Antiretroviral Therapy Adherence and Effectiveness in a Private Sector Disease Management Programme in Southern Africa

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by

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STATEMENT OF AUTHOR'S CONTRIBUTION

The work presented in this thesis is the product of several studies using a dataset provided by the Aid for AIDS disease management programme in Cape Town, South Africa. I personally was involved closely at all stages, including study design, data management and analysis, data interpretation and writing under the supervision of Professor Gary Maartens. I was responsible for checking the quality of the data collected and held in the dataset and have done all the analyses. For further dataset cleaning, I was helped by the Aid for AIDS data manager, and for advanced statistical analysis techniques, when needed, I got helpful supervision from the Department of Epidemiology and Biostatistics at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. The contribution, help and advice I have received from others (see acknowledgement section) was complementary to, and not a substitution for, my personal expertise, critical appraisal, and intellectual and scientific authorship.

The work on which this thesis is based has not, in whole or in part, been submitted towards another degree at this university or elsewhere. The University of Cape Town is empowered to reproduce either the whole or any portion of the contents for purposes of research.

NOTE FROM THE AUTHOR

In 1998, I was very grateful and fortunate to have received the Stellios M. Stelson Scholarship from the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, to work toward their Masters in Public Health (MPH) degree with supplementary funding from the Dikembe Mutombo Foundation, Atlanta, GA, USA. The Johns Hopkins MPH program, one of the top programs in the world, equipped me with tools in Epidemiology, Biostatistics and International

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2. NACHEGA JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to Non-Nucleoside Reverse Transcriptase-based HIV Therapies and Virologic Outcomes. *Ann Int Med* 2007;146(8):564-73.

3. NACHEGA JB, Hislop M, Dowdy DW, Lo M, Omer BS, Regensberg L, Chaisson RE, Maartens G. Adherence to Highly Active Antiretroviral Therapy as Assessed by Pharmacy Claims Predicts Survival in HIV-infected South African Adults. *J Acquir Immune Defic Syndr* 2006;43(1):78-84.

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5. Mills EJ, NACHEGA JB, Guyatt G, Buchan I, Orbinski J, Attaran A, Singh S, Rachlis B, Wu P, Thabane L, Wilson K, Bangsberg DR. Adherence to Antiretroviral Therapy in Africa and North America: A Meta Analysis. *J Am Med Assoc* 2006;296(6):679-90.

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GLOSSARY

AfA	Aid for AIDS
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of Variance
AUC	Area Under the Curve
CD4 count	$CD4^+$ T cell count
CI	Confidence Interval
CROI	Conference on Retroviruses and Opportunistic Infections
DNA	Deoxyribonucleic Acid
EFV	Efavirenz
GFATM	Global Fund Against AIDS, Tuberculosis and Malaria
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IQR	Interquartile Range
IRIS	Immune Reconstitution Inflammatory Syndrome
KM	Kaplan Meier
MEMS	Medication Event Monitoring System or Electronic Medication Monitoring System
µL	Microlitres
mL	Millilitres
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OR	Odds Ratio
PEPFAR	Presidential Emergency Plan for AIDS Relief
PI	Protease Inhibitor
PMTCT	Prevention of Mother-to-Child HIV Transmission
RNA	Ribonucleic Acid
ROC	Receiver Operating Characteristic
RR	Relative Risk
RT	Reverse Transcriptase
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

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ABSTRACT

Background: Adherence to highly active antiretroviral therapy (HAART) is among the most important predictors of treatment effectiveness for people infected with Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS). However, it is unclear how adherence should best be monitored in large HIV programs in sub-Saharan Africa where treatment is being scaled up. Furthermore, the precise relationship between adherence and healthcare burden and costs is not well defined. This dissertation presents the results of evaluating pharmacy refill claims data as a measure of HAART adherence and of determining the association between HAART pharmacy-claim adherence and virologic and clinical outcomes, including survival, and costs in HIV-1-infected patients enrolled in Aid for AIDS, a private-sector HIV/AIDS management programme operating in nine countries in southern Africa. Aid for AIDS collects demographic and longitudinal clinical data on participants. Patients in the program are started on HAART once they reach a certain $CD4^+$ T cell count level or develop an AIDS-defining illness, and a monthly claim submitted to the patient's health insurance provides reimbursement for the cost of HAART regimen.

Design and Methods: These investigations were accomplished using observational cohort studies. Pharmacy and clinical records of patients who enrolled in Aid for AIDS between 1998 and 2007 and who began receiving HAART at some point during that period were included. Pharmacy claim adherence is expressed as a percentage, calculated as the number of months with claims submitted divided by the number of complete months between the date of HAART commencement and (*a*) death, (*b*) withdrawal from the AfA program, or (*c*) study end, and the result multiplied by 100. The specific aims were: 1) To determine the impact of adherence as evaluated by pharmacy claim data on time to virologic suppression as well as time to failure after initial virologic suppression; 2) To determine whether there is an association between

pharmacy-claim adherence and survival; 3) To compare pharmacy-claim adherence by initial non-nucleoside reverse transcriptase inhibitor-based regimens (in particular Nevirapine vs. Efavirenz) and by virologic and clinical outcomes; 4) To compare adults to adolescents in terms of adherence measured by pharmacy claim data, clinical outcomes and virologic outcomes; 5) To evaluate the impact of pharmacy-claim adherence on direct health care costs.

Results: Of the 6288 Aid for AIDS registrants who began HAART between January 1999 and August 2004, 3805 (61%) were female and 6094 (97%) were black African. HAART adherence was >or= 80% for 3298 patients (52%) and was 100% for 1916 patients (30%). Women were significantly more likely to have adherence >or= 80% than men (54% vs 49%, P<0.001). The median (interquartile range) follow-up time was 1.8 (1.37-2.5) years. As of 1 September 2004, 222 patients had died, resulting in a crude mortality rate of 3.5%. In a multivariate Cox regression model, adherence <80% was associated with lower survival (relative hazard 3.23; 95% confidence interval: 2.37-4.39). When medication adherence was divided into five strata with a width of 20% each, each stratum had lower survival rates than the adjacent higher-adherence stratum. In a subset of 2821 patients started on non-nucleoside reverse transcriptase inhibitor-based HAART, each 10% increase in pharmacy claim adherence greater than 50% was associated with a mean absolute increase of 0.10 in the proportion of patients with sustained virologic suppression (defined as viral load <400 copies/mL) (P < 0.001). Predictors for shorter time to virologic failure after initial suppression in multivariable Cox regression included $CD4^+$ T-cell counts of 500 x 10^6 cells/mL or less (hazard ratio, 1.60 [95% CI: 1.22 to 2.10] vs. $CD4^+$ T-cell counts >200 x 10^6 cells/mL), baseline viral load greater than 10^5 copies/mL (hazard ratio, 1.39 [CI: 1.14 to 1.70]), nevirapine-based regimen (hazard ratio, 1.43 [CI: 1.16 to 1.75]), and low pharmacy claim adherence (hazard ratio, 1.58 [CI: 1.48 to 1.69], per 10% decrease in adherence to 50%). In an analysis of 154 adolescents [age 11 to 19 years] compared to 7622 adults [age ≥20 years], adolescents did not have significantly increased times to initial virologic

suppression <400 copies/mL (HR 0.86; 95% CI 0.70-1.05). However, after achieving initial suppression, adolescents had shorter times to virologic rebound >400 copies/mL (HR 2.1; 95% CI 0.63-1); this finding was restricted to patients who failed to maintain 100% adherence. Adolescents were more likely to have lower pharmacy claims adherence than adults. In a final analysis, poor pharmacy claim adherence was associated with greater hospitalisation costs.

Significance of this work: Pharmacy refill claims are an effective tool to estimate HAART adherence. This is believed to be the first demonstration of a linear association between adherence and virologic outcomes for patients on NNRTI-based HIV therapy, a finding that has important clinical and public health implications both in Africa and in developed countries. This is also believed to be the first investigation to show the association between adherence and survival in Africa, and the first evidence from Africa that efavirenz is superior to nevirapine when considering both virologic endpoints and clinical endpoints and when taking into account adherence to therapy. This work is also believed to be the first to show that adherence in adolescents in southern Africa is worse than in adults, a discovery that requires further investigation to identify reasons and to tailor appropriate interventions to improve adherence in this population. And finally, this is the first report that adherence correlates with inpatient hospitalisation costs.

Conclusion: This work shows that pharmacy refill or claim data may be a simple and effective population-level tool for monitoring treatment adherence and predicting treatment effectiveness as HAART programs in Africa are scaled up.

Chapter 1

Introduction and Literature Review

The HIV/AIDS Epidemic in sub-Saharan Africa

Of the world's estimated 35 million people living with HIV in 2007, roughly 68% live in sub-Saharan Africa.[1,2] Although domestic and international efforts to stabilize and reduce HIV incidence in sub-Saharan Africa have achieved notable accomplishments, success has been inconsistent. [3] Recently, in countries such as Uganda and Kenya, the national HIV prevalence has been reduced to less than 10%.[1] Southern Africa, however, remains one of the hardest hit by HIV. The latest report from UNAIDS suggests that this region is home to 35% of all people living with HIV infection and 32% of all deaths due to HIV/AIDS.[1] Because of a change in methodology and improvement in countries' disease-monitoring programmes [2], it is difficult to compare the most recent adult HIV statistics with those published in earlier years. However, according to these new figures, eight countries of southern Africa still have HIV-infection prevalence in excess of 15%.[1] In sub-Saharan Africa, AIDS is still the single largest cause of mortality, claiming the lives of 1.6 million adults and children in 2007 alone.[1]

Access to Antiretroviral Therapy in Africa

Until a few years ago, HIV infection almost always led to an early death from AIDS. However, since the advent of highly active antiretroviral therapy

(HAART), the disease largely has been transformed into a treatable and chronic condition in developed countries. For individuals with access to HAART, a treatment cocktail combining three or more antiretroviral drugs, the risk of opportunistic infection and death has plummeted [4-7]. The use of HAART has additional public health benefits, reducing vertical [8,9] and possibly horizontal transmission [10].

Although HAART has had a major impact on HIV infection in developed countries, its public health impact in developing nations has been limited, even though 95% of the 36 million HIV-infected individuals in the world live in low-income countries.[1] It is estimated that by December 2006, close to 2,015,000 people living with HIV/AIDS (1.8-2.2 million) were receiving treatment in low- and middle-income countries. In sub-Saharan Africa, close to 1.3 million are receiving antiretroviral therapy HAART for a coverage of 28% of the infected population, whereas three years ago only 100,000 were on treatment for a coverage of only 2%. While antiretroviral therapy coverage still needs to increase in developing countries, the rate of increase in antiretroviral access over just a few years is encouraging [2]. As an example, WHO estimates indicate that as of June 2006, the proportion of patients requiring urgent access and currently receiving ART was 65% in Botswana, 24% in Burkina Faso, 17% in Cameroon, 16.2 % in Cote d'Ivoire, 3.3% in the DRC, 8% in Nigeria, 37% in Rwanda, 18.8% in South Africa, 3.2% in Tanzania, and 61% in Uganda.[11,12] In Malawi, only 16.5% of patients requiring immediate treatment are receiving HAART, but therapy is being scaled

up in the Zomba district at a relatively unprecedented rate of 250 patients per month.

HAART's benefits in managing HIV-infected patients are clearly dramatic and life-prolonging, but the costs, feasibility, and lack of effective delivery methods remain formidable barriers to the effective and sustainable scale-up of treatment in developing countries. [13] Because of these barriers, routine use of HAART in sub-Saharan Africa and in Asia was considered to be impossible until just a few years ago.

The effort to bring anti-HIV therapies to developing countries is evolving and continues to be a major theme for the public health community, pharmaceutical companies, and governmental and non-governmental organizations. AIDS researchers in sub-Saharan Africa have been working to demonstrate the feasibility of both treatment of HIV and prevention of transmission in this setting. Activists are working diligently to make antiretroviral drugs more accessible through a variety of means, while international initiatives to increase access to HAART in sub-Saharan Africa and other resource-poor settings include discounts and marketplace competition for AIDS drugs. Examples of this include the "Accelerating Access" initiative from major pharmaceutical companies in collaboration with UNAIDS, and offers of reduced pricing and simplified dosing (fixed-dose formulations) from generic drug makers, including Cipla and Ranbaxy of India. These and other efforts have been supported in part by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the United Nations Global Fund to Fight AIDS, Tuberculosis and

Malaria (GFATM). Promising results from some of the first studies on the feasibility and early outcomes of providing HAART to large populations in resource-limited settings clearly support the effectiveness of treatment in developing countries [14,15].

Antiretroviral Treatment Adherence

Medication adherence typically refers to the extent to which individuals take medications as prescribed. Optimal adherence can been defined based on the virologic, immune, and clinical outcomes of patients whose adherence was measured during longitudinal studies. For the old unboosted protease inhibitor (PI) -based ART regimens, Paterson et al. described optimal outcome in patients who take ≥95% of the medications prescribed by their physician. [16] Currently, NNRTI-based HAART is the mainstay of initial HIV treatment in sub-Saharan Africa. While early versions of HAART required >95% adherence to be effective, accumulating data shows that NNRTI therapy can suppress HIV at moderate adherence (70-90%). [17-19, Chapter 3].

NNRTIs' longer half-life may lead to better virologic suppression at moderate adherence rates, but paradoxically lead to prolonged monotherapy and resistance during a treatment interruption, such as occurs when transport barriers prevent patients from obtaining refills (Figure 1). Indeed, a study in Kampala, Uganda, [17] of patients purchasing generic antiretroviral fixed-dose NNRTI-based combination therapy found that 65% had a treatment interruption

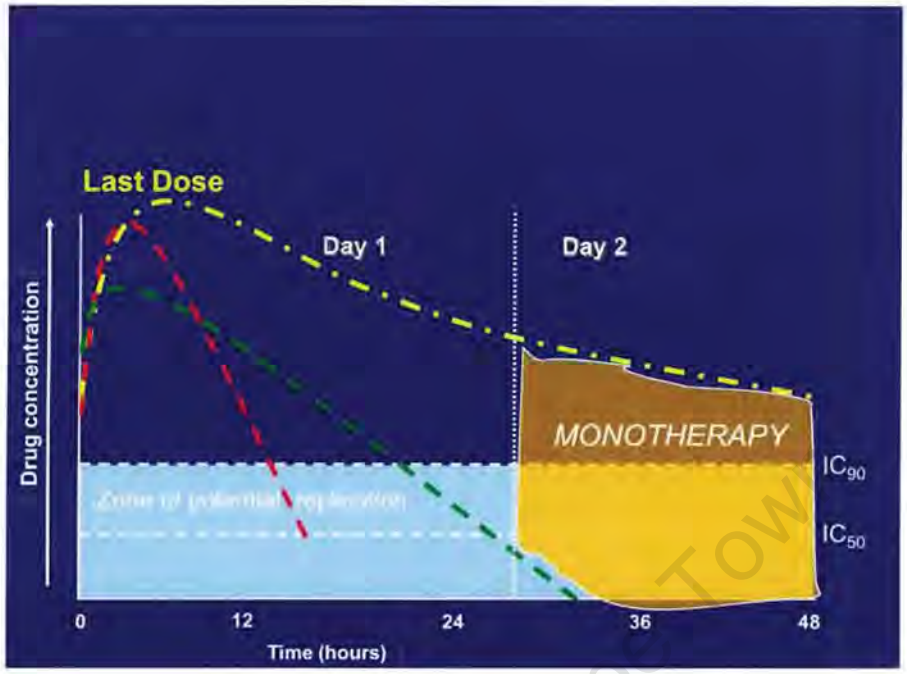


Figure 1: Stopping antiviral drugs of different half-lives (Adapted from [20]).

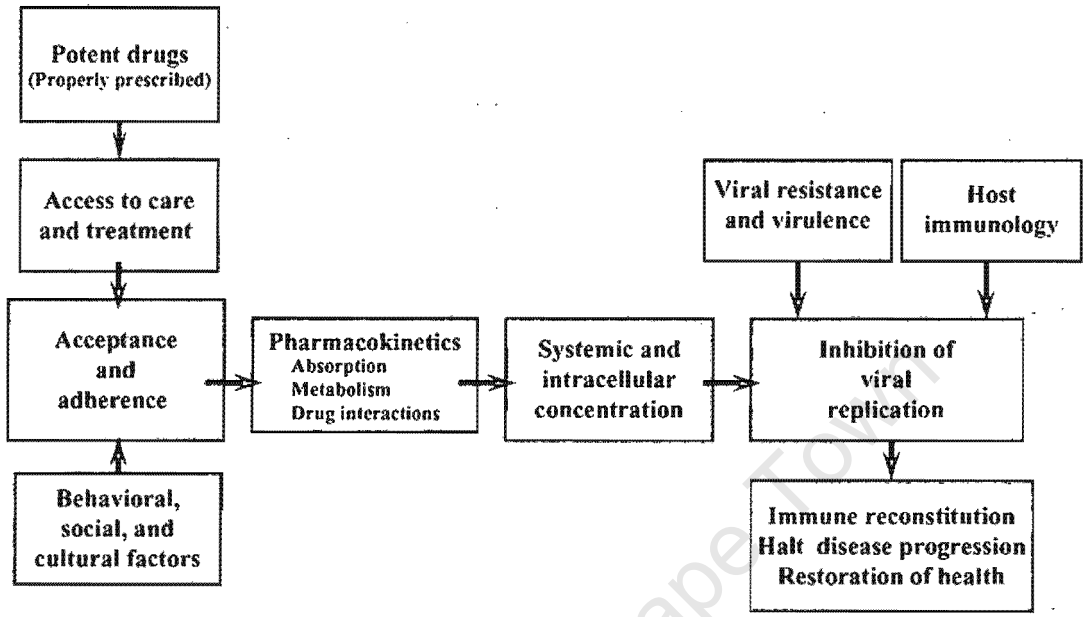
of greater than 48 hours as evaluated by adherence electronic monitors (MEMS caps), and these treatment interruptions accounted for 90% of missed doses.[17] Eight of the 62 (13%) participants who had these treatment interruptions experienced drug resistance, while none of the 33 participants without treatment interruptions greater than 48 hours had drug resistance.[17] Importantly, they also reported a significant decrease in virologic success rates (reduction of a patient's viral load), from 80% to 50%, for patients with <95% adherence.

There are a number of determinants of effective treatment of HIV infection which include biology, behaviour, and social issues. A "pathway" to treatment success was described by Friedland [21] that illustrates the critical roles in

medication adherence played by the health care system, including the development and availability of potent medications, prescription of these drugs, and regular patient access to health care and to medication, as well as by patients' own behavioural, social and cultural contributions (Figure 2). All of these factors must come together to allow excellent adherence.

The fragility of this pathway to adherence is jeopardized by the complexity of antiretroviral regimens. As an example, a South African patient taking the first-line HAART regimen must take five pills in 24 hours, which is much more complex than the regimen for patients who can afford combination pills that include several drugs in a single pill. In order to remain >95% adherent to ART, a patient could miss no more than seven out of the 150 pills the patient takes per month, and for maximal efficacy the 150 pills must be taken at the prescribed time. Moreover, like any other substance in the bloodstream, antiretroviral drugs are metabolized and excreted as time passes. [21] When patients do not accurately adhere to their regimen schedule and instead take their drugs too late or too early, blood concentrations can drop below the level necessary to suppress HIV, which may lead to drug resistance, disease progression and death, or rise to levels that are hazardous to the patient because of drug toxicity.

Figure 2. Determinants of Drug Efficacy for HIV Therapeutics. [21]



Effectively expanding or scaling up HAART access in countries with limited resources will depend on the local infrastructure and available resources. These aspects are important not just for delivering HAART and providing health care, but in monitoring treatment adherence, one of the most important predictors of therapeutic effectiveness in both developed and developing countries. Indeed, at the time the studies described herein were begun, adherence to HAART had been shown to be a major predictor of viral suppression of HIV replication [16,22,23], emergence of drug resistance [24-26], disease progression [27], and death [28,29].

Although adherence is increasingly recognized as a critical factor in treatment effectiveness, there is an urgent need for the development and

implementation of simplified, standardized treatment and monitoring algorithms that will facilitate roll-out and scale-up of programs and enable counselling and follow-up of patients, as recently recommended by WHO guidelines [2]. Required aspects of infrastructure include not only mechanisms to obtain and dispense drugs, but also to teach patients about adverse side effects, adherence and lifestyle modifications to improve treatment effectiveness.

Adherence in Sub-Saharan Africa

Historically, there has been an expectation of poor adherence in Africa [30,31] expressed at high levels of international agency decision-making [32] that has arguably contributed to the delay in antiretroviral roll-out [33]. Yet, until my colleagues and I conducted a meta-analysis to assess adherence in Africa, decisions regarding adherence had been based on anecdote and personal values. In our international research collaborative study published to coincide with the International AIDS Society (IAS) Conference in 2006, we examined reported levels of adherence measured in a variety of ways, including pill-counts, pharmacy refill data, electronic medication monitoring systems (MEMS), and self-report. [34] We found that, on average, 77% of African HAART patients (95% Confidence Interval [CI]: 68-85%) met the standard definition of good clinical adherence (≥80%) (Figure 3) compared to 55% (95% CI: 49-62%) of North American patients (Figure 4).

Figure 3. Meta-analysis of published studies showing antiretroviral therapy adherence in HAART-naive patients from sub-Saharan Africa. [34]

Source	Country	No. Adherent/ Total No.	Proportion Adherent (95% CI)
Full-Text Articles			
Byakika-Tusiime et al,[57] 2005	Uganda	207/304	0.68 (0.63-0.73)
Idigbe et al,[55] 2005	Nigeria	38/44	0.86 (0.73-0.95)
Iliyasu et al,[58] 2005	Nigeria	142/263	0.54 (0.48-0.60)
Laurent et al,[56] 2002	Senegal	51/58	0.88 (0.77-0.95)
Laurent et al,[59] 2004	Cameroon	52/60	0.87 (0.75-0.94)
Orrell et al,[53] 2003	South Africa	175/278	0.63 (0.57-0.69)
Nachega et al,[54] 2004	South Africa	58/66	0.88 (0.78-0.95)
Weiser et al,[60] 2003	Botswana	59/109	0.54 (0.44-0.64)
van Oosterhout et al,[61] 2005	Malawi	92/176	0.52 (0.45-0.60)
Abstracts			
Adedayo et al,[62] 2005	Nigeria	593/689	0.86 (0.83-0.89)
Brown et al,[64] 2004	South Africa	38/50	0.76 (0.62-0.87)
Boileu et al,[77] 2005	Burkina Faso and Mali	139/270	0.51 (0.45-0.58)
Byakika et al,[69] 2005	Uganda	25/28	0.89 (0.72-0.98)
Daniel et al,[63] 2004	Nigeria	42/53	0.79 (0.66-0.89)
Darder et al,[67] 2004	South Africa	168/192	0.88 (0.82-0.92)
Eholie et al,[78] 2004	Cote D'Ivoire	148/304	0.49 (0.43-0.54)
Ferris et al,[65] 2004	South Africa	57/74	0.77 (0.66-0.86)
Hosseinipour et al,[73] 2004	Malawi	134/141	0.95 (0.90-0.98)
Karcher et al,[68] 2004	Uganda	52/76	0.68 (0.57-0.79)
Muganzi et al,[70] 2004	Uganda	519/530	0.98 (0.96-0.99)
Okongo et al,[71] 2004	Uganda	97/100	0.97 (0.91-0.99)
Omes et al,[74] 2004	Rwanda	90/95	0.95 (0.88-0.98)
Nachega et al,[66] 2005	South Africa	3908/7812	0.50 (0.49-0.51)
Ramadhani,[79] 2006	Tanzania	125/150	0.83 (0.76-0.89)
Shihab et al,[72] 2004	Uganda	65/84	0.77 (0.67-0.86)
Tu et al,[75] 2004	Democratic Republic of Congo	30/30	1.00 (0.88-1.00)
Traore et al,[76] 2004	Burkina Faso	24/80	0.30 (0.20-0.41)
Combined			0.77 (0.68-0.85)

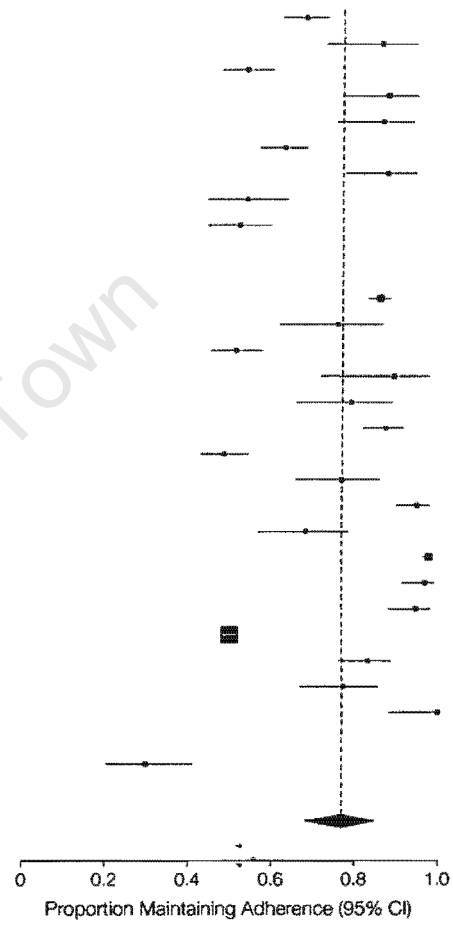
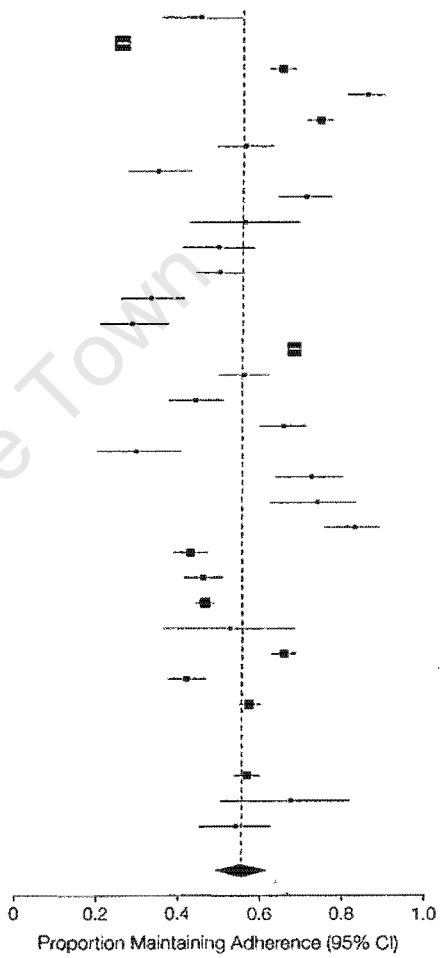


Figure 4. Meta-analysis of published studies showing overall antiretroviral therapy adherence in both experienced and HAART-naive patients from North America [34]

Source	Country	No. Adherent/ Total No.	Proportion Adherent (95% CI)
Full-Text Articles			
Acri et al,[24] 2005	United States	48/106	0.45 (0.36-0.55)
Becker et al,[25] 2002	United States	985/3788	0.26 (0.25-0.27)
Castillo et al,[48] 2004	Canada	514/788	0.65 (0.62-0.69)
Cook et al,[26] 2001	United States	188/219	0.86 (0.81-0.90)
Diamond et al,[27] 2005	United States	508/683	0.74 (0.71-0.78)
Eldred et al,[28] 1998	United States	116/207	0.56 (0.49-0.63)
Ferguson et al,[3] 2002	United States	52/149	0.35 (0.27-0.43)
Gebo et al,[29] 2003	United States	139/196	0.71 (0.64-0.77)
Graney et al,[31] 2003	United States	32/57	0.56 (0.42-0.69)
Gifford et al,[30] 2000	United States	66/133	0.50 (0.41-0.58)
Heckman et al,[32] 2004	United States	136/272	0.50 (0.44-0.56)
Hinkin et al,[33] 2004	United States	49/148	0.33 (0.26-0.41)
Ingersoll and Heckman,[34] 2005	United States	14/46	0.30 (0.18-0.46)
Johnson et al,[35] 2005	United States	1887/2765	0.68 (0.66-0.70)
Kalichman et al,[36] 2005	United States	143/255	0.56 (0.50-0.62)
Levine et al,[37] 2005	United States	98/222	0.44 (0.38-0.51)
Mohammed et al,[38] 2004	United States	179/273	0.66 (0.60-0.71)
Paterson et al,[4] 2000	United States	24/81	0.30 (0.20-0.41)
Penedo et al,[39] 2003	United States	84/116	0.72 (0.63-0.80)
Power et al,[40] 2003	United States	54/73	0.74 (0.62-0.84)
Russell et al,[41] 2004	United States	108/130	0.83 (0.76-0.89)
Schneider et al,[42] 2004	United States	238/554	0.43 (0.39-0.47)
Tesoriero et al,[43] 2003	United States	200/435	0.46 (0.41-0.51)
Tucker et al,[44] 2003	United States	888/1910	0.46 (0.44-0.49)
Wagner et al,[45] 2002	United States	21/40	0.53 (0.36-0.68)
Weiss et al,[46] 2003	United States	655/997	0.66 (0.63-0.69)
Wilson et al,[47] 2001	United States	191/454	0.42 (0.37-0.47)
Wood et al,[49] 2003	Canada	816/1422	0.57 (0.55-0.60)
Abstracts			
Montessori et al,[52] 2000	Canada	504/886	0.57 (0.54-0.60)
Robertson et al,[51] 2006	United States	25/37	0.68 (0.50-0.82)
Temoshok and Wald,[50] 2004	United States	71/131	0.54 (0.45-0.63)
Combined			0.55 (0.49-0.62)



This finding has had important implications for international assistance regarding improved access to HAART and was referred to by former U.S. President Bill Clinton at the 2006 IAS Conference as the "nail in the coffin" on discrimination regarding drug access. [35] The finding clearly indicated that there were erroneous assumptions about adherence in poverty-affected populations that adversely affected treatment, access, and clinical care.

Given the individual and public health implications associated with adherence to HAART, there is a need for a greater understanding of actual adherence rates within specific populations. In addition to evaluating levels of adherence, it is important to examine reasons for poor adherence and possible motivators to improve adherence.[36] A review of the literature shows that the most important and prevalent factors reported to negatively impact adherence in sub-Saharan Africa are: cost [36-39]; non-disclosure to a loved one or fear of being stigmatized [38,40]; alcohol abuse [36]; and difficult drug regimens [37,41]; Studies report that the majority of patients accessing ART have disclosed their HIV status to family or friends [42,43] and that those who have not appear to do worse on therapy [38,40]. Patients who do not disclose their infection are likely to have frequent treatment interruption due to the fact that tablets must be hidden and not taken in the presence of others. Encouraging voluntary HIV status disclosure in a community with access to ART may result in improved uptake of voluntary counseling and testing (VCT) and may help decrease stigma and improve adherence, although findings of qualitative studies should not be

generalized. Preliminary, as-yet unpublished data from the 2006 Dignitas Baseline Survey (DBS) suggests wide variance in urban and rural adherence patterns and identifies some factors that may affect adherence, such as transport costs to and from clinics, clinical oversight and access to pharmacy refills. [Ed Mills, PhD, personal communication]

Very few interventions have been designed that have successfully demonstrated improved adherence, and most have been limited to North American settings. [44] Knowledge of effective adherence interventions in African settings is limited. One of the most controversial program components of HAART scale-up in developing countries, including Malawi, is whether there is a need for intensive interventions such as directly observed therapy of ART, known as DOT-HAART. By having a close family member or friend to whom the patient has voluntarily disclosed their HIV status observe a patient actually take each dose, DOT-HAART is proposed to influence patient outcomes. Indeed, in settings with high HIV status disclosure rates, community-based DOT-HAART with a patient-nominated treatment accompagnateur or supporter [15,45] has been reported to be feasible and to help improve or maintain high levels of ART adherence. However, in order to separate the influence of DOT-HAART from a constellation of other services provided by the treatment program, this finding still needs to be confirmed in well-conducted randomized trials, which are underway in several African countries. Furthermore, patients who are not able to disclose due to fear of stigma, discrimination, or violence would need other culturally sensitive

adherence interventions. Other methods, such as long-term clinic-based DOT-HAART, may prove to be unfeasible given the lifelong nature of HIV treatment and paucity of clinic settings.

However, because adherence is so important for treatment effectiveness, it is critical to establish a reliable, cost-effective method for determining or estimating adherence and, eventually, to use that method to evaluate adapted, culturally appropriate interventions to improve adherence.

Relationship between Adherence and Drug Resistance

The phenomenon of HIV drug resistance continues to receive major attention because it not only threatens the patient in which it develops, but has the potential to undermine our ability to fight the HIV/AIDS pandemic by rendering current treatments ineffective, especially in the developing world where HIV salvage therapy is very costly and drugs may not even be available. [46] Like any evolutionary change, the development of resistance first occurs with a mutation of the genetic material responsible for the overall structure or function of an organism or virus. Experts estimate that a mutation occurs in the HIV genome once every time it is replicated because viral enzymes lack the proof-reading mechanisms that help limit the mutation rate in mammalian cells. [47] Therefore the potential mutation rate in HIV can be quite high if virus replication is not suppressed by medication.

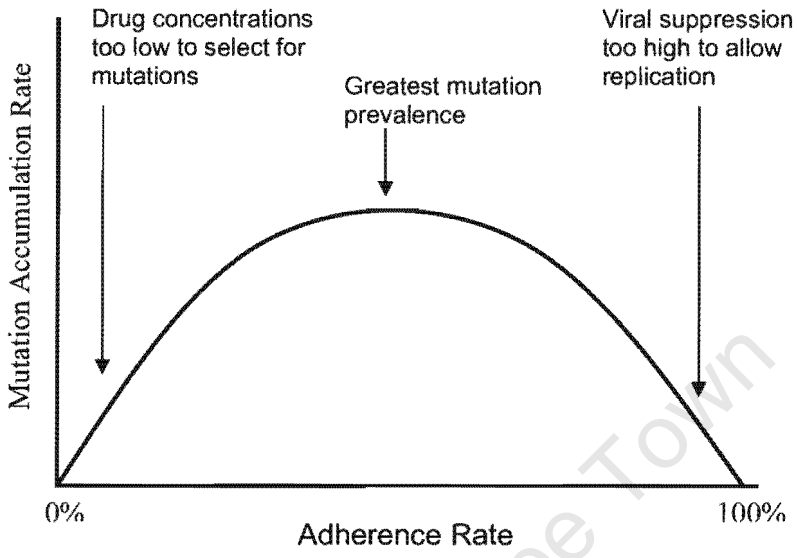
It is worth noting that not all mutations have the same impact; most either have no effect or are detrimental to the virus in some way. Occasionally though,

a genetic mutation alters an HIV particle in a way that makes it impervious to a medication in HAART. Usually the mutant HIV particle is in some way less fit than the standard, or wild-type, strain. However, when the second ingredient for evolution, selection pressure, is added, the mutant may gain the advantage. Selection pressure occurs when HAART incapacitates the wild-type strain, but is ineffective against the mutant strain, allowing it to replicate unchecked. Eventually the resistant strain is able to expand and dominate the HIV population in that individual.

It is a common belief that non-adherence to medication breeds drug-resistance. However, taking into account the evolutionary model of resistance, one can see that the relationship between adherence and resistance is much more complex. This relationship is not simply linear but parabolic (Figure 5). It is true that at the highest levels of adherence the threat of resistance is lowest because mutations cannot occur without replication. A review of studies addressing the adherence and resistance relationship reported that "the likelihood of accumulating new mutations will increase sharply with even small departures from perfect adherence, with a rise to 1.9 times higher with individuals with 90% adherence." [48] Therefore, while exceptional adherence effectively prevents resistance by stopping viral replication, moderate adherence can allow slow progression toward resistance.

However, the relationship between adherence and resistance is shaped by the fact that most mutant strains are less fit than the wild-type strains, which means a certain level of selection pressure is required before the mutant strains

Figure 5. Hypothetical curve demonstrating relationship between adherence and development of drug resistance. [48]

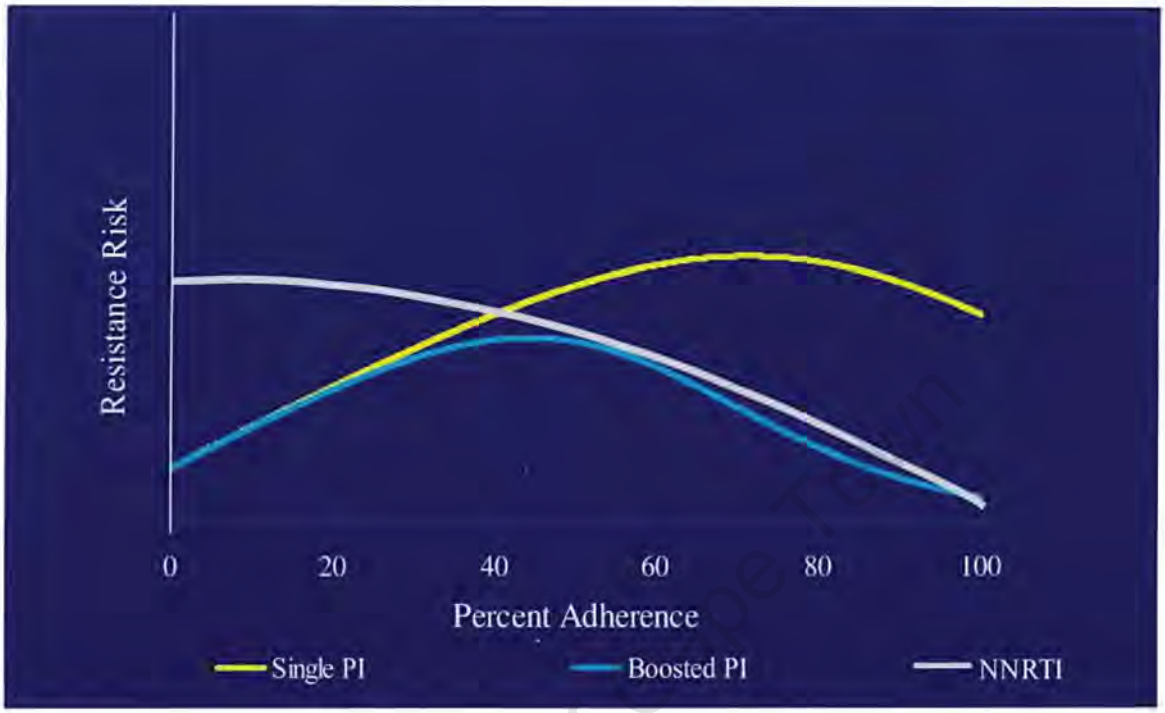


are able to out-compete the wild-type strains. As a result, low levels of adherence do not impose the necessary selection pressure on the HIV population and so mutant strains or quasi species persist at only very low levels and resistance is less likely; of course low adherence is not advisable since it allows the wild-type virus to replicate unchecked, leading to disease progression. [50] This 'u-shaped' relationship leaves moderately adherent patients at the greatest risk for the development of resistance. [48]

Recent work by Bangsberg and colleagues found that this relationship between adherence and drug resistance differs depending on the antiretroviral drug class. [50,51] Indeed, they showed that NNRTI-based drug regimens are more likely to produce resistance than PI-based because of several factors. First,

NNRTIs act on HIV's reverse transcriptase (RT) at an area removed from the active site—the location required for enzymatic activity—so NNRTI-resistance changes have little effect on RT's overall function and hence little impact on viral fitness. Also, the high potency and extended half-life of NNRTIs increase both the magnitude and duration of selection pressure and therefore promote greater resistance development even under conditions of very poor adherence or treatment discontinuation. [50,51] Finally, there is a low genetic barrier to resistance mutations for current NNRTIs, which exacerbates other factors affecting the adherence-resistance relationship for current NNRTIs. As a consequence, the threat of resistance to today's NNRTIs is highest at low adherence, rather than at moderate adherence, because even the lowest concentrations of these NNRTIs create enough selection pressure to affect HIV (Figure 6). Protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) require multiple mutations, each of which alters enzyme function and could make the virus less fit. [52] It is therefore not surprising that NNRTI resistance is seen more often than PI or NRTI resistance.

Figure 6. Resistance risk by adherence and regimen class. (Adapted from [50])



Measuring Adherence

Although adherence is of critical importance, it is only recently that adherence measures have been examined empirically. [53-55] Common methods of adherence measurement include pill counts, electronic monitoring, pharmacy record reviews, and self-report measures. [56,57] However, each method has distinct advantages and disadvantages including cost, complexity, accuracy, intrusiveness and bias. To date, there is no gold standard, and the selection of a method varies depending on availability and feasibility. Gill et al. [58] found large discrepancies among estimated adherence for different methods used within the same groups. They constructed a relative hierarchy of adherence

measurement methods, and reported that physician assessment and self-report were the least accurate, pill counts were intermediate, and electronic drug monitoring provided the most accurate surrogate of antiretroviral adherence [58].

Of note, studies of adherence measures typically rely on limited assessment of criterion-related forms of validity such as predictive or concurrent validity. In most cases, validation of an adherence measure is based on how well the measure predicts virologic outcomes. [54] While this ability is of central importance, accurate prediction of virologic outcome provides only limited information about what is actually being measured in terms of adherence behaviour. In addition, some have argued that virologic failure is an inadequate indicator of non-adherence, as several other factors (e.g., viral mutations, HIV viremia at initiation of therapy, potency of the therapy prescribed, individual differences in absorption, and drug interactions) also mediate virologic outcomes. [56,59] Assessments of content validity (i.e., how well the measurement items represent the entire universe of items or domain being assessed) and construct validity (i.e., how well a measure reflects some underlying construct or latent variable) are rare [57], and to our knowledge have only been evaluated in one very small study from Uganda, by Oyugi et al. [60]

Problems related to adherence measurement have been perpetuated by the use of the single term 'adherence' to refer to various adherence behaviours. In the case of adherence to HAART, full adherence involves a series of distinct behaviours, including continuing access to treatment, timely refilling of a prescription, correctly counting medications, and ensuring that medications are

taken at the right time of day and in accordance with dietary guidelines. The cognitive and behavioural tasks that comprise "adherence" include both prospective and retrospective memory components [61], as patients must not only remember when to perform the adherence behaviour, but they also must remember what the behaviour consists of. Below, the different adherence measurement methods available are reviewed.

Pill Count

Two types of pill counts have been used to measure medication-quantity adherence. Announced pill counts occur when patients bring their pill bottles to a practitioner who counts the remaining medications to determine the number of medications not consumed. A second type is an unannounced visit to a patient for the purpose of pill counting. [62] Adherence measured by pill count is calculated by dividing the number of pills taken by the number prescribed.

Studies employing pill counts have shown moderate associations with surrogate markers of adherence such as viral load and CD4 cell count. [54,62,63] However, in studies comparing several measures of adherence, pill counts have been found to be inferior to other methods, in particular electronic MEMS (Medication Event Monitoring System) and composite adherence measures, [54,66] although studies have reported that unannounced pill counts are more predictive of viral load than self-reported adherence measures. [64]

There are several limitations associated with pill count methods. First, as for any other adherence measure which does not demonstrate patients'

medication ingestion or therapeutic plasma drug levels, pill counts only measure medication-quantity adherence, and therefore associations with virologic outcomes can be contaminated by other unmeasured adherence behaviours. In addition, investigators must assume that medications missing at time of the pill count have been consumed. Pill counts also provide an estimate of average adherence and do not capture drug "holidays" [65]. Furthermore, when compared with other measures, some have argued that pill counts tend to overestimate adherence [63] because some subjects may dump pills prior to counting [66]. In terms of feasibility, pill counts are time-consuming and may seem overly paternalistic to some patients. [56] Unannounced pill counts, although they may be superior, are costly and likely will only be a research tool. For these reasons, and the problem of patients forgetting to bring pill bottles for counting, pill counts are not ideal for routine clinical settings.

Medication Event Monitoring System (MEMS)

Medication Event Monitoring Systems (MEMS), also known as electronic medication monitoring systems, are being used increasingly in studies of adherence. [22] These systems use a microchip placed in a medication bottle cap that records the date and time of openings and closings of the cap. [67] The bottles are placed on a communicator that downloads and displays all openings and closings for up to 30 days. The software computes the percentage of time the patient had drug coverage based on recorded dose events (i.e., openings) and the prescribed time interval between doses. [68] This method of adherence assessment is considered by many to be the most objective and accurate

method of adherence measurement [56,68,69], but it is rarely used in developing settings [22].

Adherence to antiretroviral therapy as evaluated by MEMS technology has been associated with virologic and immunological outcomes [16,23,53,64,70]. In addition, longitudinal and cross-sectional comparisons of multiple adherence measures have found that MEMS-measured adherence was more strongly associated with virologic outcome than other measures such as pill counts, self-reported adherence, and pharmacy refills. [23,53,54,64,71,72]

Despite these encouraging findings, there are numerous shortcomings for this approach. First, while MEMS is generally used to obtain information concerning medication-quantity and medication-interval adherence, MEMS, in fact, measures nothing other than pill bottle openings and cannot distinguish between a proper dose and issues such as patients taking out several pills during one bottle opening (also known as "pocket doses") as well as "curiosity events", when patients open the pill bottle out of curiosity but do not remove a pill. [16,64] Another problem arises because subjects are restricted to use of the MEMS cap and bottle and cannot use pillboxes, which are memory aids that increase medication adherence. [73] In addition, system malfunction and incorrect use of MEMS have forced exclusion of some patients in adherence assessments in some studies. [63,74]

In terms of feasibility, electronic monitoring technology is difficult to implement. A single MEMS cap costs approximately US$100 and can only be used by one patient at a time. [75] In addition, use of these devices may threaten

patient privacy and alter pill-taking behaviour as clients are forced to carry around larger or unusual pill containers. [76]

Pharmacy Refill or Claims

Pharmacy data have been used extensively to calculate medication adherence. [77,78] Pharmacy refill is defined as the number of times that medicines have been dispensed, whereas pharmacy claims refer to the number of times medicines were dispensed and subsequently claimed to gain reimbursement. The most common method of pharmacy refill adherence measurement examines the number of prescriptions picked up, although some investigators have studied medication gaps or treatment interruptions. [78] In its simplest form, medication availability is calculated as either the number of months or days' supply obtained divided by the total number of months or days in the period or the number of refills obtained divided by the expected number of refills in a given time period [78].

Several studies have shown moderate to strong associations between pharmacy-based adherence measurements and various indices of disease progression, including virologic outcome, $CD4^+$T-cell count, and AIDS-related mortality. [71,77-81] Published studies from developed settings have found a statistically significant linear trend for viral suppression across five strata of adherence as measured by pharmacy-based adherence. [79] However, other studies have found weak or no associations between pharmacy-based adherence and measures of disease progression, likely due to low statistical

power. Finally, other investigators have reported that pharmacy-based adherence measurement is inferior to measures such as MEMS. [71,82]

The predictive validity of pharmacy records reported by various investigators is surprising given that pharmacy records only measure medication pick-up adherence. It can be assumed that some individuals who fill their prescriptions do not consume all their medications and/or do not consume them on the prescribed schedule, and therefore this method may overestimate adherence. However, the advantages of this approach include the lack of participation required from patients and problems associated with patient involvement for other methods, including time involved, inaccurate recall and socially desirable responding associated with self-report. [77] While pharmacy-based adherence measurement is often easily obtained through computerized data linkages, this approach may be time consuming and less accessible for clinicians.

Despite the possible disadvantages, as a measure of adherence, pharmacy-based data (refills and claims) are relatively simple to collect and therefore may be suitable as an adherence-monitoring tool in large HIV programs. Pharmacy refill data have previously been validated as a measure of adherence in HIV-1-infected adults, but only in developed-country settings [77,79]. One way to evaluate pharmacy data measures is to define their association with outcomes in large cohort from a "real-world" setting.

SELF-REPORTED ADHERENCE

Self-report is the most commonly used method for assessing adherence to HAART due to ease of implementation and low cost, although there are considerable differences in the composition of self-report measures. [55] While most measures focus on measuring medication-quantity adherence, the specific survey items differ greatly in the use of anchors, including use of visual aids, and the number of days on which subjects are asked to report.

A meta-analysis found that self-reported measures do predict clinical outcomes associated with adherence fairly reliably. [55] This is consistent with several earlier studies examining the relationship between self-reported adherence and virologic outcomes, antiretroviral plasma levels, and other clinical outcomes. [19,83-87] However, studies comparing self-reported adherence to other measures have repeatedly found that self-report measures likely overestimate adherence and have weaker associations with virologic outcome than do objective measures. [54,56,64,67,69] However, self-report measures do not always overestimate adherence, and, to date, there is no evidence supporting this assumption in Africa. [60]

Suggestions that self-report measures overestimate adherence are typically attributed to patients' tendency to provide socially desirable responses. [88] However, this is likely an overly simple explanation for the observed discrepancies between objective measures of adherence and self-reported adherence. One obvious problem with self-reported adherence stems from the fact that subjects might have difficulty accurately recalling what they did or forgot

to do in the course of a day. Recent studies in cognitive science have indicated that while people generally remember memory successes in everyday life, our ability to remember that we have forgotten to do a particular thing is poor. [89,90]

There are measurement issues unique to self-report methods. One problem is that these measures do not provide continuous assessment of adherence due to the time parameters commonly used. The intervals used are often too short to capture fluctuations in adherence to dose schedules that may occur over weeks or months. Indeed, Lui et al. demonstrated that MEMS and pill counts produce adherence patterns with greater variation than self-report measures. [54] However, the accuracy of adherence recall will likely diminish as the period covered is increased.

Conclusion

Adherence to antiretroviral treatment is a critical factor in the success or failure of therapy for HIV infection, but no one method for measurement or estimation of adherence has been widely accepted. To monitor effectiveness of treatment and to intervene to optimize or improve treatment effectiveness as HAART scale-up proceeds in resource-limited settings such as sub-Saharan Africa, it is necessary to select a simple, affordable adherence method for use in these settings and to validate its usefulness.

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Chapter 2

Description of the Study Population, Design and Methods

Hypothesis

The hypothesis driving these investigations was that pharmacy-claim adherence would be an appropriate and easy-to-ascertain method to estimate adherence to antiretroviral treatment regimens in a private sector HIV-disease management programme in southern Africa, and that, as an estimate of actual adherence, pharmacy-claim adherence would be associated with clinical and virologic outcomes, including survival, and direct health care costs, and that pharmacy-claim adherence and outcomes are likely to depend on patient age (adult vs. adolescent) and the NNRTI used.

Overall Objective and Specific Aims

The long-term primary objective of this study was to validate pharmacy claim data as an adherence monitoring tool in HIV-infected patients in sub-Saharan Africa.

The specific aims of this study were:

1. To determine the impact of adherence as evaluated by pharmacy data on time to virologic suppression as well as time to failure after initial virologic suppression in HIV-infected patients on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (Chapter 3)

2. To determine whether there is an association between pharmacy-claim adherence and survival (Chapter 4);
3. To compare the effects of pharmacy-claim adherence by initial NNRTI-based Regimens (Efavirenz vs. Nevirapine) on virologic and clinical outcomes (Chapter 5);
4. To compare adults vs. adolescents with respect to pharmacy-claim adherence, clinical outcomes, and virologic outcomes (Chapter 6);
5. To evaluate the association between pharmacy-claim adherence and direct health care costs (Chapter 7).

Overview of Design, Patient Cohort and Statistical Considerations

Design

These specific aims were investigated using observational cohort studies.

Patient Cohort: The Aid for AIDS Programme

Data was obtained from records of HIV-1-infected patients enrolled in Aid for AIDS, a private-sector disease management programme available to beneficiaries of contracted medical insurance funds (subsidized by employers) in nine countries in southern Africa (South Africa, Malawi, Botswana, Zimbabwe, Namibia, Zambia, Mozambique, Lesotho, Swaziland) (See registration form in Appendix #1). Roughly 42,000 patients are currently [March 2008] registered in Aid for AIDS. The number of patients eligible for each analysis and the number within each analysis who were lost to follow-up or who died are reported within

each chapter. Patient data and pharmacy claims have been recorded by Aid for AIDS since June 1998. With the patient's permission, baseline demographic and clinical data, including $CD4^+$ T-cell count, HIV-1 RNA levels, and prior history of HAART, are captured in the Aid for AIDS database upon application for the program. Acceptance is subject to confirmation of HIV-1 infection and proof of eligibility. Once enrolled, patients with a $CD4^+$ T-cell count <350 cells/μL on 2 occasions or with an AIDS-defining condition are eligible for HAART. The regimen prescribed included at least 3 medications, either 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), or 2 NRTIs plus 1 protease inhibitor (PI) (ritonavir-boosted saquinavir, indinavir or lopinavir). The NNRTI-based HAART was strongly preferred as a first-line regimen per WHO recommendations. [1]

Patients obtain authorization for reimbursement of HAART expenditure by their medical insurance fund subject to (*a*) receipt of a prescription for HAART from their physician, and (*b*) review and approval of the prescription by Aid for AIDS clinical staff in accordance with pre-specified clinical guidelines (Appendix #2). A uniform 30-day (1-month) supply of the HAART regimen is dispensed to patients, either at their local pharmacy or via confidential mail-order pharmacy.

For reimbursement, a claim must be submitted to the patient's health insurance fund. Each claim contains information about the dispensed date, specific medication regimen, and quantity supplied. Nearly all antiretroviral-related claims received are reimbursed without any patient co-payment. All claims are processed through the coordinating centre at the Aid for AIDS Cape

Town office. Claims include the drug names and date of the prescription refill. There was no differential delay between countries or sites within countries with respect to returning prescriptions for processing.

Data are captured to the database via a "Disease Management System" which is designed to allow capture and display of all relevant patient treatment, results and comments. While enrolled in Aid for AIDS, patients are seen by their individual private doctors and not by the programme or special clinics. Patient calls to a dedicated phone line will reach specially trained Aid for AIDS adherence counsellors who focus on the clinical and psychological aspects of HIV and its treatment. These patient calls are routed by Aid for AIDS call centre agents to one of four adherence coordinators per site (See Appendix 4 for full job description of adherence counsellors).

Semi-annual measurement of $CD4^+$ count and viral load is recommended, but physicians are free to choose the timing and the laboratory in which these tests are performed (fully reimbursed). Physicians are asked to use the same laboratory for follow-up measurements, but the specific viral load assays used are not recorded. Therefore the cutoff limit for undetectable viral load (<50 vs. <400 copies/mL) for each measurement is not known, and so a level of <400 copies/mL was defined as evidence of viral suppression for these studies.

During follow-up, deaths were identified by notification from the attending medical practitioner, hospital case manager (for in-hospital deaths), medical fund administrator, or family member. Patients who elected to leave their insurance

fund or whose insurance fund changed to a different disease-management program were censored as lost to follow-up at the date of departure.

IDENTIFICATION OF STUDY SUBJECTS

Roughly 42,000 patients are currently registered in Aid for AIDS dataset from which the cohort samples for the studies herein were randomly selected. Each chapter of this thesis contains detailed inclusion criteria for the specific aim investigated. In general, to be included in this thesis, Aid for AIDS registrants needed to fulfill the following requirements: be domiciled in southern Africa; belong to a medical scheme; have claims data available for HAART and other medicines, hospitalizations, investigations, general practitioners and specialists consultations etc. (for adherence and cost evaluation in Chapter 7); have enough data to generate adherence measures (i.e. have at least 6 months of follow-up); be HAART-naïve (medical records indicate no HAART use prior to initiation of HAART under Aid for AIDS); and have claimed at least 1 month of HAART between January 1999 and March 2006. Of note, for specific aim#1 and #3, only patients initiated on NNRTI-based HAART regimen were included (N= 2,817).

OVERALL ANALYSIS PLAN

As mentioned earlier, pharmacy refill is defined here as the number of times that medicines have been dispensed, whereas pharmacy claims refer to the number of times medicines were dispensed and subsequently claimed to gain reimbursement. Adherence for the studies herein is based on pharmacy

claims, which imply that refills have occurred. The overall analysis plan for the specific aims presented in this thesis is shown in Table 1. For details see subsequent chapters.

Regulatory Approvals

These studies were approved by the University of Cape Town Research Ethics Committee and the Aid for AIDS Clinical Advisory Committee and Board, Cape Town, South Africa, and by the Johns Hopkins Bloomberg School of Public Health's Committee on Human Research, Baltimore, MD.

Table 1. Method of analysis, Primary endpoints, and statistical techniques used to investigate each Specific Aim. For details see subsequent chapters.

SPECIFIC AIM(S)	ANALYSIS	ENDPOINT	STATISTICAL TECHNIQUES
1,3	Viral suppression OR Viral rebound after initial suppression	Proportion of patients with VL< 400 c/ml (binary) or Time to Viral Suppression/Rebound	X^2 analysis Adjusted logistic regression Log-Linear Regression Kaplan-Meier & Cox regression
2	Survival	All-cause mortality (binary)	X^2 analysis (binary) Adjusted logistic regression K-M & Cox regression
1,2,3,4,5	Pharmacy-claim Adherence	Proportion of patients with 100% adherence (binary) and by pre-defined strata	X^2 analysis (binary exposure/outcome) Adjusted logistic regression
5	Cost analysis	Monthly inflation adjusted direct care costs in US $	Wilcoxon rank-sum test or ANOVA Adjusted linear regression Log-Linear Regression

Power Justification

In this section, we calculate that a sample size of a hypothetical 2000 patients has at least 80% power for the primary analyses of Aims 1-5. The power and sample size calculations were conducted using the software program PASS © [2] which uses methods described in Hsieh et al. [3], Shoenfeld [4],and Desu [5].

Aims 1 and 2: The primary goal of Aim 1 was to determine the proportion of patients achieving viral suppression at all measurements from one month after HAART initiation until the end of the follow-up period, accounting for other variables of interest. The primary goal of Aim 2 was to determine whether there is an association between pharmacy-claim adherence and all-cause mortality, accounting for other variables of interest. The analysis of data for both aims used logistic regression. For purposes of the sample size and power calculations, baseline probabilities of virologic suppression occurring (when all the other variables of interest were at their mean values) of 0.1, 0.4, and 0.7 were explored. The same baseline probabilities were used for death (Aim 2). Correlation between covariates of 0.2, 0.4, and 0.6 (R^2 = 0.04, 0.16, and 0.36) were explored (Table 2 and Figures 1, 2 and 3), where R^2 is the squared-correlation achieved when the primary predictor of interest (adherence) is regressed on the other independent variables in the regression. Even for relatively small effect sizes (OR = 1.3 or higher), the power is 80% or higher for the parameter configurations considered.

Table 2. Power to detect effect sizes when Total Sample Size (N) = 2000 (Specific Aims 1 and 2).

R^2	Odds Ratio	*Baseline Probability of Virologic Suppression (Aim 1) or Death (Aim 2) Occurring*		
		0.1	**0.4**	**0.7**
0.04	**1.1**	0.24	0.53	0.48
	1.2	0.67	**0.97**	**0.96**
	1.3	**0.93**	**1.00**	**1.00**
	1.4	**0.99**	**1.00**	**1.00**
	1.5	**1.00**	**1.00**	**1.00**
0.16	**1.1**	0.22	**0.96**	**0.43**
	1.2	0.61	**0.96**	**0.93**
	1.3	**0.90**	**1.00**	**1.00**
	1.4	**0.99**	**1.00**	**1.00**
	1.5	**1.0**	**1.00**	**1.00**
0.36	**1.1**	0.17	0.39	0.35
	1.2	0.50	**0.89**	**0.85**
	1.3	**0.80**	**1.00**	**0.99**
	1.4	**0.95**	**1.00**	**1.00**
	1.5	**0.99**	**1.00**	**1.00**

Figure 1. Power vs. Odds Ratio by baseline probability of viral load suppression or death with a hypothetical N = 2000 and covariates correlation (R^2) =0.04

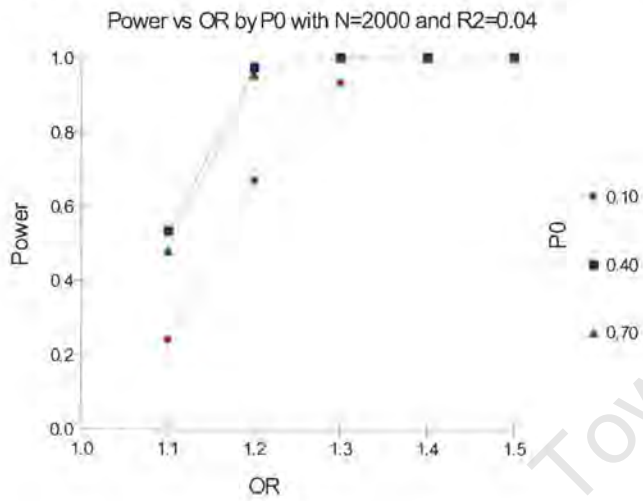


Figure 2. Power vs. Odds Ratio by baseline probability of viral load suppression or death with a hypothetical N = 2000 and covariates correlation (R^2) =1.2

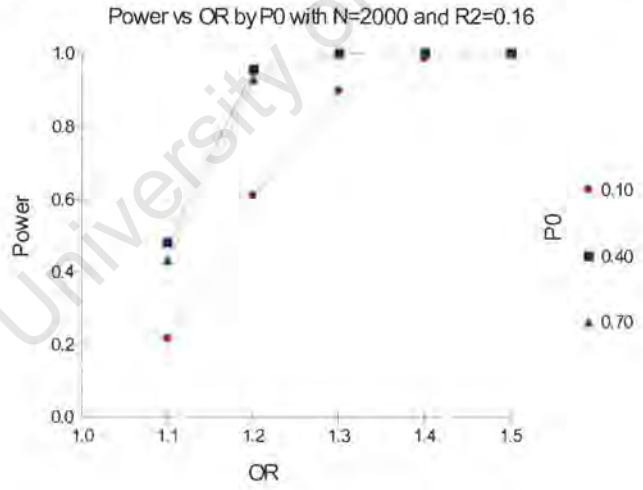


Figure 4. Power versus Hazard Ratio of virologic failure for varying covariates correlation and an event rate of 0.10

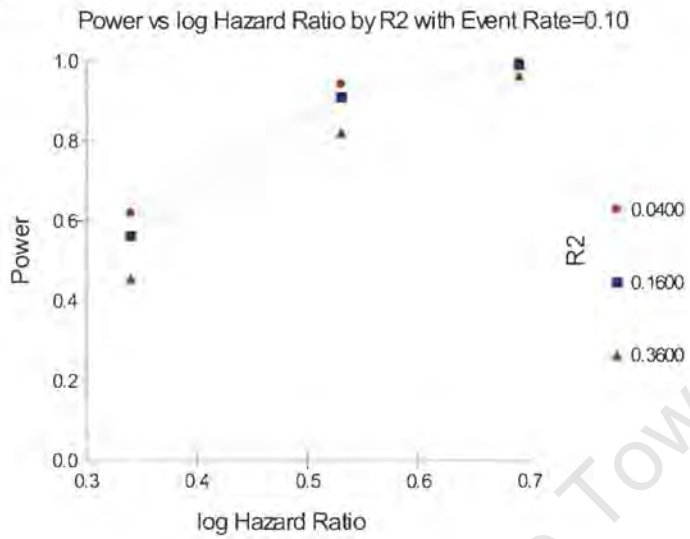


Table 3. Power when Total Sample Size (N) = 2000 (Specific Aim 3).

R^2	Hazards Ratio	*Overall Event Rate of Virologic Failure*		
		0.1	**0.5**	**0.8**
0.04	**1.4**	0.61	**1.00**	**1.00**
	1.7	**0.94**	**1.00**	**1.00**
	2.0	**1.00**	**1.00**	**1.00**
0.16	**1.4**	0.56	**1.00**	**1.00**
	1.7	**0.91**	**1.00**	**1.00**
	2.0	**0.99**	**1.00**	**1.00**
0.36	**1.4**	0.45	**0.98**	**1.00**
	1.7	**0.82**	**1.00**	**1.00**
	2.0	**0.96**	**1.00**	**1.00**

Aim 4: The primary aim is to compare adults *vs.* adolescents with respect to time to virologic failure, accounting for other covariates including adherence, *via* Cox proportional hazards regression. For purposes of the sample size and power calculation, the proportion of adults to adolescents explored was 50:1 with rates of virologic failure ranging from 0.1 (low) to 0.8 (high). Additionally, correlations between covariates of 0.2, 0.4, and 0.6 (R^2 = 0.04, 0.16, and 0.36) were explored. A high event rate and a relatively large hazard ratio is needed to achieve 80% power (Table 4, Figures 5 and 6).

Aim 5: The primary aim was to evaluate the association between pharmacy-claim adherence and direct health costs by stratifying patients using quartile adherence rates and analyzing differences in the distribution of the four adherence strata

Table 4. Power for various choices for R^2, the Hazard Ratio, and the Overall Event Rate for Specific Aim 4

R^2	Hazards Ratio	*Overall Event Rate of Biological Suppression*		
		0.1	**0.5**	**0.8**
0.04	**1.4**	0.10	0.31	0.46
	1.7	0.18	0.63	**0.83**
	2.0	0.27	**0.85**	**0.97**
0.16	**1.4**	0.09	0.28	0.41
	1.7	0.16	0.58	0.78
	2.0	0.24	**0.80**	**0.94**
0.36	**1.4**	0.08	0.22	0.33
	1.7	0.13	0.47	0.66
	2.0	0.19	0.69	**0.87**

Figure 5. Power vs. Log of baseline hazard ratio of virologic failure by covariates coefficient with event rate of 0.10

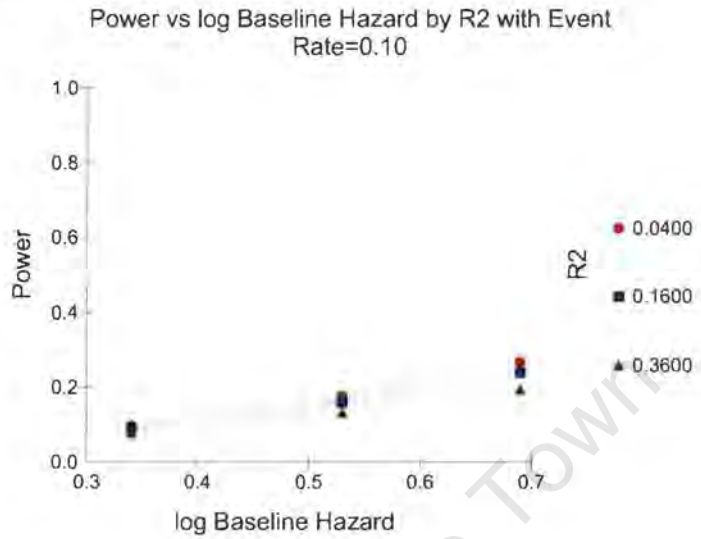
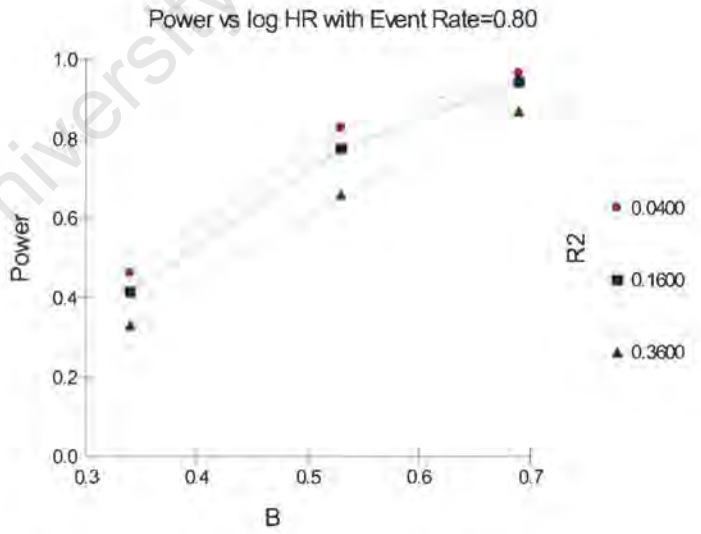


Figure 6. Power versus log of hazard ratio of virologic failure with event rate of 0.80



using the Kruskal-Wallis test, a non-parametric version of the Analysis of Variance (ANOVA). For purposes of the sample size and power calculation, the total cost excluding costs of HAART and viral load and $CD4^+$ measurements (HAART-out) was examined. The mean direct health care costs excluding HAART and viral load/$CD4^+$ measurements for the 1st (highest), 2nd, 3rd, and 4th (lowest) adherence quartiles were 155, 164.6, 178.9, and 199.7 (based on previous results). To perform the sample size calculation, cost was considered to follow a gamma distribution with a shape parameter of 2.0 (medium positive skewness). The sample sizes for each category were chosen to be 500. Given these inputs, 100% power was achieved.

General Limitations

Using Aid for AIDS patients for our study population creates some general limitations for the results reported herein. First, Aid for AIDS is a private care setting, and so our patient cohort may not share characteristics with other populations in Africa. As a result, the potential to generalize the findings in this thesis within the Aid for AIDS population or to other settings (e.g. public sector) in Africa may be limited.

However, the particular individuals included in each analysis are likely to be representative of other participants in Aid for AIDS because our study population is a large random sample of the patients from whom data could be generated and who met inclusion criteria for each specific aim. Furthermore, the findings in this thesis may be generalizable to the public-sector patient population

because the relationship between adherence and biological variables (e.g., HIV viral load) is unlikely to be influenced by factors such as socioeconomic status that may differ for public-sector programs. Moreover, our findings showing usefulness of pharmacy data as an adherence monitoring tool has been confirmed by studies from other investigators in public-sector settings both in developed countries [6] and recently in a large PEPFAR-funded public-sector HAART program in Zambia [7]. These validations of the association between pharmacy data and virologic outcomes provide strong evidence of the universality of this approach for monitoring effectiveness of antiretroviral therapy in countries hit hard by the AIDS epidemic like South Africa. [8]

The use of pharmacy claims to calculate adherence presents limitations. For instance, there is no evidence that pharmacy claim or refill data reflect the number of pills taken correctly by a patient. As a result, claims data may underestimate adherence if not all medications taken were claimed or if some were obtained via refill outside of the Aid for AIDS program, or it may overestimate adherence if some number of the pills claimed were not taken appropriately or if not all of the claimed medications were taken. However, a number of studies have found that refill compliance correlates well with other compliance behaviours such as appointment keeping, medication consumption [9] or viral load suppression [7,10]. It may be reasonably assumed that patients would not continue to refill a prescription (or, in this case, to claim medication) without intending to adhere [11]. In any case, the results presented in this thesis suggest that pharmacy claims or refill may be appropriately used as a program-

level HAART adherence measure, regardless of whether pharmacy claims directly correlate with consumption.

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Chapter 3

Relationship between Antiretroviral Adherence and Virologic Outcomes in Patients on NNRTI-based Antiretroviral Therapy

Introduction

Adherence to highly active antiretroviral therapy (HAART) has been shown to be a major predictor of viral suppression of HIV replication [1-3], emergence of drug resistance [4-6], disease progression [7] and death [8-10]. When un-boosted protease inhibitor (PI)-based HAART regimens are used, nearly perfect adherence (≥95%) is required for sustained virologic suppression [2], and emergence of drug resistance is highest at intermediate levels (70-90%) of adherence [5,11].

However, data from a prospective study conducted by Maggiolo and colleagues in Italy suggest that at intermediate levels of adherence patients on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens may have higher rates of viral suppression than those on un-boosted PI-based regimens. [12] Similarly, a study of homeless/indigent antiretroviral-experienced HIV patients in San Francisco found that, in contrast to patients on un-boosted protease inhibitors, about 70% of patients on NNRTI-based HAART with intermediate adherence (70%-90% as evaluated by pill count or electronic monitor) achieved undetectable viral load (<400 copies/mL) and lower levels of drug resistance compared to patients with low (0%-50%) adherence. [13,14] These studies were limited by small sample size and reduced generalizability to

other populations. As a result, it remains unclear whether the relationship between adherence and viral suppression in patients taking NNRTI-based HAART resembles a linear dose-response or a threshold adherence level, below which virologic failure rapidly increases.

NNRTI-based HAART is not only the preferred option for first-line treatment of HIV/AIDS worldwide [15,16], but also in the scale-up of HAART programs in resource-limited settings [17]. Given the importance of adherence for treatment success, it is also important to select and validate a method of estimating treatment adherence during HAART scale-up in resource-limited settings. One way to validate pharmacy-claims adherence as a useful tool is to determine its association with both virologic and clinical (death) outcomes, and to do so not in well controlled environment such as clinical trials, but in routine clinical practice that offers a "real-world" setting.

Materials and Methods

Study Participants

Inclusion criteria: All Aid for AIDS participants who: (a) qualified for and claimed at least one month of NNRTI-based HAART between January 1998 and March 2003; (b) were ≥18 years old at HAART initiation; (c) had no indication of prior HAART therapy in the medical record provided by the medical practitioner/attending doctor; (d) had HIV-1 RNA >400 copies/mL at HAART initiation and (e) had at least one follow-up viral load measurement recorded between 30 and 365 days after initiating HAART.

Measurement of Plasma HIV-1 RNA

As stated earlier, the frequency and timing of viral load measurements and the pathology laboratory used for analysis were at the discretion of the treating physician. The assay used to measure viral load was not recorded.

Operational Definitions, Outcome Measures, and Exploratory Variables

Pharmacy claim adherence was expressed as a percentage, calculated as the number of months with HAART claims submitted, divided by the number of complete months from HAART commencement to either (a) death, (b) withdrawal from the Aid for AIDS program, or (c) study end (September 1, 2004) with the result multiplied by 100. Patients were categorized into seven groups based on calculated pharmacy-claim adherence: <50%, 50%-59%, 60%-69%, 70%–79%, 80%–89%, 90%–99%, and 100%. Strata in increments of 10% were defined a priori; patients having <50% adherence are reported as a single stratum due to small sample size. The primary outcome was proportion of patients achieving viral suppression, defined as HIV RNA level <400 copies/mL, at all measurements from one month after HAART initiation until the end of the follow-up period. The proportion of patients achieving this viral suppression at their first viral load measurement in pre-defined six-month strata (3-9 months, 9-15 months, 15-21 months, and 21-27 months) was also measured. Age, gender, race, baseline $CD4^+$ T-cell count, specific NNRTI prescribed, date of HAART initiation, and baseline plasma HIV-1 RNA levels were investigated in relation to

both pharmacy-claim adherence and viral suppression in univariate and multivariate analyses.

Additional analyses were performed with the endpoints of time to viral suppression (HIV-1 RNA < 400 copies/mL), as well as time to viral load rebound (>400 copies/mL) among those patients who achieved initial viral suppression <400 copies/mL. In these analyses, patients who switched to protease inhibitor-based therapy were censored at the time of the switch, with the assumption that, at that time, the patient had a similar suppression status as at his/her last viral load measurement.

Statistical Analysis

Differences in baseline characteristics were assessed with two-sample Student's *t* tests (continuous variables) and χ^2 tests (categorical variables). Mean absolute increase in the proportion of patients achieving sustained viral suppression, per 10% increase in pharmacy-claim adherence, was calculated by variance-weighted, least squares regression (adherence modeled as categorical). To do this, sustained viral suppression was used as a binary-coded, dependent variable among patients with at least 50% adherence. Kaplan-Meier plots and log-rank tests were used to examine survival by strata of medication adherence. Cox proportional hazards regression was used to model the individual and simultaneous effects of baseline variables and medication adherence on time to viral suppression or failure. Plots of -log[-log(survival)] against log(analysis time) and analysis of scaled Schoenfeld residuals were used

to assess the proportionality assumption. All available variables were included a priori in multivariable models and were stratified into discrete categories, as follows: viral suppression (greater or less than 400 copies/mL), gender (male/female), race (black/other), HIV-1 RNA (greater or less than 5 $\log_{10}$ copies/mL), HAART regimen (efavirenz- or nevirapine-based) and date of HAART initiation (in four calendar-year strata). All *P* values reported are exact and 2-tailed, with a value of <0.05 considered statistically significant. Statistical analyses were performed using STATA Release 8.0 (Stata Corporation, College Station, TX, USA).

RESULTS

2,821 patients meeting all inclusion criteria were identified, of whom 1,822 (64.6%) were on efavirenz- and 999 (35.4%) on nevirapine-based regimens. The mean age (standard deviation) at HAART initiation was 37.0 (7.8) years; 1,775 patients (62.9%) were female, and 2,734 (96.9%) were black Africans (Table 2). The median (interquartile range) follow-up period was 2.2 (1.7-2.7) years, and median (interquartile range) frequency of viral load measurement was 1.2 (0.7-1.7) measurements per year. Of viral load measurements <400 copies/mL (5,513 [75.6%] of 7,290 total measurements), 65.9% were recorded as <50 copies/mL, 22.1% as <400 copies/mL, and 11.9% were recorded as between 50-400 copies/mL. The median (interquartile range) $CD4^+$ T-cell counts at HAART initiation for males and females were 130 (56-211) and 157 (69-236) cells/μL (*P*=0.002), respectively. The median (interquartile range) HIV-1 RNA levels at

HAART initiation for males and females were 5.1 (4.6-5.6) and 5.2 (4.7-5.6) $\log_{10}$ copies/mL, respectively (*P*=0.184).

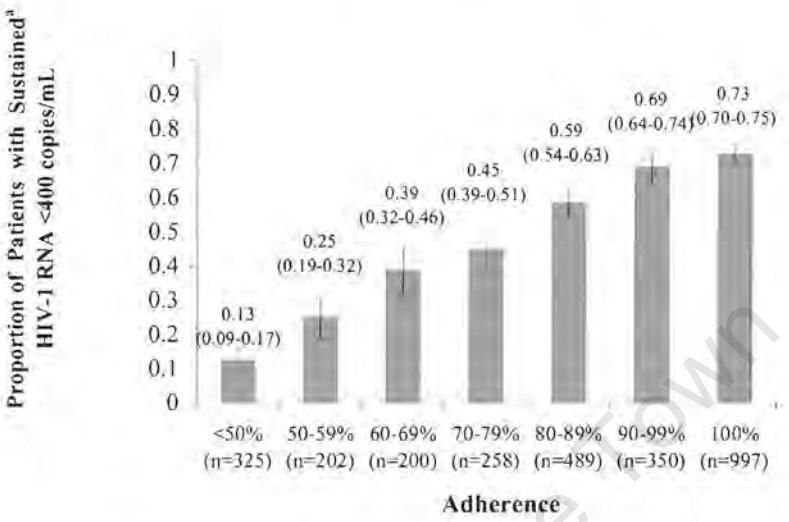
A significant dose-response relationship was identified between viral load suppression and pharmacy claim adherence across all adherence strata. Rates of sustained viral suppression in the seven adherence strata from <50% to 100% were 13% (41/325), 25% (51/202), 39% (78/200), 45% (116/258), 59% (287/489), 69% (241/350), and 73% (725/997), respectively (Table 1 and Figure 1). Thus, using simple linear regression, every 10% increase in adherence—above 50%—was associated with a mean absolute increase of 0.10 in the proportion of patients achieving sustained viral suppression of <400 copies/mL. In pairwise comparisons, each stratum of increased adherence had significantly (p<0.004) higher rates of sustained viral suppression than the preceding stratum, except for the comparisons of 100% vs. 90%-99% (p=0.168) and 60%-69% vs. 70%-79% adherence (p=0.20). Similarly, pharmacy-claim adherence, modelled as a continuous variable among patients with adherence >50%, was significantly associated with odds of achieving persistent viral suppression (p<0.001). Examination of sub-strata within the <50% adherence stratum (e.g., 40%-49%) suggested a similar dose-response pattern but this finding was limited by small sample size. A similar dose-response pattern, with viral suppression rates consistently over 70% in patients who achieved pharmacy-claim adherence rates of 80% or better, was seen when outcome was measured as viral suppression <400 copies/mL at the first viral load measurement within four pre-specified time

Table 1. Baseline Characteristics of Study Population, According to Achievement of Sustained Virologic Suppression < 400 copies /mL

Variable	Patients with sustained virologic suppression[a] (N = 1539)	Patients without sustained virologic suppression (N=1282)	Total (N = 2821)	P value[b]
Age: Mean (sd)	37.2 (7.9)	36.7 (7.7)	37.0 (7.8)	0.052
Gender				0.045
Male	545 (35.4)	501 (39.1)	1046 (37.1)	
Female	994 (64.6)	781 (60.9)	1775 (62.9)	
Race				0.012
Black	1480 (96.2)	1254 (97.8)	2734 (96.9)	
Other	59 (3.8)	28 (2.2)	87 (3.1)	
Baseline CD4				<0.001
≤50	286 (18.6)	299 (23.3)	585 (20.7)	
51-200	698 (45.3)	602 (47.0)	1300 (46.1)	
>200	555 (36.1)	381 (29.7)	936 (33.2)	
Baseline VL				<0.001
$\leq 10^5$	711 (46.2)	445 (34.7)	1156 (41.0)	
$>10^5$	828 (53.8)	837 (65.3)	1665 (59.0)	
NNRTI				<0.001
Efavirenz	1056 (68.6)	766 (59.8)	1822 (64.6)	
Nevirapine	483 (31.4)	516 (40.2)	999 (35.4)	
NRTI				<0.001
3TC + ZDV	1228 (79.8)	962 (75.0)	2190 (77.6)	
3TC + d4T	56 (3.6)	56 (1.9)	80 (2.8)	
d4T + ddI	246 (16.0)	277 (21.6)	523 (18.5)	
ddI + ZDV	9 (0.6)	19 (1.5)	28 (1.0)	
Date of HAART start				<0.001
1998-2000	21 (1.4)	36 (2.8)	57 (2.0)	
2001	503 (32.7)	582 (45.4)	1085 (38.5)	
2002	917 (59.6)	596 (46.5)	1513 (53.6)	
2003	98 (6.4)	68 (5.3)	166 (5.9)	
Pharmacy-claim adherence				<0.001
<50%	41 (2.7)	284 (22.1)	325 (11.5)	
50-59%	51 (3.3)	151 (11.8)	202 (7.2)	
60-69%	78 (5.1)	122 (9.5)	200 (7.1)	
70-79%	116 (7.5)	142 (11.1)	258 (9.2)	
80-89%	287 (18.7)	202 (15.8)	489 (17.3)	
90-99%	241 (15.7)	109 (8.5)	350 (12.4)	
100%	725 (47.1)	272 (21.2)	997 (35.3)	

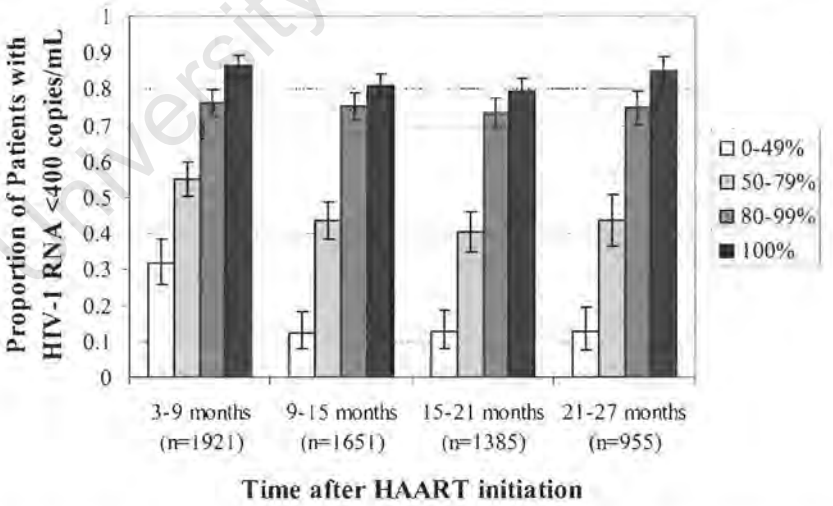
[a] Defined as less than 400 copies/mL at all of measured time points during follow-up.
[b] Based on the chi-square test (χ^2) with one degree of freedom, comparing patients who did or did not achieve sustained virologic suppression.

Figure 1. Proportion of patients at each level of pharmacy-claim adherence to NNRTI-based HAART with sustained[a] viral suppression <400 copies/mL



[a] Defined as achievement of viral load <400 copies/mL at all measured time points. Error bars represent 95% confidence intervals around the estimate of the respective proportions, based on a binomial probability distribution and using the sample sizes listed.

Figure 2. Pharmacy-claim adherence to NNRTI-based HAART and viral suppression <400 copies/mL within specified time strata after HAART initiation



N.B. For patients with more than one viral load measurement within each time stratum, only the first qualifying measurement was included in this analysis. Error bars represent 95% confidence intervals around the estimate of the respective proportions, based on a binomial probability distribution and using the sample sizes listed.

strata after HAART initiation, rather than viral suppression at all time points throughout follow-up (Figure 2).

Variables significantly associated with shorter time to viral suppression <400 copies/mL in multivariable analysis (hazard ratio, 95% confidence interval) were female gender (1.17, 1.06-1.28), baseline viral load $\leq 10^5$ copies/mL (1.28, 1.18-1.40), use of efavirenz rather than nevirapine (1.20, 1.10-1.32), and high pharmacy-claim adherence (3.79, 3.13-4.58, comparing 100% vs. <50% adherence) (Table 2). All higher pharmacy-claim adherence groups had significantly shorter time to viral suppression than the <50% group, and patients with 100% pharmacy-claim adherence had significantly shorter time to suppression than all adherence strata <90%. When pharmacy-claim adherence was modelled as a continuous variable, each 10% increase in adherence above 50% was associated with a hazard ratio of 1.19 (1.15-1.23) for time to viral suppression <400 copies/mL; this figure increased to 1.25 (1.22-1.28) when restricted to adherence in the first six months of follow-up, among a subset of patients (n = 2,436, 86.4% of total population) for whom these data were available.

Significant pre-therapy baseline multivariate predictors of shorter time to virologic failure (viral load >400 copies/mL) after prior suppression included low $CD4^+$ T-cell counts (1.60, 1.22-2.10, for ≤50 versus >200 cells/ μL); viral load $>10^5$ copies/mL (1.39, 1.14-1.70); use of nevirapine (1.43, 1.16-1.77); later date of HAART start (1.43, 1.16-1.77, for patients starting after vs. before January 1, 2002); and low pharmacy-claim adherence (10.78, 7.69-15.12, for <50% vs.

100% adherence) (Table 2). Increasing pharmacy-claim adherence was associated with longer time to failure in all strata, except that no difference in time to failure was seen in the 90-99% versus 100% adherence strata. Pharmacy-claim adherence ≥90% was associated with significantly longer time to failure than in all adherence strata <90% (Figure 3). When pharmacy-claim adherence was modelled as a continuous variable, each 10% decrease in adherence to 50% was associated with a hazard ratio of 1.58 (1.48-1.69) for time to virologic failure (Table 2, inverse of final row).

To assess the possibility of bias from differential frequency of viral load measurement, this variable was examined in strata of pharmacy-claim adherence and sustained viral suppression. In all strata of adherence, patients with sustained viral suppression received fewer viral load measurements ($p<0.001$ for global association); however, patients in strata of higher pharmacy-claim adherence had significantly more viral load measurements per year than those in lower adherence strata ($p<0.001$, non-parametric test for trend). In multivariable analysis, an increase in frequency of one viral load measurement per year was associated with a hazard ratio of 1.06 (0.998-1.13) for faster time to initial viral suppression and 1.79 (1.51-2.12) for faster time to subsequent failure. Inclusion of this variable in multivariate analyses had no effect on associations with time to suppression and mildly strengthened the association between pharmacy-claim adherence and time to failure.

Table 2. Adjusted Associations between Patient Characteristics and Time to Viral Load Suppression <400 copies/mL and Time to Subsequent Virologic Failure

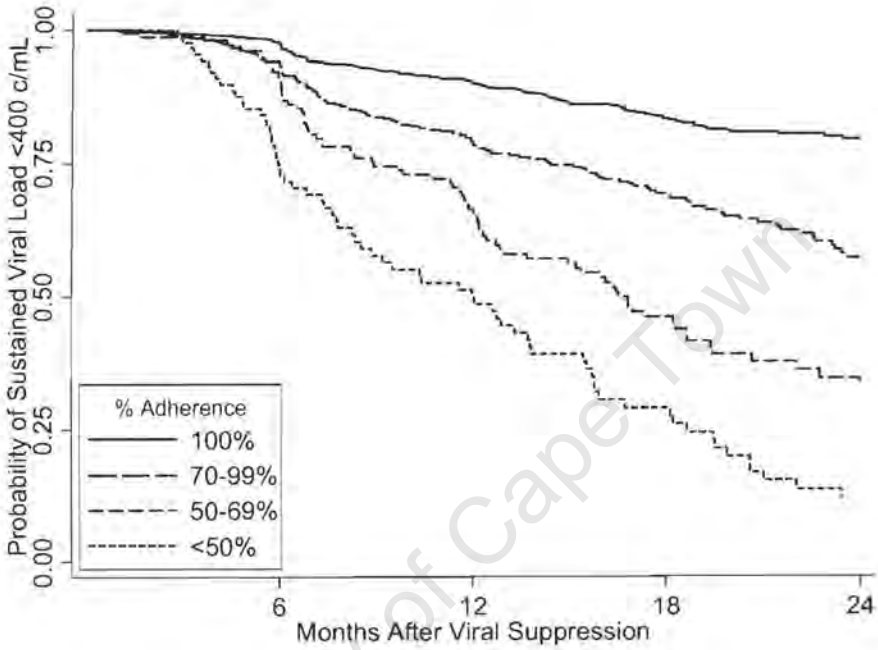
	Predictors of time to viral suppression (N = 2821)		Predictors of time to subsequent virologic failure (N = 1579)	
Variable	**Univariate HR (95% CI)**	**Multivariate HR (95% CI)** [a]	**Univariate HR (95% CI)**	**Multivariate HR (95% CI)** [†]
Age (per 10 years)	1.04 (0.98-1.10)	1.04 (0.98-1.10)	0.86 (0.76-0.98)	0.91 (0.80-1.04)
Gender				
Male	1	1	1	1
Female	1.20 (1.10-1.31)	1.17 (1.06-1.28)	1.01 (0.82-1.23)	1.17 (0.95-1.44)
Race				
Black	0.84 (0.66-1.06)	0.90 (0.71-1.15)	1.50 (0.71-3.16)	1.17 (0.55-2.49)
Other	1	1	1	1
Baseline CD4$^+$				
≤50	1	1	1.53 (1.18-1.99)	1.60 (1.22-2.10)
51-200	1.06 (0.94-1.18)	1.03 (0.92-1.15)	1.27 (1.02-1.59)	1.18 (0.94-1.48)
>200	1.16 (1.03-1.31)	1.07 (0.92-1.18)	1	1
Baseline viral load				
$\leq 10^5$	1.29 (1.19-1.41)	1.28 (1.18-1.40)	1	1
$>10^5$	1	1	1.37 (1.13-1.67)	1.39 (1.14-1.70)
NNRTI				
Efavirenz	1.19 (1.09-1.30)	1.20 (1.10-1.32)	1	1
Nevirapine	1	1	1.28 (1.05-1.55)	1.43 (1.16-1.75)
Year of HAART start			1.73 (1.05-2.85)	1.33 (0.80-2.21)
1998-2000	0.88 (0.64-1.22)	1.01 (0.73-1.40)	1	1
2001	1	1	1.03 (0.84-1.27)	1.41 (1.13-1.75)
2002	1.22 (1.12-1.34)	1.09 (0.99-1.20)	1.83 (1.12-3.00)	4.63 (2.69-7.94)
2003	1.18 (0.98-1.42)	0.81 (0.66-0.99)		
Pharmacy-claim adherence[b]				
<50%	1	1	8.27 (6.07-11.3)	10.8 (7.69-15.1)
50-59%	1.65 (1.28-2.12)	1.63 (1.27-2.10)	5.11 (3.56-7.34)	6.59 (4.52-9.63)
60-69%	2.17 (1.71-2.75)	2.16 (1.70-2.75)	4.24 (2.99-5.99)	5.24 (3.64-7.54)
70-79%	2.34 (1.87-2.93)	2.42 (1.93-3.03)	2.81 (1.99-3.96)	3.45 (2.41-4.96)
80-89%	2.90 (2.38-3.54)	2.84 (2.33-3.47)	1.81 (1.34-2.46)	2.20 (1.59-3.03)
90-99%	3.38 (2.75-4.16)	3.45 (2.80-4.24)	0.81 (0.55-1.18)	0.97 (0.65-1.45)
100%	3.78 (3.14-4.55)	3.79 (3.13-4.58)	1	1
Pharmacy-claim adherence (per 10% increase)[c]	**1.19 (1.16-1.23)**	**1.19 (1.15-1.23)**	**0.66 (0.62-0.71)**	**0.63 (0.59-0.68)**

HR (95% CI) = Hazard ratio (95% confidence interval); NNRTI, non-nucleoside reverse transcriptase inhibitor; HAART, highly-active antiretroviral therapy.

[a] Adjusted for all other variables in the table. [b] As measured by pharmacy claims.

[c] Restricted to patients with >50% adherence (n=2496); in multivariate analysis, other variables were adjusted for adherence by strata, not as a continuous variable

Figure 3. Kaplan-Meier plot of patients with sustained HIV RNA <400 copies/mL after initial viral suppression, by levels of pharmacy-claim adherence



Adherence			Number at Risk		
100%	917	816	585	345	161
70-99%	411	351	243	144	68
50-69%	162	136	81	44	18
<50%	89	64	37	19	7
Total	1579	1367	946	552	254

DISCUSSION

These data suggest that increased adherence to NNRTI-based HAART, as measured by pharmacy claims, is associated with improved virologic outcomes at all levels of adherence above 50%. This relationship holds whether virologic success is measured as sustained viral suppression throughout follow-up, time to first viral suppression <400 HIV-1 RNA copies/mL, or time to virologic failure (>400 HIV-1 RNA copies/mL) after initial suppression. For each 10% increase in pharmacy claim adherence above 50%, one can expect an additional 10% of an HIV-1-infected population to maintain complete viral suppression over a median of 2.2 years (Figure 1); a 19% (15%-23%) increase in the hazard of achieving first-time viral suppression; and a 37% (32%-41%) decrease in the hazard of virologic failure, given initial viral suppression (Table 2, final row). This study therefore documents a dose-response relationship between NNRTI-based HAART adherence as measured by pharmacy claims and viral suppression in HIV-1-infected patients.

In this study, over half of patients with 80%-89% adherence by pharmacy claims achieved 100% viral suppression. These data corroborate prior results from a randomized controlled trial indicating greater viral suppression with NNRTI therapy than unboosted protease inhibitor therapy [18] and also confirm findings from small studies conducted in Italy [12] and the United States [13,14] which found higher rates of viral suppression on NNRTI than un-boosted protease inhibitor therapy for the same levels of HAART adherence. However, pharmacy

refill/claim adherence is likely an estimate of maximum possible individual adherence, since patients may not take all claimed medications. Therefore, our measures of adherence are conservatively biased. The more reliable viral suppression with NNRTI-based than un-boosted PI-based regimens at modest levels of adherence observed in our study and others may be due to either improved potency or extended half-life of NNRTIs. [18-21]

These data add to the results of the above studies by clearly demonstrating that increased adherence to NNRTI-based HAART is strongly associated with improved virologic outcomes in a linear dose-response relationship. Furthermore, the time-to-event analyses suggest that moderate levels of adherence (70-90%) to NNRTIs often lead to viral suppression, which is not the case with unboosted PI-based HAART [6,14], and that time to virologic failure after initial suppression begins to increase at any level of NNRTI adherence below 90%. In this regard, our data suggest that there is no threshold below which decreased adherence to NNRTI-based HAART is benign.

In multivariate analysis, pre-therapy $CD4^+$ T-cell counts <50 cells/μL were associated with greater risk of subsequent virologic failure, independent of other factors. These findings are in agreement with results from other studies [22,23], but may nevertheless reflect unmeasured confounding factors associated with lower $CD4^+$ T-cell counts and hence advanced HIV disease. The fact that the relationship between adherence and virologic outcome persisted despite

adjustment for $CD4^+$ T-cell count suggests that this relationship is not explained by poor access and/or adherence among the most ill. A low baseline $CD4^+$ T-cell count may be a marker of virologic or immunological factors such as increased quasi-species diversity, which in turn may generate drug-resistant HIV-1 variants or lower HIV-specific host immunity. [23,24]

This study has several important clinical and public health implications. First, concern exists that the low genetic barrier (one single-step mutation) of the NNRTIs may result in the rapid selection of drug resistance in patients with moderate to low levels of adherence.[25,26] For that reason, some clinicians suggested that NNRTIs should be avoided in patients expected to have less than 95% adherence. The results of this study and others [13] argue against this idea. Indeed, our data suggest that NNRTI-based regimens may be an appropriate alternative to protease inhibitor-based regimens particularly in areas where adherence between 70% and 94% is expected. Nevertheless, individuals and populations on NNRTI-based HAART should benefit from increased adherence regardless of existing adherence patterns.

Second, these results suggest that good clinical outcomes can be achieved in routine clinical practice even without perfect adherence. In addition, more than 60% of patients in this cohort maintained pharmacy claim adherence >80% and had correspondingly high rates of viral suppression over a median follow-up period of 2.2 years. These data corroborate similar findings in other resource-limited settings and argue that concerns of suboptimal adherence

among patients in such settings should not delay expansion of access to HAART [27]. While it is important to ameliorate modifiable barriers to adherence prior to commencing HAART, failure to treat individuals because they may not achieve perfect adherence [28] inevitably leads to disease progression and the potential for increased morbidity and mortality. Also, failure to initiate therapy may risk significant immunologic progression, which, as shown in the present study, can increase the risk of subsequent virologic failure. The dramatic dose-response pattern between adherence and viral suppression, as well as the reasonable rates of suppression achieved at moderate levels of adherence, support the recommendations to treat all eligible HIV-1-infected individuals and to encourage maximum adherence with each patient. [29,30]

These data confirm that pharmacy claim measures are an appropriate population-level method to monitor adherence in resource-limited settings.Our study population included patients enrolled in a private managed insurance program. Only 18% of South Africans, and an even lower proportion in other developing countries, have private medical insurance [31]. Thus, while this study population may not generalize to all South Africans, our results argue for further assessment of pharmacy data as a tool to evaluate HAART adherence in public-sector programs. For example, the total proportion of person-months in which drug was dispensed to program participants could be used to assess overall adequacy of adherence within the program.

This study has several limitations in addition to those related to the nature of the cohort and the use of pharmacy claims that were discussed in Chapter 2. One additional limitation is that because adherence data were reported from pharmacies only in aggregate form, we were unable to measure individual adherence in a time-dependent fashion. As such, patient adherence may be misclassified, in that levels of adherence at the time of initial virologic suppression or failure might not be the same as adherence at the end of the study. This concern is greatest with our time-to-event analyses, in which patient adherence would ideally be classified in an ongoing fashion rather than at study end. These concerns, however, would be expected to dilute any true dose-response relationship toward the null of no association. Thus the relationship between adherence and virologic response may be even stronger than that seen in the present analysis, as suggested by the significant association between adherence and time to suppression when adherence was measured only during the first six months of therapy.

Also, these findings are subject to the potential for "reverse causation," as patients who experience poor clinical outcomes as a result of viral non-suppression may subsequently stop taking their medication.

In summary, this study from a southern African private-sector HIV-management programme suggests that increased adherence to NNRTI-based HAART regimens, as measured by pharmacy claims, is associated with

improved virologic outcome in all strata of adherence greater than 50% in a linear dose-response fashion. More than 60% of patients in this African setting maintained pharmacy-claim adherence >80% and had correspondingly high rates of viral suppression over a median follow-up of 2.2 years. The linear dose-response relationship holds in a resource-limited field setting using a very simple measure of adherence, and persists regardless of whether virologic outcome is measured as sustained viral suppression, time to suppression, or time to subsequent virologic failure. NNRTIs often lead to viral suppression at moderate adherence levels; however, maximum NNRTI adherence should be encouraged for all patients regardless of existing adherence patterns.

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Chapter 4

Relationship between Antiretroviral Adherence and Survival

INTRODUCTION

We have shown that adherence strata based on pharmacy refill claims data are associated with time to viral suppression and time to viral rebound after suppression in sub-Saharan Africa. (See Chapter 4) In order to evaluate the relationship between adherence and survival in the Aid for AIDS cohort we evaluated the association between survival and pharmacy claim adherence in HIV-1-infected adults on HAART regardless of the regimen (first line, second line, salvage therapy, etc.) during participation in Aid for AIDS. To reduce confounding, participants must have been HAART-naïve prior to enrolling in Aid for AIDS.

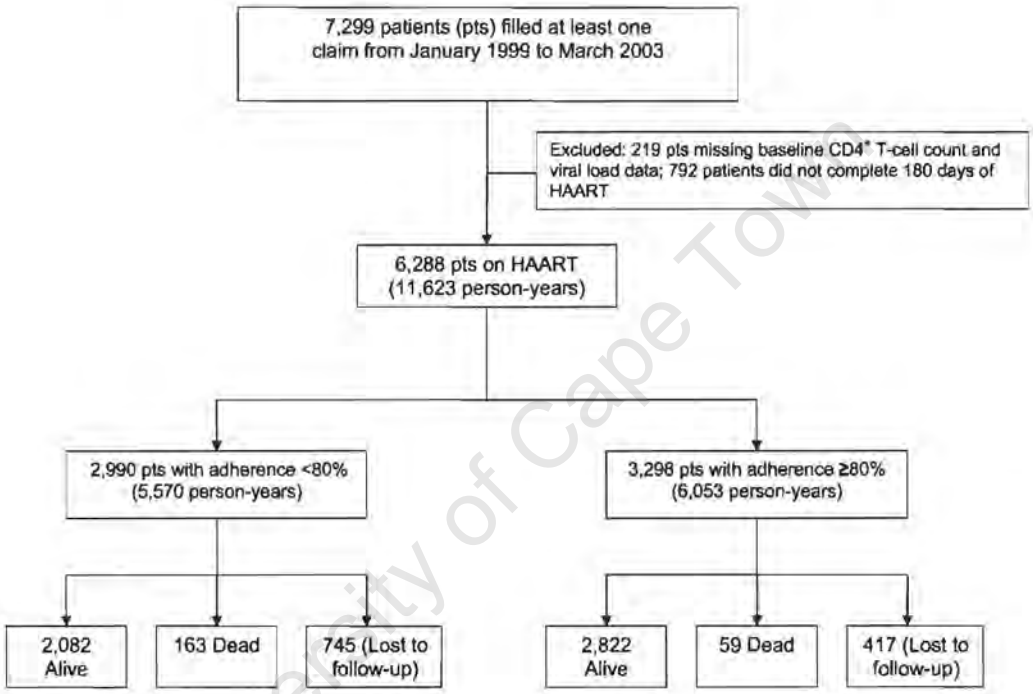
MATERIALS AND METHODS

Identification of Study Subjects

All adult (≥18 years old) HAART-naive patients with a baseline HIV-1 RNA >400 copies/mL who qualified for and claimed at least 1 month of HAART between January 1999 and March 2003 in the Aid for AIDS Programme were identified. For our primary analyses, we excluded patients who had died or had left the programme during their first 180 days of HAART (Figure 1). The rationale was to minimize bias due to patients who entered with terminal disease and so

had minimal chance of responding to therapy. Among these patients, early death may not be reflective of adherence levels.

Figure 1. Study profile and outcomes. (From [1])



Operational Definitions, Outcome Measures, and Exploratory Variables

Adherence was expressed as a percentage, calculated as the number of months with claims submitted divided by the number of complete months between the date of HAART commencement and (a) death, (b) withdrawal from Aid for AIDS, or (c) the study end on 1 September 2004, and the result multiplied

by 100. Patients were categorized into 6 strata based on calculated adherence: 0% to 19%, 20% to 39%, 40% to 59%, 60% to 79%, 80% to 99%, and 100%.

The primary outcome was all-cause mortality. Patients who elected to leave their insurance fund or whose insurance fund changed to a different disease-management program were censored as lost to follow-up at the date of departure. Age, gender, race, baseline $CD4^+$ T-cell count, and baseline plasma HIV-1 RNA levels were investigated in relation to both adherence and survival in the multivariate analyses. Secondary analyses included either death or loss to follow-up as the outcome. An additional secondary analysis included 12-month adherence, defined as the total months of HAART claimed during the first 12 months of therapy. By definition, the latter analysis was restricted to patients who survived for at least 12 months.

Statistical Analysis

Differences in baseline characteristics were assessed with contingency tables, agreement with the Pearson correlation coefficient (*r*), and statistical significance with the 2-sample Student *t* test for continuous variables and χ^2 test for dichotomous variables. Kaplan-Meier plots were used to examine survival in the 6 strata of medication adherence defined earlier. These analyses were further stratified by baseline $CD4^+$ T-cell count (≤50, 51-200, or >200 cells/μL). Cox proportional hazards regression and the log-rank test were used to model the individual and simultaneous effects of baseline variables and medication

adherence on survival. Any baseline variable associated with survival ($P < 0.1$) in univariate analysis was included in the multivariate model. All variables were stratified into discrete categories, as follows: median adherence level (≥80%, <80%, or in the 6 strata defined earlier), gender (male, female), race (black, white, other), age (18-34, 35-44, 45-54, ≥55), HIV-1 RNA (<4, 4-4.99, ≥5 $\log_{10}$ copies/mL), and date of HAART initiation (in 6-month strata). Inasmuch as $CD4^+$ T-cell count was found to modify the effect of adherence on survival, survival curves were stratified by $CD4^+$ T-cell count. The assumption of proportional hazards was assessed by inspecting graphs of -log(-log[survival]) versus log(analysis time). All *P* values reported are nominal and 2-tailed, with a value of <0.05 considered statistically significant. Statistical analyses were performed using STATA Release 8.0 (Stata Corporation, College Station, TX, USA).

RESULTS

A total of 6,288 patients were eligible for the study (Figure 1). Of these, 82% were on 2 NRTIs plus 1 NNRTI, and 18% were on 2 NRTIs plus 1 protease inhibitor. The total person-time contributed was 11,623 patient-years, and the median (interquartile range, IQR) follow-up time per participant was 1.8 (1.3-2.5) years; 3,805 patients (60.5%) were female, 6,094 (96.9%) were black Africans, and the mean age was 37 ± 8 years. The overall median (IQR) $CD4^+$ T-cell count at HAART initiation in the population was 149 (65-227) cells/μL. The median (IQR) HIV-1 RNA level was 5.16 (4.63-5.62) $\log_{10}$ copies/mL. A total of 3298

Table 1. Baseline Characteristics of the Study Population at Initiation of HAART by Adherence Level (N = 6,288). (From [1])

Variable	Low (<80%) Adherence n = 2990 (47.6%)	High (≥80%) Adherence n = 3298 (52.4%)	Total N = 6288 (100%)	P*
Gender				<0.001
Male	1257 (42.0)	1226 (37.2)	2483 (39.5)	
Female	1733 (58.0)	2072 (62.8)	3805 (60.5)	
Race				0.74
Black	2903 (97.1)	3191 (96.8)	6094 (96.9)	
White	52 (1.7)	65 (2.0)	117 (1.9)	
Other	35 (1.2)	42 (1.3)	77 (1.2)	
Age (y)				0.04
18–34	1377 (46.1)	1420 (43.1)	2797 (44.5)	
35–44	1205 (40.3)	1357 (41.1)	2562 (40.7)	
45–54	350 (11.7)	446 (13.5)	796 (12.7)	
≥55	58 (1.9)	75 (2.3)	133 (2.1)	
$CD4^+$ T-cell count (cells/μL)				0.61
≤50	603 (20.2)	682 (20.7)	1285 (20.5)	
51–200	1408 (47.1)	1515 (45.9)	2923 (46.4)	
201–350	908 (30.4)	1033 (31.3)	1941 (30.9)	
>350	71 (2.4)	68 (2.1)	139 (2.21)	
Log_{10} HIV-1 RNA (copies/mL)				0.14
<4	265 (8.9)	250 (7.6)	515 (8.2)	
4–4.99	956 (32.0)	1098 (33.3)	2054 (32.7)	
≥5	1769 (59.2)	1950 (59.1)	3719 (59.1)	
Date of HAART initiation				<0.001
Before 2001	221 (7.4)	153 (4.6)	374 (5.9)	
Jan 2001–Jun 2001	710 (23.7)	492 (14.9)	1202 (19.1)	
Jul 2001–Dec 2001	739 (24.7)	575 (17.4)	1314 (21.0)	
Jan 2002–Jun 2002	781 (26.1)	917 (27.8)	1698 (27.0)	
Jul 2002–Dec 2002	512 (17.1)	840 (25.5)	1352 (21.5)	
Jan–Mar 2003	27 (0.9)	321 (9.7)	348 (5.5)	

*χ^2 test with 1 degree of freedom was used to calculate the statistical significance (*P* value) between baseline characteristic by adherence level (≥80% vs <80%).

(52.4%) had high (≥80%) adherence, which was associated with female gender (54% vs 49%, $P < 0.001$), older age ($P < 0.04$), and later enrollment in the study ($P < 0.001$). No other significant differences in baseline characteristics were observed between the two groups (Table 1).

During the study period, 222 patients (3.5%) died and 1,155 (18%) were lost to follow-up (Figure 1). In univariate analysis, patients with adherence <80% had significantly poorer survival than those with ≥80% adherence [relative hazard (RH) 3.01; 95% confidence interval (CI): 2.24-4.06]. However, no difference in survival was seen between patients with 80% to 99% compared to those with 100% adherence (RH 0.85; 95% CI: 0.51-1.42). Below 80%, the patient's adherence level had a dose-response effect on survival, with each stratum of medication adherence having lower survival rates than the adjacent, higher-adherence stratum. This effect remained significant, but attenuated, when "death or loss to follow-up" as used as the outcome (Table 2).

Table 2. Crude Relative Hazards of Death, by Level of HAART Adherence (N = 6288) (from [1])

Adherence	N	Deaths (%)	Crude RH* (95%CI) (Death†)	*P*	Crude RH (95%CI)* (Death/Loss†)	*P*
0%–19%	501	41 (8.2)	4.28 (2.69–6.81)	<0.001	2.75 (2.29–3.31)	<0.001
20%–39%	678	42 (6.2)	3.39 (2.14–5.37)	<0.001	2.58 (2.16–3.07)	<0.001
40%–59%	823	45 (5.5)	2.83 (1.79–4.46)	<0.001	2.05 (1.73–2.45)	<0.001
60%–79%	988	35 (3.5)	1.69 (1.04–2.73)	0.03	1.36 (1.13–1.63)	0.001
80%–99%	1382	27 (2.0)	0.85 (0.51–1.42)	0.53	0.91 (0.76–1.09)	0.33
100%	1916	32 (1.7)	1	—	1	—
<80%	2990	163 (5.5)	3.01 (2.24–4.06)	<0.001	2.12 (1.90–2.37)	<0.001
≥80%	3298	59 (1.8)	1	—	1	—

*RH (95% CI) = relative hazard of mortality (95% confidence interval) using Cox proportional hazards regression analysis.
†In the column labeled "Death," confirmed death is the end point and losses to follow-up are censored, whereas in the column labeled "Death/Loss," the RH is calculated by using the combined outcome of death or loss to follow-up.

Upon varying the lag period (the period following HAART initiation during which patients who died or were lost to follow-up were excluded from analysis), the association between adherence of <80% and decreased survival remained significant using any lag period of >90 days (Table 3). Furthermore, compared with 100% adherence, 80% to 99% adherence was significantly associated with decreased survival (RH 1.38; 95% CI: 1.08-1.80) using a lag period of 455 days (15 months). At longer lag periods, the point estimate of the association between adherence and survival continued to increase, but statistical significance was attenuated by small sample size.

Other variables significantly associated with decreased survival in univariate analysis included male gender (RH 1.50; 95% CI: 1.15-1.95), $CD4^+$ T-cell count ≤200 cells/μL (RH 3.00; 95% CI: 2.12-4.28), and HIV-1 RNA $>10^5$

Table 3. Dependence of Relative Hazards of Death Estimates on Analytical Lag Period (from [1])

Adherence	Crude RH (95% CI), By Lag Period Imposed					
	Lag = 0 Days (n = 7080)	*P*	Lag = 90 Days (n = 6609)	*P*	Lag = 365 Days (n = 5776)	*P*
0–19%	1.11 (0.95–1.28)	0.19	1.99 (1.68–2.36)	<0.001	3.63 (2.85–4.62)	<0.001
20–39%	1.20 (1.06–1.37)	0.01	2.28 (1.96–2.65)	<0.001	3.05 (2.41–3.87)	<0.001
40–59%	1.07 (0.95–1.22)	0.27	1.69 (1.45–1.97)	<0.001	2.64 (2.10–3.32)	<0.001
60–79%	0.66 (0.57–0.75)	<001	1.22 (1.04–1.42)	0.014	1.67 (1.31–2.12)	<0.001
80–99%	0.37 (0.32–0.43)	<001	0.68 (0.58–0.81)	<0.001	1.18 (0.93–1.49)	0.17
100%	1	—	1	—	1	—

Lag period refers to the duration of time after HAART initiation for which outcomes (deaths and losses to follow-up) are ignored for purposes of analysis. RH (95% CI) = relative hazard of death (95% confidence interval) using Cox proportional hazards regression analysis and with death or loss to follow-up as the outcome.

copies/mL (RH 2.93; 95% CI: 1.44-5.95). After adjusting for other variables, only adherence <80% (RH 3.23; 95% CI: 2.37-4.39) and $CD4^+$ T-cell count ≤200 cells/μL (RH 2.54; 95% CI: 1.77-3.62) remained significantly and independently associated with decreased survival (Table 4).

A total of 3,267 patients had data available with which to calculate adherence at 12 months after HAART initiation. In this population, the median adherence was 83% at 12 months and 80% at the end of the study. Adherence of ≥80% at 12 months was predictive of the same level of adherence at the end of study (Pearson $r = 0.94$, $P < 0.001$). Furthermore, 12-month adherence remained highly significant as a predictor of subsequent mortality (crude RH 3.61; 95% CI: 2.29-5.68; adjusted RH 3.64; 95% CI: 2.30-5.75).

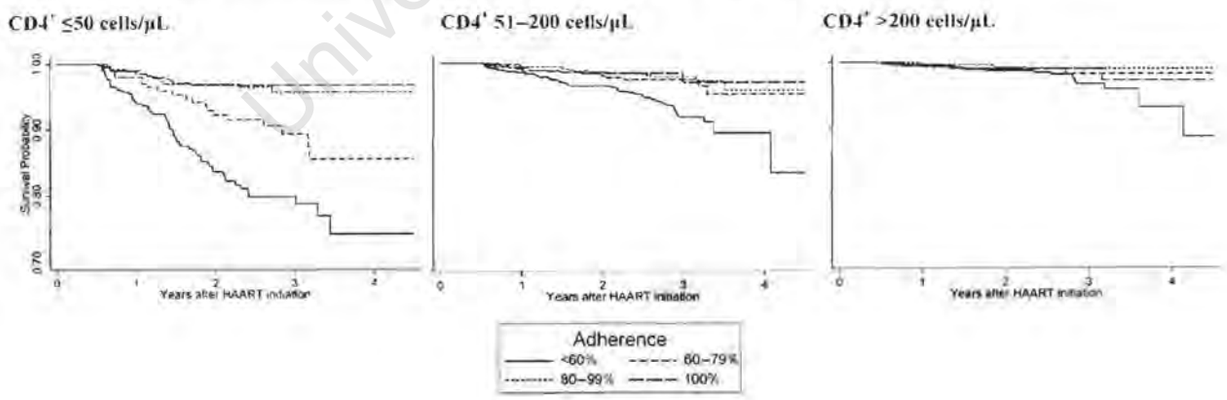
Table 4. Adjusted and Unadjusted Relative Hazards of Death by Baseline Factors Among 6,288 HIV-1-Infected Patients at HAART Initiation (from [1])

Variable	Crude RH (95% CI)*	P	Adjusted† RH (95% CI)*	P
Adherence				
<80%	3.01 (2.24–4.06)	<0.001	3.23 (2.37–4.39)	<0.001
≥80%	1		1	
Gender				
Female	1		1	
Male	1.50 (1.15–1.95)	<0.001	1.22 (0.93–1.59)	0.15
Race				
Black	1			
White	1.34 (0.59–3.03)	0.48		
Other	1.23 (0.39–3.85)	0.72		
Age (y)				
18–34	1		1	
35–44	1.21 (0.91–1.61)	0.19	1.13 (0.84–1.51)	0.41
45–54	1.06 (0.68–1.64)	0.80	1.02 (0.66–1.59)	0.92
≥55	2.03 (0.98–4.18)	0.06	2.00 (0.96–4.16)	0.06
$CD4^+$T-cell count (cells/μL)				
≤50	6.00 (4.03–8.92)	<0.001	5.13 (3.42–7.72)	<0.001
51–200	2.15 (1.43–3.22)	<0.001	1.86 (1.23–2.80)	0.003
>200	1		1	
Log_{10} HIV-1 RNA (copies/mL)				
<4	1		1	
4–4.99	1.57 (0.74–3.31)	0.24	1.37 (0.65–2.90)	0.64
≥5	2.93 (1.44–5.95)	0.003	2.01 (0.98–4.11)	0.06
Date of HAART initiation				
Before 2001	1.60 (0.98–2.60)	0.06	1.44 (0.88–2.35)	0.15
Jan–Jun 2001	0.95 (0.63–1.43)	0.82	0.85 (0.56–1.28)	0.43
Jul–Dec 2001	0.95 (0.63–1.43)	0.81	0.95 (0.63–1.42)	0.79
Jan–Jun 2002	1		1	
Jul–Dec 2002	1.07 (0.70–1.65)	0.75	1.19 (0.77–1.83)	0.44
Jan–Mar 2003	0.93 (0.42–2.06)	0.86	1.39 (0.62–3.13)	0.43

*RH (95% CI) = relative hazard of death (95% confidence interval) using Cox proportional hazards regression analysis.
†Adjusted for adherence, gender, age, $CD4^+$ T-cell count, HIV-1 RNA, and date of HAART initiation.

No significant interactions were detected between adherence (at <80% vs ≥80% threshold) and any baseline variable as predictors of survival. Although the interaction between adherence and $CD4^+$ T-cell count did not achieve statistical significance ($P = 0.09$), the effect of poor (<80%) adherence on survival was greatest in those with low $CD4^+$ T-cell count, with a crude relative hazard of 4.54 (95% CI: 2.83-7.29) in the most immunosuppressed (≤50 cells/μL) versus 2.39 (95% CI: 1.51-3.78) and 2.08 (95% CI: 1.00- 4.31) in patients with $CD4^+$ T-cell count of 51 to 200 and >200 cells/μL, respectively (Figure 2). Treating $CD4^+$ T-cell count as continuous variable rather than a categorical one did not change the findings. In addition, inclusion of patients with missing baseline data did not change any univariate point estimate of relative hazard by more than 5%.

Figure 2. Kaplan-Meier product limit estimates of cumulative progression to death by HAART adherence, as assessed by pharmacy claims (N = 6,288). (From [1])



Each 20% decrease in pharmacy-claim adherence below 80% was associated with a decrease in survival in dose-response fashion, even when death or loss to follow-up was used as the outcome. Indeed, in some cases, the reason for loss to follow-up may be due to imminent death, and in some cases, not. Both extremes of these scenarios were investigated in the survival analysis, one in which patients were censored from the analysis on leaving the insurance fund or a more conservative scenario where these patients were considered deceased. Compared to those with 100% adherence, patients with adherence of 80% to 99% had significantly better survival when using a lag period of <90 days (Table 4). This counter-intuitive finding does not persist when using a lag period of >90 days, suggesting that it reflects deaths among patients enrolling with advanced disease, for whom 100% adherence corresponds to a small number of claims made and in whom death is less likely to be a consequence of non-adherence. In addition, our finding of no significant difference in survival comparing those with 80% to 99% versus 100% adherence does not refute the need for nearly perfect (at least 95%) adherence for optimal outcomes. Rather, this finding reflects the inadequacy of even a 6-month lag period in excluding all patients with advanced disease, coupled with the inability of 100% monthly pharmacy claims to distinguish between those patients who are truly adherent from those patients who fill claims but do not actually ingest all of their medication. Finally, these results suggest that pharmacy claims may be a valid marker of adherence in AIDS patients on HAART for at least 3 to 6 months, but

that claims should not be used to predict individual outcomes, particularly in the months immediately after HAART initiation.

In this observational cohort study, half of enrolled HIV-1-infected patients claimed more than 80% of their prescriptions, and one third claimed <60%. For patients who had been on HAART for at least 12 months, 62% claimed >75% of their prescriptions. These rates are relatively lower than those reported in studies from developed countries that used pharmacy records. Hogg et al. [2] reported that among 1,282 HIV-1-infected individuals, 74% had adherence >75% and 57% had adherence >95% in their first year on HAART, based on pharmacy refill data. In addition, in a 1-year retrospective review of pharmacy refill data for 100 patients in Canada, Ostrop et al reported >80% adherence in 75% of patients. [4] The lower rate of adherence found in this study also differs from previous studies in sub-Saharan Africa that reported a high proportion (>80%) of patients with excellent (>95%) adherence [5-8] using different adherence measures and in developed countries (mean adherence range: 54%-84%) using electronic bottle monitors. [9-13] This discrepancy is likely to reflect difference in adherence measurement tools used or a selection bias leading to overestimation of preliminary studies reported from Africa [14-18], most of which were cross-sectional, measured adherence by self-report, were with short-term follow-up, and included patients participating in ongoing randomized trials with rigorous exclusion criteria and substantial structural support. It is also likely that the adherence support and treatment readiness programs in the public sector could

result in higher adherence than individualized private doctors can accomplish in the private sector.

Given the direct dose-response relationship between pharmacy-claim adherence and both virologic outcomes (Chapter 3) and survival, and the need to evaluate pharmacy-data as a tool for public HIV/AIDS programs, such as those sponsored by public agencies (GFATM, PEPFAR, Médecins Sans Frontières), it could be useful for those programs to consider tracking pharmacy data as a measure of adherence. Such public-private partnerships are essential in countries such as South Africa, where the private sector has greater resources.[19]

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Chapter 5

Effectiveness of Efavirenz- versus Nevirapine-based Regimens for Initial Antiretroviral Therapy in HIV-infected African Adults

INTRODUCTION

A preliminary analysis of results obtained in Chapter 3 suggested that patients treated initially with efavirenz might have better virologic outcomes than those treated with nevirapine. In the present study, the effectiveness of efavirenz vs. nevirapine was evaluated in detail for both virologic and clinical outcomes.

The World Health Organization recommends that initial HAART regimens in resource- limited settings include an NNRTI -- specifically, either efavirenz or nevirapine.[1,2] Despite the two drugs' widespread use in such settings, direct comparisons of their effectiveness have been limited. One of the few trials was the 2NN Study [3], a multicentre, open-label, randomised trial in which 1216 antiretroviral therapy-naive patients were assigned nevirapine (400 mg) once daily, nevirapine (200 mg) twice daily, efavirenz (600 mg) once daily, or nevirapine (400 mg) and efavirenz (800 mg) once daily, plus stavudine and lamivudine, for 48 weeks. The primary endpoint was the proportion of patients with treatment failure (less than 1 $\log_{10}$ decline in plasma viral load in the first 12 weeks or two consecutive measurements of more than 50 copies/mL from week 24 onwards) or disease progression. This trial, with approximately one-third of study participants from South Africa, reported comparable efficacy for efavirenz

and nevirapine at 48 weeks (viral load <50 copies/mL in 70% and 65% of subjects, respectively; p=0.193).[3] However, nevirapine could not be declared non-inferior as the investigator could not show equivalence within the 10% limits of the treatment groups even though the study was adequately powered for such an analysis and nevirapine was associated with more serious toxicity (including 2 deaths).[3] Moreover, in a collaborative study of 12 cohorts from Europe and North America, as well as in a cohort of Veterans Affairs patients in the United States, efavirenz was associated with better virologic outcomes than was nevirapine.[4,5] Furthermore, meta-analyses of data from clinical trials, mostly conducted in the developed world, suggest that efavirenz-based regimens achieve higher rates of virologic suppression than do nevirapine-containing regimens.[6]

Currently, when used with two NRTIs, efavirenz is recommended over nevirapine for initial treatment by both the U.S. Department of Health and Human Services [7] and the International AIDS Society-USA guidelines [8], based on its more favorable toxicity profile and efficacy data from multiple clinical trials.[5,9-12] A World Health Organization survey, however, found that most (67%) countries in sub-Saharan Africa recommended a first-line regimen of stavudine (d4T), lamivudine (3TC) and nevirapine.[13]

Reasons for the wider use of nevirapine in sub-Saharan Africa include its low cost, availability in generic, fixed-dose, combination regimens (stavudine-lamivudine-nevirapine prescribed as Triomune® or Maxivir® in Africa, at a cost of

approximately US $17 to $32 per month) [14,15], and safety in pregnant women. However, strong evidence that efavirenz produces more favorable virologic and clinical outcomes in a resource-limited population might influence such recommendations and speed efforts either to reduce the cost of efavirenz (US$34 per month, not including the cost of NRTIs) [15] or to develop a generic efavirenz-containing fixed-dose combination regimen for use in resource-limited settings. Therefore, the magnitude of any differential treatment effect of efavirenz vs. nevirapine in southern Africa is likely to help shape policy decisions moving forward.

We followed our preliminary observations with an observational cohort study using pharmacy-claim adherence and both virologic and clinical outcomes to provide a more conclusive investigation of the relative effectiveness of these two NNRTIs in our patient cohort.

MATERIALS AND METHODS

Study Population and Data Source

Records from HAART-naïve HIV-1-infected adults enrolled in Aid for AIDS from January 1998 to September 2004 were evaluated (See Chapter 2 for other details).

Analytic Variables and Definitions

The primary exposure variable for the current analysis was the initial NNRTI used (efavirenz or nevirapine). Patients were defined as being on efavirenz- or nevirapine-based HAART from the time their first pharmacy claim was authorized until either (a) authorization for that drug lapsed for 30 days, (b) another NNRTI or protease inhibitor was prescribed and authorized by Aid for AIDS, or (c) the study's end (September 1, 2004).

The primary outcome was time to virologic failure, defined as (a) two separate measurements of viral load ≥400 c/mL, each taken more than six months after HAART initiation, or as (b) a switch to another NNRTI or protease inhibitor after at least one such measurement. Secondary outcomes included time to all-cause mortality, time to viral-load suppression <400 c/mL, and discontinuation of initial NNRTI without virologic failure.

Potential confounders that we evaluated are shown in Table 1. Pharmacy-claim adherence was expressed as a percentage, calculated as the number of months with HAART claims submitted divided by the number of complete months from HAART commencement to either (a) death, (b) withdrawal from the Aid for AIDS program, or (c) study's end, with the result multiplied by 100. According to the specific analysis, adherence was analyzed either as a binary variable with a cut-off of 100%, 90%, or 80%; in discrete pre-defined strata; or as a continuous variable among patients with at least 50% adherence. Short-course HAART was a policy recommendation for prevention of mother-to-child transmission (pMTCT)

of HIV in this population and single-dose nevirapine was never used because of the risk of developing NNRTI resistance. [16]

Statistical Analysis

Differences in baseline characteristics were assessed with two-sample Student's t tests (continuous variables) and χ^2 tests (categorical variables). Kaplan-Meier plots were used to estimate survival probability according to initial NNRTI and adherence status (100% vs. <100%; >90% vs. <90%; >80% vs. <80%). Cox proportional hazards regression was used to model the individual and simultaneous effects of the initial NNRTI, baseline variables, and pharmacy-claim adherence on time to virologic failure, viral suppression, and regimen discontinuation. Plots of -log[-log(survival)] against log(analysis time) and analyses of scaled Schoenfeld residuals were used to assess the proportionality assumption (p = 0.67 for efavirenz vs. nevirapine on time to virological failure). All available variables were included a priori in multivariate models and were stratified into discrete categories as follows: sex (male/female), race (black/other), CD4 count (≤50, 51–200, or >200 cells/μL), viral load (greater or less than 5 $\log_{10}$ copies/mL), prior history of antiretroviral therapy for pMTCT (yes/no), initial NRTI combination (zidovudine/lamivudine, stavudine/lamivudine, stavudine/didanosine, or zidovudine/didanosine), and date of HAART initiation (in four calendar-year strata). All *P* values reported are exact and 2-tailed, with a value of <0.05 considered statistically significant. Statistical analyses were

performed using STATA Release 8.0 (Stata Corporation, College Station, TX, USA).

RESULTS

A total of 2817 patients met inclusion criteria, of whom 1822 (64.7%) were started on efavirenz and 995 (35.5%) on nevirapine. The most frequently prescribed NRTI pairs were zidovudine/lamivudine (n=2187, 77.6%), stavudine/didanosine (n=523, 18.6%), and stavudine/lamivudine (n=79, 2.8%). Compared to patients initially treated with efavirenz, those treated with nevirapine were significantly younger, were more likely to be female, were less immunosuppressed as determined by $CD4^+$ T-cell count, had lower viral loads, started treatment earlier in calendar time, and were more likely to receive zidovudine/lamivudine ($p<0.01$ for all comparisons; Table 1).

Patients started on nevirapine did not differ from those started on efavirenz in terms of frequency of viral-load measurements (median 1.08 per year, IQR 0.59–1.60, for nevirapine; 1.10, 0.71–1.58, for efavirenz; $p = 0.15$ for difference) or time to first post-HAART viral load measurement (median 122 days, IQR 92–209, for nevirapine; 114 days, 92–204, for EFV; $p = 0.19$ for difference). Women with baseline $CD4^+$ T-cell count ≥250 cells/μL were more likely to start on nevirapine (n=157, 23.4%) than efavirenz (n=203, 18.5%); exclusion of these patients did not materially change results.

Median (interquartile range [IQR]) length of follow-up was 1.9 (1.0–2.6) years among patients started on nevirapine and 2.0 (1.3–2.6) among those started on efavirenz (p=0.009 for difference; Table 1). During this time, patients started on nevirapine were significantly less likely than those started on

Table 1. Characteristics of Study Population, by Initial NNRTI Regimen

Variable	Efavirenz QD (n=1822)	Nevirapine BD (n=995)	Total (N = 2817)	P value[a]
Age: Mean (sd)	37.5 (7.6)	36.0 (8.0)	37.0 (7.8)	<0.001
Follow-Up Duration: Median (IQR), in yrs	2.0 (1.3-2.6)	1.9 (1.0-2.6)	2.0 (1.2-2.6)	0.009
Sex				<0.001
Male	723 (39.7)	323 (32.5)	1046 (37.1)	
Female	1099 (60.3)	672 (67.5)	1771 (62.9)	
Race				0.46
Black	1769 (97.1)	961 (96.6)	2730 (96.9)	
Other	53 (2.9)	34 (3.4)	87 (3.1)	
Baseline CD4				<0.001
≤50	407 (22.3)	176 (17.7)	583 (20.7)	
51-200	879 (48.2)	420 (42.2)	1299 (46.1)	
>200	536 (29.4)	399 (40.1)	935 (33.2)	
Baseline VL				0.003
$\leq 10^5$	709 (38.9)	445 (44.7)	1154 (41.0)	
$>10^5$	1113 (61.1)	550 (55.3)	1663 (59.0)	
pMTCT				<0.001
Yes	84 (4.6)	142 (14.3)	226 (8.0)	
No	1738 (95.4)	853 (85.7)	2591 (92.0)	
Initial NRTI				<0.001
3TC + ZDV	1321 (72.5)	866 (87.0)	2187 (77.6)	
3TC + d4T	59 (3.2)	20 (2.0)	79 (2.8)	
d4T + ddI	432 (23.7)	91 (9.2)	523 (18.6)	
ddI + ZDV	10 (0.6)	18 (1.8)	28 (1.0)	
Date of HAART start				<0.001
1998-2000	10 (0.6)	46 (4.6)	56 (2.0)	
2001	620 (34.0)	462 (46.4)	1082 (38.5)	
2002	1072 (58.8)	441 (44.3)	1513 (53.6)	
2003	120 (6.6)	46 (4.6)	166 (5.9)	
Pharmacy-claim adherence				<0.001
<50%	206 (11.3)	119 (12.0)	325 (11.5)	
50-79%	410 (22.5)	248 (24.9)	658 (23.4)	
80-99%	511 (28.1)	327 (32.9)	838 (29.7)	
100%	695 (38.1)	301 (30.2)	997 (35.4)	

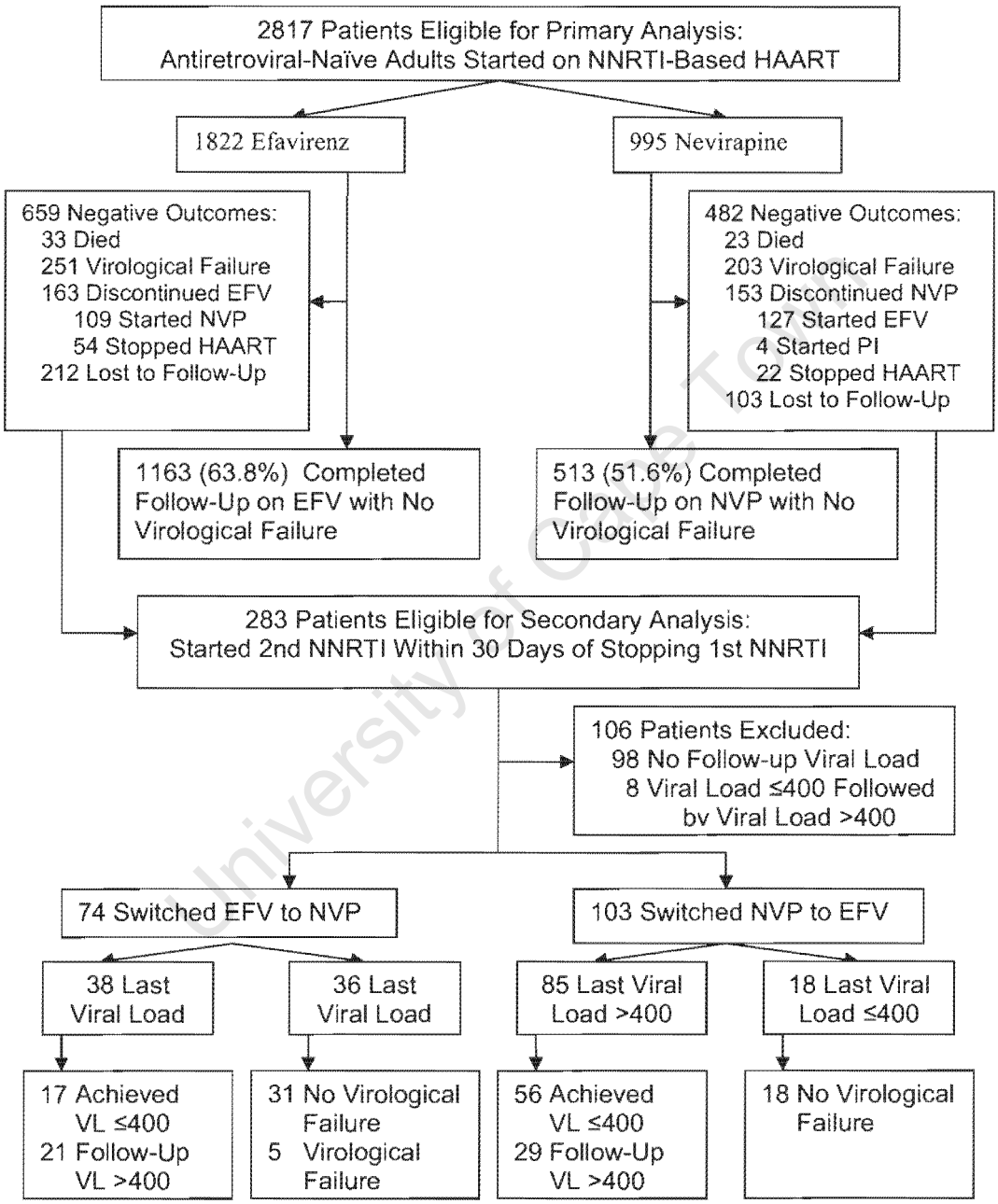
[a] Based on the Student's t-test or chi-square test (χ^2) with one degree of freedom, comparing patients initiated on efavirenz versus those initiated on nevirapine.

efavirenz to achieve high adherence, whether defined as 100% (30.2% vs. 38.1%, p<0.002) or >90% (44.8% vs. 49.4%, p<0.02). Patients started on nevirapine were significantly more likely to experience virologic failure (20.4% vs. 13.8%, p<0.001) and NNRTI discontinuation without virologic failure (15.4% vs. 8.9%, p<0.001). The crude proportions of patients who died (2.3% for NVP vs. 1.8% for EFV, p=0.36) or were lost to follow-up (10.4% vs. 11.6%, p=0.30) were comparable in the two patient groups (Figure 1).

After adjusting for other variables, patients initially treated with efavirenz experienced a significantly shorter time to virologic suppression (<400 c/mL) than did those treated with nevirapine (median time to suppression 5.5 months on NVP versus 4.8 months on efavirenz, multivariate HR 1.27, 95% CI 1.15–1.40) (Table 2). Similarly, patients on nevirapine were more likely to experience virologic failure than were those given efavirenz (HR 1.52, 1.24–1.86) (Table 2). Other variables significantly associated with faster time to virologic failure in multivariate analysis included lower baseline $CD4^+$ T-cell count (HR 1.52, 1.16–1.99, for ≤50 vs. >200 cells/μL), initial use of stavudine/didanosine (HR 1.48, 1.15–1.91, vs. zidovudine/lamivudine) or zidovudine/didanosine (HR 2.35, 1.07–5.18), calendar year of HAART initiation (HR 1.57, 1.29–1.90, per later year), and, as reported before, pharmacy-claim adherence (HR 11.74, 8.48–16.25, for <50% vs. 100% adherence) [6].

The increased risk of virologic failure associated with nevirapine use was restricted to patients with <90% adherence in univariate analysis (Figures 2, 3

Figure 1. Characterization of Study Participants



and 4), but was observed in all patients after adjustment for potential confounders (multivariate HR = 1.46, 1.17–1.84, in patients with <90% adherence; 1.63, 1.04–2.54, in those with ≥90% adherence). In multivariate analysis, patients initially treated with nevirapine had a significantly higher risk of both death (HR 2.17, 1.31-3.60) and of NNRTI discontinuation in the absence of virologic failure (HR 1.67, 1.32–2.11) than did patients initially treated with efavirenz (Table 4), presumably due to toxicity.

In a secondary analysis, outcomes in patients who switched from efavirenz to nevirapine or vice versa were compared, after excluding patients who either had no viral-load measurement after NNRTI switch or who switched NNRTI after achieving virologic suppression and subsequently experiencing virologic failure (viral load ≥400 c/mL). Of 177 eligible patients, 54 (34.2%) switched while virologically suppressed (i.e., last known viral load measurement <400 copies/mL). Of these 54, 4 of 18 patients (22.2%) who switched from nevirapine to efavirenz had a single viral-load measurement ≥400 c/mL, and none experienced virologic failure, as defined here, over a median 0.81 (IQR 0.65–1.49) years of follow-up. By contrast, 9 of 36 patients (25.0%) who switched from efavirenz to nevirapine had at least one viral-load measurement ≥400 c/mL, and 5 (13.9%) experienced virologic failure over a median 0.93 (IQR 0.53–1.40) years of follow-up. In time-to-event analysis, the univariate risk or hazard of virologic failure was 3.92 (95% CI 1.61–9.55) for patients who switched to nevirapine compared to those remaining on efavirenz.

Table 2. Adjusted Associations between Patient Characteristics and Time to Initial Viral Suppression <400 copies/mL

Variable	Univariate HR (95% CI)	Multivariate HR (95% CI) [a]
NNRTI		
Efavirenz	1.21 (1.10-1.33)	1.27 (1.15-1.40)
Nevirapine	1	1
Age		
(per 10 years)	1.04 (0.99-1.10)	1.05 (0.99-1.11)
Sex		
Male	1	1
Female	1.20 (1.10-1.32)	1.11 (1.01-1.22)
Race		
Black	0.84 (0.66-1.07)	0.87 (0.68-1.11)
Other	1	1
Baseline $CD4^+$		
≤50	1	1
51-200	1.02 (0.91-1.15)	0.95 (0.84-1.06)
>200	1.14 (1.00-1.28)	1.12 (0.98-1.27)
Baseline viral load		
$\leq 10^5$	1.28 (1.17-1.40)	1.41 (1.29-1.55)
$>10^5$	1	1
pMTCT		
Yes	1.10 (0.94-1.28)	1.27 (1.07-1.50)
No	1	1
NRTI pair		
3TC + ZDV	1	1
3TC + d4T	1.55 (1.22-1.97)	1.08 (0.84-1.37)
d4T + ddI	0.92 (0.82-1.03)	0.82 (0.73-0.92)
ddI + ZDV	0.44 (0.25-0.78)	0.43 (0.23-0.79)
Year of HAART start		
1998-2000	1.00 (0.72-1.39)	2.27 (1.58-3.27)
2001	1	1
2002	1.22 (1.11-1.33)	1.23 (1.12-1.36)
2003	1.13 (0.93-1.37)	1.08 (0.88-1.33)
Pharmacy-claim adherence		
50% vs. <50%	1.05 (0.77-1.42)	0.84 (0.61-1.14)
per 10% increase above 50%	1.14 (1.11-1.18)	1.15 (1.12-1.18)

[a]Adjusted for all other variables in the table, plus frequency of viral load measurement and time to measurement of first viral load.

Table 3. Adjusted Associations between Patient Characteristics and Time to Study Outcomes

Variable	Hazard Ratio (95% Confidence Interval) for Association with Specified Outcome					
	Virological Failure[a]		Death		Regimen Discontinuation (Without Virological Failure)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
NNRTI						
Efavirenz	1	1	1	1	1	1
Nevirapine	1.48 (1.23-1.78)	1.52 (1.24-1.86)	1.46 (0.91-2.34)	2.17 (1.31-3.60)	1.84 (1.48-2.30)	1.67 (1.32-2.11)
Age						
(per 10 yrs)	0.88 (0.78-1.00)	0.87 (0.76-1.00)	1.14 (0.84-1.53)	1.08 (0.79-1.47)	0.95 (0.82-1.10)	1.09 (0.94-1.26)
Sex						
Male	1.27 (1.06-1.54)	1.08 (0.89-1.33)	1.52 (0.95-2.42)	1.22 (0.76-1.98)	0.74 (0.58-0.94)	0.82 (0.64-1.06)
Female	1	1	1	1	1	1
Race						
Black	1	1	1	1	1	1
Other	1.02 (0.56-1.85)	1.10 (0.60-2.02)	1.95 (0.71-5.36)	2.13 (0.77-5.94)	0.93 (0.48-1.81)	1.00 (0.51-1.94)
Baseline CD4*						
≤50	1.67 (1.30-2.16)	1.52 (1.16-1.99)	5.60 (2.75-11.44)	5.50 (2.65-11.39)	0.93 (0.69-1.25)	1.05 (0.77-1.43)
51-200	1.42 (1.14-1.76)	1.29 (1.02-1.62)	2.25 (1.10-4.61)	2.14 (1.03-4.44)	0.74 (0.57-0.94)	0.76 (0.59-0.99)
>200	1	1	1	1	1	1
Baseline viral load						
$\leq 10^5$	1	1	1	1	1	1
$>10^5$	1.36 (1.12-1.65)	1.25 (1.02-1.53)	1.56 (0.94-2.58)	1.12 (0.67-1.88)	0.97 (0.77-1.21)	1.07 (0.85-1.35)
pMTCT						
Yes	1	1	1	1	1	1
No	0.98 (0.70-1.38)	1.12 (0.77-1.62)	5.69 (0.79-40.95)	4.33 (0.58-32.22)	0.46 (0.34-0.63)	0.56 (0.40-0.78)
NRTI pair						
3TC + ZDV	1	1	1	1	1	1
3TC + d4T	0.81 (0.40-1.63)	1.33 (0.65-2.72)	1.26 (0.31-5.20)	1.83 (0.43-7.74)	1.08 (0.57-2.02)	1.28 (0.67-2.43)
d4T + ddI	1.36 (1.08-1.73)	1.48 (1.15-1.91)	2.05 (1.21-3.46)	2.30 (1.31-4.05)	0.70 (0.51-0.98)	0.73 (0.52-1.03)
ddI + ZDV	1.90 (1.01-3.60)	2.35 (1.07-5.18)	1.89 (0.26-13.76)	1.97 (0.19-20.91)	1.31 (0.49-3.52)	1.23 (0.41-3.73)
Year of HAART start						
1998-2000	1.42 (0.87-2.33)	0.66 (0.36-1.21)	1.36 (0.32-5.73)	0.62 (0.11-3.45)	1.21 (0.57-2.59)	0.94 (0.40-2.22)
2001	1	1	1	1	1	1
2002	1.12 (0.92-1.37)	1.18 (0.95-1.46)	1.00 (0.60-1.66)	1.11 (0.64-1.91)	0.97 (0.77-1.24)	1.11 (0.86-1.42)
2003	2.60 (1.64-4.14)	5.37 (3.20-9.02)	1.33 (0.46-3.84)	1.28 (0.38-4.31)	1.66 (1.09-2.52)	2.76 (1.70-4.48)
Pharmacy-claim adherence						
<50%	7.22 (5.32-9.79)	11.74 (8.48-16.3)	3.43 (1.84-6.39)	3.85 (1.93-7.66)	1.20 (0.82-1.75)	1.43 (0.95-2.16)
50-59%	5.19 (3.61-7.45)	7.48 (5.07-11.04)	1.05 (0.36-3.08)	1.19 (0.39-3.61)	1.33 (0.86-2.07)	1.57 (1.00-2.47)
60-69%	4.13 (2.86-5.98)	6.35 (4.34-9.30)	1.25 (0.47-3.35)	1.37 (0.50-3.78)	1.04 (0.64-1.69)	1.14 (0.69-1.86)
70-79%	3.68 (2.58-5.25)	4.05 (2.82-5.82)	1.01 (0.38-2.72)	1.06 (0.38-2.94)	1.47 (1.00-2.15)	1.72 (1.15-2.57)
80-89%	2.14 (1.53-2.99)	2.91 (2.07-4.10)	1.05 (0.49-2.26)	1.10 (0.49-2.47)	1.31 (0.95-1.79)	1.47 (1.05-2.07)
90-99%	0.73 (0.47-1.14)	0.92 (0.59-1.45)	0.83 (0.35-1.99)	0.89 (0.35-2.24)	1.03 (0.70-1.49)	1.16 (0.78-1.74)
100%	1	1	1	1	1	1

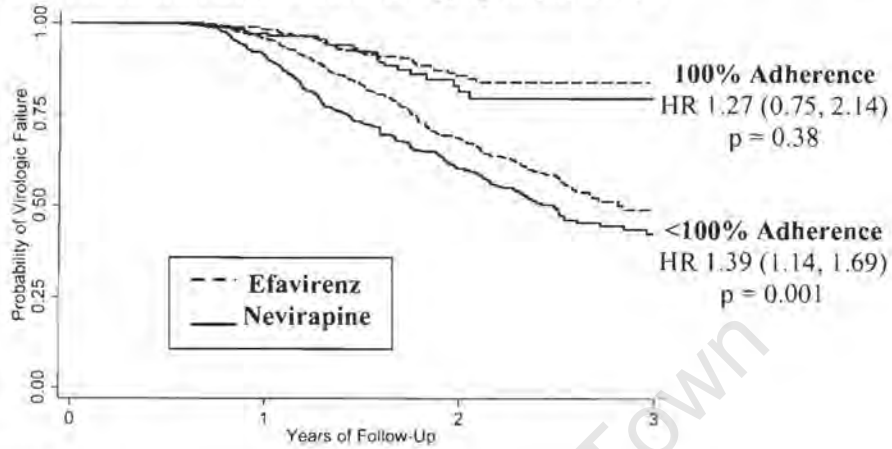
[a] Defined as either two detectable viral load measurements (>400 copies/mL) more than 6 months after starting HAART, or switch to an alternative HAART regimen following a single detectable viral load measurement. Multivariate results in this column are also adjusted for time to first viral load and frequency of viral load measurement.

The remaining 123 (65.8%) of the 177 patients switched NNRTIs before achieving known virologic suppression (Figure 1); 78 (63.4%) of these patients had no viral-load measurement between HAART initiation and NNRTI switch. After adjusting for confounders including time to next viral load measurement, patients who switched from nevirapine to efavirenz before virologic suppression had a comparable chance of achieving subsequent suppression compared to those who remained on nevirapine (HR 0.86, 95% CI 0.65–1.13). By contrast, those who switched from efavirenz to nevirapine achieved suppression significantly more slowly than did those who remained on efavirenz (HR 0.58, 95% CI 0.35–0.93) (Figure 5).

DISCUSSION

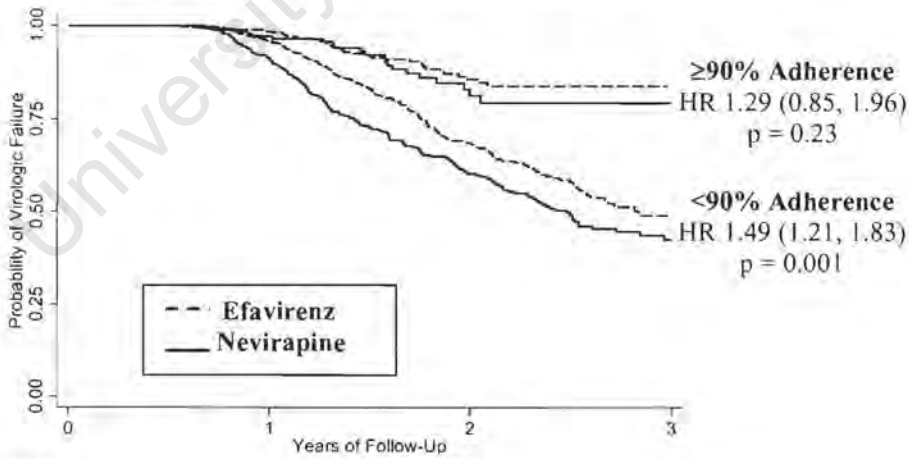
This observational study found that in the setting of a private-sector antiretroviral management program in southern Africa, nevirapine was less effective than efavirenz when used in an initial NNRTI-based HAART regimen. Specifically, the initial use of nevirapine was associated with a 52% increase in the risk of virologic failure and more than a doubling in the risk of all-cause mortality than efavirenz, after adjusting for adherence, NRTI backbone, baseline viral load, prior use of pMTCT treatment, sex, age, calendar time, frequency of viral load measurement and time to measurement of first viral load. Furthermore, switching from efavirenz to nevirapine was associated with significantly worse virologic outcomes than was switching from nevirapine to efavirenz.

Figure 2. Time to Virologic Failure for Patients with 100% Pharmacy Claim Adherence and Those with <100% Adherence, by Initial NNRTI



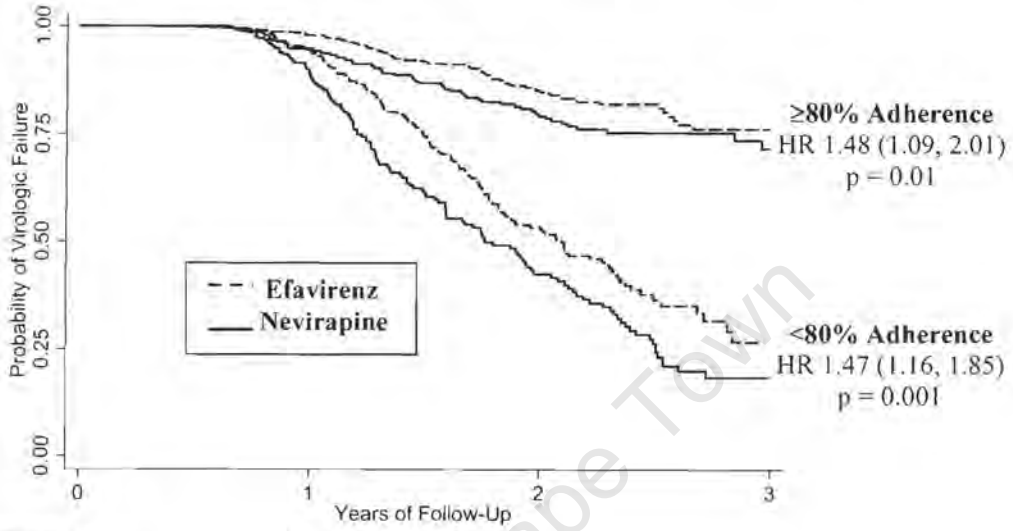
NNRTI/Adherence		Number at Risk		
EFV/100%	695	399	108	12
EFV/<100%	1127	610	236	23
NVP/100%	301	147	46	8
NVP/<100%	694	359	150	33
Total	2817	1515	540	76

Figure 3. Time to Virologic Failure for Patients with ≥90% Pharmacy Claim Adherence and Those with <90% Adherence, by Initial NNRTI



NNRTI/Adherence		Number at Risk		
EFV/≥90%	900	534	186	21
EFV/<90%	922	475	158	14
NVP/≥90%	446	240	102	27
NVP/<90%	549	266	94	14
Total	2817	1515	540	76

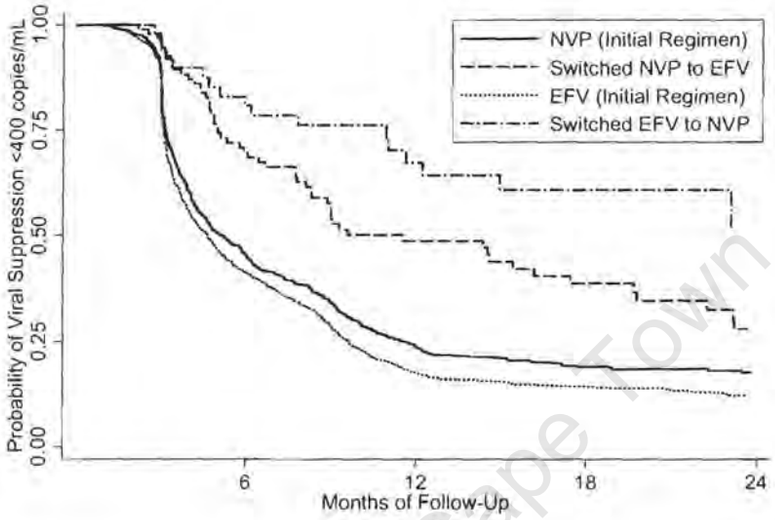
Figure 4. Time to Virologic Failure for Patients with ≥80% Pharmacy Claim Adherence and Those with <80% Adherence, by Initial NNRTI



NNRTI/Adherence		Number at Risk		
EFV/≥80%	1206	704	247	28
EFV/<80%	616	305	97	7
NVP/≥80%	628	340	141	32
NVP/<80%	367	166	55	9
Total	2817	1515	540	76

These data are consistent with comparable studies from the developed world. An analysis of the Antiretroviral Therapy Cohort Collaboration (ART-CC), which combined data from 12 HIV/AIDS cohort studies, found that 12% of patients who started with regimens that included efavirenz still had detectable viral loads at six months compared to 22% of patients started on nevirapine (OR 2.19, 95% CI 1.83–2.62). [4] ART-CC also found that the adjusted hazard ratio for all-cause mortality for the nevirapine group was 2.28 (95% CI, 1.20–4.36)

Figure 5. Time to Virologic Suppression, by Initial and Second NNRTI Regimen



Regimen	Number at Risk			
NVP (Initial)	381	142	76	43
EFV (After NVP)	41	24	17	9
EFV (Initial)	678	217	120	43
NVP (After EFV)	14	13	11	4
Total	1114	396	224	99

during the first 6 months. [4] Of note, the ART-CC study was unable to control for adherence, which is perhaps the most important determinant of treatment outcome. A study of Veterans Affairs (VA) patients (97% male) in the United States reported worse virologic and immunological outcomes with nevirapine compared to efavirenz in univariate analysis and after adjustment for adherence. However, this study of VA patients did not evaluate virologic failure after initial suppression and did not report clinical outcomes. [5]

There are only two clinical trials that have directly compared efavirenz and nevirapine. Nunez and colleagues reported from Spain the results of a small trial in which 64 HAART-naive patients started stavudine and didanosine with either nevirapine or efavirenz.[17] In an intent-to-treat analysis, 64% of patients in the nevirapine and 74% in the efavirenz arm had viral load <50 copies/mL at 48 weeks (P =0.43). It is worth noting that this study had only 14% power to detect a significant difference between the two arms. On the another hand, in the multicenter 2NN trial [3], which was powered to demonstrate non-inferiority of nevirapine compared to efavirenz, the investigators could not show equivalence within the 10% limits of the treatment groups and nevirapine was associated with more serious toxicities, including two drug-related deaths, and did not satisfy the protocol criteria for non-inferiority. Among the South African subjects enrolled in 2NN, the rates of failure of nevirapine (50.0%) and efavirenz (38.3%) [3], defined as virologic failure or NNRTI switch, were comparable to failure rates in the present study among patients who failed to complete follow-up on the initial NNRTI regimen (48.4% and 36.2%, respectively). Thus, the preponderance of existing evidence suggests that initial treatment with efavirenz achieves better virologic outcomes than initial treatment with nevirapine, and this study is the first to demonstrate this difference in a large population of patients from sub-Saharan Africa. Furthermore, these results provide evidence of the superiority of efavirenz in routine clinical practice, where issues not captured in efficacy trials—including adherence under non-controlled conditions, provider prescription patterns, and

drug interactions related to treatment of endemic co-infections (e.g., tuberculosis)—may be critical.

The better virologic and clinical outcomes observed with efavirenz have important clinical and public health implications, particularly when guidelines are being developed for initial antiretroviral programs in resource-limited settings. However, other factors, including the lower cost of nevirapine, different side-effect profiles, the requirement for more careful clinical and laboratory monitoring with nevirapine [18-20], the greater teratogenicity potential of efavirenz, and complex drug interactions (e.g., with rifampicin) [21], must also be considered. A formal cost-effectiveness analysis comparing the two agents may aid decision making. Furthermore, our results suggest that the as yet unquantified risk of birth defects with efavirenz [22] may need to be weighed against the increased risk of virologic failure on nevirapine. Efforts to lower the price of efavirenz and to develop generic, efavirenz-based, fixed-dose combinations should be given high priority.

Another important determinant of virologic outcome that may favour efavirenz in this setting is the increase in efavirenz half-life in individuals who are homozygous for the CYP2B6 position 516 TT polymorphism. This genotype was found in 3.4% of European-Americans in the AIDS Clinical Trials Group study A5097s [23], close to 50% of participants in a study from Ghana [24] and 13.1%

of participants in a South African study [25]. That polymorphism may result in greater rates of discontinuation due to CNS toxicity [26], improved efficacy due to prolonged half-life, or both. It is also possible that patients with the polymorphism who miss one or more doses because of mild toxicity may have the impact of the missed dose balanced by the altered pharmacokinetics, which results in a half-life long enough to maintain levels beyond a single day. Indeed, at lower levels of adherence (i.e., <90%), efavirenz outperforms nevirapine, an effect that becomes more pronounced as adherence drops. This suggests that efavirenz is more forgiving of missed doses than is nevirapine, which might in part explain the differential effectiveness in a clinical setting in which perfect adherence is not the norm. Of note, this adherence effect disappears in multivariate analysis adjusted for confounding to include adherence. In the absence of genotypes for the study population, the fact that in our population, efavirenz outperformed nevirapine to a degree similar to that seen in populations with low prevalence of this polymorphism [4,5] would appear to suggest that the polymorphism is less likely to account for our findings.

The current study has some limitations in addition to those outlined in Chapter 2. First, due to its observational design, the results of our study are subject to the potential for both unmeasured confounding and bias. Of particular concern is selection bias: patients more likely to adhere to HAART may have been more likely to be prescribed efavirenz than nevirapine. A second limitation

is the possibility of temporal bias, as physicians were more likely to prescribe nevirapine during the early years of the study. However, it is reassuring that the estimated magnitude of efavirenz's effect (versus nevirapine) was comparable in patients with 100% versus <100% adherence (although the estimated effect in patients with 100% adherence was not statistically significant). Also reassuring is the fact that patients who enrolled later in calendar time—and who were thus more likely to receive efavirenz—had significantly shorter times to virologic failure in univariate analysis than those enrolled earlier. Additional limitations of this study are the small sample size for our secondary analyses of mortality and NNRTI switch and our exclusion of patients with neither six months of follow-up nor a subsequent viral load measurement, both of which hinder application to the general population of patients initiating HAART. Finally, our analysis of the drugs' effectiveness after NNRTI switch could not consider the clinical indication for switching regimens because that information was not captured in our database.

Given the rapid pace at which antiretroviral programs are being rolled out in this region of the world, as well as the frequency with which such programs use nevirapine as a first-line NNRTI agent, the assumption that efavirenz and nevirapine are equally effective should be reassessed. Our results and those from other studies underscore the critical need for a large, randomized, clinical trial in resource-limited settings to definitively compare efavirenz and nevirapine.

Furthermore, efforts to develop lower-cost formulations of efavirenz, including generic, fixed-dose, combination regimens, should be accelerated.

In conclusion, this study found that among adults enrolled in a private-sector HIV management program in southern Africa, the use of efavirenz in initial HAART regimens was associated with more rapid viral suppression, less frequent treatment discontinuation, and a lower risk of virologic failure or death compared to nevirapine, even when accounting for adherence as estimated by pharmacy claims. Also, patients with detectable viral loads who switched from nevirapine to efavirenz had rates of future virologic suppression that were comparable to those of patients remaining on nevirapine, whereas those who switched from efavirenz to nevirapine had significantly lower suppression rates than those remaining on efavirenz.

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Chapter 6

Virologic Outcomes and Antiretroviral Therapy Adherence in Adolescents Compared with Adults in Southern Africa

INTRODUCTION

The goal of combination antiretroviral therapy (ART) is the sustained suppression of human immunodeficiency virus (HIV) replication. Although large studies of HIV-infected adults [1-4] and children [5,6] have been conducted, there are relatively few data in adolescents describing the virologic outcomes of ART. According to the World Health Organization (WHO), the number of adolescents on ART continues to increase, reflecting successful treatment of perinatally-infected children, infections during early adolescence, and expanding worldwide access to ART [7]. Because of unique behavioural characteristics, adolescents may have worse adherence to ART [8,9], increasing the risk of both morbidity and drug resistance. As a result, measurement of adherence and virologic outcomes in this population is important.

Existing data on ART adherence and outcomes in adolescents come almost exclusively from the developed world. For example, the REACH (Reaching for Excellence in Adolescent Care and Health) Project in the U.S. found that only 41% of adolescents on ART reported >95% adherence and that factors associated with poor adherence included depression, pill burden,

advanced HIV status, alcohol use, and dropping out of school [8,10]. In another study, the Pediatric AIDS Clinical Trial Group (PACTG) 381 cohort included 120 adolescents infected via high-risk behaviors and treated with at least two NRTIs plus either a protease inhibitor or an efavirenz-containing HAART regimen. Of the 120 subjects starting ART, 44 (37%) stayed on study treatment for the 3 years of observation. Twenty-nine (24%) subjects reached and maintained undetectable viral loads. Poorer adherence was the main predictor of virologic failure. [11]

In these studies, however, adolescent data were not directly compared to data from adults, and it also is uncertain whether this adolescent data could be generalized to sub-Saharan Africa, currently home to 70% of all people living with AIDS [7]. Therefore, we investigated adherence and virologic outcomes in adolescents compared to adults enrolled in *Aid for AIDS*, a large private-sector HIV management program in southern Africa.

METHODS

Data source

We evaluated records from HIV-1-infected adults and adolescents enrolled in *Aid for AIDS* who initiated ART, defined as a minimum of two NRTIs plus one NNRTI (Efavirenz or Nevirapine) or a boosted protease inhibitor (PI), between January 1999 and August 2006 and met the following criteria: (1) no

known prior exposure to ART; (2) age ≥11 years old at ART initiation; (3) at least 6 months of follow-up data available; (4) baseline (pre-ART) HIV viral load >400 copies/mL; and (5) at least one known viral load measurement after ART initiation. Follow-up continued from initiation of ART until a) change in ART regimen, b) loss to follow-up, c) death, or d) study end in February 2007 (six months after the last eligibility date).

Our primary analyses compared adolescents (defined as age 11–19 years) to adults (age ≥20 years), based on age at ART initiation. The primary outcomes were virologic suppression (HIV viral load ≤400 copies/mL) and viral rebound, defined as virologic failure (viral load >400 copies/mL) after achieving virologic suppression. The cutoff of 400 copies/mL was selected because measurements were performed at a variety of laboratories, some of which measured HIV viral load using assays with a limit of detection of 400 copies/mL. Adherence was classified as ≤50%, 51-67%, 68-84%, 85-99% and 100% of possible pharmacy refills. Other covariates in the analysis included sex, race, $CD4^+$ T-cell count and viral load at programme enrolment, year of ART initiation and number of viral load measurements.

Statistical analysis

Two analytic methods to compare virologic suppression in adolescents versus adults were used. In the first, four pre-specified time points +/- 3 months

of 6, 12, 18 and 24 months after ART initiation were used, and at each the following were recorded: (a) pharmacy refill adherence to that point, and (b) last available post-ART viral load measurement. We then used virologic suppression at each time point as the dependent variable in a log-linear model, with adolescent status as an independent variable. Both univariate and multivariate (including all covariates listed above) models were analyzed. The Pearson χ^2 Goodness-of-Fit statistic was used to assess model fit. The second analysis employed a Cox proportional hazards model to evaluate the association between adolescent status and time from virologic suppression to virologic rebound. The assumption of proportional hazards was assessed by the model-based test for the time-by-log(t) interaction.

All *p* values reported are 2-tailed, with a value of <0.05 considered statistically significant. Fisher's exact test and the Wilcoxon rank-sum test were used in two-way comparisons of binary and continuous variables, respectively. Statistical analyses were performed using STATA Release 8.2 (Stata Corporation, College Station, TX, USA).

RESULTS

7,776 eligible patients were included, of whom 154 were adolescents and 7,622 were adults as defined in this analysis. Characteristics of the study cohort are shown in Table 1. Adolescents were more likely than adults to be female

(72.7% vs. 62.3%, P =0.01), initiate ART in 2003 or later (40.3% vs. 50.1%, P =0.02), and have shorter follow-up duration (median 27 months, inter-quartile range [IQR] of 18.1-43.7 vs. 36.9 [IQR: 23.6-54.5], P <0.001).

In a subset of patients with adherence data available through 6, 12, and 24 months of follow-up, adolescents had consistently and significantly lower adherence than adults. Adolescents claimed medication for a median of 4/6 (IQR 3-5), 8/12 (IQR 5-10), and 15/24 (IQR 8-19) months, versus 5/6 (IQR 3-6), 10/12 (IQR 6-12), and 19/24 (IQR 12-23) months for adults ($p \leq 0.001$ at all time points). Similarly, the percentage of adolescents achieving 100% adherence was 20.7% at 6 months, 14.3% at 12 months, and 6.6% at 24 months, compared to 40.5%, 27.9%, and 20.6% for adults ($p<0.01$ at all time points, Table 1).

The proportion of adolescents achieving viral suppression was lower than for adults, although the differences were significant only at 12, 18, and 24 months after ART initiation (Table 1). Patients achieving 100% 12-month adherence were significantly more likely to exhibit virologic suppression at 12 months, whether adolescent (91% of perfect adherers suppressed at 12 months vs. 45% of others, $p=0.007$) or adult (86% vs. 59%, $p<0.001$). The association between adolescent status and lower rates of virologic suppression persisted despite adjustment for potential confounders, although adjustment for adherence did weaken the measured association (Table 2).

Table 1. Demographic and clinical characteristics of study population

Variable	Adolescent (n = 154)	Adult (n = 7,622)	Total (n = 7,776)	P†
Age, yrs*	16.4 (11.9-18.8)	36.1 (31.5-42.0)	36 (31.2-41.9)	<0.001
Female, n (%)	112 (72.7)	4,749 (62.3)	4,861 (62.5)	0.01
Black, n (%)	125 (94.0)	7,301 (95.8)	7,426 (95.8)	0.28
Baseline‡ $CD4^+$ T-cell count, cells/μL*	144 (27-246)	146 (64-242)	146 (64-242)	0.24
Baseline‡ viral load, log_{10}-copies/mL, n (%)	5.1 (4.5-5.6)	5.1 (4.6-5.5)	5.1 (4.6-5.5)	0.59
Follow-up time, mos*	27 (18.1-43.7)	36.9 (23.6-54.5)	36.7 (23.4-54.4)	<0.001
# of viral loads per patient, n*	2 (1-3)	2 (1-4)	2 (1-4)	0.007
$CD4^+$ T-cell count, cell/μL*				
6 months	295 (135-482)	246 (142-377)	247 (142-378)	0.28
12 months	281 (154-538)	276 (159-412)	276 (159-413)	0.96
18 months	263 (157-439)	308 (177-464)	308 (177-464)	0.72
24 months	172 (44-451)	339 (187-496)	338 (186-496)	0.02
Pharmacy-claim adherence at specified times post-ART, %*				
6 months	66.7 (50.0-83.3)	83.3 (5.0-100)	83.3 (50.0-100)	<0.001
12 months	66.7 (41.7-83.3)	83.3 (50.0-100)	83.3 (50.0-100)	0.001
24 months	62.5 (33.3-80.0)	80.0 (50.0-95.8)	80.0 (50.0-95.8)	<0.001
Total	72.7 (36.5-95.8)	81.0 (50.0-95.8)	81.0 (50.0-95.8)	0.15
100% Adherence, n (%)				
6 months	17/82 (20.7)	2835/7005 (40.5)	2852/7087 (40.2)	<0.001
12 months	11/77 (14.3)	1868/6693 (27.9)	1879/6770 (27.8)	0.007
24 months	4/61 (6.6)	1173/5684 (20.6)	1177/5745 (20.5)	0.004
Viral suppression, n (%)				
6 months	58/92 (63.0)	2711/3912 (69.3)	2769/4004 (69.2)	0.20
12 months	32/70 (45.7)	1982/3190 (62.1)	2014/3260 (61.8)	0.006
18 months	24/53 (45.3)	1651/2741 (60.2)	1675/2794 (60.0)	0.03
24 months	17/39 (43.6)	1456/2337 (62.3)	1473/2376 (62.0)	0.02
Viral rebound, n (%)§				
6 months	14/45 (31.1)	396/2,390 (16.6)	410/2435 (16.8)	0.02
12 months	14/33 (42.4)	384/1905 (20.2)	398/1938 (20.5)	0.004
18 months	7/18 (38.9)	335/1560 (21.5)	342/1578 (21.7)	0.09
24 months	6/16 (37.5)	297/1229 (24.2)	303/1245 (24.3)	0.24
Ever-suppressed, n (%)	93/154 (60.4)	5504/7622 (72.2)	5597/7776 (72.0)	0.002

* Data are given as median (inter-quartile range)

† P-values are calculated using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for binary variables.

‡ Data collected at program enrollment.

§The denominator consists only of patients who had initially suppressed viral load

Table 2. Relative risks for virologic suppression in adolescents, compared to adults

Time of follow-up	Unadjusted		Adjusted for all variables other than adherence †		Completely adjusted ‡	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
At 6 months* (92 adolescents, 3912 adults)	0.91 (0.78-1.07)	0.24	0.85 (0.71-1.02)	0.09	0.94 (0.77-1.15)	0.56
At 12 months* (70 adolescents, 3190 adults)	0.74 (0.57-0.95)	0.02	0.67 (0.48-0.92)	0.01	0.77 (0.55-1.07)	0.12
At 18 months* (53 adolescents, 2741 adults)	0.75 (0.56-1.01)	0.06	0.82 (0.59-1.15)	0.25	-	-
At 24 months* (39 adolescents, 2337 adults)	0.70 (0.49-1)	0.05	0.70 (0.47-1.05)	0.08	0.76 (0.51-1.14)	0.18

* Time is measured in months after HAART initiation.

† Includes gender, race, baseline CD4, baseline viral load, ART initiation before 2003, and # of viral load measurement per patient-months. A total of 16 adolescents and 30 adults at 6 months, 16 adolescents and 43 adults at 12 months, 12 adolescents and 93 adults at 18 months, and 5 adolescents and 40 adults at 24 months had at least one missing data point and were excluded from this analysis.

‡ Categorized in strata of ≤50%, 51-67%, 67-84%, 85-99% and 100% and baseline variables as described in (†). Missing adherence data leading to additional exclusion of 30 adolescents and 302 adults at 6 months, 23 adolescents and 202 adults at 12 months, and 10 adolescents and 100 adults at 24 months. No adherence data up to 18 months.

In the subset of patients who achieved initial virologic suppression (N = 5504 adults and 93 adolescents, of which 3805 adults and 62 adolescents had at least one viral load measurements after initial suppression), the proportion of adolescents with viral rebound was higher than for adults (31.3% vs. 16.6%, p = 0.02 at 6 months; 42.4% vs. 20.2% at 12 months, p = 0.004; 38.9% vs. 21.5% at 18 months, p = 0.09; and 37.5% vs. 24.2%, p = 0.24 at 24 months) (Table 1). The association between adolescent status and higher rate of viral rebound was sustained in both unadjusted and adjusted models (Table 3). Adolescents were less likely than adults to experience immunologic recovery on ART as evidenced by their median $CD4^+$ T-cell count (IQR): 295 (135-482) vs. 246 (142-377), p = 0.26 at 6 months; 281 (154-538) vs. 276 (159-412) at 12 months, p = 0.96; 263 (157-439) vs. 308 (177-464) at 18 months, p = 0.72; and 172 (44-451) vs. 339 (187-496), p = 0.02 at 24 months) (Table 1).

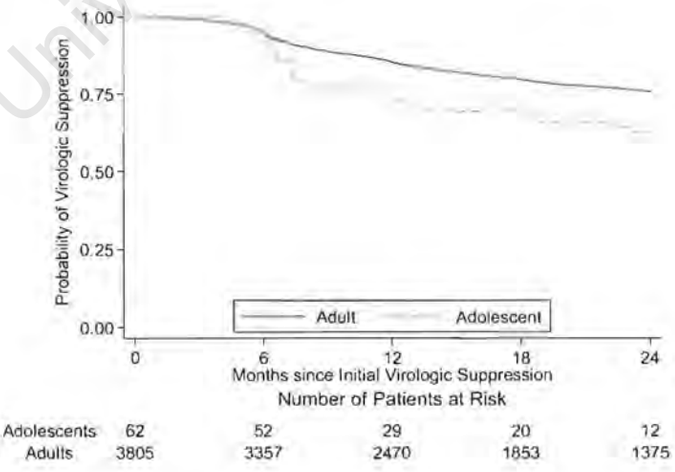
In Cox proportional hazards analysis in the subset of patients who achieved initial virologic suppression, adolescents had a significantly shorter time to viral rebound when unadjusted (HR 2.10 [1.43-3.08]; p = 0.001) and adjusted for both baseline characteristics and adherence (HR 2.03 [1.31-3.13]; p = 0.001) (Figure 1).

Table 3. Relative risks for viral rebound in adolescents, compared to adults

Model	Unadjusted		Adjusted for all variables other than adherence †		Completely adjusted ‡	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
At 6 months* (45 adolescents, 2390 adults)	1.88 (1.20-2.93)	0.005	2.02 (1.24-3.30)	0.005	2.35 (1.72-3.21)	<0.001
At 12 months* (33 adolescents, 1905 adults)	2.10 (1.40-3.16)	<0.001	1.82 (1.10-3.00)	0.02	1.75 (1.22-2.51)	0.002
At 18 months* (18 adolescents, 1560 adults)	1.81 (1.01-3.26)	0.05	2.12 (1.23-3.65)	0.01	-	-
At 24 months* (16 adolescents, 1229 adults)	1.55 (0.82-2.94)	0.18	1.69 (0.95-3.00)	0.07	1.65 (1.06-2.58)	0.03

* Time is measured in months after HAART initiation.
† Includes gender, race, baseline CD4, baseline viral load, ART initiation before 2003, and # of viral load measurement per patient-months. A total of 8 adolescents and 29 adults at 6 months, 10 adolescents and 13 adults at 12 months, 3 adolescents and 13 adults at 18 months, and 2 adolescents and 8 adults at 24 months had at least one missing data point and were excluded from this analysis.
‡ Categorized in strata of ≤50%, 51-67%, 67-84%, 85-99% and 100% and baseline variables as described in (†). Missing adherence data leading to additional exclusion of 10 adolescents and 164 adults at 6 months, 6 adolescents and 118 adults at 12 months, and 3 adolescents and 25 adults at 24 months. No adherence data up to 18 months.

Figure 1. Time to rebound in adolescents compared to adults. P for log-rank test <0.001



Number of Patients at Risk

Adolescents	62	52	29	20	12
Adults	3805	3357	2470	1853	1375

DISCUSSION

Our results suggest that HIV-infected adolescents on ART in southern Africa have poorer adherence rates and virologic outcomes than their adult counterparts. In this study, adolescents were approximately 50% as likely as adults to maintain perfect adherence at all time points and 70-75% as likely to be virologically suppressed (≤400 copies/mL) at 1 and 2 years after ART initiation. Lower rates of virologic suppression among adolescents were largely explained by more rapid viral rebound. Furthermore, adolescents were less likely than adults to experience long-term immunologic recovery; despite having nearly identical initial $CD4^+$ T-cell counts, adolescents experienced very small increases in $CD4^+$ T-cell counts after two years, from a median of 144/mL to 172/mL vs. increases in adults from a median of 146/mL to 339/mL ($p = 0.02$).

Low medication adherence in the very population most likely to benefit from optimal adherence (i.e. those who would have the longest life expectancy on successful ART) underscores the urgent need to identify risk factors that contribute to poor adherence in HIV-infected adolescents in sub-Saharan Africa. Such knowledge would help guide the design of targeted interventions to achieve or maintain high adherence rates in this population.

These results also suggest that pharmacy refill data may be a useful tool for adherence monitoring in adherence-intervention studies in sub-Saharan

Africa. Given the limited availability of second line and salvage antiretroviral therapy regimens in this region, preserving long-term success of first-line ART is critical, particularly in adolescents, who would be expected to live longer than HIV-infected adults by virtue of their younger age, if both groups are able to achieve equivalent treatment success.

Although no studies of adherence barriers in HIV-positive adolescents in resource-limited settings are available, it is useful to consider the limited data related to adolescents' adherence to medication regimens in general. In a survey from Finland, Kyngas reported factors that affect medication adherence in adolescents with a chronic illness such as asthma, epilepsy, rheumatoid arthritis and insulin dependent diabetes mellitus. [14] Adherence in this population was promoted by good motivation, a strong sense of normality, a positive attitude towards the disease and treatment, energy and will-power, experience of results, support from the parents, nurses and physicians, and a feeling that the disease was not a threat to social well-being. [14] If these factors may be applicable to HIV-positive adolescents in resource-limited areas, it is of great concern, since it is known that adults in these settings have a significant fear of stigma associated with disclosure of their HIV-positive status. [15,16] Therefore is might be possible that the very nature of HIV infection and particular cultural perspectives of it could combine to reduce adolescents' ART adherence compared to that of both children and adults.

Knowledge of barriers to adherence and risk factors for non-adherence in adults have been reported and include cost [17,18] in countries where ART is not free of charge; non-disclosure to a loved one or fear of being stigmatized [15,16]; substance (mostly alcohol) abuse [15]; and complexity of the drug regimen [15,19]. In a qualitative study in Uganda, Bikaako-Kajural et al. found that structural factors including poverty and stigma were barriers to both ART and cotrimoxazole adherence, even in children who had complete disclosure and a supportive relationship with parents. [20] If these factors are shared by adolescents, then interventions to encourage voluntary testing and disclosure of HIV status, or to reduce the cost and complexity of antiretroviral therapy, might also improve adherence rates in this age group. Further research on barriers to ART adherence in adolescents is sorely needed.

Our study has certain limitations. First, although our study population is among the largest cohorts on ART under observation in sub-Saharan Africa, our sample size for this analysis was limited by the small proportion of these patients who were adolescents, particularly at long follow-up times. Furthermore, our dataset is limited in certain adherence data missing at different timepoints for both adults and adolescents. However, using the statistical imputation technique to account for missing data did not change the results in one way or another. Finally, our dataset was not structured to capture reasons for non-adherence. As

a result of these limitations, further studies on ART adherence in African adolescents are needed to determine whether the results from this study are fully generalizable (e.g. to the public sector), and to describe relationships that could not be measured with the limited data in the current database. Ultimately, studies of interventions to improve adherence in this vulnerable population will be essential to maximize the number of HIV-infected infants who successfully survive into adulthood.

In conclusion, compared with adults, adolescents in southern Africa are less adherent to ART and have lower rates of virologic suppression at all time points after ART initiation, and experience more rapid viral rebound. Studies to determine barriers to adherence in adolescents and interventions to address them are sorely needed in this setting.

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Chapter 7

Pharmacy Claim-Adherence Predicts Direct Health Care Costs for HIV-infected Adults

INTRODUCTION

Previous studies have shown that antiretroviral therapy (ART) is cost-effective for HIV-infected patients in both resource-rich [1] and resource-limited settings [2,3]. Adherence to ART is known to influence virologic outcomes [4], drug resistance [5,6] and survival [7, and see Chapter 3]. However, the relationship between adherence and overall healthcare costs or healthcare burden is not well defined. Cost models suggest that excellent adherence would be cost-effective [8], and a recent review shows that health care costs are higher for people with more advanced disease [9]. For example, a 2002 study in France estimated that the average cost (in 2001 U.S. dollars) of treating a patient with a $CD4^+$ T-cell count >500 cells/mL was $1015, while the average cost of treating a patient during a month in which an AIDS-defining event occurred was $3,795, and during a patient's last month of life was $14,655. [10]

The most robust cost data is from developed countries [9]. Thus, it is increasingly important to measure treatment-related costs in resource-limited settings where advanced end-of-life care may be unavailable, and the burden of HIV/AIDS is greatest. Studies of HIV-related costs in resource-limited settings

are beginning to emerge. In Botswana, higher out-of-pocket costs have been shown to reduce the likelihood of achieving viral suppression in the first month on ART, underscoring the value of keeping such costs as low as possible. [11] A recent retrospective study of 212 patients in a public-sector HIV-management programme in South Africa reported that health care costs are highest for HIV-infected patients who die before starting antiretroviral therapy or who die within the first year on therapy. [12] Furthermore, they found that health care costs were about 50% lower for patients in the second year on treatment, largely due to reduced hospitalization and associated costs. Others recently have modelled the cost-effectiveness of various treatment options, including no treatment, for HIV-infected patients in the Ivory Coast. [13]

Although cost information is becoming available, there is no data available on adherence and total direct health care costs for HIV-infected people in sub-Saharan Africa. Understanding the relationship between adherence and direct health care costs of HIV-infection will help inform evaluation of interventions to improve treatment adherence, which may be an important next step to optimize the benefit of ART scale-up in Africa. To clarify the relationship between adherence and direct health care costs, we evaluated direct monthly costs of patients on ART enrolled in Aid for AIDS, one of the largest HIV/AIDS managed care programs in southern Africa, and correlated program cost data with patient characteristics, including adherence.

MATERIALS AND METHODS

Study Population

This retrospective cohort analysis includes all HIV/AIDS patients from Aid for AIDS over a 5 year period from March 19, 1999, to September 1, 2004. We included all participants who met the following eligibility criteria: (a) at least 18 years old; (b) qualified for ART for at least six months and submitted claims; (c) antiretroviral treatment-naïve upon entry to the Aid for AIDS database. Pharmacy-claim adherence was expressed as a percentage, calculated Adherence was calculated as the number of months with ART claims submitted, divided by the number of complete months from ART commencement, to withdrawal from the Aid for AIDS program, or study end, with the result multiplied by 100.

Treatment costs were obtained directly from the Aid for AIDS database and were categorized into physician consultations, hospitalisations, investigations, non-ART medications, ART, and other costs. The primary sources of medical cost data were claims from physicians, hospitals, laboratories, and pharmacies. Direct monthly costs per patient were categorized as above and were totalled both with ART and laboratory investigations ($CD4^+$ T-cell count and Viral Load) expenses (ART & labs-in) and excluding ART and laboratory investigations expenses (ART & Investigations-out). Due to data restrictions, these analyses were conducted from the perspective of a third-party payer, and so costs to

patients and to other elements of society (e.g., the national health-care system) were not included. Patient baseline exploratory variables collected included age, gender, baseline $CD4^+$ T-cell count, and HIV viral load.

Statistical Analysis

Statistical analyses were based on medians because costs were not normally distributed as documented by the degree of skewness (comparison median values to means). Adherence rates were categorized by quartile. Study groups at baseline were compared using trend test (Wilcoxon rank-sum test for trend across ordered strata) for continuous variables and the chi-squared statistic for categorical variables. Log-binomial regression was used to assess associations of covariates with total health care costs (categorized as above or below the median value). To eliminate the contribution of ART and investigations to total cost, we repeated the model using costs excluding these cost categories. Patients were further categorized into a binary variable of never-hospitalised or ever-hospitalised depending on whether hospitalisation cost was zero (never-) or non-zero (ever-) to assess associations of hospitalisation with potential covariates. Hospital charges among those ever-hospitalised were assessed using the same techniques as used for total health care costs.

All *P* values reported are exact and 2-tailed, with a value of <0.05 considered statistically significant. Statistical analyses were performed using STATA Release 8.0 (Stata Corporation, College Station, TX, USA).

RESULTS

A total of 4,631 patients met study inclusion criteria. The demographic, clinical and health care cost characteristics of study population are shown in Table 1. Median (Inter-quartile range, IQR) age was 36.4 (31.6-41.9) years, 59.8% of patients (n=2,768) were female; 98% (n=1,135) were black. Median (IQR) duration of follow-up was 29 (24-36) months, of which 14 (10-20) were HAART-authorized. The median (IQR) $CD4^+$ cell count at entry was 155 (67-234) cells/μL, and viral load was 5.2 (47-56) $\log_{10}$ copies/mL. Pharmacy-claim adherence medians (total range) for the 1st through the 4th quartile were 100% (95.7-100%), 90% (83.3-95.7%), 70.6% (52.6-83.3%), and 30% (3.2-52.6%), respectively. Overall median (IQR) monthly cost areas were $288.38 ($165.29-$402.83) for HAART; $34.53 ($0-$174.12) for hospitalisations; $40.74 ($23.35-$69.42) for consultations; $64.32 ($37.78-$98.9) for investigations; $41.04 ($23.96-$62.3) for non-ART medications; and $17.16 ($3.09-$36.65) for other costs. Overall proportion of patients who had ever been hospitalised was 61.7% and median (IQR) monthly hospital charge of this subset was $563 ($388-$796). HAART was responsible for more than twice as many charges as any other cost category in total costs (ART was 45%, hospitalisations, the second largest factor, were 22% of total costs), but hospitalisation costs increased with lower adherence (15% to 38% of total costs from 1st to 4th quartile) (Figure 1).

Table 1. Baseline and health care cost characteristics of study cohort by quartile of adherence*

Variable	1st Quartile n = 1158	2st Quartile n = 1158	3st Quartile n = 1157	4st Quartile n = 1158	Overall n = 4631	P‡
Adherence rate, %§	100 (95.7-100)	90 (83.3-95.7)	70.6 (52.6-83.3)	30 (3.2-52.6)	83.3 (3.2-100)	
Age, yr	36.8 (31.9-41.9)	36.2 (31.6-42.2)	36.4 (31.5-41.6)	36.1 (31.3-41.9)	36.4 (31.6-41.9)	0.08
Female, n (%)	743 (64.2)	717 (61.9)	713 (61.6)	595 (51.4)	2,768 (59.8)	<0.001
Black race, n (%)	1,121 (96.8)	1,110 (95.8)	1,130 (97.7)	1,135 (98)	4,496 (97.1)	0.01
Follow-up time, mo	27 (24-32)	27 (24-32)	30 (25-37)	28 (20-35)	29 (24-36)	0.62
Baseline CD4, cells/μL	158 (66-237)	156 (69-237)	144 (64-229)	160 (68-237)	155 (67-234)	0.89
Baseline viral load, log_{10}-copies/mL	5.2 (4.6-5.6)	5.2 (4.7-5.7)	5.2 (4.7-5.7)	5.2 (4.7-5.6)	5.2 (4.7-5.6)	0.12
Monthly cost areas, US$						
HAART Med.	432 (356-531)	358 (277-414)	251 (186-320)	96 (51-151)	288 (165-403)	<0.001
Hospitalization	13 (0-142)	32 (0-163)	39.22 (0-178)	61 (0-227)	34 (0-174)	<0.001
Consultation	43 (25-71)	41 (24-66)	40 (24-70)	40 (22-68)	41 (23-69)	0.02
Investigation	76 (51-112)	67 (44-97)	61 (38-97)	48 (23-87)	64 (38-99)	<0.001
Non-ART Med.	43 (25-69)	41 (25-61)	42 (24-64)	39 (22-58)	41 (24-63)	<0.001
Other	17 (3-37)	18 (5-37)	17 (3-36)	19 (1-36)	17 (3-37)	0.11
Total	699 (552-935)	596 (484-798)	510 (372-725)	358 (207-605)	563 (388-796)	<0.001
Total excl¥	154 (83-322)	159 (83-332)	165 (84-336)	180 (82-372)	164 (83-342)	0.03
Ever-Hospitalised Patients, n (%)	635 (54.8)	722 (62.4)	726 (62.8)	773 (66.8)	2,856 (61.7)	<0.001
Monthly hospital charge, US$†	123 (48-272)	120 (43-262)	128 (54-303)	146 (61-336)	129 (51-291)	0.001

* Data are entered as median (inter-quartile range), unless otherwise specified.
‡ P-values are calculated using the Wilcoxon rank-sum test for continuous variables or Chi-squared test for categorical variables
§ Values in parentheses correspond to total (not inter-quartile) ranges.
† Hospital charges among patients who were hospitalised.
¥ Total health care cost excluded HHART medications and viral load/CD4 count measures

Figure 1. Contributions to total cost of each cost category for each adherence quartile (1st = highest adherence quartile)

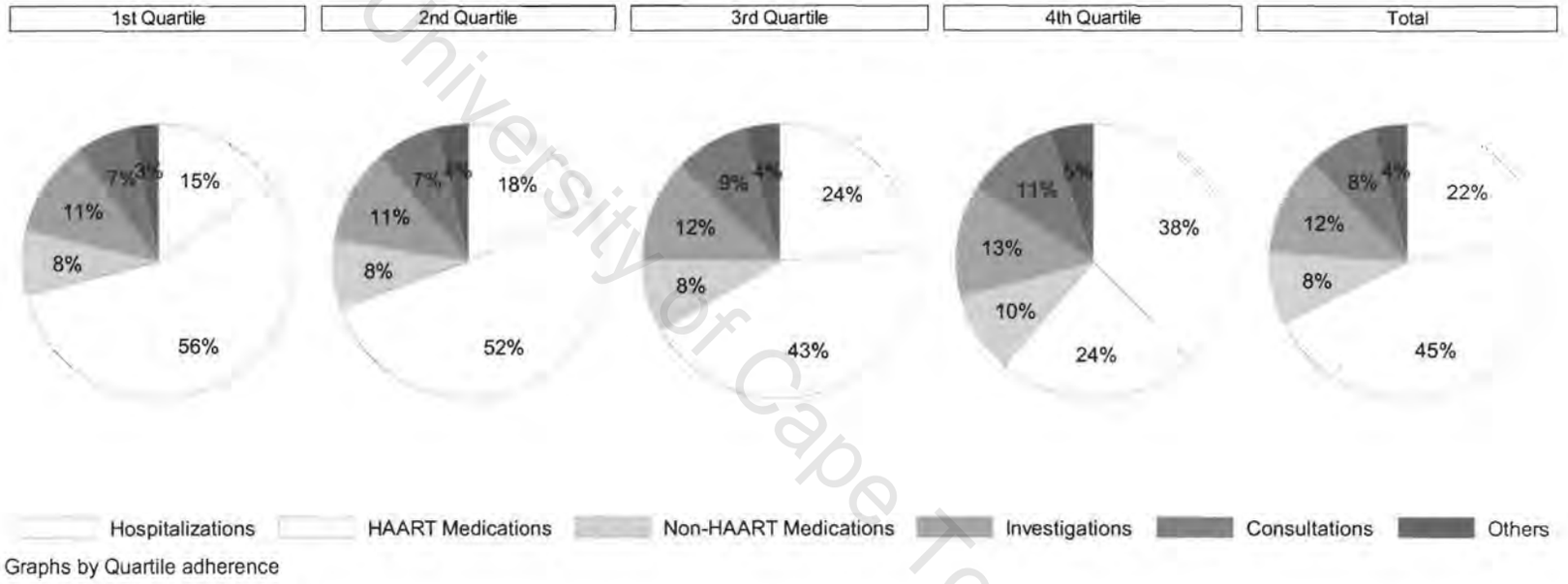
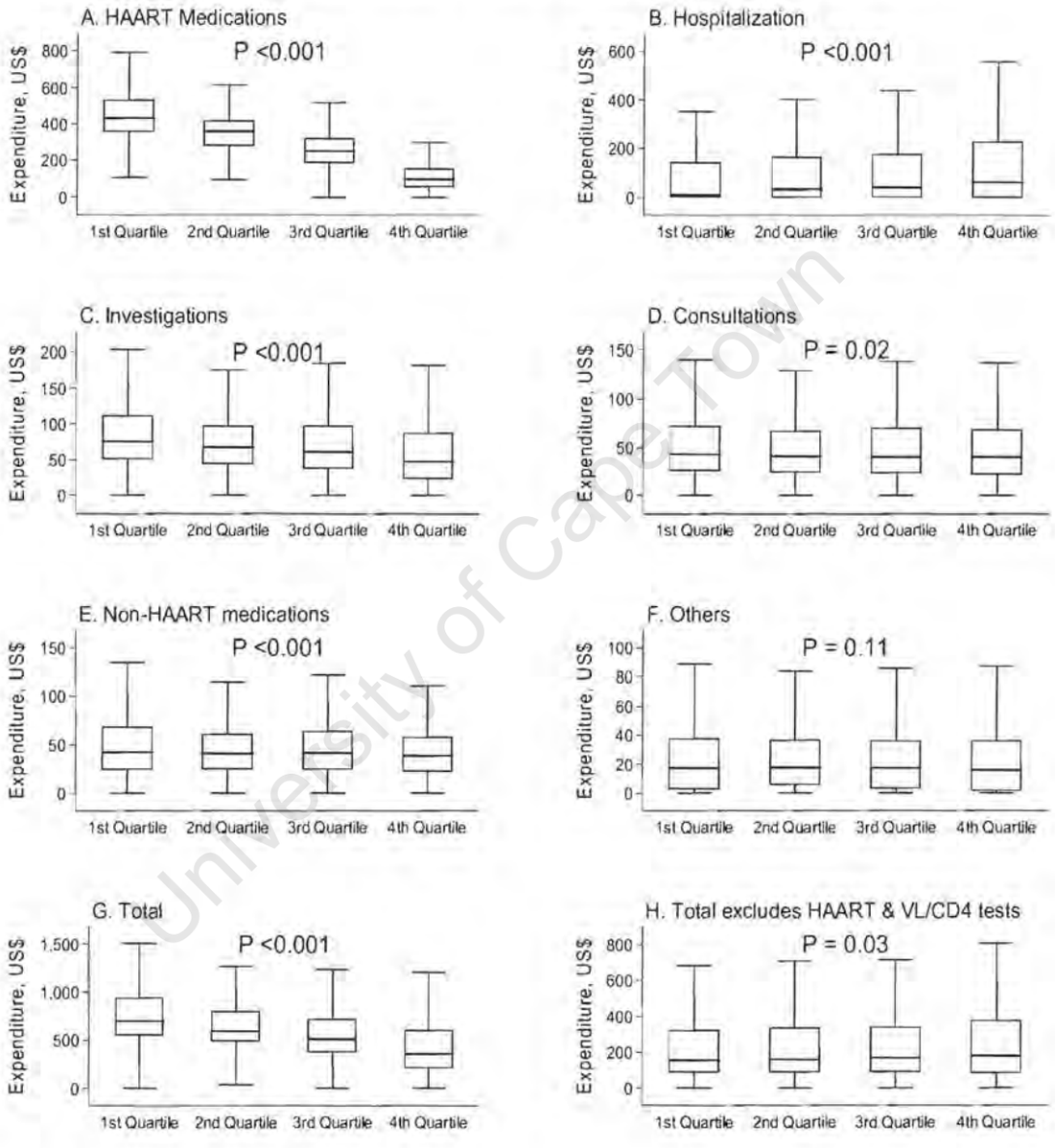


Figure 2. Boxplots of health care cost areas by quartile adherence.

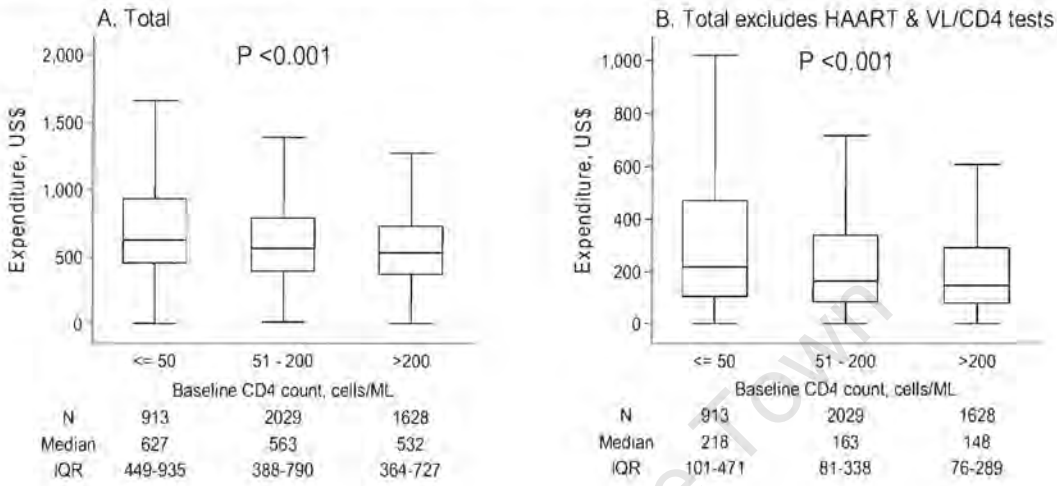


All P-values were from Wilcoxon rank-sum test.
Abbreviations: VL, viral load measurement; CD4, CD4 cell count.

As shown in Table 1 and Figure 2, patients with higher adherence incurred significantly higher monthly total costs (median [IQR] from lowest to highest adherence strata were ($358 [$207-$605] to $699 [$552-$935], P for trend <0.001), including costs related to ART ($96 [$51-$151] to $432 [$356-$531], p for trend <0.001) and investigations ($48 [$23-$87] to $76 [$51-$112], P for trend <0.001), but had significantly lower costs due to hospitalisation ($61 [$0-$227] to $13 [$0-$142), P for trend <0.001). After removing ART and investigation costs from the total, the reverse trend was seen in which patients with higher adherence incurred significantly lower monthly total costs (median [IQR] from highest to lowest adherence strata were $154 [$83-$322] to $164 [$83-$342], P for trend = 0.03).

Patients with lower $CD4^+$ T-cell count at entry had higher total health care costs [median (IQR) $627 ($449-$935), $563 ($388-$790), and $532 ($364-$727) for patients with ≤50, 51-200, and >200 cells/μL respectively, p<0.001] (Figure 3). This trend persisted when costs of HAART and laboratory investigations were ignored (Figure 3).

Figure 3. Monthly health care costs by baseline CD4 cell count. All P-values were from Wilcoxon rank-sum test. Abbreviations: VL, viral load measurement; CD4, CD4 cell count.



In both univariate and multivariable analysis, both male sex (adjusted relative risk (RR): 0.83, CI: 0.78-0.88) and higher baseline CD4 cell count (RR: 0.89, CI: 0.86-0.92, per 100 cell increase) were associated with lower costs, while adherence rate was associated with higher total cost (relative risk [95% CI] comparing higher to lower adherence strata versus lowest stratum were 2.56 [2.31-2.83], 2.03 [1.83-2.26], and 1.43 [1.27-1.61], respectively). When total cost excluding HAART and investigations above the median was used as a dependent variable, such predictors as male sex and baseline $CD4^+$ cell count were associated with lower total costs (RR: 0.78, CI: 0.73-0.83 and RR: 0.91, CI: 0.88-0.94, respectively), and higher adherence rate was associated with lower

total cost (RR [95% CI] comparing higher to lower adherence strata versus lowest stratum were 0.88 [0.81-0.95], 0.91 [0.84-0.98], and 0.93 [0.86-1], respectively).

When hospitalisation cost above the median was considered as a dependent variable, predictors that were associated with lower hospitalisation costs were age (RR: 0.95; CI: 0.91-0.99, per 10 year increase), male sex (RR: 0.76; CI: 0.72-0.81), higher baseline $CD4^+$ T-cell count (RR: 0.87; CI: 0.84-0.9), and higher adherence rate (Relative risks [95% CI] comparing higher to lower adherence strata versus lowest stratum were 0.77 [0.7-0.83], 0.86 [0.79-0.93], and 0.88 [0.82-0.95], respectively); and predictors that were associated with the higher cost were higher baseline viral load (RR: 1.06; CI: 1.02-1.11) and non-black race (RR: 1.25; CI: 1.08-1.44) (Table 2).

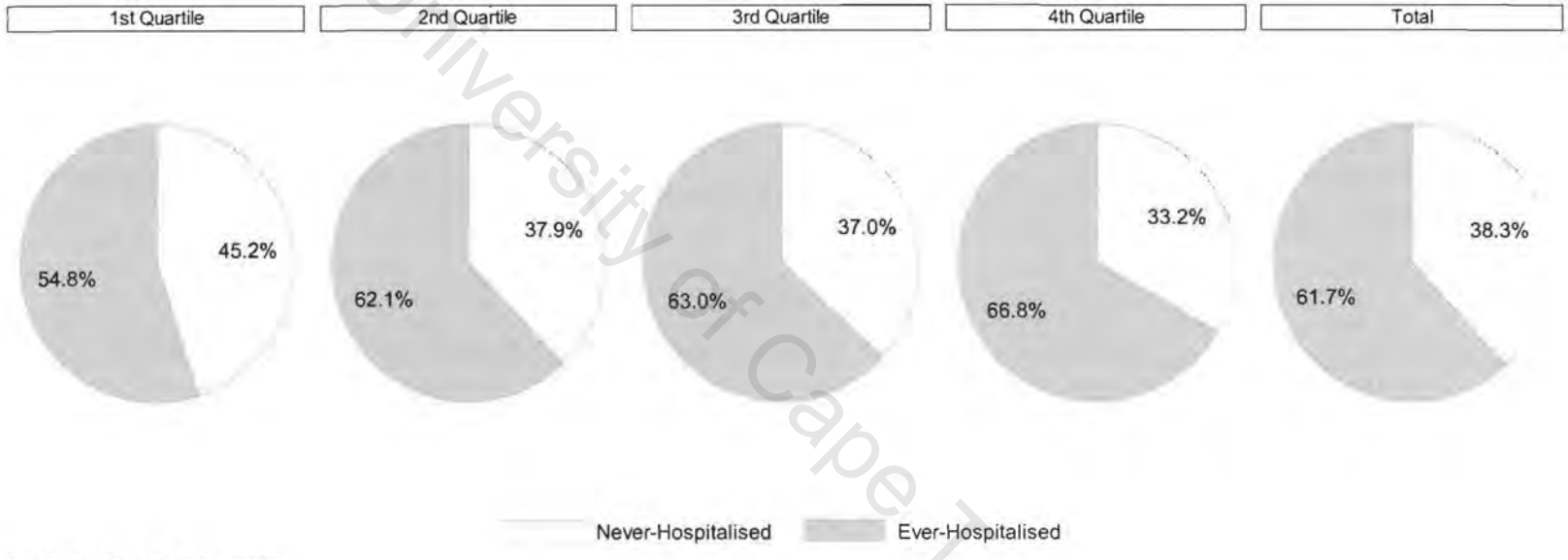
A significantly smaller proportion of the higher adherence strata were ever-hospitalised (54.8% in highest adherence stratum to 66.8% in lowest adherence stratum, P <0.001) (Figure 4). In log-binomial analysis using hospitalisation status as a dependent variable, predictors significantly associated with lower probability of being hospitalised were age (RR: 0.95; CI: 0.92-0.98),

Table 2. Log-binomial regression analysis of factors associated with health care cost above the median

Variable	Univariate		Multivariate	
	RR (95% CI)	P	RR (95% CI)	P
a. Total health care cost (HAART and VL/CD4-in*)				
Age, per 10 years	1.02 (0.98-1.06)	0.26	1.03 (0.99-1.06)	0.12
Male (vs. Female)	0.8 (0.75-0.85)	<0.001	0.83 (0.78-0.88)	<0.001
Non-black (vs. Black)	0.9 (0.75-1.09)	0.28	0.86 (0.71-1.04)	0.11
Baseline CD4, per 100 cells	0.89 (0.87-0.92)	<0.001	0.89 (0.86-0.92)	<0.001
Baseline VL, per 1 $\log_{10}$-copy	1 (1-1.08)	0.16	1 (0.96-1.04)	0.89
Adherence (4th quartile as ref.)				
1st quartile	2.59 (2.35-2.85)	<0.001	2.56 (2.31-2.83)	<0.001
2nd quartile	2.04 (1.83-2.26)	<0.001	2.03 (1.83-2.26)	<0.001
3rd quartile	1.46 (1.3-1.63)	<0.001	1.43 (1.27-1.61)	<0.001
b. Total health care cost (excludes HAART and VL/CD4 measures†)				
Age, per 10 years	0.98 (0.95-1.02)	0.40	1 (0.97-1.05)	0.68
Male (vs. Female)	0.81 (0.76-0.86)	<0.001	0.78 (0.73-0.83)	<0.001
Non-black (vs. Black)	1.02 (0.86-1.21)	0.80	1.07 (0.9-1.26)	0.44
Baseline CD4, per 100 cells	0.91 (0.88-0.94)	<0.001	0.91 (0.88-0.94)	<0.001
Baseline VL, per 1 $\log_{10}$-copy	1.07 (1.03-1.12)	0.002	1.04 (1-1.09)	0.07
Adherence (4th quartile as ref.)				
1st quartile	0.91 (0.84-0.98)	0.02	0.88 (0.81-0.95)	0.001
2nd quartile	0.93 (0.86-1.01)	0.09	0.91 (0.84-0.98)	0.02
3rd quartile	0.96 (0.89-1.04)	0.29	0.93 (0.86-1)	0.06
c. Hospitalisation cost				
Age, per 10 years	0.92 (0.89-0.96)	<0.001	0.95 (0.91-0.99)	0.01
Male (vs. Female)	0.78 (0.74-0.83)	<0.001	0.76 (0.72-0.81)	<0.001
Non-black (vs. Black)	1.16 (1-1.34)	0.05	1.25 (1.08-1.44)	0.003
Baseline CD4, per 100 cells	0.87 (0.85-0.9)	<0.001	0.87 (0.84-0.9)	<0.001
Baseline VL, per 1 $\log_{10}$-copy	1.11 (1.06-1.16)	<0.001	1.06 (1.02-1.11)	0.01
Adherence (4th quartile as ref.)				
1st quartile	0.79 (0.73-0.86)	<0.001	0.77 (0.7-0.83)	<0.001
2nd quartile	0.88 (0.82-0.95)	0.001	0.86 (0.79-0.93)	<0.001
3rd quartile	0.91 (0.84-0.98)	0.02	0.88 (0.82-0.95)	0.001

* Monthly total health care cost including HAART medications and investigations costs
† Monthly total health care cost excluding HAART medications and investigations costs

Figure 4. Proportion of each adherence quartile hospitalised since beginning HAART.



male sex (RR: 0.83; CI: 0.79-0.87), and higher baseline $CD4^+$ T-cell count (RR: 0.92; CI: 0.9-0.94). Those significantly associated with higher probability of being hospitalized included non-black race (RR: 1.11; CI: 0.98-1.26), higher baseline viral load measurements (RR: 1.06; CI: 1.03-1.1), and lower adherence rate (RRs [CI] comparing higher to lower strata vs. highest one were 1.13 [1.06-1.21], 1.14 [1.07-1.23], and 1.24 [1.16-1.33], respectively) (Table 3).

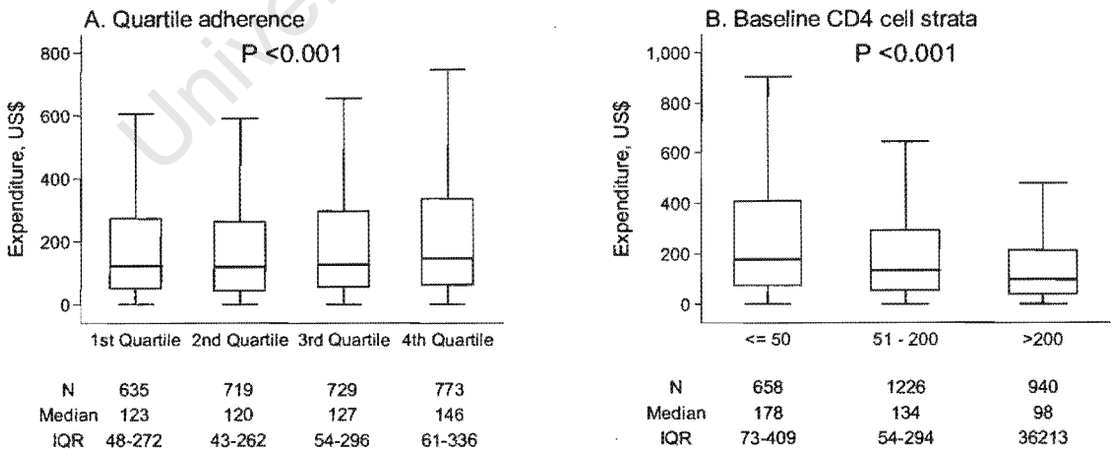
Among those having ever been hospitalised, median (IQR) monthly hospital charges were $123 ($48-$272), $120 ($43-$262), $128 ($54-$303), and $146 ($61-$336) from highest to lowest adherence strata (P for trend across strata <0.001) (Table 1 and Figure 5). Lower baseline $CD4^+$ count significantly incurred higher hospital charge (median [IQR] monthly hospital charges were $178 [$73-$409], $134 [$54-$294], and $98 [$36-$213] for $CD4^+$ strata of ≤50, 51-200, and >200 cells/μL, respectively, P for trend <0.001) (Figure 5). Using log-binomial model with hospital charge above the median in this subset indicated that only lower adherence rate associated with higher hospital charge, but only highest versus lowest strata had shown significance level <0.05 (adjusted P = 0.01) (Table 3).

Table 3. Log-binomial regression analysis of factors associated with being hospitalized and hospital charge above the median among ever-hospitalized patients

Variable	Univariate n = 2856		Multivariate n = 2763	
	RR (95% CI)	P	RR (95% CI)	P
a. Being hospitalized				
Age, per 10 years	0.93 (0.9-0.96)	<0.001	0.95 (0.92-0.98)	<0.001
Male (vs. Female)	0.84 (0.8-0.88)	<0.001	0.83 (0.79-0.87)	<0.001
Non-black (vs. Black)	1.06 (0.93-1.2)	0.37	1.11 (0.98-1.26)	0.09
Baseline CD4, per 100 cells*	0.92 (0.9-0.94)	<0.001	0.92 (0.9-0.94)	<0.001
Baseline VL, per 1 log_{10}-copy†	1.09 (1.05-1.13)	<0.001	1.06 (1.03-1.1)	0.001
Adherence (1st quartile as ref.)				
2nd quartile	1.13 (1.06-1.21)	<0.001	1.13 (1.06-1.21)	<0.001
3nd quartile	1.15 (1.07-1.23)	<0.001	1.14 (1.07-1.23)	<0.001
4rd quartile	1.22 (1.14-1.3)	<0.001	1.24 (1.16-1.33)	<0.001
b. Hospital charge above the median				
Age, per 10 years	1.01 (0.96-1.06)	0.75	1.01 (0.96-1.06)	0.63
Male (vs. Female)	0.96 (0.89-1.04)	0.30	0.91 (0.84-0.98)	0.02
Non-black (vs. Black)	0.98 (0.79-1.21)	0.83	1 (0.8-1.25)	0.99
Baseline CD4, per 100 cells	0.88 (0.85-0.92)		0.88 (0.84-0.91)	
Baseline VL, per 1 log_{10}-copy	1.05 (0.99-1.11)	0.10	1 (0.94-1.05)	0.89
Adherence (1st quartile as ref.)				
2st quartile	0.99 (0.89-1.11)	0.89	1.01 (0.9-1.13)	0.87
3nd quartile	1.02 (0.91-1.14)	0.74	1.02 (0.91-1.13)	0.78
4rd quartile	1.12 (1.01-1.24)	0.04	1.14 (1.03-1.27)	0.01

* Data excluded due to missing were 32 patients in univariate model
† Data excluded due to missing were 91 patients in univariate model

Figure 5. Monthly hospital charge by quartile adherence and baseline CD4 cell count. All P-values were from Wilcoxon rank-sum test.



DISCUSSION

In this study of 4631 patients in a private health management programme in southern Africa, better adherence to ART was associated with higher total costs. For example, comparing the most-adherent to the least-adherent quartiles of patients, total costs were $699 (IQR: $552-$935), compared to $358 (IQR: $207-$605). This reflects the fact that 45% of grand total claimed charges were for ART medication, and ART-related costs were substantially higher in patients with better pharmacy-claim adherence. Among those with higher adherence, hospitalisation costs were significantly lower than for those with lower adherence levels, but these costs represented only 22% of total charges.

In a multivariate linear regression model, variables significantly associated with non-ART related expenditures included ART adherence, $CD4^+$ T-cell count per 100 mm^3 increase, and non-black race. The peak in cost seen around the initiation period is largely due to hospitalisation and investigations, as most people have a low $CD4^+$ T-cell at entry and are therefore prone to opportunistic infections and other HIV-related morbidity. Immune reconstitution syndrome (IRIS) may also be partially responsible for the increased cost in the period around initiation of ART, as IRIS patients are also likely to be hospitalised.[14]

These findings have important clinical and public health implications. First, our results indicate that non-ART and non viral load/$CD4^+$ T-cell count measurements costs decrease with improving adherence in a "dose-dependent" manner. Good adherence also clearly has clinical benefits, with better survival [7,15] and, as shown in this study, decreased hospitalisation costs. These clinical benefits are likely to result in further savings in indirect costs, but we did not measure these. Second, our data show that ART costs are a major proportion of total costs. The cost effectiveness of ART in South Africa is highly dependent on antiretroviral costs. [3] Although antiretroviral costs have dropped with the advent of access pricing and availability of generics, further reductions are necessary to expand access in resource-limited settings. Third, the observation that lower $CD4^+$ T-cell count categories tend to incur more cost than higher ones is likely due to the fact that late presenters are more likely to require hospitalisation for opportunistic diseases. Public health interventions that improve earlier access to ART treatment programs could reduce these complications and expenditures and are urgently needed in low-income countries, where ART is commenced with more advanced disease than in high-income countries. [16]

Strengths of our study include its description of the financial expenditure patterns in relation to adherence of a local South African HIV-infected population from a reliable database of a managed care organisation that has many years of experience in healthcare funding. The database includes low- to medium- income

patients registered for treatment. Furthermore, the health care costs are actual expenditures.

Limitations include the status of Aid for AIDS as a private managed care organisation that administers claims across 30 different medical aid schemes, and different schemes may have different treatment protocols. The patients were treated by different physicians whose treatment practices may be different despite Aid for AIDS guidelines. Furthermore, there is a lack of data on costs outside the Aid for AIDS scheme and hence the results are not necessarily generalizable to the public sector. Although health care costs are higher for more advanced disease, individuals receiving more effective treatment will live longer and thus over their lifetimes are likely to incur higher total health care costs (even if their average monthly health care costs are lower). Therefore it is generally desirable to evaluate antiretroviral therapy in terms of cost-effectiveness, including social costs and benefits, but such an analysis was beyond the scope of this work. Finally, our analyses were based median values and from a payer or policy perspective. However, from a budgetary viewpoint, median differences are less informative because the payer or policymaker still needs to provide resources for high cost outliers, making mean costs remain the best source for forecasting future costs.

In summary, poor levels of adherence, as assessed by pharmacy claims in a private-sector managed care program, are associated with greater overall non-ART related expenditures in HIV-infected South African adults on NNRTI-based ART. The decrease in non-ART costs was insufficient to offset the increased cost of HAART in patients who were highly adherent. Further research should prospectively investigate the impact of improving adherence on health care and social costs as well as on clinical outcomes.

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Chapter 8:

Overall Discussion, Conclusions and Future Research

As the number of patients on highly active antiretroviral therapy (HAART) grows worldwide, developing simple, affordable ways of monitoring patients after treatment initiation has become a major public health priority. Since the central paradigm of antiretroviral therapy is suppression of viral replication, and since costs of second line HAART are higher than first-line regimens [1], monitoring efforts should, to whatever extent possible, focus on preserving the virologic effectiveness of first-line combinations. Failure to identify patients on partially suppressive regimens may result in selection of viral resistance mutations, which have been associated with more rapid disease progression and death [2-4].

In the developed world, the standard of care for monitoring virologic response involves measuring plasma HIV-1 RNA levels [5]. These assays are often unavailable in most countries in the developing world due to financial and technical constraints [6]. Since $CD4^+$ counts are comparatively inexpensive, World Health Organization (WHO) guidelines for scaling up antiretroviral therapy in resource-limited settings advocate use of $CD4^+$ T-cell count criteria to identify patients on failing HAART regimens [7]. Thus, $CD4^+$ T-cell count is considered an essential tool for monitoring patients on HAART [8], and there is a widespread

movement to incorporate cheaper, less technologically demanding $CD4^+$ T-cell count assays into clinical care in the developing world [9].

Quantifying and monitoring adherence levels to HAART using pharmacy data is one potentially useful and low-cost method of monitoring patients at high risk for virologic failure in resource-limited settings [10]. The work presented in this thesis and in other published works clearly show that adherence to HAART is strongly associated with virologic response in a dose-dependent manner and with survival in developing and developed countries (Chapters 3, 4, 5) [11-16]. Furthermore, among patients on first-line therapy, lapses in adherence usually precede immunologic declines, and, unlike $CD4^+$ T-cell count pharmacy refill or claim adherence data are readily accessible to clinics that dispense HAART, require little to no technical sophistication to compile, and directly measure a variable on which providers can intervene. Although $CD4^+$ T-cell count monitoring in patients on HAART is deeply ingrained in HIV care [5,7], if adherence assessments are as accurate as $CD4^+$ T-cell count changes for identification of patients with virologic failure, sites currently performing or planning measurements for treatment monitoring could instead monitor adherence, thereby preserving scarce resources for triaged virologic monitoring [17,18] or for other treatment-related activities. Recently, using a validated computer simulation model of HIV infection, the effect of antiretroviral therapy was used to compare survival, use of second-line regimens, and development of

resistance resulting from different strategies, based on viral load, $CD4^+$ T-cell count, or clinical observation alone, for determining when to switch to second-line regimens. In that study, Phillips and colleagues found only modest benefits of viral load or $CD4^+$ T-cell count monitoring over clinical monitoring alone for patients on a first-line regimen of stavudine, lamivudine, and nevirapine. [19]. The Phillips model assumes patients with drug-resistant virus will do as well in Africa as their counterparts in North America, which might not prove correct.

The limited empirical data to compare with Phillips and colleagues' model, however, are supportive. The ART-LINC (Antiretroviral Treatment in Lower Income Countries) collaboration found no evidence of improved mortality in programmes with viral-load testing. [20] Furthermore, preliminary results from one of two randomised trials examining this question in Africa do not show significant survival benefits from adding viral-load measurements to $CD4^+$ T-cell count monitoring. [21] In that ongoing study, 1094 HIV-infected ART-naïve adults with a $CD4^+$ T-cell count of <250 cells/mm^3 or World Health Organization (WHO) stage 3 or 4 were offered ART and randomized to 1 of 3 monitoring groups: A) clinical monitoring, with quarterly $CD4^+$ T-cell count and viral loads; B) clinical monitoring and quarterly $CD4^+$ T-cell count; or C) clinical monitoring alone. The use of routine CD4 cell count monitoring was associated with fewer new AIDS-defining events or mortality compared to clinical monitoring alone. The clinical monitoring-only arm was stopped early due to an unexplained increase in

mortality (not due to undocumented virologic failure) compared to the other arms, although mortality was still low (13% with a 3 year follow-up). The results from the other randomized study in Africa are anticipated within the next year; the Development of ART (DART) for Africa is comparing clinical versus laboratory-based treatment monitoring in Uganda and Zimbabwe and will add to this discussion. [22]

To add to this discussion, it worth noting that a recent work using pharmacy claim data from the Aid for AIDS cohort, our collaborative research group found that adherence levels outperformed $CD4^+$ T-cell count changes in the first year after HAART (areas under the curve [AUCs] for adherence and $CD4^+$ T-cell count changes were 0.79 and 0.68 [difference = 0.11; 95% CI 0.06-0.16], respectively, at 6 months and 0.85 and 0.75 [difference = 0.10; 95% CI 0.05-0.14], respectively, at 12 months; P <0.001 for both comparisons). When used to detect breakthrough viremia, adherence and $CD4^+$ counts were equally accurate (AUCs of 0.68 vs. 0.67 [difference = 0.01; 95% CI -0.06-0.07]; P>0.5). The results did not change if virologic failure was defined as >10,000 copies/mL. [23] One can therefore consider that pharmacy-claim adherence assessments are as accurate as $CD4^+$ T-cell count for identification of virologic failure on HAART. It would seem prudent that WHO guidelines for antiretroviral therapy scale-up in resource-limited settings should include an adherence-based monitoring approach.

As recommended by WHO [7], NNRTI-based HAART regimens (using efavirenz or nevirapine) are the cornerstone of initial antiretroviral therapy in Africa. Among the specific findings of work reported in this thesis was the association of efavirenz-based initial HAART regimens with superior virologic and clinical outcomes, compared to nevirapine-based regimens, even when accounting for treatment adherence. This suggests efavirenz might be the preferred NNRTI for initial HAART in resource-limited settings, but its higher cost and potential teratogenicity are important considerations in implementation. Furthermore, it is worth discussing the possibility of unmeasured confounding that might account for efavirenz outperforming nevirapine in real world. In particular, our dataset did not consider capture tuberculosis treatment information. Indeed, concomitant rifampicin-based anti-tuberculosis treatment significantly reduces nevirapine concentrations, and sub-therapeutic trough nevirapine concentration occurs in a significant proportion of patients, which is one reason efavirenz is recommended for patients being treated with rifampicin. [18] While preliminary reports from Spain, Malawi and Thailand suggested that these sub-therapeutic levels of nevirapine were not associated with virologic failure [23-25], emerging data from South Africa shows a significant association with virologic failure for concomitant nevirapine and rifampicin-based tuberculosis treatment [26]. Even though tuberculosis information wasn't captured, it is unlikely that interaction of nevirapine with rifampicin-based tuberculosis treatment accounts for the findings in Chapter 5, in part because our findings are similar to

results from many cohorts in the developed world where tuberculosis is not endemic. It is clear, however, that there is a critical need for a large randomized clinical trial in resource-limited settings to definitively compare efavirenz and nevirapine and to assess the impact of rifampicin-based tuberculosis treatment on nevirapine-based HAART regimens.

While informative, the finding that switching from nevirapine to efavirenz had no significant virologic effect, whereas switching from efavirenz to nevirapine resulted in significantly slower time to suppression (HR 0.58, 95% CI 0.35–0.93) and faster time to failure (HR 3.92; 95% CI 1.61-9.55) versus remaining on EFV, need to be interpreted with cautious given the limited sample size of these secondary analyses. Furthermore, this finding may have been confounded by physician prescribing pattern. Indeed, efavirenz induces the metabolism of co-administered drugs through the induction of CYP3A4. It is often necessary to switch from efavirenz to nevirapine because of intolerance or teratogenicity concerns. In a pharmacokinetic study, Winston et al. [27] found that when switching from efavirenz to nevirapine, individuals should commence on 200 mg twice daily and not to dose-escalate nevirapine, as the latter practice was associated with sub-therapeutic drug levels that might lead to virologic failure.

The present work clearly demonstrates the impact of adherence on survival (Chapter 4). It is also significant that adherence was particularly

important in patients presenting with low CD4 cell counts, a finding not only pertinent to Africa but also to the developed world. Although it may be expected that patients in Africa often present with low CD4 counts, in the United Kingdom, more than 50% of patients present with CD4 counts below 200 cells/mL. The lower the CD4 count at HAART initiation, the more important near perfect adherence is for better survival. As a result, there is a critical need for patients to access HAART before CD4 counts drop below 200 cells/mL. Furthermore, for those who start HAART with CD4 below 100 cells/mL, perfect adherence is required until CD4 counts recover to 200 cells/mL or higher, which can take 6 to 12 months or longer.

The findings on adolescents' adherence (Chapter 6) is very relevant now that children born with HIV disease or infected perinatally or through breastfeeding are reaching this stage in life. In addition, adolescents also become infected due to high-risk sexual behaviour. There is limited data on the attitudes and beliefs adolescents have regarding HIV infection and/or its treatment, but it is well known anecdotally that many adolescents rebel as they seek their independence, and therefore it is possible that even those who were once highly adherent children could be at risk for reduced adherence during adolescence. Understanding adolescents' attitudes concerning HIV and HIV therapy would inform the design of targeted interventions for this special population. We discuss in Chapter 6 adolescents' adherence for treatment of

other chronic non-infectious diseases, but it would be quite interesting to have information regarding adolescents' treatment adherence for chronic infectious diseases such as tuberculosis.

The relationship between adherence and healthcare costs (Chapter 7) is vitally important for all countries where antiretroviral drugs are the major cost burden for HIV care. Even with the limits of the analyses, such documentation is rare for any healthcare system and extremely so in resource-limited settings. All statistical analyses of healthcare costs reported in this thesis use median (inter-quartile range) because costs were not normally distributed, as evidenced by the degree of skewness (difference between medians and means, data not shown). However, it is important to acknowledge the limitation of focusing on median values from a payer or policy perspective. From a budgetary viewpoint, median differences are less informative because the payer or policymaker still needs to provide resources for high cost outliers; therefore mean costs remain the best source for forecasting future costs. Furthermore, although costs are higher for patients with poor adherence and more advanced disease, individuals experiencing more effective treatment will live longer and are likely to incur higher total healthcare costs (even if their average monthly healthcare costs are lower). As a result, an important next step to the work reported herein is evaluation of cost-effectiveness of high adherence to ART, which will need to take into account social costs and contributions by healthier individuals to get a

true picture of the value of effective ART in resource-limited settings. Such an analysis was beyond the scope of this thesis and would require data outside the Aid for AIDS dataset.

Conclusions

The work presented in this thesis establishes the usefulness of pharmacy-claim adherence in the Aid for AIDS cohort, and application of this method revealed its usefulness in addressing research questions. In particular, we were able to show that pharmacy-claim adherence is strongly associated with virologic and clinical outcomes in adults in a linear dose-dependent manner, that it can be used to reveal differences in treatment efficacy (with efavirenz being more effective in initial HAART than nevirapine), and that adolescents have significantly lower pharmacy-claim adherence than adults. We also showed that high adherence significantly reduces hospitalisation and health care costs while increasing total cost due to HAART. Efforts to decrease HAART cost should also be a priority on the agenda of private and public partnership.

Future Research

These conclusions offer much opportunity for future study. First, it is clear that a large randomized clinical trial will be needed to fully evaluate the relative effectiveness of efavirenz vs. nevirapine for initial HAART regimen in Africa.

This work also showed data that adolescents have lower adherence levels that adults enrolled in Aid for AIDS (Chapter 5), a finding that underscores the need to study adherence levels in a larger group of adolescents and to investigate barriers to adherence in this special population. Although some barriers might be the same as those faced by adults (cost, infrastructure problems, fear of stigma, etc.), culturally appropriate interventions to address barriers need to be developed specifically for adolescents and for adults and evaluated in each population. Pharmacy-data adherence should offer a low-cost and straightforward way to establish baseline adherence and to measure the effect of adherence interventions in both developing and developed countries. Importantly, the effect of interventions could be tracked individually, if necessary, and not just cohort-wide.

We also were able to show that pharmacy-claims adherence levels are indirectly related to total, non-HAART direct health care costs. Because there are so few studies published on the association between costs and HAART adherence, this finding, too, is cause for further study both from private and public sectors, in both the developing and the developed world. These critically needed data will be helpful to conduct cost-effectiveness evaluation of adherence interventions in sub-Saharan Africa using real world data.

Furthermore, to apply pharmacy-claim adherence outside of research or particular cohorts will require work to solve barriers to placing into routine operation systematic monitoring of adherence using pharmacy refill and/or claims data. For example, there must be ready access to drug refill information as well as conversion of these data into an adherence metric at the time a patient is seen, which may be difficult in some settings at this time. One approach might be to link pharmacy and patient care records by computer, so the pharmacy refill adherence calculation would be automatically provided to the clinical medical record when a patient is seen. But provision of adherence data to patients at the point of care doesn't have to rely on computer technology. In Botswana, for example, patients present to providers a paper pharmacy card on which dates of medication dispensing (and pill counts) are noted. [Bisson G, personal communication] Providers can calculate adherence directly using these cards. It is clear that widespread application of pharmacy data adherence monitoring would take at least some scale-up, but it is reassuring that the technological requirements for this approach are flexible and can be made minimal.

The flexibility of pharmacy-claim adherence, its ability to identify patients at high risk of virologic failure not just after virologic failure, and its ability to offer providers information on a modifiable patient behavior are good reasons for clinics to move towards organizing pharmacy data so they can be used in routine patient care. This would allow clinicians or HAART program officers opportunities

to intervene with targeted adherence interventions to prevent drug resistance and death, and as we demonstrated in this thesis, improvements in adherence should be cost-saving.

In short, pharmacy-claims or refill adherence should be a tool with great utility in evaluating HIV treatments, adherence interventions, and in routine monitoring of patients on antiretroviral medication in many settings for many years to come.

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aid for aids

2 June, 2008.

Jean Nachega: Ph D Thesis: Inclusion of *Aid for AIDS* Clinical Guidelines

This is to confirm that I have given permission to Jean Nachega to include a copy of the *Aid for AIDS* Clinical Guidelines (sixth edition) in the appendix section of his thesis submission.

L D Regensberg MB ChB (Cape Town) MRCP (London)
Senior Manager: Clinical
Aid for AIDS

AfA aid for aids

Aid for AIDS Programme — APPLICATION FORM - CONFIDENTIAL

FIRST PAGE – TO BE COMPLETED BY APPLICANT

PRINCIPAL (MAIN) MEMBER DETAILS

Member's first name:		Surname:		
Medical Scheme:		Gender:	MALE	FEMALE
Membership number:		Option/Plan:		

PATIENT DETAILS

Patient's Surname:		Dependant Code:		
First Name:		Gender:	MALE	FEMALE
ID number:		Date of Birth:	D D M M Y Y Y Y	
Postal address of choice for **confidential** mail:				
		Postal Code:		

Treatment Support is a vital part of the AfA programme. Contact details must be supplied in order that we can provide you with this support.

Telephone numbers:	HOME: CODE		WORK: CODE		FAX: CODE	
Cellphone:			E-mail: (please print)			

How often would you like AfA to contact you per year? :	0	1	2	3	4	6	Would you like to receive SMS notification of registration of your application?	NO	YES
What time of days is the best time for AfA to contact you?	MORNING			AFTERNOON			Would you like to receive information via SMS on a regular basis?	NO	YES
What is your first language							What is your second language?		
Do you have access to an Employee Assistance Programme	NO	YES	If YES, please specify, including contact number:						

OTHER DOCTORS OR SPECIALISTS (that you are seeing in addition to the doctor filling in this form):

Name of Doctor	Speciality	Telephone Number		Fax Number	
		CODE		CODE	

I/we understand that all personal clinical information supplied to the Aid for AIDS (AfA) programme will be used to determine access to specific benefits for people with HIV infection. The programme's medical staff will review this information in order to make recommendations regarding the provision of these benefits. Your doctor, however, retains responsibility for your care, irrespective of the benefits so authorised.

I/we therefore, authorise any doctor, hospital, clinic, laboratory and/or medical facility in possession of any medical information regarding myself, the applicant or any dependant (also newly born baby), to provide the AfA programme with information that it may require. I/we warrant that the information in this application form is correct.

I acknowledge that benefits authorised by the Aid for AIDS programme are subject to scheme rules and that noncompliance to the programme could result in my benefits from this programme being cancelled.

I understand that acceptance onto Aid for AIDS means that an AfA treatment support counsellor will contact me. (unless indicated otherwise above).

PATIENT'S SIGNATURE:		D D M M Y Y Y Y
		DATE

PLEASE FAX COMPLETED FORM WHERE POSSIBLE TO 0800 600 773

PAGES 2 – 4 : TO BE COMPLETED BY THE ATTENDING MEDICAL PRACTITIONER

DETAILS OF THE DOCTOR WHO WILL BE PROVIDING ONGOING CARE:

Doctor's Surname:		Initials:		Qualifying Degree:	
Practice Number:		SAMDC Registration Number:		E-mail address:	
Postal Address:				Postal Code:	
Physical Address:				Postal Code:	
Telephone Numbers:	CODE		Fax NO: CODE		Cellphone:

1. CLINICAL HISTORY (Current diagnosis and medication recorded under Point 4.)

1.1	When was HIV infection first diagnosed? (Please attach reports.)										D	D	M	M	Y	Y	Y	Y
1.2	Is the patient currently being treated for tuberculosis?	YES	NO	If Yes, start date?							D	D	M	M	Y	Y	Y	Y
1.3	Has the patient previously been exposed to antiretrovirals?	YES – MTCT prophylaxis	YES - Other	NO	If YES, please provide details below:													
1.4	Previous antiretroviral Exposure Note: If the application is for a baby please list mom's previous ART history.																	

Drugs	Date Treatment Started	Date Treatment Ended	Duration (months)	Reason for discontinuation

1.5	Current combination patient is taking:								
1.6	Please list all other medication the patient is taking, including prophylaxis:								
1.7	Is the patient allergic to any medication?	Sulphonamides?	YES	NO	Other allergies?	YES	NO	Please Specify:	

INFORMATION REQUIRED TO PREVENT ADVERSE SIDE-EFFECTS OF CERTAIN DRUGS:

1.8	Is there a history of heavy alcohol intake? (i.e. more than 4 drinks per day for a long period of time)	YES	NO
1.9	Is there a history of recreational drug use? (Cannabis, Cocaine, Ecstasy, LSD etc.)	YES	NO
1.10	Is there a history of depression or psychiatric illness? If yes, specify treatment:	YES	NO

2. CLINICAL EXAMINATION

2.1	If female:	Pregnant	Not Pregnant	If pregnant, expected date of delivery:	D	D	M	M	Y	Y	Y	Y
2.2	Expected mode of delivery:	NVD	C / S	Expected date of C / S:	D	D	M	M	Y	Y	Y	Y
	(Please specify in Section 4 whether i/v or oral medicines are preferred during labour.)											
2.3	Weight					kg	**2.4**	Height					cm	
2.5	WHO Clinical Staging													

Adult / Adolescent	
Clinical Stage 1	**Please tick**
Generalised lymphadenopathy	
Clinical Stage II	
Weight loss, <10% of body weight	
Minor mucocutaneous conditions	
Shingles within the last five years	
Recurrent upper respiratory tract infections	
Clinical Stage III	
Weight loss (= _____kg), >10% of body weight	
Unexplained chronic diarrhoea > 1 month	
Oral candidiasis	
Oral hairy leukoplakia	
Pulmonary tuberculosis	
Severe bacterial infections (i.e. pneumonia)	
Clinical Stage IV	
HIV wasting syndrome	
AIDS defining opportunistic infection*. Please specify: _____	

*** For list of AIDS defining opportunistic infections, please see AfA Clinical Guidelines booklet or www.aidforaids.co.za**

Paediatric	**Please tick**
Clinical Stage I	
Generalised lymphadenopathy	
Clinical Stage II	
Unexplained chronic diarrhoea	
Severe persistent or recurrent candidiasis outside the neonatal period	
Weight loss or failure to thrive	
Persistent Fever	
Recurrent severe bacterial infections	
Clinical Stage III	
Severe failure to thrive	
Progressive encephalopathy	
Malignancy	
Recurrent septicaemia or meningitis	
AIDS defining opportunistic infection*. Please specify: _____	

2.6	Is there any degree of peripheral neuropathy?	YES	NO	If Yes, please specify:	Mild	Moderate	Severe
2.7	Is there any other significant clinical finding?	YES	NO	If Yes, please specify:			

3. SPECIAL INVESTIGATION RESULTS (Please provide copies of reports. Please supply as many results as possible.)

Date Test Performed (DD/MM/YYYY)	CD4 count (cells / mm)	CD4 % (must be provided for children)	Viral Load (copies / ml)

Additional Investigations	Test Done?		If yes, results	Date Test Performed
Tuberculin skin test	NO	YES	mm	
Blood count(s) (Essential prior to approval of Zidovudine)	NO	YES		
Baseline ALT (Essential prior to approval of Nevirapine	NO	YES		
Creatinine clearance or serum creatinine (Essential for patients with renal failure)	NO	YES		

4. MEDICATION (NB: Generic equivalents will be authorised unless otherwise stated)

4.1 ANTIRETROVIRAL THERAPY	Strength (e.g. 10mg)	Directions (e.g. 1 tds)	Period in use (months)	Period required (months)

4.2 Other Medication Required (associated with the management of HIV)

DIAGNOSIS	MEDICINES	Strength (e.g. 10mg)	Directions (e.g. 1 tds)	Period in use (months)	Period required (months)

N.B.: Approval for ongoing antiretroviral therapy will only be considered if the result and date of a recent CD4 count is supplied. Only medication recommended in the Aid for AIDS Clinical Guidelines will be considered for reimbursement. Please refer to these guidelines or contact Aid for AIDS on 0800 22 7700, or at afa@afadm.co.za for further information. Motivations will however always be considered. Please contact AfA for assistance if required.

ACKNOWLEDGEMENT BY EXAMINING DOCTOR:

I certify that the above particulars are – to the best of my knowledge and belief – true and accurate, having conducted a personal examination and procured the test and/or other diagnostic investigations referred to. I acknowledge that the Aid for AIDS programme will rely on such particulars when making any recommendation regarding payment for treatment to the relevant medical scheme. I acknowledge that telephonic discussions will be taped for medico-legal purposes.

This refers specifically to patient:				
	Surname	**Name**	**Doctor's Signature**	**Date**

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CONTENTS

Introduction

Of the estimated 38.6 million people living with HIV/AIDS worldwide, approximately 24.5 million (65%) live in Sub-Saharan Africa (UNAIDS Global Report 2006).

Africa, and in particular Sub-Saharan Africa, thus remains the global epicentre of the epidemic. HIV/AIDS poses a major threat to development, as most infections occur in young economically active adults. In addition, we are faced with falling life expectancy, rising infant mortality, and an increase in the number of AIDS-orphans.

The private sector has not escaped the epidemic. Research indicates that the prevalence of HIV infection among medical scheme beneficiaries is between 6 and 8 percent. Amendments to the regulations under the Medical Schemes Act (No. 131 of 1998) relating to prescribed minimum benefits for HIV infection now ensure that from 1 January 2005, all medical scheme beneficiaries have access to highly active antiretroviral therapy (HAART) to at least the extent provided for the public sector, as well as the necessary monitoring tests. In addition, schemes must cover the following:

- HIV voluntary counselling and testing
- Co-trimoxazole as preventive therapy
- Screening and preventive therapy for TB
- Diagnosis and treatment of sexually transmitted infections
- Pain management in palliative care
- Treatment of opportunistic infections
- Prevention of mother to child transmission of HIV
- Post-exposure prophylaxis following occupational exposure or sexual assault

With respect to companies there is ample evidence to support the need for a comprehensive approach to managing HIV/AIDS in the workplace, including the provision of HAART. Benefits include reduced absenteeism and retraining costs, increased productivity and morale and less reliance on employee benefits. The number of companies providing HIV treatment for their employees through Aid for AIDS (AfA) continues to grow.

The aim of AfA is to facilitate the clinical and financial management of each patient by the responsible medical practitioner, within the framework of a comprehensive and confidential disease management programme, with access to reasonable benefits within the budget of the medical scheme or company concerned. Provision has been made not only for evidence-based combinations of antiretroviral therapy, but also effective prophylaxis, immunization and the treatment of HIV related conditions. The programme facilitates access to relevant investigations and hospitalization. Most importantly, it assists with regular follow-up, and monitoring of adherence to therapy, without which the benefits of the programme would soon be lost.

Further services offered include the provision of a total management solution incorporating voluntary counselling and testing (VCT) campaigns, impact analyses, surveillance surveys, KAP studies and workplace HIV/AIDS policies.

Confidentiality has been ensured by the creation of a restricted access unit within our Cape Town offices, with a dedicated computer and communication system, so that neither the employer nor the medical scheme can identify HIV positive beneficiaries.

The following guidelines, now in their sixth edition, have been extensively revised in consultation with experienced colleagues throughout South Africa and neighbouring countries, and continue to reflect national as well as international best practice. AfA has access to an expert panel of "hands-on" HIV specialists and is therefore able to assist with advice on all aspects of managing HIV infection. Practitioners are thus welcome to contact AfA for additional assistance.

Management of HIV Infection in Adults

Diagnosis

The diagnosis of HIV infection is made by demonstrating the presence of HIV antibodies. Screening tests will detect antibodies to both HIV 1 and HIV 2 (HIV 2 is very rare in Southern Africa, but should be considered if HIV was acquired in West Africa – special tests are required for this, discuss with the laboratory). The most frequently used method to detect antibodies in the laboratory is the enzyme-linked immunosorbent assay, or ELISA. Although the ELISA has 100% sensitivity (no false negatives – but see notes on the "window period" below) it has a specificity of 99.7%, i.e. rare false-positives may occur. A positive screening ELISA should therefore always be confirmed by a second test. The preferred confirmatory test is an additional HIV ELISA from another manufacturer. Alternative confirmatory tests, including HIV Western Blot and qualitative HIV PCR, are only indicated in special circumstances. A separate specimen should be sent for the confirmatory tests in order to avoid the possibility of a mislabelled specimen. The rapid HIV test (whole blood, serum or saliva) is an acceptable screening test. A positive result should always be confirmed with a laboratory HIV ELISA or a second rapid test from a different manufacturer.

As with other infectious diseases diagnosed by antibodies (e.g. tickbite fever), antibody tests will be negative in early HIV infection – this is the so-called "window period". In most individuals, antibodies develop within 3–6 weeks of infection. No test is available that will eliminate the "window period". Antigen tests (P24) and especially nucleic acid amplification tests (e.g. PCR) are more sensitive than antibody tests and become positive sooner. However, the nucleic acid amplification tests (e.g. PCR) have a significant false positive rate. These tests should generally only be requested when there is clinical evidence of primary infection (also called the seroconversion illness) and must always be confirmed by subsequent positive antibody tests.

Pre- and Post-Test Counselling

The purpose of HIV testing is not simply to identify infected individuals, but also to educate both seropositive and seronegative people about prevention and limiting transmission of the virus. Prior to HIV testing, pre-test counselling is essential. Counselling should always be done in the client's home language. Informed consent for HIV testing should be obtained in writing. Short courses in basic counselling are available at organisations such as LifeLine and ATICC.

Issues that should be covered include:

- Confidentiality.
- The definition of HIV and AIDS.
- Transmission of HIV infection.
- Risk factors and how to reduce the risk of exposure.
- The meaning of a negative HIV test.
- The concept of the "window period".
- Possible reactions to a negative or a positive result.
- The social support available.
- The meaning of a positive test.
- The personal and practical implications of performing the test.
- The procedure and when to expect a result.
- How to reduce risk and protect sexual partners.
- The return appointment – as soon as possible, preferably within 24 hours.
- The need to avoid blood / plasma / organ donation.

Post-test counselling is equally important. Issues that should be discussed include:

- The significance of either a negative or positive result.
- If negative, suggest re-testing in three months (if appropriate).
- If positive, explain that the person is both infected and infectious.
- Possible routes of transmission and prevention strategies.
- The person's comprehension of the result and its significance.
- Who s/he wishes to tell about the result.
- The importance of notifying sexual partners.
- Social support available.
- The likely progression of infection.
- The availability of care programmes, such as Aid for AIDS.
- Medical follow-up.

Initial Examination and Staging

If HIV positive, a complete physical examination should be performed, with particular attention to the skin, mouth, anogenital region and lymph nodes. Evaluation of the mental state and peripheral nerves is also important. Body weight and height must be recorded.

If the patient belongs to an AfA contracted scheme or company, this examination will be part of their application to the programme. Please contact Aid for AIDS on 086 0100 646 for more information on how to apply, or consult the relevant section of the Clinical Guidelines (see page 105).

Patients should be staged clinically according to the WHO disease staging system outlined on the next page. This is valuable both in terms of prognosis and the initiation of antiretroviral therapy.

WHO Clinical Staging of HIV/AIDS for Adults and Adolescents with Confirmed HIV Infection (2006)

Clinical Stage I

Asymptomatic
Persistent generalized lymphadenopathy

Clinical Stage II

Unexplained moderate weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections

Clinical Stage III

Unexplained severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8g/dl), neutropaenia (<0.5×10^9 per litre) and/or chronic thrombocytopaenia (<50×10^9 per litre)

Clinical Stage IV (AIDS)

HIV wasting syndrome*
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy**
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis)
Recurrent septicaemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B-cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis

Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

* HIV wasting syndrome: weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>1 month) or chronic weakness and unexplained prolonged fever (>1 month).

** HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.

Baseline Investigations

These should include the following:

- Full blood count and differential count.
- Liver and renal function tests. An ALT level may be done instead of full LFTs.
- VDRL or RPR.
- Hepatitis B serology.
- PAP smear.
- Mantoux (Tuberculin skin test).
- Urinalysis.
- Pregnancy test.

Other important baseline investigations include a **CD4 count** and a **quantitative HIV PCR** (viral load).

The **CD4 cell count** is the most clinically useful laboratory indicator of the degree of immune suppression and stage of disease. The CD4 count assists in deciding when to start antiretroviral therapy. (See page 32.) The count is also useful in differential diagnosis, e.g. cryptococcal meningitis is unlikely if the CD4 count is above 200, and infection with CMV or non-tuberculous mycobacteria virtually only occurs once the CD4 count is below 50.

Apart from the absolute count, the percentage of lymphocytes which are CD4 may be used. The CD4% is routinely used in preference to absolute counts in paediatrics (see paediatric section), as the normal CD4 counts in children are much higher. In adults the CD4% is useful when evaluating significant changes in the CD4 count, which may be associated with transient lymphopaenia due to intercurrent infection. In this case, the CD4% will be unchanged.

The CD4 count may be affected by other infections (e.g. tuberculosis). The CD4 count falls by 25 percent during pregnancy. The count may also vary by up to 20 percent from day to day. Due to the variability in CD4 counts, major therapeutic decisions should not be taken on the basis of a single count. This includes particularly the initiation of antiretroviral therapy, especially when the patient has no clinical evidence of advanced immune suppression. Single counts have limited value, sequential assessments provide the most useful information.

In uninfected individuals, the CD4 count is about 1000 cells/µl. In HIV infection, mild immune suppression occurs once the count drops below 500. These persons are at low risk for opportunistic infections. Skin rashes due to bacterial or fungal infection, and herpes zoster may occur. These become more common once the count falls below 350 with moderate immune suppression.

Once the count is below 200, there is significant immune suppression and a high risk of opportunistic infections and AIDS-defining conditions. However, patients can be asymptomatic despite very low CD4 counts.

The CD4 count should be performed every 4–6 months.

The **viral load** measures the amount of HIV in the blood, and indicates how fast the virus is replicating. There are several techniques for measuring viral load. The same technique and laboratory should be used for follow-up tests. Viral load is critically important in monitoring responses to ART. It also has prognostic value as patients with high viral loads (>100 000 copies/ml) experience more rapid declines in CD4 count, whilst those with low viral loads (<1 000 copies/ml) have very slow CD4 declines. Viral load measures are calculated and reported in copies/ml, as well as in $\log_{10}$ values. In early HIV infection, the viral load may be in the millions – it settles to a plateau level (known as the "set point") after 4–6 months.

Transient increases in viral load occur with intercurrent infections and immunizations, so the test should not be done under these circumstances. Tests should be done at least two weeks after any intercurrent infection or vaccination. Viral load results may also vary by up to three times (0.5 log), for example from 5 000 to 15 000, or 50 000 to 150 000. These changes appear to be large, but are within the margin of error of the test. Therefore, decisions to change antiretroviral therapy should never be based on the results of only one test.

Viral loads are useful in monitoring the response to antiretroviral therapy (ART). A baseline viral load prior to initiating ART is required. Thereafter the test should be repeated 6–8 weeks after starting ART. At this point the viral load should show at least a >10 fold (1 $\log_{10}$) decrease. Thereafter the viral load should be done every 4–6 months. After 6 months of highly active antiretroviral therapy (HAART) the ideal response would be a viral load below the limit of detection of the assay. There is no point in monitoring the viral load if the patient is not on antiretroviral therapy.

Laboratory Tests

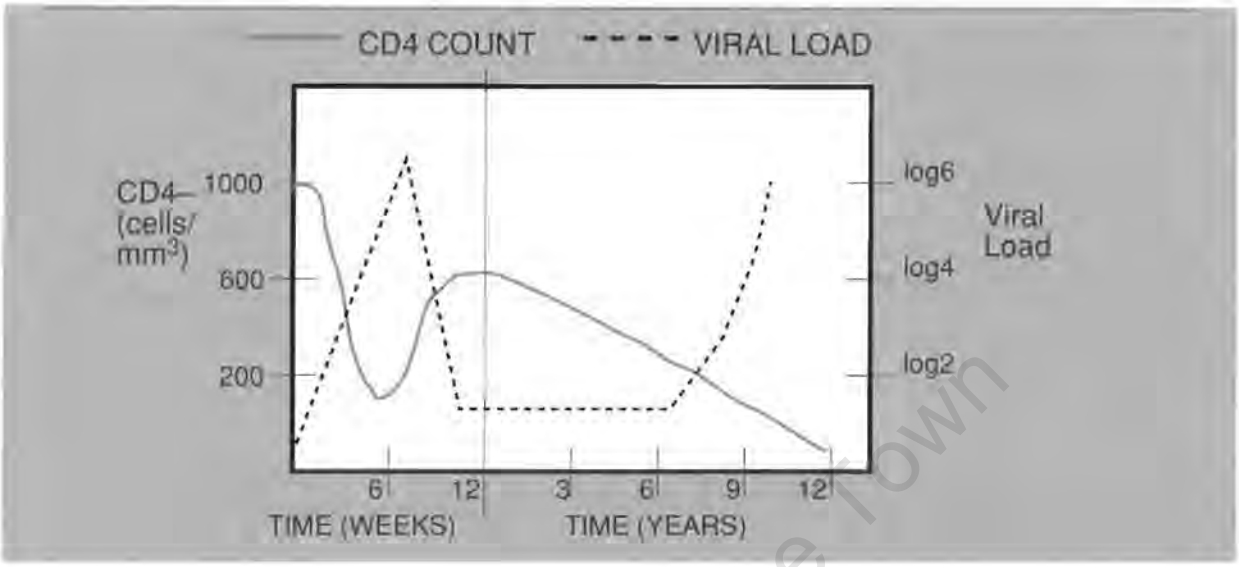
Test	Appropriate Sample
HIV antibody test	Clotted blood
Viral load test	Blood in EDTA (purple-topped) tube. Send to lab within six hours.
CD4 cell count	Blood in EDTA (purple-topped) tube
Hepatitis B serology	Clotted blood
Syphilis serology	Clotted blood
Full blood count	Blood in EDTA (purple-topped) tube
Serum chemistry	Clotted blood
PCR (qualitative)	Blood in EDTA (purple-topped) tube

HIV Disease Progression

HIV infection is characterised by slowly progressive immune deficiency with a prolonged period of clinical latency, which is highly variable but on average lasts eight years. If untreated, patients eventually develop one or more serious morbid events, which are known as the AIDS-defining illnesses. Death occurs as a result of these illnesses, or from general cachexia. The rate of declining immunity is variable. A very small proportion of patients don't experience disease progression. These patients (called long term non-progressors) have a good immune response and have very low viral loads. Patients with high viral loads progress more rapidly. The rate of

disease progression is dependant on the viral load "set point" (the lowest level to which the viral load falls after seroconversion). If the set point is high, disease progression will be rapid, whilst a low set point is associated with slow progression to AIDS. Once the CD4 count is less than 50, median survival without ART is 12 months.

The natural history of HIV illness



Prevention of Opportunistic Infections

Primary prophylaxis is given to prevent common opportunistic infections and is very effective.

Co-trimoxazole Prophylaxis

All patients with CD4 counts of less than 200 as well as those with WHO stage 3 or 4 disease (irrespective of CD4 count) should receive co-trimoxazole 480–960 mg (1–2 single strength tablets) daily. The lower dose causes fewer side effects, but most studies have been with the higher dose. Prophylactic co-trimoxazole prevents Pneumocystis pneumonia (PCP) and toxoplasmosis. It also reduces the frequency of bacterial infections, including bacterial pneumonia, and some protozoal causes of diarrhoea (Isospora belli and Cyclospora species). If the patient is on antiretroviral therapy and the CD4 count is rising, it has been shown to be safe to withdraw the drug once the CD4 count is consistently above 200. This also applies to co-trimoxazole used as secondary prophylaxis.

Hypersensitivity to sulphonamides is common in advanced HIV infection. Provided the reaction is not life threatening, co-trimoxazole can be continued with antihistamine cover or stopped and rechallenged, or desensitisation (see below) attempted. Those unable to tolerate co-trimoxazole, or allergic to sulphonamides, may be given Dapsone 100 mg daily, although this is less effective. If the allergic reaction took the form of a Stevens-Johnson syndrome, neither co-trimoxazole nor dapsone should be used as cross reactions may occur.

A simple slow method for co-trimoxazole desensitization (safe and effective in about two thirds of cases) appropriate for prophylxis is as follows (see page 20 for rapid desensitization regimen when patients present with acute infections such as toxoplasmosis and PCP):

(Use co-trimoxazole suspension 240 mg/5ml)

DAY 1	1.25ml daily
DAY 2	1.25ml bd
DAY 3	1.25ml tds
DAY 4	2.5ml bd
DAY 5	2.5ml tds
DAY 6	1 tablet (480 mg) daily

Rechallenge and desensitization should be done under antihistamine cover, starting the day before. After the initial rechallenge dose the patient should be observed for several hours.

Tuberculosis Prophylaxis

Preventive therapy is effective, but trials have shown that only patients with a positive tuberculin skin test benefit from preventive therapy (in HIV infection a Mantoux of over 4 mm induration is considered positive). Prophylaxis should also be offered to HIV infected patients who have had recent contact with open tuberculosis, or are at high risk (e.g. health care workers and underground miners). Preventive therapy should be given irrespective of the CD4 count. Isoniazid (INH) 300 mg daily for six months has been shown to be effective, and is the best-studied regimen. Patients must be followed up every month and asked specifically about symptoms of hepatotoxicity (nausea, vomiting and jaundice). Pyridoxine (vitamin B6) 25–50 mg daily should be given concurrently to reduce the risk of peripheral neuropathy.

Before commencing TB prophylaxis, active tuberculosis should always be excluded. Further investigations to exclude TB must be done if any of the following symptoms are present

- Cough >2 weeks
- Night sweats or fever for >2 weeks
- Observed weight loss >1.5kg per month

If any of the above symptoms are present, two sputum smears and one sputum TB culture (current Department of Health guidelines) should be carried out.

A screening chest x-ray is **not** required before initiating preventative therapy.

TB preventive therapy should not be administered at TB clinics as HIV positive patients may be exposed to multidrug resistant TB.

Malaria Prophylaxis

Most cases of malaria in sub-Saharan Africa are due to Plasmodium falciparum. Falciparum malaria has a higher mortality rate and is more common in HIV infected persons, especially those with a low CD4 count and pregnant women.

Preventing malaria

- Avoid mosquito bites by using insecticide impregnated bed nets and topical insect repellants. Repellants should be applied to all exposed skin (avoiding the face) especially between dusk and dawn. Electric mosquito pads may also be used.
- Chemoprophylaxis: Mefloquine or doxycycline is recommended. A combination of atovoquone and proguanil (Malanil®) is also effective, but is more expensive and has potential drug interactions with certain antiretrovirals. Mefloquine is the agent of choice in pregnancy.

Immunizations

Live vaccines (e.g. yellow fever) should be used with caution and avoided in patients with a CD4 count less than 200 as they could lead to life-threatening disease. Response to immunisation is very poor if the CD4 count is less than 200. Use of the currently available polysaccharide pneumococcal vaccine has been shown to be harmful in a large Ugandan study, and should thus not be given unless there are other indications (e.g. splenectomy or chronic lung disease). Annual influenza immunization should be given. Hepatitis B immunization may be given if the person is antibody negative.

Nutritional Support

HIV infection is a protein-wasting illness primarily in the late stages and weight loss is common. In addition, there are a number of treatable causes of weight loss. These include unrecognised depression, poor dentition and HIV-associated oral conditions, for example thrush. Opportunistic infections (especially those causing prolonged diarrhoea), tuberculosis and malignancies can cause rapid weight loss. Antiretroviral drugs may also cause weight loss by several mechanisms: anorexia, nausea, diarrhoea or symptomatic hyperlactataemia.

The HIV wasting syndrome is an AIDS-defining condition and is defined as weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>1 month) or chronic weakness and unexplained prolonged fever (>1 month). This is a diagnosis of exclusion. If the weight loss is rapid (>1 kg/month) then investigations should be done to rule out underlying opportunistic infections or malignancy. In this context a C-reactive protein is helpful, as it tends to be raised with opportunistic diseases but not with HIV per se.

Nutritional support with protein and carbohydrate supplements may be indicated if there is documented weight loss of greater than 10% of body weight over any period. This seems to improve well-being, but does not increase life expectancy. The use of anabolic steroids should not be considered unless serum testosterone levels are low.

People living with HIV should be encouraged to eat a balanced diet but with increased energy and protein intake to counter the increased energy requirements and protein-wasting.

Micronutrients, especially zinc and selenium, have an important role in immunity. Increased oxidative stress and immune dysfunction are common in HIV infection. A number of studies have confirmed low levels of micronutrients, especially in patients with advanced disease. Trials assessing the benefits of micronutrient supplementation have generally been inconclusive. There is evidence that high doses of vitamin A and zinc are harmful. A recent meta-analysis failed to show conclusive benefit, but supported the use of a supplement at doses of RDA (recommended daily allowance).

Any balanced multivitamin/mineral formulation can be used, and will be funded by most medical schemes and companies contracted to Aid for AIDS. Preparations containing very high doses of fat-soluble vitamins (A, D, E and K) and zinc should be avoided as these are harmful.

Patients should be discouraged from using unconventional nutritional supplements or alternative remedies, which are scientifically unproven. Some of these have turned out to be toxic.

Of particular concern is the African wild potato (hypoxis), which has been reported to cause bone marrow depression and CD4 count decline. Patients should be advised to avoid these products, pending the outcome of properly conducted efficacy and safety studies.

Management of weight loss and the maintenance of adequate nutrition become particularly difficult in advanced disease. The advice of a dietician is recommended.

Minor HIV/AIDS-related Conditions

Oral Lesions

Common conditions include thrush, aphthous ulcers and oral hairy leukoplakia. Also common are periodontal diseases such as linear gingivitis and the more serious periodontal necrotising ulceration. As periodontal disease is common, good dental hygiene is important and regular dentist visits are advised. Chlorhexidine rinses may also be useful.

Oropharyngeal candidiasis is common, and a WHO stage 3 defining condition. Therefore it is an indication to start prophylactic co-trimoxazole (irrespective of the CD4 count). Oral candidiasis may manifest in one or more of the following ways; pseudomembranous plaques (white plaques which may be scraped off the mucosal surface with or without bleeding); erythematous candidiasis (presenting as single or multiple red patches); angular cheilitis (presenting as linear fissures or ulcers at the corners of the mouth); hyperplastic candidiasis (presenting as white, adherent plaques on the buccal mucosa); or median rhomboid glossitis.

Treatment of oral candidiasis:

Topical: (troches or lozenges are more effective because of the longer contact time)
- Amphotericin B lozenges 10 mg 6-hourly for 5–10 days
- 0.5% gentian violet solution painted in the mouth 3 times per day
- Nystatin suspension (100 000 IU/ml) 1ml four times per day
- Daktarin® oral gel is helpful for angular cheilitis

Systemic (only for lesions that fail to respond to topical therapy):
- Fluconazole 50–100 mg for 7 days or 150 mg STAT
- Itraconazole oral solution 200 mg/d for 7 days

Relapses following topical and systemic treatment are common.

Systemic antifungals should be used judiciously as repeated use may result in infection with Candida species that are resistant to azole antifungals. In particular, prophylactic use of antifungals is not recommended because of the risk of developing resistance. In the presence of dysphagia or odynophagia, a clinical diagnosis of oesophageal candidaisis is made, which requires systemic treatment (fluconazole 100 to 200 mg daily for 14 days). This is an AIDS-defining condition.

Oropharyngeal or oesphageal ulcers occur frequently in advanced disease. The commonest cause is non-specific ulcers related to HIV. These are deep, painful ulcers that may cause considerable tissue destruction. They may respond to topical steroids (Kenalog in Orabase® or a steroid inhaler aimed at the lesions), but, a course of prednisone 30 mg daily is required for severe lesions or oesophageal involvement. Thalidomide has also been found to be effective, but is difficult to obtain and requires MCC authorisation. Other causes of ulcers include cytomegalovirus and herpes simplex virus.

Salivary gland disorders

Salivary gland enlargement, especially the parotids, is extremely common. It is usually due to a benign disorder of lymph-epithelial cysts. Sicca symptoms may co-exist. The salivary gland involvement is a marker for the diffuse infiltrative lymphocytic syndrome (DILS), which may cause lymphoid interstitial pneumonitis and a variety of auto-immune disorders (e.g. polymyosistis, mononeuritis). Large cysts may be treated with aspiration and instillation of sclerosant. Alternative treatments include low dose irradiation or superficial parotidectomy. The glands may also regress on HAART.

Peripheral Neuropathy

Peripheral neuropathy is common in HIV infection. It may present at any stage of the illness, but becomes more common in late disease, occurring in about a third of AIDS patients. It presents as a symmetrical mixed sensorimotor neuropathy in a typical "glove and stocking" distribution. It is slowly progressive. Paraesthesiae and depressed ankle jerks are seen in early disease, progressing to loss of sensation. Mild peripheral weakness may occur. It is important to exclude toxic neuropathy due to drugs. The drugs which most often cause peripheral neuropathy in HIV medicine are isoniazid and the antiretrovirals stavudine and didanosine. Drug-induced neuropathy develops much more rapidly than HIV neuropathy and is usually more painful.

The management of peripheral neuropathy should commence with a trial of B complex vitamins (or pyridoxine alone with isoniazid). The most effective drug for paraesthesiae is amitriptyline in low doses starting at 10–25mg at night. Carbamazepine should be avoided as it has many drug interactions with non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Lamotrigine has been shown to be beneficial in clinical trials and does not have the same drug interaction problems as carbamazepine. Regular simple analgesia is also helpful.

Neuropathy induced or exacerbated by drugs generally reverses if the drug is stopped, but partial recovery should be expected if the neuropathy was severe. Mild cases of neuropathy due to these drugs can be treated as for HIV neuropathy and the drug continued or, in the case of stavudine, the dose may be decreased. However, the offending drug should be sustituted if the neuropathy is more severe or if it progresses.

Lymphadenopathy

This is a common feature of HIV infection, typically occurring early in the illness and persisting for months to years. It may also indicate the presence of malignancy (e.g. Kaposi's sarcoma or lymphoma) or tuberculosis, which is an extremely common cause in Southern Africa. Rapid enlargement of a node, asymmetric enlargement, or lymphadenopathy associated with constitutional symptoms (even if the nodes are symmetrical), warrants further investigation. Lymph node needle aspiration (using a wide bore needle such as 19G) should be undertaken for microscopy. One slide should be air-dried and sent for staining for acid-fast bacilli (70 percent yield in tuberculosis). The other slide should be fixed and sent for cytology. If this is unhelpful, excision biopsy should be considered.

Haematological Conditions

Thrombocytopaenia resembling immune thrombocytopaenia is a common problem in HIV infection. It is steroid-responsive, but is also an indication for HAART unless it is mild (platelet count >50). Thrombotic thrombocytopaenic purpura is also HIV-associated and should be treated in conjunction with a haematologist – HAART should also be given.

Bone marrow suppression is common in advanced disease. This may be due to bone marrow infiltration (TB, malignancies, fungi) or due to HIV-induced hypoplasia/dysplasia – a bone marrow biopsy is necessary to distinguish these two disorders. Pure red cell aplasia may complicate parvovirus infection and responds to high dose gamma globulin.

Skin Lesions

Skin lesions are very common and become more common as the CD4 count falls. If there is any uncertainty in diagnosis, the advice of a dermatologist should be obtained and a biopsy performed. Scabies should not be forgotten as a common cause of pruritus.

Common conditions include:

Xeroderma

Dry skin is very common in late-stage HIV infection and may be associated with pruritus. Therapy: aqueous cream or other emollients. Antihistamines may assist with the pruritus.

Seborrhoeic Dermatitis

Lesions are commonly found in the hairline, nasolabial folds and eyebrows, but may be extensive. Therapy: low dose topical steroids and selenium sulphide shampoo.

Folliculitis

Several types are seen – infective, acneform and eosinophilic. Therapy: topical benzoyl peroxide and antibiotics (e.g. erythromycin) may be effective. If severe or refractory refer to dermatologist.

Papular, Pruritic Eruption ("Itchy red bump disease")

Common and difficult to manage. Darker-skinned patients often experience marked post-inflammatory hyperpigmentation. Therapy: antihistamines (older sedating agents given at night are preferred) and steroid creams, often mixed with an emollient such as aqueous cream. The cause is thought to be an exaggerated response to insect bites and measures to reduce these (e.g. regular treatment of pets, mosquito nets) should be implemented.

Molluscum Contagiosum

This is commonly found with low CD4 cell counts. Therapy: local curettage if limited number of lesions.

Dermatophytosis

This may involve the skin, scalp or nails. Therapy: topical antifungals should be used for limited skin disease only. Extensive skin involvement or infection of the scalp or nails must be treated with oral antifungals:

Tinea corporis/cruris/pedis: Terbinafine 250 mg daily for 2 weeks OR Griseofulvin 500 mg daily for 4 weeks OR fluconazole 150 mg per week for 2–4 weeks.

Tinea capitis: Terbinafine 250 mg daily for 4 weeks OR Griseofulvin 500 mg daily for 4–8 weeks.

Tinea unguium (fingernails): Terbinafine 250 mg daily for 6 weeks OR Griseofulvin 500 mg daily for 8 weeks OR Itraconazole 200 mg BD for one week, repeat after 1 month.

Tinea unguium (toenails): Terbinafine 250 mg daily for 12 weeks OR Griseofulvin 500 mg daily for 12 weeks OR Itraconazole 200 mg BD for one week, repeat monthly for 3–4 months.

NB: There are drug interactions between certain ARVs and itraconazole. See tables on page 43.

Herpes Simplex

Many asymptomatic carriers develop symptomatic disease with HIV infection. With advancing immune suppression, large chronic mucocutaneous ulcers develop, particularly in the anogenital region and around the mouth. The lesions may be very extensive. Therapy: Oral acyclovir 400 mg three times a day for 5–10 days. Frequent recurrences should be treated with suppressive therapy: acyclovir 400 mg BD for 6 months, but acyclovir-resistant HSV may develop.

Herpes Zoster

May be the first sign of HIV infection. May affect multiple dermatomes and may be recurrent. Therapy: Valaciclovir 1g tds or acyclovir 800 mg five times daily or famciclovir 250 mg tds – all for one week. Pain management is critically important – opiates are often necessary acutely. Amitriptyline 10–100 mg nocte is useful for prolonged pain (but should be started early if pain is not settling within a few days). Soothing antibacterial creams are useful (e.g. povidone-iodine, silver sulfadiazine).

Management of Sexually Transmitted Infections (STIs)

Syndromic management for common presentations:

GENITAL ULCER (exclude genital herpes clinically)	benzathine penicillin 2.4MU IM STAT PLUS erythromycin 500 mg 6 hourly for 5 days
VAGINAL DISCHARGE (exclude candidiasis clinically)	ceftriaxone 125mg IM (OR cefixime 400 mg PO) STAT PLUS doxycycline 100 mg 12 hourly for 7 days PLUS metronidazole 2g STAT
URETHRAL DISCHARGE	ceftriaxone 125mg IM (OR cefixime 400 mg PO) STAT PLUS doxycycline 100 mg 12 hourly for 7 days

Management of specific infections:

Syphilis (if there are no clinical signs for staging, regard as latent)	
primary and secondary	benzathine penicillin 2.4MU IM as a single dose
Penicillin allergy	doxycycline 100 mg 12 hourly for 14 days
latent	benzathine penicillin 2.4MU IM at weekly intervals for 3 weeks
Penicillin allergy	doxycycline 100 mg 12 hourly for 28 days
neurosyphilis	penicillin G 5MU 6 hourly IV for 10 days followed by benzathine penicillin 2.4MU IM weekly for 3 weeks
Gonorrhoea	ceftriaxone 125mg IM STAT OR cefixime 400 mg PO STAT
Penicillin allergy	ciprofloxacin 500 mg PO STAT (NB high rates of resistance in SA currently) OR spectinomycin 2g IM STAT
disseminated/arthritis	ceftriaxone 1g IM/IV daily for 7 days
Chlamydial infection	doxycycline 100 mg 12 hourly for 7 days (14 days for lymphogranuloma venereum)
Chancroid	erythromycin 500 mg 6 hourly for 7 days OR ciprofloxacin 500 mg 12 hourly for 3 days

Trichomonas	metronidazole 2g STAT
Bacterial vaginosis	metronidazole 2g STAT OR metronidazole 400 mg 12hourly for 7 days

Major Opportunistic Infections

Bacterial pneumonia

Diagnosis: as for community-acquired pneumonia in HIV negative patients. Higher rate of bacteraemia.

Treatment: Ceftriaxone OR cefotaxime OR co-amoxiclav OR levofloxacin/moxifloxacin (other quinolones not suitable) for 5–10 days. In severe pneumonia add a macrolide (e.g. clarithromycin) – except if a quinolone was used (these have good cover against Legionella spp, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*).

Maintenance treatment: Co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART (reduces the incidence of bacterial pneumonia and prevents other opportunistic infections).

Candidiasis of oesophagus/trachea

Diagnosis: clinically with oropharyngeal thrush and odynophagia/dysphagia or on endoscopy.

Treatment: fluconazole 100–200 mg daily for 14–21 days.

Maintenance treatment: not indicated. Although recurrences are common, disease is not life-threatening and azole-resistant Candida strains develop. Co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART (to prevent other opportunistic infections).

Cryptococcosis

Diagnosis: culture of Cryptococcus neoformans from any site or by positive cryptococcal antigen in blood or CSF.

Treatment: Amphotericin B 0.7mg/kg/day IV for 14 days followed by fluconazole 400 mg daily for 8 weeks. Patients with initial raised intracranial pressure should have daily lumbar puncture, removing sufficient CSF to lower pressure to <20 cm H_2O.

Maintenance treatment: fluconazole 200 mg daily until CD4 count rises to >100 on HAART (minimum of 6 months). Co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART (to prevent other opportunistic infections).

Cryptosporidiosis

Diagnosis: stool examination.

Treatment: no effective therapy available – loperamide and oral rehydration solution. Responds well to HAART.

Maintenance treatment: none. Co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART (to prevent other opportunistic infections).

Cytomegalovirus (CMV)

Disease outside the reticuloendothelial system is seen in advanced disease (CD4 <50). The diagnosis and treatment of the site of CMV disease differ, so they will be discussed separately.

Treatment is currently extremely expensive, but the morbidity of CMV disease is severe (e.g. retinitis, the commonest site, results in irreversible blindness). The most affordable treatment options are given. Early initiation of HAART is essential in all cases. Zidovudine is best avoided in combination with gancyclovir as both agents suppress the bone marrow. Co-trimoxazole two single strength (480 mg) tablets daily should also be prescribed until CD4 count rises to >200 on HAART (to prevent other opportunistic infections).

1. CMV retinitis

Diagnosis: fundoscopy by an ophthalmologist.

Treatment: Gancyclovir 5mg/kg bd IV for 14 days (patient should be admitted to hospital).

Maintenance treatment: Intravitreal ganciclovir 2mg once a week. Discontinue when CD4 count is >100 on HAART (in consultation with an ophthalmologist).

2. CMV GIT (colitis/oesophagitis)

Diagnosis: histology of biopsy of ulcer.

Treatment: Gancyclovir 5mg/kg bd IV for 14–21 days (patient should be admitted to hospital).

Maintenance treatment: not necessary.

3. CMV CNS

Diagnosis: PCR of CSF.

Treatment: Gancyclovir 5mg/kg bd IV for 14–21 days.

Maintenance treatment: Valgancyclovir 900 mg daily. Discontinue when CD4 count is >100 on HAART.

4. CMV pneumonitis

Diagnosis: histology of lung biopsy. Usually there is another pathogen causing disease (especially Pneumocystis).

Treatment: usually not necessary – treatment of co-pathogens usually results in resolution of disease. An induction course of ganciclovir 5mg/kg bd IV for 14 days may be indicated in severe disease.

Herpes simplex virus ulcers

Diagnosis: usually clinical – shallow, painful spreading muco-cutaneous ulcers. As disease advances spontaneous healing is delayed and then does not occur.

Treatment: acyclovir 400 mg TDS OR valacyclovir 500 mg BD OR famciclovir 125mg BD for 7–14 days.

Maintenance treatment: not usually indicated. Although recurrences are common, disease is not life-threatening and resistant mutant strains develop. Recurrences can usually be dealt with by repeated treatment courses. In exceptional cases acyclovir 400 mg BD for 6 months can be

used (AfA authorisation required). Co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART (to prevent other opportunistic infections).

Histoplasmosis

Diagnosis: culture of *Histoplasma capsulatum* from any source. Biopsy of mucocutaneous lesions suggestive.

Treatment: Amphotericin B 0.7mg/kg daily IV for 3–10 days initially followed by itraconazole 200 mg bd for 12 weeks.

Maintenance treatment: Itraconazole 200 mg daily until CD4 count rises to >100 on HAART (minimum of 6 months) – minimal data. Co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART (to prevent other opportunistic infections).

Isosporiasis

Diagnosis: special stain of stool.

Treatment: Co-trimoxazole 4 single strength (480 mg) tablets bd for 14 days.

Maintenance treatment: Co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART.

Microsporidiosis

Diagnosis: demonstration of the organism on stool (special stains or PCR) or on small bowel biopsy.

Treatment: some strains respond to albendazole 400 mg bd for 21 days – no therapy for other strains. Responds well to HAART.

Maintenance treatment: none. Co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART (to prevent other opportunistic infections).

Non-tuberculous mycobacterial infection (disseminated)

Diagnosis: culture from blood or bone marrow – usual organism is *Mycobacterium avium complex*. Culture from sputum is unhelpful and is NOT an indication for treatment.

Treatment: Clarithromycin 500 mg bd **plus** ethambutol 800 mg daily to be continued until the CD4 count has increased to >100 on HAART (minimum duration 12 months). When the non-nucleoside reverse transcriptase inhibitors and clarithromycin are used together the clarithromycin levels are decreased. Azithromycin 500 mg / day should be used as an alternative.

Maintenance treatment: see above. Co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART (to prevent other opportunistic infections).

Pneumocystis pneumonia

Diagnosis: special stains of broncho-alveolar lavage or induced sputum (following ultrasonic nebulisation of hypertonic saline). Clinical diagnosis is suggested by bilateral interstitial ("ground glass") infiltrate on CXR, history of progressive dyspnoea <12 weeks, and hypoxia (spontaneous or on effort as assessed by >5% desaturation).

Treatment: Co-trimoxazole one single strength (480 mg) tablet per 4kg body weight (maximum 16 tablets/day) given in divided doses 6–8 hourly for 21 days. All hypoxic patients should be given adjunctive prednisone 40 mg BD for days 1–5, 40 mg daily for days 6–10 and 20 mg daily

for days 11–21. There are extremely limited options available in South Africa for patients with co-trimoxazole intolerance. Pentamidine, trimethoprim (given with dapsone) and primaquine (given with clindamycin) are no longer registered in South Africa - MCC permission must be sought for any of these (primaquine is easier to get currently). The only available alternative therapy is atovaquone 750 mg BD – this is only suitable for mild PCP and is extremely expensive. Some clinicians have used clindamycin plus dapsone, but there is no published evidence of efficacy with this combination.

Co-trimoxazole desensitisation should be considered for patients with moderate to severe PCP and a history of intolerance to co-trimoxazole. The rapid desensitisation regimen listed below was successful in 19/22 patients with no significant problems in the 3 who failed. However, a further 3 patients had to subsequently discontinue due to the development of a rash (Clin Infect Dis 1995;20:849).

Use co-trimoxazole suspension 240mg/5ml. Co-trimoxazole suspension will need to be diluted appropriately. Please consult your pharmacist or contact AfA. Desensitisation must be conducted in hospital and should be done WITHOUT antihistamine or steroid cover.

Time (hours)	Dose (mls of undiluted co-trimoxazole susp)
0	0.0005
1	0.005
2	0.05
3	0.5
4	5
5	two single strength tablets
Followed by full dose	

Maintenance treatment: co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART.

Progressive multifocal leukoencephalopathy

Diagnosis: non-enhancing lesions on MRI together with positive PCR for JC virus on CSF. Definitive diagnosis requires brain biopsy (seldom necessary).

Treatment: no effective therapy available. Responds poorly to HAART, with many cases experiencing exacerbation due to immune reconstitution.

Salmonella bacteraemia

Diagnosis: blood culture of non-typhoidal salmonella.

Treatment: ciprofloxacin 500 mg bd for 4–6 weeks.

Maintenance treatment: co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART (even if the salmonella was resistant to co-trimoxazole – other opportunistic infections will be prevented).

Tuberculosis (TB)

HIV infection increases the risk of TB substantially, with the risk doubling shortly after seroconversion, and increasing further in advanced disease. TB may affect the lungs, be disseminated or limited to extrapulmonary sites. Disseminated or extrapulmonary TB is regarded as an AIDS defining condition, although African studies have shown that all forms of tuberculosis have a better prognosis than other AIDS-defining illnesses. All forms of TB may occur at any CD4

count, but extrapulmonary, disseminated and non-cavitaitory pulmonary TB are typically seen when the CD4 count is <200. In advanced disease, the chest x-ray may be clear with positive TB culture in the sputum.

It is important to try and confirm the diagnosis of tuberculosis. The sputum smear is less likely to be positive in HIV infection, but remains the best initial test. At least two sputum specimens should be sent for smear. Smears of lymph node aspirates also have a high yield. Biopsy is also useful to obtain a rapid diagnosis – this can be from affected tissues (e.g. lymph node, lung pleura) or from bone marrow or liver if disseminated disease is suspected. All biopsy material should also be sent for mycobacterial culture, which has a high yield. Other specimens which give good culture yields are sputum, caseous material from cold abscesses/node aspirates, pleural/ascitic/pericardial fluid, early morning urine and blood (using special mycobacterial culture bottles). Nucleic acid amplification tests (e.g. PCR) offer the promise of a rapid diagnosis, but these tests are not very reliable if the smear is negative and culture confirmation is always necessary.

In advanced disease TB can progress rapidly. Therefore TB treatment will often be necessary before culture results are available. For pulmonary TB it is reasonable to commence TB treatment if two sputum smears are negative, there has been no response to a course of antibiotics, and the chest x-ray is compatible with TB. However, at least one and preferably 2 specimens should be sent for culture before starting TB therapy. As noted above, biopsy should also be considered.

HIV positive patients respond to TB treatment just as well as HIV negative individuals. Treatment should be initiated according to national guidelines (in South Africa: rifampicin, isoniazid, pyrazinamide and ethambutol in a fixed dose combination tablet, with the addition of streptomycin for re-treatment cases) and all cases should be referred to their nearest TB clinic for management. TB is a notifiable disease.

For managing patients on TB and antiretroviral therapy please see page 32.

Toxoplasmosis

Diagnosis: is made on CT/MRI scan showing enhancing mass lesions. CD4 count is nearly always <200. Toxoplasma IgG (not IgM) positive. Rapid treatment response confirms the diagnosis (brain biopsy is definitive but seldom necessary).

Treatment: Co-trimoxazole four single strength (480 mg) tablets BD for 4 weeks, then two BD for 12 weeks. For co-trimoxazole intolerance clindamycin 600 mg qid **plus** pyrimethamine 50 mg daily **plus** folinic acid 15mg daily (to prevent bone marrow suppression from pyrimethamine – folic acid is ineffective) for 6 weeks.

Maintenance treatment: co-trimoxazole two single strength (480 mg) tablets daily until CD4 count rises to >200 on HAART.

In general, initiation of HAART should be delayed until any active opportunistic infection is under control to avoid the development of immune reconstitution inflammatory syndrome (IRIS).

Management of HIV-Associated Kaposi's Sarcoma (KS)

Background to HIV-associated KS

- KS is a malignancy of lymphatic endothelial origin.
- It is associated Human Herpes Virus-8 (HHV-8) also known as KS Herpes Virus (KSHV).
- KS may involve the skin, oral cavity, lymph nodes or viscera (especially lung and intestines). Lymphoedema is a common complication.
- 80–90% of cases of visceral KS will have oral or skin involvement.
- The typical CXR appearance of pulmonary KS is a reticulonodular appearance spreading from the hilar regions bilaterally. The diagnosis is confirmed by visualizing endobronchial KS lesions on bronchoscopy (biopsy poses a risk of haemorrhage). Pulmonary KS may be associated with intrathoracic adenopathy and/or pleural effusions which are typically bloody or serosanguinous.
- CXR is a useful screen for pulmonary KS.
- KS is a WHO Stage 4 defining illness, regardless of CD4.
- The incidence of KS has been dramatically reduced by HAART (92% reduction in Swiss cohort).
- Although most cases are diagnosed on the typical macroscopic appearance of skin and oral lesions, certain cases should have biopsy confirmation. Atypical skin lesions should be biopsied (punch biopsy or excision biopsy) to differentiate from angiomas, dermatofibromas, etc. Nodular lesions that enlarge rapidly should be biopsied to exclude bacillary angiomatosis that is due to Bartonella infection.
- Lymph nodes >2cm should be biopsied to exclude TB and lymphoma.
- Atypical oral lesions should be biopsied to exclude other malignancies such as lymphoma, squamous carcinoma and salivary gland tumours.

Treatment principles

- All patients with KS should be pretest counselled and have consented HIV testing.
- All HIV positive patients with KS should be commenced on HAART regardless of CD4 as KS is a Stage 4 defining illness. This should always be the first-line therapeutic intervention.
- Co-trimoxazole prophylaxis should be commenced given that this is a Stage 4 defining illness.
- Regression and resolution of mucocutaneous KS on HAART alone is well described. There are also case reports of regression of pulmonary KS lesions on HAART alone.
- HAART prolongs the time to treatment failure of KS chemotherapy.
- It is important to investigate for and exclude co-existent opportunistic infections (particularly TB), especially if the patient is going to receive chemotherapy which will immunosuppress them further.
- Treatment decisions need to be individualized and are based on: extent of disease, rate of growth of lesions, symptoms, CD4 count and general condition. Quality of life is an important factor in decision-making regarding intensity of chemotherapy and decisions as to when palliative therapy becomes appropriate.
- Local therapy is appropriate for localized skin and oral lesions and options include:
  - Intralesional chemotherapy (vinblastine)
  - Local radiotherapy
  - Liquid nitrogen cryotherapy for small lesions
  - Topical alitretinoin gel 0.1%.
- Systemic chemotherapy is preferred in the following patients:
  - >25 skin lesions

- Rapidly progressive disease
- Visceral involvement
- Extensive oedema
- "B"symptoms (fever, night sweats, significant constitutional symptoms)
- Failure to respond to local therapy and HAART

- Patients who have a poor performance status and/or very low CD4 tend to tolerate chemotherapy less well. If their poor performance status is due to a factor that is remediable in the short term such as an opportunistic infection then chemotherapy should be delayed until after this has been addressed. However, if it is related to disseminated KS then obviously chemotherapy cannot be delayed. In patients with poor performance status and/or CD4<100 it may be appropriate to adopt a low intensity chemotherapy regimen for initial therapy. And in certain patients who are too ill to tolerate any chemotherapy palliative therapy alone may be more appropriate.

A suggested general approach is:

Cutaneous and oral lesions:
- Commence HAART.
- If lesions don't regress after 3–6 months then local therapy or systemic chemotherapy depending on extent.

Disfiguring or symptomatic (pain, obstructing airway/swallowing, etc) lesions:
- Commence HAART and local therapy.
- If don't regress after 3–6 months then systemic chemotherapy.

Extensive skin disease / visceral involvement:
- HAART and systemic chemotherapy, with the commencement staggered a week apart.

Standard chemotherapy regimens

3 options:

1. Adriamycin (doxorubicin), bleomycin, vincristine combination therapy
   2 weekly × 6–8 cycles
   Adriamycin 10–20 mg/m^2
   Bleomycin 10 mg/m^2
   Vincristine 1,2mg/m^2 (maximum dose 2mg)

2. Paclitaxel
   100 mg/m^2 every 2 weeks (better tolerated) or
   135mg/m^2 every 3 weeks

3. Liposomal anthracycline
   Liposomal daunorubicin 40 mg/m^2 every 2 weeks
   or liposomal doxorubicin 20 mg/m^2 every 2–3 weeks

Liposomal anthracyclines have been demonstrated to be superior to conventional combination chemotherapy (bleomycin and vincristine with or without non-liposomal doxorubicin) in terms of response rates and side effects. One study showed a response rate of 46% for liposomal doxorubicin vs 25% for non-liposomal doxorubicin, bleomycin plus vincristine ($p < 0.001$).

Paclitaxel has been found to be effective even in patients with anthracycline-resistant disease. Two studies demonstrated response rates of 59% and 71% respectively in patients who had previously failed at least one regimen.

Liposomal anthracyclines are better tolerated than paclitaxel in terms of side effects. Paclitaxel is associated with more neutropaenia, thrombocytopaenia, myalgia and arthralgia. Paclitaxel is therefore usually reserved for second line therapy.

Low-intensity chemotherapy regimens

1. Vincristine + bleomycin 2 weekly 6–8 cycles
   Bleomycin 10 mg/m^2
   Vincristine 1,2mg/m^2 (maximum dose 2mg)

2. Vincristine alternating vinblastine 2 weekly, 6–8 cycles
   Vincristine 1,2mg/m^2 (maximum dose 2mg)

   Alternating with vinblastine 4mg increasing by 1mg increments each cycle to maximum 8mg dose watching FBC/neutrophil count

HAART with chemotherapy

Given the increased risk of myelosuppression when combining chemotherapy with zidovudine, it is preferable to use tenovir or stavudine rather than zidovudine when commencing HAART around the time of chemotherapy.

There are several potential drug interactions when combining HAART and the above chemotherapy agents:
- NNRTIs may reduce levels of paclitaxel and vincristine/vinblastine.
- PIs may increase levels of these agents potentially increasing toxicity.
- There is no interaction with the anthracyclines.

It is also worth noting that stavudine and the vinca alkaloids share the common side effect of causing peripheral neuropathy. In addition, patients may have pre-existing HIV neuropathy and if this is manifesting with disabling symptoms then consideration should be given to omitting vinca alkaloids from the chemotherapy regimen.

Prognosis

Prognosis depends on the extent of KS at diagnosis. In patients with limited disease 3 year-survival in the HAART era is 88%, but even those patients with disseminated disease have a fair medium term prognosis. Patients with pulmonary KS have a 46% 3 year-survival when treated with chemotherapy and HAART (Nasti, et al, J Clin Onc 21(15): 2876-2882).

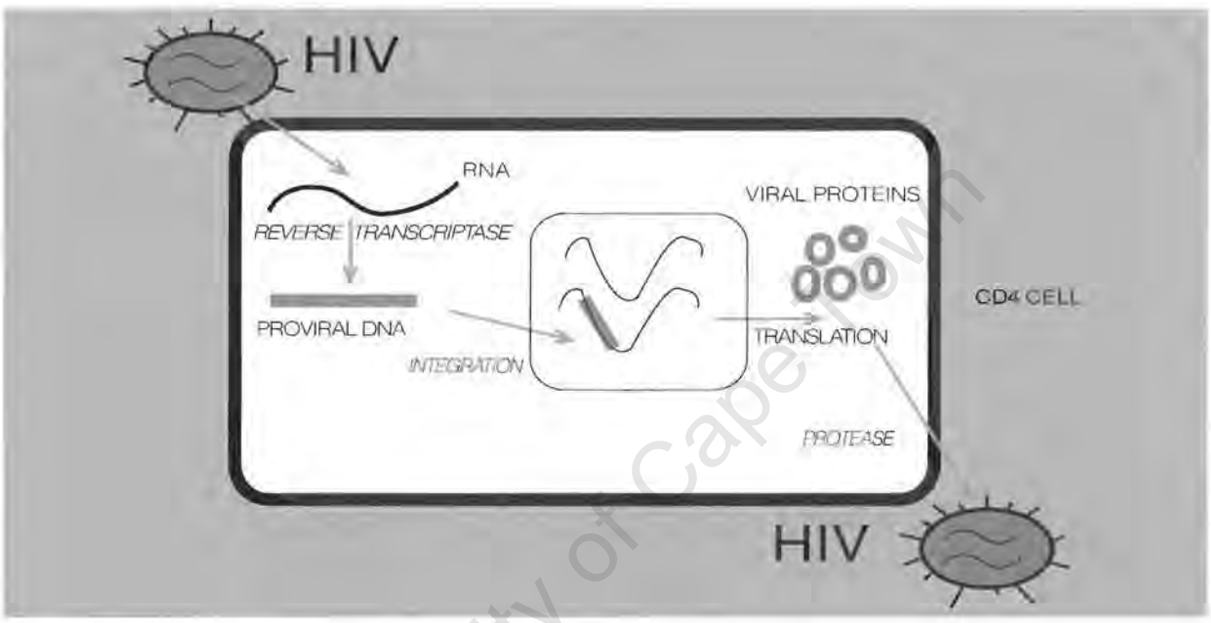
Antiretroviral Therapy in Adults

The primary goals of antiretroviral therapy are:
- to prolong life expectancy.
- to improve quality of life.
- to prevent development of opportunistic infections and other AIDS-related conditions.
- to reconstitute immune function.
- to suppress viral replication as far as possible and for as long as possible.
- to prevent transmission of the virus.

Antiretroviral Drugs

Drugs currently available in Southern Africa block viral replication by inhibiting two viral enzymes – either HIV reverse transcriptase or the HIV protease. A fusion inhibitor (enfuvirtide) which blocks entry of the virus into the cell is commercially available overseas, but is very expensive. At this stage it is only available in an injectable formulation. Attachment inhibitors blocking co-receptor (chemokine) binding, integrase inhibitors which prevent integration of DNA into the cell nucleus, and maturation inhibitors are under investigation.

The HIV lifecycle



Drugs that inhibit reverse transcriptase fall into three classes: nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). These drugs block the conversion of viral RNA into proviral DNA and thus inhibit genetic integration of the virus. NRTIs and NtRTIs resemble the natural nucleotide building blocks of DNA so that when the reverse transcriptase tries to add the drug to a developing strand of DNA, it cannot be completed. NRTIs need to be activated first by phosphorylation. NtRTIs are partly phosphorylated as they already possess one of the 3 phosphate groups necessary for activity. NNRTIs inhibit activity of the reverse transcriptase directly.

Protease inhibitors act at a later stage and interfere with HIV protease, which cleaves viral polyproteins into functional end products. This prevents the formation of mature infectious virus and results in the release of immature non-infectious viral particles.

As many of the antiretroviral drugs now have generic equivalents, trade names have been omitted from the section which follows.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Class side effect

All NRTIs impair mitochondrial function by inhibiting mitochondrial DNA γ-polymerase. This can cause steato-hepatitis or symptomatic hyperlactataemia or lactic acidosis (see pg 37).

The NRTIs vary in their ability to do this: stavudine = didanosine > zidovudine > lamivudine = abacavir = tenofovir.

Zidovudine (AZT)
This nucleoside analogue mimics thymidine and was the first effective antiretroviral drug. Zidovudine has good CNS penetration and is effective in HIV related encephalopathy and dementia.

Side-effects: include initial nausea, vomiting, headaches and myalgia, which may be dose-related and improve as tolerance develops. Anaemia and neutropaenia may occur. These are also dose-related, and occur more frequently in advanced disease. Macrocytosis (not related to vitamin B12 / folate deficiency) occurs in nearly all patients, and may in fact be used to confirm compliance. Myopathy with raised CK is a rare side effect after long term use. Hyperlactataemia risk – moderate.

Dose: 250–300 mg bd. The dose may be reduced to 200 mg bd if side-effects or a significant drop in the haemoglobin (Hb) or neutrophil count occur (see table on pg 36 on haematological toxicity). The drug need only be discontinued if the Hb falls below 6.5 g/dl or the neutrophil count below 0.5×10^9/l. Thrombocytopaenia however does not occur and zidovudine is in fact indicated for the treatment of HIV-induced thrombocytopaenia. A fixed dose combination product is available which contains 300 mg zidovudine and 150 mg lamivudine per tablet. The dose is one tablet twice a day.

Stavudine (d4T)
Stavudine is also a thymidine analogue and has good CNS penetration. Drug combinations should include either stavudine or zidovudine but never both, as they interact antagonistically. The two drugs have a very similar resistance profile and there is extensive cross-resistance. Stavudine is associated with significant toxicity, and many international guidelines recommend against its use for initial therapy. Lower doses should be considered (see below).

Side-effects: Peripheral neuropathy which generally occurs after a few months in up to 20% of patients. Anaemia and neutropaenia have been reported, but are less common than with zidovudine. Macrocytosis may also occur. Lipo-atrophy (loss of subcutaneous fat) is a common and cosmetically distressing side effect. Stavudine should be avoided in women with a body mass index >28 or weight >75kg due to the increased risk of hyperlactataemia. Hyperlactataemia risk – high.

Dose: 40 mg bd (30 mg bd if weight <60kg). Consider reduction of dose with peripheral neuropathy (40 mg to 30 mg and 30 mg to 20 mg). There is evidence from a meta-analysis that lower doses (30 mg bd if weight >60kg) are as effective and less toxic.

Lamivudine (3TC)
This is a cytosine analogue which is also active against hepatitis B. It may be used in combination with either zidovudine or stavudine, but never on its own. In common with the non-nucleoside reverse transcriptase inhibitors early viral resistance is a problem in the absence of a suppressive regimen.

Side-effects: are remarkably few. Peripheral neuropathy and rash have been reported. Pancreatitis is rare and has only been reported in paediatric patients. Flares of hepatitis B may occur if the drug is discontinued. Hyperlactataemia risk – low.

Dose: 150 mg bd.

Didanosine (ddI)
This is an adenosine analogue. It is generally used as part of combination therapy with either zidovudine or stavudine, although the combined toxicity associated with stavudine and

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Resistance to NNRTIs can arise very rapidly, as it requires only a single mutation. There is cross-resistance between both NNRTIs currently available. These drugs should NEVER be used as single agents or added as a sole new agent to a failing regimen. A non-nucleoside triple therapy combination is as effective as triple therapy with a protease inhibitor, even in patients with advanced disease and is associated with fewer long term side effects. Therefore, in common with international and national guidelines, AfA promotes the use of NNRTI regimens as first-line therapy. NNRTIs are metabolised by the liver and both efavirenz and nevirapine are inducers of liver enzymes (efavirenz also inhibitis some isoenzymes of the cytochrome P450 system). There are thus many potential drug interactions – please see page 42.

Nevirapine

Side-effects: The most important is a generalized hypersensitivity rash. This occurs in about 15% of patients, and generally within the first 6 weeks of therapy. Nevirapine has been discontinued because of rash in 7% of patients. See table below for management of the rash. Abnormal liver enzymes occur commonly (10–20%), especially in the first 8 weeks, but clinical hepatitis is uncommon (2%). Liver function (sufficient to measure ALT only) should be monitored at two, four and eight weeks, and three monthly thereafter – see table on page 37 for managing abnormal liver function tests. Hepatitis and rash occur more commonly in women with a CD4 count >250 and in men with a CD4 count >400 – nevirapine should generally be avoided in these patients (unless the CD4 count has risen to these levels on HAART, in which case there does not appear to be an increased risk).

Dose: One 200 mg tablet daily for two weeks, then 200 mg bd. The dose needs to be increased as the drug induces its own metabolism. If the patient is switching from efavirenz to nevirapine the lead in dose is not necessary as efavirenz is an hepatic enzyme inducer. A fixed dose combination product is available which contains 40 mg stavudine, 150 mg lamivudine and 200 mg nevirapine. The dose is one tablet twice a day after the lead-in period.

Managing NNRTI rash:

Description of Rash	Action
Mild to moderate rash (may include pruritus)	Continue dosing without interruption. No dose escalation during lead-in until rash resolves. If nevirapine is interrupted for >7 days, reintroduce with 200 mg/day lead-in.
Any rash with one or more of the following associated features: ▪ Elevated ALT ▪ Fever ≥ 38°C ▪ Blistering ▪ Mucosal lesions (oral/conjunctival/genital) ▪ Facial oedema ▪ Myalgia/arthralgia	Permanent discontinuation. No reintroduction.
Severe rash ▪ Extensive erythematous or maculopapular rash ▪ Moist desquamation ▪ Serum sickness-like reactions ▪ Stevens-Johnson syndrome ▪ Toxic epidermal necrolysis	Permanent discontinuation. No reintroduction.

Antihistamines (see interactions table on pg 43) may be used for symptomatic treatment. As there is evidence that prophylactic use of oral corticosteroids aggravates the risk and possibly the severity of the rash, the use of corticosteroids to treat the rash is not recommended.

There is a small risk of developing a rash with efavirenz in patients discontinuing nevirapine because of hypersensitivity. However, most experts advise against switching to efavirenz if the skin rash was life-threatening (e.g. Stevens-Johnson syndrome).

Efavirenz

Side-effects: CNS side-effects are very common, including insomnia, dizziness, delusions and inappropriate behaviour, acute depression, impaired concentration, somnolence and abnormal dreams. The symptoms usually begin during the first or second day of therapy, are generally mild and resolve after several weeks. Despite these side effects the drug is generally well tolerated in the long term. Dosing at bedtime (or, in shift workers, at the beginning of the off shift as the drug has a long half life) improves the tolerability.

Hypersensitivity rash is common in the first 6 weeks, but this is usually milder than with nevirapine (efavirenz has been discontinued because of rash in 1.7% of patients).

Teratogenicity has been noted in animal studies and 4 cases of myelomeningocoele have now been reported in humans. Efavirenz is therefore contraindicated in pregnancy. Barrier contraception should always be used in combination with other methods of contraception. Women of childbearing age should undergo pregnancy testing prior to initiation of efavirenz.

Self-limiting gynaecomastia has been described. Patients on efavirenz may have false positive urinary cannabis tests.

Dose: 600 mg once daily.

Protease Inhibitors (PIs)

All protease inhibitors are liver enzyme inhibitors, although the most potent is ritonavir. In addition, some cytochrome P450 isoenzymes are induced by ritonavir. This results in significant drug interactions with many drugs metabolized by the liver, including other PIs – see page 42. This enzyme inhibition can be exploited therapeutically – low dose ritonavir may be combined with most other PIs prolonging their half-lives and often also the peak drug levels. Adverse effects such as diarrhoea and nausea are common. A metabolic syndrome consisting of lipodystrophy, dyslipidaemia (elevated triglycerides and LDL-cholesterol, especially the former) and insulin resistance occurs commonly with prolonged use. Fasting lipograms and glucose should be done before initiating PIs and six monthly thereafter. Diarrhoea, nausea and vomiting are common side effects of all PIs. PI-induced diarrhoea may be successfully treated with loperamide/psygillium husk/calcium carbonate 900 – 1200 mg daily. There is a degree of cross-resistance between most PIs currently available.

Lopinavir/ritonavir

This is a fixed combination of lopinavir and ritonavir. It is useful when PI resistance has developed, but is also widely used in patients without prior PI experience. Its place in sequencing antiretrovirals remains debateable as it has excellent activity, both as a first line protease inhibitor and as a salvage agent. There is a high potential for dyslipidaemia. The drug requires refrigeration, but is stable below 25 degrees centrigrade for 42 days following opening of packaging. A tablet which doesn't require refrigeration should be available shortly.

Dose: 400 mg/100 mg (3 capsules) bd. Four capsules bd if used with efavirenz or nevirapine because of drug interaction. If used with rifampicin, the dose should be doubled (i.e 6 capsules bd) or additional ritonavir (300 mg bd) should be added.

Indinavir

Side-effects: These are relatively frequent and include nephrolithiasis (patients need to drink at least 1.5 litres of fluid daily, with increased fluid intake in hot climates), unconjugated hyperbilirubinaemia and hair loss. Nephrolithiasis is not an indication to stop the drug, but should be managed by increasing fluid intake. There is a moderate potential for dyslipidaemia. It is recommended to give ritonavir and indinavir in combination, which prolongs the half-life of indinavir and allows for 12 hourly dosing with no food restrictions.

Dose: 800 mg bd + ritonavir 100 mg bd with plenty of fluids.

Ritonavir

Ritonavir is well absorbed orally. Its properties as a powerful liver enzyme inhibitor are utilised in combinations with other protease inhibitors. In adults it is almost always used to boost other protease inhibitors, rather than used on its own because of its poor GIT tolerability in full doses. There is a high potential for dyslipidaemia.

Side-effects: These include nausea, diarrhoea, headaches and perioral paraesthesia. Raised liver enzymes may occur and drug interactions are extremely common. GIT side effects are very common at full doses.

Dose: The drug may be given 600 mg bd with meals. Starting with a lower dose, 300 mg bd, and escalating it gradually over 10–12 days may improve tolerability. It is currently most commonly used in doses of 100–200 mg in combination with other protease inhibitors, as a cytochrome P450 inhibitor. The drug requires refrigeration, but is stable below 30 degrees centrigrade for 1 month following opening of packaging.

Saquinavir

Saquinavir should never be used without boosting by ritonavir.

Side-effects: These include diarrhoea (up to 20 percent), nausea and abdominal pain. There is a low potential for dyslipidaemia.

Dose: Saquinavir: 400 mg bd + ritonavir 400 mg bd. Alternatively saquinavir 1000 mg bd may be combined with ritonavir 100 mg bd. Saquinavir may also be combined with lopinavir and ritonavir as a salvage regimen (saquinavir 800–1000 mg bd, lopinavir/ritonavir 400 mg/100 mg bd).

Nelfinavir

This is available as a 250 mg tablet and a 50 mg/g oral powder. Nelfinavir is expensive compared to other protease inhibitors which limits its use. Nelfinavir lowers the serum concentration of oral contraceptives. Alternative contraceptive measures should be used.

Side-effects: The most frequent side-effect is diarrhoea of mild to moderate intensity. Other side effects include skin rash, nausea, vomiting and abdominal pain. There is a low potential for dyslipidaemia.

Dose: 750 mg tds or 1250 mg bd with a meal or light snack.

Antiretroviral Drugs

NUCLEOSIDE ANALOG REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)		
Chemical Name	**Dose**	**Common side-effects**
Zidovudine(AZT)	250 mg bd 300 mg bd	Nausea, headache, fatigue, neutropaenia, anaemia, myalgia
Stavudine(d4T)	>60kg: 40 mg bd <60kg: 30 mg bd	Peripheral neuropathy
Didanosine (ddI)	>60kg: 200 mg bd or 400 mg daily <60kg: 125mg bd or 250 mg daily on empty stomach	Peripheral neuropathy, nausea, pancreatitis
Lamivudine (3TC)	150 mg bd	Headaches, nausea
Abacavir	300 mg bd	Hypersensitivity
NUCLEOTIDE ANALOG REVERSE TRANSCRIPTASE INHIBITORS (NtRTIs)		
Chemical Name	**Dose**	**Common side-effects**
Tenofovir (TDF)	300 mg daily with food	Nephrotoxicity
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)		
Chemical Name	**Dose**	**Common side-effects**
Nevirapine	200 mg daily for two weeks, then 200 mg twice daily	Rash, hepatitis
Efavirenz	600 mg nocte	CNS effects, rash Teratogenic
PROTEASE INHIBITORS (PIs)		
Chemical Name	**Dose**	**Common side-effects**
Indinavir	800 mg bd + ritonavir 100 mg bd	Kidney stones, nausea, diarrhoea, hair loss, dyslipidaemia and insulin resistance (low potential)
Ritonavir	600 mg bd (start with 300 mg bd). Take with food.	Diarrhoea, nausea, abdominal pain, dyslipidaemia and insulin resistance (high potential).
Saquinavir	400 mg bd + ritonavir 400 mg bd	Diarrhoea, nausea, abdominal pain, dyslipidaemia and insulin resistance (high potential)
Nelfinavir	750 mg tds OR 1.25g bd. Take with meals.	Diarrhoea, dyslipidaemia and insulin resistance (low potential)
Lopinavir / ritonavir	400 mg / 100 mg (3 capsules) bd	Diarrhoea, nausea, dyslipidaemia and insulin resistance (high potential)

Principles Of Antiretroviral Therapy (ART)

Getting Started

The HIV infected person's willingness to accept and adhere to a complex and costly regimen of drugs is essential before embarking on therapy. Without this commitment, there is little chance of success. It is recommended that therapy only be commenced after at least two consultations with extensive counselling. Including a patient-nominated "treatment buddy" in the counselling sessions is extremely helpful and assists patients in getting used to the idea of lifelong therapy.

Timing of when to commence ART is not a simple decision. Recently published international guidelines promote starting ART in later disease than was formerly the case. These changes were made because of increasing recognition of long term toxicity, that therapeutic options are limited and virological resistance is increasing. Furthermore, studies show that provided ART is started before the CD4 count is less than 200, outcome is excellent and immune reconstitution occurs in most cases. The new WHO and SA HIV Clinicians Society guidelines have moved away from using viral load as an indication to start therapy. A high viral load is associated with a more rapid decline in the CD4 count, and such patients should have their CD4 count monitored more frequently (e.g. 3 monthly). Because CD4 counts are variable, decisions to start ART purely on the basis of CD4 counts should ONLY be considered when the CD4 count has been repeated (after at least 6 weeks).

Guidelines for starting ART in adults:

The patient MUST be ready for treatment.

AND

The patient has a WHO stage 4 condition (except TB – see below).

OR

One CD4 count less than 350 AND a WHO stage 3 condition (except TB – see below).

OR

Stage 1 and 2 with two CD4 counts less than 350 done at least 6 weeks apart.

ART in the Patient with TB

- TB *per se* should not be used as an indication to start HAART (even if it is extrapulmonary TB, which is WHO stage 4) because TB occurs with a very wide spectrum of immune deficiency in countries with a high TB incidence.
- TB should always be managed by public sector TB Clinics.
- If the patient is already on ART the regimen should be changed, if possible, to be compatible with rifampicin (see interaction table on the next page).
- When ART is commenced in a patient on TB therapy, the patient's symptoms may temporarily worsen as part of immune reconstitution – the patient should be specifically warned about this.
- If the patient is not yet on ART, the timing of commencement of ART should be guided by the CD4 count as TB occurs at any stage of HIV in countries where TB is endemic:
  - CD4 >200 commence ART after completing tuberculosis therapy (providing the patient fulfils the criteria above – i.e. the CD4 count must be <350). The CD4 will usually rise when TB has been treated.

- CD4 50–200 delay ART until after the intensive phase of tuberculosis therapy (2 months). At this stage the number of anti-tuberculous drugs is reduced with less chance of shared toxicity and there is less risk of the immune reconstitution inflammatory syndrome (see below) developing. If the patient has other serious HIV-related illness ART should be introduced once the patient is stabilised on tuberculosis therapy.
- CD4 <50 ART should be introduced once the patient is stabilised on tuberculosis therapy (approximately 2 weeks).

The immune reconstitution inflammatory syndrome (IRIS) following commencement of HAART may cause a flare up of the tuberculosis, as well as other opportunistic infections. It commonly occurs when HAART is commenced within the first 2 months of anti-tuberculous therapy, and in patients with advanced disease. Return of TB symptoms and paradoxical enlargement of TB lesions (nodes, pulmonary infiltrates, effusions, tuberculomas etc.) are usual manifestations. Drug-resistance should be considered in all IRIS cases. The management of IRIS is uncertain – steroids may have a role in severe cases.

Rifampicin has significant drug interactions with the protease inhibitors and NNRTIs. When antiretroviral therapy is indicated it is preferable to use a regimen which does not interact significantly with rifampicin (see table below). If the patient is already on ART, therapy should be changed to allow rifampicin to be used.

ART Interactions with rifampicin

NRTIs	No significant interactions.
Efavirenz	Mild reduction in efavirenz levels, no dose adjustment necessary.
Nevirapine	Moderate reduction in nevirapine levels, dose increase to 300 mg BD should be considered. Limited experience – concern about shared hepatotoxicity. Therapeutic drug monitoring advised.
Ritonavir (full dose)	No significant interaction*.
Lopinavir/ritonavir (Kaletra®)	Additional ritonavir 300 mg bid OR Kaletra® double dose needs to be given to counteract the enzyme inducing effect of rifampicin. Therapeutic drug monitoring advised.
Ritonavir + saquinavir both 400 mg bid	No significant interaction*.
All other PIs	Marked reduction in PI levels – avoid.

* Elevation in liver enzymes and hepatitis has been described in healthy volunteers on rifampicin who are taking saquinavir 1000 mg bd with ritonavir 100 mg bd. The manufacturer has advised that this combination is not used with rifampicin. If using protease inhibitors with TB medicines, the ALT should be monitored. If using saquinavir and ritonavir monitor ALT at baseline, 2 weeks, 4 weeks and monthly whilst on TB medicines.

Shared side-effects of TB therapy and ART

Side effects	ART	Tuberculosis treatment
Nausea	didanosine, zidovudine, ritonavir, saquinavir	pyrazinamide
Hepatitis	nevirpine, efavirenz	rifampicin, isoniazid, pyrazinamide
Peripheral neuropathy	stavudine , didanosine	isoniazid
Rash	nevirapine, efavirenz	rifampicin, isoniazid, pyrazinamide

Selecting Drug Combinations

Antiretroviral drugs must always be combined in order to delay or prevent the emergence of HIV resistance. Monotherapy, for example with zidovudine, should only be used for prophylaxis. A number of different combinations have been shown to be effective in reducing the number of opportunistic infections and other HIV related conditions, and delaying the onset of AIDS. In order to achieve virological suppression it is essential to use combinations of potent drugs, typically "triple therapy" with two NRTIs and an NNRTI or boosted PI.

Dual NRTIs form the backbone of virtually all antiretroviral combinations.

Dual NRTI Combinations

Recommended combinations
Stavudine + lamivudine
Tenofovir* + lamivudine
Zidovudine + lamivudine
Tenofovir*+ emtricitabine*
Zidovudine + didanosine
Hazardous combinations
Stavudine + didanosine
Tenofovir* + didanosine
Antagonistic combinations
Stavudine + zidovudine

* These drugs are not registered at time of publication, but South African registration is imminent.

The recommended combinations are all effective, but do differ in terms of patient acceptability and cost. Hazardous combinations are best avoided because of increased risk of toxicity and, in the case of tenofovir and didansine, reduced efficacy. Selection should be individualized: patients with a history of ethanol abuse should not be given didanosine, for example, because of the risk of pancreatitis. Patients with unexplained severe anaemia or neutropaenia should avoid zidovudine. Abacavir use is restricted because of expense – it may be substituted in most combinations if toxicity occurs and no other options are available (discuss with AfA). Adverse reactions may occur with any of these drugs (see table on page 31).

If a patient has received previous antiretroviral therapy, it may be necessary to select a different combination depending on their adherence, response and the genetic barrier to resistance of the drugs. For example, a patient failing an initial regimen of stavudine, lamivudine and nevirapine is likely to have resistance to NNRTIs and lamivudine, thus zidovudine (which has cross-resistance with stavudine) can be combined with didanosine and a PI (as per the current South African public sector guidelines) – the reason why stavudine is not continued in this setting is that it is hazardous to combine it with didanosine.

The addition of a PI or NNRTI to the dual NRTI backbone ("triple therapy" or HAART) results in a highly potent combination, which should result in sustained suppression of viral replication in >80% of adherent patients. The preferred initial regimen is to add an NNRTI to the dual NRTIs because the protease inhibitors have significant long-term toxicity.

Two NRTIs plus a protease inhibitor are recommended if the NNRTI regimen fails or is not tolerated. Lopinavir/ritonavir is the most affordable protease inhibitor and has a very high barrier to resistance, therefore AfA recommends its use whenever a PI is required.

The use of two PIs with ritonavir boosting (e.g. saquinavir + lopinavir / ritonavir) is currently being evaluated for salvage therapy.

Patients who are unable to tolerate NRTIs (e.g. because of lactic acidosis) can use a combination of a NNRTI (efavirenz or nevirapine) with lopinavir and ritonavir. The dose of lopinavir and ritonavir should be increased to 4 capsules twice a day when used with a NNRTI. This combination is as effective as conventional HAART. If they have failed a NNRTI regimen before, then lopinavir / ritonavir alone should be tried, with the option of adding saquinavir or NRTIs with low potential risk of lactic acidosis if there is poor response. Expert advice is recommended in these situations.

Monitoring Therapy

CD4 & VL Monitoring

Regular monitoring of the CD4 count and viral load is critical to identify poor adherance to therapy or treatment failure early. The CD4 count should be performed every 4–6 months. The viral load should be done 6–8 weeks after commencing antiretroviral therapy and then every 4–6 months together with the CD4 count. The purpose of the early viral load test is to detect an adequate viral load response (more than 1 log reduction). These tests should not be done following vaccination or if an intercurrent infection is present, as this will transiently increase the viral load.

With HAART, at least a ten-fold (1 log) drop in the viral load can be expected within 8 weeks and the viral load should be undetectable after 16–24 weeks of therapy. The viral load is the most important test for monitoring response to therapy. Virological failure is defined as a rise of viral load by >1 log from the lowest point or a sustained increase to >5 000 copies/ml. These criteria should be used when deciding to change the first regimen. This is often not possible in patients who are on their second or third regimens as there are currently very limited treatment options. Patients failing a PI-containing regimen have been shown to continue benefiting clinically and immunolgically despite a high viral load. One explanation for this is that the viral mutations necessary for the development of resistance cripple the virus.

The CD4 count rises rapidly within 4 weeks on starting HAART and then more gradually. The average rise in CD4 is about 150 in the first year and about 80 per annum thereafter, but this is extremely variable. In some patients (about 10–20%) the CD4 count fails to rise despite a suppressed viral load – there is no point in changing their HAART regimens.

Clinical monitoring is also important, including general well-being and sustained weight gain. Changes to therapy should not be based only on laboratory results. However, it is important to note that an intercurrent clinical event should not be an indication for changing therapy if the viral load is suppressed. Furthermore, clinical deterioration and CD4 decline both occur after many months of virological failure as defined above. Thus, the main criterion for changing the initial HAART regimen is virological failure.

Managing Drug Toxicity

Haematological Toxicity

Patients on zidovudine, stavudine, or co-trimoxazole may experience abnormalities in their full blood counts. Macrocytosis (unrelated to vitamin B12 / folate deficiency) is seen with zidovudine and stavudine. Significant anaemia and neutropaenia (NOT thrombocytopaenia) are commonly seen with zidovudine and occasionally with stavudine, and may respond to reduced doses (zidovudine 200 mg BD and stavudine 30 or 20 mg BD depending on the weight). Regular monitoring (monthly for the first three months of therapy and thereafter three monthly) of FBC is essential for all patients on zidovudine.

Haematological toxicity with co-trimoxazole is more frequent with prolonged high doses used for treating opportunistic infections. This can result in pancytopaenia and may respond to folinic (not folic) acid and reduced dose. Neutropaenia may rarely occur with prophylactic doses of co-trimoxazole.

Before blaming drugs for haematological toxicity it is important to recognise that advanced HIV disease and many opportunistic diseases (especially TB) can be associated with cytopaenias.

Haemoglobin (Hb)	≥ 9.5 No action.	8–9.4 Repeat 4 weeks.	7–7.9 Repeat 4 weeks. Reduce dose.	6.5–6.9 Repeat 2 weeks. Reduce dose.	<6.5 Stop drug.
Neutrophils	≥ 1.5 No action.	1–1.5 Repeat 4 weeks.	0.75–1 Repeat 2 weeks.	0.5–0.75 Repeat 2 weeks. Reduce dose.	<0.5* Stop drug.
Platelets	≥ 100 000 No action.	75 000–100 000 Repeat 4 weeks.	50 000–75 000 Repeat 2 weeks.	20 000–50 000 Repeat 2 weeks. Reduce co-trimoxazole dose.	<20 000 Stop co-trimoxazole.

* If the neutrophil count is <0.5 the patient should be given ciprofloxacin 500 mg bd until the count rises.

Hepatotoxicity

All currently available antiretrovirals can cause hepatotoxicity. Furthermore, infection with hepatitis B or C is common in HIV-infected patients and flares of viral hepatitis may be induced by commencing ART (part of immune reconstitution) or on withdrawing certain antiretrovirals (e.g. lamivudine and tenofovir in patients with hepatitis B). Baseline liver function tests should be done before starting ART – if the baseline result is abnormal then hepatitis B and C should be excluded.

Nevirapine is most often associated with hepatotoxicity (subclinical increase in liver enzymes

15%, clinical hepatitis 2%). Patients starting nevirapine should have their ALT monitored regularly – after two weeks, four weeks and 2 months on nevirapine. Thereafter 3 monthly if no problems.

Many other drugs commonly used in HIV infected patients, notably anti-tuberculous therapy (including prophylactic isoniazid) may also cause hepatitis. NRTIs may result in steatohepatitis – this generally causes mild elevation of liver enzymes, affecting GGT and alkaline phosphatase more than the transaminases. Patients on indinavir may develop unconjugated hyperbilirubinaemia resembling Gilbert's Syndrome. This generally does not require treatment.

Transaminases	<2.5 × ULN Repeat 2 weeks.	2.5–5 × ULN Repeat 1 week.	5–10 × ULN Stop relevant drugs. Hepatitis screen.	>10 × ULN Stop all drugs. Hepatitis screen.
GGT / Alk Phos	<2.5 × ULN Repeat 4 weeks.	2.5–5 × ULN Repeat 2 weeks.	5–10 × ULN Ultrasound.	>10 × ULN Ultrasound.
Bilirubin	<2.5 × ULN Repeat 4 weeks.	2.5–5 × ULN Repeat 2 weeks. See text.	5–10 × ULN See text.	>10 × ULN See text.

ULN = upper limit of normal

NB: Hepatotoxic drugs should be discontinued at lower levels of LFT abnormalities if there are symptoms of hepatitis.

If a NNRTI is discontinued the NRTI backbone should be continued for a week to prevent NNRTI resistance from developing.

The most important drug reactions elevate the transaminases. In severe reactions request a viral hepatitis screen. Where other liver enzymes are involved (GGT or Alkaline Phosphatase) or if conjugated bilirubin is elevated, a liver ultrasound should be done to exclude biliary obstruction or hepatic infiltration. A very common cause of this picture is fatty liver due to NRTIs (especially stavudine).

Elevated Lactic Acid

Asymptomatic elevated lactate is common in patients on NRTIs (10–20% per annum) and is due to mitochondrial toxicity. Provided this is asymptomatic there is no reason to stop NRTIs. There is in fact no need to monitor lactate levels in asymptomatic patients as this does not predict the development of lactic acidosis. Symptomatic hyperlactataemia without acidosis occurs in 1–2% per annum. Lactic acidosis is rare (about 0.1% per annum) and presents as a life-threatening acute illness with acidosis. Lactic acidosis carries a poor prognosis (50% mortality). Obese women are at high risk of developing symptomatic hyperlactataemia.

The risk of lactate elevation is as follows:

stavudine = didanosine > zidovudine > lamivudine = abacavir = tenofovir

The combination of didanosine and stavudine seems the most likely to cause this condition. Lactic acidosis is a complication that may be observed in patients treated with all of the currently available nucleoside reverse transcriptase inhibitors.

Early recognition is the most important safeguard: If NRTI therapy is discontinued after early detection, symptoms resolve in most cases. Symptomatic hyperlactataemia is often seen in patients doing well on ART – they often have some other evidence of toxicity thought to be mediated by mitochondrial toxicity (especially peripheral neuropathy).

Signs and symptoms of hyperlactataemia are non-specific and may include:

- Nausea and vomiting (especially new onset)
- Malaise
- Liver dysfunction (due to steatosis)
- Lethargy
- Abdominal pain
- Weight loss
- Hyperventilation
- Tachycardia

More severe features may be seen in patients with lactic acidosis:

- Cyanosis
- Decreased level of consciousness
- Hypotension

Other causes of lactic acidosis should be considered (e.g. severe sepsis). In unclear cases an important clue that the cause is NRTI-induced is that the lactate persists for weeks, whilst with other causes it resolves rapidly when the underlying condition is treated.

Laboratory Diagnosis

Plasma lactate level needs to be taken without a tourniquet in a fluoride tube, sent to the laboratory on ice and processed immediately. The normal level is <2 mmol/l. Levels of 2–5 are mild, 5–10 moderate and >10 severe with high mortality.

Lactic acidosis is diagnosed when lactate levels >5 are associated with acidosis (characterized by low pH, low bicarbonate and increased anion gap).

Tests to look for other causes or triggers of acidosis should be sought (see under treatment below).

Treatment of Symptomatic Hyperlactataemia/Lactic Acidosis

Early intervention with discontinuation of all ART is essential in lactic acidosis and severe hyperlactataemia. Lactate levels resolve slowly over weeks. It is essential to establish whether lactic acidosis is present (see above), as this needs intensive care admission and a careful search for other causes or triggers of lactic acidosis (e.g. sepsis, myocardial infarction, pancreatitis – but note that pancreatitis can also co-exist with NRTI-induced hyperlactataemia).

- Maintenance of airway patency
- Delivery of oxygen
- Monitoring cardiac rhythm
- Respiratory and / or haemodynamic support to improve tissue perfusion
- Most clinicians would empirically add a broad spectrum antibiotic, e.g. third generation cephalosporin, pending cultures as sepsis is a common cause of lactic acidosis

Unfortunately there is no evidence to support any particular therapy in lactic acidosis, but good supportive care in an intensive care unit should be instituted:
Bicarbonate replacement is controversial. High dose vitamin B complex (riboflavin and thiamine are thought to be important) may have a role in therapy.

Following recovery from symptomatic hyperlactataemia reintroduction of ART with NRTIs does carry some risk. After symptomatic hyperlactataemia NRTIs that are less associated with hyperlactaemia could be used with regular lactate monitoring. In confirmed cases of lactic acidosis NRTIs should be stopped and not used again. Specialist advice (available from AfA) should be sought in all cases.

Hyperlipidaemia

Fasting lipids (total cholesterol and triglycerides) should be done at baseline in all patients starting protease inhibitors. This should be repeated in 3–6 months and then annually thereafter. Lifestyle modification should be advised for all elevations (stop smoking, lose weight if relevant, increase exercise, reduce cholesterol and saturated fat intake).

Levels which may require additional therapy:
Triglycerides >10 mmol/l or total cholesterol > or equal 7.5 mmol/l (after diet) provided there are no significant IHD risk factors.

Fibrates are the drugs of choice as they are more potent for elevation in triglycerides (which is the commonest PI-induced dyslipidaemia) and are not associated with drug interactions. There are marked drug interactions with most of the statins, which should be avoided EXCEPT for low dose atorvastatin (5–10 mg) or pravastatin.

Lipodystrophy

Lipodystrophy may result from long-term use of the protease inhibitors, usually in combination with the NRTIs (especially stavudine). Changes include lipohypertrophy (e.g. buffalo hump, breast enlargement, accumulation of abdominal fat, peripheral lipomata) and lipoatrophy (e.g. thin extremities, loss of facial fat). Lipoatrophy is particularly associated with stavudine. Metabolic disorders (increased glucose and increased lipids) may be associated. Some reversal is possible on switching to antiretroviral therapy that is less associated with this problem, but resolution is seldom complete and is very slow. Furthermore, patients on PIs have generally failed NNRTIs, so a switch is not really possible. Diet and aerobic exercises help for visceral fat accumulation. In extreme cases surgery may be necessary (e.g. for buffalo humps and lipomata).

Protease Inhibitor Induced Diarrhoea

Diarrhoea is a common presentation in patients with HIV. It impacts significantly on quality of life, and can lead to malnutrition, loss of weight, associated immunosuppression, and susceptibility to opportunistic infections. It may diminish absorption of medications, and adversely affect adherence to antiretroviral agents. Diarrhoea is associated with a multitude of aetiologies and is a common adverse effect of the protease inhibitor class of antiretrovirals.
PI induced diarrhoea is more common in patients with lower CD4 counts, and in those treated with nelfinavir > ritonavir (also a component of the combination PI Kaletra®) > saquinavir > indinavir. The following treatments of PI induced diarrhoea have shown benefit in clinical trials: bulk forming agents (oat bran, psyllium husk), calcium carbonate, and antimotility agents such as loperamide. Often, combinations of the agents are used to control symptoms.

Compliance/Adherence

If the individual drugs of an antiretroviral regimen are not taken correctly or omitted, there is a considerable risk of selection for resistant HIV strains. Adherence of 95% or more has been shown to be associated with the best virological response, with a progressive reduction in response for adherence below this level. Adherence also predicts survival – 80% adherence or greater is associated with the lowest death rates. It is crucial, therefore, that time is spent on carefully explaining the need to take the drugs correctly and how to deal with possible adverse effects. It is difficult to predict who is likely to be compliant. Factors which are associated with poor adherence include:

- untreated depression
- active substance abuse
- lack of insight
- failure to disclose HIV status
- adolescents and young adults

It is critical that adherence to therapy is assessed before drug combinations are changed because of suspected viral resistance.

The doctor should ensure that the patient is ready and prepared to commit to life-long therapy and spend time explaining what is required and the need to take therapy exactly as prescribed. There should be no rush to initiate therapy in the vast majority of patients.

Methods to assist with maintaining adherence:

- Negotiate a plan with the patient to ensure commitment to a regimen.
- Take time – never rush into beginning a HAART regimen.
- Depression is common in HIV/AIDS – always exclude this before therapy or if adherence is poor.
- Recruit "treatment buddies" to support the patient if possible.
- Pay attention to "minor" side effects, particularly involving the GIT.
- Use memory aids such as diaries, pill-boxes etc.
- Provide information to assist the patient in fully understanding their drug regimen, and in taking their medications adequately.
- Plan ahead for medication refills, financial assistance etc.
- Avoid recreational drug and alcohol abuse.
- Regularly monitor HAART adherence at each clinical visit (the most pragmatic measure of adherence is whether patients have collected their medication on time).
- Reassure and consider treating "minor", transient side effects – especially nausea, diarrhoea, hypersensitivity reactions and neuropsychiatric side effects.
- Plan regimens to avoid food restrictions where possible.
- Attempt to avoid regimens which require large pill burdens (the number of pills is associated with poor adherence – try to minimise non-ART medication).

Viral Resistance and Changing Therapy

Resistance should be suspected if the viral load starts increasing in a patient who is adhering to ART. Ensure that the viral load was not done after vaccination or an acute infection. Minor transient increases in viral load (less than 1000 copies/ml), "viral blips", are not indications to change therapy. A high viral load should be confirmed with a second reading within 3 months where possible.

Failure of therapy may be defined as follows:

- A sustained increase in viral load >5 000 copies/ml.
- A decline in viral load of less than 1 log within 6 – 8 weeks after commencing antiretroviral therapy.
- A rise of viral load by >0.5 log (3 fold) from the lowest point.

If treatment failure has occurred, then a completely new combination should be selected. This may be difficult if the patient has been exposed to multiple agents, particularly since there is often cross-resistance within classes of antiretrovirals. For example, if a patient fails therapy with 2 NRTIs and a NNRTI, one could change to two different NRTIs and a PI. Ideally, changing therapy should include 3 or at least 2 "clean" drugs (never used before or unlikely to be cross-resistant).

Resistance testing by genotyping is now available in South Africa – the genes encoding for reverse transcriptase and protease are sequenced to see if known resistance mutations are present. Resistance testing MUST BE DONE WHILST THE PATIENT IS ON THERAPY as the wild type (sensitive) virus rapidly overgrows resistant mutants. It is an extremely expensive test and requires pre-authorisation from AfA.

NB:

- Sometimes the test shows no resistant mutations and the reason for failing is that the patient is not taking their medication – it is essential to ensure adherence before doing the test.
- Resistance to drugs which were previously used will often not be detected (the resistant mutations are archived and will re-appear on exposure to the old drug).
- The patient must be taking ART when the test is done.
- Genotyping can not be done if the viral load is less than 1000 copies/ml.

Even when there appears to be viral resistance it is worthwhile continuing with therapy if there are no treatment options whilst awaiting new drugs – studies have clearly shown that continuing therapy confers significant clinical benefit. This is due to reduced viral fitness as a result of the mutations required to develop resistance.

Refer to section on Monitoring Therapy for more information on virological failure. If intolerance occurs to a drug, then only the offending drug needs to be stopped and a new one added unless the viral load is increasing. For example, stavudine may be used in place of zidovudine if the patient develops neutropaenia.

Please Note

ALL resistance profile assessments may be referred to the AfA clinical committee for opinion. Making decisions on future regimens involves clinical and financial decisions, and our clinical team can assist with such decisions.

Interrupting Therapy

Therapy with antiretroviral drugs should not be interrupted except in exceptional circumstances (e.g. severe toxicity), or if HAART was only prescribed to prevent mother to child transmission. Interruptions have been shown to increase the risk of resistance and even death (in trials of repeated structured treatment interruptions). If HAART has to be interrupted and the combination includes a drug with a long half-life e.g. nevirapine or efavirenz, this should be stopped a week earlier to reduce the risk of resistance developing.

Interactions with Antiretroviral Drugs

Patients receiving antiretroviral therapy frequently take other medication, which may be chronic, acute or over the counter. There are numerous potential drug interactions with antiretroviral therapy. Interactions could be on the basis of shared side effects, impaired absorption or altered metabolism.

In general, the nucleoside reverse transcriptase inhibitors do not interact with the pharmacokinetics of other drugs with the exception of the old buffered formulation of didanosine, which has an antacid that may interfere with absorption of other drugs (the enteric coated formulation is free of interactions). Most relevant interactions are with protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

The basis of these drug interactions is interference with hepatic metabolism. PIs and NNRTIs are metabolised by the liver and other drugs that induce and/or inhibit hepatic enzymes which affect the levels of PIs or NNRTIs. Both PIs and NNRTIs in turn induce and/or inhibit hepatic enzymes, which leads to potentially adverse reactions with many other drugs. Enzyme induction may lead to sub-optimal drug levels – when this involves antiretroviral drugs this could lead to the development of HIV resistance. Enzyme inhibition leads to elevation of drug levels, potentially causing toxicity.

The accompanying tables list drugs interacting with either the PIs or NNRTIs. The list is not comprehensive. When the drug interaction leads to marked alteration of drug levels, co-administration should be avoided – this is indicated in the table. In other instances a dose adjustment of the interacting drug MAY be necessary. If the patient is clinically stable on the co-administered medication with no evidence of toxicity, then a dose adjustment may not be necessary. Drug levels (e.g. theophylline) or effect (e.g. prothrombin time with warfarin) should be checked where this is possible.

Further information on drug interactions can be obtained from the package inserts, the South African Medicines Formulary, by contacting an AfA pharmacist or from the following website: www.hiv-druginteractions.org/

Alternatives listed in the table are drugs from a similar class that do not have significant drug-drug interactions.

PIs without ritonavir boosting generally have less marked effect of increasing levels of interacting drugs, but there is a greater chance that interacting drugs that are enzyme inducers can lower PI levels.

Alternatives	Comment	Efavirenz	Nevirapine	INTERACTING DRUG (ID)	Ritonavir boosted PI*	Comment	Alternatives
lorazepam, oxazepam, temazepam	Not recommended - use alternative	↓ level ID	↓ level ID	**Alprazolam**	↑level ID	Not recommended - use alternative	lorazepam, oxazepam, temazepam
	May need dose increase	↓ level ID	↓ level ID	**Amiodarone**	↑↑level ID	AVOID – ID levels toxic	
				Amitriptyline	↑level ID	Consider reduced dose of ID	
	All calcium channel blockers affected. May result in poor response	?↑level ID	↓ level ID	**Amlodipine**	↑level ID	All calcium channel blockers affected. Consider reduced dose of ID	
	Uncertain significance. Monitor closely for efficacy	?↓ level ID	?↓ level ID	**Artemether-lumefantrine**	↑level ID	Lumefantrine levels predicted to increase - discontinue PI until malaria cured and monitor for cardiac toxicity	
				Atenolol	↑level ID	Consider reduced dose of ID	
fibrates, fluvastatin, pravastatin, rosuvastatin		↓ level ID	↓ level ID	**Atorvastatin**	↑level ID	Use low dose of ID (5 to 10 mg). Monitor for myopathy	fibrates, fluvastatin, pravastatin, rosuvastatin
				Atovaquone	? ↓ level ID	Probably not significant	
				Azithromycin	↑level ID	Uncertain significance	
				Bisoprolol	↑level ID	Consider reduced dose of ID	
	Consider reduced dose of ID with efavirenz	↑level ID	↓ level ID	**Bupropion**	↑level ID	Consider reduced dose ID	
valproate, levetiracetam, gabapentin, topiramate, lamotrigine	Not recommended (unless levels of NNRTIs and carbamazepine measured)	↓ level ID & ↓ level NNRTI	↓ level ID & ↓ level NNRTI	**Carbamazepine**	↑↑level ID & decr level PI	Not recommended (unless levels of PI and carbamazepine measured)	valproate, levetiracetam, gabapentin, topiramate, lamotrigine

Alternatives	Comment	Efavirenz	Nevirapine	INTERACTING DRUG (ID)	Ritonavir boosted PI*	Comment	Alternatives
				Carvedilol	↑level ID	Uncertain significance	
				Chloroquine	↑level ID	Probably not significant	
				Chlorpromazine	↑level ID	Consider reduced dose of ID	
metoclopramide		AVOID	↓ level ID	**Cisapride**	↑↑level ID	AVOID – ID levels toxic	metoclopramide
	Uncertain significance	?↓ level ID	↓ level ID	**Citalopram**	↑level ID	Avoid high doses of ID	
azithromycin	Use azithromycin for MAC	↓ level ID	↓ level ID	**Clarithromycin**	↑level ID	Reduce dose of ID only if renal impairment	azithromycin
				Clindamycin	↑level ID	Uncertain significance	
lorazepam, oxazepam, temazepam	Consider increased dose of ID	?↓ level ID	↓ level ID	**Clonazepam**	↑level ID	Reduce dose of ID	lorazepam, oxazepam, temazepam
				Clozapine	↑level ID	Use low doses of ID	
		?↓ level ID	NA	**Cyclophosphamide**	↑level ID	Reduce dose of ID	
	Monitor levels of ID	↓ level ID	↓ level ID	**Cyclosporin**	↑level ID	Reduce dose of ID Monitor level of ID	
	Increased dose ID may be necessary	↓ level ID	↓ level ID	**Dexamethasone**	↑level ID	Reduce dose of ID	
				Dextropropoxyphene	↑level ID	Reduce dose of ID	
lorazepam, oxazepam, temazepam	Not recommended - use alternative	?↑or↓ level ID	↓ level ID	**Diazepam**	↑↑level ID	AVOID – ID levels toxic	lorazepam, oxazepam, temazepam
				Digoxin	↑level ID	Monitor level of ID	
sumatriptan	AVOID – ID levels toxic	↑↑level ID	?AVOID	**Dihydroergotamine**	↑↑level ID	AVOID – ID levels toxic	sumatriptan
	All calcium channel blockers affected	? ↑level ID	↓ level ID	**Diltiazem**	↑level ID	All calcium channel blockers affected. Consider reduced dose of ID	
	Consider switch to nevirapine	↑level ID	NA	**Disopyramide**	↑level ID	Reduce dose of ID	

Alternatives	Comment	Efavirenz	Nevirapine	INTERACTING DRUG (ID)	Ritonavir boosted PI*	Comment	Alternatives
	Consider increased dose of ID	?↓ level ID	↓ level ID	**Docetaxel**	↑level ID	Consider reduced dose of ID	
				Ergometrine	↑↑level ID	AVOID – ID levels toxic	
sumatriptan	AVOID – ID levels toxic	↑↑ level ID	?AVOID	**Ergotamine**	↑↑level ID	AVOID – ID levels toxic	sumatriptan
				Erythromycin	↑level ID	Reduce dose of ID	
	Use additional contraceptive method. Avoid low dose oestrogen OC with nevirapine	↑level ID	↓ level ID	**Ethinyloestradiol**	↓ level ID	Use additional contraceptive method. Avoid low dose oestrogen OC	
valproate, levetiracetam, gabapentin, topiramate, lamotrigine		?↓ level ID	↓ level ID	**Ethosuximide**	↑level ID	Reduce dose of ID	valproate, levetiracetam, gabapentin, topiramate, lamotrigine
				Fentanyl	↑level ID	Reduce dose of ID	
	Consider switch to nevirapine	↑level ID	NA	**Flecainide**	↑↑level ID	AVOID – ID levels toxic	
	Monitor liver function. Consider switch to efavirenz	NA	? Incr level nevirapine	**Fluconazole**	NA		
				Fluoxetine	↑level ID	Reduce dose of ID	
lorazepam, oxazepam, temazepam		?↓ level ID	↓ level ID	**Flurazepam**	↑↑level ID	AVOID – ID levels toxic	lorazepam, oxazepam, temazepam
				Fluticasone	↑↑level ID	AVOID - Cushing's syndrome reported	beclomethasone, budesonide less likely to cause systemic effects
fibrates, pravastatin	Monitor for myopathy with efavirenz or use alternative	↑level ID	↓ level ID	**Fluvastatin**	?↑ level ID	Reduce dose of ID	fibrates, pravastatin

Alternatives	Comment	Efavirenz	Nevirapine	INTERACTING DRUG (ID)	Ritonavir boosted PI*	Comment	Alternatives
metformin		?↓ level ID	↓ level ID	**Glipizide**	↑level ID	Consider reduced dose of ID	metformin
				Haloperidol	↑level ID	Reduce dose of ID	
fluconazole	Consider increased dose of ID or use alternative	↓ level ID	↓ level ID	**Itraconazole**	↑level ID	Reduce dose of ID or use alternative	fluconazole
fluconazole	AVOID with nevirapine	?↓ level ID	↓↓ level ID & ↑level NNRTI	**Ketoconazole**	↑level ID & ↑level PI	Reduce dose of ID	fluconazole
				Lamotrigine	↓ level ID	Consider increased dose of ID.	valproate, levetiracetam, gabapentin, topiramate
	Uncertain significance	?↓ level ID	↓ level ID	**Lansoprazole**	? ↑level ID	Uncertain significance	
	Consider reduced dose ID	↑level ID	NA	**Lignocaine**	↑level ID	Consider reduced dose of ID	
				Loperamide	↑level ID	Reduce dose of ID	
cetirizine		?↓ level ID	NA	**Loratidine**	↑level ID	Reduce dose of ID	cetirizine
fibrates, fluvastatin, pravastatin, rosuvastatin		?↑↑level ID	↓ level ID	**Lovastatin**	↑↑level ID	AVOID – ID levels toxic.	fibrates, fluvastatin, pravastatin, rosuvastatin
	Consider increased dose of ID	↓ level ID	↓ level ID	**Methadone**	↓ level ID	Consider increased dose of ID	
				Metoprolol	↑level ID	Uncertain significance	
				Metronidazole	Possible disulfiram reaction	Ritonavir formulations contain alcohol	
	Consider switch to nevirapine	↑level ID	NA	**Mexiletine**	↑level ID	Reduce dose of ID	

Alternatives	Comment	Efavirenz	Nevirapine	INTERACTING DRUG (ID)	Ritonavir boosted PI*	Comment	Alternatives
lorazepam, oxazepam, temazepam	AVOID with efavirenz	↑level ID	↓ level ID	**Midazolam**	↑↑level ID	AVOID – ID levels toxic	lorazepam, oxazepam, temazepam
amitriptyline, fluoxetine		?↓ level ID	↓ level ID	**Mirtazepine**	↑level ID	Consider reduced dose of ID	amitriptyline, fluoxetine (avoid high doses with PI)
				Morphine	↓ level ID	Consider increased dose of ID	
	All calcium channel blockers affected	? ↑level ID	↓ level ID	**Nifedipine**	↑level ID	All calcium channel blockers affected. Consider reduced dose of ID	
				Nortriptyline	↑level ID	Consider reduced dose of ID	amitriptyline, fluoxetine (avoid high doses with PI)
	Consider increased dose of ID	?↓ level ID	↓ level ID	**Olanzepine**	↓ level ID	Consider increased dose of ID	
	Consider increased dose of ID	?↓ level ID	↓ level ID	**Paclitaxel**	↑level ID	Consider reduced dose of ID	
				Paroxetine	↑level ID	Reduce dose of ID	
				Perphenazine	↑level ID	Consider reduced dose of ID	
				Pethidine	↑↑level ID	AVOID – ID levels toxic	morphine (may need increased dose), tramadol (may need decreased dose)
valproate, levetiracetam, gabapentin, topiramate, lamotrigine	Not recommended (unless levels of NNRTI and phenobarbitone measured)	?↓ level ID & ?↓ level NNRTI	↓ level ID & ↓ level NNRTI	**Phenobarbitone**	↑level ID	Not recommended (unless levels of PI and phenobarbitone measured)	valproate, levetiracetam, gabapentin, topiramate, lamotrigine

Alternatives	Comment	Efavirenz	Nevirapine	INTERACTING DRUG (ID)	Ritonavir boosted PI*	Comment	Alternatives
	NNRTI levels appear to be adequate - levels should be monitored	↓ level NNRTI	↓ level NNRTI	**Rifampicin**	↓ level PI	Can overcome this by increasing ritonavir boosting dose to 400 mg bd	
				Risperidone	↑level ID	Reduce dose of ID	
metformin	Consider switch to efavirenz or use alternative	NA	↓ level NNRTI	**Rosiglitazone**	NA		
amitriptyline, fluoxetine		?↓ level ID	↓ level ID	**Sertraline**	↑level ID	Reduce dose of ID	
		?↓ level ID	↓ level ID	**Sildenafil**	↑level ID	Reduce dose of ID to 25mg per 48 hours	
fibrates, fluvastatin, pravastatin, rosuvastatin		?↑ level ID	↓ level ID	**Simvastatin**	↑↑level ID	AVOID – ID levels toxic	fibrates, fluvastatin, pravastatin, rosuvastatin
	Monitor level of ID	?↓ level ID	↓ level ID	**Sirolimus**	↑level ID	Reduce dose of ID Monitor level of ID	
		?↓ level ID	↓ level ID	**Stanazol**	↑level ID	Consider reduced dose of ID	
	Monitor levels	?↓ level ID	↓ level ID	**Tacrolimus**	↑level ID	Reduce dose of ID Monitor level of ID	
		?↓ level ID	↓ level ID	**Tadalafil**	↑level ID	Reduce dose of ID, maximum 10 mg per 72 hours	
cetirizine	AVOID with efavirenz	↑↑level ID	↓ level ID	**Terfenadine**	↑↑level ID	AVOID – ID levels toxic	cetirizine
		?↓ level ID	↓ level ID	**Testosterone**	↑level ID	Consider reduced dose of ID. Monitor level of ID	
				Theophylline	↓ level ID	Monitor level of ID	
		?↓ level ID	NA	**Tramadol**	↑level ID	Consider reduced dose of ID	

Alternatives	Comment	Efavirenz	Nevirapine	INTERACTING DRUG (ID)	Ritonavir boosted PI*	Comment	Alternatives
lorazepam, oxazepam, temazepam	AVOID with efavirenz	↑↑level ID	↓ level ID	**Triazolam**	↑↑level ID	AVOID – ID levels toxic	lorazepam, oxazepam, temazepam
		?↓ level ID	↓ level ID	**Vardenafil**	↑↑level ID	AVOID – ID levels toxic	
	All calcium channel blockers affected	? ↑level ID	↓ level ID	**Verapamil**	↑level ID	All calcium channel blockers affected. Consider reduced dose of ID	
	Consider increased dose of ID	?↓ level ID	↓ level ID	**Vinblastine**	↑level ID	Consider reduced dose of ID	
	Consider increased dose of ID	?↓ level ID	↓ level ID	**Vincristine**	↑level ID	Consider reduced dose of ID	
fluconazole	AVOID with efavirenz	↓ level ID and increased level NNRTI	↓ level ID	**Voriconazole**	↓ level ID	AVOID ID levels subtheapeutic	fluconazole
	Monitor INR closely	↑level ID	↓ level ID	**Warfarin**	↓ level ID	Consider increased dose of ID. Monitor INR closely	
lorazepam, oxazepam, temazepam		?↑or↓ level ID	↓ level ID	**Zolpidem**	↑level ID	Reduce dose of ID	lorazepam, oxazepam, temazepam

Drug Dosages in Renal Failure

For peritoneal dialysis the dose given under creatinine clearance <10 should be given daily. For haemodialysis the dose given under creatinine clearance <10 should be given daily, but must be given after dialysis on dialysis days as some of the drug will be dialysed out.

Formula to estimate creatinine clearance:

$$\frac{(140 - \text{age}) \times \text{ideal weight(kg)}}{0.82 \times \text{serum creatinine } (\mu\text{mol/L})}$$

Good estimate for men, for women multiply total by 0.85

Drug	Creat. clearance 10–50	Creat. clearance <10
Zidovudine	unchanged	300 mg daily
Didanosine	>60 kg 200 mg daily <60 kg 150 mg daily	>60 kg 100 mg daily <60 kg 75mg daily
Lamivudine	150 mg daily	50 mg daily
Stavudine	>60 kg 20 mg 12 hourly <60 kg 15mg 12 hourly	>60 kg 20 mg daily <60 kg 15mg daily
Abacavir	unchanged	unchanged
Tenofovir	AVOID	AVOID
PIs	unchanged	unchanged
Nevirapine	unchanged	unchanged
Efavirenz	unchanged	unchanged
Co-trimoxazole	480 mg daily	480 mg three times a week
Fluconazole	half dose	quarter dose

Sources: Bartlett JG. Medical care of patients with HIV Infection 2003.
The Sanford guide to antimicrobial therapy 2003.

ART Dosages in Liver Impairment

Drug	Prescribing with liver impairment
NRTIs	
Abacavir	Reduce adult dose to 200 mg bd for mild to moderate liver impairment. Contraindicated in severe hepatic impairment.
Didanosine	Use with caution. Recent reports implicate didanosine use as a risk factor for the development of hepatic decompensation in patients being treated for cirrhosis due to hepatitis C. Avoid co-administration of didanosine with stavudine in patients with liver disease in view of the likely increased risk of lactic acidosis.
Lamivudine	Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HIV and have discontinued lamivudine*.
Stavudine	No adjustment of dose is necessary. Avoid co-administration of didanosine with stavudine in patients with liver disease in view of the likely increased risk of lactic acidosis.
Tenofovir	No dosage adjustment necessary. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HIV and have discontinued tenofovir*.
Zidovudine	Decrease dose to 200 mg bd.
NNRTIs	
Efavirenz	Caution should be exercised in administering efavirenz to patients with liver disease.
Nevirapine	Contraindicated in severe hepatic impairment, accumulation may occur with moderate hepatic impairment but no specific recommendations on dose reductions can be made due to limited data.
PIs	
Indinavir	Reduce adult dose to 600 mg 8 hourly in mild to moderate hepatic impairment.
Lopinavir/ ritonavir	Lopinavir is highly metabolized in the liver and concentrations may be increased in patients with hepatic impairment. Pharmacokinetic studies have not been done, but reduced adult dose to 2 capsules bd should be considered in severe liver disease.
Nelfinavir	Dose reduction advised – limited data suggests doses of 500 mg bd to 750 mg bd.
Ritonavir	No adjustment for mild hepatic impairment or moderate impairment (monitor closely). No data on severe impairment.
Saquinavir	There have been reports of worsening liver disease and development of portal hypertension after starting saquinavir in patients with severe liver disease and the use of saquinavir should be avoided.

Patients co-infected with hepatitis B should preferably be treated with the dual NRTI backbone of tenofovir plus lamivudine (or the similar NRTI emtricitabine). This dual NRTI therapy should not be discontinued even if HIV resistance develops. (May cause flare-up of hepatitis B.)

HAART and Porphyria

There is very limited information on the safety of antiretrovirals in patients with acute porphyria. It is likely that nucleoside reverse transcriptase inhibitors will be safe. The protease inhibitors are thought to be unsafe, with one report of an attack induced by indinavir. There is no data on non-nucleoside reverse transcriptase inhibitors. Close monitoring of patients with acute porphyria needing HAART is advised – contact the porphyria service at the University of Cape Town for advice: +27 (0)21 406 6332.

Guidelines on Artificial Ventilation, ICU Care and Withdrawal of Therapy in HIV Infected Patients

- Criteria for withholding or discontinuing ventilation in HIV infected individuals should be the same as those for individuals without HIV. The doctor treating the patient must ultimately make these decisions.
- Patients who require ventilation for conditions which are not directly related to HIV have a similar outcome to patients without HIV.
- The commonest HIV related indication for ventilation is pneumonia, either due to conventional bacteria or *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*). Both have similar in-hospital mortality to patients without HIV who require ventilation for community-acquired pneumonia.
- Highly active antiretroviral therapy (HAART) has dramatically improved the outcome of patients with advanced HIV disease. All patients registered with AfA have access to HAART. Thus, provided there is a reasonable prospect of surviving intensive care unit admission, patients should receive artificial ventilation. The exception is patients who have documented failure of all available HAART regimens – this should be discussed with AfA in each case.
- HAART takes weeks to months to achieve clinical benefit, so introducing HAART in a newly-diagnosed HIV infected patient on a ventilator is unlikely to affect their outcome. It may in fact worsen outcome due to the early paradoxical deterioration seen in the first few weeks of starting ART in patients with advanced HIV.
- Nearly all of the HIV related conditions are either treatable or will regress on HAART. However, if a progressive condition has failed to respond to a reasonable trial of HAART or specific therapy then ventilation would be futile. Examples of conditions that fall into this category are visceral Kaposi's sarcoma, lymphoma and progressive multifocal leukoencephalopathy.
- Under the following circumstances, it would be reasonable to consider withdrawing active therapy, apart from supportive / nursing care:
  - If the patient requests it.
  - If the patient has an untreatable AIDS condition.
  - If there has been no response to an adequate trial of HAART.
  - If the patient has a poor quality of life.

The views of the patient, involved healthcare professionals and relatives should always be taken into account.

NB: The use of laboratory tests e.g. $CD4$ count or viral load to determine when to stop therapy is not acceptable as benefit can still be gained from HAART even in patients with advanced disease.

Pregnancy and Mother-to-Child Transmission Prophylaxis

Pregnant women who are HIV positive may be offered termination of pregnancy, depending on local legislation in this regard. Those who wish to continue with the pregnancy should receive comprehensive counselling. Counselling includes information on options to dramatically reduce the risk of mother to child transmission through antiretroviral strategies and improved prognosis in adults.

HIV can be transmitted to the infant in utero, perinatally (the commonest mode of transmission) or by breastfeeding. Without intervention the risk of transmission is 20–40%. The risk is halved with the use of zidovudine or single dose nevirapine monotherapy. Additional benefit is obtained by not breastfeeding and by offering elective Caesarean section (this does not provide additional benefit if the viral load is very low). With a combined approach using HAART, rates of transmission of approximately 1% are achievable. Transmission is particularly unlikely if the maternal viral load is undetectable at delivery.

Pregnant women who require treatment with antiretroviral therapy (see guidelines for initiating therapy) should be initiated on HAART, although drugs should be avoided in the first trimester if at all possible. Zidovudine should be used as a component of HAART in pregnancy as there is most experience with this drug. Protease inhibitors or nevirapine (liver function must be carefully monitored on nevirapine) can be used in pregnancy. Lopinavir/ritonavir and nelfinavir appear to be well tolerated and safe in pregnancy, although the blood glucose should be carefully monitored.

Women who become pregnant while taking antiretrovirals, should generally continue with their drug regimen provided this has been shown to be effective. Zidovudine should be substituted for stavudine as discussed above. An exception is efavirenz as it has been shown to be teratogenic – termination of pregnancy should then be offered. (Note: women of childbearing age and on efavirenz should be on adequate contraception and counselled to avoid pregnancy.) While efavirenz is contraindicated in pregnancy it may be considered in late pregnancy if no alternatives exist. Fatal lactic acidosis has been reported in pregnant women treated with the combination of stavudine and didanosine, which should therefore be avoided.

CD4 counts are about 25 percent lower in pregnancy, falling to a nadir at the end of the first trimester. The CD4 percentage remains unchanged. The CD4 count rises to pre-pregnant levels 3 months after delivery. If the count is less than 200, daily co-trimoxazole should be given as primary prophylaxis.

Elective Caesarean section before the onset of labour reduces the risk of transmission substantially and should be offered. If the viral load is <1000 copies/mL, Caesarean section does not appear to add further benefit.

The following MTCT prophylaxis regimens are recommended for women who **do not** need long term HAART:

1. HAART commencing in the second trimester. This is the most effective form of mother-to-child transmission prophylaxis. Zidovudine, lamivudine and lopinavir/ritonavir or nelfinavir is recommended. Nevirapine is associated with a higher risk of hepatitis and rash in women with a CD4 count >250, so it should generally be avoided in this setting.
2. Monotherapy with zidovudine during the last 12 weeks of pregnancy is an option for women with detectable virus but levels below 1000 copies/ml, but this may not be as effective as short course HAART.

3. Women who present late (in labour) should be given nevirapine 200 mg stat together with zidovudine and lamivudine for 7 days to prevent nevirapine resistance. The baby should be given a stat dose of nevirapine (2mg per kg) as soon as possible after birth.

The use of dual nucleoside therapy only (e.g. zidovudine and lamivudine) as MTCT prophylaxis is discouraged because of the risk of developing lamivudine resistance.

In all cases infants should receive zidovudine suspension for 6 weeks (4mg/kg/dose bd starting 8–12 hours after birth). Full blood counts should be done at 2 to 3 weeks to exclude anaemia or neutropaenia. If there is evidence of zidovudine resistance, alternative regimens should be considered for the infant — please contact the AfA programme.

Breastfeeding increases the risk of transmission and should be discouraged. AfA will authorize payment for milk supplements. Formula feeds will be authorized for six months (2kg a month). Women who elect to breastfeed should be counselled to exclusively breastfeed without addition of water, formula milk, juices, cereals or solids. Breastfeeding should be limited to 4 to 6 months and weaning should be abrupt.

A qualitative HIV PCR should be performed on the infant at 4–6 weeks to determine if infection has occurred. The HIV ELISA may be positive for up to 15 months because of maternal antibodies. Genotyping may be appropriate in infants who become HIV infected despite PMTCT in order to assist with selection of antiretroviral therapy.

After delivery, women who commenced HAART with CD4 counts above 350 should discontinue antiretrovirals, with counselling, in order to limit toxicity and preserve future options. HAART can be recommenced when criteria for initiating therapy are fulfilled.

Emergency Post-Exposure Prophylaxis (e.g. needle-stick injury, rape)

Prophylaxis is indicated after exposure to HIV infected body fluids (e.g. rape or needle-stick injury) and should commence as soon as possible. It is unclear whether delayed initiation of post-exposure prophylaxis is of benefit – animal models suggest that there is no benefit after 24 hours. The duration of prophylactic treatment should be four weeks. Please contact the AfA programme immediately for authorisation.

Zidovudine plus lamivudine for 4 weeks is not registered for use after rape, but will be funded provided that the doctor accepts responsibility for off-label use.

If exposure occurs on the weekend, please ensure your patient gets the necessary medication after exposure. Begin with a starter pack. You can then contact AfA, first thing on Monday morning, to complete the post exposure prophylaxis (PEP) application form and to arrange reimbursement for further PEP medication.

Exposure	HIV status of source patient		
	Unknown	Positive	High risk*
Intact skin	No PEP	No PEP	No PEP
Mucosal splash/ Non-intact skin	Consider AZT + 3TC	Recommend AZT + 3TC	Recommend AZT + 3TC

Exposure	HIV status of source patient		
	Unknown	Positive	High risk*
Percutaneous (sharps)	Recommend AZT + 3TC	Recommend AZT + 3TC	Recommend AZT + 3TC + lopinavir/ ritonavir
Percutaneous (needle in vessel or deep injury)	Recommend AZT + 3TC	Recommend AZT + 3TC + lopinavir/ ritonavir	Recommend AZT + 3TC + lopinavir/ ritonavir

* Terminal AIDS, seroconversion illness or known to have a high viral load

Nevirapine should not be used for PEP as it has been associated with severe hepatotoxicity in this setting. The neuropsychiatric side-effects of efavirenz also make this drug unsuitable as a third agent. Stavudine may be used as an alternative to zidovudine if this is poorly tolerated (nausea and headache are common early side effects of AZT). If the source patient is already on antiretroviral therapy an alternative combination should be considered if the patient is known to be failing therapy – specialist advice is recommended.

Follow-Up Monitoring

- HIV serology (must be done in the laboratory for medico-legal reasons):
  - Necessary at the time of exposure to ascertain the patient's HIV status (PEP must NOT be given to HIV-infected individuals as there is no benefit and there is a risk of lamivudine resistance).
  - Needs to be done 6 weeks, 3 months and 6 months after exposure to determine whether the patient has become infected. Current laboratory antibody tests (ELISA) should be positive within 3 months, but the 6 month test is retained for medico-legal reasons.
  - **NOTE: Tests for diagnosing HIV before the antibody becomes positive (e.g. PCR) should NOT be done as these tests are too sensitive with most of the positive results being false positives. This causes unnecessary stress.**

- Full blood count:
  - Necessary to get baseline results, 2 weeks and 4 weeks after exposure to ensure that the zidovudine is not suppressing the bone marrow.

If a patient has been exposed to HIV, condoms should be used until the three-month HIV ELISA test is negative. Patients should be counselled regarding the need to complete the four week course of prophylaxis as side-effects to treatment are common. Anti-emetics such as cyclizine are helpful in treating nausea, which is a common side effect.

Hospitalization

Experience acquired since AfA was initiated in 1998 confirms that the need for hospitalization is reduced by the use of effective antiretroviral therapy. Savings on expected hospitalizations are the basis for providing antiretroviral therapy. The duration of hospitalization can be shortened by the judicious use of step down facilities and home nursing. Hospitalization always requires reimbursement authorization. Please refer to individual scheme rules for details regarding hospital case management. Hospitalization is not covered for members of corporate programmes. Such patients should either contact their medical schemes or be referred to a state hospital.

HIV in children

Introduction

HIV infection in children may follow a more rapid course than in adults. Nevertheless, observational studies in Europe and USA show that up to 50% of infected children may survive up to 10 years of age without the need for antiretrovirals. Supportive care and ART both contribute significantly to improved survival and quality of life. HAART has been associated with a 70% decline in mortality in a European study. In the Family Clinic at Tygerberg Academic Hospital, mortality has declined. In a survey from the preHAART era, 46 of 274 (16.8%) children died. In contrast, the mortality declined to 9.6% in children receiving HAART over a 30 month period, with almost 50% of mortality in the first month of treatment, in children with advanced disease.

Route of Infection

- Mother-to-child transmission – this is by far the most important route, accounting for 95% of paediatric HIV.
  - Transplacental (in utero) (± 10% of total through mother-to-child transmission)
  - Peri-partum (in utero or birth canal) (± 60%)
  - Breastfeeding (± 30%)
- Sexual abuse
- Blood product transfusion – this route is now extremely rare but is possible where a donor donated blood in the window period.
- Unexplained – in a small number of children, no obvious cause is found. Possible causes include the following:
  - Not the genetic offspring of the parents
  - Occult sexual abuse
  - Surrogate breastfeeding
  - Nosocomial infection through re-use of contaminated equipment such as disposable razor blades, breast milk pumps or unlabelled breast milk
  - Use of contaminated equipment during immunization
  - Scarification

Prevention of Vertical Transmission

See page 54 in the Adult Guidelines.

Diagnosis of HIV in Infants and Children

Passively acquired maternal antibodies may persist for up to 18 months. Detection of HIV antibodies in children thus only confirms infection after 18 months of age.

To determine the infection status of an HIV exposed infant in the first 18 months, the qualitative polymerase chain reaction (PCR) test for HIV specific DNA or RNA must be performed. This can already detect up to 90% of infected infants by 2 weeks of age in the absence of breastfeeding. Quantitative HIV RNA (viral load) assays should preferably not be requested, as they are more expensive and less sensitive than the qualitative PCR assays.

The first PCR test should be carried out at 4 to 6 weeks of age. It may be performed earlier if symptomatic disease is suspected. A negative test should be repeated 1 to 2 months later to exclude laboratory errors or prolonged incubation. A positive test should also be repeated. The confirmatory test may be done as a viral load, especially if early HAART is contemplated.

NB: The baby must be registered with the medical scheme before any investigations can be authorized by Aid for AIDS for payment.

Where the mother has elected to breastfeed, HIV infection cannot be excluded until 6 weeks after the last breastfeed either by a PCR if under 18 months of age or antibodies if older than 18 months. For the latter, the 4th generation elisa antigen/antibody test should be used, especially in the first 3 months post cessation of breast feeding. Significant amounts of lamivudine and nevirapine can be absorbed by breast feeding infants. This poses a significant risk to infected infants for developing resistance to these agents.

Resistance testing
Resistance testing should be undertaken on all infants infected despite mother-to-child transmission prophylaxis. This is most likely to occur where it was commenced late in pregnancy. Single dose nevirapine and lamivudine in the mother are most associated with resistance in infants.

Management of HIV Exposed Infants

Commence co-trimoxazole prophylaxis against *Pneumocystis jiroveci pneumonia* (PCP) at four to six weeks of age on all exposed infants. This may be discontinued once the second PCR is shown to be negative. As PCP can occur in HIV-exposed uninfected infants, we recommend continuing PCP prophylaxis up to 6 months of age.

The dose is 5mg/kg/day of the trimethoprim component (trimethoprim 40 mg/5ml of co-trimoxazole). In infected infants continue the prophylaxis for the first year of life and then maintain if the CD4 is less than 15%.

Commence an appropriate multivitamin preparation such as Abidec® 0.6ml daily.

Clinical Grounds for Suspicion of HIV Infection

Although the majority of HIV infected children will be detected through mother-to-child transmission prevention programmes, HIV infection should still be suspected in children presenting with the following conditions:

- Failure to thrive
- Recurrent or chronic diarrhoea
- Infection with unusual organisms
- Recurrent oral candidiasis
- Recurrent infections
- Recurrent pneumonia
- Severe pneumonitis in the first year of life
- Invasive bacterial disease such as arthritis, osteitis, mastoiditis
- Unexplained arthropathy
- Unexplained cardiomyopathy
- Unexplained anaemia or thrombocytopaenia
- Generalised lymphadenopathy and hepatosplenomegaly
- Severe herpes simplex stomatitis, varicella zoster or chicken pox
- Enlarged parotids or digital clubbing (older child)
- Severe dermatitis
- Recto-vaginal and peri-anal fistulae
- Chronic otorrhoea

Classification

We recommend using the revised WHO Classification for Infants and Children (www.WHO.int) and also the treatment guidelines, which take recent data into account. Note that CD4 percentage is best used until 5 years of age. The Immunological Classification supersedes that of the CDC, which does not take age of child into account.

Note that although pulmonary tuberculosis is a Stage III event, ART need not necessarily be started if the CD4 percentage and other clinical parameters are within acceptable limits.

Table I. WHO clinical staging of HIV for infants and children with established HIV infection

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2[a]
Unexplained persistent hepatosplenomegaly Papular pruritic eruptions Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Unexplained persistent parotid enlargement Lineal gingival erythema Herpes zoster Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Fungal nail infections

Clinical stage 3[i]
Unexplained moderate malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5 °C, intermittent or constant, for longer than one month)
Persistent oral candidiasis (after first 6 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Lymph node TB
Pulmonary TB
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8.0 g/dl), neutropenia (<0.50 x $10^9/L^3$) or chronic thrombocytopenia (<0.50 x $10^9/L^3$)
Clinical stage 4[i] [ii]
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site)
Extrapulmonary TB
Kaposi sarcoma
Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after the neonatal period)
HIV encephalopathy
Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month
Extrapulmonary cryptococcosis (including meningitis)
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis
Disseminated non-tuberculous mycobacteria infection
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
HIV-associated cardiomyopathy or nephropathy

(i) Unexplained refers to where the condition is not explained by other causes.
(ii) Some additional specific conditions can be included in regional clasifications (e.g. Penicilliosis in Asia, HIV associated rectovaginal fistula in Africa).

Presumptive and definitive criteria for recognizing HIV-related clinical events in infants and children with established HIV infection

Clinical event	Clinical diagnosis	Definitive diagnosis
Stage 1		
Asymptomatic	No HIV-related symptoms reported and no clinical signs on examination.	Not applicable
Persistent generalized lymphadenopathy (PGL)	Persistent swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites (excluding inguiral), without known cause.	Clinical diagnosis
Stage 2		
Unexplained persistent hepatosplenomegaly	Enlarged liver and spleen without obvious cause.	Clinical diagnosis
Papular pruritic eruptions	Papular pruritic vesicular lesions.	Clinical diagnosis
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onchomycosis is uncommon without immunodeficiency.	Clinical diagnosis
Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responding to antifungal treatment but may recur.	Clinical diagnosis
Lineal gingival erythema (LGE)	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding.	Clinical diagnosis
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring.	Clinical diagnosis
Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red; facial, more than 5% of body area or disfiguring. Giant molluscum may indicate advanced immunodeficiency.	Clinical diagnosis
Recurrent oral ulcerations (two or more in six months)	Aphthous ulceration, typically with a halo of inflammation and yellow-grey pseudomembrane.	Clinical diagnosis
Unexplained parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause; usually painless.	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, may be haemorrhagic on erythematous background and may become large and confluent. Does not cross the midline.	Clinical diagnosis
Recurrent upper respiratory tract infection (URTI)	Current event with at least one episode in past six months. Symptom complex: fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB), persistent or recurrent ear discharge.	Clinical diagnosis
Stage 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to -2 standard deviations (SDs), not explained by poor or inadequate feeding and/or other infections, and not adequately responding to standard management.	Documented loss of body weight of -2 SDs, failure to gain weight on standard management and no other cause identified during investigation.
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily) not responding to standard treatment.	Stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (intermittent or constant for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever of >37.5 °C with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.
Oral candidiasis (after first 6 weeks of life)	Persistent or recurring creamy white soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Microscopy or culture.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	Clinical diagnosis
Lymph node TB	Nonacute, painless "cold" enlargement of lymph nodes, usually matted, localized in one region. May have draining sinuses. Response to standard anti-TB treatment in one month.	Histology or fine needle aspirate for Ziehl Neelsen stain. Culture.

Clinical event	Clinical diagnosis	Definitive diagnosis
Pulmonary TB (History of contact with adult with smear positive PTB)	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In older children, productive cough and haemoptysis as well	Isolation of M. Tuberculosis on sputum culture, +/- abnormal CXR.
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest in-drawing nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous six months	Isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	Clinical diagnosis
Symptomatic LIP	No presumptive clinical diagnosis.	CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise induced fatigue. Characteristic histology.
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/ or wheezes on auscultation.	CXR; may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8g/dl), or neutropenia (<0.50 x $10^9/L^3$) or chronic thrombocytopenia (<0.50 X $10^9/L^3$)	No presumptive clinical diagnosis.	Laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelminthics as outlined in IMCI.

Clinical event	Clinical diagnosis	Definitive diagnosis
Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss not explained by poor or inadequate feeding or other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of -3 SDs, as defined by WHO IMCI guidelines.	Documented weight loss of >-3 SD +/- oedema.
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI.) Usually of rapid onset especially in infants under 6 months of age. Response to high-dose cotrimoxazole +/- prednisolone.	CXR, typical bilateral perihilar diffuse infiltrates; microscopy of induced sputum or BAL or NPA.
Recurrent severe bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous six months.	Culture of appropriate clinical specimen.
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Culture and/or histology.
Oesophageal Candida (or Candida of trachea, bronchi or lungs)	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids) or retrosternal pain worse on swallowing (food and fluids) responds to specific treatment. In young children, suspect particularly if oral Candida observed and food refusal occurs and/or difficulties/crying when feeding.	Macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary/ disseminated TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis.	Positive microscopy showing AFB or culture of Mycobacterium tuberculosis from blood or other relevant specimen except sputum or BAL. Biopsy and histology.
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules.	Macroscopic appearance or by histology.

Clinical event	Clinical diagnosis	Definitive diagnosis
CMV retinitis or CMV infection affecting another organ, with onset at age over 1 month	Retinitis only: may be diagnosed by experienced clinicians: typical eye lesions on fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Histology or CMV demonstrated in CSF by culture or DNA-PCR.
CNS toxoplasmosis with onset at age over 1 month	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy.	Positive serum toxoplasma antibody AND of available single/multiple intracranial mass lesions on neuro imaging (CT or MRI).
Extrapulmonary cryptococcosis including meningitis	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy.	Isolation of Cryptococcus neoformans from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF or blood.
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: – failure to attain, or loss of, developmental milestones, loss of intellectual ability; or – progressive impaired brain growth demonstrated by stagnation of head circumference; or – acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances.	Neuro imaging demonstrating atrophy and basal ganglia calcification, exclusion of other causes.
Disseminated mycosis (coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive clinical diagnosis.	Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture.

Clinical event	Clinical diagnosis	Definitive diagnosis
Disseminated mycobacteriosis other than TB	No presumptive clinical diagnosis.	Non-specific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung.
Chronic cryptosporidiosis (with diarrhoea)	No presumptive clinical diagnosis.	Cysts identified on modified ZN stain.
Chronic Isospora	No presumptive clinical diagnosis.	Identification of isospora.
Cerebral or B cell non-Hodgkin lymphoma	No presumptive clinical diagnosis.	CNS imaging: at least one lesion with mass effect; histology of relevant specimen.
Progressive multifocal leukoencephalopathy (PML)	No presumptive clinical diagnosis.	Progressive neurological disorder together with white matter lesions on neuroimaging or positive polyomavirus JC (JCV) PCR on CSF.
Symptomatic HIV-associated nephropathy	No presumptive clinical diagnosis.	Renal biopsy.
Symptomatic HIV associated cardiomyopathy	No presumptive clinical diagnosis.	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography.

A. Immunological

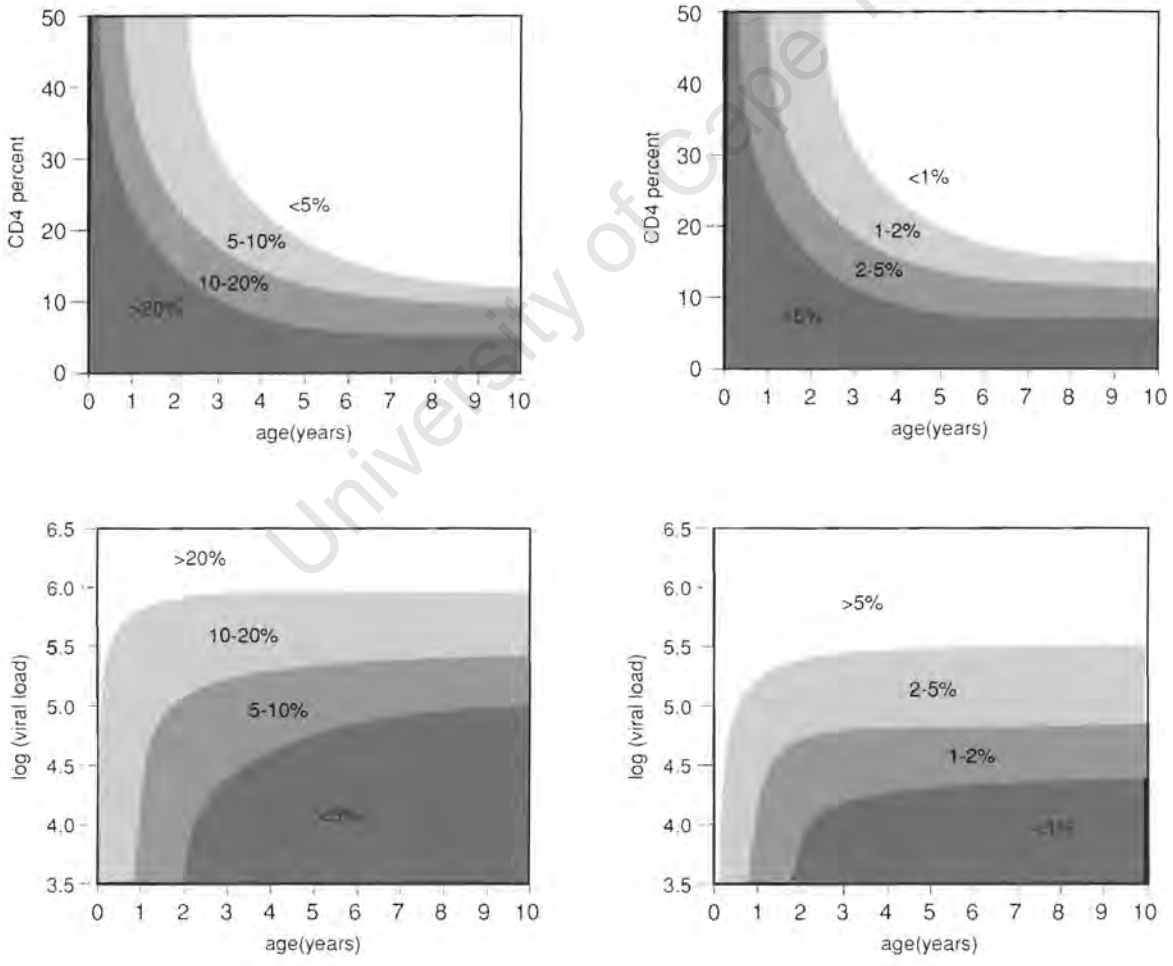
Because there is a gradual decline in CD4 cell numbers up to 5 years of age, more reliance is placed on CD4 cell percentages that remain constant. One should, however, note percentage and absolute numbers as well as the CD4 / CD8 ratio to gain a full appreciation of immunological status. CD8 cells may be elevated in response to HIV and a low CD4 cell percentage may give a false impression of immune suppression. After 5 years of age, one can use the CD4 count instead of percentage. The immunological classification is shown in Table II.

Table II. WHO classification of HIV-associated immunodeficiency in infants and children

Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	<11 months (%)	12–35 months (%)	36–59 months (%)	>5 years (cells/mm^3)
Not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 or <15%

Source: Based on WHO global and regional consultations.

A new development is the understanding that the significance of a specific CD4 percentage and count are age-related. For example, a CD4 percentage of 25% at 6 months of age has >20% risk of AIDS within a year while a percentage of 15% at 10 years of aqe has a risk of <5% (see figure). A risk calculator is available at www.www.ctu.mrc.ac.uk/penta/hppmcs



Risk of developing AIDS or death, by CD4 percentage or a viral load, is age-related. www.ctu.mrc.ac.uk/penta/hppmc/graphs.htm

The Management of a Newly Diagnosed Child

Perinatally Acquired HIV Infection Reflects a Family Disease

- Survival of infected and uninfected children is intimately linked with survival of the parents.
- Every effort should be made to screen and counsel family members and refer for appropriate therapy.

Important points when counselling parents of HIV infected children:

- Be hopeful. HIV is a chronic disease with many opportunities for positive intervention.
- Encourage economic advancement as a survival mechanism.
- Explore the possibility of joining a medical aid society.
- Discuss the routes of acquisition of HIV in children.
- Discuss infant feeding. Breastfeeding in an already infected infant should continue. In an exposed infant, exclusive breastfeeding with abrupt weaning between 4 and 6 months of age is an alternative to exclusive formula feeding in many communities. Mixed feeding is extremely dangerous.
- Anything that weakens the body will strengthen HIV. Any factor that strengthens the body will weaken HIV.
- The parents should contemplate the need for planning for the child in the event of advanced disease in the parent.

History

- Carefully note details of maternal and infant ARV use including drugs and duration
- Also note feeding choices for neonates and infants

Clinical Assessment

- Record the child's weight, height and head circumference.
- Check the perinatal details including maternal RPR results, and previous weights on the "Road to Health" card.
- Check the immunization status on the "Road to Health" card.
- Check for generalized lymphadenopathy, hepatosplenomegaly, parotid enlargement, digital clubbing or oral thrush.
- Check dental hygiene and refer to dentist if necessary.
- Actively exclude tuberculosis (TB) in family members. Always inquire about the possibility of TB or coughing and weight loss in family members or friends. If a family member has active tuberculosis, the child should be fully investigated for TB, with chest X-ray, gastric washing, etc. If negative, tuberculosis prophylaxis should be given. If positive, the child should be referred to a TB clinic for treatment. A Mantoux skin test with ≥ 5 mm induration is considered positive. Any response to a percutaneous skin test such as a Tine test should be considered positive. (Prophylaxis: INH 5–10 mg/kg daily or three times weekly for between 6 and 9 months or INH and rifampcin 10 mg/kg for 3 months.)

Baseline Investigations

- RPR – only necessary if mother's status during pregnancy is uncertain.
- Chest radiograph – this is extremely valuable as many children develop chronic lung disease or TB.
- Full blood count and differential count.
- CD4 count.
- Urinalysis (dipstick).
- Viral load is not obligatory but may aid clinical decision making.
- Hepatitis B serology if the child has not been immunized against hepatitis B.
- Mantoux
- Stool for microscopy, culture and sensitivity, and parasites – especially if diarrhoea.
- Liver functions.
- Gastric aspirates – daily (three times) where TB is suspected.

Immunizations

- All routine childhood immunizations should be given.
- Avoid measles immunization only in severely immunosuppressed patients. If given at nine months this immunization should be repeated at 12 months instead of at 18 months.
- Varicella vaccine can be given safely to asymptomatic infants and children.
- Influenza vaccine is worth giving each year for infants over 6 months of age. If given for the first time, give 2 doses a month apart.

Routine Medication

- Parasite infestations: mebendazole or albendazole every six months (start from 12 months).
- Mebendazole: 100 mg twice daily for three days (100 mg = 5ml or one tablet) or 500 mg stat if over 5 years of age.
- Albendazole: if under 10kg, 200 mg stat (suspension 20 mg/ml). if over 10kg, give 400 mg stat (tablets 200 mg).
- PCP prophylaxis: co-trimoxazole for all HIV exposed infants in the first year of life unless two negative PCRs. For confirmed HIV infection or if unable to do PCR, measure CD4 percentage at one year of age. If under 15 percent, co-trimoxazole should be continued. Dosage: 5mg/kg/day of trimethoprim component (co-trimoxazole: trimethoprim 40 mg/5ml). This may be given 3 times weekly (Monday, Wednesday and Friday). An alternative is dapsone 2mg/kg daily or 4mg/kg/week. Co-trimoxazole may be of benefit to children with recurrent bacterial infections.

Nutritional Support

- A balanced diet should be given. Advice from a dietician should be sought if dietary problems or inadequate intake is suspected.
- Multivitamins (vitamin A 3 000iu per day).
- If there is the possibility of an inadequate diet, include prophylactic iron to prevent iron deficiency (ferrous gluconate 8mg/kg/day; 1mg elemental iron/kg/day).
- Folic acid – 2.5mg daily may benefit symptomatic children.
- (Note: there are no data to support giving anabolic steroids.)

Follow-Up

All HIV exposed infants should be seen at 4–6 weeks of age. Thereafter, patients should be seen every 3–6 months. The patient should be seen at monthly intervals on initiation of ART or if there is a change of clinical importance.

Monitoring

Height and weight

The Road to Health chart is a valuable tool for monitoring well-being. Failure to maintain growth is suggestive of progressive HIV infection or superimposed infection such as TB. Recent data, however, suggests that weight may decline in children responding adequately to ritonavir-containing triple therapy.

CD4 lymphocytes

CD4 counts are much higher in infancy than in adults but the percentage remains constant. A CD4 percentage <15% should be viewed in the same light as a CD4 count <200/µl in adults. Absolute CD4 counts are useful for monitoring response to antiretrovirals.

Viral load

Levels in infants are far higher in the first year of life than in adults. They decline to adult values by two to three years of age. By two months of age most infected infants have viral loads above 100 000 copies/ml, ranging from undetectable to 10 million copies/ml. Generally, the higher the viral load, the more rapid the disease progression, although in children there is considerable overlap. Levels >299 000 copies/ml have been correlated with rapid disease progression and death in infants below one year of age. Viral load assays are of value in monitoring treatment with antiretrovirals.

Combination of CD4 percentage and viral loads

This has a higher predictive value than either parameter alone (see table 3).

Table 3. Baseline CD4% and HIV copy number: risk of dying

HIV RNA (copies/ml)	Baseline CD4%	Patients (number)	Deaths (%)
≤ 100 000	≥ 15	103	15
	<15	24	63
>100 000	≥ 15	89	36
	<15	36	81

Mean age 3.4 years; mean follow-up 5.2 years
(Mofenson et al J Infect Dis J 1997; 175: 1029–38)

Viral Load for Monitoring ART

Many experts feel that undetectable viral load levels, while useful, are not essential for successful ART in children and excellent and sustained clinical and immunological responses are seen in the absence of undetectable viral loads.

Initial virological response may be slower than seen in adults (8–12 weeks) especially if the initial viral load is >1 million copies/ml.

Suppression to an undetectable viral load can occur in more than 50% of infants and is less likely to be associated with failure.

A baseline value followed by a second value at 3 months, and thereafter 6 monthly is a reasonable approach.

For children on triple therapy, suppression < 10-fold (1 log) and dual NRTI therapy < 5-fold (0.7 log) is regarded as insufficient.

In children who have responded with durable but not absolute viral suppression, a reproducible increase > 3-fold (0.5 log) in children ≥ 2 years and > 5-fold (0.7 log) are possible indications to switch antiretroviral agents. Many experts would defer a change in therapy in the absence of immunological or clinical progression.

Adapted PENTA (Paediatric European Network for Treatment of AIDS) guidelines for the use of antiretroviral therapy, 2004

M Sharland, S Blanche, G Castelli, J Ramos and DM Gibb on behalf of the PENTA Steering Committee

To access the full PENTA guidelines and references, see: www.ctu.mrc.ac.uk/penta/. Certain of the drugs and procedures referred to below may not yet be available in South Africa. Availability of HIV genotyping will depend on scheme benefits and AfA pre-approval.

There have been few major advances in paediatric HIV management over the last 2 years. Decisions about starting antiretroviral therapy can now be based on recent large meta-analysis of the predictive value of CD4 and HIV RNA viral load (VL) in nearly 4000 untreated children, which is discussed in these updated guidelines. Risk estimates for progression to AIDS and death using surrogate markers can now be broken down by age, allowing more accurate discussion with families. In addition, there is increasing recognition of the problems of long-term adherence, drug resistance and cumulative toxicity in adults and children. The controversy over whether to treat asymptomatic infants continues. For older children more data on the efficacy of ritonavir boosted protease inhibitor (PI) regimens suggests that these may be the PI option of first choice. There is still no adult or paediatric trial evidence on which to base decisions about whether to start with PI- or non-nucleoside reverse transcriptase inhibitor (NNRTI)- based regimens, but the PENPACT 1 trial, which is addressing this question, is ongoing. There are increasing moves to provide simpler anti-retroviral therapy (ART) regimens, including once daily dosing, but these lag behind adult regimens because of the paucity of pharmacokinetic data. Resistance assays should now be performed in all HIV-infected infants exposed to ART in pregnancy. Therapeutic drug monitoring may be very important in children because of high between- and within-child variability in drug absorption and metabolism. A trial to evaluate this should start shortly in Europe (PENTA 14 trial). The value of resistance tests for choices of ART regimens remain unproven (the PERA will report late in 2004), but resistance assays are increasingly being used. The issue of when to switch therapy also remains unanswered and is being addressed within the PENPACT 1 trial. Regular formal assessment of adherence is now the standard of care, and routine monitoring in the clinic for the lipodystrophy syndrome (LDS) and other ART toxicities is increasingly important. These guidelines will be updated again in 2006.

1. Introduction

The care of children with HIV infection is complex. The Paediatric European Network for Treatment of AIDS (PENTA) 2004 guidelines provide a review of the evidence base for treatment. They clearly demonstrate the marked limitations of the evidence and the strong continuing need for the clinical trials within the PENTA network, particularly to address strategies aimed

at reducing life-time toxicity of antiretroviral therapy (ART), while maintaining or increasing long-term efficacy. Many clinical and treatment issues cannot be covered in the guidelines. PENTA therefore believes that paediatric HIV specialists need to be involved in the care of all HIV-infected children, either directly or as part of a clinical network. More work needs to be done to define specialist centres. There is also a need to improve the training of paediatricians specialising in the care of children with HIV.

The successful identification of HIV among pregnant women and reduction of perinatal transmission has dramatically reduced the number of children born with HIV in Europe. Perinatal transmission, however, is still high in some countries in Eastern Europe, and older children migrating from high prevalence countries continue to present to paediatricians in Europe with advanced disease. For these reasons and because HIV-infected children are living much longer with antiretroviral therapy, the number of children under care has increased in many European countries. Overall, the cohort of children with HIV in Europe is increasing in age and starting to enter adolescence. Many clinics are now collaborating with adult services to assist transition from paediatric to adult care. These 2004 guidelines were developed using a full review of Medline and international HIV conferences.

The PENTA Guidelines should be read in conjunction with both the US paediatric HIV guidelines (www.aidsinfo.nih.gov/guidelines) and national guidelines. The PENTA and US guidelines are now very similar with regard to when to start therapy, what to start with and the appropriate dosing of drugs.

The aim is to maximize the efficiency of highly active antiretroviral therapy (HAART), while minimizing long-term toxicity.

2. When to start treatment

2.1 Background

The PENTA 1 trial of early vs. deferred zidovudine monotherapy remains the only randomized trial evaluating when to start ART in children. Recommendations on when to start combination therapy in both adults and children are based on cohort data that provide an estimate of the risk of progression to AIDS or death based on the child's current CD4 percentage and viral load (VL). Recommendations based on surrogate marker data cannot give an absolute risk. Emphasis should be placed on serial measurements of CD4%, VL and clinical assessment. VL and CD4% fluctuate with intercurrent illness, physiological and test variability. The trend in 3–4 repeated measurements of CD4% and VL is very important. Rapid clinical, virological or immunological failure is of particular concern. Starting ART is rarely an emergency. Time spent preparing and educating the family is never wasted. Starting ART should be a fully informed choice supported by the family if it is to succeed. It is preferable not to start ART the first time you meet a family. Older children should know why they are taking treatment, with full or partial disclosure. With increasing recognition of the long-term problems of resistance and toxicity associated with ART, it should only be started when the risk of progression is 'significant', although consensus about the definition of 'significant' remains unclear. Risk assumptions should be discussed fully. Some families may be more risk averse, while in others concerns around the burden and toxicity of ART means they will accept a higher risk of clinical progression. There is a balance between the need for acting as the child's advocate with formal child protection in families rigidly opposed to ART, and respecting a family's need to adjust to the diagnosis and treatment.

The meta-analysis now provides very useful risk levels for progression to AIDS or death over the subsequent 6 and 12 months using the child's current age, CD4% and VL. Individual risk levels can be obtained from a calculator on the PENTA website (www.pentatrials.org). Table 2 provides a summary of the risk of progression to AIDS and death over the subsequent 12 months by current age and CD4%. Care must be taken in the interpretation of the risk generated from the meta-analysis for an individual child. The data is a pooled retrospective analysis of the longitudinal cohorts and trials in the pre-HAART era, and a strong calendar time effect was observed.

Although the analysis is adjusted for cotrimoxazole prophylaxis, it is very likely that progression to AIDS will be slower in prospectively followed children in 2004 than it was 10–15 years earlier. There could also be different practices and populations in individual countries that influence outcome. Surrogate marker-based risk of progression varies considerably by age, so the PENTA guidelines use five age bands (<1, 1–3, 4–8, 9–12 and 13–17 years).

Table 2 Risk of progression to AIDS and death over the next 12 months based on current age and CD4%

	CD4 5%		CD4 10%		CD4 15%		CD4 20%		CD4 25%		CD4 30%		CD4 35%	
Age	AIDS	Death	AIDS	Death	AIDS	Death	AIDS	Death	AIDS	Death	AIDS	Death	AIDS	Death
3/12	71	56	60	39	49	27	40	19	34	14	28	10	25	8
6/12	65	47	51	30	40	19	31	12	25	9	20	6	18	5
1	56	36	40	20	29	12	21	7	16	4	13	3	11	3
2	46	26	29	12	18	6	12	3	9	2	7	1	6	1
3	39	20	22	8	13	4	8	2	6	1	5	<1	5	<1
4	34	16	18	6	10	3	6	1	4	<1	4	<1	4	<1
5	31	14	15	5	8	2	5	<1	4	<1	3	<1	3	<1
6	28	12	12	4	6	1	4	<1	3	<1	3	<1	3	<1
7	26	11	11	3	5	1	3	<1	3	<1	2	<1	2	<1
8	24	10	9	3	4	<1	3	<1	2	<1	2	<1	2	<1
9	22	9	8	2	4	<1	2	<1	2	<1	2	<1	2	<1
10	20	8	7	2	3	<1	2	<1	2	<1	2	<1	2	<1

In formulating these guidelines a risk of progression to AIDS in the subsequent 12 months of >10% and a risk of death in the next 12 months of >5% was considered to be unacceptable (based on data from the HIV Pediatric Prognostic Markers Collaborative Study (HPPPMCS) analysis). These are pragmatic levels and may change with time as further evidence of the efficacy and toxicity of ART become available. Combination ART is very affective in reducing the incidence of major new opportunistic infections and organ disease. There is a need to assess the more subtle risks of HIV progression in untreated children, including mild cognitive impairment and organ disease, and balance these against the emerging long-term toxicity of HAART.

2.2 Infants

Clinical Data

Infants who present with clinical AIDS have a high risk of dying before receiving ART, therefore all infants presenting with clinical stage C disease should start ART as soon as possible after treatment of their AIDS-defining illness. Surrogate markers are poor predictors of rapid disease progression in infancy and rapid clinical deterioration often occurs in the presence of high

CD4%. Infants not started on ART should therefore be very closely monitored clinically and for CD4 and VL values (e.g. every 1–2 months). Lymphadenopathy and/or hepatosplenomegaly (stage A disease) are not good indicators of clinical deterioration; failure to thrive or any stage B disease is an indication to start ART, as is any indication of neurodevelopmental deterioration.

Immunological and virological data

There is a complex balance between the immediate clinical and immunological benefits of early ART in asymptomatic infants, vs. concerns about the long-term development of resistance and toxicity to ART if initiated early. The major clinical concern is the development of an irreversible AIDS-defining illness, especially encephalopathy, because there are no good markers to determine which infants will develop rapidly progressive disease and which will be asymptomatic throughout childhood without treatment. Recent European cohort data in the era of widespread antenatal testing suggest that the development of encephalopathy is rare in prospectively identified and treated infants under care compared with historical controls.

There are also concerns about the early use of ART in asymptomatic infants. Infants often have very high VL values, and high rates of virological non-response can lead to the early development of resistance. Causes of poor response include inadequate pharmacokinetic levels, particularly for PIs, and poor adherence due to the difficulties of administering complex and unpalatable regimens to asymptomatic infants. Some infants started early on HAART lose HIV antibody and HIV-specific immune responses, probably related to the absence of HIV antigen presentation.

The high risk of short-term progression in infants means that it may be more appropriate to consider the risk of progression to AIDS or death over the next 6 months rather than 1 year. At 6 months of age there is an approximate risk of developing AIDS in the subsequent 6 months of 10% when an infant's CD4% falls below 35%, increasing to a 15% risk when the CD4% reaches 25%. Infants with a CD4% between 30 and 35% and falling should start ART. It is still acceptable, after full discussion with the parents and documentation of the risks involved, not to treat asymptomatic infants with no evidence of clinical progression, with HIV RNA VLs of less than 1 million copies/mL, and a stable CD4% of over 35%. Many expert clinicians feel that they would prefer to offer parents the option of treating all asymptomatic children identified in the first year of life.

2.3 Children

Clinical data

All children with an AIDS defining illness should start ART following discussion with their family. The evidence for clinical benefit of ART in children with AIDS is so strong that complete parental refusal to treat is now a child protection issue in Europe. Symptomatic disease (stage B) includes conditions with differing predictive values. In particular, children with lymphocytic interstitial pneumonitis (LIP) may have stable clinical course many years after diagnosis apart from recurrent chest infections.

Immunological data

1–3 years old. The risk of encephalopathy and rapid clinical progression is still high in this age group. It is therefore more appropriate to use a CD4 percentage of <20 as the trigger to initiate therapy.

4–8 years old. Previous PENTA guidelines used a cut off CD4 count of <15% for the initiation of therapy. This corresponds to an adult absolute count of around 250 cells/mm^3. Within this age band, data from the meta-analysis suggests that a CD4% of 15% is still an appropriate level to start therapy. Discussion with the family, however, should be initiated at higher levels and a

CD4 % of 15% considered at the lower end of the range for treatment initiation; it would not be considered safe to delay therapy in a child with a rapidly falling CD4% below 15%.

9–12 years old. From the meta-analysis data, death was very rare in older children with a CD4% >10%, the 1-year risk of progression to AIDS being under 10%. Although a CD4% of 15% is still a reasonable level to initiate therapy in this age group, there is less urgency than in the younger child. Absolute CD4 count can also be used to guide ART in this age group (CD4 200–350 cells/mm^3, consider ART; CD4 <200 cells/mm^3,must start ART).

13–17 years old. There are few data on the risk of progression in newly diagnosed adolescents. In parts of Europe, increasing numbers of older children are presenting who were born and spent their early childhood in high prevalence countries (some are long-term non-progressor). There is a need for further data in this group. At present it seems reasonable to use current adult guidelines for starting therapy within the range of CD4 absolute count between 200 and 350 cells/mm^3. Social and adherence factors are often critical to the success of ART in adolescents.

HIV RNA viral load

VL is an independent predictor of progression to AIDS and death, although weaker than CD4%. Children with low VLs (<4 log) are unlikely to progress rapidly.

- For infants a VL >1 000 000 copies/mL is associated with a risk of developing AIDS over the subsequent year of >10%.
- For children aged 1–3 years a VL >250 000 copies/mL is associated with a risk of developing AIDS over the subsequent year of >10%.
- For children aged 4–12 years, an approximate VL of >250 000 copies/mL is associated with a risk of developing AIDS over the subsequent year of >10%.
- Children with a VL of <10 000 copies/mL at all ages up to 12 years have a risk of developing AIDS over the subsequent year of <3%.

A summary of when to start ART is given in Table 3.

Table 3 Summary of recommendations on when to start antiretroviral therapy – grade A+

Infants

1. Clinical
   Start all infants with WHO III and IV if ≤11 months.
2. Surrogate marker
   Start all infants with CD4% <25–35%.
   Strongly consider starting with a VL>1million copies/mL.
   Many experts treat all asymptomatic infants.

Children aged ≥12 months to 36 months

1. Clinical
   Start all children with stage IV and consider for III (CD4-guided for TB, LP, Oral Hairy Leucoplakia) disease.
2. Surrogate marker
   Start all children with a CD4% <20% and consider between 20 and 24%
   Strongly consider starting with a VL>250 000 copies/mL.

Children aged 36 to 59 months

1. Clinical
   Start all children with stage IV and consider for III (CD4-guided for TB, LP, Oral Hairy Leucoplakia) disease.

2. Surrogate marker data
   Start all children with a CD4 15–19%.
   Strongly consider starting with a VL>250 000 copies/mL.

Children aged ≥5 years

1. Clinical
   Start all children with stage IV and consider for III (CD4-guided for TB, LP, Oral Hairy Leucoplakia) disease.
2. Surrogate marker data
   Start all children with CD4 < 350 cells × 10^6/l but with less urgency than in a younger child.
   Strongly consider starting with a VL>250 000 copies/mL.

Adolescents aged 13–17 years

1. Clinical
   Start all adolescents with stage C disease.
2. Surrogate marker data
   Start all adolescents with a CD4 absolute count between 200 and 300 cells/mm^3.

3. Which ART regimen to start

There are no adequately powered randomized trials allowing direct comparison of different HAART regimens in children. Discussion with the family about which antiretroviral drugs to start should include consideration of the taste and volume of syrups, pill size and numbers, crushability, storage and food requirements, and number of times a day drugs must be taken. It is good practice to show the family the medicines at an early stage. Details of early (e.g. nausea, vomiting, diarrhoea) and late side effects of drugs should be discussed and documented.

3.1 Infants

Treatment in infants is difficult, because drug absorption, interactions and metabolism differ from older children, and higher doses may be needed. In addition, many infants have very high VL values. The results of early treatment including a PI in 31 infants in the French perinatal cohort showed a high frequency of virological failure, and VL levels less than 500 copies/mL were observed in only 53% of children after 6 months and 18% after 24 months on therapy. Failure was associated with genotype resistance relatively early (e.g. at 6 months), even with protease inhibitor drugs.

Table 4 Summary of recommendations on which ART to start – grade B+

Infants

either

2 NRTI[1] + 1 PI (Lopinavir/r)

or

2 NRTI[1] + 1 NNRTI (Nevirapine)

Children

either

2 NRTI[1] +1 PI (Lopinavir/r)

or

2 NRTI[1] + 1NNRTI (Efavirenz or Nevirapine[2])

[1]Dual NRTI combination recommended: abacavir plus lamivudine – most durable combination; zidovudine plus lamivudine or didanosine; didanosine plus lamivudine. D4T is not recommended as first line therapy.
[2]Nevirapine would be the preferred NNRTI for children under the age of 3 years of age.

Sub-optimal doses of drugs or incomplete adherence could contribute to treatment failure. Nevertheless among the infants treated with ART before the age of 6 months only one child developed an opportunistic infection during the first 18 months of life and none developed encephalopathy. This represents a significant decrease in HIV disease progression compared with natural history data in the pre-HAART era.

3.2 Children

3.2.1 PI –based combinations

The first two studies of PI-based triple regimens (two nucleoside reverse transcriptor inhibitors (NRTIs) plus ritonavir (RTV) (PACTG 338 trial) and NRTIs plus NFV (PACTG 377) reported that approximately 40–50% of children receiving these drugs achieved plasma HIV-1 RNA of <400 copies/mL by 24 weeks. Poor results in PACTG 338 could be due to the unpleasant taste and poor gastrointestinal tolerability of RTV. In PACTG 377 a higher proportion of children receiving a four-drug regimen including all three classes of drugs appeared to respond virologically compared with those on three-drug regimens, but numbers were small. In adults there are no data suggesting that four-drug regimens are more effective than three-drug regimens, and because data are sparse in children this should not normally be recommended.

The large non-randomized study of Saez-Llorens et al. demonstrated that the liquid formulation of lopinavir and ritonavir (LPV/r) is safe and well tolerated by HIV-infected children. Substantial and persistent antiviral activity and improved immune function were observed in 88% of the ART-naïve /PI-naïve enrolled subjects, with 69% of the children achieving a VL of <50 copies/mL at week 48. Despite the concern over possible increased long-term lipodystrophy with a ritonavir-boosted PI, the improved VL and CD4 data suggest that first-line PI use in children should possibly be ritonavir-boosted, as in adults. Paediatric data from the other new ritonavir boosted PIs, fosamprenavir, atazanavir and tipranavir are awaited.

Table 5 Advantages and disadvantages of specific ART drugs

Combination with best clinical evidence	Pro	Contra
NRTI AZT + 3TC	– best results in adult ACTG 384 – palatable liquid formulation – co-formulation in a single pill	– bone marrow toxicity
AZT + ddI	– extensive experience – ddI in a single pill for a o.d. dose	– bone marrow toxicity – pancreatic toxicity – food interference
3TC + ABC	– most durable over time – no food interference – palatable liquid formulation – can be given once daily	– potential ABC hypersensitivity
D4T + 3TC	– palatable liquid formulation – no food interference – synergetic activity	– d4T toxicity: lactic acidosis, lipoatrophy, peripheral neuropathy

AZT +ABC	– palatable liquid formulation – no food interference	– potential ABC hypersensitivity – bone marrow toxicity
ddI + 3TC	– possibility of once daily administration	– food interference – pancreatic toxicity
Not recommended		
AZT + d4T		– drug interaction
ddI + d4T		– higher combined risk of lipodystrophy
NNRTI		
NVP	– liquid formulation – no food interference	– resistance with single mutation – rash and hepatic side-effects
EFV	– once day administration – no food interaction	– resistance with single mutation – neuro psychiatric side-effects
PI		
LPV/r	– high syrup concentration, low volumes – high genetic barrier	– poor taste of syrup – large capsules
NFV	– few adverse effects – should be given with food	– diarrhoea – high variability in blood levels – high pill burden
RTV		– poor palatability – gastrointestinal intolerance

Table 6 New ART either currently or soon available

Drug	Class	Advantages	Problems	Tolerance in children
Tenofovir	Nucleotide reverse transcriptase inhibitor (NA)	Once daily; Low mitochondrial toxicity profile	Some cross resistance with NA	Nephrotoxicity – tubular leak osteoporosis
Emtricitabine	Nucleoside reverse transcriptase inhibitor	Once daily	Cross resistance to 3TC	Unknown
Atazanavir	Protease inhibitor	Once daily; Low incidence of lipid disturbance	Cross resistance to other PIs Ritonovir boosting required	Hyperbili-rubinaemia
Tipranavir	Protease inhibitor	Active in PI-resistant virus	Must be boosted by ritonavir	Unknown
Fosamprenavir	Protease inhibitor	Pro drug of amprenavir; Lower pill burden	Must be boosted by ritonavir	Unknown
Enfuvirtide	Fusion inhibitor	New class; No cross resistance	Subcutaneous injection twice/ daily	Painful local reaction

3.2.2 NNRTI-based combinations

Due to the major concerns about metabolic toxicity associated with PI use, there is increasing interest in NNRTI-based combinations as first-line regimens. However, there remain few data on NNRTI use in children. Dosing of NVP using a surface area formula is preferable than using the mg/kg recommendations, because the latter was not used in clinical trials, generally results in lower doses and recommendations include a curious step in recommended dose at age 8 years that is not evidence-based.

3.2.3 Triple NRTI-based regimens

These are not recommended based on poor results in adult studies.

3.3 Once daily therapy

This may become an option in the future once more information becomes available.

3.4 Immune reconstitution syndrome

This sydrome is increasingly recognized in patients with very low CD4 cell counts. Symptoms, which may be similar to those of an opportunistic infection, occur around 6 weeks later concurrent with a rapid rise in CD4 cell count. CMV disease, BCGosis and tuberculosis have been seen in South Africa.

Table 4 gives a summary of which ART to start with. Table 5 gives the advantages and disadvantages of specific combinations and Table 6 lists newer antiretroviral drugs.

4. Treatment Failure

The failure of first-line therapy may be virological and/or immunological and/or clinical. Treatment failure is usually virological at first, followed by immunological and eventually clinical failure. Clinical failure can be simply defined as the recurrence or non-disappearance of B and C disease. Similarly, immunological failure may be considered as the non-correction or reappearance of low CD4 percentage (generally 20%, but could be lower in older children, or CD4 count in adolescents). The definition of virological failure is more complex and a consensus has not yet been reached. The overall aim of treatment is to reduce VL to levels below the lowest detection threshold (<50 copies/mL) as rapidly as possible and to maintain undetectable levels for as long as possible. A large number of children on treatment, however, have a detectable VL between 1000 and 50 000 copies/mL, but continue to have excellent clinical response and maintain high CD4% values. The presence of continued viral replication is associated with increasing cumulative risk of the acquisition of resistance mutations, which may eventually drive immunological and clinical failure as well as compromise subsequent combinations, due to the cross-resistance induced by many resistance mutations. There have been few longitudinal studies of the emergence of resistance mutations in children, but there is no reason to believe that the data obtained in adults differ from those in children. There is, therefore, a general risk of resistance linked to the rate of residual viral replication, although this risk depends on the drugs used. The cut-off point defining 'acceptable' levels of residual VL and its duration have not yet been determined.

4.1 Causes of failure

Poor adherence, inadequate pharmacokinetic levels or inadequate potency of the drugs chosen can all contribute to antiretroviral treatment failure. Genetic differences in drug metabolism are also likely to be important. Drug level variability is high in children, who may benefit from

individual 'tailoring' of drug doses following drug level measurement. If poor adherence is identified and improved early, it may not necessarily lead to resistance. NNRTIs, however, are particularly likely to select mutations conferring complete resistance to the class within only a few days of viral replication.

4.2 Second-line treatment after initial treatment failure

The choice of treatment should be based on careful analysis of the causes of failure, the previous regimen used and possibly on the results of resistance genotyping. If, for example, a genotype shows no resistance mutations, non-adherence may be very likely and would suggest improving this rather than switching therapy. An alternative combination of drugs that are easier to take may be appropriate. If the child was initially treated with two NRTIs and one NNRTI, a general consensus is to use two new NRTIs and a PI. If, however, the child was treated with two NRTIs and a PI, the choice may include switching to two NRTIs and a NNRTI, but could also include a different ritonavir-boosted PI, if cross-resistance is not a risk.

4.3 Multiple ART failure

The problem of multidrug resistance is growing in paediatric HIV. It is sometimes possible to reintroduce drugs previously prescribed to the child that were originally poorly tolerated. This may be the case, for example, for drugs such as didanosine (now available in the form of enteric coated capsules). Reintroducing drugs for which resistance mutations have been identified in the past, but do not seem to be present in the most recent genotype evaluated is likely to result in rapid selection of the mutant strain, which although undetectable at the time of testing has been archived in long-lived cells. Below are some principles for salvage treatment.

- The use of new drugs, evaluated in adults, but for which paediatric use has not yet been fully evaluated may be justified (possibly with some measurement of drug levels if available). If these drugs are to be effective, they must be included with a regimen containing at least one other and ideally two new active agents to achieve the best chance of success. It is better to wait and change when three new drugs are available. It is very unwise unless really necessary to add a new drug to a failing regimen.
- Salvage combinations may include more than three drugs. Combinations of four or five drugs are possible (Mega-HAART). Seek specialist advice.
- Even in the absence of a mutation conferring resistance specific to a new PI, the susceptibility of a resistant strain to other molecules of this class may be altered, with an increase in IC50, necessitating the use of higher doses. There are adult data suggesting that the dose of lopinavir/r should be increased in patients with NNRTI or PI resistance.

4.4 Resistance assays

Drug resistance may develop with only one mutation or may require several. Single mutants are often present within the virus quasi-species prior to treatment, and are selected by replication in the presence of the antiretroviral drug. For some drugs a single point mutation is associated with resistance (3TC or NNRTIs), while for other drugs (ABC, TDF or PIs) a number of mutations may be required for resistance to develop. Resistance can be overcome for certain drugs by increasing drug levels, for example PIs with RTV boosting. Resistance to antiretroviral drugs may be assessed by phenotypic or genotypic assays. Currently, only genotyping is routine.

At present a genotypic resistance assay should be performed in all HIV-infected infants exposed to any ART during pregnancy, and in children failing their second or subsequent regimens. If a resistance assay is not performed a sample should be stored for subsequent analysis if necessary. A list of the common resistance mutations is shown in Table 7.

4.5 Therapeutic drug monitoring (TDM)

The link between plasma concentrations of antiretroviral drugs and efficacy has been strongly suggested in several retrospective or observational studies, mainly for NNRTIs and PIs. The PENTA 14 study is a randomized trial comparing different levels of TDM in children compared to no TDM. Data on target normal ranges for drug levels in children are very limited. Approximate adult peak and trough ranges are given in Table 8. At present drug monitoring should be considered in children failing PI- or NNRTI-containing regimens, treatment with another antiretroviral or other drug having a potential interaction especially if cotreatment with rifampicin for TB (e.g. PI/NNRTI combination), and in infants and children on drugs where dosage recommendations are based on very limited data. Further information is available at www.hiv-druginteractions.org.

Table 7 Common HIV mutations and associated ART resistance

Resistance mutations	ART associated resistance
NRTIs	
M41L, D67N, K70R, L210W	TAMs (thymidine associate mutations)
T215 Y, K219Q, K219E	High level resistance to most NRTIs except 3TC
M184V	3TC
69 Insertions	Occur after TAMS High level resistance to most NA
K65R	ABC TDF
Y115F	ABC
L74V	ddI
NNRTIs	
K103N	EFV and NVP
Y181C Y188C	NVP and EFV
PIs	
D30N N88D N88S	NFV and other PIs
L90M G84V	SQV and other PIs
V82A V82T V82F	RTV IDV and other PIs
I47V I50V	APV LPV and other PIs
I84V L10I L10F K20R K20M M36I M46I M46L I54V I54L A71V A71T	Increasing number of mutations seen on failing therapy High level resistance to most PIs

Table 8 Target ART trough and peak plasma concentrations (Cmin, Cmax,ng/mL) (data taken from studies on adults)

Nevirapine	3 500 – 8 000
Efavirenz	1 000 – 5 000
Indinavir	150 – 800
Nelfinavir	1 000 – 4 000
Saquinavir	100 – 3 000
Amprenavir	400 – 3 000
Lopinavir	1 000 – 8 000

5. Adherence

There is evidence that adherence to HAART predicts and is related to the virological and clinical response to therapy. Therefore an important challenge when starting therapy is to convince parents and children to be fully adherent. Poor family social circumstances compound adherence difficulties, and careful social assessment and plans for family support should always precede starting or changing therapy. When changing therapy because of poor adherence, it is important to recognize that treatment failure is not always overcome by more simple regimens.

A high level of adherence to the complex antiretroviral regimens is critical for virological efficacy because resistance develops rapidly when drug levels are not maintained within a therapeutic range, rendering these drugs ineffective in the future as well as other antiretrovirals of the same class as a result of cross-resistance. Adult studies have found that more than 90% adherence with antiretroviral medications is required for prolonged viral suppression. In children adherence may be suboptimal because of complex factors relating to the child, the caregivers, the medication and their inter-relationships. Barriers to adherence in children include the lack of liquid formulations of some drugs, high volume, poor palatability, high pill burden, frequent daily dosing requirements, dietary restrictions and toxicity. In addition, specific psychological issues in children include the knowledge of their HIV status and the concern of the patient or caregiver about the disclosure to other family members, friends or school.

In the PACTG 377 trial there was a trend towards poorer adherence with regimens of four drugs, and with regimens including medications requiring three times daily dosing. Poor adherence to PI drugs was related to poor palatability leading to children refusing to take them. In children some medicines can now safely be given once a day (3TC, ABC, ddI, FTC, EFV, TDF). In PENTA 5, one of the few prospective studies carried out on adherence, difficulties in taking the medications in the study were more frequently reported in the first months of therapy, suggesting that more efforts to improve adherence should be put in place at the initiation of therapy and when a new regimen is started.

5.1 Measuring Adherence

There is no gold standard direct method for measuring adherence. A number of indirect methods and strategies have been used to assess adherence in clinical studies. Most studies in children have been cross-sectional and used single methods to measure adherence, such as self-report, caregivers interview or questionnaire. The number of doses missed in the preceding week has been shown to be a useful measure of adherence. Various aids for monitoring adherence have been proposed (www.bhiva.org/chiva and see www.fstrf.org/qol/ql_forms.html). Receipt of medication should be monitored using pharmacy records, and a paediatric pharmacist is an important member of the clinical team. Drug level monitoring may be useful, but can only be used as a guide because inter-individual variability is high in children, and finding a correct plasma level on the day of the sample does not guarantee that compliance is continuous.

Some form of formal evaluation of adherence should ideally be integrated into routine childcare. Regular (every 3–6 months) assessment of adherence performed by questionnaire can be useful. This should be combined with pharmacy record information and documented in the clinical notes. Despite the advances in simplifying antiretroviral regimens and in monitoring adherence, many children are non-compliant and intervention is required. If possible, supervised administration with the help of family members, specialist nurses, psychologists and social organizations should be attempted. In selected cases, and particularly if drugs are poorly

tolerated by mouth, a gastrostomy (G) tube may be a useful option to improve adherence. In some studies with small numbers of patients, G-tubes have been well tolerated by younger HIV-infected children, and caregivers have been satisfied with the procedure because it resulted in shorter medication administration times, fewer behavioural problems and better adherence and virological response. They can be removed once the child is taking oral medication well.

6. Toxicity

Although there are fewer data on toxicity in children than in adults, the complete spectrum of metabolic complications observed in adults has been reported in children. The increasing prevalence of reported metabolic abnormalities observed in children treated with HAART is now of major concern.

6.1 Lipodystrophy syndrome (LDS)

Despite difficulties in assessment and the lack of a standardized definition, fat redistribution in LDS is increasingly recognized in children. It is of great concern, because of its potential metabolic consequences and the impact that body changes may have in self-image leading to poor adherence and treatment failure. The commonest clinical picture seen is facial and limb lipoatrophy, but truncal obesity and buffalo hump also occur, with or without elevations in blood lipid levels. Current cross-sectional studies in paediatric clinics in Europe have reported the prevalence of LDS to range from 2% to 33% as assessed on clinical grounds and anthropometric measurements. In a large recent European questionnaire survey including 374 children with a median age of 5 years, an overall prevalence of clinical LDS was reported to be 28%. There is a need for longitudinal data on LDS and a substudy of the PENPACT 1 trial is ongoing.

Several studies in adults have observed abnormalities in fat distribution by dual energy X-ray absorbiometry (DEXA) before clinical signs are recognized. DEXA provides accurate information about subcutaneous fat, whereas CT or MRI scanning may be useful to tell between abdominal subcutaneous fat stores of the overweight child and intra-abdominal visceral fat seen in LDS. Risk factors for LDS include puberty, female sex, advanced disease and duration of time on ART. There is an association with PI use, and peripheral lipoatrophy is clearly linked to D4T use, especially if combined with ddI (D4T + ddI combinations should be avoided if at all possible).

In children hypercholesterolaemia appears to be more common than hypertriglyceridaemia. RTV-boosted PIs have been most associated with abnormal blood lipids, cholesterol, triglycerides and low density lipoprotein. All children on RTV-boosted PIs including LPV should have fasting blood lipids measured at least annually. Consideration should be given to switching the PI to an NNRTI or abacavir in children with markedly elevated blood lipids. There is very limited experience of statins in children.

Table 9 Summary of suggested routine monitoring of a child on ART

Every 3 months
Height and weight.
Formal adherence questionnaire and pharmacy records check.
Clinical examination for lipodystrophy syndrome.
FBC, electrolytes, liver function tests, calcium, phosphate and alkaline phosphatase (amylase if on ddI).
CD4 count and percentage.
Viral load.

Annual
Tanner pubertal stage.
Fasting blood lipids if on ritonavir boosted PI.

Resistance testing
Resistance testing – infants born of mothers on ART, and all children failing second and subsequent regimens

6.2 Mitochondrial toxicity

Mitochondrial toxicity may result from therapy with NRTIs, and severe lactic acidosis is a rare but serious toxicity attributed to this class of antiretrovirals. Large prospective adult studies have estimated an incidence of symptomatic hyperlactataemia of 0.4–0.8 per 100-patient-years. The predictive value of random lactate determinations is low, suggesting that routine lactate should not be checked in clinical practice in the absence of symptoms. There are also difficulties in determining venous lactate in optimal conditions. Even true hyperlactataemia is usually asymptomatic and may be transient. Isolated case reports of fulminant severe lactic acidosis and death have been seen in children. Treatment with mitochondrial multivitamin rescue can be considered. A high index of suspicion is necessary for mitochondrial toxicity because early symptoms are non-specific. A special situation occurs in children born to HIV-infected mothers exposed to NRTIs in utero in whom the prevalence of transient hyperlactataemia is greater, suggesting reversible mitochondrial dysfunction. Although the great majority of children are asymptomatic, these infants may have a slightly higher risk of mitochondrial disorders including neurological dysfunction.

6.3 Osteoporosis

There have been increasing reports of osteonecrosis and abnormalities of bone mineral metabolism in patients on HAART. Osteonecrosis usually results from circulatory insufficiency, and the areas most involved are the femoral and humeral heads. A large cross-sectional study using MRI detected avascular necrosis of the hip in 4% of adults, even before clinical symptoms developed. In children, a large case-controlled study has suggested that Legg-Calve-Perthe's disease is nine-fold more frequent in HIV-infected children than in the general population. The incidence of osteopenia and osteoporosis is increased in adults treated with HAART, although the association with PIs is not clear. The pathogenesis is not obvious, although decreased bone mineral content may be a result of mitochondrial toxicity (and associated with NRTI use). An association has been reported between osteopenia in children and ART, including duration of time on ART.

The consequence of decreased bone mineral density is unknown, but is of great concern due to the fact that the physiologic peak value of bone mass density is achieved in young adults and may be permanently impaired in HIV-infected children as a result of osteopenia, with the subsequent risk of pathological fractures. Although to date reports of bone fractures are rare, observational data from the PACTG 219 study indicate that they may be more common in HIV-infected children. Biphosphonates have demonstrated some benefit in the treatment of osteopenia and osteoporosis in HIV-infected adults and should be considered in children with pathological fractures and severe osteoporosis.

6.4 Diabetes

Altered glucose homeostasis is seen in adult patients treated with HAART. Although fasting glucose levels remain normal in most adults, impaired glucose tolerance and hyperinsulinaemia are not uncommon in PI-treated patients, and the incidence of diabetes mellitus is increased in PI-treated compared with untreated HIV-patients. In contrast, to date, impaired glucose tolerance has been infrequently reported in children and diabetes is very rare. The true prevalence of insulin resistance is difficult to assess in clinical practice, but may assume greater importance as children remain on HAART for longer periods of time.

A summary of the suggested minimum routine clinical monitoring for a child on ART is given in Table 9. Table 10 summarized prescription and administration information, and Table 11 summarized toxicities of antiretrovirals.

These guidelines are available on the PENTA website www.pentatrials.org. They will be updated again in 2006.

Table 10 Summary of prescribing and administration information for antiretrovirals

Dosage (oral unless specified)

Names of drug	Neonatal (<30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5) / adult	Formulations	Special instructions
Nucleoside / Nucleotide reverse transcriptase inhibitors (NRTIs / NtRTIs)						
Zidovudine (ZDV, AZT, Retrovir)	Oral Term: 4mg/kg b.d. or 2mg/kg q.d.s Premature: ≥ 30 weeks: 2mg/kg b.d for 2 weeks then 2mg/kg t.d.s. ≤ 30 weeks: 2mg/kg b.d. for 4 weeks then 2mg/kg t.d.s. IV Term: 1.5mg/kg q.d.s Premature: 1.5mg/kg b.d.	Oral 1–3 months: 4mg/kg b.d. or 2mg/kg q.d.s. IV 1–3 months: 1.5mg/kg q.d.s.	Oral Over 3 months: 360 to 480 mg/m²/day in two divided doses Intravenous (IV) infusion Over 3 months: Intermittent: 120 mg/m² q.d.s. or continuous: 20 mg/m²/h	250–300 mg b.d.	Capsules: 100 mg, 250 mg. Tablets combined with lamivudine: Zidovudine 300 mg, lamivudine 150 mg (Combivir) Syrup: 10 mg in 1 mL Infusion: 10 mg in 1 mL, 20 mL vials	Large volume of syrup not well tolerated in older children. Infusion: Dilute with 5% dextrose to a concentration of ≤ 4mg/mL. Intermittent infusion is given over 1 h
Didanosine (ddI, dideoxyinosine, Videx)	100 mg/m² every 12 hours	1 to 8 months of age: 100 mg/m² every 12 hours After 8 months of age: 120 mg/m² every 12 hours		<60kg: 250 mg o.d. or 125mg b.d. ≥ 60 kg: 400 mg o.d. or 200 mg b.d.	Capsules: 125mg, 200 mg, 250 mg, 400 mg (Tablets: 25mg, 200 mg) Oral suspension: 10 mg in 1 mL	Enteric coated capsules ideally to be taken at least 2 hours before or after food. Tablets: Rarely used in children. To ensure sufficient antacid each dose to be taken as 2 tablets (child under 1 year 1 tablet) chewed, crushed or dispersed in water or clear apple juice. Oral suspension: 1-month expiry. Store in a refrigerator. Ideally taken 1 h before or 2 h after food. May be less important in children.
Stavudine (d4T, Zerit)	Under study: (ACTG332) 1mg/kg b.d.	Over 3 months and <30 kg: 1mg/kg b.d. ≥ 30–60 kg: 30 mg b.d.		<60 kg: 30 mg b.d. ≥ 60 kg: 40 mg b.d.	Capsules: 15mg, 20 mg, 30 mg, 40 mg Oral solution: 1mg in 1 mL	Oral solution: 1-month expiry. Store in a refrigerator. Large volume of syrup.

Table 10 (cont.)

Dosage (oral unless specified)

Names of drug	Neonatal (<30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5) / adult	Formulations	Special instructions
Nucleoside / Nucleotide reverse transcriptase inhibitors (NRTIs / NtRTIs)						
Lamivudine (3TC, Epivir)	2mg/kg b.d.	Over 1 month: 4mg/kg b.d. or 8mg/kg o.d. (PENTA 13). Maximum 300 mg daily.		150 mg b.d. or 300 mg o.d	Tablets: 100 mg, 150 mg Tablets combined with: zidovudine – see zidovudine, abacavir and zidovudine – see abacavir Oral solution 10 mg in 1ml.	Well tolerated. Use oral solution within 1 month of opening.
Abacavir (ABC, GW1592U89, Ziagen)	2mg/kg b.d.	1–3 months: 8mg/kg b.d. under study. Over 3 months: 8mg/kg b.d. or 16mg/kg o.d. (PENTA 13) Maximum 600 mg daily.		300 mg b.d. or 600 mg o.d.	Tablets: 300 mg Tablets combined with zidovudine and lamivudine: abacavir 300 mg, zidovudine 300 mg, lamivudine 150 mg (Trizivir) Oral solution: 20 mg in 1ml.	Must caution parents about risk of serious hypersensitivity. Patients should not interrupt therapy without consulting their doctor.
Non-nucleoside analogue reverse transcriptase inhibitors – (NNRTIs)						
Nevirapine (NVP, Viramune)	Inadequate data but 2–5mg/kg o.d. has been used. Post Exposure Prophylaxis (combined with 2 NRTIs) 2mg/kg o.d. for 14 days then stop due to long half-life. Continue NRTIs for 4 weeks in total. If treatment is to continue increase to 4–5mg/kg o.d. after 14 days and increase again at 2 months	Inadequate data. 150–200 mg/m^2/day o.d. for 14 days then, if no rash, increase to 300–400 mg/m^2/day in 2 divided doses. Alternatively: 2 months – 8 years: 4mg/kg o.d. for 14 days then 7mg/kg b.d. Maximum 400 mg daily. 8–16 years and <50kg: 4mg/kg for 14 days then 4mg/kg b.d. ≥ 50 kg: adult dose.		Over 16 years: 200 mg o.d. for 14 days then 200 mg b.d. 400 mg o.d. unlicensed.	Tablets: 200 mg Suspension: 10 mg in 1 mL	Few data on use with PI. Practice is to increase PI dose by about 30%. Suspension: shake well. Store at room temperature.

Table 10 (cont.)

Dosage (oral unless specified)

Names of drug	Neonatal (<30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5) / adult	Formulations	Special instructions
Non-Nucleoside analogue reverse transcriptase inhibitors (NNRTIs)						
Efavirenz (EFV, Sustiva)	Unknown	Inadequate data in children <3 years or <13 kg. capsules: Over 3 years: 13–15 kg, 200 mg o.d. 15–20 kg, 250 mg o.d. 20–25 kg, 300 mg o.d. 25–32.5 kg, 350 mg o.d. 32.5–40 kg, 400 mg o.d. Over 12 years and/or ≥ 40 kg: 600 mg o.d.		600 mg o.d Tablets: 600 mg	Capsules: 50 mg, 100 mg, 200 mg Tablets: 600 mg	Bedtime dosing is recommended especially during the first 2–4 weeks to improve tolerability of CNS side effects. The bioavailability of Sustiva oral solution is lower than that of the tablets or capsules. Capsules may be opened and added to food. Contents have a peppery taste.
Protease inhibitors (PIs)						
Indinavir (IDV, Crixivan)	Do not use in neonates due to risk of kernicterus	The safety and efficacy of the capsules is not established in children less than 4 years. >3 months – 17 years: 500 mg/m² t.d.s. Patients with a small surface area may require 300–400 mg/m² t.d.s With low dose ritonavir: 2–18 years: Indinavir 350 mg/m² b.d. With ritonavir 125mg/m² b.d.		800 mg t.d.s With low dose ritonavir: Indinavir 400 mg b.d. with ritonavir 400 mg b.d. Indinavir 800 mg b.d. with ritonavir 100–200 mg b.d.	Capsules: 100 mg, 200 mg, 333mg, 400 mg	Take on an empty stomach 1 h before or 2 h after a meal (or can take with a light meal). In combination with ritonavir food restrictions do not apply. Adequate hydration is required to reduce risk of nephrolithiasis (at least 2.5 pints in adults) If given with ddI give at least 1 h apart on an empty stomach. NVP or EFV are likely to reduce IDV levels. Store in original container with desiccant.
Ritonavir (RTV, Norvir)	Under study (PACTG-354) 350 mg/m² b.d.	>1 month of age: 350 to 400 mg/m² of body surface area twice daily with a maximum dose of 600 mg twice daily.	>1 month of age: 350 to 400 mg/m² of body surface area twice daily with a maximum dose of 600 mg twice daily. Start with 250 mg/m² to minimize risk of nausea and vomiting. Increase stepwise to full dose over 5 days as tolerated. Dose range 300 – 400 mg/m² b.d.	600 mg b.d. starting with 300 mg b.d. and escalating over 5 days or more as tolerated. Low dose to boost other PIs: e.g. 100 mg b.d.	Capsules: 100 mg Oral solution: 80 mg in 1 mL	Take with food to increase absorption and reduce gastrointestinal side effects. If RTV is given with ddI there should be 2 h between taking each of the drugs. Oral solution must be kept in the fridge and stored in the original container. Can be kept at room temperature if used within 30 days. To minimize nausea and vomiting escalate dose over 5 days or so as tolerated. Oral solution contains 43% alcohol and is very bitter. Do not mix it with water. To increase tolerability: • Mix solution with milk, chocolate milk or ice cream. • Dull the taste buds before giving, with ice or lollies. • Coat the mouth with peanut butter before the dose. • Give strong tasting food straight after the dose e.g. cheese, chewing gum.

Table 10 (cont.)

Dosage (oral unless specified)

Names of drug	Neonatal (<30 days)	Infant (1–12 months)	Paediatric (Tanner stages 1–3)	Adolescent (Tanner stages 4–5) / adult	Formulations	Special instructions
Protease Inhibitors (PIs)						
Saquinavir (SQV, Invirase, Fortovase)	Unknown	Unknown	Under study: 50 mg/kg t.d.s. With nelfinavir: 33mg/kg t.d.s.	Over 16 years: Fortovase 1.2g t.d.s. or 1.6 g b.d. With low dose ritonavir: Fortovase 1 g b.d. or Invirase 1 g b.d. with ritonavir 100 mg b.d.	Capsules: 200 mg hard gelatine (Invirase), 200 mg soft, gel-filled (Fortovase)	Take within 2 h after a meal. SQV concentration increased by giving with grapefruit juice. Photosensitivity can occur – sunscreen or protective clothing advised. Fortovase and Invirase are not interchangeable.
Nelfinavir (NFV, Viracept)	Under study: 40 mg/kg b.d. (PACTG-353) 50–75mg/kg b.d. as infant PEP	<1 year: 75mg/kg b.d. Preferably avoid. >1 year: 60 mg/kg b.d. • <12 months of age: 75mg/kg twice daily • 12-24 months of age: 60 mg/kg twice daily • >2 years of age: 55mg/kg twice daily with a maximum of 1250 mg twice daily		750 mg t.d.s. 1250 mg b.d.	Tablets: 250 mg, 625mg Oral powder: 50 mg/g	Take with food to enhance absorption. Can crush tablets and disperse in water then mix with milk / chocolate milk. Crushed tablets can be mixed with food. Do not mix with acidic food or juice due to poor taste. Adolescents need higher doses than adults do. If given with ddI NFV should be given 2 h before or 1 h after ddI.
Lopinavir/ritonavir (LPV/r,Kaletra)	No data on dosing for children <6 months old.	6 months – 12 years All doses given b.d. with food		Without NVP or EFV: 400/100 mg (3 capsules or 5 mL) b.d. With NVP or EFV: 533/133.3mg (4 capsules or 6.67 mL) b.d.	Capsules: lopinavir 133.3mg with ritonavir 33.3mg. Oral solution: lopinavir 80 mg with ritonavir 20 mg in 1 mL	Higher doses used with NNRTIs or if previously PI experienced. Liquid formulation has a low volume but a bitter taste. Capsules are large Take with food to enhance absorption – especially the liquid. Store in the fridge. Can be kept at room temperature for 6 weeks. ddI should be taken 1 h before or 2 h after LPV/r. 5 mL oral solution = 3 capsules. Kaletra® and rifampicin: Add extra ritonavir so that the lopinavir and ritonavir doses are the same i.e. add 60 mg ritonavir per 1ml Kaletra®.
		Weight (kg)	Lopinavir/Ritonavir dose (mg/kg) No NVP or EFV	Lopinavir/ritonavir dose (mg/kg) With NVP or EFV or, susceptibility		
		7 – <15	12/3	13/11.25		
		15 – 40	10/2.5	11/2.75		
		>40	3 capsules i.e. 400 mg / 100 mg	4 capsules i.e. 533mg/133.3mg		
		Equivalent to:	230/57.5mg/m² BD	300–133.3mg / m² BD		

Names of drug	More common side effect	Less common (more severe)	Rare
Abacavir (ABC, GW1592U89, Ziagen)		Approximately 1–3% of children develop a potentially fatal hypersensitivity reaction. Symptoms include fever, fatigue, malaise, nausea, vomiting, diarrhoea and abdominal pain or respiratory symptoms e.g. shortness of breath. Physical finding include lymphadenopathy, ulceration of mucous membranes and maculopapular or urticarial skin rash. Hypersensitivity can occur without a rash. Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase and lymphopenia. Most common in first 6 weeks of therapy. In patients with suspected hypersensitivity Abacavir should be stopped. Do not rechallenge as hypotension and death have occurred on re-challenge. Cases of mitochondrial toxicity have been reported (Section 6.2). Some of these have been fatal.	
Emtricitabine (FTC, Emtriva)		Headache, diarrhoea, nausea, rash and skin discoloration (hyperpigmenatation on palms and/or soles, predominantly seen in non-Caucasian patients). Cases of mitochondrial toxicity have been reported (section 6.2). Some of these have been fatal.	

Names of drug	More common side effect	Less common (more severe)	Rare
Tenofovir disoproxil fumarate (Viread)	Evidence of tubular leak syndrome i.e. renal toxicity including increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calcuria and decreases in serum phosphate have been seen. Hypophosphataemia in >10%. Patients at risk of renal impairment should be monitored closely.	Approximately 1% discontinued due to gastrointestinal side effects.	At high doses tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals. These effects have not been seen in adults taking tenofovir for up to 1 year. It is unknown if these effects will occur in the longer term or in children. Cases of lactic acidosis and severe hepatomegaly with steatosis have been reported with use of the nucleoside analogues. Some of these have been fatal.
Non-nucleoside analogue reversa transcriptase inhibitors (NNRTIs)			
Nevirapine (NVP, Viramune)	Skin rash in 10%. If mild and systemically well can sometimes treat through with antihistamines. Some are severe requiring hospitalisation. Can be life threatening including Stevens-Johnson syndrome, toxic epidermal necrolysis, fever, nausea, headache and abnormal liver function tests.	Hepatitis which may rarely lead to severe and life-threatening and in some cases fatal liver damage. Very rarely – liver failure and granulocytopenia. Hypersensitivity reactions including, but not limited to severe rash or rash with fever, blisters, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, general malaise and/or significant hepatic abnormalities.	Manufacturers recommend frequent monitoring of LFTs for the first 3 months. The risk of hepatic events is greatest in the first 6 weeks but the risk continues past this period and monitoring is recommended through out treatment.
Delavirdine (DLV, Rescriptor)	Headache, fatigue, gastrointestinal complaints and rash (may be severe).		

Names of drug	More common side effect	Less common (more severe)	Rare
Efavirenz (EFV, Sustiva)	Skin rash, CNS system (somnolence, insomnia, abnormal dreams, 'Spacey kids', confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalisation, hallucinations, euphoria). Best avoided if previous psychological problems.		Teratogenic in primates (use in pregnancy should be avoided).
Protease inhibitors (PIs)			
Indinavir (IDV, Crixivan)	Nausea, abdominal pain, headache, metallic taste, dizziness and asymptomatic hyperbilirubinaemia (10%).	Renal stones/nephritis (4%) and exacerbation of chronic liver disease. Lipodystrophy Syndrome (section 6.1)	Hyperglycaemia, ketoacidosis, diabetes and haemolytic anaemia.
Ritonavir (RTV, Norvir)	Nausea, vomiting, diarrhoea, headache, abdominal pain and anorexia.	Circumoral paresthesias and increases in liver enzymes. Lipodystrophy syndrome (section 6.1).	Pancreatitis, hyperglycaemia, ketoacidosis, diabetes and hepatitis.
Saquinavir (SQV, Invirase, Fortovase)	Diarrhoea, abdominal discomfort, headache, nausea, paresthesias and skin rash.	Lipodystrophy syndrome (section 6.1).	Hyperglycaemia, ketoacidosis and diabetes.
Nelfinavir (NFV, Viracept)	Diarrhoea (mild – moderate)	Abdominal pain. Lipodystrophy syndrome (section 6.1).	Hyperglycaemia, ketoacidosis and diabetes.
Lopinavir/ritonavir (LPV/r,Kaletra)	Diarrhoea, nausea and vomiting.	Lipodystrophy syndrome (section 6.1).	Pancreatitis, hyperglycaemia, ketoacidosis, diabetes and hepatitis.
Amprenavir (APV, Agenerase)	Vomiting, nausea, diarrhoea, perioral paresthesias and rash	Life-threatening rash including Stevens-Johnson syndrome in 1% of patients. Lipodystropy syndrome (section 6.1).	New onset diabetes mellitus, hyperglycaemia, exacerbation of pre-existing diabetes mellitus, haemolytic anaemia.

Names of drug	More common side effect	Less common (more severe)	Rare
Fosamprenavir	In adults diarrhoea, nausea, vomiting, abdominal pain and flatulence, headache, hypertriglyceridaemia and rash occurred commonly i.e. 1–10%	Life-threatening rash including Stevens-Johnson syndrome in <1% of patients. Lipodystrophy syndrome (section 6.1).	New onset diabetes mellitus, hyperglycaemia, exacerbation of pre-existing diabetes mellitus, haemolytic anaemia.
Atazanavir	Asymptomatic elevations in unconjugated bilirubin (30% patients), jaundice (10% patients) headaches, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhoea and paresthesias.	Prolongation of PR interval on ECG.	Pancreatitis, hyperglycaemia, ketoacidosis, diabetes and hepatitis.
Tipranavir	In adults diarrhoea, nausea, fatigue, headache and vomiting are common.	Lipid abnormalities and hepatotoxicity.	
Fusion inhibitors			
Enfuvirtide (T20, Fuzeon)	98% patients get local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritis and ecchymosis. Usually mild or moderate in severity but can be more severe.	Unclear association with an increased rate of bacterial pneumonia.	Hypersensitivity reactions including fever, nausea and vomiting, chills, rigors, hypotension, elevated liver transaminases. Immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis and Guillan-Barre syndrome. Therapy should not restart following signs and symptoms consistent with hypersensitivity reactions.

Opportunistic Conditions

Bacterial Infections (Recurrent)

Febrile episodes should be managed similarly to those occurring in other immunocompromised children. There is a reasonable chance that a febrile episode may indicate serious invasive bacterial disease including: pneumonia, meningitis, septicaemia and osteitis. Where this is suspected, blood cultures should be drawn and parenteral antibiotics given, pending the results. Generally, an aminoglycoside should be given with a ß lactam antibiotic.

Viral upper and lower respiratory tract infections are also common as are secondary bacterial complications such as otitis media and sinusitis. A useful approach is to use amoxicillin / clavulanate and amoxicillin, both at 45mg/kg/day; thus giving high enough levels of amoxicillin for activity against *S. pneumoniae* with intermediate penicillin resistance (also useful as follow-up therapy for pneumonia).

Bronchiectasis

Common in children where initiation of HAART has been delayed.
Tuberculosis is often superimposed.
Children with LIP may have concomitant bronchiectasis.
CT scan is useful to confirm diagnosis.
Localized bronchiectasis may be amenable to surgical excision.
Chest physiotherapy is important (twice daily – home programme).
Caregivers should be trained with regard to daily physiotherapy and postural drainage.

Candidiasis

Oral
Miconazole gel, 4–6 hourly is effective for the treatment of oral thrush OR nystatin suspension, infants should receive 1ml (100 000u) and older children 2ml (200 000u) 4–6 hourly.

Oesophagus/trachea
Diagnosis: clinically with oropharyngeal thrush and odynophagia/dysphagia. Suspect in patients with drooling. Infants are irritable and appear uncomfortable. Therapy is with fluconazole at 3–6mg/kg/day for 14 days. It is often reasonable to conduct a therapeutic trial rather than attempting to confirm the diagnosis.

Treatment: fluconazole 3–6mg/kg/day for 14–21 days.

Maintenance treatment: not indicated: although recurrences are common, disease is not life-threatening and azole-resistant Candida strains develop.

Nappy rash
Often associated with a *Candida* infection.
They can usually be treated topically with Nystatin® cream bd.
The nappy area needs meticulous attention, as it may be a nidus for bacterial superinfection.

Cryptococcosis
Diagnosis: culture of *Cryptococcus neoformans* from any site or by positive cryptococcal antigen in blood or CSF.

Treatment: Amphotericin B 0.7–1mg/kg/day IV for up to 14 days followed by fluconazole 10–20 mg/kg/day for 8 weeks. Patients with initial raised intracranial pressure should have daily lumbar puncture, removing sufficient CSF to lower pressure to <20 cm H_20.

Maintenance treatment: fluconazole 10 mg/kg/day until CD4 percentage >20% if >6 years of age and >25% if 2 to 6 years of age on HAART (minimum of 6 months). Co-trimoxazole 5mg/kg/day (to prevent other opportunistic infections) until CD4 percentage >20% if >6 years of age and >25% if 2 to 6 years of age on HAART (minimum of 6 months).

Cryptosporidiosis
Diagnosis: stool examination.

Treatment: no effective therapy available – loperamide and oral rehydration solution helpful. May respond well to HAART. Aggressive nutritional and fluid support.

Maintenance treatment: None. Co-trimoxazole prophylaxis (to prevent other opportunistic infections).

Cytomegalovirus (CMV)

Pneumonitis
Causes severe interstitial pneumonitis, often with PCP. Occurs most commonly in the first year of life in infants not on co-trimoxazole prophylaxis. The most common situation is where the mother had not been tested in pregnancy.

Diagnosis: CMV-IgM suggestive. pp65 antigenaemia test good evidence. Lung biopsy definitive but seldom done.

Treatment: The role of ganciclovir is uncertain but likely to be beneficial. Dosage 10 mg/kg/day in 2 divided doses IVI for 2 to 3 weeks. Treat for PCP and bacterial pneumonia.

Zidovudine is best avoided in combination with gancyclovir as both agents suppress the bone marrow.

Early initiation of HAART essential, preferably while still receiving ganciclovir to avoid Immune Reconstitution Inflammatory Syndrome (IRIS).

CMV retinitis
Diagnosis: fundoscopy by an ophthalmologist.

Treatment: Ganciclovir 5mg/kg bd IV for 14 days (patient should be admitted to hospital).

Maintenance treatment: Ganciclovir 5mg/kg/day. Discontinue when CD4% is >14% on HAART (in consultation with an ophthalmologist). Treatment should be continued for at least 6 months.

CMV GIT (colitis/oesophagitis)
Seldom diagnosed in infants.
Diagnosis: histology of biopsy of ulcer.

Treatment: Ganciclovir 5mg/kg bd IV for 14–21 days (patient should be admitted to hospital).

Maintenance treatment: not necessary.

Diarrhoea (non-specific)
May be persistent and associated with failure to thrive.

Investigations

Often no pathogen is found on stool culture.
Culture for bacterial pathogens.
Stool microscopy for *Giardia* and *Cryptosporidium*.

HIV Encephalopathy
Signs and symptoms include:
- Regression of or failure to achieve developmental milestones.
- Motor signs including spastic diplegia, ataxia and pseudobulbar palsy.
- Acquired microcephaly.
- Expressive language delay in toddlers.
- Behavioural and concentration difficulties in older children.

Differential Diagnosis

Tuberculosis, CNS lymphoma and toxoplasmosis should be excluded.

Investigations

CT or MRI—former for cerebral atrophy and / or calcification of basal ganglia; and latter for white matter changes (all features of HIV encephalopathy). Lumbar puncture may need to be done to exclude subacute meningitis (bacterial, mycobacterial or cryptococcal).

Herpes simplex virus ulcers (including stomatitis)
Diagnosis: usually clinical – shallow, painful spreading muco-cutaneous ulcers. As disease advances spontaneous healing is delayed and then does not occur.

Treatment: acyclovir 2 years and over give 400 mg 8hourly for 5 days; Under 2 years, give 200 mg 8 hourly for 5 days
Give intravenously at 25mg/kg/day in 3 divided doses if unable to swallow. Analgesia – paracetamol 10–15mg/kg 6 hourly.

Isosporiasis
Diagnosis: special stain of stool.

Treatment: co-trimoxazole 10 mg/kg/day of trimethoprim 12 hourly for 3 weeks.

Maintenance treatment: co-trimoxazole 5mg/kg/day until CD4% >15%.

Management of HIV-Associated Kaposi's Sarcoma (KS) in children

Background to HIV-associated KS
- KS is a malignancy of lymphatic endothelial origin and is most common malignancy seen in children.
- Almost 100% of cases are associated Human Herpes Virus-8 (HHV-8) also known as KS Herpes Virus (KSHV).
- KS may involve the skin, oral cavity, lymph nodes or viscera (lung, intestines and rarely other organs such as the liver and bone marrow). Lymphoedema is a potential complication. Skin lesions usually subcutaneous.
- The typical CXR appearance of pulmonary KS is a reticulonodular appearance spreading from the hilar regions bilaterally. The diagnosis is confirmed by visualizing endobronchial KS lesions on bronchoscopy (biopsy poses a high risk of haemorrhage). Pulmonary KS may be

associated with intrathoracic adenopathy and/or pleural effusions which are typically bloody or serosanguinous.
- CXR is a useful screen for pulmonary KS. Faecal occult blood is a useful screen for GIT involvement.
- KS is a WHO Stage 4 defining illness.
- Although most cases are diagnosed on the typical macroscopic appearance of skin and oral lesions certain cases should have biopsy confirmation. Atypical skin lesions should be biopsied.
- Lymph nodes >2cm should be biopsied to exclude TB and lymphoma.
- Atypical oral lesions should be biopsied to exclude other malignancies such as lymphoma, squamous carcinoma and salivary gland tumours.

Treatment principles
- All HIV positive patients with KS should be commenced on HAART regardless of CD4 as KS is a Stage 4 defining illness. This should always be the first-line therapeutic intervention.
- Regression and resolution of mucocutaneous KS on HAART alone is well described. There are also case reports of regression of pulmonary KS lesions on HAART alone.
- HAART prolongs the time to treatment failure of KS chemotherapy.
- It is important to investigate for and exclude co-existent opportunistic infections (particularly TB), especially if the patient is going to receive chemotherapy, which will immunosuppress them further.
- Refer to paediatric oncologist.

Lymphoid Interstitial Pneumonitis (LIP)
Occurs in at least 40 percent of children with perinatal HIV. Usually diagnosed in children over one year of age. This is in contrast to *Pneumocystis jiroveci pneumonia* (PCP), which is more common below one year of age. Median survival is five times longer for children with lymphoid interstitial pneumonitis (LIP) than PCP.

LIP is characterised by diffuse infiltration of pulmonary interstitium with CD8+ T lymphocytes and plasma cells. It may progress to hypoxaemia. Superimposed bacterial infections are common and bronchiectasis may develop.

Clinical

Symptoms include: slowly progressive tachypnoea, cough and wheezing.

Signs include: clubbing, parotid enlargement, generalised adenopathy, hepatosplenomegaly. Bacterial superinfection is common.

Radiological: reticulonodular infiltrates associated with hilar adenopathy.

Diagnosis: the least invasive is obviously a diagnosis of exclusion. A lung biopsy may be needed to exclude tuberculosis. A CT scan of the lungs may be necessary to exclude bronchiectasis (consult a pulmonologist).

Management

HAART
Lung function in older children may identify those with reversible bronchoconstriction that may benefit from an inhaled bronchodilator and inhaled steroid therapy.

Treatment: prednisone 2mg/kg/day for 4–6 weeks. Wean to 0.5mg/kg on alternate days if possible and according to symptoms. Treat only if the child is symptomatic.

Microsporidiosis

Diagnosis: demonstration of the organism on stool (special stains or PCR) or on small bowel biopsy.

Treatment: one strain (E intestinalis) responds to albendazole 400 mg bd for 5 days – if >2years. Responds well to HAART.

Maintenance treatment: none.

Mycobacterium Avium Complex (MAC infection disseminated)

Diagnosis: culture from blood, lymph node biopsy or bone marrow – usual organism is *Mycobacterium avium* complex. Culture from sputum is unhelpful and is NOT an indication for treatment.

Treatment: clarithromycin 15mg/kg/day in 2 divided doses **plus** ethambutol 20 mg/kg/day. For extensive disease add ciprofloxacin 30 mg/kg/day in 2 divided doses. Consider adding amikacin 15mg/kg daily until good response. Initiate HAART and stop MAC treatment after 12 months if CD4% >15.

Maintenance treatment: see above. Co-trimoxazole.

Mycobacterium Tuberculosis

Diagnosis

History: History of exposure to adult with tuberculosis, cough >14 days and failure to thrive.
Examination: Generalised lymphadenopathy, hepatosplenomegaly, consolidation and pleural effusion, unusual features of PTB in HIV disease include otorrhoea, finger clubbing and presentation as an acute lung infection.
Chest X-ray: bronchopneumonia with hilar adenopathy, miliary changes and pleural effusions.
Mantoux ≥ 5 mm.
Microbiology: acid fast bacilli on Ziehl-neelsen, confirmed by culture on early morning gastric aspirate, induced sputum, CSF pleural and ascitic fluids.

Management

The source/index case should be identified and treated.
All contacts should be screened for tuberculous infection.
Monitor the nutritional status of the child to assess response to treatment.
Only symptomatic pleural effusions should be drained.

Drug treatment

Refer to state sector clinic.
Directly observed therapy short course using fixed drug combination is recommended to avoid drug resistance.
Treatment should be given five times per week in both the intensive and the continuation phases.
In special circumstances (for example, those who stay far from health facilities and have no DOT supporter), treatment may be given three times per week, in the continuation phase only.
HIV infected children with tuberculosis should be treated as per standard treatment protocol.
Regimens: used fixed drug combinations rifampicin and INH for 6 to 9 months and PZA added for 1st 2 months.

Adjust treatment dosages to body weight.

All children with severe forms of tuberculosis (meningitis, spine, peritonitis, miliary, bones) should be managed using 4–drug therapy daily (INH + rifampicin + PZA + ethionamide) at double the standard dose for 2 months during the initial phase and INH + rifampicin daily × 5 per week for 7 months in the continuation phase.

Ethionamide is preferred to ethambutol for children under 8 years of age.

All HIV infected children of any age in contact with an adult who is TB infected should be screened for tuberculosis. If negative, the child should receive chemoprophylaxis.

Congenital Tuberculosis

Acquired through placental blood flow or via the passage of swallowed maternal blood during delivery or via inhalation of the bacilli during the neonatal period.
The incidence is increasing in the HIV era.
Diagnosis: Positive vaginal swabs or sputum for *M.tuberculosis* in the mother.
Hepatosplenomegaly and a suggestive chest × ray.

Drug treatment

Neonates born of mother with active tuberculosis and who do not have signs of TB:

- INH plus Rifampicin for 3 months.

Then place a Mantoux and if negative, BCG is given and TB treatment discontinued.
If Mantoux is positive or TB suspected full TB treatment is given and the child followed up. At 6 months, BCG should be given if child does not have symptomatic HIV.

Pneumonia

Bacterial

Diagnosis: as for community-acquired pneumonia in HIV negative.

Treatment: ceftriaxone OR cefotaxime OR co-amoxiclav for 5–10 days. In severe pneumonia add aminoglycoside. Consider treating for PCP.

Maintenance treatment: Ensure that co-trimoxazole prophylaxis continues if frequent.

Pneumocystis pneumonia

Diagnosis: Most common in 1st 6 months of life where antenatal screening had not been done and where co-trimoxazole prophylaxis was not given. Special stains of broncho-alveolar lavage or induced sputum (following nebulisation of hypertonic saline). Suspect in any infant presenting with severe pneumonitis and requiring oxygen. Clinical diagnosis is suggested by bilateral interstitial ("ground glass") infiltrate on CXR. Hypoxia common.

Treatment: co-trimoxazole 20 mg/kg/day in 4 divided doses intravenously for 21 days. Change to oral therapy at same dosage once patient is stable. Consider giving hypoxic patients prednisone 2mg/kg/day for 7 days and then wean, over a week (may exacerbate concomitant CMV pneumonitis). There are limited options available in South Africa for patients with co-trimoxazole intolerance – rechallenge should be attempted. Rechallenge or desensitise rapidly with co-trimoxazole under antihistamine cover. This option is risky if the original co-trimoxazole hypersensitivity was life-threatening.
Maintenance treatment: co-trimoxazole 5mg/kg/day until CD4 percentage >20% if >6 years of age and >25% if 2 to 6 years of age on HAART (minimum of 6 months).

Progressive multifocal leukoencephalopathy

Diagnosis: non-enhancing lesions on MRI together with positive PCR for JC virus on CSF. Definitive diagnosis requires brain biopsy (seldom necessary).

Condition	Treatment options	Dosage	Duration	Prophylaxis
Salmonella bacteraemia	Ceftriaxone	50 mg/kg/day (can change to po and adjust according to sensitivity of organism).	7 to 10 days (4–6 weeks if recurrent)	N/R.
Tuberculosis	Standard short-course		6–9 months.	
Cytomega-lovirus	Short-course ganciclovir Long-term ganciclovir for retinitis not supported.	5mg/kg bd for one day then 5mg/kg/day.	2–3 weeks.	N/A.
Isosporiasis	Co-trimoxazole	10 mg/kg/day (trimethoprim) qid × 10 days, then 5mg/kg/day bd × 3 weeks.	4 weeks.	Co-trimoxazole 5mg/kg trimethoprim daily.
Cryptospo-ridiosis	None available.	N/A.	N/A.	N/A.
Bacterial pneumonia	Cefuroxime + Gentamicin	150 mg/kg/day tds IV 5mg/kg/day tds.	10 days.	
Mycobac-terium avium-intracellulare	Best results clarithromycin + ethambutol + rifabutin (adults). Clarithromycin Ethambutol Rifabutin Ofloxacin Amikacin or streptomycin	 15mg/kg/day bd 25mg/kg/day 5mg/kg/day-dosage under study. If cannot obtain, use rifampicin 20 mg/kg/day. 20 mg/kg/day. 20 mg/kg/day.	Ongoing.	
Bacterial meningitis	Cefotaxime OR ceftriaxone consider adding vancomycin if S.pneumoniae suspected or cannot be excluded.	200 mg/kg/day tds IVI 100 mg/kg/day daily, IVI; 60 mg/kd/day qid IVI.	7–14 days 7–14 days.	

* Adjunctive prednisone 2mg bd for seven days should be given to hypoxic patients.

Specific Issues for Adolescents

What about adolescents?

There is little expertise in treating adolescents in South Africa. They are at high risk for acquiring HIV and more vertically infected children can be expected to survive to this age. Compliance may be an especially important issue. Also the issue of disclosure of diagnosis has ramifications on compliance. For adolescents with early sexual development (Tanner stage 1 and 2) paediatric dosages should be used and for more advanced sexual maturity (Tanner stage 3 and 4), adult dosages are indicated.

Sexually active adolescents are at risk of contracting HIV. Pre-emptive counselling should take place. Perinatally infected children will rarely reach adolescence and if they do, they will need counselling regarding modes of transmission and prevention of transmission. Open discussion is encouraged.

Adult treatment guidelines are appropriate for post-pubertal adolescents (Tanner 5). Non-compliance is problematic. Strategies such as more frequent visits and intensive counselling should be introduced to promote adherence.

Tanner Staging for Boys

Stage	Pubic Hair	Penis	Testes
1	None.	Preadolescent.	Preadolescent.
2	Scanty, long, slightly pigmented.	Slight enlargement.	Enlarged scrotum, pink texture altered.
3	Darker, starts to curl, small amount.	Longer.	Larger.
4	Resembles adult, less than adult.	Larger, glans and breadth increase in size.	Larger, scrotum dark.
5	Adult distribution, spread to medial surface of thighs.	Adult.	Adult.

Tanner Staging for Girls

Stage	Pubic Hair	Breasts
1	Preadolescent.	Preadolescent.
2	Sparse, lightly pigmented, straight, medial border labia.	Breast and papilla elevated as small mound; areola diameter increased.
3	Darker, beginning to curl, increased amount.	Breast and areola enlarged, no contour separation.
4	Coarse, curly, abundant but less than adult.	Areola and papilla form secondary mound.
5	Adult feminine triangle, spread to medial surface of thighs.	Mature; nipple projects, areola part of general breast contour.

Application to Aid for AIDS (AfA) Programme

Who, why, how?

Who is Eligible to Apply?

- Any beneficiary of a scheme option contracted to AfA or
- Any employee who meets the eligibility rules of a corporate HIV treatment programme contracted to AfA or
- Any member of a NGO or other public sector based treatment programme for which AfA provides disease management support.

Any of the individuals mentioned above with confirmed HIV infection may apply to join the programme. It is not necessary to wait until the patient qualifies for antiretroviral therapy, or has AIDS before they apply. Early application to the programme allows access to monitoring tests, vaccinations, immunizations and vitamin supplements. Applicants will also be counselled regarding the importance of adherence to therapy and monitored by the AfA Treatment Support Consultant. They may also contact the AfA Treatment Support Line, who can explain their treatment or offer advice on changes in lifestyle.

What Benefits are available for individuals registered on the AfA programme

AfA manages the benefits specified by the rules of a medical scheme or of the funders of a treatment programme. These rules may specify detail such as:

- A monetary limit on the cost of treatment and / or
- Designated service provider for the supply of treatment including:
  - A defined network of doctors,
  - A specified medicine provider, or
  - A specified laboratory service
- Defined clinical protocols (for example they may specify that treatment may only be provided in accordance with state treatment protocols).

AfA is required to recommend treatment in accordance with the specified rules. Treatment and monitoring tests will only be included on individualised treatment plans if they are allowable within the benefits funded by the medical scheme or treatment programme.

AfA authorises reimbursement of the following:

- Antiretroviral therapy (guidance as to antiretroviral therapy that will be considered for payment can be found in this booklet under the sections on antiretroviral therapy.)
- Treatment and prophylaxis for HIV related opportunistic infections.
- Immunisations
- Vitamins
- Pathology monitoring tests. The following tests are generally covered with the number per year being specified by individual scheme or programme rules:

- CD4 count
- Quantitative PCR – Viral Load
- Qualitative PCR – For infants post MTCT prophylaxis
- Full Blood Count
- ALT
- Triglyceride
- Cholesterol
- Blood Glucose
- HIV genotyping (only if approved by the AfA clinical committee)

Application Procedure

To maintain confidentiality, application forms are only available from the AfA programme. Application forms can be obtained by contacting AfA on 0860 100 646.

There are different application forms for medical schemes, corporate programmes and public sector based programmes – please confirm with AfA which application form is required.

Signed consent from the individual applying to join the programme is essential. Non medical scheme programmes mostly have separate detailed consent forms which must be completed and sent with the application form. Applications to register on the programme cannot be processed without the applicable consent form being completed and signed.

Once the application form is received, the applicant should consult his / her doctor, for an examination and completion of the form. The doctor will be paid a fee either under the tariff code 0199, or as otherwise specified under the rules of the treatment programme for this procedure. It is not necessary for medical providers to submit an account for this purpose – AfA undertakes to ensure that the appropriate payment is made.

Copies of the original laboratory reports should be faxed or posted, together with the completed application form, to the AfA programme.

Once received, the application will be reviewed by the AfA medical team. One of the consultants will contact the doctor, where necessary, and reimbursement for a holistic treatment plan will be agreed on. Applicants can join the programme before a CD4 count and viral load has been done, but antiretroviral therapy (except vertical transmission prophylaxis and post-exposure prophylaxis) cannot be authorised without these results.

An authorisation letter confirming acceptance onto the programme will be posted to the doctor and patient. This letter also specifies the treatment to be reimbursed and suggested investigations. The letter may be faxed on request. Details of the claiming procedure are sent to the patient and may also be obtained on request.

There will be regular telephonic contact with the patient in order to assist their doctor with monitoring compliance and counselling.

Application for Post-Exposure Prophylaxis (PEP)

As this is an emergency, the application procedure has been modified to facilitate authorisation of PEP within 24 hours. In this instance, the doctor or patient should telephone the AfA programme immediately and request a PEP application form. This will be faxed straight away and once completed, should be returned to the AfA toll-free line. Authorisation will take place immediately and the doctor will be notified (again via fax) regarding the authorised medicines.

If exposure occurs on the weekend, please ensure your patient gets the necessary medication at least 24 hours after exposure. Begin with a starter pack. You can then contact AfA, first thing on Monday morning, to complete the PEP application form and to arrange reimbursement for further PEP medication.

Motivation for Medication, Investigations / Procedures

Certain drugs require motivation before they will be authorised for payment by AfA. The number of these drugs has been kept to a minimum to reduce the administrative burden.

Motivation is required for:

- Reimbursement of changes to antiretroviral therapy.
- Ganciclovir (short courses).
- Ethambutol and azithromycin or clarithromycin for MAC infections.
- Pentamidine (nebulized). (No longer generally available)
- Chemotherapy for lymphoma.
- Anabolic steroids.
- Fluconazole, if prescribed for longer than two weeks.
- Ketoconazole or itraconazole, if prescribed for longer than two weeks.
- Nutritional supplements (other than vitamins) or enteral nutrition.
- Valaciclovir, famciclovir and acyclovir, if prescribed for longer than seven days (in adults).

If the clinical criteria are met, reimbursement for these drugs will not be refused.
Motivation is also required for all HIV drug resistance testing and CD4 counts or viral load estimations where the number recommended for reimbursement is exceeded.

To motivate, please contact the AfA programme or submit your motivation with the application form if your patient is applying for the first time.

<u>In order to process all applications timeously please ensure:</u>

- The patient is a valid member of the medical scheme option or is eligible for participation in a particular corporate or NGO based treatment programme.
- The medical scheme option is contracted to AfA.
- The application form contains:
  - The doctor's and the patient's signature (main member if patient is a minor).
  - The doctor's and the patient's contact telephone numbers.
  - The patient's weight and length. This is to ensure correct dosing.
  - Contact details to ensure confidential correspondence.

The AfA programme:

- Will never compromise the doctor's professional responsibility.
- Will take all reasonable steps to ensure patient confidentiality.

The success of the programme will depend largely on co-operation from, as well as communication with, both patients and providers of care. Notification of the occurrence of HIV-related events, treatment changes as well as hospitalization is necessary in order to route claims to the appropriate benefit.

We request that results of follow-up investigations (e.g. CD4 counts and viral loads) be faxed or posted to AfA in order for us to assist with monitoring the patient's progress. This is vital if the programme is to succeed. Please request pathology laboratories to send copies of tests to AfA, toll-free, on 0800 600 773.

Obtaining Medicines

Patients may obtain their medicines from a dispensing doctor, pharmacist or courier pharmacy. Certain medical schemes or other treatment programmes may have chosen a designated service provider for the supply of medicines authorised by AfA. Details of such arrangements can be confirmed with AfA.

Medicine providers will require a valid prescription (dated within the last 6 months) from the treating doctor. Members will present their letter of approval from AfA, listing the medicines authorised, plus a matching prescription (if medicines are dispensed by a pharmacy).

AfA transmits details of medicines authorised to scheme / programme claims administration systems. Real-time or EDI claiming mechanisms can therefore be used by providers to submit claims for medicines. In the event of paper claims needing to be submitted, please send these directly to AfA rather than the medical scheme or employer group. This is in the interests of patient confidentiality and prompt payment.

A list of all antiretroviral drugs including the amount you will be reimbursed is available on request from AfA.

Additional or Unauthorised Drugs

Should an AfA patient present you with a prescription for a drug that does not appear on their treatment plan, please contact the AfA programme. Our consultant will check for authorisation of the additional drug, and if approved, the drug may be dispensed and claimed for payment. If the drug is not authorised, it will be processed against the patient's Routine Medicine Benefit subject to the relevant scheme rules. Please submit accounts for these drugs as normal medicine claims. It is, however, best to pre-authorise the patient's HIV medication with the AfA programme to maintain patient confidentiality.

Other drugs, and medication used on a short-term basis for 'minor' HIV related illnesses will, in general be funded from the patient's Routine Medicine Benefit and will be subject to scheme rules.

Changing Therapy

Should the patient's doctor wish to change their treatment, AfA should be contacted immediately to authorise the changes for payment, and to update their records. Once authorised for payment, changes to treatment will be confirmed in writing. Letters will be sent to the doctor and the patient. If medication is obtained from a pharmacy, a prescription matching the updated treatment plan is required, in order for the medicines to be dispensed.

Claims for unauthorized medicines will be rejected.

Claiming Procedures

All claims for treatment authorised by AfA that are not claimed via online real-time claiming mechanisms should be submitted directly to the programme to ensure confidentiality. Please submit accounts to the following address:

Claims
P.O. 38597
Pinelands
7430

Faxing claims

Accounts may also be faxed to AfA on the following fax number: 0800 600 773.

When faxing claims please include the name and telephone number of a contact person in case the fax does not come out clearly.

Claim Queries

Please feel free to contact the Aid for AIDS programme if you are:

- Querying scheme options contracted to AfA.
- Querying whether a patient remains a valid member of a scheme or is eligible to join a treatment programme.
- Requesting an application form.
- Checking to see whether medicines for HIV / AIDS treatment have been authorised by the programme.
- Updating medication.
- Querying claims for HIV / AIDS treatment sent to the programme.
- Querying the drug pricing.

Please contact the relevant Hospital Benefit Management Programme (HBMP) regarding payment for hospitalisation. AfA will be able to direct you to the correct HBMP.

Aid for AIDS Internet Programme

Website: www.afadm.co.za/dms

The website facility allows:

- ❑ Providers to confirm medicine authorisations online.
- ❑ For the registration of employees of certain contracted companies and members of medical schemes outside South Africa with AfA electronically via the internet.

Please contact AfA to arrange access to this facility if desired.

CONTACT INFORMATION		
Aid for AIDS		
Phone (toll-free):	0800 227 700	(doctors and pharmacists only)
Phone:	0860 100 646	(for application forms, general queries and the Treatment Support Line)
Fax (toll-free):	0800 600 773	
Postal address:	AfA programme P.O. Box 38597 Pinelands 7430	
E-mail:	afa@afadm.co.za	

Courier Pharmacies		
Direct Medicines HIV unit:	+27 (0)11 456 8075 0861 444 410 0861 444 415	(phone) (phone) (fax)
Chronic Medicine Dispensary:	0860 633 420	
Freeway Pharmacy:	+27 (0)11 893 2962	
Pharmacy Direct HIV unit:	0860 103 810 0866 114 000/1/2/3	(phone) (fax)

CRISIS + HELP LINES	
Lifeline	0861 322 322
AIDS Helpline	0800 012 322
AIDS Law Project	+27 11 356-4100 (phone) +27 11 339-4311 (fax)

PUBLIC SECTOR ACCREDITED ANTIRETROVIRAL TREATMENT SITES
Please contact AfA for details

USEFUL WEB ADDRESSES	
Aid for AIDS	www.aidforaids.co.za
The Body	www.thebody.com (general info).
AIDSMAP	www.aidsmap.com
AVERT	www.avert.org
AIDSLINE	www.medscape.com then click on AIDSLINE.
HAART for Africa	www.haart4africa.com (Useful source of patient information sheets in a range of SA languages)
CDC	www.cdc.gov/hiv
Drug Interactions	www.hiv-druginteractions.org
John Hopkins HIV Guide	www.hopkins-aids.edu
SA HIV Clinicians Society	www.sahivcliniciansociety.org
UNAIDS	www.unaids.org
HIV AIDS Clinic	www.hivaidsclinic.com (online HIV training)

Notes

Adherence Measurement Methodology

[Author: Michael Hislop, MSc, Senior Data Analyst, Aid for AIDS Programme |Created: 2004-11-01 | Modified: 2005-01-11]

1. Introduction

This document describes an enhanced version of an adherence measurement methodology described previously (see Adherence_Methods_200311.doc).

The motivation for developing this methodology was two folds;

1. To make it possible to measure adherence for fixed periods, e.g. in first six months, year, two years, etc. In the original methodology it was only possible to express adherence as months with ART claims submitted as percentage of total months authorised. For example, if a patient had been on ART for 48 months, it was not possible to look at adherence in the first 12 or 24 months only. This limitation makes it less accurate to compare adherence in patients who have been on therapy for different lenghths of time, as the likelihood of good adherence decreases in relation to the duration of therapy.
2. To reduce the chances of counting two discrete dispensed dates, occurring within one month, as one rather than two claims, as was likely in the original methodology.

In addition to these two important factors, a careful audit of the active periods that beneficiaries were on each option was also required, to ensure that the 'period of exposure' was reported as accurately as possible.

2. General methodology

Overview of Adherence Measurement Methodology.

1. Medicine details extract from 2003, contains claims up to 200306 and complete treatment months up to 200303, for Medscheme beneficiaries associated with AFA at the time of the extract.
2. From medicine details, create a summary of claims for ART at a beneficiary, drug name, and dispensed date level. The drug level summary permits the allocation of a line by line drug equivalence, e.g. COMBIVIR has an equivalence of two.
3. Include only patients who have been authorised on full ART prior to 2003-03-01, i.e. patients must have started full ART before medicine claims cut-off.
4. From the first level summary, create a second level summary at a beneficiary, dispensed date, and script (sum of equivalence) level.
5. Some ART claims were missing in the medicine details extract, but were present in the claims data in a summarised form as AFA authorised claims (BRO code). Any BRO claim for more than R300, missing from medicine details, was inserted into the second level ART claims summary.
6. The effective date of ART commencement was established. It was assumed that effective ART commencement date was the earliest date that ART was dispensed, but only if ART was dispensed at earliest, in the month before AFA ART authorisation.
7. The number of days between ART dispensed and the effective date that ART was started was calculated in the second level ART claims summary. The number of months between ART dispensed and ARTstart was calculated based on the interval in days since ARTstart, divided by 30.4375.
8. From the second level summary, a third level summary was created at a beneficiary, months since ART start and sum of equivalence level. In some cases there were duplicates, i.e. multiple dispensed dates associated with the same dispensed month. More often than not, these were 'borderline' dispensed dates associated with the incorrect dispensed month. Incorrectly assigned

duplicates were identified based on whether they might be preceding or succeeding missing records in the sequence of claims.

9. Remaining patients with more 'actual dispensed months' than 'months relative to ART start', were manually checked, as this was suggestive of duplication.
10. A final adherence summary was generated by (i) creating a table containing all complete months relative to the start of ART that each beneficiary was active on each option, and (ii) flagging the active months where claims occurred.
11. Due to a significant number of errors in the beneficiary option level membership data, this data was put through a review and validation process to ensure that dates were plausible.

3. Source data.

1. Distinct ART drugs from the database of all reimbursable medicines (t_Drug_List), 100 in total.
2. Applicant data from the *Aid for AIDS* system.
3. ART authorisation data from the *Aid for AIDS* system.
4. Membership data for Medscheme associated AfA patients from Medscheme Datawarehouse.
5. Detailed Medicine claims data from Medscheme Datawarehouse.
6. Script level claims data from Medscheme Datawarehouse.

4. Beneficiaries for medicine claims extract and adherence analysis.

4.1. Introduction

This section describes the preparation of membership data of the medical scheme options against which AFA patients have been claiming for ART. At the time of preparing the data for this adherence analysis, only membership data for Medscheme administered schemes was available. A patient can belong to one option at a time, and may change from one option to another within a scheme, or may change from one scheme to another over time. It is essential to ensure that the duration of option membership is accurate, as this provides the period during which ART claims should be submitted. For example, if option duration is incorrectly given as twelve months, when it should be six months, and the patient has claimed for six months, adherence will be reported as 50% when it should, in fact, be 100%. To ensure that the data is as accurate as possible, two keys steps are taken, (i) the membership database is carefully checked to ensure that all the options to which patients have belonged are extracted, and (ii) that the dates on which patients joined and left these options are as accurate as possible. The first step ensures that all possible medicine claims data for each option that a patient belonged to can be extracted, and the second step ensures that the duration of option membership is not exaggerated.

4.2. Source data

There are several sources for medical scheme option membership data;

1. Application data (t_Application) in the Aid for AIDS system provides beneficiary numbers for patients who are currently on Medscheme administered options.
2. The AfA system also captures previous beneficiary numbers of AfA patients *whilst the patients were registered on the programme* (t_Application_History). This table also contains a lot of rubbish data which has to be excluded via a tedious audit process.
3. The Medscheme Datawarehouse has a database of all options to which Medscheme administered beneficiaries have ever belonged (DATAWARE.BENEFICIARIES). Via a number of steps it is possible to link patients to their option membership history via any current or previous Medscheme option membership numbers. Unfortunately, a significant number of these membership records are either void (never activated or claimed against), or have incorrect option joined or left dates. A painstaking consolidation process, described below, is required to audit this data.

4.3. *Method*

1. Extraction of beneficiary extract against which Medicine Details data was extracted.
    a. Extract all Medscheme patients and all non-Medscheme patients who are still associated with a Medscheme MemNum, e.g. Sizwe Medical Scheme, into AFA_Extract..Applicants_CRAM on 2003-06-13.
    b. Data loaded up in Datawarehouse as **BONZETM.APPLICANTS_CRAM** (24,977 rows).
    c. Extract all MemberNumbers & DepNums in CLAIMSP.BENEFICIARIES associated with the INTERNAL_NUMBER of these beneficiaries (5,166) into **AfA_DW_Beneficiaries_030623** on 2003-06-23. Total rows: 30,143.
    d. Prepare App_MemNum_History on 2003-07-03, a table containing all current and previous beneficiary numbers recorded for patients registered on AfA. There are 29,901 beneficiaries in App_MemNum_History with Medscheme-like MemNums.
    e. Add 1,927 extra BenNums from App_MemNum_History which were not extracted via AfA_DW_Beneficiaries_030623 methodology, most likely because the numbers were from a previous scheme to which the patient belonged.
    f. Final total, **32,070** beneficiary numbers. Merged data loaded up in Datawarehouse as **JOEV.REQ5117** on 2003-07-05. (4 excluded due to errors).
2. Extraction of beneficiary extract used to determine duration of option membership.
    a. Beneficiaries extracted on 2004-05-28 (AfA_DW_Beneficiaries_040528) by a method similar to the one described above.
    b. 35,655 Medscheme beneficiaries identified via AFA data in application and application history data (App_MemNum_History). Data loaded into Medscheme Datawarehouse as CLIFFORDG_DBA.MICHAEL_MEMBER_LIST.
    c. With join from CGMML to the Datawarehouse beneficiaries table on the medical scheme identification number (INTERNAL_NUMBER), 41,428 beneficiary records were identified. With join from CGMML to beneficiaries on the option beneficiary number, 2,262 beneficiary records were identified. The latter were not joined in the first instance due to missing or incorrect INTERNAL_NUMBER. In total, 43,690 beneficiary membership records could be identified. Some of these were invalid, and deleted, yielding a final total of **43,597** beneficiary membership records.
3. Audit of beneficiary extract used to determine duration of option membership.
    a. From beneficiaries extracted on 2004-05-28 (AfA_DW_Beneficiaries_040528), include only beneficiary records for patients on full ART who were *authorised* on ART prior to '2003-03-01' (authorised on ART for at least one month prior to claims cut-off) (21,473 of 43,597).
    b. These beneficiary records then subjected to an audit to determine whether the option membership duration was valid for adherence analysis. To this end, two flags were added to indicate (i) record should be excluded and the reason for exclusion, and (ii) record had been modified and reason for modification. For the latter, A and C indicate changes in Joined Date, B and D indicate changes in Left Date, and E indicates Left Date changed to date deceased (A & B identified in first iteration as patients having sum of the individual durations of option membership being longer than the interval between the earliest date joined and latest date left. C & D were identified via an audit process in Excel.). The results of the audit process are described in the table below.

Total	Difference	Percent	Description
21,473			Patient on full ART.
21,292	-181	0.8%	Exclude: [A] ARTstart >= '2003-03-01'
21,277	-15	0.1%	Exclude: [B] beneficiaries with implausible overlap in option membership or NULL dates.
	531	2.5%	FIX beneficiary joined / left data for those with overlapping option membership.
18,395	-2,882	13.5%	Exclude: [C] JoinDate2 >= '2003-03-01'
	8,001	43.5%	Active beneficiaries (LeftDate2 IS NULL)
	4,921	26.8%	LeftDate2 > '2003-03-31'

17,674	-721	3.9%	Exclude: [D] LeftDate2 <= JoinDate2
16,919	-755	4.3%	Exclude: [E] Fedhealth membership data a shambles. Exclude from analysis.
	18,327	85.3%	Beneficiaries with claims.
	921	5.4%	Beneficiaries with death date before option left date.
16,914	-5	0.0%	Exclude: [F] JoinDate2 IS NULL and MinTreatDate IS NULL
15,889	-1,025	6.1%	Exclude: [G] LeftDate2 < ARTStart.
	5,832		Option level ART start modified due to ARTStart < JoinDate2.
	711	4.5%	Beneficiaries with claims after date left.
	14,679		Distinct App_ID in ##DWBens

5. Medicine claims extract.

5.1. Introduction

This section provides the method used to extract medicine claims data for AfA patients from Medscheme Datawarehouse. It should be possible to associate all Medscheme beneficiary numbers of AfA patients with claims data from Medscheme Datawarehouse. No claims implies that the beneficiary either (i) never submitted a single claim (*unlikely with legitimate beneficiary numbers*), (ii) was registered under a non-functional beneficiary number (*possible with membership errors, e.g. patients temporarily captured under multiple member numbers*), or (iii) was somehow not joined to the claims table for data extraction (*unlikely*).

5.2. Method

1. Data extracted on 2003-07-11 by Joe Vala of Medscheme Datawarehouse.
2. JOEV.REQ5117 joined to DATAWARE.MEDICINE_DETAILS or DATAWARE.EVENT_HEADER on MemberNumber only. *Therefore claims for entire family, and not only the patient in question, were extracted.*

In total, data was extracted for 78,262 beneficiaries (6,261,220 lines). Of these **30,054** Beneficiary_Numbers associated with Aid for AIDS patients (via AfA_DW_Beneficiaries_030709 [Beneficiaries from JOEV.REQ5117]) (**3,848,791** lines).

6. Beneficiary level ART claims summary.

6.1. Introduction

From the detailed medicine claims data, it is necessary to create a beneficiary level summary of ART claims per month. This can then be compared to the months that beneficiaries were actually authorised on ART to derive a measure of their adherence to therapy.

6.2. Method

1. From medicine details, create a first level summary of claims for ART at a beneficiary, drug name, and dispensed date level, *including only patients who have been authorised on full ART prior to 2003-03-01*, i.e. patients must have started full ART before medicine claims cut-off. There are **341,897** ART drug claims in this table.
2. This drug level summary permits the allocation of a line by line drug equivalence, e.g. COMBIVIR has an equivalence of two. When the drug level data is later summed per month (to a script level), the sum of equivalence indicates whether the claim was complete, either dual or triple therapy.
3. All claims for single use ART, e.g. 'RETROVIR / 3TC STARTER PACK','RETROVIR IV 20ML' were excluded (**262**) from the adherence analysis, as these drugs should not be a component of on-going therapy.
4. From the first level summary, create a second level summary at a beneficiary, *dispensed date*, and script (sum of equivalence) level, creating a table of **159,195** 'script' lines per dispensed date. In some cases, patients claim one or more of their drugs on a different dispensed date in the same

month. It is therefore necessary to evaluate whether the drugs dispensed on different dates are actually part of the same script for the same month.

5. Some ART claims are missing in the medicine details extract, but are present in the claims data in a summarised form as AFA authorised claims (**BRO** code). Any BRO claim for more than R300, missing from medicine details, was inserted into the second level ART claims summary, **1,733** records, yielding a total table size of 160,928 records.
6. In order to determine the relative interval between a dispensed date and the commencement of therapy, it necessary to establish the effective date of ART commencement. The *effective* date of ART commencement was taken as the earliest date that ART was dispensed, but only if ART was dispensed at earliest, in the month before the authorisation of ART by AFA staff.
7. Once this is done, the number of days between ART dispensed and the effective ART start date, could be calculated in the second level ART claims summary. The number of months between ART dispensed and ARTstart, was then calculated from the number of days between ART dispensed and ART start, by incrementing in intervals of *30.4375* days.
8. From the second level summary, create a third level summary by beneficiary, months since ART start and sum of equivalence, containing 150,016 records. In some cases there are duplicates, i.e. multiple dispensed dates associated with the same dispensed month. More often than not, these are 'borderline' dispensed dates associated with the incorrect dispensed month. Incorrectly assigned duplicates were identified based on whether they coincide with missing records in the sequence. There were 4,227 misallocated scripts based on gaps in the sequence, yielding a new total of 154,243 records.
9. There were some remaining patients with more 'actual dispensed months' than 'months relative to ART start', suggestive of duplication. These were manually reviewed, through which an additional 403 misallocated duplicates were identified and added to the claims sequence, yielding a final row count of **154,646** months of ART claims.

7. Beneficiary level adherence summary.

7.1. Introduction

The beneficiary level ART adherence summary is created in two steps, (i) a table containing all complete months that each beneficiary was active on each option, and (ii) the ART claims summary described above is used to associate each claimed month to the relevant active month on each option.

7.2. Method

1. Create a table of complete active months that each beneficiary was on each option relative to the start of ART.
2. This is done by calculating the number of days between starting ART and leaving the option, then dividing the number of days by 30.4375 and rounding down the result to the smallest integer (Floor function) to obtain complete active months.
3. For example, if a beneficiary started ART on 16 March 2002, and left the option on 28 September 2003, then that beneficiary would have FLOOR(561/30.4375) = 18 active month on the option during which therapy should have been claimed.
4. If a beneficiary changed option, then the first active month was taken as the first complete month. For example, if a patient joined a new option 18.4 months after commencing therapy, then the first active month was taken as 20.
5. A potential limitation of this method is that active claim months can be lost. For example, if the patient in the last example left the previous option shortly before joining the next, then the last complete month on the first option would be 18, and the first complete month on the second option would be 20. Patients were given a slight benefit of the doubt in that if an actual claim occurred in month 19, then that month was added in as an active month.
6. In total there were **228,483** active months for patients on therapy in which ART should have been claimed.

7. Once the active months have been derived, the next step is to figure out in which of these months claims were actually submitted. This is done by associating active months with the equivalent month in which ART was claimed from the beneficiary level ART claims summary described above, in total **154,646** (68%).

8. Patient level adherence summary.

8.1. Introduction

The final adherence result needs to be expressed at a patient level. To do this, the beneficiary level adherence measure needs to be summarised at a patient level.

8.2. Method

1. The numerator is calculated as the sum of complete unique months that the patient was active on each option.
2. The denominator is calculated as the sum of complete unique active months in which the patient submitted claims for ART.
3. The patient level adherence is calculated as the first over the second, expressed as a percentage.

Date of implementation: 05/02/2008
Review: last – 05/02/2008 & next -05/05/2008

Job Description of an Adherence Counselor

PURPOSE

To outline the various functions and specific aspects involved in a counselors role.

BACKGROUND

Counsellors
These are specially trained counsellors that focus on the clinical and psychological aspect related to HIV.

DESCRIPTION

All patient calls from the 08601006465 line requiring intervention by a counsellor needs to be routed by the AFA call centre agents to 1 of the 4 adherence co-ordinators.

Qualities of a counselor

- The adherence Co-ordinator must be well informed about HIV and AIDS
- She/he is a professional person with a medical background and able to respond to clinical issues.
- Must understand all Antiretroviral drugs, and their side effects
- Must not be judgmental
- Must be polite and empathetic and understanding towards the patients
- Must respect patients view's, cultures and decisions.
- Must be friendly at all times
- Must be able to cope with own stress
- Must be able to speak at least two African languages e.g. Xhosa, Sotho, Zulu or Tswana
- Professional secrecy/ Confidentiality is essential

Problems that may affect Compliance

- Denial
- Depression
- Cultural beliefs e.g. using traditional medicines
- Not well informed about HIV/AIDS/AfA
- Unable to get treatment frequently from the supplier due to travelling problems
- Suppliers delaying to order the drugs
- Patient is not aware that the Rx is ongoing
- Side effects
- Patient sharing the medication
- Language barriers – instructions in English
- Unhealthy lifestyle – unsafe sex and alcohol abuse.
- Confidentiality e.g. Hiding the medication from other family members or partners.
- Pill Burden

How to over-come these problems

- Patients must be treated with respect and dignity at all times. Their needs, wants and preferences must always be taken into consideration when advice is given.
- Allow the process to be patient driven.
- Give information about HIV, AIDS and AfA.
- Encourage patients to be open about their status.
- Encourage good patient/doctor/counsellor relationship at all times
- Translate correspondence into pt's language.
- Refer clients to a counselling centre or a Psychologist in their area
- If pt's insist on using any traditional medicines advise them not to take a Jug of the stuff at a time, always encourage pts to still take their anti-retrovirals
- Advise them to look for moral support within the family
- They need to accept themselves and live with the virus
- Reassure clients all the time

Incoming Calls

- The caller must be identified
- If a caller is a family member of a patient, do not divulge any information about the patient but do answer any general questions that may be asked.
- If the caller is a member, describe the AFA programme and explain the difference between HIV and AIDS.
- Explain the importance of follow-ups.
- Give basic lifestyle advice on the use of condoms, diet, rest, exercise, compliance, abuse of alcohol, and the use of vitamins.
- If patient needs ongoing counselling refer to the counseling centre/psychologist in the pt's area.
- Check patient's file and explain pt's situation in detail e.g. the CD4, VL, FBC and PCR.

Outgoing Calls

The adherence co-ordinators will initiate calls to patients as follows:

For a Patient on the programme with no Rx authorised.

- Explain the programme, HIV and AIDS
- Explain the antiretroviral's, CD4, VL and FBC.
- Explain that treatment must be authorised, unauthorised treatment will not be paid for by AfA programme.
- Explain the importance of follow up tests
- Explain why the patient is not getting treatment and what will happen in future
- Stress the importance of safe sex, balanced diet, rest, exercise and use of vitamins.
- Patients can phone AfA for any queries
- Reassure patient at all times
- Need to be understanding and not judgmental

For a Patient that is accepted on the Programme with treatment authorised.

- Explain about the programme, difference between HIV/AIDS
- Reassure patient at all times
- Explain the importance of taking the treatment as prescribed, everyday, every month and at the same time.
- If the patient experiences any side effects to go back to the Dr. and never to stop Rx.
- Discuss treatment with the patient: one drug at a time e.g. (Videx, how to take it).
- Try not to please the patient by saying that your viral load is low.
- Explain about the follow-up CD4, VL, FBC and PCR and why these need to be monitored
- Advise on healthy life style and the usage of condoms, exercise, rest, balance diet, vitamins, abuse of alcohol and strict compliance and why.

Follow up Calls

- Follow up calls must be made to ensure compliance for patients who are very sick and with low CD4
- Patients with compliance problems may be due to side effects
- Patients who have been hospitalized
- Pregnant patients
- PEP patients

At all times, if you are unable to contact a patient, send a contact letter and make a note in the note pad, every time you work on a file.

VTP – Vertical Transmission Prophylaxis

- Patients must be contacted before they deliver and they need to understand what VTP is.
- If patient is on ongoing treatment she must be told that she must not stop Rx after delivery.
- Advise mother to take syrup with her to the hospital as baby will have it 8hrs after delivery
- Never breastfeed the baby
- Ask the Dr. to motivate for formula
- Explain the importance of follow-up test (CD4, VL, FBC and PCR)
- Basic education on healthy lifestyle