Retrospective Analysis of Outcomes in the Programme of Fast-tracking of Antiretroviral Therapy for Patients Admitted to a Palliative Care Centre after Diagnosis of Opportunistic Infections

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Submitted towards partial fulfilment for the degree M Phil Palliative Medicine at the University of Cape Town.

STUDENT NUMBER: EDWCHR003

DATE: 14 January 2010

SUPERVISOR: Dr. Liz Gwyther

DECLARATION

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26 January 2010

ACKNOWLEDGEMENTS

1. Dr. H Holst, CEO McCord hospital - support to develop the palliative care centre for People Living with HIV/AIDS.

2. Dr .Richard Murphy, Infectious Diseases Unit, Harvard Medical School – data analysis and biostats support.

3. Dr.H.Sunpath, Clinical Head of Medicine –mentorship and supervision of clinical care.

4. Roma Maharaj -Monitoring and evaluation officer at Siyaphila –maintaining the quality of data collection

5. Ansuri Singh, Fiona Samed and Daniel Wong –research assistants in data management.

6. Palliative care interdisciplinary team at Siyaphila –excellent team work to make the programme a success

7. Dr.Liz Gwyther, UCT –mentorship for and supervision of research.

8. Dr.S.Fakroodeen, Director Highway hospice, Durban –inspiration for AIDS palliative care

9. Patients and relatives of Siyaphila-our greatest inspiration to excel in our work

ABSTRACT

Title: **Retrospective Analysis of Outcomes in the Programme of Fast-tracking of Antiretroviral Therapy for Patients Admitted to a Palliative Care Centre after Diagnosis of Opportunistic Infections.**

Background : Although national guidelines in South Africa recommend starting antiretroviral therapy (ART) mainly to outpatients with WHO stage four disease and /or CD4 count of 200 cells/uL, immediate ART initiation after opportunistic infection (OI) treatment in the inpatient wards at several international sites has been shown to reduce the adverse outcomes of AIDS progression and death. This study describes a retrospective analysis of the effect of immediate initiation of ART after acute OI including tuberculosis in ART-naive patients hospitalised in Durban, South Africa.

Methods: Eligible patients who were admitted with acute OI were initiated on immediate ART in a palliative care centre. We conducted a retrospective quantitative analysis of patient information at admission and 24 weeks. The primary and secondary endpoints were 24-week mortality and virological outcome respectively. A convenience sampling was used covering a nine month period.

Results: 93 patients were enrolled (50% women, median age 37 years). The median CD4 cell count in this group with advanced AIDS was 21 cells/uL. OIs included pulmonary tuberculosis, 17%, tuberculosis meningitis, 11% and other extra pulmonary tuberculosis, 37%; cryptococcal meningitis, 13% and Pneumocystis pneumonia, 11%. The median number of days to ART after initial treatment for OI was 15 (IQR 12-20). During 24 weeks of follow-up, 8% experienced a serious

Immune Reconstitution Inflammatory Syndrome (IRIS) event; IRIS occurred in one of 12 patients with baseline cryptococcal meningitis and there was one IRIS-associated death. Among patients who remained in care, at 24 weeks 92% achieved virological suppression and the median improvement in CD4 cell count was 90 cells/uL with two-thirds achieving an improvement to above 100 cells/uL. The overall mortality in this clinically advanced patient group was 20% (95% CI: 13 -29%) and loss to follow-up was 6%.

Conclusion: Current South African policies of discharging patients after hospital admission for management of OIs for follow up and initiation of antiretroviral treatment at ARV clinics result in poor patient outcomes as described by reports from South Africa. In contrast, this study demonstrates the feasibility and effectiveness, under routine programme conditions, of a rapid, supervised inpatient ART initiation. Further research is needed to reduce the known high rate of early mortality among patients with advanced HIV disease.

Abstract (365 words)

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ACRONYMS AND ABBREVIATIONS

AIDS –Auto Immune Deficiency Syndrome

ART –Antiretroviral therapy

DHHS-Department of Health and Human Sciences

HIV –Human Immunodeficiency Virus

OI –Opportunistic Infection

PLWHA-People Living With HIV/AIDS

UNAIDS –United Nations AIDS

WHO-World Health Organisation

INTRODUCTION

Current South African policies of discharging patients after hospital management of OIs for follow up and initiation of antiretroviral treatment at ART clinics result in poor patient outcomes as described by reports from South Africa .[1] The proposed study seeks to describe the feasibility and effectiveness, under routine programme conditions, of a rapid, supervised inpatient ART initiation.

Guidelines on when to start ART in resource poor settings

At the International AIDS Society (IAS) meeting in Cape Town in July 2009, the president of the South African HIV Clinicians Society, Dr .F. Venter made a comprehensive assessment of the evidence used in various settings to decide about the most appropriate CD4 count at which to initiate ART.[2] His arguments are summarised in this paragraph. In South Africa, the threshold in the public health system remains 200cells/uL, based on the Department of Health guidelines published in 2004. In the private sector, medical schemes are generally using a threshold of 350cells/uL, based on the Southern African HIV Clinicians Society Guidelines. Other Sub- Saharan countries generally use a 200 threshold as well. Meanwhile, Europe and North America also initiate at first CD4 count below 350cells/uL.[3]

The 350 cells/uL threshold is supported with evidence from several studies: The When to Start Consortium, in an analysis of 15 cohorts studies, found a greater than two times hazard ratio for progression to AIDS or death in people with CD4 counts from 100 to 200cells/uL compared to people with CD4 counts of 201 to

300cells/ul.There was also a significant difference in progression between the CD4 count strata 151- 250cells/uL and 251- 350cells/uL.[3] In 2005 the CIPRA HT 001 study was done in Port-au-Prince, Haiti. Eight hundred and sixteen volunteers with CD4 counts between 200 and 350cells/uL were randomized to either start ART immediately or defer until their CD4 count dropped below 200cells/uL, the current standard in Haiti. The Data Safety Monitoring Board stopped the trial in May 2009 when it found clear evidence favouring the earlier treatment group. In the immediate group six people died versus 23 in the deferred group. Twice as many people contracted tuberculosis in the deferred group and these results are statistically significant. [4]

Francois Venter presented three pertinent issues affecting the discussion for the adult ART programme on when to start at the symposium at IAS 2009.[2]

1. In developed countries, the average patient initiates treatment with a CD4 count of 150 to 200cells/uL. In Sub-Saharan Africa the CD4 count for initiation has increased from 50cells/uL to about 100cells/uL. Venter pointed out that this was despite a large increase in testing in South Africa over the same period, with only about 20% of tested patients eligible for ART according to current guidelines.

2. Many people die waiting for treatment. For example, of 4570 patients followed up for at least one year in a cohort in Free State Province, South Africa, 53.2% died. Of these, 87% died before receiving ART. The challenge is to decide whether treatment should start (irrespective of CD4 count) earlier to reduce non-AIDS morbidity.

3. Earlier ART will have an effect on the outcome of opportunistic infections. There are high rates of opportunistic infections above CD4 counts of 200cells/uL in

resource poor settings. Additional concerns in resource –poor settings about opportunistic infections are related to the high burden of tuberculosis. There were also concerns about the greater risk of bacterial and fungal infections including cryptococcal meningitis, pneumococcal infection, salmonella, and malaria, even at higher CD4 counts.

Venter's analysis provides an excellent summary of the complex issues affecting when to start. His presentation shows that problems with systems are at least as important as changing guidelines. Even in developed countries many patients start late, being well within the guideline recommendations. The situation is much worse in resource-poor settings. The proposed study at the sub acute wards of McCord Siyaphila centre was done using current guidelines of the national South African ART rollout plan. However the main research question deals with a description of the inpatient ART model of care that will enable the clinicians to reduce the mortality among very ill patients admitted to the medical wards. The inpatient programme has the potential to reduce the mortality that is due to the long delays common to the outpatient ART model.

Revised ART guidelines.

In late 2009, both the Department of Health and Human Services (DHHS) in the USA and WHO guidelines raised the CD4-cell-count threshold for starting treatment. For the past several years, the results of several large cohort studies have shown that starting ART at CD4 counts of 350 cells/uL or even higher would protect against a variety of adverse outcomes.[3] The DHHS now suggests starting treatment when CD4 counts fall below 500 cells/uL, while the WHO recommends 350 cells/uL as

the threshold. [5,6] New WHO recommendations endorse earlier ART initiation for HIV-infected adolescents and adults and an even more aggressive approach for those co infected with tuberculosis or hepatitis B virus.

Meanwhile, in the developing world, treatment is seldom initiated until CD4 counts drop below 200 cells/ uL or clinical AIDS develops. Previous WHO guidelines have taken a cautious approach to HIV treatment because of the lack of resources and clinical infrastructure in many of the most severely affected countries. These new recommendations are much more aggressive, reflecting the latest evidence on the benefits of early treatment. Still, in many resource-constrained settings, practitioners have not yet been able to widely adopt the standards set by the WHO in 2006 and will therefore find it challenging to implement the new recommendations.

Clearly a progressive approach will be needed, with incremental implementation according to the availability of resources and the potential impact of individual strategies on morbidity and mortality. Of course, these findings that led to change of guidelines address only some of the challenges. Studies of the cumulative, long-term, treatment-related side effects associated with early versus late ART will supply information to address the other challenges. Each patient's personal risk-benefit calculation will continue to weigh heavily in all treatment decisions.

The national recommendations of 2009 for expedited ART includes adults with a CD4 < 100 cells/uL, adults with unexplained ongoing loss of weight, pregnant women qualifying for ART, and adults recently hospitalised with an HIV-linked condition including TB. [7]

Stages of HIV/AIDS disease

The human immunodeficiency virus (HIV) infection is primarily an infection of the immune system and over a number of years destroys the cells of the immune system especially the CD4 T-lymphocytes (helper) cells and thus causes the acquired immune deficiency syndrome (AIDS).The HIV/AIDS pandemic has resulted in a high rate of morbidity and mortality and at present the highest prevalence of people living with HIV are in sub-Saharan Africa. The medical aspect of the disease due to an immune deficient system renders the patient vulnerable to opportunistic infections (OI) and malignancies. The psychosocial aspects of the disease have also to be considered as it is associated with stigma. Many patients at McCord hospital seek medical attention only when the disease is far advanced because of stigma and a poor family support system. The WHO staging system which assesses the immune system is based on the clinical condition of the patient and it divides them into four stages. As most patients present in stage 3 and 4 of the disease it is important to know the clinical staging system. (Appendix 1)

Effect of the HIV/AIDS pandemic in public hospitals in Durban, South Africa

The HIV/AIDS pandemic has posed a number of challenges to the health care system in South Africa, especially in the care of patients who are in stage four of the disease and hospitalised for an opportunistic infection (OI). Patients often require prolonged hospitalisations for the treatment of the opportunistic infection. ART is the only recommended treatment for HIV /AIDS and arrests morbidity and mortality effectively. Over the past decade, HIV infection has become the most significant and urgent health crisis in South Africa (SA). This epidemic resulted in a large-scale,

comprehensive approach to treatment and care starting in 2003-2004.[8] The province of KwaZulu-Natal and particularly its largest city, Durban, have been especially affected, where the prevalence of infection is estimated to be between 31.8-40.8%. [9] A proportion of these patients present for the first time to the acute care medical services with advanced HIV/AIDS disease. Durban, the largest city in KwaZulu-Natal has only seven public hospitals that care for the patients seeking admission to the hospitals.

The McCord –Siyaphila centre in Durban.

McCord Hospital is located in central Durban and was established in 1909 as a missionary hospital to care for Zulu patients. It is now a semi-private district level hospital that has developed a comprehensive HIV/AIDS care and treatment programme to care for patients at all stages of their illness. Approximately 50% of the admissions to the medical wards are HIV patients in stage four of the disease. There are only 45 beds in the medical wards, with the average length of stay being ten days. This constrains the number of new patients that can be admitted daily and may also lead to the premature discharge of patients from the acute medical wards. Therefore a new palliative care centre, Siyaphila (meaning “We are well” in Zulu), was commissioned at McCord Hospital in May 2006 to provide sub-acute and ongoing inpatient care. The value of this in-patient programme is that it is linked to an acute care ward and the outpatient ART clinic of the hospital. Patients who develop intercurrent illnesses after transfer to the sub-acute ward could be referred back for acute care. Patients are also seen by the same team in the ART clinic on discharge so that continuity of care and early management of adverse events post-ART initiation could be expedited.

The role of ART and the integration of palliative care and HIV/AIDS care.

Palliative care as defined by the WHO is an approach which improves the quality of life of patients and their families facing life-threatening illness. Care is provided through the prevention, assessment, and treatment of pain and other physical, psychosocial, and spiritual problems. In the past palliative care was considered as a last resort and the patient either had disease specific treatment or palliative care. This was an 'either/or' scenario. Comprehensive palliative care in the context of HIV/AIDS, integrates palliative care in the continuum of care together with disease specific or disease-modifying treatment. This is the 'both-and' scenario.[10]

The palliative care centre at Siyaphila is able to provide this comprehensive care by providing both disease modifying treatment (treatment of OI and ART) and palliative treatment (pain and symptom control and supportive treatment addressing the psychological, social, spiritual, and cultural needs of the patient and family, including bereavement care). All medical inpatients are offered the option of being transferred to Siyaphila for ongoing inpatient care.

The comprehensive inpatient model for provision of ART to very ill patients admitted to Siyaphila.

Once patients have been started on appropriate treatment for the opportunistic infection and their condition is improving, they are transferred to Siyaphila centre. With the help of the multidisciplinary team (doctors, nurses, HIV counsellors, social worker, psychologist, dietician and physiotherapist) at the palliative care centre, those eligible for ART are enrolled on the ART programme. The eligibility criteria for ART initiation at Siyaphila are based on the clinical and social criteria from the 2004

department of health guidelines (WHO stage four disease and or CD4 count <200cells/uL and disclosure to one person).

In addition the Siyaphila criteria for inpatient ART initiation are:

1) Patient resides in the greater Durban area

2) Patient has disclosed HIV status to at least one person who could then be the treatment supporter

3) Patient is able to swallow his pills

4) Patient is able to afford staying in the palliative care centre at least for two weeks
Patients with HIV/AIDS were triaged to receive one of the two protocols of care that is advocated. This was designed for use at McCord hospital by consultants in HIV medicine as standard of care. [11]

(1)**Terminal care**: Patients with the following conditions are considered for end of life care according to palliative care principles: irreversible end-organ damage, advanced malignancies and /or are unable to take oral medication for various irreversible medical reasons. Among the diagnoses were: end stage renal disease with multiple co morbidities, advanced malignancies (Kaposi's sarcoma, lymphoma, carcinoma of the cervix), intractable cardiac failure with cardiomyopathy, pulmonary hypertension with poor prognosis, severe soft tissue sepsis and complicated central nervous infections with poor prognosis.

(2) **Sub-acute and ongoing care of treatable clinical conditions:** Treatment for the opportunistic infection was completed in the sub acute ward. Antiretroviral

therapy (ART), which is the cornerstone of palliative care in AIDS, is offered to patients who are eligible as described in the Siyaphila criteria above.
Siyaphila centre offers a package of healthcare that is patient-centred and comprehensive to incorporate the following components:

Clinical Care: This involves ongoing treatment of the OI until the patient has recovered sufficiently to become physically independent. ART is then provided from the first line regimen recommended by the department of health being Stavudine, Lamivudine and Efavirenz. The interdisciplinary team consists of doctors practicing different medical specialties. This expert multidisciplinary team approach expedited the care of the clinical problems and enabled patients to go onto ART earlier. A palliative care physician trained in HIV medicine worked closely with a specialist family physician who was also trained in HIV medicine and infectious disease physician .The infectious disease specialist and specialists in other fields of internal medicine were available for consultation at all times. ART initiation was expedited because of the skills of the medical team.

Spiritual Care: Consistent with the priority to treat total pain, a team of trained counselors and spiritual care givers help the patients deal with spiritual issues that cause them distress.

Psychological Care: A team of psychologists with a visiting psychiatrist assist patients to overcome psychological barriers in their care before and after ART initiation. Cognitive function and AIDS related dementia is also assessed before and after ART initiation.

Social Care: Patients and their families require various types of care including, financial help, patient treatment support and relationships in the home. They help

individuals and family members to maintain links to care services. Support group services are also provided on site.

Physical Rehabilitation: Physical therapy and nutritional interventions are very important for successful rehabilitation.

End of Life Care: Symptom management, supportive care through the patient's terminal phase of HIV/AIDS illness is provided by the interdisciplinary team. Bereavement counseling for the family is commenced and appropriate follow up done.

HIV Counseling Services: Trained lay HIV counselors are involved in ART literacy training before and after ART initiation. Group sessions are held with the entire interdisciplinary team before discharge of patients.

Community support and follow up: Those who are not eligible for ART are discharged to care providers and programmes in the area where they reside. The Sinikithemba ("we give hope "in Zulu) ART clinic at Mc Cord hospital is available to all patients commenced on ART at Siyaphila. Support group services at the hospital provide ongoing support.

Conclusion.

The delay in ART initiation due to long waiting lists in the clinic and the high mortality from this delay are important issues to be addressed. Another system of care like an inpatient expedited initiation programme that provides ART for the very ill patients will be described in this proposed study**.** A pilot study described below was done at McCord hospital on patients discharged from the acute medical ward. This study was the basis to do further work to provide expedited ART to very ill patients. Furthermore, the guidelines to start ART at CD4 counts <350 will further reduce the mortality from opportunistic infections. These guidelines are currently under review

by the department of health. However the expedited ART programme for certain categories of patients with CD4 <200 cells/uL are already approved by the department of health in 2009. [5]

AIMS AND OBJECTIVES OF RESEARCH

Aims

To analyse an inpatient programme for early ART initiation after diagnosis of opportunistic infections as well as 24 week outcomes.

Objectives

The objectives were

1) To determine the number of patients initiated on early ART who would otherwise have ART delayed.

2) To estimate the prevalence of adverse events, including IRIS.

3) To describe clinical and biochemical outcomes at six months.

4) To determine the rates for mortality and lost to care among patients enrolled.

5) To determine the predictors of early mortality.

6) To make recommendations to develop a protocol and system of care for early ART initiation in patients admitted to the acute medical wards of a district hospital.

LITERATURE REVIEW

Sources and purpose of review.

The literature search focused on the review of articles to assess the efficacy of expedited ART in very ill patients after the diagnosis of an opportunistic infection. The second challenge was to examine different systems of care to provide ART for patients admitted to a health centre. Literature review for international and South African articles was done by computer search using the key words "inpatient ART". Data from randomized controlled trials [12,13] and from the case controlled study done in an academic hospital in Cape Town [1] and several observational studies [14,15,16] are cited below. The randomised controlled studies showed good validity of the results when comparing the early and deferred ART groups. The case controlled study also compared two groups who initiated ART early, but in different settings. The data analysis showed good scientific rigor. However all these studies demonstrate the improved mortality outcomes after inpatient ART initiation. The prevalence of opportunistic infections differed between developed and developing countries and thus the search for local data from South Africa was an important aspect of the review.

Pilot study describing a historical control group at Mc Cord Hospital.

In a pilot study done by Murphy et al in an inpatient population group in 2006, the mortality rate was 52 % in patients discharged after treatment for an acute OI who did not access ART within four months. [17] The barriers to access ART in this study was not clearly described. However mortality was associated with lower CD4 count and the sickest patients were unable to access ART.

In this study including 49 patients conducted at McCord Hospital between December 2006 and August 2007, the researchers evaluated ART uptake (secondary outcome) and mortality (primary outcome) six months after admission for an acute OI. For the 20 patients (44%) who initiated ART, the median time from discharge to commencing an ART regimen was 82 days. Among the 25 patients (56%) who did not initiate ART, 13 died (mortality 52%). Overall, two-thirds of patients with higher entry level CD4 counts (50 –200 cells/uL) successfully accessed ART after receiving treatment for an OI versus 32% of patients with lower entry level CD4 counts (<50 cells/ uL) (p=0.06). Failure to initiate ART after admission for an OI was associated with an almost 13 fold increased risk of death.

The effect of ART soon after the diagnosis of various opportunistic infections common worldwide.

ART reduces overall mortality among persons with HIV-1infection. According to the Morbidity and Mortality Weekly Report (MMWR) of the Centre for Disease Control, Atlanta [18] dated 2004, providing ART in the setting of acute OIs has advantages that outweigh the disadvantages. ART initiation is especially indicated in the setting of acute OIs for which there is no known alternative treatment options. Kaposi's sarcoma (KS),[16] chronic diarrhoea caused by cryptosporidiosis and microsporidiosis,[17] and progressive multifocal leukoencephalopathy (PML),[18] have been shown to respond to ART and guidelines recommend immediate ART initiation.

The timing of initiation of ART in the setting of acute OI is currently an area of great interest. There is some concern for potential drug-drug interactions, toxicities and immune reconstitution inflammatory syndrome (IRIS) that may worsen the clinical

condition of the patient.[18] In Uganda, Bisson G. et al demonstrated better outcomes in starting ART together with treatment for cryptococcal meningitis.[19] Zolopa A. et al demonstrated the improvement in mortality rates for inpatients starting ART within two weeks of diagnosis of OIs.[12] This group was compared in a large, multicentre, randomised controlled trial to a group that started ART treatment two months after the diagnosis of an OI. The OIs treated were pneumocystis pneumonia, cryptococcal meningitis and toxoplasmosis. However patients with tuberculosis were not included in this study.

Studies that describe the timing of early ART after diagnosis of opportunistic infections common in South Africa.

The study in South Africa by Faesan S. et al also confirmed that the presence of TB at the start of ART did not adversely affect outcomes. [20] Other studies cited below demonstrate the relative safety of treating the most common opportunistic infections, namely cryptococcal meningitis and tuberculosis in South Africa, with ART early in the course of the disease, within weeks rather than months. Additionally, they conclude that the presence of an OI is not an absolute contraindication to start ART early. Lawn SD et al, in Cape Town described the challenges of the outpatient model of ART provision [21] in a study that followed patients for 34 days after enrolment. In the programme pre-treatment and early treatment deaths together accounted for 87% of deaths and were independently associated with advanced immunodeficiency at enrolment. The possible causes of late access to the ART programme were identified as: delays in health care access, health system delays, or inappropriate treatment criteria.

To address the question of timing of ART in TB, which is the commonest opportunistic infection in South Africa, a trial by the Centre for AIDS Programme of Research in South Africa was reported in 2008.[13] The Starting Antiretrovirals at three Points in TB (SAPIT) study supports the use of early ART in patients with acute OIs (within two months) after initiation of anti tuberculosis treatment irrespective of CD4 count. HIV and TB co-infected patients assigned randomly to receive ART, together with their TB treatment (integrated arm), were compared to patients assigned to receive ART upon completion of TB treatment (sequential arm). There was a mortality rate of 11.6 per 100 person-years in the sequential arm compared to the mortality rate of 5.1 per 100 person-years in the integrated arms. The early integrated arm started ART as soon as possible within the first two months of TB treatment and the late integrated arm started ART as soon as possible after completing the two months intensive phase of TB treatment. The ideal timing of initiation of ART to maximize benefit and minimize morbidity and mortality remains unclear but would appear to be within the first months of initiating anti-tuberculosis treatment.

Initiation of antiretroviral therapy (ART) is often delayed in patients with newly diagnosed AIDS and tuberculosis (TB), to avoid immune reconstitution inflammatory syndrome (IRIS) and a tangle of possible drug interactions and adverse effects. However, results from the CAMELIA trial [22]in Cambodia add to the growing body of evidence indicating that earlier ART is better. A total of 661 HIV-infected, ART-naive patients with smear-positive TB and CD4 counts <200 cells/uL (median, 25 cells/uL) were randomized to initiate Efavirenz + Stavudine +Lamivudine either two weeks or eight weeks after starting a standard four-drug regimen for TB. At one year, overall

mortality was 34% lower in the early-ART group than in the late-ART group, and a multivariate
analysis confirmed that late receipt of ART was an independent predictor of death. Among survivors, the virologic efficacy of ART was excellent in both groups.

These results confirm and extend the findings described above, of two other important trials: ACTG A5164, which showed the importance of early ART during treatment for opportunistic infections other than TB [12],and SAPiT, which showed that integrating ART into TB treatment is better than deferring it until after TB treatment is complete.[13] The analysis of early versus late ART in SAPiT is still pending, but one wonders whether simultaneous initiation of HIV and TB treatment could reduce early mortality rates even further.

IRIS and the effect of timing of ART

IRIS was found to be more common in the early treatment arm compared to the late treatment arm in most recent studies .[12,22] However there were no deaths from the IRIS event The benefits seem to outweigh the risks of IRIS. What is required is clinical vigilance and sound management strategies. Treatment of the OI early together with the continuation of ART is warranted. Patient information will enable patients to present early for clinical assessment, especially after discharge.

IRIS was not significantly different in the ACTG trial [12] between early (8/141patients) and deferred group (12/141patients). IRIS developed at a median of 33 days .There was no significant difference in IRIS between groups on steroids (6%) vs. those not on steroids (9.8%).For the spectrum of OIs (PCP) seen IRIS should not be a reason

to defer ART. In the SAPIT T trial [13] there were no IRIS deaths, in the integrated arm there were 52 /429 (12.1 %) cases of IRIS ,compared to 8 /213 (3.8 %) cases of IRIS in the sequential arm, which was statistically significant .(p value of <0.05).Ten patients with IRIS were hospitalised in the integrated arm and none in the sequential arm. Only four patients were on steroid treatment. In the CAMELIA study [22], IRIS was two to three times more frequent in the early arm (p< .0001).IRIS was not aggressive in its clinical presentation and was relatively easy to manage. This study supports a much earlier (within two weeks) initiation of ART in HIV/TB compared to other studies.

Different systems of care for the provision of inpatient ART

Academic hospital medical wards.

Eshun-Wilson et al evaluated the outcomes in patients commencing ART after OI during hospitalisation at a South African academic hospital between January 01, 2004 and March 31, 2008. [13] Selected patients were initiated on ART as inpatients among those admitted to the acute care ward. The controls were patients who attended the infectious diseases outpatient department during that period. Forty eight patients (80%) were admitted with AIDS-defining illnesses, the commonest admission diagnoses were Kaposi's sarcoma (seven cases), tuberculosis (seven cases), and non-Hodgkin's lymphoma (six cases). Eleven patients died before hospital discharge and six before follow up appointment. In the case-control analysis, patients who had been hospitalised and discharged for initiation of ARVs as outpatients had a greater risk of dying (odds ratio = 7.33; 95% confidence interval =

2.8 to 19.23) and were more likely to be lost to follow-up (odds ratio = 4.07; 95% confidence interval = 1.32 to 12.52). There were only 15 previously hospitalised patients with viral load measurements at 12 months.

The reasons for poor follow up were the great distances that patients had to travel to the hospital. The patients were referred to clinics that were located far away from the city centre. The median CD4 count in the hospitalised group and control group was 91 and 64.5 cells /uL respectively .The commonest AIDS-defining illnesses in the outpatient group were disseminated tuberculosis (19 cases) and oesophageal candidiasis (11 cases). It was established that there was a higher mortality among hospitalised patients, as these patients were admitted due to the severity and extent of their illnesses.

The high numbers lost to follow up among patients discharged from the hospital wards was noteworthy. Previous studies had suggested that up to 50% of patients who are lost to follow-up in low-resource settings have died.[22] Patients who had been initiated on ART while in hospital and who returned for follow-up and remained on ART had favourable treatment outcomes. This is similar to the findings by Soria A et al, [23] which showed good virological outcomes and adherence in an Italian cohort of patients commencing ART during hospitalisation. However, both studies are small making it difficult to draw meaningful conclusions from the results. Patients discharged from the wards who do remain in care have comparable treatment outcomes to those of more clinically stable patients. It will be ideal to place the very ill patients in a programme linked to a home-based care network. An improved system for patient follow-up and earlier initiation of ART was recommended to improve outcomes in hospitalised patients in these settings.

ART in an intensive care unit

It is possible to provide patients that are admitted in an advanced stage of disease with ART in the intensive care unit (ICU). A retrospective study conducted in Brazil adds to the evidence supporting early ART in patients with acute OIs. [24] This study suggests that those benefits might begin to accrue even sooner. The study involved 278 HIV-infected patients who were admitted to a Brazilian intensive-care unit (ICU) between late 1996 and late 2006. Eighty percent had AIDS-defining conditions, with the most common opportunistic infections being tuberculosis and pneumocystis pneumonia. The use of ART in the ICU (whether initiated then or previously) was associated with a 50% reduction in six month mortality; the benefit was statistically significant only if ART was used within the first four days after ICU admission. Survival curves for patients who initiated ART in the ICU versus those who did not, diverged within the first 25 days after admission; subsequently, similar numbers of patients died within each group. The rate of IRIS that was detected in the ICU was quite low (~1%), but this may be related to the difficulty of identifying IRIS in critically ill patients in a retrospective study. Mortality rates were high both in the ICU (55%) and six months after admission (69%). The benefit of ART in the ICU setting seemed mainly to be to improve survival rate at six months.

Palliative care inpatient unit.

Jameson described the success of an inpatient palliative care unit in treating both patients with cancer and HIV.[26] The inpatient unit was developed as a public-private partnership in Grahamstown to address the problems of the two diverse groups in the community; the affluent, elderly patients with cancer and the younger, often unemployed patients with AIDS. The author conducted the study on the 51 patients

admitted to the palliative care unit in the first three months following the opening of the ward (1 March-31May 2006). Of these patients, 36 (70%) had AIDS and 15 had cancer (30%).Patients had to fulfil the criteria of being a hospice patient and also have a primary care giver at home to care for the patient on discharge. Criteria for hospice care for HIV/AIDS patients include all patients in stage 3 or 4 disease and not only terminally ill patients. These patients require ongoing treatment for AIDS defining conditions and symptom management. The patients were admitted from the HIV clinic, medical ward and the hospice. The palliative treatment involved pain and symptom relief with the use of morphine for pain, dyspnoea, and diarrhoea, haloperidol for nausea and confusion, non-steroidal anti-inflammatory drugs for pain, lorazepam for anxiety and other medications commonly used in the palliative care setting. All AIDS patients were on ART. The outcome in 16 cases was death (6 had cancer).The AIDS patients stayed longer (average length of stay being 8.3 days) because of side-effects to ART or immune reconstitution syndrome (IRIS) as compared to the cancer patients (average length of stay being 3.8 days). The death rate in the first 3 months was 38% in the cancer patients and 33% in the AIDS patients. In the following two months the death rate was 33% in the cancer patients and 19% in the AIDS patients. Though the numbers were small the drop in the death rate may be related to earlier initiation of ART and application of palliative care principles in the treatment of AIDS patients. Larger studies are needed to establish the mortality benefit of early ART initiation.

Inpatient community health centre.

The Keiskamma AIDS Treatment (KAT) Programme was established in Hamburg, Eastern Cape in July 2004 in response to community needs – identified through

routine work in the local primary clinics. People living with HIV/AIDS who are too sick or too poor to access facility based resources were able to get ART through the Keiskamma AIDS Treatment Programme. [27] The study followed the progress of 174 patients in the period from July 2004 to February 2006. Members of the community were employed as nursing staff, caregivers, community health workers and drivers. Due to the remoteness and economic conditions of the communities, the effectiveness of the KAT Programme depended on three key components: 1) availability of in-patient facilities, 2) transportation and 3) a network of home- based care workers.

Keiskamma AIDS Treatment centre was established in an old house with 20 beds and patients stayed for one to two weeks and were educated about their illness and ART. Many of the patients were very sick and unable to care for themselves. Those who had an opportunistic infection were treated where possible. A high proportion of patients had TB. Patients left the centre once they had started ART. Transport was provided through two light delivery vehicles with drivers who not only brought patients to the Keiskamma AIDS Treatment centre but also took patients to the secondary and tertiary facilities for specialist consultation. The home- based care workers were able to monitor adherence in the communities and provide contact with the Keiskamma AIDS Treatment centre.

The study classified the 174 patients as ambulant or bedridden, CD4 count at treatment initiation was taken as baseline CD4. Possible patient outcomes at six months were:

1) Good response -viral load (VL) < 400copies / ml or CD4 count >250 cells/uL

2) Poor response -VL >400 copies /ml or CD4 count <250 cells/uL

3) Died

4) Lost to follow up

5) Insufficient data

6) transferred out (to other ART programmes.)

Most of the patients were female (74%) and about half were bedridden (42%) which makes a programme like this very beneficial in communities that are in the lower socioeconomic group. Baseline CD4 counts reflected that most of the patients had very advanced immunosuppression. Thirty seven percent were in the range of 0 -49 cells/uL and 26 % were in the range of 50 -99 cells/uL. Only 11 % had CD4 cells > 200 cells/uL. Of the patients with baseline CD4 counts 0-99 cells/uL, 56 %were bedridden and unlikely to have accessed conventional facility-based care. Although more bedridden patients died (43%) compared to ambulant patients (5%) the outcome was still considered as successful as the bedridden patients were extremely ill at treatment before the ART had therapeutic effect. The success of the programme was probably linked to the in-patient facility where ART counselling could be done and patients made ready for ART. The transport system made it possible for those who needed it most (the sickest and the poorest). The community health workers played the key role by providing an extensive support network. Community based ART programmes can be useful adjuncts to the facility based system. Effective treatment programmes must address the needs of the community. The study also provided evidence that no one should be regarded as too sick to access ART. Resources and effort need to be expended to bring these patients into

care and thus the necessity to work within the Government HIV/ART programme for sustainability.

Conclusions.

The literature review supported the efficacy of ART early in the course of stage four disease; especially after diagnosis and treatment of an acute opportunistic infection. However all these studies were reported on small numbers of patients and were done at a time when there was limited evidence for the efficacy for early inpatient ART initiation in very ill patients. The majority of HIV/AIDS patients are admitted to a district level public hospital in South Africa. This type of programme has not been established as a standard of care in this setting. There was a high early mortality when patients were discharged from the acute care wards with no access to ART within the first few months. The outpatient programme linked to some hospitals has several challenges to deal with very ill patients as well as a limitation on the numbers that could be seen in the clinic. Various inpatient programmes have been described which were based in the ICU, academic hospitals, community health inpatient centres and palliative care wards. What would be the best inpatient programme will depend on the needs of the community served by the programme. Thus, the rationale for the proposed study was to describe a unique system of care that is suitable to deal with the early provision of ART to very ill patients admitted to a district level public sector hospital.

Though AIDS has become a chronic manageable disease, because of ART, the morbidity and mortality remains high. A dynamic and integrated framework of both curative and palliative care are needed to meet the needs of the HIV positive

throughout the course of their illness. Decisions regarding the goals of care with respect to medical and psychosocial issues need to be more collaborative with patient focussed care.[28]

Thus a successful palliative care programme needs to have a national policy to ensure good standards, funding for education and training of health care workers and availability of necessary drugs for pain and symptom management.[29]

METHODOLOGY

Study Design

The study was a quantitative retrospective analysis through review of clinical records, of a cohort of HIV positive inpatients who were initiated on ART after the diagnosis of an OI.

Study Site

The study site was a palliative care centre (Siyaphila) attached to McCord hospital in Durban and the outpatient clinic, Sinikithemba.

Study population and sampling

The study population consisted of HIV positive patients admitted to Siyaphila from the acute care medical ward of Mc Cord hospital to which they had been admitted with the diagnosis of an acute opportunistic infection.

The study cohort was chosen as a convenience sample. The study sample consisted of the first consecutive 100 patients who were initiated on ART at Siyaphila between November 2006 and May 2007. Three hundred and fifty eight patients were admitted during this period.

Data collection:

Data extraction sheets

Two data collection sheets were designed

1) Initial data collection at time of admission (Appendix 2)

2) Six month follow up data collection sheet (Appendix 3)

The researcher developed the set of questions that were relevant to the study in consultation with colleagues and supervisor. The important data to be collected was formulated in order to answer the key research objectives. Demographic data and baseline clinical and laboratory data were needed to be compared with outcomes at six months. The optimal time for ART initiation was a key measurement and thus the time lines for admission and discharge were crucial. A record of the clinical progress before and after discharge was enumerated according to anticipated adverse events associated with the ART regimens used.

The researcher developed the initial and a follow up data sheet in consultation with the consultant of Medicine at McCord hospital. The source of data for the initial data collection sheet was the inpatient notes and discharge summary. The discharge summary was designed by the clinicians as a standard of care document for all inpatients to facilitate the handover of patients to the next level of care. The main source for the follow up data was the electronic patient record system used in the outpatient ART clinic at McCord hospital. Data recorded in the electronic records were consistent with department of health guidelines. It recorded clinical, immunological and biological outcomes mainly. Other laboratory data was limited to save costs.

Data collection process.

Data was collected by the researcher from the hospital database comprising of the inpatient files and discharge summaries from Siyaphila for the initial data sheet. The data was recorded for the first 100 patients who started ART. For the six- month follow-up data, the electronic patient record (EPR) and the patient files from the outpatient ART clinic-Sinikithemba ("We give hope" in Zulu), was used. The incidence of missing data was to be minimized by searching for information in all three records: the inpatient file, the electronic patient record and the outpatient file.

VALIDITY AND BIAS

Measures to ensure validity of data

Most data collection was carried out by trained volunteer research assistants who checked each entry twice. The consistency of data collection was ensured by using a customised data collection sheet as included in the appendices.

Reduction of bias

Selection bias:

All patients admitted consecutively from the acute care wards who were considered sick enough to be sent to *Siyaphila* were included in the study population. The same patients who were discharged were followed up by the research clinician over the six month follow up.

Information bias:

Data was validated by triangulating it from different sources in the hospital database before it was entered onto the patient data collection sheet. When information was missing on the electronic patient record, patient files were reviewed.

Confidentiality

The names of patients were not being disclosed .The data collection sheets were numbered. The data collection forms were identified by unique number ensuring anonymisation of the data.

Data analysis

An Excel spread sheet and Access database were created by a research assistant to record and identify key clinical and laboratory data at baseline and at six months for each patient. Data analysis was done using a standard statistical package. The statistical package used was the SPSS (Version 19.0, Chicago, IL).

The final outcome measures were: mortality at 24 weeks and virological and clinical outcomes including clinical complications. at 24 weeks.

Other data analysed were:

1. Demographic data,

2. Prevalence of different types of OIs,

3. Time of initiation of ART from date of diagnosis of OIs,

4. Prevalence of adverse events on ART,

5. Prevalence of different types of IRIS and

6. Clinical markers.

Ethical considerations

Consent

All patients joining the ART programme at Sinikithemba signed a contract as part of the help expand ARV therapy (HEART), a President's Emergency Plan for AIDS Relief (PEPFAR) initiative, consenting to the use of clinical information for research. Data was extracted from hospital database of patient records. Patients were not identified from the records. Permission from the medical superintendent at McCord hospital was obtained (Appendix 4)

Privacy

The data collection sheets were stored in a locker in the researcher's office. Information linking patients to the forms were kept in a separate site from the research data. The identity of the patient was not known to the research assistant who did the data entry, and thus the privacy of the patient was respected.

Ethics approval

Application to the Mc Cord Hospital Research Ethics committee. (Appendix 5)

Application to the UCT Post graduate ethics committee. (Appendix 6)

RESULTS

Three hundred and fifty eight patients were referred from the acute care medical wards of Mc Cord Hospital to Siyaphila centre. Only 93 patients (26 % of those admitted) were started on inpatient ART and were found to be eligible for analysis. Seven patients were excluded from the study because they had initiated ART at other sites and were changing service provider from other sites to McCord hospital. (Figure 1).

Figure 1 Inclusion of first 100 patients in immediate ART after OI diagnosis and discharge from the acute medical wards of Mc Cord Hospital to Siyaphila centre, from November 2006.

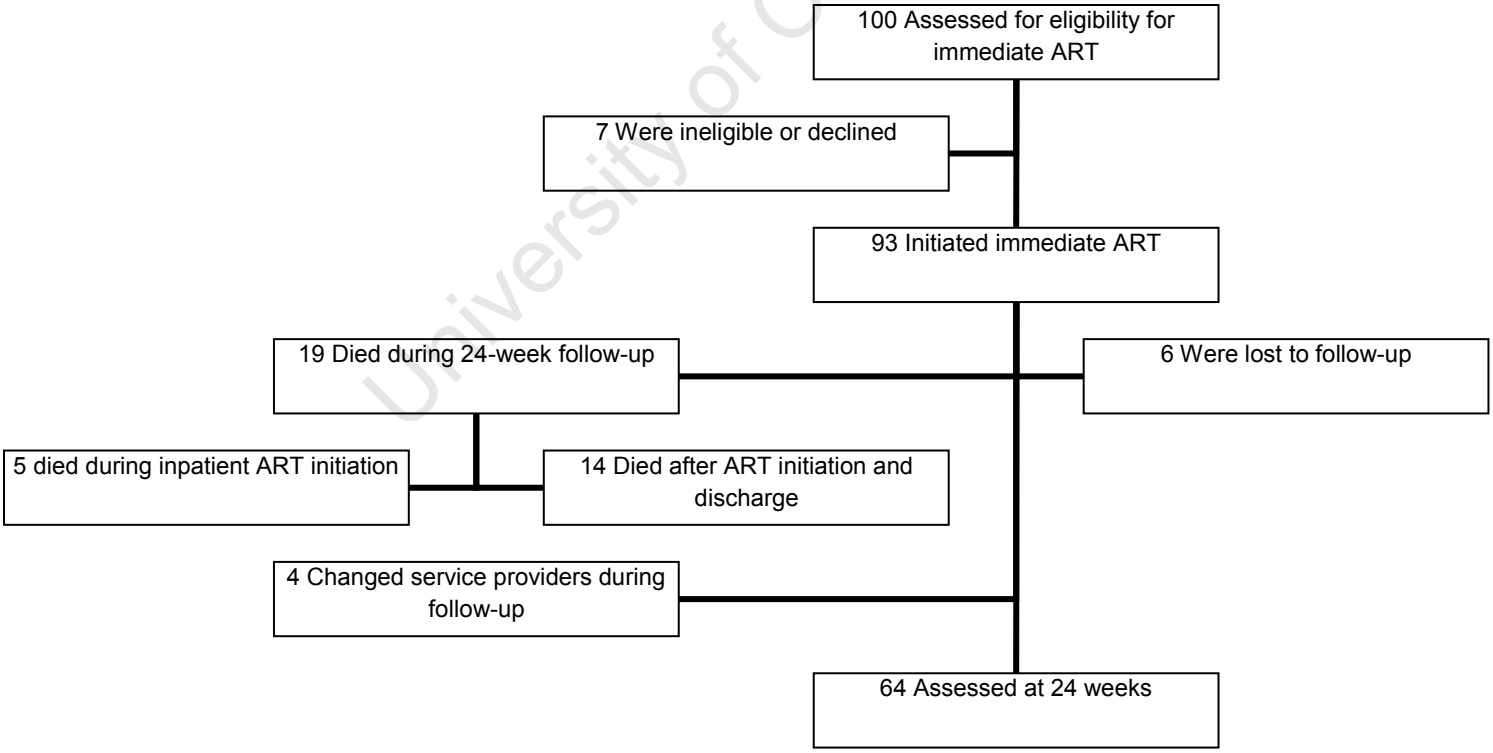

Table 1(A): **Baseline characteristics of first 100 patients at the time of OI when admitted to the acute care wards from November 2006 to May 2007.**

The median age in the cohort was 37 years and women constituted 45 % of the cohort. The majority of the patients were of black ethnic background (90 %). The median baseline haemoglobin was 9.9 g/dl (IQR 8.2 -11.3). The median baseline albumin was 25 g/l (IQR 20 -29). (See Table 1A)

Demographics and weight	**Patients N=93**
Median Age (years) [IQR]	37 [31-45]
Women no. (%)	46 (49)
Ethnicy no. (%)	
Black	84 (90)
Non-black	9 (10)
Median baseline weight (kg) [IQR] 2	54 [47-60]
Baseline weight < 45 kg – no. (%)	14 (15)
Other baseline laboratory parameters	
○ Median baseline hemoglobin (g/dl) [IQR] *	9.9 [8.2-11.3]
○ Median baseline albumin (g/l) [IQR] *	25 [20-29]
○ Median baseline creatinine (ul/l) [IQR] *	78 [66-97]

Table 1(B): **Baseline characteristics of first 100 patients at the time of OI when admitted to the acute care wards from November 2006 to May 2007.**

Acute OI- no. (%)	N= 93
Tuberculosis	
o Pulmonary	15 (16)
o Extrapulmonary	34 (37)
o Meningitis	10 (11)
Cryptococcal Meningitis	12 (13)
Pneumocystis neumonía	10 (11)
Chronic diarrhoea (>14 days)	4 (4)
Toxoplasmosis of the brain	4 (4)
Bacterial pneumonia	3 (3)
HIV-associated cardiomyopathy	1 (1)
Median baseline weight (kg) [IQR] 2	54 [47-60]
Baseline weight < 45 kg – no. (%)	14 (15)

Tuberculosis was the commonest OI, seen in 63 % (n=59) of the patients of which15/93 had pulmonary TB (16 %), 10/93 patients had TB meningitis (11%) and 34 /93 had other extra pulmonary TB (37 %). The diagnosis in the remaining 41 % were cryptococcal meningitis (13%), pneumocystis pneumonia (11%), chronic diarrhoea (4%), toxoplasmosis of the brain (4%), bacterial pneumonia (3%) and HIV –related cardiomyopathy (1%) (Table 1 B).

Table 1(C): **Baseline characteristics of first 100 patients at the time of OI when admitted to the acute care wards from November 2006 to May 2007.**

Other clinical characteristics	
Median baseline CD4 count (cells/uL) [IQR]	21 [9-44]
Baseline CD4 cell count category (%)	
0-49 cells/ul	69 (76)
50-99 cells/ul	11 (12)
100-199 cells/ul	10 (11)
200-349 cells/ul	1 (1)
Acute OI- no. (%)	

The median CD4 cell count in this group was 21cells/uL. The majority of the patients (75%) had a CD4 count in the range of 0 to 49 cells/uL. (Table 1 C)

Table 2(A): Initial 24-week outcomes after immediate ART commenced at Siyaphila from November 2006 to May 2007.

Outcome	Patients N=93
Timing of ART initiation achieved Median days from admission with OI to ART initiation – no. [IQR]	15 [12-20]
ART regimen initiated no. (%)	
D4T – 3TC – EFV	92 (99)
D4T – 3TC – NVP(Nevirapine)	1 (1)
24-week Virological Outcomes	
Intent-to-treat viral suppression <400 c/mol no, (%)	54 (58)
As-treated (AT) viral suppression <400 c/mL no. (%)	54 (92)
24-week Immunologic Outcomes	
Median CD4 count improvement (cells/uL) (IQR)	90 (49-156)
CD4 cell count > 100 cells/uL at 24 weeks, no. (%)	41 (66)
24-week Weight Gain, kg. (IQR)	8.0 (3.3-14.6)

Thirty eight patients (40%) were started on ART within two weeks of an OI diagnosis. The median days to ART initiation from admission with an opportunistic infection were 15 days (IQR 12 -20). Most of the patients (99%) were commenced on Regimen 1 a consists of Stavudine (D4T), Lamivudine (3TC) and Efavirenz (EFV). At twenty four weeks, the intent to treat viral suppression (< 400 copies/ml) was 58 % seen in 54/93 patients. The viral suppression in the as treated group of 54/93 patients was 92 %. The median CD4 count improvement at twenty four weeks was

90 cells/uL (IQR 49 -156). Fourty one (66%) of the patients on ART achieved a CD4 count of >100 cells/uL. The median 24 week weight gain in the group was 8 kg. (Table 2 A)

The overall mortality rate at 24 weeks among the 93 patients was 20% (95%CI 13-29%).Fourteen patients (15 %) died after discharge and 5 died prior to discharge from Siyaphila (5%). A median day to death in all patients was 51 days (IQR 16 - 106).There was a loss to follow up of 6% and four patients (4%) changed service provider .(Table 2B)

Table 2(B): Initial 24-week outcomes after immediate ART commenced at Siyaphila from November 2006 to May 2007.

24-week Vital Outcomes	N =93
Overall mortality (%)	19 (20)
Mortality before Siyaphila discharge	5 (5)
Mortality after discharge	14 (15)
Median days to death, (IQR)	51 (16-106)
24-week Programme Outcomes	
Loss to follow-up (%)	6 (6)
Changed service provider	4 (4)

Table 2(C): Initial 24-week outcomes after immediate ART commenced at Siyaphila from November 2006 to May 2007.

Serious IRIS Events and Adverse events	N =93
IRIS events requiring admission, no. (%)	7 (8)
Tuberculosis	5 (5)
Cryptococcal meningitis	2 (2)
Pneumocystis pneumonia	1 (1)
IRIS-associated deaths	1 (1)
Change to Zidovudine (AZT)-3TC-EFV no. (%)	13 (14)
Peripheral neuropathy	9 (10)
Lactic acidosis	1 (1)
Pre-emptive switch with an increase in BMI to >28 kg/m2	1 (1)
Change to D4T-3TC-NVP	
Neuropsychiatric event	2 (2)

Adverse events were managed at an outpatient level and seven patients (8%) required admission for IRIS. The details of how these patients with IRIS presented is not known, however there was only one death in this group out of 8 patients. Five had tuberculosis, two had cryptococcal meningitis and one had pnuemocystis pneumonia. Most TB IRIS cases were self-limiting. One patient who had IRIS cryptococcal meningitis died. Thirteen patients (14%) changed regimen by six months to Zidovudine, Lamivudine and Efavirenz. The main reason for change was due to Stavudine related peripheral neuropathy (9/13). (Table 2 C)

Table 3(A) : Univariate Analysis of Factors Associated with 24-Week Mortality after Acute OI and ART initiation in the first 100 patients at Siyaphila from November 2006.

Characteristics	N	no. (%)	P
All subjects	93	19 (20)	
Ethnicity			
Black	84	17 (20)	
Non-Black	9	2 (22)	0.7
Gender			
Female	46	5 (11)	
Male	47	14 (30)	0.03
Age			
0-29 years	21	3 (14)	
30 – 39 years	38	6 (16)	
40 – 49 years	26	7 (27)	
> 50 years	8	3 (38)	0.4
Initial CD4 cell count			
0-49 cells/ul	69	14 (20)	
50-99 cells/ul	11	2 (18)	
100-199 cells/ul	11	2 (18)	0.9

A univariate analysis was performed to assess risk factors associated with 24 week mortality after acute opportunistic infection and ART initiation. Demographic data like

ethnicity, gender and age were assessed as risk factors. Only male gender was predictive of higher mortality (30 % for males vs. 11 % for females) and was statistically significant (p <0.03).Baseline CD4 count ranges 0-49, 50 -99 and 100 to 200 cells /uL was not predictive of mortality. (Table 3 A)

Table 3(B) : Univariate Analysis of Factors Associated with 24-Week Mortality after Acute OI and ART initiation in the first 100 patients at Siyaphila from November 2006.

Time from OI therapy to ART			
0-14 days no,(%)	38	6 (16)	
>15 days no.(%)	55	13 (25)	0.3
Opportunistic infection			
Tuberculosis	59	12 (20)	
Other OI	34	7 (21)	0.9
Hemoglobin baseline			
<9	31	7 (23)	
>9	59	12 (20)	0.7
Albumin baseline			
<20	23	7 (30)	
21-25	28	5 (18)	
26-30	19	4 (19)	
>30	15	2 (13)	0.6

Twenty four week mortality among the 55 patients started on ART after 15 days was 25 % (13/55 patients). Only 6 out of the 38 patients who initiated ART between 0 to 14 days died by 24 weeks (mortality 16 %).This was not statistically significant in the univariate analysis (p=0.3).Having tuberculosis compared to other opportunistic infections was also not predictive of greater mortality at 24 weeks (p =0.9).Baseline haemoglobin and albumin was also not predictive of greater mortality. (Table 3 B)

DISCUSSION

Introduction

In a pilot study done by Murphy et al [17] in an inpatient population group in 2006, the mortality rate was 52 % in patients discharged after treatment for an acute OI who did not access ART within four months. The reported results from the present study of a 20 % (95%CI 13-29%) mortality at six months in the ART cohort is an important outcome. Both the studies enrolled a similar cohort from the same hospital with a similar prevalence of different OIs. In this pilot study, patients were discharged without ART and formed the historical control group. There are no other comparable studies done in a district hospital.

One study in South Africa was done on an inpatient cohort in a community health centre.[27] More bedridden patients died (43%) compared to ambulant patients (5%). The outcome was still considered as successful as the bedridden patients were extremely ill at treatment before the ART had therapeutic effect. .In another study[13] at an academic hospital in Cape Town, 17/48 (34 %) patients among those hospitalised died (11 before discharge and 6 after discharge) .It is not clear to what extent linkage to care after discharge was appropriately arranged. for these patients. The discussion will focus on how the integration of palliative care with HIV care worked in reducing mortality in this group of very ill patients.

The challenge of treating the sickest patients

The literature search provides evidence that earlier ART initiation soon after diagnosis of an opportunistic infection reduces morbidity and mortality among people

living with HIV/AIDS. Clinicians are often reluctant to initiate ART early due to the complexities of treating patients with multiple co morbidities for which they get admitted. Starting ART increases the pill burden, and has the potential to increase drug interactions and drug adverse events. This group of patients requires an extensive diagnostic work up and management by experienced clinicians. However, if clear guidelines for the timing of ART are available, more patients could initiate ART early.

The challenge of the inpatient expedited ART programme is to limit treatment related complications in patients presenting with acute opportunistic infection. Prolonged hospitalisation of People Living with HIV/AIDS may be required to surmount the considerable barriers discussed above. One additional challenge linked with providing an optimal service for patients are the unique needs that each patient brings to the therapeutic encounter and the need for individualised attention. These unique needs include multiple opportunistic infections, psychosocial co morbidities, severe poverty, and alternative belief systems which may call into question the efficacy of allopathic medicines.

The need for an appropriate follow up plan

The Siyaphila programme describes the management of the largest cohort of PLWHA at a district hospital. Patients were followed up at a clinic linked to the hospital. This clinic is accessible by public transport to the patients who live in the greater Durban area. A large number of patients are lost to follow up in many studies among those discharged from acute care hospital wards. This was seen in a recent

study in an academic hospital in Cape Town. Very ill patients were discharged to clinics for follow up that were situated far away from their place of residence.

The benefits of the Siyaphila follow up plan

The inpatient stay of patients in Siyaphila after ART initiation is crucial to monitor and treat anticipated adverse events and drug toxicities from combined opportunistic infection treatment and ART. The variable time to initiate ART after initial admission for different clinical conditions emphasizes the need for an individualised approach about the optimal time to initiate ART. Different conditions and clinical presentations require different durations of treatment for the presenting problem. Those patients that have associated physical and psychosocial co-morbidities require a longer time for ART readiness preparation. A detailed follow-up plan was created upon discharge for all patients leaving Siyaphila regardless of whether ART was initiated or not. All patients commenced on ART, had follow up appointments at the outpatient ART clinic after two weeks. Thereafter they were seen at four and eight weeks of follow up. The good clinical response (92 % of the 64 patients followed up at 24 weeks had virological suppression <400 copies/ml) from such an expedited programme of ART initiation has made such an intensive programme worthwhile.

Outcomes of the Siyaphila programme

The prevalence of the various opportunistic infections in this study is representative of what can be expected in most of the country. The distribution of baseline CD4 counts in this population (three quarters of the patients below 50 cells/uL) differs from that typical for ART initiates in South Africa. Patients who are admitted to the

wards are generally sicker than patients seen in the clinics. They are sick enough to require admission for acute care of life threatening clinical conditions. The Siyaphila programme offers a critical additional entrance point into care for typically non-ambulatory patients with advanced disease who have been shown under routine conditions to have low ART uptake after discharge. [17] Late presentation is likely to have arisen for various reasons including poor health care access, late HIV testing and, in some patients, the impact of denial and/or stigma. It is encouraging that mortality at 24 weeks after ART was 20 % only. The majority of those very ill patients survived and was doing well at six months.

Twenty six percent (93 /358) of the patients in the study group that were evaluated for transfer to Siyaphila center for immediate ART were found to be eligible to start ART as inpatients. This evaluation was done based on biomedical and psychosocial criteria for ART readiness. These patients started treatment on ART after treatment for the HIV linked condition within a median of fifteen days from date of initial ward admission. This time falls within the time lines set by the national guidelines for expedited ART initiation.[7]

Benefits of the programme to common infections in SA

Tuberculosis is the commonest co-infection in HIV positive patients and comprises approximately sixty percent of all admissions. The use of the Siyaphila facility helped to provide isolation for cases of open TB as they posed a major challenge to infection control in the medical wards. The other OIs were cryptococcal meningitis, pneumocystis pneumonia, toxoplasmosis of the brain and chronic diarrhoea.

Among the 93 (26 %) patients initiated on ART at Siyaphila five died during the in-patient stay and 14 died after discharge. Only one patient with IRIS died during follow up post discharge, having been treated for cryptococcal meningitis. IRIS was diagnosed in 8 %. These results demonstrate that the mortality due to IRIS is low in this setting and would not preclude any patient from qualifying for expedited ART initiation and being discharged for follow up.

The mortality has been reduced now that ART is commenced soon after treatment of cryptococcal meningitis. [30] The greatest challenge in treating patients with ART after the management of cryptococcal meningitis is the management of IRIS cryptococcal disease which can be life threatening. However studies from the United States of America suggest that an equal or greater risk exists in patients in whom ART is delayed. [31] The prolonged stay in of these patients in the wards affords an opportunity for monitoring adverse events of treatment. Patients can also be counseled on ART readiness, and ART could be commenced before discharge from the wards.

Univariate analysis of risk factors for poor outcome

In the univariate analysis, male gender had a threefold increased risk of death by 24 weeks compared to females (p-0.03). The possible reason for this is seen anecdotally in the medical wards because of the late presentation of males to the hospital for care. This poor health seeking behaviour of males needs to be addressed**.** A difference in baseline CD4 cell count by gender was explored. There was no difference in baseline CD4 cell count (median baseline CD4 cell count among men, 20 cells/uL; women 26 cells/uL). Formal test of significance below using

analysis of variance showed a p value = 0.49 which was statistically significant for comparison of mean CD4 cell count by gender.

The non ART cohort

The patients that were not initiated on ART before discharge are not included in this analysis. These patients received standard care under current guidelines. They were treated for the HIV–linked condition for which they were admitted. ART readiness training was provided for them and eligible patients were discharged to ART sites in the area of their residence. They are among patients for whom the cost of in-patient care at Siyaphila would have been prohibitive. Siyaphila is a state subsidised hospital and patients pay higher fees than that paid at fully owned state hospitals. These patients were discharged to government ART clinics where they would be able to access lifelong care. Some patients died soon after admission due to terminal medical conditions as they presented in an advanced stage of illness. All these patients received good pain and symptom management according to standard palliative care guidelines. They were referred to home based care organizations that provide adequate pain management and appropriate symptom control as long as the patients require.

Limitations of the study

The limitation of this study lies in the lack of follow up data on patients in this study who did not initiate ART at Siyaphila. A pilot study was done at McCord hospital during the same period of this study .[17] these patients did not enter the Siyaphila ART programme. The mortality among this group was about thirty percent at six

months. This programme attempted to address this challenge by the expedited ART programme.

Concluding remarks

The programme to start ART as soon as possible after a patient is admitted to the hospital is not the most popular method of ART initiation. However the potential to reduce the high mortality among this patient population is clearly demonstrated by this study. This programme catered for those patients with the most advanced disease. The cost of inpatient care at Siyaphila is considerably lower than the daily costs in an acute care medical ward. From a cost point of view, the challenge is to establish a similar programme that can be scaled up. This must be balanced with the high costs to families and the health care system.[32] the linkages to outpatient primary care follow up was very effective. As the clinic is based on the hospital campus most patients and their families are made familiar with the procedure of enrolment and follow up in the clinic before discharge. The electronic patient record system in the hospital and clinic facilitates this linkage of care .Only those patients that are bed bound upon discharge are referred to home based care networks in the area of their residence. This programme must involve disease specific treatment together with optimal pain and symptom control. It makes it possible to help bed-ridden patients who otherwise may not be able to access an outpatient programme. With this understanding, we predict based on our experience at Siyaphila that high uptake of ART can be achieved. Effort and resources should be spent to include such patients into inpatient treatment programmes such as this. This study provides evidence that nobody should be considered too sick to access ART.

CONCLUSIONS AND RECOMMENDATIONS

It is acknowledged that the conclusions in this study were not derived from data in this study. These data are summarised from a review of the latest literature .These findings were proven in some randomised controlled trials already published. The study at Siyaphila has operationalised the findings of these randomised controlled trials and demonstrated good mortality outcomes at six months. This was done in the context of an inpatient programme .The Siyaphila model has demonstrated that HIV care and palliative care can be integrated to operationalise an expedited ART programme for the sickest patients.

The objectives of the study outlined in the study protocol were achieved and described in the results section. Different opportunistic infections require different protocols of treatment as seen in previous reports. Recommendations for ART initiation in a sub acute ward of district hospitals will be made based on evidence in the literature from trials already published. And the best practice guidelines described in the Siyaphila programme.It must be noted however that the Siyaphila programme started before the results of the randomized trials were published. The protocols used were based on expert advice and current literature or guidelines as described in the literature search.

The value of an interdisciplinary team in the wards

The 24 week mortality in the programme was 20 % and was due to the effective role of the interdisciplinary team. One important challenge linked with providing an

optimal service for patients are the unique needs that each patient brings to the therapeutic encounter and the need for individualised attention. These unique needs include multiple opportunistic infections, psychosocial co morbidities, severe poverty, and alternative belief systems which may call into question the efficacy of allopathic medicines. With this understanding, we predict based on our experience at Siyaphila that high uptake of ART can be achieved. At Siyaphila this has required the use of staff with intimate knowledge of the patient population and an ability to communicate effectively which included counsellors, spiritual care givers and psychologists as formal components of the care team. The multidisciplinary health team was a key component to the success of the programme providing crucial support required for the ART preparation and training of extremely ill patients.

The use of a sub acute care ward for fast tracking ART initiation

The use of a sub acute care ward linked to the acute care wards for patients with advanced HIV allowed us to provide a very high level of care for a portion of the population. Their needs have not been met by the ART roll-out as it currently exists at a reasonable cost. Though innovative this programme has provided ART in a way consistent with the aims articulated by the HIV AIDS National Strategic Plan for South Africa.

Care of patients who did not access ART

The interdisciplinary team provides care for patients in the non-ART cohort. These patients are not eligible for ART for various reasons. Terminally ill patients were

offered optimal treatment for symptoms and bereavement support for patients and families. Care was individualized for all patients depending on the clinical needs.

Recommendations

Protocols for sub acute care in patients with advanced HIV disease are made based on findings from this study. Experts at McCord Hospital were involved in designing recommendations for early ART initiation after diagnosis of opportunistic infections. This study provides crucial pilot data that can combine existing best practice reports and recommendations by the South African HIV Clinicians Society. These based recommendations can lead to broader discussions for the development of an in-hospital based model of care for advanced HIV infection.

Based on evidence and best practice, the following guidelines are suggested for when to initiate ART after diagnosis of an acute opportunistic infection.

a) Pulmonary and extra pulmonary tuberculosis: Begin ART once the patient has demonstrated no early adverse effect of tuberculosis therapy as early as one week after TB treatment initiation.
b) Cryptococcal meningitis: Amphotericin B is recommended for at least 14 days with monitoring for renal dysfunction and hematological toxicity (anaemia) prior to initiation of ART.
c) Pneumocystis pneumonia: After a week of acute treatment, which generally will include corticosteroids and high dose cotrimoxazole, ART is recommended as early as one week after PCP therapy initiated.
d) For all other AIDS associated opportunistic infections and associated illnesses, begin ART within a week of opportunistic infection diagnosis.

e) For conditions for which there is no effective disease directed therapy, consider starting ART earlier viz. Microsporidosis, Cryptosporidiosis, Kaposi's sarcoma and PML.

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APPENDIX 1

WHO STAGING OF HIV/AIDS

WHO Stage 1

Seroconversion illness/asymptomatic infection

Persistent generalized lymphadenopathy

Performance status 1(fully active and asymptomatic)

WHO Stage 2

Less than 10%weight loss

Herpes zoster

Minor mucocutaneous manifestations

Recurrent upper respiratory tract infections

Performance status 2(symptomatic but near fully active)

WHO Stage 3

More than 10%weight loss

Chronic diarrhoea for >one month

Prolonged fever

Oral candida, chronic vaginal candidiasis/ Oral hairy leukoplakia

Severe bacterial infections

Pulmonary tuberculosis (TB)

Performance status 3(in bed <50% of normal daytime)

WHO Stage 4(AIDS)

Extrapulmonary TB

Pneumocystis carinii pneumonia

Cryptococcal meningitis

Herpes simplex virus ulcer >1 month

Oesophageal candidiasis

Toxoplasmosis

Cryptosporidiosis

Isosporiasis

Cytomegalovirus (CMV)

HIV wasting syndrome

HIV encephalopathy

Kaposis's sarcoma (KS)

Progressive multifocal leukoencephalopathy (PML)

Disseminated mycosis

Atypical mycobacteriosis

Non-typhoid Salmonella bacteraemia

Lymphoma

Recurrent pneumonia

Invasive cervical carcinoma

Performance status 4(confined to bed>50% of normal daytime

APPENDIX 2

PATIENT DATA COLLECTION FORM: INITIAL FORM

Date form completed: ----------/----------/----------

Day Month Year

Study ID number: ----------

Date of ward admission: ----------/----------/----------

Day Month Year

Date of birth: ----------/----------/----------

Day Month Year

Gender: Female Male

Ethnic group: Black White Indian Coloured

What was the final diagnosis?

Medical problems / Opportunistic infections	
1. Pulmonary Tb (see below)	11. T gondii
2. Tb meningitis (see below)	12. Kaposi's sarcoma
3. Extra pulmonary Tb (not TBM)	13. CMV of any organ
4. PCP	14. HIV associated dementia
5. Cryptococcus meningitis	15. HIV wasting
6. Diarrhoea > 14 days	16. Mycobacterium avium
7. Herpes Zoster	17. Recurrent pneumonia
8. Esophageal candidiasis	18. Cardiac failure
9. Diabetes	19. Renal failure
10. Hypertension	20. Liver disease-cause
	21. Other (specify----------

Clinical exam:

Current weight : ----------kg Date: ----------/----------/--

Baseline blood test

Latest CD4 count _____ Date: ----------/----------/----------

Latest Viral load _____ Date: ----------/----------/----------

Latest FBC/Hb _____ Date: ----------/----------/----------

Latest albumin_____ Date: ----------/----------/----------

Treatment:

Treatment given for OI: ---------- Date: ----------/----------/----------

Day Month Year

Other treatment given :_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Date of admission to Siyaphila: ----------/----------/----------

Day Month Year

Date of commencement of ARVS: ----------/----------/----------

Day Month Year

ARV regimen: ----------

Progress at Siyaphila: ----------

Date of discharge from Siyaphila: ----------/----------/----------

Day Month Year

Patient concerns/other comments :----------

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-

APPENDIX 3

PATIENT DATA COLLECTION FORM: FOLLOW –UP VISITS

Study ID number: ----------

Date ----------/----------/----------Completed by _____

Day Month Year

Clinical exam:

Current Weight: ----------kg Date: ----------/----------/----------

Day Month Year

Did the patient experience any of the ffg or get admitted to the hospital since the last visit? What were the dates?

Medical problems / Opportunistic infections	
1. Pulmonary Tb (see below)	11. T gondii
2. Tb meningitis (see below)	12. Kaposi's sarcoma
3. Extra pulmonary Tb (not TBM)	13. CMV of any organ other than
4. PCP	14. HIV associated dementia
5. Cryptococcal meningitis	15. HIV wasting
6. Diarrhoea > 14 days	16. Mycobacterium avium
7. Herpes Zoster	17. Recurrent pneumonia
8. Esophageal candidiasis	18. Cardiac failure
9. Diabetes	19. Renal failure
10. Hypertension	20. Liver disease-cause

Did the patient have any of the ffg adverse events after ARVs?

Adverse event	Date
Peripheral neuropathy	
Anaemia	
Lactic acidosis /Hyperlactatemia	
Rash	
Drug induced liver injury	
Neuropsych symptoms	
IRIS – TB	
IRIS – CRYPTO	
IRIS – PCP	
IRIS – OTHER	

Is the patient not in the clinic for one of the ffg reasons

Cause	Date
Lost to follow up	
Changed to service provider	
Death	
Stopped taking medicines	
Other	

BLOOD TESTS

Latest CD4 count_____Date----------/----------/----------

Day Month Year

Latest Viral Load-_____Date----------/----------/----------

Day Month Year

Latest FBC ____/Hb_____ Date----------/----------/----------

Day Month Year

Latest ALB_____Date----------/----------/----------

Day Month Year

Has there been any change in treatment ?

Additional

Comments/ concerns :----------

APPENDIX 4

McCORD HOSPITAL

26th February 2008

Dr Christina Edwin
By hand

Dear Dr Edwin,

RESEARCH

This serves to grant support for undertaking the following research at the McCord Siyaphila Centre:

> Retrospective Analysis of outcomes in the program of fast-tracking of antiretroviral therapy for patients admitted to a palliative care centre after diagnosis of opportunistic infections.

I understand that this research project is being done towards a Masters degree in Palliative Medicine at University of Cape Town.

We wish you success in your career.

Yours sincerely

Dr Helga Holst
Chief Executive Officer

APPENDIX 5

McCORD HOSPITAL

6 March 2008

Dear Dr Edwin

Retrospective Analysis of Outcomes in the Programme of Fast -Tracking of Anti-Retroviral Therapy for Patients Admitted to a Palliative Care Centre after Diagnosis of Opportunistic Infections

I refer to your application to undertake research at McCord Hospital. Your study proposal was reviewed by the McCord Research Ethics Committee on the **25 January 2008**.

I have the pleasure in informing you that this study has been approved.

Attached please find the Committee Clearance Certificate, with the MREC study number.

Please also complete and sign the document acknowledging the terms and conditions for undertaking research at McCord Hospital. The signed document should be returned to the Research Coordinator.

Why we wish you every success in your research.

Sincerely

Dr Juliet Giddy
Acting Chair: McCord Research Ethics Committee

APPENDIX 6

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: [illegible]

06 June 2008

REC REF: 334/2008

Dr C [illegible]
c/o Dr L Gaydon
Public Health & Family Medicine

Dear Dr [illegible]

PROJECT TITLE: RETROSPECTIVE ANALYSIS OF OUTCOMES IN THE PROGRAMME OF FAST-TRACKING OF ANTI-RETROVIRAL THERAPY FOR PATIENTS ADMITTED TO A PALLIATIVE CARE CENTRE AFTER DIAGNOSIS OF OPPORTUNISTIC INFECTIONS

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 15th June 2009.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

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