A Retrospective Cohort Study: The retention in care of HIV positive pregnant and breastfeeding patients universally initiated on lifelong ART ('OptionB+') in the Klipfontein/Mitchells Plain substructure in Cape Town

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PLAGIARISM DECLARATION

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PART A
Research Protocol

Introduction

South Africa has one of the highest Human Immunodeficiency Virus (HIV) prevalence rates at 12.2% in 2012 of which 14.4% were female.[1] The Joint United Nations Programme on HIV/AIDS(UNAIDS) 2014 Gap Report confirmed the epidemic in Sub-Saharan Africa and reported one in every four new HIV infections to occur in adolescent and young females.[2]

Unsurprisingly the wellbeing of these women and their unborn children has become key in the global fight against HIV/AIDS. The World Health Organisation (WHO) has supported this by advocating elimination of new paediatric HIV infections and keeping mothers alive by 2015.[3]

Several challenges threaten the success of PMTCT in developing countries. In Malawi, high HIV prevalence rates complicated by factors such as short birth intervals and late antenatal bookings decreased the effectiveness of the program.[7] In addition insufficient laboratory resources in many centres cause delayed CD4 testing, unnecessary deferral of ART initiation and consequently higher risk of MTCT and maternal morbidity and mortality.[7]

Attempting to improve access to and uptake of patients in ART care Malawi launched 'Option B+' as pilot program in 2011, rolling out rapid testing and same day lifelong ART initiation for all HIV positive pregnant and breastfeeding women.[7] Concerns around long term feasibility of the regimen surfaced,[8] but largely positive outcomes ultimately led to updated WHO ART guidelines in 2012.[9]

Experiencing similar challenges to Malawi South Africa implemented revised ART guidelines in April 2013 with the Western Cape following Malawi's suit with 'Option B+'.[10]

Unsurprisingly concerns regarding patient retention on 'Option B+' have surfaced. Hypotheses propose attrition peaks at ART initiation and postpartum after cessation of breastfeeding with different suggestions of possible contributing factors.[11]

Considering the valid concerns around 'Option B+' on the background of evident positive outcomes and the lack of local evidence further research is imperative. While positive outcomes will affirm the value of 'Option B+' the results of this study will contribute to development of retention strategies and decisions around regimen choices for individual provinces.

Study title

The retention in care of HIV positive pregnant and breastfeeding patients universally initiated on lifelong ART ('OptionB+') in the Klipfontein/Mitchells Plain substructure in Cape Town.

Literature Review *(Extensive literature review in Part B)*

Reducing vertical transmission

Before the introduction of PMTCT programs the HIV infection rate amongst breastfed infants in developing countries was estimated as high as 25% - 35% in the first 6 months.[15]

Literature searches on HIV PMTCT revealed a lack of international data with the majority originating from Sub-Saharan Africa. One of the most significant, the Kesho Bora study, was conducted in Burkina Faso, Kenya and South Africa between 2005 and 2008.[12] This randomised control trial compared HIV MTCT in breastfeeding mothers on triple ART to that in breastfeeding mothers on AZT and single dose nevirapine prophylaxis.[12]

The outcomes of this trial changed the face of PMTCT and global views on HIV exposed infant feeding practices. It showed a 43% relative risk reduction in infant HIV infection at 12 months in the triple ART group with no significant difference between the two groups at birth or 6 weeks postpartum.[12] Similar outcomes were demonstrated looking at feeding practices with a relative risk reduction in HIV transmission of 48% in the triple ART group compared to the AZT/single dose nevirapine group.[12]

With results this significant it is important to confirm validity of the results. Including five study sites across three countries, having a large study population and conducting a randomised control trial improved study outcomes' significance.[12] Authors were transparent with the selection process and follow up not concealing confounding factors or difficulties encountered.[12]

The study's most relevant publications, the MTCT and breastfeeding results, were transparent and appropriately used odds ratios and relative risk reduction. Confidence intervals and p-values aided in interpreting statistical significance of results and thus relevance in clinical practice.[12]

These controversial but indisputable results significantly impacted the future of HIV PMTCT. With clear evidence that ART in pregnancy and breastfeeding decreases HIV MTCT the WHO revised its guidelines to include these new findings.[5]

Retention is key

Adherence is vital in all patients on ART, but especially in HIV positive pregnant and breastfeeding women to preserve maternal health, reduce drug resistance and prevent HIV MTCT.[16] Studies have shown that adherence rates as low as 70–80 % sufficiently suppress the virus[16], but they emphasize much more favourable outcomes with better adherence. In pregnant and breastfeeding women this is particularly essential to ensure the lowest possible risk of MTCT and to aim to eliminate new vertical HIV infections by 2015.[3]

In a systematic review of ART adherence during pregnancy and breastfeeding compiled in 2012, collective international data showed a statistically significant higher retention rate of 75.7% in the

antepartum period compared to a mere 53% in the postpartum period (p=0.005).[16]

It is evident that patient retention in ART care prior to 'Option B+' was suboptimal with adherence rates below even the lowest acceptable rate to achieve viral suppression. In addition, adherence during pregnancy seems superior to the postpartum period, most likely due to mothers' instinctive motivation to protect their unborn child with external pressures influencing their behaviour after delivery.[16]

Nonetheless, 'Option B+' continued to raise questions. While it markedly increases ART accessibility and availability[7] it demands patient dedication and capacity to adhere to the regimen. Only with successful combination of these factors can the goal to eliminate HIV MTCT be fully achieved.[16]

Research on ART patient retention during pregnancy, prior to roll-out of the 2012 WHO ART Guidelines, were conducted in Johannesburg in 2010.[17] This retrospective cohort study revealed much higher attrition rates in patients initiated on 'Option A' compared to patients eligible for triple ART.[17] Only 40.3% of 'Option A' patients were retained during antenatal care with a mere 22.6% returning for the required repeat CD4 count after delivery.[17] Antenatal retention of ART eligible patients was higher at 48.9% with a further 8.4% LTFU six months postpartum, still suboptimal compared to international data.[17]

Recognising the need for improved patient retention and identifying compounding factors in developing countries contributed to the development of the current WHO ART Guidelines and ,in certain settings ,'Option B+'.

A pilot study conducted in Cape Town in 2011 implemented `'Option B+' principles similar to the Malawian guidelines at the time[7] and ultimately every HIV positive pregnant patient received triple ART regardless of CD4 count or WHO staging.[4] Results revealed remarkable ART initiation of 91% at first antenatal booking visit with longer antenatal ART exposure and consequently complete viral load suppression at delivery in 75.8% of patients and a negligible vertical transmission rate of 0.9%.[4]

The success of rapid ART initiation demonstrated by this and other studies further supported the international shift to 'Option B/Option B+' with undoubted benefits to both mother and baby.[4, 7, 18] In appropriate settings, specifically developing countries, this simplified algorithm seemed the long awaited solution to major obstacles and the publication of revised international guidelines only a matter of time.

<u>The birth of 'Option B+'</u>

It has now widely been accepted that ART improves maternal HIV viral load suppression and consequently leads to improved HIV PMTCT.[4] Despite widely implemented ART regimens such as 'Option A' several factors (especially in Sub-Saharan countries) serve as potential barriers to early and rapid initiation.

Malawi identified this problem early on, and proposed 'Option B+' as a feasible alternative regimen.[18] In a 2011 Lancet article, Schouten et al discuss the motivation behind this decision, and identify difficult access to CD4 testing, high fertility rates, late antenatal bookings and extended breastfeeding as major barriers to ART initiation.[19] The article supports 'Option B+'s' intended treatment protocol and identifies 'Option B+'s' strengths as its early defined treatment goals and improved patient recruitment.[19]

The Malawian Ministry of Health (MOH) implemented 'Option B+' in 2011 with promising expectations of decreased morbidity, mortality and better PMTCT.[18] Indeed, initial routine monitoring by the MOH showed positive outcomes with a seven fold increase in PMTCT coverage during the first year and retention at 6 months of 82,6% and 76,9% at 12 months.[7] These results sparked global interest, as they made the proposed UNAIDS/PEPFAR (Presidents emergency plan for AIDS relief) goal of eliminating new HIV infections in children by 2015 all the more attainable.[3] Developing countries facing PMTCT challenges similar to those in Malawi now had the potential to show equally promising outcomes, and soon Uganda, Rwanda and Haiti adopted 'Option B+' into their PMTCT policies.[18]

Nevertheless, despite 12 month retention rates comparable to those prior to implementing 'Option B+', questions regarding lifelong retention of patients surfaced.[18] Considering that patients on this regimen often have high CD4 counts and no Stage 3 or 4 defining illnesses, risk of LTFU after cessation of breastfeeding became a growing concern.[18]

Twelve months after the introduction of 'Option B+' the MOH conducted a more extensive study and the results were published in AIDS Journal in 2014.[7] This study consisted of two study arms, the first exploring selected facilities' patient retention in care (factoring possible site-level predictors of patient LTFU) and the second determining LTFU in pregnant and breastfeeding women on 'Option B+' compared to non-pregnant women starting ART for their own health.[7]

Results reflected previous programmatic data on 'Option B+', with similar LTFU rates of 17% and 22% at 6 and 12 months after ART initiation respectively.[7] Additionally outcomes showed women initiating ART during pregnancy to be five times more likely to become LTFU compared to non-pregnant women.[7] Patients initiated during breastfeeding had the highest attrition risk at twice that of pregnant ART starters.[7] Large numbers of study participants, the inclusion of multiple sites, including both facility level and individual data in separate study arms all added to improve generalisation of findings.

Unsurprisingly, Malawi's pilot project sparked controversy, with Coutsoudis et al. criticising 'Option B+' in a Lancet 2013 publication and a debating editorial comment in AIDS Journal in 2014.[8, 20] While the editorial questions the feasibility of 'Option B+', it maintains a balanced appraisal and encourages further research.[20] Instead Coutsoudis

et al. label 'Option B+' as "extreme", criticise Malawi's "test and treat" approach and warn about pressure on countries to adopt the new regimen.[8] This criticism seems biased as the authors do not engage with the several positive and negative aspects of this issue. In a subsequent Lancet correspondence the WHO dismisses the criticism and supports the generally accepted positive but cautionary view on 'Option B+' encouraging further research on the matter.[20]

In 2012 the WHO incorporated 'Option B+' into the revised PMTCT Guidelines providing much needed confidence for further roll out whilst continuing to provide alternative regimen options to settings which found it less viable.[9]

Subsequently, South African National ART Guidelines were revised in 2013 with national implementation in April 2013.[10] These guidelines advocate 'Option B' in pregnant HIV positive women with the Western Cape Department of Health opting for 'Option B+' as part of their provincial guidelines.[10]

One year after implementation of 'Option B+ in the Western Cape, important questions remain unanswered. Despite successes with increased access and availability of ART, growing concerns regarding long term retention exist.

The proposed study aims is to appreciate the attrition rate in the Hanover Park/Mitchells Plain ART community and to better understand the challenges faced. Recommendations and suggested interventions to promote retention can then then be made. Optimistically, this study will prompt further research, influence policy development and ultimately add value to both national and international PMTCT knowledge.

Aims

1) To determine the retention in care of HIV positive pregnant and breastfeeding women universally initiated on lifelong ART ('Option B+') at Hanover Park Community Health Centre (CHC) and Mitchells Plain Community Health Centre (CHC) in the Klipfontein/Mitchells Plain substructure in Cape Town.

2) To compare retention in care of pregnant and breastfeeding women initiated on ART using 'Option B+' to HIV positive women initiated on ART because of their own health (i.e. CD4 count<350cells/ul or WHO stage 3 or 4).

Objectives

1) To identify all HIV positive and ART naïve pregnant women initiated on ART using 'Option B+' at Hanover Park CHC and Mitchells Plain CHC between April 2013 and Aug 2013.

2) As a control identify non-pregnant, ART naive HIV positive women initiated on ART with a CD4 count<350cells/ul or WHO stage 3 or 4 at Hanover Park CHC and Mitchells Plain CHC between April 2013 and Aug 2013.

3) To compare the retention rate of patients in the pregnant group to that in the non-pregnant group at 1, 3, 6, 12 and 15 months post initiation of ART.

4) To conclude what impact 'Option B+' implementation has had on patient retention in ART care in the Hanover Park/Mitchells Plain communities.

5) To explore possible determinants of LTFU in patients initiated on 'Option B+' in the Hanover Park/Mitchells Plain communities.

6) To make recommendations to optimise retention of pregnant HIV positive patients in ARV Care.

Methodology

Study Design

Retrospective cohort study.

Study Site(s)

The Western Cape Primary Health Care model includes 479 facilities in 6 districts (5 rural and 1 metro). The Cape Town metro district consists of four sub-structures.

ART services in the Western Cape have mostly been decentralised with most patients receiving care at primary care level. Primary level ART care is based on a nurse driven service model with doctor support aiming to increase accessibility.

Successful integration of antenatal and PMTCT services has been implemented across the province. Most pregnant and breastfeeding HIV positive patients attend one site for ART, antenatal and postnatal care simplifying management and improving continuity of care. Advantages include increased patient centeredness and better resource allocation.

At both facilities pregnant women are initiated on ART at the onsite MOU and follow up continued at the onsite ART clinic. ART initiation and follow up of non-pregnant patients take place at the same facilities' ART clinics.

Hanover Park CHC

This 24 hour facility is located on Hamlyn Walk in Hanover Park, Cape Town and forms part of the Klipfontein/Mitchells Plain substructure. It provides primary health care, 24 hour accident and emergency services, midwifery and has an ART Clinic on site. The unit works closely with the onsite MOU serving a large population of pregnant and breastfeeding women living with HIV.

Mitchells Plain CHC

This 24 hour facility is located on First Avenue in Eastridge, Mitchells Plain, Cape Town. It also forms part of the Klipfontein/Mitchells Plain substructure serving a similar patient population profile to Hanover Park CHC.

Services offered at Mitchells Plain CHC are comparable to those described at Hanover Park CHC and the working relationship between the ART clinic and MOU is based on the same model.

Study site selection

The study would be best conducted at a primary health care centre that has an onsite MOU as well as integrated ART services. The ART clinic should have implemented 'Option B+' from April 2013 in

order to be included in this study. Sites using electronic record keeping systems (ERKS) is preferable (although not considered an exclusion criteria) due to the accessibility and probable accuracy of patient information.

Several CHC's in the Cape Town metro have both an MOU and ART clinic offering integrated services. To the researchers' knowledge all sites providing ART care in the Western Cape rolled out 'Option B+' in April 2013 with very few, if any exceptions.

Record keeping and data capturing vary between sites ranging from paper-based records to sophisticated ERKS depending on availability and suitability.

Hanover Park and Mitchells Plain CHC were selected on the basis of convenience. The principal researcher is based at Hanover Park CHC for the majority of the study period simplifying the data collection process. In addition, having both the principal investigator and co-supervisor permanently based at the facility made it the most practical option. Both Hanover Park and Mitchells Plain CHC are located within the Klipfontein/Mitchells Plain substructure serving a similar patient profile with comparable clinical challenges.

Participants

Participants will be assigned to two cohort groups based on the pre-specified selection criteria.

The control group will consist of HIV positive, non-pregnant, female patients initiated on ART at Hanover Park and Mitchells Plain ART Clinics during the specified period. Owing to current ART guidelines participants should have a CD4 count<350cells/µl or be WHO stage 3 or 4 at ART initiation.

The cohort group will include pregnant patients that booked at Hanover Park and Mitchells Plain MOU during the specified period. Only women testing HIV positive and that are ART naïve at antenatal booking will be included in the study. In accordance with 'Option B+' guidelines, patients in this group could have any CD4 count or WHO clinical stage at initiation.

Participants will not be excluded based on other demographic characteristics. However, during data analysis, multivariate logistics regression will be used to account for any confounding variables.

Participant sampling

Patient sampling will start by accessing MOU ACTS (Advise, Counsel, Test, Support) registers at the two included sites. These registers document each antenatal patient's HIV rapid test result, making it ideal data sources. However, like all registers, they are paper based and depend on individual counsellor vigilance and accuracy, which is variable.

As an additional data source, each facility's ERKS will be utilised. Hanover Park ART clinic makes use of Tier.net whilst Mitchells Plain ART clinic stores patient data on Ekapa.

Basic operation of both sites' ERKS is similar with user friendly interfaces simplifying data retrieval. Another advantage of this data collection method is accuracy as each clinical visit is captured on the

system daily. Both sites' ERKS allow criteria selection to filter data and produce a patient sample. Sampling the cohort group will use "pregnant at ART start" and "April 2013 – Aug 2013" as filters. Participants in the control group will be selected using "female" and "non-pregnant" as filters within the same period as the cohort group.

Sample sizes are projected as 200 cohort group participants with 400 included in the control group. Sample sizes are based on programmatic data obtained from the Hanover Park ART administrative clerk and are mere estimations. Should patient sampling reveal more participants meeting the inclusion criteria or produce less patients in either group sample sizes may be affected.

Data Collection

Data collection will be conducted primarily by the principal researcher.

The MOU ACTS registers will be primarily used to identify all pregnant patients that tested HIV positive at the MOU during the specified time period and to capture each included participant's demographic data using the data collection tool. *(See Part D)*

Ekapa and Tier.net will be accessed to determine participant retention as either "Yes" or "No" at the first visit and 1, 3, 6, 9, 12 and 15 months post ART initiation in the respective groups. "First visit" will refer to a patient's first subsequent visit to the ART Clinic after initiation of ART.

Using these crucial points in care to determine patient retention researchers will be able to identify both patients "never returning for follow up" and those "lost to follow up". We define "never returning for follow up" as a patient not returning for ART care after their initial visit. This becomes especially important in the cohort group in which the MOU initiate pregnant HIV positive women on ART at their booking visit with continued follow up at the ART clinic. Patients will be classified as LTFU should they not attend ART care for 90 days or longer after their last ART clinic visit. The researchers base these definitions on current standard of practice (SOP) at the study sites as well as a review of existing studies.[7, 14] To account for reasons other than true attrition additional outcomes will be added such as "transfer out" and "death".

Relevant patient demographic data will be collected using the same data collection tool. This will include age, divided into four subcategories, employment status, marital status, residing suburb, baseline CD4 count, WHO clinical stage and their counselling rate prior to initiation. The researchers hypothesise that these factors potentially contribute to patient retention and will discuss its relevance in the final report.

The investigators recognise the possibility of insufficient electronic patient data in which case individual patient folders will be accessed to obtain the required information.

Data Collection Tool *(See Part D)*

Collection of data will be done using a pre-programmed Excel spread sheet. Data will be

captured directly onto the spread sheet by the principal researcher throughout the data collection process.

Data Analysis

The raw data collected will be entered into a biomedical statistics program such as BioStrata to compare retention rates between the two groups using odds ratios. Logistic regression will be used to account for possible confounding variables.

We are projecting to recruit 200 experimental subjects and 400 control subjects. Prior data indicates that the retention rate among controls is 0.83. We will be able to detect true retention rates of 0.727 or 0.916 in exposed subjects with probability (power) of 0.8. The Type I error probability associated with this test of the null hypothesis that the failure rates for experimental and control subjects are equal is 0.05. We will use a continuity-corrected chi-squared statistic or Fisher's exact test to evaluate this null hypothesis.

The projected statistical analysis is based on a review of the current available literature. The expected retention rate of 0.83 is derived from the recently conducted Malawian study owing to its relevance and actuality.[7] Should more appropriate literature become available during data analysis or the number of study participants change due to unforeseen circumstances this might influence the projected detectable retention rates as outlined above. In this instance the investigators will clearly outline and discuss the reasons and impact it will have in the final document.

Ethical Considerations

Application for ethics approval will be submitted to both the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (UCT) and the Department of Family Medicine Research Committee.

Considering the retrospective study design exclusively involving accessing patient records without direct patient interaction individual informed consent will be difficult to acquire. Since data is in the care of the facilities and remains the property of the Western Cape Department of Health, consent to gain access to patient information will be obtained from the facility managers. *(See Part D)* They will act as custodians of the folders, but as proxy representatives of the patients.

The data collection process is outlined above. Expected duration of data collection is projected at thirty days up to a maximum of ninety days in the event of encountering unforeseen circumstances.

Confidentiality of patient information will be maintained with patient identification done only through folder numbers. Should a patient's folder need to be accessed for information the patient's identity will be kept confidential and only known to the researcher responsible for data collection. In addition only patient information required to conduct the study will be collected, particularly with regards to patients' personal data to ensure optimal patient privacy.

Collected data will be stored electronically in the care of the principal researcher and stored anonymously protecting misuse by a third party. Collected data will be stored for 5 years from completion of the study to allow for perusal or inclusion in future studies with permission from the principal investigator and facility managers of the included study sites.

Results will be kept confidential and if published patient identity will remain anonymous.

No monetary incentives, compensation or payment in kind will be offered to either study participants or facilities involved. The investigators have no conflicts of interest to declare.

On conclusion of the study, results will be disseminated to the facility managers involved as well as to the ARV/Wellness Clinic managers of each facility. The results will be included in the proposed Masters dissertation of the principle researcher and submitted for grading to the UCT Department of Family Medicine and the College of Medicine South Africa. Study results will be made available to interested governing bodies to promote further interest in the study field and make recommendations to positively impact future PMTCT policies and patient retention in care.

Budget

Funding to conduct the research will be applied to through the University of Cape Town School of Public Health and Family Medicine.

	Activity	**Amount (ZAR)**	**Description**
Equipment & Consumables	Printing	R300	Letters of permission, Proposal documents, Application Forms, Data Collection Sheets
	Telephone	R200	R100/month x 2 months
	Transport	R300	R3/km (AA rates) x 100km
Human Resources	Proofreading	R1000	R10/page x 100 pages
	Biostatistician	R200	R50/hour x 4 hours
Final Report	Printing & Binding	R1000	Printing & Binding for dissemination & submission
Other	Presentation of results at conference	R1000	Conference enrolment fee
Total cost		R4000	

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PART B
Literature Review

a) Definitions

- **Option A** recommends zidovudine (AZT) to all human immunodeficiency virus (HIV) positive pregnant and breastfeeding women not qualifying for lifelong triple antiretroviral treatment (ART) from 14 weeks gestation with single dose nevirapine and tenofovir/emtracitibine 3 hourly in labour.
- **Option B** recommends universal ART to all HIV positive pregnant and breastfeeding women. Patients with CD4 counts less than 350 cells/µl or at World Health Organisation (WHO) stage 3 or 4 continue ART lifelong while those not meeting these criteria discontinue ART one week after cessation of breastfeeding.
- **Option B +** recommends lifelong ART to all pregnant and breastfeeding HIV positive women regardless of CD4 count or WHO clinical staging.

b) Objectives

- To identify current published literature on the prevention of mother to child transmission (PMTCT) of HIV among pregnant and breastfeeding women, retention in long term ART care and 'Option B+'.
- To select literature relevant to the proposed research project by applying defined inclusion criteria.
- To critically appraise selected literature using evidence based medicine principles to determine the quality and level of the evidence.
- To provide a context and rationale for the aims, objectives and outcomes of the proposed research project to be conducted.

c) Literature search strategy

UCT Libraries' online portal served as the base for the literature search using the following databases: MEDLINE, WorldCat.org, Academic OneFile, SA ePublications Journal Collection, Science Direct, BioMed Central, Google Scholar and Pubmed.

Keywords used to search for literature included 'human immunodeficiency virus', 'pregnant', 'breastfeeding', 'mother to child transmission', 'vertical transmission', 'CD4', 'adherence', 'compliance', 'retention', 'attrition', 'antiretroviral treatment', 'Option B+', 'international', 'Sub-Saharan Africa', 'South Africa'.

d) Quality, Inclusion & Exclusion Criteria

The principal researcher screened the identified literature for relevance and only included peer reviewed articles, articles published in English and papers published up to 1 April 2015.

e) Literature Review

Extensive research has been conducted on HIV PMTCT with overwhelming evidence demonstrating the effectiveness of ART in reducing vertical transmission of HIV during pregnancy and breastfeeding when compared to no ART or short course PMTCT.[1,2] Subsequently, patient adherence became important, with retention in

care receiving increased research interest. Retention rates vary significantly between studies, depending on factors such as patient population, institutional differences and treatment protocols.[3]

The introduction of 'Option B +' in Malawi in 2010 served as a global pilot program for universal life long ART initiated during pregnancy and breastfeeding.[4] Despite the program's positive outcomes, concerns have been raised regarding patient retention in care, especially among patients initiated on ART at CD4 counts above 350 cells/ųl or WHO Stages 1 or 2.[4, 5]

Despite controversies the WHO revised ART guidelines in 2012 allowing for both 'Option B' and 'Option B +' as regimen options depending on individual region factors.[6] In 2013 the South African Department of Health adopted 'Option B' as the national standard of care while the Western Cape adopted 'Option B +'.[7] Similar to the Malawi program, patient retention has been questioned in the Western Cape especially taking into consideration the discrepancy with national guidelines.

Defining the problem

Despite the evident importance of retention in care, no definition for lost to follow up (LTFU) has been standardised with inconsistencies in available published research.[8] Patient misclassification as either LTFU or "in active care" is a major obstacle in determining true attrition rate impacting comparison between facilities and implementation of interventions.[8]

In an attempt to generate an empirical LTFU definition for adults on ART Chi, Yiannoutsos et al conducted a systematic review on available literature in 2011.[8] The authors obtained data from the International Epidemiology Database to Evaluate Adult Immunodeficiency Syndrome (IeDEA) which contains information from 7 international regions consisting of 41 countries' facilities specifically including regions with the highest incidence of HIV.[8]

The primary analysis of this study identified the most accurate definition of LTFU to be 180 days since the patient's last visit with a narrow 95% confidence interval of 173 – 181 days.[8] Further analysis showed that applying this definition had a sensitivity of 77,6%(95% CI: 77,3% - 78%), specificity of 97,1%(95% CI: 97% - 97,2%), positive predictive value of 89,9%(95% CI: 89,6% - 90,2%) and a negative predictive value of 93%(95% CI: 92,8% - 93,1%).[8] Misclassification of patients as LTFU or "in active care" only amounted to 7,7%, the lowest rate in all threshold comparisons.[8] Furthermore, the high positive and negative predictive values of the suggested definition supported by narrow 95% confidence intervals are compelling.[8] Nonetheless, considering the significant heterogeneity among regions, the authors identify a standardised global LTFU definition as a potential study limitation.[8] This implies that in certain contexts, locally applicable LTFU definitions tailored to unique challenges may be more appropriate than the article's recommended definition.[8]

Vertical transmission reduction

Before introduction of PMTCT programs, HIV infection rate among breastfed infants in developing countries was estimated to be as high as 25% - 35% in the first 6 months.[9] This shifted global research towards HIV PMTCT and ultimately led to the birth of the *UNAIDS Global plan towards the elimination of new HIV infections among children and keeping their mothers alive*.[10]

One of the most significant studies that revolutionised HIV PMTCT is the Kesho Bora study conducted in Burkina Faso, Kenya and South Africa between 2005 and 2008.[1] This blinded, randomised control trial compared HIV MTCT in breastfeeding mothers on triple ART to that in breastfeeding mothers on antepartum zidovudine and single dose nevirapine prophylaxis in labour.[1] The study primarily aimed to compare HIV vertical transmission between the groups by determining infant HIV status at 6 weeks and 12 months postpartum.[1]

The results of this trial revolutionised PMTCT and views on feeding practices in HIV exposed infants worldwide. HIV MTCT in the triple ART group was 5.4% at 12 months (95% CI: 3.6 – 8.1%) and 9.5% (95% CI: 7.0 – 12.9%) in the control group.[1] This translates into a statistically significant 43% relative risk reduction in HIV MTCT 12 months postpartum in patients on triple ART compared to those on the zidovudine/nevirapine PMTCT regimen (p=0.029).[1]

In resource limited settings where breastfeeding is vital, the Kesho Bora study unequivocally demonstrated that triple ART during pregnancy and breastfeeding significantly reduces HIV MTCT.[1]

In 2009, the Kisumu Breastfeeding Study conducted in Kenya published results confirming the findings of the Kesho Bora study.[2] This single arm clinical intervention trial assessed HIV MTCT reduction using triple ART initiated at 34 weeks gestation until 6 months postpartum while exclusively breastfeeding when compared to single dose nevirapine.[2] Results showed HIV MTCT rates of 4.2% (95% CI: 2.7% - 6.4%) at 6 weeks postpartum and 6.7% (95% CI: 4.8% - 9.4%) at 18 months.[2] Most importantly, Kisumu's finding of 5.0% (95% CI: 3.4% - 7.4%) cumulative transmission rate 6 months postpartum correlates with Kesho Bora's vertical transmission rate at 6 months of 4.9% (95% CI: 3.1% - 7.5%).[1,2] Given these findings, it is evident that triple ART initiated in pregnancy and breastfeeding significantly reduces HIV MTCT compared to zidovudine/nevirapine.[1,2]

Retention is Vital

Adherence is vital in all patients on ART, but especially in HIV positive pregnant and breastfeeding women to preserve maternal health, diminish the development of drug resistance and prevent MTCT of HIV.[11] Studies determining the required level of ART adherence to sustain virological suppression in patients on current ART regimens have shown that adherence rates as low as 70–80% sufficiently suppress the virus.[11] However, these studies emphasize that much more favourable outcomes can be achieved with better adherence, thereby continuing to highlight the importance of optimal ART adherence.[11]

In pregnant and breastfeeding women this is particularly important to ensure the lowest possible risk of MTCT and to achieve the WHO target of eliminating new vertical HIV infections by 2015.[10]

A 2010 retrospective cohort study conducted by Clouse et al. in Johannesburg, South Africa, looked at LTFU of newly diagnosed HIV positive pregnant women before and after delivery.[12] The authors shared international concerns of increased postpartum LTFU once infants are no longer at risk of vertical transmission.[12]

The study defines LTFU as one month or longer since last scheduled visit.[12] Considering the average global consensus of 180 days since last visit, this definition seems stringent and could overestimate attrition.[12] The authors calculated the cumulative retention of ART eligible patients (i.e. those with CD4 cell counts <350 cells/µl or WHO Stage 3 or 4) as 40.5% (95% CI: 32.3 - 49.0%) from testing, through delivery, until 6 months after ART initiation.[12] Of note, even at the upper limit of a rather wide 95% confidence interval (49%), retention remains poor.[12] The same calculation for the ART ineligible group showed an even lower 22.6% cumulative retention from booking through 6 months postpartum (95% CI: 15.9 – 30.6%).[12] As with the ART eligible group, the wide 95% confidence interval does not necessarily alter the conclusion that retention in ART care during pregnancy is poor.[12]

Additionally, a baseline CD4 cell count of >350 cells/µl was shown to be strongly associated with LTFU.[12] Patients with CD4 cell counts >350 cells/µl at antenatal booking had a 3.3 times higher risk of becoming LTFU compared to their lower CD4 cell count counterparts (aHR 3.30; 95% CI: 1.95 – 5.58).[12] Conversely, being over 30 years of age at ART initiation was associated with increased retention in longterm care (aHR 0.49; 95% CI: 0.30 – 0.81).[12]

The study resonates global concerns that retention of pregnant HIV positive patients in ART care is suboptimal, especially during the postnatal period.[12] Indeed, results in patients with CD4 cell counts>350 cells/µl are alarming, with less than a quarter of these patients still in care 6 months after ART initiation.[12]

It is evident that retention before implementation of 'Option B+' was suboptimal, with overall adherence rates below even the lowest acceptable rate to achieve viral suppression.[12] Furthermore, postpartum adherence (particularly once infant HIV exposure ceases) declines progressively, with concerning implications regarding resistance and maternal health.[12]

A progressive PMTCT pilot study implementing rapid ART initiation in pregnancy was launched in Cape Town in 2011.[13] It applied 'Option B+' principles similar to those in the Malawian guidelines at the time providing triple ART to all HIV positive pregnant patients regardless of CD4 cell count or WHO staging.[13] Investigators aimed to demonstrate the program's proposed benefits (which included markedly increased uptake in antenatal ART care and significantly reduced perinatal HIV transmission rates) in an attempt to motivate for national adoption of 'Option B+'

guidelines.[13] Their results revealed a remarkable ART initiation rate of 91% at antenatal booking visit.[13] Consequently, antenatal ART exposure was optimised with complete viral load suppression at delivery in 75.8% of patients and a negligible vertical transmission rate of 0.9%.[13]

The marked success of rapid ART initiation demonstrated by this study supported the international shift to 'Option B/B+' with undoubted benefits to both mother and infant as shown in literature to date.[4, 13, 15] In appropriate settings, specifically developing countries, this simplified algorithm seems the long awaited solution to major obstacles and the publication of revised guidelines only a matter of time.

The birth of Option B+

In 2010 the WHO revised PMTCT guidelines to include 'Option B' as well as the already well established 'Option A'.[14] Nonetheless, several factors, especially in Sub-Saharan countries, continued to complicate ART initiation and served as barriers to early initiation with consequent inadequate maternal viral load suppression before birth.[16]

Malawi identified shortcomings in their PMTCT program early on and implemented 'Option B+' as a feasible alternative regimen.[15] In a 2011 Lancet article, Schouten et al debate the proposed regimen and identify limited access to CD4 cell count testing, high fertility rates, late antenatal booking and extended breastfeeding as major barriers to timeous implementation of PMTCT ART in Malawi.[16]

Responding to widespread criticism of Malawi's immediate adoption of 'Option B+' without a preceding pilot project, the authors propose the regimen's excellent safety profile, limited access to CD4 cell count testing and the urgency of expanding the country's PMTCT coverage as adequate motivation for the decision.[16] Schouten et al additionally refute global concerns of increased attrition rates among healthy women with high CD4 cell counts in long term ART care.[16] They cite continuous viral load suppression in short succession pregnancies, reduction of opportunistic infections and a decreased maternal mortality rate as compelling reasons in support of life long triple ART.[16]

The Malawian Ministry of Health (MOH) implemented 'Option B+' in 2011 with promising expectations of decreased morbidity and mortality and improved HIV PMTCT.[4] Initial outcomes were positive, with a seven fold increase in PMTCT coverage during the first year and a retention rate of 76,9% 12 months after ART initiation.[4] Despite retention comparable to that prior to 'Option B+', concerns around long term sustainability continued to surface.[15] Sceptics suspected high attrition rates among patients with high CD4 cell counts or WHO stage 1 or 2 particularly once infants were no longer at risk of vertical HIV transmission.[15]

These concerns prompted a study by the MOH published in AIDS in 2014 aiming to accurately determine retention rates among 'Option B+' patients in Malawi.[4]

The study conducted by Tenthani et al, consisted of two parts. One explored general patient retention

at Malawian ART facilities, and the second aimed to determine LTFU among pregnant and breastfeeding women on 'Option B+' compared to non-pregnant women starting ART for their own health.[4]

At facility level the investigators' primary outcome determined the proportion of pregnant HIV positive patients LTFU 6 months after ART initiation.[4] Data for this part of the study was obtained through MOH quarterly HIV program reports containing information from governmental audits.[4] Considering the lack of external audits and independent data, information bias cannot be definitively excluded in this study arm.[4]

Facility selection included all ART/PMTCT clinics in Malawi.[4] Although this ensures a comprehensive assessment of the national retention rate it has potential pitfalls. Significant differences in facility sizes increase the possibility of variable intensity patient care.[4] Similarly, faith-based and private clinics could provide different standards of care compared to public clinics further complicating comparison.[4] To compensate for this heterogeneity amongst facilities, investigators appropriately use random-effects meta-regression.[4] After determining the proportion of patients LTFU at each facility researchers calculate site-specific log odds and performed a meta-analysis to determine predictors of LTFU among 'Option B+' women in Malawi.[4]

The patient level section of the study complements facility level outcomes, but also measures individual patient retention through a retrospective cohort design comparing 'Option B+' patients to a non-pregnant female control group.[4] The researchers identify no follow up visit after ART initiation and the proportion of patients LTFU as primary outcomes.[4] A clear patient selection flow diagram demonstrates exclusion criteria such as male gender or age less than 50 years which decreases potential confounding factors that could impact study outcomes. However, authors only include facilities using electronic medical recordkeeping systems, consequently excluding Northern Malawian facilities using paper-based records.[4] This potentially renders the study sample non-representative of the entire Malawian HIV positive female population.[4]

The study's data collection occurred in three cohort groups, with pregnant and breastfeeding women initiated on 'Option B+' as the two intervention groups and non-pregnant women initiating ART for own health as the control group.[4] Tenthani et al applied identical selection criteria, follow up and outcome criteria for all groups, excluding potential bias.[4] Results showed an overall attrition rate of 17.1% 6 months after ART initiation.[4]

Patient level data analysis found pregnant patients five times more likely (aOR 5.0, 95% CI: 4.2 – 6.1) and breastfeeding women twice as likely to be LTFU (aOR 2.2, 95% CI: 1.8 – 2.8) compared to women starting ART for own health.[4]

Researchers attempted to identify predictors of LTFU as an additional outcome.[4] Patients at urban facilities demonstrated a 1.4 times greater risk of attrition than those at rural facilities, but a 95% confidence interval of 1.0 – 2.0 renders this result

statistically less significant.[4] Similar limitations invalidate attrition risk comparison between different types of facilities.[4] Six months after ART initiation 29.4% (95% CI: 27.6 – 31.3%) of 'Option B+' pregnant women and 16.1% (95% CI: 14.3 – 18.0%) among 'Option B+' breastfeeding patients were classified as LTFU.[4] Compared to a 6 month attrition rate of 9.6% (95% CI: 8.7 – 10.6%) among women initiating ART for own health, the higher rate of LTFU among 'Option B+' patients is evident.[4]

The study has certain limitations with the most significant being incomplete data from electronic records attributed to the retrospective study design and short follow up time.[4] Most studies report on retention for up to at least 12 months after ART initiation to better reflect true attrition rate. The limited 6 month follow up by Tenthani et al could overestimate retention and consequently render study outcomes difficult to compare and extrapolate globally.[4]

Malawi's pilot project reignited global controversy around 'Option B+'. In a Lancet 2013 publication Coutsoudis et al. question 'Option B+' feasibility and label Malawi's program "extreme" and an unscientific "test and treat" approach.[18] In response, the WHO dismisses Coutsoudis et al's criticism and supports the global positive but cautionary view on 'Option B+'.[19] They suggest implementing 'Option B+' in resource limited settings, should the advantages of the program outweigh potential pitfalls.[19]

Zimbabwe implemented 'Option B+' in September 2013. Motivated by global concerns, retention in ART care were scrutinised in a retrospective cohort study by Dzangare et al in 2014. They showed six month LTFU amongst 'Option B+' women of 15.9%, significantly less than Malawi's 29.4% at the same time post ART initiation.[22]

The study additionally identified age and gravida status as significant risk factors for attrition. Adolescent females were found to be more at risk of attrition. This is evident in the finding that women aged between 20 – 25 years were 0.2 times as likely to be LTFU (aRR 0.2, 95% CI: 0.1 – 0.5, p=0.000) than those aged 15 – 19 years. Additionally women that were gravida 3 were 7.4 times more likely to be LTFU compared to primigravidas (aRR 7.4, 95% CI: 1.7 – 32.5, p = 0.008). Despite demonstrated statistical significance ($p<0.05$), the wide 95% confidence interval of the latter result renders it less generalisable.[22]

Although this study resonates with prior research findings, its small study sample and inclusion of only two rural districts in Zimbabwe further limits its extrapolation value. However, as the authors aptly identify, the study serves to confirm the importance of 'Option B+' in PMTCT and highlights the need for continued research and interventions to reduce attrition.[22]

After implementing 'Option B+' in 2013 Ethiopia similarly lacked data on patient retention. A retrospective cohort study published in the Journal of the International AIDS society in March 2016 explored LTFU rate among pregnant women initiated on 'Option B+' between March 2013 and April 2015.[23]

The investigators had clearly defined selection criteria and definitions such as LTFU being 90 days after the last clinic visit. This definition is in keeping with the majority of international research simplifying direct comparison between studies. Participant selection occurred through an all-inclusive method and all participants excluded from the study was accounted for with valid reasons avoiding selection bias.[23]

The study outcomes showed a 6 month attrition rate of 11.9% (95% CI: 8.9 - 16.0%) and LTFU at 12 months of 15.7% (95% CI: 12.0 - 20.4%). Although this is lower than the attrition rate found in other studies, it could be attributed to different PMTCT models between countries, varying LTFU definitions and other study setting incompatibilities.[23] Considering the impact these factors could potentially have on the study outcomes, the results should be interpreted cautiously and further research conducted.

Another Ethiopian-based study is in keeping with previous studies' findings that ART initiation rate and age are significant predictors of LTFU. Women that had same day ART initiation were twice as likely to be LTFU (aHR 1.9, 95% CI: 1.1 to 3.2, p=0.032) compared to those initiated at a later stage. Possible reasons cited include the inability to disclose and lack of readiness to commit to lifelong treatment. Additionally, age between 18 and 24 years was associated with a 2.3 times increased risk of attrition (aHR 2.3, 95% CI 1.2 to 4.5, p=0.017). With narrow confidence intervals and statistically significant p-values these outcomes can be considered valid and generalizable to other settings.[23]

The incorporation of 'Option B+' into the revised WHO PMTCT Guidelines affirmed confidence in its use in eligible, resource limited settings.[6] Subsequently, South Africa published revised National ART Guidelines in 2013 adopting 'Option B' as the main regimen with the Western Cape Department of Health opting to implement 'Option B+'.[7,20]

f) Gaps & Future Research

Two years after the implementation of 'Option B+' in the Western Cape, important questions remain unanswered. While success is evident in the increased uptake of pregnant patients in ART care, decentralisation of services and expanded nurse-initiated ART coverage, growing concerns remain regarding patient retention in long term ART care, especially once infants are no longer at risk of vertical transmission.[21]

Despite several recent publications investigating 'Option B+' retention and long term outcomes it is imperative that continued research be conducted.

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PART C

Abstract, Results & Discussion

A Retrospective Cohort Study: The retention in care of HIV positive pregnant and breastfeeding patients universally initiated on lifelong ART ('OptionB+') in the Klipfontein/Mitchells Plain substructure in Cape Town

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Background: The implementation of 'Option B+' has increased uptake and access to antiretroviral (ART) care. However, growing concerns exist regarding retention, especially once vertical transmission risk ceases. Considering the importance of adherence to achieve virological suppression and avoid resistance research on retention is crucial. This study compares the retention of women initiated on 'Option B+' to that of women initiating ART for their own health. Additionally possible predictors of loss to follow-up (LTFU) were explored.

Methods: Women initiating ART between 1 April and 31 August 2013 were allocated to either the pregnant (n=228) or non-pregnant (n=177) cohort. Retrospective review of electronic recordkeeping systems and patient folders measured retention up to 15 months after ART initiation. Demographic data was captured to explore predictors of LTFU. To avoid outcome bias with participants transferred out, analysis included a 'worst case' scenario assuming LTFU of all these participants and a 'best case' scenario assuming continued retention in care.

Results: At 6 months 'best case' analysis showed 28.1% of pregnant women LTFU compared to 16.9% of non-pregnant women with a 1.3 times greater attrition risk among pregnant cohorts (RR 1.29; 95% CI 1.09 – 1.54; p=0.009). 'Worst case' analysis at 6 months showed pregnant women at 1.4 times larger LTFU risk (RR 1.42; 95% CI 1.20 – 1.67; p<0.0001). Despite 'best case' analysis LTFU at 15 months increased to 41.2% in the pregnant group compared to 30.5% in non-pregnant patients and pregnant women remained at a 1.2 times greater attrition risk (RR 1.22; 95% CI 1.03- 1.44; p=0.03). Significant predictors of LTFU were age over 41 years (HR 17.2; 96% CI 1.8 - 163.0; p=0.013) and WHO clinical stage 3 (HR 4.2; 95% CI 1.6 - 10.8; p=0.004). Marital status, employment, baseline CD4 cell count and clinic distance were not significant predictors.

Conclusion: Similar to previous research, we found HIV positive pregnant women at significantly higher risk to be LTFU compared to non-pregnant women. Given the global focus on the elimination of vertical HIV transmission and retention in ART care, we hope our findings will enrich the ongoing conversation on how best to implement and revise PMTCT guidelines.

Keywords: Attrition, Retention, Antiretroviral, Option B+, Predictors, Pregnant.

Extensive research has been conducted on Human Immunodeficiency Virus (HIV) prevention of mother-to-child transmission (PMTCT) with overwhelming evidence demonstrating the effectiveness of antiretroviral treatment (ART) in reducing vertical transmission of HIV during pregnancy and breastfeeding. [1, 2]

Adherence rates as low as 70–80 % can sufficiently suppress the virus, but much more favourable virological outcomes are possible with increased adherence.[3] In pregnant and breastfeeding women, suppression is particularly important to ensure the lowest possible risk of mother-to-child transmission (MTCT) and to eliminate new vertical HIV infections.[4, 5] Retention rates between studies vary significantly, depending on factors such as patient population, institutional differences and treatment protocols.[6]

Several challenges threaten the success of PMTCT in developing countries including high HIV prevalence rates complicated by factors such as short birth intervals and late antenatal bookings.[7] Furthermore, insufficient laboratory resources cause delayed CD4 cell count testing, unnecessary ART deferral and consequently higher MTCT and maternal morbidity and mortality.[7]

In response, Malawi launched the 'Option B+' pilot program in 2011, implementing rapid testing and same day lifelong ART initiation for all HIV positive pregnant and breastfeeding women.[7] Concerns around long term feasibility of the regimen surfaced,[8] but largely positive outcomes ultimately led to updated World Health Organisation (WHO) ART guidelines in 2012.[9]

Shortly after the release of updated guidelines several countries including Zimbabwe and Ethiopia followed suit and implemented 'Option B+'.[19,20] Equally alarming attrition rates echoed existing global concerns, but the studies demonstrated much improved PMTCT access and availability complicating criticism of the program.[19,20]

Experiencing similar challenges, South Africa revised its ART guidelines in April 2013 with the Western Cape implementing 'Option B+'.[10]

Three years after the implementation of 'Option B+' in the Western Cape, important questions remain unanswered. While success is evident in increased accessibility, decentralisation of services and expanded nurse-initiated ART coverage, growing concerns remain regarding retention in long term care, especially once vertical transmission risk ends.[11]

Definitions

- **Option A:** Zidovudine (AZT) to HIV positive pregnant women not qualifying for lifelong triple ART from 14 weeks gestation with single dose nevirapine and tenofovir/emtracitibine 3 hourly in labour. [12]
- **Option B:** Universal ART to all HIV positive pregnant women. Patients with CD4 counts less than 350 or WHO stage 3 or 4 continue lifelong while others discontinue ART one week after cessation of breastfeeding. [9,10]
- **Option B +**: Lifelong ART to all pregnant and breastfeeding HIV positive women regardless of CD4 count or WHO clinical staging. [9,10]
- **Lost to follow up:** Not attending ART care for 90 days or longer after the last visit. The definition is based on current standard of practice at the study sites and a comprehensive literature review. [6,13]
- **Never returning for follow up:** Never returning to ART care after the first visit.
- **Transfer Out:** Transfer to another ART facility documented in the clinical notes or on the ERKS.

Evidently, further research in this area is crucial for the ongoing development of retention strategies and future decisions around regimen choices for individual provinces.

Study Outcomes

The primary outcome aims to determine the retention of HIV positive pregnant and breastfeeding women initiated on 'Option B+' in the Klipfontein/Mitchells Plain substructure in Cape Town and compare this to the retention of HIV positive women initiated on ART for their own health (CD4 count<350 cells/ųl or WHO clinical stage 3 or 4).

The study's secondary outcome aims to explore possible predictors of LTFU among 'Option B+' patients.

Study Site(s)

Western Cape ART services have been decentralised mostly to primary care level, with successful integration of antenatal and PMTCT services across the province. Attending one site for ART, antenatal- and postnatal care has advantages such as increased patient centredness and better resource allocation.

Hanover Park Community Health Centre (CHC) and Mitchells Plain CHC were selected as study sites for reasons such as having onsite Midwife Obstetric Units (MOU), integrated ART services, and implementation of 'Option B+' from 1 April 2013 in accordance with the provincial ART guidelines.

At both facilities pregnant women are initiated on ART at the onsite MOU and follow up continued at the ART onsite clinic. ART initiation and follow up of non-pregnant patients take place at the very same facilities' onsite ART clinics.

Participants

Participants included were female, ART naïve (i.e. no exposure to previous PMTCT or triple ART), older than 16 years of age, and initiated ART between 1 April and 31 August 2013.

Participants were assigned to one of two cohort groups based on their pregnancy status at ART initiation. The cohort group consisted of pregnant women who started antenatal care at the study sites during the specified time period and met the other inclusion criteria. Under 'Option B+' guidelines, participants in this group could have any CD4 count and WHO clinical staging at initiation.[9, 10]

The control group consisted of non-pregnant, HIV positive women who initiated ART at the included ART sites during the study period. Owing to the provincial adult ART eligibility guidelines at the time these participants had CD4 counts <350 cells/ųl and/or were WHO clinical stage 3 or 4.[10]

Participants were not excluded based on other demographic characteristics.

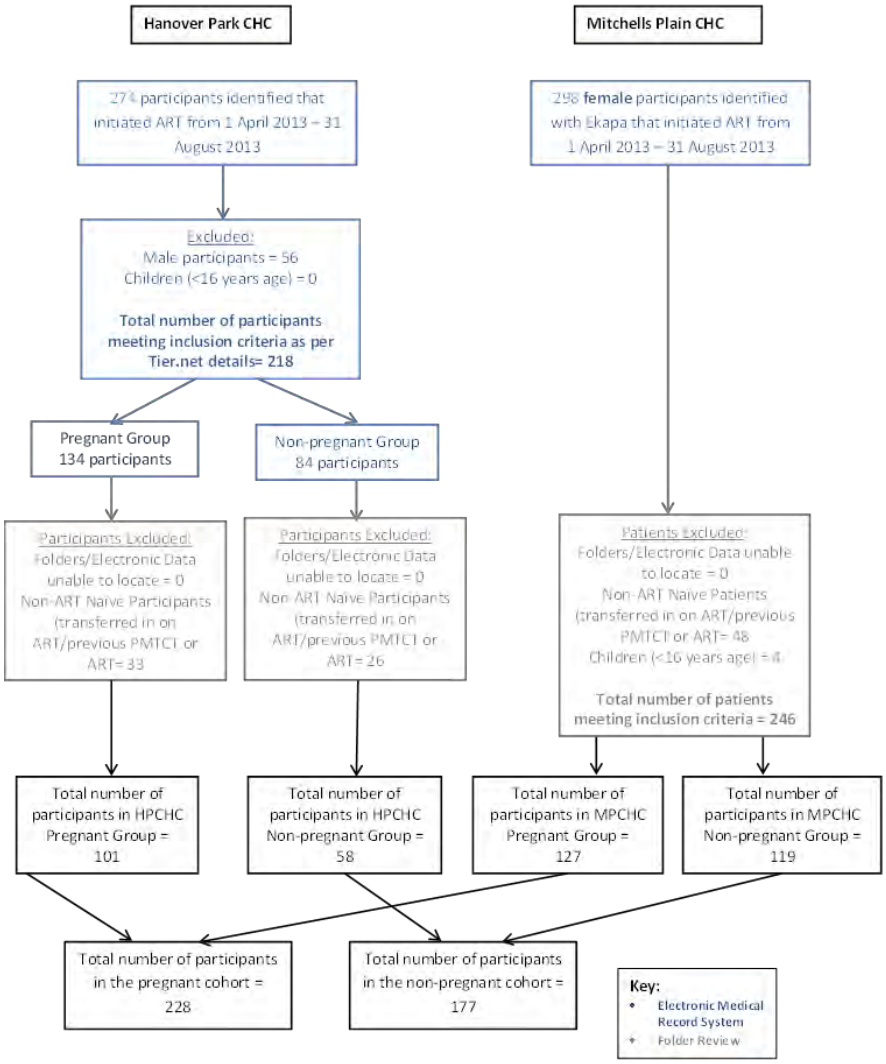
Participant Sampling

The initial proposal to sample participants using the MOU Advise, Counsel, Test, Support (ACTS) registers at the two study sites was amended due to certain limitations. These included the registers' lack of comprehensive patient information and concerns regarding counsellor vigilance in recording every tested patient, thereby increasing the likelihood of missing patients during sampling.

As a result the respective electronic record keeping systems (ERKS) at the study sites were used to

identify participants meeting the selection criteria. Hanover Park CHC has Tier.net as an ERKS while Mitchells Plain CHC uses Ekapa. Dedicated ERKS data capturers at ART sites ensure more accurate electronic records thereby significantly decreasing the possibility of incomplete participant sampling when used as a data source.

Figure 1. Participant Selection



Patient selection with Tier.net was done applying the filters "female", "pregnant", "non-pregnant" and "1 April 2013 – 31 August 2013", consequently generating two cohort groups from the onset.

Due to innate differences in Ekapa it was not possible to similarly apply these filters during sampling at Mitchells Plain CHC. Instead, collaboration with the University of Cape Town's information technologists generated a combined list of participants meeting the inclusion criteria. Unfortunately pregnancy status could not be differentiated and cohort allocation could only be done after individual folder review.

Following participant selection *(Figure 1)* the pregnant cohort group comprised of 228 participants and the non-pregnant control group included 177 women.

Data Collection

The principle investigator used pre-programmed Excel spread sheets as data collection tools. Participant demographic data was collected through individual folder reviews and cross-checked or supplemented with ERKS.

Retention in care was determined through clinical notes review to ascertain participant attendance at the first visit and 1, 3, 6, 9, 12 and 15 months after ART initiation. To account for reasons other than true attrition 'transfer out' and 'death' were additional outcomes.

Ethical Considerations

Ethics approval for the study was granted by both the Human Research Ethics Committee of the University of Cape Town (HREC 607/2014) and the Western Cape Provincial Research Ethics Committee.

Data Analysis

Data was captured using Excel version 14.0.0 (Microsoft, USA, 2011) and analysis performed with SPSS version 22.0.0.0 (IBM, USA, 2015).

Patient demographic characteristics were described as proportions (%). The skewness and kurtosis scores confirmed normal distribution of data. To calculate and quantify LTFU, risk ratios were calculated for each cohort. Odds ratios are additionally included in the results.

To avoid outcome bias with participants transferred to other facilities, analysis included a 'worst case scenario' assuming LTFU of all these participants and a 'best case scenario' assuming continued participant retention in care.

The Pearson's $\chi 2$ test (with its accompanying contingency coefficient) or Fischer's exact test were used to calculate the statistical significance of the different proportions and risk ratios. Independent Sample t-tests were used to test additional hypotheses. The Cox proportional hazards regression model was used to determine predictors of LTFU, expressed as hazard ratios with 95% confidence intervals. The log-rank test was used to test the significance of observed differences. Statistical significance was accepted as $p<0.05$.

Results

A total number of 274 patients initiated ART at Hanover Park CHC between 1 April and 31 August 2013 *(Figure 1)*. After excluding males and participants younger than 16 years of age, 218 participants were identified and allocated to the pregnant (134) and non-pregnant (84) cohorts respectively. Folder and ERKS review excluded non- naïve ART participants and subsequently generated the final Hanover Park cohorts of 101 pregnant and 58 non-pregnant participants.

The Ekapa database identified 298 new ART patients at Mitchells Plain CHC during the study period. As clarified earlier the exclusion of 48 ART non-naïve patients and 4 children preceded cohort allocation, finally producing the site's study groups of 127 pregnant and 119 non-pregnant participants.

Baseline patient demographic data is outlined in *Table 1*. When comparing age, distribution across the four age categories was not similar, but differences between similar ranges were statistically significant. ($p<0.0001$)

81.1% of pregnant cohorts live within the City of Cape Town's ideal 5 kilometer travelling distance from the clinic compared to 70.1% of non-pregnant females residing in the same radius. ($p=0.01$)

CD4 cell count distribution between the pregnant and non-pregnant group differed, with the majority of non-pregnant females (97.8%) having baseline CD4 cell counts < 350 cells/µl ($p<0.0001$). The 4 non-pregnant women with baseline CD4 cell counts > 350 cells/µl qualified for ART based on their WHO clinical stage. In the pregnant cohort, CD4 cell counts were fairly equally distributed with around 28% participants in each of the categories above 200 cells/µl. ($p<0.0001$)

The majority of participants in both cohorts had a baseline WHO stage of 1 at 91.2% of pregnant and 43.5% of non-pregnant women respectively. ($p<0.0001$)

Table 1. Baseline Patient Demographic Data			
	Pregnant % (n)	**Non-pregnant % (n)**	**p-value**
Number of Patients	228	177	
Age (yrs)			<0.0001
≤ 20	8.8 (20)	2.8 (5)	
21 – 30	62.7 (143)	39.6 (70)	
31 – 40	27.6 (63)	40.1 (71)	
≥ 41	0.9 (2)	17.5 (31)	
Employment Status			0.25
Employed	35.1 (80)	38.4 (68)	
Unemployed	49.1 (112)	51.4 (91)	
Unknown	15.8 (36)	10.2 (18)	
Marital Status			0.39
Married	26.7 (61)	26.6 (47)	
Single	71.5 (163)	69.5 (123)	
Unknown	1.8 (4)	3.9 (7)	
Distance from Clinic			0.01
≤ 5km	81.1 (185)	70.1 (124)	
≥ 5km	18.9 (43)	29.9 (53)	
CD4 cell count			<0.0001
≥ 500	27.7 (63)	1.1 (2)	
350 – 499	28.9 (66)	1.1 (2)	
201 – 349	28.9 (66)	54.9 (97)	
≤ 200	13.6 (31)	42.9 (76)	
Unknown	0.9 (2)	0 (0)	
WHO Stage			<0.0001
1	91.2 (208)	43.5 (77)	
2	4.4 (10)	23.7 (42)	
3	3.5 (8)	25.4 (45)	
4	0.9 (2)	6.8 (12)	
Unknown	0 (0)	0.6 (1)	
Known HIV + > 6 months prior to ART			<0.0001
Yes	24.1 (55)	52.6 (93)	
No	69.7 (159)	46.3 (82)	
Unknown	6.2 (14)	1.1 (2)	
Counselling Rate			<0.0001
Same Day	59.6 (136)	11.3 (20)	
Rapid Rate	5.7 (13)	44.1 (78)	
Normal Rate	0.5 (1)	28.2 (50)	
Unknown	34.2 (78)	16.4 (29)	

Table 2. Comparison of LTFU at different time intervals after ART initiation (Worst Case for TFO)						
	Pregnant Cohort n (%)	**Non-Pregnant Cohort n (%)**	**Pregnant Cohort Relative Risk (RR) (95% CI)**	**p-value**	**Risk Difference (RD)**	**Pregnant Cohort Odds Ratio (OR) (95% CI)**
First Visit	12 (5.3)	7 (4)	1.13 (0.79 – 1.61)	0.64	- 0.01	1.35 (0.52 – 3.50)
Month 1	19 (8.3)	18 (10.2)	0.90 (0.65 – 1.25)	0.60	- 0.04	0.80 (0.41 – 1.58)
Month 2	27 (11.8)	19 (10.7)	1.05 (0.81 – 1.36)	0.75	- 0.01	1.02 (0.55 – 1.89)
Month 3	43 (18.9)	26 (14.7)	1.13 (0.92 – 1.39)	0.29	- 0.04	1.35 (0.79 – 2.30)
Month 6	97 (42.5)	42 (23.7)	1.42 (1.20 – 1.67)	<0.0001	- 0.19	2.3 (1.54 – 3.68)
Month 12	133 (58.3)	70 (39.5)	1.39 (1.17 – 1.66)	0.0002	- 0.19	2.14 (1.43 – 3.19)
Month 15	146 (64)	75 (42.4)	1.48 (1.23 – 1.79)	<0.0001	- 0.22	2.42 (1.62 – 3.62)

Table 3. Comparison of LTFU at different time intervals after ART initiation (Best Case for TFO)						
	Pregnant Cohort n (%)	**Non-Pregnant Cohort n (%)**	**Pregnant Cohort Relative Risk (RR) (95% CI)**	**p-value**	**Risk Difference (RD)**	**Pregnant Cohort Odds Ratio (OR) (95% CI)**
First Visit	12 (5.3)	6 (3.4)	1.19 (0.85 – 1.67)	0.47	- 0.02	1.58 (0.58 – 4.31)
Month 1	19 (8.3)	15 (8.5)	0.99 (0.73 – 1.36)	1.00	- 0.002	0.98 (0.48 – 1.99)
Month 2	27 (11.8)	16 (9.0)	1.13 (0.88 – 1.45)	0.42	- 0.02	1.35 (0.70 – 2.59)
Month 3	38 (16.7)	20 (11.3)	1.20 (0.97 – 1.48)	0.15	- 0.05	1.57 (0.88 – 2.80
Month 6	64 (28.1)	30 (16.9)	1.29 (1.09 – 1.54)	0.009	- 0.11	1.91 (1.17 – 3.11)
Month 12	84 (36.8)	50 (28.2)	1.18 (0.99 – 1.40)	0.07	- 0.09	1.48 (0.97 – 2.26)
Month 15	94 (41.2)	54 (30.5)	1.22 (1.03 – 1.44)	0.03	- 0.11	1.60 (1.06 – 2.41)

Interestingly, the majority of pregnant participants were diagnosed HIV positive within 6 months of ART initiation at 69.7% compared to 46.3% in the control group. ($p<0.0001$)

In keeping with 'Option B+' the majority of pregnant cohorts received same day counselling (59.6%) or their counselling rate was unknown leaving only 14% of pregnant women not counselled according to the guidelines.

The 'worst case scenario' showed 42.5% of HIV positive pregnant women to be LTFU 6 months after ART initiation compared to only 23.7% of their non-pregnant counterparts. *(Table 2)* Assuming retention of all transferred out pregnant women decreased this proportion to 28.1% pregnant and 16.9% non-pregnant women LTFU at 6 months. ($p=0.009$) *(Table 3)*

At fifteen months, LTFU was 64% in the 'worst case' pregnant group compared to an equally suboptimal, but much lower, proportion of 42.4% in patients on ART for their own health. ($p=0.0002$) Regardless of assuming the optimistic 'best case scenario' retention of pregnant cohorts at 15 months remained comparatively poor with a 41.2% attrition rate. ($p=0.03$)

We further calculated the risk of HIV positive pregnant women to be LTFU relative to that of non-pregnant HIV positive patients. Both odds ratios and relative risk were calculated and are included in the results. However relative risks were primarily used in interpretation of study findings since outcome frequencies were greater than 10% and odds ratios could potentially overestimate the difference between cohorts.[21]

At 6 months after ART initiation, 'worst case' pregnant cohorts were 1.4 times more likely to be LTFU (RR 1.42; 95% CI 1.20 – 1.67; $p<0.0001$) and despite assuming the 'best case scenario' attrition risk was still 1.29 times greater in this group. (RR 1.29; 95% CI 1.09 – 1.54; $p=0.009$) Moreover, the comparison at 15 months remained similar with a 1.2 times larger attrition risk in the pregnant, 'best case' cohort (RR 1.22; 95% CI 1.03 – 1.44; $p=0.03$) and an unchanged 1.4 times greater LTFU risk assuming the 'worst case' scenario. (RR 1.48; 95% CI 1.23 – 1.79; $p<0.0001$)

The risk difference between cohorts at 15 months showed non-pregnant women to be at 0.2 times ('worst case') and 0.1 times ('best case') less risk of being LTFU compared to their non-pregnant counterparts.

Most of the factors investigated in this study were not statistically significant predictors of LTFU. *(Table 4)* Assuming the 'worst case' demonstrated that age over 41 years predicted a 17.2 times greater risk of LTFU, but the accompanying wide 95% confidence interval decreases its significance. (HR 17.2; 96% CI 1.8 – 163.0; $p=0.013$)

Table 3. Cox Regression Analysis for predictors of LTFU among pregnant HIV positive patients on ART ('Worst Case')

Variable	n (%)	HR (95% CI)	P - value
Age (yrs)			
≤ 20	20 (8.8)	R	
21 – 30	143 (62.7)	1.3 (0.5 – 3.5)	0.57
31 – 40	63 (27.6)	1.0 (0.4 – 2.7)	1.00
≥ 41	2 (0.9)	17.2 (1.8 – 163.0)	0.013
Employment Status			
Unemployed	80 (35.1)	R	
Employed	112 (49.1)	0.8 (0.5 – 1.3)	0.35
Marital Status			
Single	61 (26.7)	R	
Married	163 (71.5)	0.6 (0.4 – 1.1)	0.12
Clinic Distance			
≤ 5 km	185 (81.1)	R	
≥ 5 km	43 (18.9)	1.3 (0.7 – 2.3)	0.45
CD4 Cell Count (cells/ul)			
≥ 500	63 (27.7)	R	
351 – 499	66 (28.9)	1.9 (0.9 – 3.5)	0.05
201 – 349	66 (28.9)	1.4 (0.7 – 2.7)	0.29
≤ 200	31 (13.6)	1.2 (0.5 – 2.7)	0.66
WHO Clinical Stage			
1	208 (1.2)	R	
2	10 (4.4)	0.6 (0.2 – 2.0)	0.42
3	8 (3.5)	4.2 (1.6 – 10.8)	0.004
4	2 (0.9)	0.0 (0.0 – 6.9)	0.96
Known HIV + Status			
< 6 months	55 (24.1)	R	
> 6 months	159 (69.7)	1.5 (0.9 – 2.4)	0.15
Counselling Rate			
Normal	1 (0.5)	R	
Rapid	13 (5.7)	0.02 (0.001 – 0.2)	0.001
Same Day	136 (9.6)	0.02 (0.001 – 0.2)	0.001

Table 5. Cox Regression Analysis for predictors of LTFU among pregnant HIV positive patients on ART ('Best Case')

Variable	n (%)	HR (95% CI)	P - value
Age (yrs)			
≤ 20	20 (8.8)	R	
21 – 30	143 (62.7)	2.2 (0.5 – 9.7)	0.29
31 – 40	63 (27.6)	2.1 (0.5 – 9.2)	0.34
≥ 41	2 (0.9)	39.9 (3.2 – 496.5)	0.004
Employment Status			
Unemployed	80 (35.1)	R	
Employed	112 (49.1)	0.7 (0.4 – 1.1)	0.14
Marital Status			
Single	61 (26.7)	R	
Married	163 (71.5)	0.6 (0.3 – 1.1)	0.08
Clinic Distance			
≤ 5 km	185 (81.1)	R	
≥ 5 km	43 (18.9)	0.7 (0.3 – 1.7)	0.41
CD4 Cell Count (cells/ul)			
≥ 500	63 (27.7)	R	
351 – 499	66 (28.9)	1.9 (0.9 – 4.0)	0.09
201 – 349	66 (28.9)	1.0 (0.5 – 2.3)	0.92
≤ 200	31 (13.6)	1.0 (0.4 – 2.7)	0.96
WHO Clinical Stage			
1	208 (1.2)	R	
2	10 (4.4)	1.0 (0.3 – 3.4)	0.97
3	8 (3.5)	6.3 (2.2 – 17.8)	< 0.001
4	2 (0.9)	0.0 (0.0 – 7.8)	0.97
Known HIV + Status			
< 6 months	55 (24.1)	R	
> 6 months	159 (69.7)	1.3 (0.7 – 2.5)	0.36
Counselling Rate			
Normal	1 (0.5)	R	
Rapid	13 (5.7)	0.01 (0.001 – 0.2)	0.002
Same Day	136 (59.6)	0.01 (0.001 – 0.2)	0.001

Being WHO stage 3 at ART initiation had a 4.2 times larger attrition risk. (HR 4.2; 95% CI 1.6 – 10.8; p=0.004) The risk of being LTFU if pre-ART initiation counselling was rapid (three sessions done over two days) or all done on the same day was much lower than the risk if only one session was done per week. (HR 0.02; 95% CI 0.001 – 0.2; p=0.001) However, having only one participant in the normal counselling rate group could be the reason for this finding.

Applying the 'best case scenario' to the same model yielded similar outcomes with age ≥ 41 years (HR 39.9; 95% CI 3.2 – 469.5; p=0.04), WHO clinical stage 3 (HR 6.3; 95% 2.2 – 17.8; p<0.001) and counselling rate (HR 0.01; 95% CI 0.001 – 0.2; p=0.02) being possible predictors of LTFU in the pregnant group.

Discussion

Pregnancy is associated with several physical, emotional and social challenges. The added burden of an HIV positive diagnosis in pregnancy and pressure to start ART potentially threatens patient buy-in and commitment to lifelong treatment.[3]

We found HIV positive pregnant women at least twice as likely to be LTFU as women starting ART for their own health with 36.8% ('best case') and 58.3% ('worst case') LTFU 12 months after ART initiation. Results correlate with a Johannesburg-based study which similarly found 57.5% attrition among pregnant women within 13 months of testing HIV positive.[14]

One of the most pertinent 'Option B+' studies to date (conducted in Malawi in 2014) demonstrated a 6 month attrition rate of 16.1%.[7] At 6 months our study showed a much higher 42.5% ('worst case') and 28.1% ('best case) LTFU rate during pregnancy with an approximately 1.4 times greater attrition risk compared to non-pregnant women.

Despite the statistical significance (p<0.05) of the findings, it is notable that the confidence intervals (precision) of some of the risk ratios are wide and range from close to unity (one), which raises uncertainty about the findings. Nonetheless, the results would likely be more convincing, with narrower confidence intervals in a larger scale study.

Interestingly research conducted in Zimbabwe and Ethiopia after the implementation of 'Option B+' demonstrated much lower six month attrition rates of 15.9% and 11.9% among pregnant women respectively.[19,20] This lower rate compared to our and Malawi's study findings could be attributed to potentially different implementation of 'Option B+' models between countries, varying LTFU definitions and other study setting incompatibilities.

Evaluation of the study outcomes seems to support our hypothesis that HIV positive pregnant women only remain in care until delivery or the cessation of breastfeeding. Several reasons have been suggested with the most probable being mothers' motivation to protect their unborn children, with external social and emotional pressures influencing their behaviour after delivery.[3] This is demonstrated by the increasing LTFU over time, up to a considerable 41.2% or

1.2 times greater attrition risk at 15 months even when assuming the optimistic 'best case' scenario.

Another possible explanation could be most pregnant women's good physical health at ART initiation. The daily pill burden, possible side effects, as well as the implications of regular clinic visits, while completely asymptomatic, could explain the lack of incentive to remain in care. Previous studies support this hypothesis, demonstrating higher attrition among patients at WHO stage 1 or 2.[13,15] Although our study showed a 4.2 times higher attrition risk at WHO stage 3, the small subgroup sample means this finding should be viewed with caution.

With the 'test and treat' premise of 'Option B+', attrition could also be a result of inadequate patient preparation to start and adhere to lifelong medication. We showed counselling rate to be a significant predictor of LTFU, but considering that the majority of pregnant women received same day counselling, with only one participant counselled at the normal rate, deriving conclusions from this cohort would be problematic.

Research has shown that disclosure and the recruitment of a treatment supporter prior to initiation has a positive impact on ART adherence.[16, 17] With the 'test and treat' approach of 'Option B+' this is clearly not possible and could potentially impact the risk of attrition. However, disclosure has been found to be suboptimal even prior to the implementation of 'Option B+' with fears around social isolation and stigmatisation cited as possible reasons.[18] Moreover, pregnant and breastfeeding women initiated on 'Option A' and 'Option B' have had equally concerning attrition rates, potentially highlighting issues with PMTCT in general, instead of 'Option B+' specifically.[3, 14]

Evaluating predictors of LTFU revealed age over 41 years, WHO stage 3 and counselling rate as significant predictors of LTFU. Other factors such as employment, marital status and baseline CD4 cell count were not statistically significant predictors. As mentioned earlier, the skewed distribution of pregnant participants in the three significant categories (with less than ten participants each) potentially undermine the results. Nevertheless, their statistical significance could be confirmed and shown to be more generalizable, should the study be repeated on a larger scale.

The study's retrospective design has certain limitations that could impact findings. Inadequate recordkeeping could result in incorrect or missing data which could change study outcomes by altering baseline data input.

To avoid observer bias and "favourable" data capturing the principal researcher had predetermined categorical variables with clearly assigned values. However, the risk of recording bias in retrospective studies is more difficult to exclude completely. Although care was taken to correctly record data from the clinical notes illegible clinician handwriting was unavoidable at times.

Considering the study's limitations in light of its significant findings, it is advisable that further research be conducted in this area. Studies with larger numbers of participants and more sites

could improve both the statistical, and more importantly clinical, significance of the findings.

Conclusion

The findings of our study confirm both national and sub-Saharan research to date, where HIV among adolescent and young females is most prevalent.[4] It confirms the suspected much higher attrition risk pregnant women have as early as 6 months after ART initiation and their increasing LTFU rates over time.

Given the importance of adherence to achieve virological suppression and avoid resistance, interventions to improve retention are imperative. However, the inability of this and previous research to identify significant modifiable risk factors for LTFU among pregnant women makes intervention programs difficult to develop. However, we alternatively suggest continuous counselling and education of women throughout pregnancy. In addition, actively tracing patients who become LTFU could improve retention, but might be challenging in resource-limited settings.

The elimination of vertical transmission and retention in ART care remains a priority in the global HIV community. While our study hopefully enriches ongoing conversations on the implementation and revision of the PMTCT guidelines, further research to continuously improve and positively impact this important issue is recommended.

Conflicts of interest

The authors have no conflicts of interest to declare.

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PART D
Supporting Documents

Author Guidelines

JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

INFORMATION PRIOR TO SUBMISSION (available from: http://www.jiasociety.org/index.php/jias/about/submissions)

Aims and scope The JIAS welcomes submissions on HIV-related topics from across all scientific disciplines, including but not limited to:

- Basic and biomedical sciences
- Behavioural sciences and epidemiology
- Clinical sciences
- Health economics and health policy
- Operations research and implementation sciences
- Social sciences and humanities, including political sciences and media

The JIAS places high priority on submissions from operational research and implementation science as publication of such material can provide valuable information on various algorithms for monitoring and providing support for comprehensive, yet affordable and sustainable treatment, prevention and care programmes in different contexts. Submission of HIV research carried out in low- and middle-income countries is strongly encouraged. The JIAS accepts submissions in the categories of Research, Short Report, Review, Debate, Commentary and Letter to the Editor.

Ethical policies

The JIAS is a member of the Committee on Publication Ethics (COPE) and endorses the World Association of Medical Editors' (WAME's) Policy Statement on Geopolitical Intrusion on Editorial Decisions. All submitted manuscripts are scanned for plagiarism and may be rejected if significant overlap with other published material is detected. Work presented in submitted manuscripts may not have been previously published; nor may the same manuscript be submitted for consideration to another journal simultaneously. Any misconduct by authors in reporting their data, for example, falsification, will lead to rejection of their manuscript and other consequences decided on by the Editors. Please see COPE and International Committee of Medical Journal Editors (ICMJE) for further information on ethical issues in publishing.

Authorship

It is understood that all authors listed on submitted manuscripts have read and agreed to its content, and meet the authorship requirements as detailed by ICMJE here. In brief, contributors can be listed as authors if they:

1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; AND

2) have been involved in drafting the manuscript or revising it critically for important intellectual content; AND

3) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All contributors who do not meet the criteria for authorship should be listed in the Acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help or writing assistance, or a head of department, who provided only general support.

Ethical approval

Experimental research described in the manuscript must have been performed with the approval of an appropriate ethics review board. Research carried out on humans must be in compliance with the Helsinki Declaration, and any experimental research on animals must have followed internationally recognized guidelines. A statement on the ethical aspects, including the consent procedure followed, must be included in the Methods section of the manuscript. The Editors may reject manuscripts where the research has not been carried out within an ethical framework. For all articles that include information or photographs relating to individuals, written and signed consent from each patient to publish must also be made available if requested by the Editors. Confidentiality of study participants must be ensured at all stages of research and reporting.

Competing interests

Authors are required to submit a statement on competing interests, which exist when personal or financial relationships with persons or organizations may influence the interpretation of the data or how the author's work is presented. For details, see ICMJE's policy on competing interests here. In brief, all financial competing interests must be disclosed in this statement (reimbursements, fees, funding, salary payments from or ownership of any stocks or shares in an organization that may in any way gain or lose financially from the publication of the manuscript, either now or in the future, or applications for patents relating to the content of the manuscript), as well as non-financial competing interests (such as political, personal, religious, ideological, academic and/or intellectual interests) that are related to the work submitted. The competing interest statement should be included in the manuscript and will be published in the final article. If no competing interests exist, please state in this section, "The author declare that they have (or The author declares that he/she has) no competing interests."

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The involvement of scientific (medical) writers or anyone else who assisted with the preparation of the manuscript content should be acknowledged, along with their source of funding, as described in the European Medical Writers Association (EMWA) guidelines on the role of medical writers in developing peer-reviewed publications.

MANUSCRIPT PREPARATION

File formats

Accepted files formats are OpenOffice, Microsoft Word, RTF or WordPerfect; in addition, a PDF copy of the manuscript needs to be prepared. Tables and figures should be inserted in the main text. Additional files, such as supporting information or large datasets, can be submitted in any file format and should be uploaded as a separate file. Footnotes are not allowed.

Style and language

Use line spacing of 1.5 and an easily readable font, for example, Times New Roman, size 12. Do not use underlining, but use of bold and italics is acceptable. Set the text unjustified to the left and use portrait page setup. Your manuscript must contain line numbers to facilitate editors' and reviewers' comments. All submissions must be in UK English (International) and UN-accepted terminology should be followed. No capitalization should be used except for grammatically correct use, official names and titles, and abbreviations.

Acronyms should be used sparingly, and not in headings or in the Abstract. Only commonly known acronyms may be used, and they should be spelt out at first use followed by the abbreviation in brackets. SI units should be used, with litre and molar being permitted.

Title page

On the title page, you should mention the title of the manuscript, list all authors' names in full, and list any study groups if applicable. Each authors' affiliation should be numbered in superscript consecutively and listed underneath, including department, institution, city and country. The corresponding author should be marked with the symbol § in superscript and full contact details should be provided, including a telephone number with country code. Authors who have contributed equally to the work should be marked with the symbol * in superscript. Deceased authors should be marked with the symbol ^ in superscript. The email addresses of all authors should be listed by their initials. A list of six to eight keywords should be provided, preferably alternate words to those found in the abstract in order to improve search hits for the article in repositories.

Abstract

The Abstract should not exceed 350 words and should be structured according to the headings of the selected article category (see below), excluding the heading, Discussion for Research articles. Avoid using abbreviations and do not cite references in the Abstract. If you are reporting results from a controlled health care intervention, please include your trial registry, together with your unique identifying number at the end of the Abstract. For randomized controlled trials, follow the CONSORT extension for abstracts.

Main text

More information on the different article categories is provided below, including specific section headings and word limits. Information on the different sections in the manuscript is further detailed below, as well.

Article categories

Research - full reports of data from original research studies Headings: Introduction, Methods, Results, Discussion, Conclusions.

Word limit: 3500 words

Numbers of figures and tables: Unlimited

Additional files: Yes Manuscript template

Article sections

Introduction The Introduction section should introduce the topic to readers without specialist knowledge in that area and must clearly outline the current state of knowledge in this field, the motivation and the aim of the study or the article.

Methods The Methods section should include all information necessary to repeat the study, in particular, the study design, how data was collected and analyzed, clarifying the choice of methods that were made. If applicable, you should describe the setting of the study, the dates the study were conducted, and the sample or participants, as well as necessary power calculations and materials, including statistical packages, used. Interventions and programmes should be described in detail. Generic names for drugs or any molecules should be used. All studies involving humans or animals require a statement on ethical approval, and for the former, the consent procedure that was followed. Please include the names of the ethics review board(s) that approved the study. If the research study was specific to one sex/gender, the reasons for this should be clearly stated.

Results This section should include only data and findings from the authors' study. Presentation of statistical results should mention confidence intervals and levels of significance where appropriate. Quotes from qualitative study participants of less than three lines should be quoted in the text using quotation marks. For quotes longer than three lines, place the quote in a separate, indented paragraph and introduce it with a colon. No quotation marks are needed in this case. Details of the participant can be added in round brackets following the quote, but should not contain identifiable information to ensure confidentiality. Clarifications within the quotation should be placed in square brackets. Submitting authors are strongly encouraged to include data disaggregated by sex (and, whenever possible, by race) and provide a comprehensive analysis of gender and racial differences. The authors should include the number and percentage of men, women and, if appropriate, transgender persons who participated in the research study. Anatomical and physiological differences between men and women (height, weight, body fat-to-muscle ratios, cell counts, hormonal cycles, etc.), as well as social and cultural variables (socio-economic, education, access to care, etc.), should be taken into consideration in the presentation of data and/or analysis of the results.

Discussion In the Discussion section, you should discuss your main findings and place these within the context of the current body of knowledge in the field. Limitations of the study, for example, selection bias, can also be discussed, and should address how these influence the results and conclusions. If statistically significant differences were found between men and women or between different racial or cultural groups in the effects of the studied intervention, the implications, if any, for clinical and/or public health should be adequately discussed.

Conclusions In your Conclusions section, state your key messages from the study and explain their importance and relevance, as well as implications. Future studies and recommendations can be included in this section. The conclusions drawn must be strictly based on the data provided.

Figures Figures should be integrated into the text at the appropriate place. Figures should be cropped as closely as possible and have the header: "Figure 1. Title of figure". All figures need to be cited in the text in consecutive order. Legends should be provided underneath the figures, listing any abbreviations or meanings of symbols used. If several figures are included, please ensure that symbols are used consistently. Sufficient information needs to be provided for the figure to stand alone, including labels of axes. Please ensure that figures are legible in black and white print and also compatible with colour blindness. If figures are copied or adapted from another source, authors must seek permission prior to publication and these should be clearly cited as such. If the complete figure spans more than one page, authors should upload the figure as an additional file instead. High-resolution illustrations are recommended for optimal viewing performance in the final article.

Tables Tables must be created within the word file in the correct place and should have the header: "Table 1. Title of table". All tables should be cited in the text in consecutive order. The tables should not contain colour or shading, and no vertical, visible lines. A legend can be provided underneath the title, listing any abbreviations or meanings of symbols used. If several tables are included, please ensure that symbols are used consistently. If tables are copied or adapted from another source, permission must be sought by the authors prior to publication and these should be clearly cited as such. If a table spans more than one page, authors may want to consider uploading the table as an additional file instead.

References All external sources of information should be referenced within the text, the tables and figures, using consecutive numbering in square brackets, e.g. [1], [3-5], [3,4]. The references should be up to date and adequately reflect the current state of knowledge in the field. Citation bias, for example, by country or point of view must be avoided. Numbers of references are unlimited for all article categories and should be formatted in standard Vancouver style; see Sample references from ICMJE. Unpublished observations, personal communications and manuscripts currently under consideration should be cited in the text in round brackets and not in the reference list.

Data Collection Tool

Data Collection Sheet - Hanover Park ART Clinic										
		Patient Demographics								
Folder number	Date ART start	Pregnant	Age	Employed	Address	CD4 at start	WHO at start	Counselling Rate	Feeding	Baby PCR

Data Collection Sheet - Hanover Park ART Clinic

Retention of Patient						Reason for Loss to follow up		
First Visit	Month 1	Month 3	Month 6	Month 12	Month 15	Transfer Out	Death	Unknown

Denominator Reference Tool

Denominator	Data Specifier			
Pregnant	Yes	No		
Age	<20 = A	20-30 = B	30-40 = C	>40 = D
Employed	Yes	No		
Address (Suburb)				
CD4	>500 = A	350-500 = B	200-350= C	<200= D
WHO	1	2	3	4
Counsel Rate	Same Day= S	Rapid= R	Normal= N	
Feeding	Breast= B	Formula= F		
Baby PCR	Negative= N	Positive= P		
Retention	Yes	No		
Transfer Out	Yes	No		
Death	Yes	No		
Unknown	Yes	No		

Letters to Facility Managers

Hanover Park CHC
c/o Hamlyn Walk & Hanover Park Ave
Hanover Park

23 October 2014

Dear Sr APPLE

Re: **A Retrospective Cohort Study: The retention in care of HIV positive pregnant and breastfeeding patients universally initiated on lifelong ART ("OptionB+") in the Klipfontein/Mitchells Plain substructure in Cape Town**

My name is Adelein Engelbrecht and I am currently enrolled in the Masters of Family Medicine degree at the University of Cape Town. As a Master's student I need to conduct research that will improve the quality of health care services we provide to the community.

I have an interest in HIV antiretroviral care and the current "Option B+" and would like to conduct a research project at **Mitchells Plain Community Health Centre (CHC)** to determine the retention of patients universally initiated on "Option B+" between April – August 2013 in ART care.
I have received ethical approval from the University of Cape Town (Ref 607/2014) and would like to perform my research **at Mitchells Plain CHC** in 2014/2015, subject to provincial ethical approval (submitted and pending). I will also seek permission from the facility manager at **Hanover Park CHC.**

The study will be a retrospective cohort study involving review of the MOU ACT5 register as well as access to patient data on the ART clinic's electronic recordkeeping system. Information not obtained from these sources will be accessed through patient folder reviews. This study does not involve any patient contact and thus no individual patient consent will be obtained. However, ethical considerations remain a priority and anonymity of patients as well as complete confidentiality of patient information will be maintained throughout.

The data collection process will in no way interfere with the daily patient care at **Mitchells Plain CHC** and will not jeopardise staff's daily function. I will arrange an appropriate time with the managers of the MOU and ART Clinic to access their data in order to avoid hampering their daily function. For access to the identified folders that will need review I will arrange an appropriate system and time with your administrative staff to review these folders. Folder reviews will be done on site and will not be removed from the premises. I would like to request a room (tearoom/consultation room/boardroom) to conduct the folder reviews in.
The expected time required to perform data collection at your facility is two – four weeks depending on several contributing factors.

All collected data will be stored on my personal computer with back up data stored on two external hard drives in a secure manner at my home. All data will be kept confidential and anonymous.

Once my research is complete I will disseminate the findings of the research to each facility involved in the study and it will be included in my Masters dissertation.

Thanking you in advance for this opportunity.
Yours sincerely,

Dr AM Engelbrecht

c/o Hamlyn Walk & Hanover Park Ave
Hanover Park

23 October 2014

Dear Sr Pienaar /Sr Abrahams

Re: **A Retrospective Cohort Study: The retention in care of HIV positive pregnant and breastfeeding patients universally initiated on lifelong ART ("OptionB+") in the Klipfontein/Mitchells Plain substructure in Cape Town**

My name is Adelein Engelbrecht and I am currently enrolled in the Masters of Family Medicine degree at the University of Cape Town. As a Master's student I need to conduct research that will improve the quality of health care services we provide to the community.

I have an interest in HIV antiretroviral care and the current "Option B+" and would like to conduct a research project at **Hanover Park Community Health Centre (CHC)** to determine the retention of patients universally initiated on "Option B+" between April – August 2013 in ART care.
I have received ethical approval from the University of Cape Town (Ref 607/2014) and would like to perform my research **at Hanover Park CHC** in 2014/2015, subject to provincial ethics approval. I will also seek permission from the facility manager at **Mitchells Plain CHC.**

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The data collection process will in no way interfere with the daily patient care at **Hanover Park CHC** and will not jeopardise staff's daily function. I will arrange an appropriate time with the managers of the MOU and ART Clinic to access their data in order to avoid hampering their daily function. For access to the identified folders that will need review I will arrange an appropriate system and time with your administrative staff to review these folders. Folder reviews will be done on site and will not be removed from the premises. I would like to request a room (tearoom/consultation room/boardroom) to conduct the folder reviews in. The expected time required to perform data collection at your facility is two – four weeks depending on several contributing factors.

All collected data will be stored on my personal computer with back-up data stored on two external hard drives in a secure manner at my home. All data will be kept confidential and anonymous.

Once my research is complete I will disseminate the findings of the research to each facility involved in the study and it will be included in my Masters dissertation.

Thanking you in advance for this opportunity.
Yours sincerely,

Dr AM Engelbrecht

Consent Forms Facility Managers

I, N. J. DAVID understand that Dr AM Engelbrecht will be conducting research at MITCHELL'S PLAIN CHC in the form of a retrospective cohort study entitled "The retention in care of HIV positive pregnant and breastfeeding patients universally initiated on lifelong ART ("OptionB+") in the Klipfontein/Mitchells Plain substructure in Cape Town."

I understand that:

- I am the acting custodian for patients involved in the study
- Patient identity will be kept anonymous
- Patient information will be kept confidential
- The study will not involve patient contact, but only a review of the MOU ACTS register, ART electronic recordkeeping system and patient folders where necessary
- The research process will not interfere with/hamper the facility's daily function or patient care
- Patient folders will not leave the premises but might be accessed for information on site
- Collected data will be securely stored on the principal investigator's personal computer as well as two back-up hard drives for 5 years
- Collected data will be included in the principal investigator's master's dissertation and will be disseminated to all facilities included in the study
- I have the right to decline the inclusion of this facility in the study

Print Name N. J. DAVID

Signature

Date 23 Oct 2014

Place Signed MP CHC

Who to Contact:
You may contact me, Adelein Engelbrecht (MRXALI002, adelein@gmail.com, 0725930080), my supervisor, Dr. T. Motsohi (tshepo.motsohi@westerncape.gov.za) my faculty, the Department of Family Medicine UCT (0214066510) or the UCT Ethics Committee.

I, Vuyelwa Pienaar understand that Dr AM Engelbrecht will be conducting research at Hanover Park CHC in the form of a retrospective cohort study entitled "The retention in care of HIV positive pregnant and breastfeeding patients universally initiated on lifelong ART ("OptionB+") in the Klipfontein/Mitchells Plain substructure in Cape Town."

I understand that:

- I am the acting custodian for patients involved in the study
- Patient identity will be kept anonymous
- Patient information will be kept confidential
- The study will not involve patient contact, but only a review of the MOU ACTS register, ART electronic recordkeeping system and patient folders where necessary
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- Collected data will be securely stored on the principal investigator's personal computer as well as two back-up hard drives for 5 years
- Collected data will be included in the principal investigator's master's dissertation and will be disseminated to all facilities included in the study
- I have the right to decline the inclusion of this facility in the study

Print Name Vuyelwa Pienaar

Signature _

Date 23/10/2014

Place Signed Hanover Park CHC

Who to Contact:
You may contact me, Adelein Engelbrecht (MRXALI002, adelein@gmail.com, 0725930080), my supervisor, Dr. T. Motsohi (tshepo.motsohi@westerncape.gov.za) my faculty, the Department of Family Medicine UCT (0214066510) or the UCT Ethics Committee.

Human Research Ethics Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: lameez.emjedi@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

08 September 2014

HREC REF: 607/2014

Dr T Motsohi
Public Health & Family Medicine
Falmouth Building
Medical School

Dear Dr Motsohi

PROJECT TITLE: A RETROSPECTIVE COHORT STUDY: THE RETENTION IN CARE OF HIV POSITIVE PREGNANT AND BREASTFEEDING PATIENTS UNIVERSALLY INITIATED ON LIFELONG ART (OPTION B+) IN KLIPFONTEIN/ MITCHELLS PLAIN SUBSTRUCTURE IN CAPE TOWN (MMed-candidate- A Engelbrecht)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

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

However, please note that the PI must sign section 8.3 of the FHS013 form, and not the student investigator. Please provide a revised signature page of the FHS013 form.

Approval is granted for one year until 30 September 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

We acknowledge that the following MMed Candidate Dr Alida Engelbrecht will also be involved in this study.

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

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS