Economic evaluation of models of prevention of mother-to-child transmission of HIV intervention for large scale implementation

By

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Abstract

Background

Huge successes have been seen in the prevention of mother-to-child transmission of HIV (PMTCT) towards its elimination. Now amidst a landscape of universal antiretroviral therapy (ART), focus has been placed on different models of care to support and retain mother-infant pairs in the vulnerable postpartum phase.

Methods

The aim was to establish economic evidence for scaling-up approaches and models of care for PMTCT particularly during the postpartum period in Southern Africa. The economic data were collected during three studies, Safe Generations (Eswatini), MCH-ART and PACER (South Africa), using mixed bottom-up and top-down methodology. Outcomes of these studies were used to estimate the cost-effectiveness using an incremental cost effectiveness ratio (ICER, calculated by the difference in cost divided by the difference in effects) of lifelong ART in comparison to Option A (the standard of care at the time) in Eswatini; and to estimate the annual costs, cost-effectiveness and budget impact of three models of care (Model I: Routine Care - mothers in general ART and infants in well-baby clinics; Model II: Integrated Care - mothers-infant pairs in integrated care in midwife obstetric unit; and Model III: Community Care - mothers in community adherence clubs and infants in well-baby clinics) in South Africa, from the provider and patient's perspectives. Costs are presented in 2019 United States Dollars (US $).

Results

Lifelong ART can be considered cost-effective in Eswatini with an ICER of US $984 per mother retained in care to six months postpartum. In Cape Town, South Africa, Routine Care cost US $226 per mother-infant pair per annum; Integrated Care cost US $341; and Community Care cost US $254. Annual patient costs (direct and indirect costs) for Models I-III, were US $30-55, US $23-45 and US $76 per mother-infant pair respectively. Comparatively Community Care was the most cost-effective model with an ICER of US $97 per mother-infant pair retained and mother virally suppressed. Scaling-up Community Care nationally in South Africa would require US $5 720 096 more than Routine Care, 0.2% of the total health budget for 2020/21.

Conclusions

This work has generated novel empirical data in the form of new cost estimates and cost comparisons across different models of care. It has also provided a unique comparison of the different models of care using a cost-effectiveness analysis; and further a novel budget impact analysis of different approaches to rolling these strategies out. This data has helped to fill the gap in the evidence base for instance lifelong ART was implemented in Eswatini as a direct result of the Safe Generations study findings. Community Care was found to be cost-effective and if scaled up nationally in South

Africa would only require a small increment of the total health budget. However, we recommend a mixture of models of care to cater for the needs and preferences of patients. Decision makers can use the empirical findings to help set realistic budgets in Southern Africa and explore ideal model implementation to support mother-infant pairs in the crucial postpartum phase.

Acknowledgements

I entered the Health Economics Unit through a small door, and it was Edina Sinanovic who welcomed me in when I arrived. Edina has been an incredibly supportive supervisor with just the right mix of encouragement, understanding, boundaries, expectation, kindness and technical knowledge. I feel exceptionally lucky to have been able to learn from Edina as a role model, mentor, colleague and friend.

The Health Economics Unit is often described by those in it as a family. And it really is an amazingly warm place to work. I am grateful to my colleagues, daily hugs and encouragement from Olufunke Alaba, understanding from Sue Cleary, advice and warm smiles from Jon Ataguba, wit and a bigger picture of health economics from Tommy Wilkinson, a listening ear from Latiefa Adams, a ready story from Vanessa Daries, kind words from Amarech Obse and Vimbayi Mutyambizi-Mafunda, a reminder to keep running from Geetesh Solanki, and an institutional culture of sharing from Di McIntyre.

Also, to Landon Myer who insightfully set up and ran all of the projects to which this Doctor of Philosophy (PhD) is linked as well as leading the School of Public Health and Family Medicine as Head of Department effortlessly. He modestly says that he knows little of Health Economics, but this is no longer the case as his sharp mind learns easily. I appreciate Landon's non-linear way of looking at things that make them more interesting.

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Thanks, and appreciation also go to all my co-authors and those that worked on the research projects Safe Generations, MCH-ART and PACER. Linked to Chapter Three: We

would like to acknowledge the Eswatini Ministry of Health for their involvement in the SG Study as well as FLAS Manzini and the Alliance Church who all provided relevant cost data. Thanks to the ICAP teams in New York and Eswatini as well as the researchers at the University of Cape Town who contributed to this work. This study (Chapter is funded by the United States Agency for International Development (USAID), through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), USAID Award Number: AID-OAA-A-12-00020. USAID is the donor and advisory institution for this study. They are not directly engaged with the study. USAID employees consequently have no contact with study participants and no access to individually identifiable private information. This study was also supported in part by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme Corporation. The opinions expressed in this paper are those of the authors and do not necessarily represent those of the United States Government or Merck Sharp & Dohme Corporation. Further details about this work can be requested from the corresponding author; however, a data repository has not been established.

Linked to Chapter Four: We would like to acknowledge the women that comprised these cohorts and staff that tirelessly care for them. Funding: CMD receives a NIH T32 grant, NIAID T32 AI007433, and ALC receives a NIH Research Project Grant, R01 HD 079214.

Preface

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy in the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. The work on which this thesis is based is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or in the case of multi-authored published papers, constitutes work for which the candidate was the lead author.

This thesis includes published manuscripts, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town. I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board (on 01/10/2020) to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publications. The following manuscripts (one published, one in press and two prepared for submission) are included in the thesis and are presented as self-contained chapters in the following order:

a.) Cunnama L, Abrams EJ, Myer L, Gachuhi A, Dlamini N, Hlophe T, Kikuvi J, Langwenya N, Mthethwa S, Mudonhi D, Nhlabatsi B, Nuwagaba-Biribonwoha H, Okello V, Sahabo R, Zerbe A, Sinanovic E. Cost and cost-effectiveness of transitioning to universal initiation of lifelong antiretroviral therapy for all HIV-positive pregnant and breastfeeding women in Swaziland. Tropical Medicine & International Health. 2018;23(9):950-9.
b.) Cunnama L, Abrams EJ, Myer L, Phillips TK, Dugdale CM, Ciaranello AL, Zerbe A, Iyun V, MacQuilkan K, Daries V, Sinanovic E. Provider- and patient-level costs associated with providing antiretroviral therapy to women living with HIV in South Africa: A cost comparison of three models of care. In press. 2020.
c.) Cunnama L, Abrams EJ, Myer L, Phillips TK, Zerbe A, Iyun V, Sinanovic E. Cost-effectiveness analysis of three postpartum models of care for women living with HIV in Cape Town, South Africa. Upcoming.
d.) Cunnama L, Myer L, Abrams EJ, Sinanovic E. Scaling-up postpartum models of care for mother-infant pairs in South Africa: A budget impact analysis. Upcoming.

The contribution of the candidate to each manuscript is outlined at the start of each chapter (Chapters Three to six). The candidate was the lead and corresponding author on all manuscripts, prepared the datasets for analysis, and drafted all versions of the manuscripts. All co-authors reviewed and approved the submitted manuscripts and the candidate reviewed co-author comments and integrated them into the manuscripts prior to submission.

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SIGNATURE: Signed by candidate DATE: 16 April 2021

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Abbreviations

3TC	Lamivudine
AA	Automobile Association
ALT	Alanine aminotransferase
ANC	Antenatal care visit
ART	Antiretroviral therapy
ARVs	Antiretroviral medicine
AST	Aspartate aminotransferase
AZT	Zidovudine
BCG	Bacillus Calmette-Guérin
CACs	Community-based/ community adherence clubs
CD4	Cluster of differentiation 4
CEA	cost-effectiveness analysis
Cells/µl	Cells per microliter
CEPAC	Cost-Effectiveness of Preventing AIDS Complications
COVID-19	Coronavirus Disease 2019
CSIR	Council for Scientific and Industrial Research
CTX	Cotrimoxazole
CUA	cost utility analysis
DALY	Disability adjusted life year
DTaP-IPV-Hib-HBV	Diphtheria, tetanus, acellular pertussis, inactivated polio vaccine, haemophilus influenzae type B and hepatitis B combined vaccine
EFV	Efavirenz
eMTCT	Elimination mother-to-child transmission of HIV
FBO	Faith-based organisation
Focused Care	Focused maternal and child health ART service
FTC	Emtricitabine
GDP	Gross domestic product
HAART	Highly active antiretroviral therapy
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
HREC	Human Research Ethics Committee

ICER	Incremental cost-effectiveness ratio
LMICs	Low- and middle-income countries
LTFU	Lost to follow up
M2M	Mother to Mothers
MCH	Maternal and Child Health
MCH-ART	Strategies to Optimize ART Services for Maternal and Child Health
MoH	Swaziland/ Eswatini Ministry of Health
MOU	Midwife Obstetric Unit
MSF	Médecins Sans Frontières
MTCT	Mother-to-child transmission of HIV
NGO	Non-government organisation
NHLS	South African National Health Laboratory Services
NICE	National Institute for Health and Care Excellence
NICHD	National Institute of Child Health and Human Development
NVP	Single- dose nevirapine
OPV	Oral polio vaccine
PAC-ART	Postpartum Adherence Clubs for Antiretroviral Therapy
PACER	Postpartum Adherence Clubs to Enhance Support
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugated vaccine
PEPFAR	United States President's Emergency Plan for AIDS Relief
PHC	Primary care/ health care clinics
PhD	Doctor of Philosophy
PLWHA	People living with HIV and AIDS
PMTCT	Prevention of mother-to-child transmission of HIV
PrEP	Pre-exposure prophylaxis
QALY	Quality adjusted life year
RNA	Ribonucleic acid
RV	Rotavirus vaccine
SA	South Africa
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard deviation
SDG	Sustainable Development Goals

SG	Situkulwane Lesiphephile - Safe Generations
SOC	Standard of Care Model
SZL	Swazi Lilangeni
TB	Tuberculosis
TDF	Tenofovir
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
US $	United States Dollars
USAID	United States Agency for International Development
VL	Viral load
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
WHO-CHOICE	WHO's Choosing Interventions that are Cost-Effective project
WLH	Women living with HIV
WTP	Willingness to pay

1 Chapter One: Introduction and overview

1.1 Structure of the thesis

This first section of this thesis is an introduction and overview which contains a brief background and rationale for the thesis, establishes its aims and objectives, and provides an outline of the contents. This includes a summary of the methodology used to address the aim and objectives of the thesis. This is followed by a comprehensive literature review (Chapter Two), then the four results chapters (Chapters Three-Six), and a discussion and conclusion (Chapter Seven) to bring together the contents of the four results chapters summarizing the key messages for policy makers. A reference section and appendices are also included at the end of the dissertation.

1.2 Overall aim

The aim of the proposed research was to evaluate the cost and cost-effectiveness of different models of prevention of mother-to-child transmission of human immunodeficiency virus (HIV) (PMTCT) for women living with HIV (WLH) and their infants, in order to estimate the national budget for large scale implementation in South Africa and Southern Africa generally, taking into consideration the change to the lifelong antiretroviral therapy (ART) (Option B+) approach.

1.3 Specific objectives

1. To compare the costs and effects of the Option B+ approach to the Option A approach to prevention of mother-to-child transmission of HIV (PMTCT) from a provider's perspective in a cost-effectiveness analysis

2. To estimate the costs of three models of care for mother-infant pairs during the postpartum phase (at 12 months postpartum) from a provider and patient's perspective and b.) to estimate the costs of the pregnancy phase for mothers from a provider's perspective

3. To compare the costs and effects of three models of care for mother-infant pairs during the postpartum phase (12 months postpartum) from a provider and patient's perspective in a cost-effectiveness analysis

4. To estimate the budget impact of nationally scaling-up models of care for the postpartum period

1.4 Situating this dissertation

Table 1 displays the relationship between four specific objectives the analytic methods and the main outcomes. The conceptual framework for the dissertation can be visually seen in Figure 1 which shows how the objectives build on each other to fulfil the study aim.

As South Africa had already changed over to lifelong ART for pregnant women, for this dissertation the Option B+ approach (lifelong ART) was evaluated and compared to the Option A approach, in Eswatini. This was done during the Implementation Science Study

called Situkulwane Lesiphephile - Safe Generations (SG) for which Professor Elaine Abrams was the Principle Investigator. The SG study was funded by the United States Agency for International Development (USAID), through the United States President's Emergency Plan for AIDS Relief (PEPFAR), USAID Award Number: AID-OAA-A-12-00020. In April 2018, the King of Swaziland, King Mswati III, changed the name of Swaziland to Eswatini (the 'Kingdom of eSwatini'), however as this work was published prior to this official name change, Swaziland will be used in Chapter Three of the dissertation (1).

Further to the work done to assess the cost-effectiveness of lifelong ART, it was necessary to assess which of the evolving models of care during the postpartum period are best suited to the context under the Option B+ approach. Three postpartum models were evaluated in a high HIV burden peri-urban context in South Africa with the intention to provide evidence to aid policy decision-making around the costs and cost-effectiveness of these models. Data generated through a budget impact analysis provides information on the financial requirement for the potential national scale-up of these models in South Africa. This work was accomplished during the Strategies to Optimize ART Services for Maternal and Child Health (MCH-ART) study for which Professors Elaine Abrams and Landon Myer were the principal investigators and later the supplement study Postpartum Adherence Clubs to Enhance Support (PACER). Funding was provided by PEPFAR through the National Institute of Child Health and Human Development (NICHD), Grant Number 1R01HD074558 for MCH-ART and PACER. We recommend that, if possible, the reader first read each primary outcome paper (2-5)

This Doctor of Philosophy (PhD) study is situated within an economic evaluation framework, as it aimed to value costs and outcomes and to maximise the health effects

of PMTCT models of care given the costs and available resources. It intended to assist decisions on where scare resources for PMTCT and postpartum care should be positioned for applicable scale-up in South Africa and Southern Africa generally.

1.5 Ethical considerations

This research in this doctorate did not pose any risks for the participants. Information provided for use in this study, such as salary data, remained confidential and anonymity was maintained.

The Faculty of Health Science's Human Research Ethics Committee (HREC) at the University of Cape Town reviewed the PhD proposal and granted ethical approval HREC number 461/2016 (see Appendix 1 for the letter of approval and subsequent renewal approval).

Proposals for SG, MCH-ART (trial number NCT01933477, April 2013-December 2016) and PACER (trial number NCT02417675 February 2015-October 2016) studies were reviewed and approved by HREC at the University of Cape Town and Columbia University Institutional Review Board (see Appendices 2-4), and there was individual written informed consent.

1.6 Summary of the methodology used

Here we briefly outline the methodology utilised to address the aim and objectives of the thesis. For Chapter Three, the empirical cost data for the cost-effectiveness analysis

was collected during the Implementation Science Study SG. The PhD candidate traveled to Eswatini to liaise with research staff, meet Ministry of Health Officials, collect costs using an ingredients-based approach, presented a capacity building workshop and research presentation at an Eswatini national conference and fed back results to stakeholders in a workshop once the work was complete. Data collection in Eswatini also entailed observing in clinics, helping staff fill in timesheets and going through HIV registers. The effectiveness measure of retention of mothers at six months postpartum, was utilised for the cost-effectiveness analysis. Data analysis took place in a custom-built tool within Microsoft Excel by the PhD candidate.

Empirical cost data were collected for this cost analysis from a provider and patient's perspective as presented in Chapter Four. This was done during the MCH-ART study and later the supplement study, PACER. We compared three models of postpartum care for mother-infant pairs, namely Model I - Routine Care, Model II – Integrated Care and Model III – Community Care. Patient costs were collected through time-in-motion studies conducted by the PhD candidate as well as through a questionnaire as part of the larger MCH-ART and PACER studies. Postpartum care activities in the midwife obstetric unit (MOU) (and antenatal care activities), general ART clinics and community adherence clubs were observed, informal interviews were undertaken with staff, space was measured, inventory was taken, and registers were assessed. Additional information was sourced from Provincial Department of Health, the City of Cape Town and others. A short section on the pregnancy phase costs for mothers in the MOU from a provider's perspective, which has not been published, is also included in the PhD at the end of Chapter Four. Data analysis was performed by the PhD candidate, utilising a

custom-built tool within Microsoft Excel as well as in the interface RStudio, using R Programming.

In Chapter Five, costs which were collected (as described under Chapter Four) were inflated to 2019 United States Dollars using the consumer price index. These inflated costs were then combined with the MCH-ART and PACER overall study outcomes to produce a cost-effectiveness analysis assessing the cost per mother-infant pair retained and virally suppressed at 12 months postpartum. Viral suppression was defined as HIV ribonucleic acid (RNA) <50 copies/mL. Data analysis took place in a custom-built tool within Microsoft Excel as well as in the interface RStudio, using R Programming by the PhD candidate.

For Chapter Six, data analysis took place in an adapted National Institute for Health and Care Excellence (NICE) Budget Impact Template in Microsoft Excel. Epidemiological data for these calculations were obtained from publicly available datasets. This budget impact analysis assessed the financial requirement of scaling-up the most cost-effect model of care, Model III (from Chapters Four and Five) to cater for all postpartum WLH in South Africa. Further to this we explored different scenarios of scale-up, with a mixture of the three models of care, as a slightly increased budgetary requirement may produce a suite of care that will both cater to mother-infant pair preferences and better assist with retention in care leading to improved outcomes.

Table 1: Relationship of analytic methods to specific objectives

Specific objective	Study	Analytic method	Main outcome
1. *To compare the costs and effects of the Option B+ approach to the Option A approach to PMTCT from a provider's perspective in a cost-effectiveness analysis*	*Safe Generations in Eswatini*	*Provider costs:* estimation of total and unit costs based on collection of capital and recurrent costs *Cost-effectiveness:* linking the costs and outcomes to establish the cost-effectiveness of the two approaches to PMTCT	• Cost-effectiveness analysis • ICER: the cost per mother retained at 6 months postpartum • Total and unit costs of treatment under the Option A and Option B+ approaches • Cost-effectiveness information to support decision making for both Eswatini and Southern Africa generally
2. *To estimate the costs of three models of care for mother-infant pairs during the postpartum phase (at 12 months postpartum) from a provider and patient's perspective and b.) to estimate the costs of the pregnancy phase for mothers from a provider's perspective*	*MCH-ART* (Models I – Routine and II – Integrated Care) *and PACER* (Models I - Routine and III - Community Care). *in Cape Town, South Africa*	*Provider costs:* estimation of total and unit costs based on collection of capital and recurrent costs *Patient costs:* using time motion tools to evaluate the loss of productive time by patients as well as use of questionnaires to assess the direct and indirect travel costs	• Total and unit costs of providing postpartum ART care for mother-infant pairs in three different models of care • Total and unit costs of the pregnancy phase of care to support budgeting in South Africa and Southern Africa generally
3. *To compare the costs and effects of three models of care for mother-infant pairs during the postpartum phase (at 12 months postpartum) from provider and patient's perspective in a cost-effectiveness analysis*	*MCH-ART* (Models I – Routine and II – Integrated Care) *and PACER* (Models I - Routine and III - Community Care). *in Cape Town, South Africa*	*Cost-effectiveness:* linking the costs and outcomes to establish the cost-effectiveness of the three models of care	• Cost-effectiveness analysis of the three postpartum models of care • Ranking the models in terms of cost-effectiveness • ICER: the cost per mother-infant pair retained and virally suppressed in care 12 months postpartum • Information generated to support decision making in South Africa and Southern Africa generally
4. *To estimate the budget impact of nationally scaling-up models of care for the postpartum period*	*MCH-ART* (Models I – Routine and II – Integrated Care) *and PACER* (Models I - Routine and III - Community Care). *in Cape Town, South Africa*	*Budget impact analysis:* ranking the models of care in terms of cost-effectiveness (Objective 3). Estimate the budget impact of scaling up-the model nationally by using national data	• Budget impact analysis • To assist resource allocation and decision making around the PMTCT programme in South Africa in terms of nationally scaling-up postpartum models of care

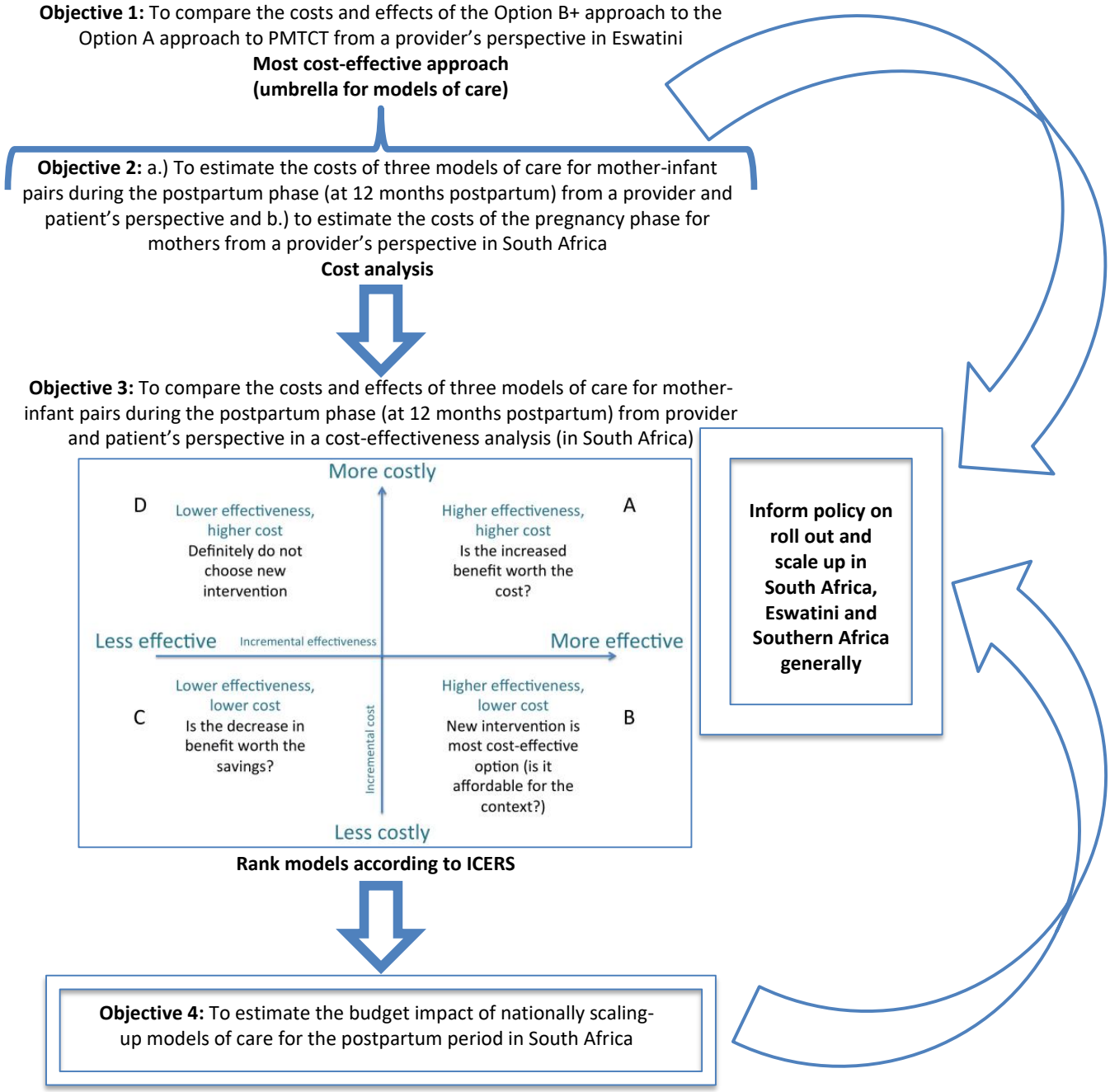

Figure 1: Links between objectives (cost-effectiveness plane adapted from Gray et al. 2011(6))

2 Chapter Two: Literature review

We find ourselves in the general context of there being a worldwide movement towards universal health coverage outlined in the Sustainable Development Goals (specifically under SDG 3.8), which should include financial risk protection as well as quality, safe and efficacious essential services that are accessible in terms of affordability (7). The crucial part of Universal Health Coverage relating to health economics is the financial risk protection, to prevent catastrophic spending on health care (8) while still incorporating factors such accessibility and services of high quality.

Mothers who acquire HIV prior to pregnancy or during pregnancy are at risk of vertical transmission of HIV to their babies. Perinatal modes of transmission are during pregnancy (in utero), during birth and delivery (intrapartum) and postpartum during the breastfeeding period (9). It is also possible for infants to obtain HIV through horizontal transmission linked to blood products, needles or other equipment, or breastmilk (either expressed or delivered through surrogate breastfeeding) which is contaminated with HIV and sexual abuse (10, 11). It is unclear how much these modes of transmission contribute to the paediatric HIV burden overall, one study suggests 11.5%(11), however, there have been several studies which report on the issue of horizontal transmission in children (10, 12-14). The United Nations four pronged approach to PMTCT was established in 2002, and consists of: Prong I) prevention of HIV in women of reproductive age; Prong II) preventing unintended pregnancies in women living with HIV; Prong III) preventing transmission of HIV from mother-to-child; and Prong IV) the treatment and care including support of both women living with HIV and their infants (and families) (15, 16). In South Africa we are privileged to have three

iterations of National Strategic Plans for HIV, Tuberculosis (TB) and Sexually Transmitted Infections (STIs). The most recent version published in 2019 are fully costed and include budgets for HIV (17).

The overall aim of the dissertation was to evaluate the cost and cost-effectiveness of different models of PMTCT for WLH and their infants, taking into consideration the change to the lifelong ART (Option B+) approach to inform decision making, in order to estimate the national budget for large scale implementation. Given this, the aim of this literature review is to provide context and background for the reader, surrounding PMTCT in low- and middle-income countries (LMICs) such as those found in Sub-Saharan Africa and the previous economic evidence generated.

This literature review will situate the reader, with a summation of the literature surrounding the topics of antiretroviral therapy (ART), the impact of Coronavirus Disease 2019 (COVID-19), HIV preventions specifically for the prevention of mother-to-child transmission of HIV (PMTCT), models of care, health economics specifically economic evaluation and budget impact analysis (BIA). It will also provide an overview of where we were with relevant literature when the parent studies, Situkulwane Lesiphephile - Safe Generations (SG), Strategies to Optimize ART Services for Maternal and Child Health (MCH-ART) and Postpartum Adherence Clubs to Enhance Support (PACER) were conceived and initiated. And flow into more up to date data on where we are now in terms of HIV prevention programmes, specifically for postpartum period and the costs and cost-effectiveness of these, ending with the conclusion and unanswered questions.

2.1 HIV/AIDS

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), which attacks and weakens people's immune systems has infiltrated many different communities worldwide since the epidemic began (18). Incidence of HIV has declined over time from 2.8 million cases in 2000 to 1.7 million in 2018, and deaths from 1.4 million to 770 000 in the same time period (19). Globally, it has been estimated that 3 million lives had been lost to the virus, while there were around 38 million people living with HIV and AIDS (PLWHA) at the end of 2019 (18).

Diagnosis of HIV/AIDS through a simple blood test identifies the presence of antibodies to the virus (18). Voluntary testing for HIV should include counselling and be linked to prevention, treatment and care services (18, 20). As there is no cure for HIV infection, prevention is necessary and, for instance, this can take the form of barrier contraception methods (18, 20). Prevention of HIV infection will be discussed in more detail below.

2.1.1 ART

With the advent of ART, PLWHA are able to live longer than without treatment and continue to have productive lives (21). In 2012, there were a reported 9.7 million people on ART in LMICs which was a remarkable scale up from 300 000 people in 2002 (22). The 2016 World Health Organization (WHO) recommendations for starting lifelong ART were a cluster of differentiation 4 (CD4) cell count of below 500 cells per microliter (cells/µl), or starting regardless of CD4 count for certain population groups, such as those with active TB (23) and pregnant women. Advances were then made such

as the development of fixed dose combination ART that is taken once daily in adults, which has been a major improvement in HIV treatment (24). This simplifies administering treatment and eases supply chain management (24). Same day initiation of ART (on the day of HIV testing) has been recommended since 2017 in South Africa and coverage of this practice has increased over time (25).

The Joint United Nations Programme on HIV/AIDS (UNAIDS) had set the ambitious target of making sure that by 2020 90% of PLWHA know their HIV status; 90% of those with a confirmed HIV infection receive sustained ART; and that 90% of those individuals receiving ART are virally suppressed (26). Further to this is the goal to completely eliminate the AIDS epidemic by 2030 (27). Eswatini (formerly Swaziland) is one of the seven African countries that has now reached and surpassed this target with 98%, 98% and 97% for each of the three categories respectively (PLWHA know their status, receive ART and are virally suppressed). South Africa is moving in the right direction particularly in the first and third category with 92%, 75% and 92%, for 2019. The second category has yet to be met despite South Africa being known as having the world's largest ART programme, with 5.2 million individuals on treatment in 2019 (28).

A large randomised control trial (which was run for 16 months before being ceased so that the control group could join the intervention group) determined that taking ART continuously reduces the risks of opportunistic infections and death in comparison to intermittent use of ART (29). Study results by Lundgren et al. (30) added to evidence on ART initiation, supporting the early start of ART for adults with CD4 counts above 500 cells/μl (30). If started early it was shown that PLWHA will benefit from a 50% reduced

risk in becoming ill or dying in comparison to those who had delayed treatment (only starting treatment once their CD4 count was below 350 cells/μl) (30).

ART guidance now promotes universal treatment which is for both clinical as well as public health benefit whereas the emphasis previously was on treatment of PLWHA who were the most clinically unwell (19). The treatment cascade in the era of universal ART, sees the patient moving from testing to linkage to care, initiating ART and then being retained on ART in both the short and long term (31). Globally the effect of universal ART has been that both the incidence as well as the number of deaths from HIV/AIDS have declined over time (19). Other positive effects such as the reduction of incident TB cases by a staggering 75%, has been noted in Ethiopia since the shift to universal treatment (32). At the end of 2019, 25.4 million PLWHA had accessed ART globally (18, 33).

However, when evaluating outcomes in South Africa before and after universal treatment was implemented, Hirasen and colleagues (34) found that under universal treatment there was more loss to follow up, which in part they ascribed to PLWHA starting ART when clinically well, which may inhibit attributing benefits to taking medication as no improvement may be noted (34).

2.1.2 The impact of COVID-19

At the time of writing in 2020, an emergent virus 'Severe Acute Respiratory Syndrome Coronavirus 2' (SARS-CoV-2) which causes COVID-19, had led to a global pandemic which is expected to have far reaching impact on the progress that is being made on the

90, 90, 90 goals set by UNAIDS (35). Efforts to model the effects of COVID-19 on HIV have indicated that the deaths for those with HIV could increase by 10% in high burden settings such as South Africa over the next five years (36). In a bold statement by the Lancet HIV, it is stated "*Given advances in prevention, testing, and treatment, every HIV infection and death in 2020 is preventable*" however they go on to say that COVID-19 is threatening the progress that has being made by disrupting services (35). There is advocacy for patients to be served outside of healthcare facilities for instance in community adherence clubs (CACs) and to be given extended refills of their ART in order to facilitate less frequent engagement with large groups and individuals seeking care with COVID-19 infection (37).

2.1.3 Investment in prevention

HIV prevention encompasses education; mobilising resources; empowering females; supplying condoms; pre-exposure prophylaxis (PrEP), voluntary medical male circumcision (VMMC) and targeting key at risk and vulnerable populations such as pregnant women (38).

The estimated amount that will need to be invested in HIV care in order to reach the SDG for HIV/AIDS elimination (among other infectious diseases) by 2030 (SDG 3.3) is US $32 billion in 2020. The goal being to reduce the number of incident infections to lower than 500 000 (by 2020). UNAIDS has put forward the concept that a quarter of this budgeted investment should be directed at HIV prevention (38).

2.1.4 PMTCT

Mother-to-child transmission of HIV (MTCT) is responsible for almost all new HIV infections in children around the world (39). Mothers who find out about their HIV status when accessing antenatal care at clinics are faced with the challenge of ensuring that their infants are born HIV negative, through the use of PMTCT programmes (23). It is important to note that, even with the reduction of MTCT, children will continue to be exposed to HIV (24) and be infected with HIV. There is a global effort to eliminate paediatric HIV as well as ensure maternal health and longevity (39) and maintain health of HIV exposed uninfected infants primarily through safe breastfeeding. This is particularly in light of the huge reduction seen in high-income countries where transmission rates were as low as 1% in 2013 (24) now countries such as Cuba (2015), Armenia and Thailand (2016), Malaysia (2018), Sri Lanka and the Maldives (2019) have succeeded in the elimination of MTCT (eMTCT) as validated by WHO (40). The global performance indicator for the complete elimination of incident cases of paediatric HIV as well as ensuring maternal health and sustained well-being by 2021 laid out by UNAIDS (27) is on track for two of the outcomes for the output titled "Access and quality of comprehensive eMTCT services improved" . These outcomes are lifelong ART being offered to pregnant women living with HIV (92% in 2018) and offering HIV testing to their partners (82% in 2018). The outcomes that are still 'in progress' relate to offering repeat testing to those pregnant and breastfeeding women not living with HIV (49% in 2018), and the engagement of women in the eMTCT strategy improvement and realisation (68% in 2018) (27).

There are now more than 80% of pregnant and breastfeeding women living with HIV accessing ART worldwide with the proportion as high as 93% in Eastern and Southern Africa (27). However accessing care is only a part of the picture of PMTCT as the global MTCT rates are unexpectedly high at 13%, suggesting that poor retention in care and late timing of ART initiation among other factors are playing roles continued MTCT (27).

There has been a shift to a more universal approach to PMTCT over time. The use of antenatal care as an access point to testing and treating women with HIV is successful and advantageous, as has been found after success in PMTCT programmes (24). However decreased levels of MTCT rely on early and robust antenatal care with good coverage and patients following the PMTCT cascade (24). Loss to follow up is high for women who are pregnant and HIV positive. Approximately 49% of women who are HIV positive are lost to follow up between antenatal care initiation and delivery of their child globally (41).

PMTCT is the poster child for prevention in that eMTCT in infants is an imminent and attainable goal (38). In a systematic review PMTCT was also found to have the lowest median incremental cost effectiveness ratio of US $1 144/HIV infection averted and US $191/DALY (disability adjusted life year) averted when compared to other HIV prevention interventions of VMMC, PrEP, treatment as prevention (TasP), other biomedical interventions, behaviour change, and structural interventions (42).

2.1.5 The history of PMTCT

In the early 1980s, it was discovered that paediatric HIV infections were due to MTCT (24). However, at this time if a woman was HIV positive the only option to ensure HIV was not transmitted to the infant was to avoid pregnancy, as no preventative interventions had been established (24). Now mothers protect their infants from infection through taking prophylactic ART during pregnancy and breastfeeding and giving post exposure prophylaxis to their infants.

In the first decade of the 2000's, the WHO guidelines for PMTCT changed four times, which emphasises the dynamic nature of PMTCT programmes (24). LMICs made their best attempt at adopting each recommendation in turn, sometimes with the result that implementation challenges have hampered their success and have created confusion (24). Botswana was the first African country to have a PMTCT programme in the late 1990s, which comprised a short course of zidovudine (AZT) and a single dose of nevirapine (24). In countries such as Kenya and Eswatini there has been a drive to integrate sexual and reproductive health services and HIV services, with the idea that this would benefit patients, improve service delivery and result in cost savings (43).

Previously the Option A approach to PMTCT was utilised, for instance in countries like Eswatini and South Africa. The Option A approach separated pregnant mothers into two categories, either eligible or ineligible for lifelong treatment based on their CD4 count (this CD4 count threshold was 200 then 250, then 350, and then 500 cells/μl). Those ineligible mothers were only given prophylactic monotherapy treatment during their pregnancy period (which differed from the triple ART given to eligible women). The

WHO also identified another approach to PMTCT called the Option B approach. The Option B approach uses treatment as prophylaxis for all but differentiates between those above and below the threshold of a CD4 count of 350 cells/μl. Initially women all start the same triple ART, however those women with a CD4 count below 350 cells/μl are started at diagnosis and continue for life, whereas those with a CD4 count above 350 cells/μl start ART from around 14 weeks gestation and cease treatment one week after stopping breastfeeding (44).

There has been a global move to the Option B+ approach, which places all pregnant mothers who are HIV positive on lifelong ART regardless of their CD4 count (23). This approach was first suggested in Malawi as a public health approach to PMTCT, in response to an identified need to start treatment prior to receiving, often delayed, CD4 count results (45). Option B+ is now referred to as lifelong ART.

The value of lifelong ART is the potential reduction in both vertical (MTCT) and horizontal (between sero-discordant couples) transmission of HIV and reducing maternal morbidity and mortality (44). As well as individual benefits in starting ART early for those women who start lifelong treatment under the PMTCT programme, such as reduced risk of TB due to early initiation (46). There is growing evidence of individual benefit with very early ART, but concerns have been raised about retention in care with this approach. Lifelong ART automatically provides PMTCT for subsequent pregnancies (if women are adherent), which along with reduced horizontal transmission, may be a significant public health benefit.

The Option B+ approach was in line with evidence for starting treatment earlier on, as it allowed pregnant women to start ART regardless of their CD4 count, which reduced harm from treatment interruption and had public health, PMTCT and individual benefits from treatment for all. Additionally, the study by Lundgren et al. (30) called for progress within the health system to improve HIV diagnosis and linkage to care, which the Option B+ approach aimed to do.

PMTCT has been a large public health achievement as it has globally prevented the infection of hundreds of thousands of children with HIV (24). Despite the improvements of the PMTCT programmes, the access and movement of pregnant women through the treatment cascade is still crucial to the success of the programme (24). Hence, if women do not access antenatal care, they may not be initiated on treatment during pregnancy (24). For those who do access antenatal care, the loss to follow up of HIV positive pregnant women in Sub-Saharan Africa countries between first antenatal care registration and delivery was found to be around 49% by a systematic review (41). This may be especially relevant where delivery is not in a health facility.

2.1.6 PMTCT Implementation influences and challenges

Challenges for PMTCT still centre on retention and adherence of patients (44) as well as on late presentation for antenatal care. In addition, the way to refer mothers into HIV treatment and care programmes remains a concern (44). The Safe Generations study in Eswatini found an overall retention of 39% of mother-infant pairs from first antenatal care visit until six months postpartum, and 53% when only assessing universal ART (5). WLH in rural Uganda and urban South Africa were compared and found to have 90%

ART adherence during the postpartum period and 40% respectively , whereas this was 91% and 74% during the pregnancy phase (47). Emotional support has been recommended as an aid to retain WLH, especially in the postpartum period (47). For example emotional support can be in the form of encouragement or reminders about ART, from a peer or treatment buddy or family member (48).

In Zimbabwe, a study was conducted to assess the implementation of a rural PMTCT programme between 2001 and 2003. The authors found that following up the mothers (loss to follow up) as well as collection of test results were the largest challenges (49). This could be partly due to the mobility of the population studied as well as monitoring of follow up only taking place in hospitals and not in clinics, posing limitations such as patient transport (49). The training health care workers receive in counselling services also has influence on the care provided and should be an aspect that is focused on (49).

Lack of follow up was also highlighted in another South African study, with the additional concern that PMTCT services were not well integrated into routine care. For instance, there was a lack of clarity around the roles of staff in well baby services as to who should be doing testing for HIV exposed infants as well as poor recording of essential PMTCT information in files (50). In a further South African study, pregnant women had concerns that the 'rules' that governed how they received care and the timing of treatment were not made explicit (51). The authors of the study raised the suggestion that women should be empowered in the ANC setting and perhaps this would help overcome this challenge (51).

2.1.7 PMTCT in Sub-Saharan Africa

It is in Sub-Saharan Africa that the burden of HIV is most heavy. It has been estimated that 2 million HIV infant infections have been prevented, as a result of ART during the pregnancy and postpartum phases for mothers (52). Of 160 000 incident cases in children (0-14 years of age) in 2018 worldwide, approximately 139 200 were in Sub-Saharan Africa. There has been a decrease in the number of incident HIV cases in Sub-Saharan Africa for those aged between 15-49 years of age by 37% between 2010 and 2017 (2.14 per 1000 uninfected in 2017) (53). Mukose and colleagues (54) in Uganda costed lifelong ART (Option B+) in four facilities and found the largest driver of costs to be the ART itself, with the unit cost for the mother-infant pair being US $442 (in 2014 US $) over a two year period. Another study in Ethiopia, had similar findings of ART being the cost driver for PMTCT services for mother-infant pairs, with a per person year cost range of US $319-1099 (also in 2014 US $) among the 12 facilities that they studied (55). Sarkar et al. (42) in their systematic review found that the median cost-effectiveness for PMTCT interventions and services in 17 studies in the Sub-Saharan African context was US $1 144 per HIV infection averted and US $191 per DALY averted (in 2018 US $) (42). There are of course elements of the literature included in the review by Sarkar et al. (42), which makes comparability difficult such as the divergent settings and different timing of the studies such as before or after the introduction of lifelong ART. Malawi, Zambia and South Africa were the most highly represented countries in their systematic review each accounting for four estimates between 2009 and 2016 (42). The authors caution that focus should shift to vulnerable and under studied populations to better serve their policy decisions through the provision of costing work.

2.1.8 PMTCT in South Africa

The HIV pandemic began in South Africa around 1990 and has been on the increase since (56). South Africa has made good headway with reducing new paediatric HIV infections, since the PMTCT programme was established in 2002 (56). Prior to this a pilot PMTCT programme was initiated in 1998 in the Western Cape at two midwife obstetric units (MOUs) in Khayelitsha by the Provincial Department of Health (56). After the formal initiation of the PMTCT programme, the government extended the PMTCT programme, in 2003, to all pregnant mothers and their children, and those pregnant women with CD4 counts of less than 200 cells/µl were deemed eligible for highly active antiretroviral therapy (HAART) (56) as was anyone with CD4 count less than 200.

The national PMTCT accelerated plan was launched in 2008 by the Minister of Health, which had the ambition to decrease MTCT from 12% to less than 5% between 2008 and 2011 (56). Between 2009 and 2012, there was a 46% decrease in new HIV infections in children in South Africa, with a 7% MTCT rate in 2012, which had decreased from a 13% MTCT rate in 2009 (39). Coverage of ART for pregnant WLH in PMTCT programmes in South Africa was in excess of 95% in 2019 and 302 936 WLH had received ART (28).

The Minister of Health endorsed the idea of exclusive breastfeeding in 2011, with the rationale to improve child health, which had the implication that freely provided formula milk distribution should be ceased (56). In 2012, in South Africa, the coverage

of ART was 83% in pregnant women and the number of newly infected women had decreased by 28%, which contributed to lower HIV transmission rates and a decreased number of HIV infected infants (39). South Africa moved from the Option A approach, which was implemented in 2010 (56), to Option B in 2013 (in all but name), and then to the Option B+ approach of immediate initiation of ART being recommended for all pregnant and breastfeeding women at the beginning of 2015 (57).

One study found that in the peri-urban setting of Gugulethu in South Africa, 58% of pregnant women enrolled in antenatal care had found out about their HIV status during pregnancy (58). However in South Africa there is a tendency to present late for the first antenatal visit and only around 40% of pregnant women attend prior to 20 weeks (56) and early initiation generally leads to better outcomes. With this in mind the adoption of lifelong ART was prudent, especially for the coverage of subsequent births.

2.2 Infant HIV testing

There is some discussion around the best timing of infant HIV testing using HIV polymerase chain reaction (PCR) testing, as ART is taken by both mother and infant in the PMTCT programme and may impact on the results of the HIV PCR test (59, 60). In South Africa, a large proportion of women attend a health facility for delivery, which could allow for high levels of coverage of testing at birth but may require point of care testing to be successful (59, 60) and will not detect intrapartum transmissions. PMTCT reduces the proportion of intrapartum transmissions more than the in-utero transmissions especially due to late antenatal care bookings and therefore a PCR done

at birth detects more infections than a delayed PCR. The in-utero transmissions are at extremely high risk of rapid progression if not treated early.

2.3 Postpartum HIV care

Transition to postpartum HIV care (which is part of Prong III and IV of PMTCT) from receiving as ART during the antenatal period through PMTCT programmes is a crucial step in the treatment cascade and presents a vulnerability where mother-infant pairs may be lost to follow up. Where integration has taken place and mother-infant pairs are continue in care within PMTCT such as part of the Strategies to Optimize ART Services for Maternal and Child Health (MCH-ART) study, it may be that women are protected during the particularly vulnerable stage of shifting from antenatal to postpartum care by delaying movement to general ART services (61). In Nigeria, the use of an integrated PMTCT intervention resulted in 85% of mother-infant pairs being retained at 6 weeks postpartum and 75% at 12 weeks which is close to a staggering ten times higher than in the control arm of the study, where 9% and 7% of and mother-infant pairs at the same time points (62). Qualitative work which has investigated the ways in which mothers personally navigate the health care system provide value insight into the barriers and facilitators to postpartum care for women living with HIV (WLH) (61). For instance, it seems that stigma in areas of Cape Town, South Africa still remains an obstacle around which women negotiate their health care, seeking care where they will not be recognised and keeping their folders out of sight (61). Two factors which seem to be important in remaining in care are improved understanding and knowledge of the rationale for receiving care as well as social support, such as being able to openly

discuss treatment with families, a partner or friend. Both of these factors may enhance the motivation of WLH and empower them to take their treatment seriously (61).

2.4 Models of care/ differentiated care

Two aspects that have been focused on in the WHO Consolidated Guidelines are decentralised HIV treatment and care, as well as task shifting for this care (20). With this in mind several models, including community-based care, have been suggested and implemented. World Vision has identified 20 countries, including South Africa, Eswatini, Mozambique and Lesotho, that could potentially implement further community-based PMTCT programmes (63).

Other models have been used for HIV care, for instance the Médecins Sans Frontières (MSF) community ART group approach in Mozambique, where groups of six individuals collect medication in a rotation, so that only one individual travels to the clinic in a given month (64, 65). This approach has been used for PLWHA generally and not specifically for pregnant HIV positive mothers.

Limited experience in the utilisation of the Option B+ approach necessitated research into the implementation of the approach, as well as recommendations regarding its cost-effectiveness in the Southern African setting. Previous work has been done around modelling the two PMTCT approaches (Option A and B+), and this work indicates that the cost-effectiveness of Option A and Option B+ are comparable, or that Option B+ has a potential to be more cost-effective than Option A (66).

In order to improve retention and adherence under the lifelong ART, innovative strategies need to be implemented which can simplify the treatment and enhance adherence (67). For instance increasing peer support, and decreasing the time spent waiting at clinics, as well as the number of clinic visits, in an attempt to strengthen adherence (67). And so, the evolution on lifelong ART is the idea of different models of care or differentiated care or differentiated service delivery, which can unburden facilities, simplify care, enhance adherence and improve the experience of patients as recommended by the WHO (20). We are reminded that the focus of differentiated care should be on the patients' needs, hence the term 'client-centred approach' (68)

A lot of work has been done to create frameworks for differentiated care that enable countries to develop context specific models of care tailored to the needs of their population. Breastfeeding WLH in the postpartum phase are one of the specific populations that has been highlighted as needing to benefit from differentiated care (69).

Integrating ART delivery and care with other health services is another part of differentiated care that has been endorsed by WHO (20). Integrating PMTCT into primary health care was a step on its own in South Africa given the history of political 'AIDS denialism' (70). There are of course arguments for integrating care with other diseases such as cervical cancer which was found to be cost-effective in one site in Kenya (71) and tuberculosis. Nugent et al. (72) wisely add the need to consider how HIV positive and HIV negative individuals' chronic healthcare needs can be managed in an integrated, sustainable and affordable way. However, Nugent et al. (72) and Golovaty et

al. (73) caution that more economic work is required on the integration of HIV and non-communicable diseases prior to uptake.

In Tanzania, a PMTCT programme being integrated into maternal and child health services was costed and revealed an average annual cost of US $160 for the 12 included facilities per patient on ART for 2017 (74). This value ranged from US $ 101-812 depending on the type of facility which was mostly related to the cost of personnel in differing facility levels. A crucial point that the authors make is that as we see improvement in the coverage and health of PLWHA in particular WLH in the antenatal period, it will most likely become more costly to detect a case of HIV. However, if services are integrated (as they were in Tanzania and as part of the MCH-ART study (2, 74)) with maternal and child health services then it is likely that the costs of detecting HIV in WLH will be absorbed more easily alongside the provision of routine antenatal services as the costs at the facility level will be shared for instance the personnel costs (74). The benefit of integrated care is further advantageous when one considers the inverse relationship that was observed between the number of tests performed and the cost per test. The average yield of positive tests from the total number of women testing for HIV found in the study was a low 1.1% (74).

Coincidently, Zegeye et al. (55), also costed PMTCT services in 12 facilities in Ethiopia (55). However, their costing was of PMTCT services as a whole as opposed to integrated care. A marked difference was found between facilities in rural and urban settings, with costs being above three times higher in urban settings (US $1 099 compared to US $319 annually per mother-infant pair in rural settings in 2014) despite higher volumes of patients (i.e. diseconomies of scale) (55).

Enhancement of models can be assisted through means such as peer support and the involvement of technology (75). Three studies in South Africa showed differences from the status quo. These studies included providing point of care CD4 testing and counselling (rapidly provided in one case) in two instances and accompanied transport from home to the facility among other interventions in the third (76-78). When point of care CD4 testing was provided with counselling in mobile clinics, linkage to care was improved in comparison to the standard of care, although still surprisingly low at the three month post-test stage (moving from 29% of individuals amongst those in standard of care to 38% in the point of care CD4 and counselling intervention arm). Shamu et al. (78) ultimately recommend that a mix of offerings work best to aid linkage to care, such as accompanied transport (particularly for children), triage in queues to fast-track patients, and team work, however the strategies they suggest have not yet been costed.

2.5 Health care prioritisation

In assessing different models of care, one needs to look at priority setting. Health care prioritisation intends to direct resources towards the areas of highest need and where impact will be achieved leading to equity (79, 80) . Lack of prioritisation can lead to research uptake, which is based on convenience and not necessarily on the most pressing health concerns (79). For quite some time there has been a clear promotion of cost-effectiveness as a tool to help with priority setting (81) and there are institutions such as the United Kingdom National Institute for Clinical Excellence (NICE), which regulates adoption of technologies through the use of cost-effectiveness analyses (81).

Currently, there is not a body such as NICE in South Africa. Importantly, the adoption of new practices or technologies is not always required, as the tools to tackle ill health can be found in existing interventions (79). Cost-effectiveness is often the first question posed while the second question of affordability is also crucial to examine (72).

The resources available for health research in LMICs remain low despite the large burden of disease in those countries (79, 80). In LMICs, the expectancy is that research should be in line with the health needs of the community and hence be prioritised accordingly (79) but this is not always the case. Some of the identified challenges in priority setting in LMICs relate to participation with stakeholders, availability of data and capacity limitations (79).

2.6 Economic evidence for PMTCT

The economic problem we face in healthcare is based on the basic definition of economics, unlimited wants due to the variety and demand of illnesses (choice) and healthcare needs and limited resources to address these needs (constraints). Resources in terms money for paying for technology and healthcare providers salaries; but also healthcare providers time and capacity; infrastructure, for instance provision of quality space; limited funds for diagnostic tests, medication (new and existing) and consumables needed to provide quality services among others (82, 83).

Inefficiency in spending on healthcare has an impact on the healthcare sector in that the value we could have gained is lost, referred to as an opportunity cost. However, the

impact ripples further than the healthcare sector as the opportunity cost can also be felt in the education sector, housing sector and social services (82).

Economic evaluation recognises that looking at the effectiveness of a programme is necessary but not sufficient for decision-making and therefore one should also incorporate the costs of the programme (84). Therefore, economic evaluation looks at both the costs and consequences of different competing and comparable options (83, 85, 86). An economic evaluation can be seen as a useful tool in deciding where scarce resources should be placed (85).

2.6.1 Cost-effectiveness analysis

A cost-effectiveness analysis is a type of economic evaluation where in essence we are looking to maximise the health benefits, taking into consideration the cost and available resources (85). The first step is to estimate the cost and effectiveness measures of the comparable health interventions for a population. In the form of a ratio one then looks at the incremental cost effectiveness ratio (ICER), which is a difference in costs divided by a difference in effectiveness (84). Therefore in a cost-effectiveness analysis we are looking at a measure of the incremental cost per unit of additional effect (85).

The Second Panel on Cost-Effectiveness in Health and Medicine was formed to align efforts in cost-effectiveness analysis, in an attempt to make the estimates more precise and informative. One of their recommendations is to use an "Impact Inventory" to better illustrate where and how costs were collected (82). Another aim which is echoed by the International Decision Support Initiative Reference Case for Economic Evaluation and

the Reference Case for Global Health Costing is that of quality and comparability (87-89). A reference case's role is to provide a set of methodological standards that one aspires to - in this case when performing a costing or cost-effectiveness analysis. Cost-effectiveness analysis has the ability to inform investments in new programmes (aiding decisions in incorporating new technology or not) as well as advising disinvestments in programmes, technology and interventions that are not cost-effective (82).

A cost-effectiveness analysis is a tool that can be used to aid decision making. However, it does not make the decision for us, deliberation is still needed, for instance in thinking about the context and affordability of introducing a new cost-effective technology. It would be impossible to implement all the interventions that are found to be cost-effective to the health benefit of all, unless we had unlimited resources (82) in which case we would not need to care about cost effectiveness..

2.6.2 Cost and cost-effectiveness analyses investigating HIV/AIDS and PMTCT

Importantly, one can see that costs fall after the first year of treatment which is credited to decreased hospital costs, but on the other hand costs rose if a patient passed away before the second year of treatment (90). When assessing the outpatient cost of initiating ART (for general adult ART services) in four different sites in South Africa, it was found that on average the cost was US $928 for the first year of treatment of a patient, with the inputs comprising 47% for medication, 19% for laboratory testing, 16% for the outpatient visits and 19% for the infrastructure and other fixed costs (91). However, for a patient to be reported as in care and responding to treatment, the cost increased by 55% on average (to US $1 438) (91). Another study estimated the average

costs for ART care in South Africa to be US $404 per patient for the first month of treatment, US $2 502 (per patient year of observation) in the first year and US $1 372 (per patient year of observation) in the second year (90). It has been established that HAART is cost-effective and can be cost saving, for instance when locally manufactured drugs are used (92).

For patients who were considered stable on their ART medication, the cost of down referring from a doctor-led, hospital based ART clinic to a nurse-led, primary health care facility (in Johannesburg) saw a reduction in costs by 11% from US $551 to US $492 over a year's duration (93). This strategy was found to be more cost effective than the hospital based, doctor-led approach (93).

When assessing the expansion of ART services based on CD4 counts, escalating to all CD4 count levels (i.e. universal coverage) was estimated to decrease the number of HIV infections in South Africa by 3.3 million, a reduction of 45% (94). The estimated cost reduction would be US $10 billion over 40 years, with the breakeven point at 2023 (94). In 2004 and 2005, the total budget for the South African National PMTCT Programme was approximately US $11 594 265, of which the Western Cape received 6.8% (95). This was a huge increase from the piloting PMTCT support provided in 2001 and 2002 of approximately US $1 511 567 (95).

Unit costs per patient for providing PMTCT services in the Western Cape in 2002 were calculated for a hospital (Paarl Hospital) and clinic (Phola Park Clinic) (95). The researchers found that for counselling and testing the unit cost was US $5, whereas the unit cost for delivery was US $21 and the unit cost for follow up care was US $26 (95).

A QALY is an effectiveness measure that uses the multi-dimensional aspects of quality and quantity of life years gained. In order to inform the quality of life years gained on a scale from zero to one, individuals are asked to evaluate their health using a measure such as the EQ-5D which is a tool is used to measure health across different diseases/ health states which uses five dimensions of health (83, 88, 89). In a study that assessed the cost effectiveness of accelerating the initiation of ART among pregnant women in Cape Town, South Africa (96), the authors found that the accelerated plan cost US $880 per women for one year as opposed to the standard of care services which cost US $220. The ICER was US $1 160 per QALY (quality adjusted life year) saved, meaning that the expedited programme was highly cost effective in South Africa when using the WHO national gross domestic product (GDP) per capita standard (96). Importantly this work also underlines the potential for South Africa to swiftly initiate pregnant women onto ART in antenatal care clinics (96). However, the use of multiples of the GDP as a threshold indicator is no longer recommended (indeed it may have been misrepresented for quite some time) (97). What is now recommended is the use of a full evaluation of the 'benefits package' for the particular area of interest such as HIV where all cost-effective items are included as far as the budget allows, with the final additional item is deemed non-cost-effective or above the 'threshold'.

Another study in Zimbabwe looked at a model comparison between single dose nevirapine, Option A, Option B and Option B+ (98). The authors found that by replacing single dose nevirapine (lifetime cost of US $5 760 for the mother-infant pair) with either Option A (lifetime cost of US $5 710) or B (lifetime cost of US $5 630), improved the outcomes for the mother and infant and was cost saving. Option B+ further improved

outcomes for the mother and had a lifetime cost of US $6 620. The ICER for Option B+ was US $1 370 per life year saved when compared with Option B, which is comparable to other ART related interventions in LMIC settings, although not cost-effective when using the WHO GDP standard for Zimbabwe (98).

Similarly, it was found that Option B+ would avert a greater number of both vertical and horizontal transmissions in comparison to Option A or B, with a reduced cost in South Africa, Kenya, Zambia and Vietnam (99).

In comparison to self-administered ART, a cost utility analysis found that directly administered antiretroviral therapy not to be cost-effective in the Sub-Saharan African setting (100).

2.7 Scaling up

Scaling up refers to 'expanding the coverage of health interventions' (101) with the aim to improve health outcomes, benefit more individuals, and support policy and programme development at large or national scale, which requires increased resources (101). With the change to lifelong ART there will be very high numbers of clinically well patients, who are stable on ART and who do not need to be regularly monitored by a doctor.

In eight African countries the scale up of PMTCT programmes was supported by strengthening the policy environment, ensuring consistent unifying national plans and then leveraging funds for the programmes both nationally and internationally (102).

One way to scale up PMTCT is to task shift to health care workers at a lower cadre such as community health care workers (101). The context within the country is significant, and so involving innovative practices that have been locally driven or implemented can be beneficial (101, 103). An important part of ensuring scale up is through the presentation of alternative health interventions with demonstrated effectiveness, which is also important when trying to gain local budget commitment (104). By ensuring strong management practices one can allow some flexibility in implementation of a new programme, which can decrease the resistance to the inclusion of new treatment practices (104). One must also allow sufficient time for scale up to occur (104), as well as ensuring that the programme is equitable in terms of providing for the deprived and vulnerable sections of society (101). Increasing coverage should be weighed up against upholding quality care (101).

The constraints of scaling up models of care could be linked to the health system, the staff involved, available or unavailable resources (such as supply shortages), the management context within the facility or setting, and the organisational culture and leadership (105). Through the understanding of the circumstances and setting that the intervention will be scaled up under, one can hope to overcome some of the constraints faced (105). WHO suggests three important ways to help overcome constraints: identifying and understanding the environmental factors at play; identifying opportune timing and opportunities; and, as the scale up evolves, assessing any changes in the environment and adapting to these changes (105).

In Ghana, the successes of community-based PMTCT scale up was assessed, where nurses were sent into the community and the local leaders where engaged in the process of PMTCT and it's scale up. It was suggested that using staff from the area eased cultural understanding, continuous review by management allowed for evolution of the programme and a common vision by the management aided scale up (106). For scale up to be successful, it is also important to anticipate unintended outcomes and to engage key actors (107).

In Gugulethu, in Cape Town, South Africa, one of the constraints to scale up of the community based HIV treatment programme has been the lack of physical space, leading to the relocation of services several times (108). A success in the scale up has been the linking of an available low cadre staff member to each client who helps with adherence and retention (108). Adherence and retention are particularly important in the context of scaling up, especially when other staff members may not be able to provide the focused support that would be possible in a smaller scale programme.

Uganda was one of the countries to roll out differentiated care at a national level, and a qualitative study has provided insight into some of the challenges at an individual, community and health system level (109). Stigma was found to be a concern in Uganda, which was the case in other settings too (35, 109).

2.8 Budget impact analysis

In order to inform scale up, a budget impact analysis can provide a component of a comprehensive economic evaluation that takes the point of view of the health care

decision maker (110, 111). Information is needed around the costs of scaling up health care interventions, such as improving maternal and child health and combating HIV/AIDS (103). It is important to assess the current treatment provided and the new treatment that may be incorporated, so that resource requirements can be estimated. Sullivan et al. (110) provide a framework for budget impact analysis allowing for transparency and easy replication. If possible, a budget impact analysis should be done alongside a cost-effectiveness analysis. Although one can estimate the increased finances that will be necessary to scale up an intervention, it may be that the health system constraints mean that the capability does not exist to deliver the intervention (101, 112). A projection for programmatic change from Option A to Option B+ within Cameroon, found that over a five-year period, the cost would be US $28.9 million more than would be spent on Option A (113). However, the price somewhat plateaus once women experience a future pregnancy. A large portion of the increased cost results from women who were not previously on ART, although they were eligible, due to low coverage rates (113).

The budgeted funds for Eastern and Southern Africa for 2020/2021 is 283 million in total (including core global, non-core funds and country envelopes) which is 27% of the global budget (27) towards the ultimate goal of ending the AIDS epidemic by 2030. The national budget for healthcare in South Africa for 2020/21 is US $3.2 billion, while the Medium Term Expenditure Framework for the HIV and AIDS Component of the 'HIV, TB, Malaria and Community Outreach Grant' for the same financial year is US $1.3 billion (114-116). In total the National Strategic Plan details that the anticipated budget for HIV, TB and STI is R37.5 billion or US $2.1 billion for the 2020/21 period which includes

funding from the South African Government, PEPFAR and USAID, Global Fund and estimated private sector ART funding (17).

2.9 Conclusion and unanswered questions

Given the above structured literature review the following research gaps in the evidence-base on the optimal approaches and models of care for PMTCT, especially during the postpartum period for WLH and their infants, the empirical costs of the models and the costs to the patient, outcomes in terms of maternal retention and viral suppression and the ideal combination of models and financial implications of scale-up emerge:

- Further research into ways of retaining mothers in care and ensuring adherence is necessary in the southern African context
- There is limited cost-effectiveness evidence from novel models of care for ART provision particularly for postpartum WLH and their infants, but also for pregnant WLH
- Innovative models need further exploration and development to aid the aim of eliminating paediatric HIV
- Evidence on the cost-effectiveness as well as the costs to the patient of different models of PMTCT care is lacking
- There is little economic information, regarding scale up of innovative models of care under the lifelong ART (Option B+) approach to PMTCT, especially on the costs of different models of care at scale, the best combination of models and where capacity will be surpassed leading to system failure

- There is a need to look at the roll of task shifting to community health care workers for PMTCT
- Current cost information for PMTCT services would be valuable for budget making purposes
- At the time that this work started pragmatic information was needed surrounding starting individuals on ART regardless of CD4 count, such as the feasibility and capability of the health system to absorb the additional workload. And more empirical, rather than modelled evidence is needed regarding the Option B+ approach in Southern Africa

On the basis of these knowledge gaps, the broad objective of this study is to evaluate whether improved approaches and models of care which cater to the preferences of mother-infant pairs can result in better maternal outcomes (retention and viral suppression), lower or similar costs from the provider and patient's perspective, and implementation of these approaches and models based on cost-effectiveness evidence and financial guidance from budget impact analysis.

3 Chapter Three: Cost and cost-effectiveness of transitioning to universal initiation of lifelong antiretroviral therapy for all HIV-positive pregnant and breastfeeding women in Swaziland

This manuscript was published in Tropical Medicine and International Health in 2018 and was completed to fulfil Objective 1.) To compare the costs and effects of the Option B+ approach to the Option A approach to PMTCT from a provider's perspective in a cost-effectiveness analysis. Formal permission was obtained by the publisher John Wiley and sons (license number: 4914720577301). Lucy Cunnama was the first author with input from all co-authors, in particular Edina Sinanovic, Elaine Abrams and Landon Myer. The citation is as follows (117):

Cunnama L, Abrams EJ, Myer L, Gachuhi A, Dlamini N, Hlophe T, Kikuvi J, Langwenya N, Mthethwa S, Mudonhi D, Nhlabatsi B, Nuwagaba-Biribonwoha H, Okello V, Sahabo R, Zerbe A, Sinanovic E. Cost and cost-effectiveness of transitioning to universal initiation of lifelong antiretroviral therapy for all HIV-positive pregnant and breastfeeding women in Swaziland. Tropical Medicine & International Health. 2018;23(9):950-9.

Abstract

Objectives

To assess the costs and cost-effectiveness of transitioning from antiretroviral therapy (ART) initiation based on CD4 cell count and WHO clinical staging ('Option A') to universal ART ('Option B+') for all HIV-infected pregnant and breastfeeding women in Swaziland.

Methods

We measured the total costs of prevention of mother-to-child HIV transmission (PMTCT) service delivery at public sector facilities with empirical cost data collected at three points in time: once under Option A and again twice after transition to the Option B+ approach. The cost per woman treated per month includes recurrent costs (personnel, overheads, medication and diagnostic tests) and capital costs (buildings, furniture, start-up costs and training). Cost-effectiveness was estimated from the health services perspective as the cost per woman retained in care through 6 months postpartum. This analysis is nested within a larger stepped-wedge evaluation, which demonstrated a 26% increase in maternal retention after the transition to Option B+.

Results

Across the five sites, the total cost for PMTCT during the study period (from August 2013 to October 2015, in 2015 US $) was US $868,426 for Option B+ and US $680 508 for Option A. The cost per woman treated per month was US $183 for a woman on ART under Option B+, and US $127 and US $118 for a woman on ART and zidovudine (AZT), respectively, under Option A. The weighted average cost per woman treated on Option B+ was US $826 compared to US $525 under Option A. The main cost drivers were the start-up costs, additional training provided and staff time spent on PMTCT tasks for Option B+. The incremental cost-effectiveness ratio was estimated at US $912 for every additional mother retained in care through six months postpartum.

Conclusions

The cost and cost-effectiveness outcomes from this study indicate that there is a robust economic case for pursuing the Option B+ approach in Swaziland and similar settings

such as South Africa. Furthermore, these costs can be used to aid decision making and budgeting, for similar settings transitioning to test and treat strategy.

3.1 Introduction

Option B+, which provides lifelong antiretroviral treatment (ART) for all HIV-positive pregnant and breastfeeding women, was by WHO in 2013 and has been adopted by the majority of Sub-Saharan African countries (118, 119). Experience with implementation of Option B+ is evolving as most countries have only just transitioned or are transitioning from Option A. Option A provides differentiated treatment based on CD4 cell count and WHO stage; those with a CD4 count ≤350 (≤500 in some countries) receive lifelong ART, while women with >350 receive zidovudine (AZT) prophylaxis while pregnant, single- dose nevirapine (NVP) and 7 days of AZT or tenofovir (TDF) and lamivudine (3TC) at delivery and NVP for infants while breastfeeding (44). Option B+ provides ART (efavirenz (EFV)+3TC or emtricitabine (FTC)+TDF) with 6 weeks of daily NVP for infants.

Evaluation of the cost-effectiveness of Option B+ is insufficient. To date, most research on the cost-effective- ness of the Option B+ approach has been assessed through economic modelling (120, 121). In a review of published literature measuring outcomes relating to infant and maternal outcomes (122), varied cost-effectiveness results were noted in the data from African countries, with models running from 10 years to a lifetime span, which would incorporate future pregnancies. Due to differences in assumptions, input costs and effects within models the conclusion on cost-effectiveness was not consistent. The most comprehensive of the studies found Option B+ to be cost-

effective in terms of infant and partner infections averted (99). However, there may have been partiality towards Option B+, and there is a clear need for ongoing cost- and cost-effectiveness data on universal ART strategies, including Option B+, in low- to middle-income countries (LMICs).

Limited experience in the utilisation of Option B+ at the time necessitated research into implementation of the approach, as well as recommendations regarding its cost-effectiveness. Empirical information on the costs of PMTCT services is important to better utilise resources, for future modelling and to assess the impact of alternative approaches (123). The aim of this research was to estimate and compare the costs and cost-effectiveness of Option B+ versus Option A in Swaziland.

3.2 Methods

The Safe Generations (SG) Study (ClinicalTrials.gov identifier: NCT01891799) was an implementation science research study, designed to evaluate the Option B+ approach to PMTCT. The Swaziland Ministry of Health (MoH) supported the SG Study because among others, cost and cost-effectiveness data were critical in informing Option B+ roll-out costing and planning. The primary outcome for the evaluation was maternal retention in care, defined as the proportion of women with any clinic attendance documented within 56 days of delivery or estimated due date (antenatal retention) and clinic attendance documented within 84 days of 6-months postpartum (postnatal retention). These definitions were based on 1 month after the longest possible ART-dispensing interval during the antenatal and postnatal periods (1 and 2 months, respectively). One of the secondary objectives was to compare the cost-effectiveness of

Option A and B+. Other outcomes included the proportion of women initiating antiretroviral medications during pregnancy, time from first antenatal care visit (ANC) to ART initiation, and the proportions of infants testing HIV- positive. The step wedge design allowed comparison between Option A (the standard of care when the study started) and B+, as transition occurred. There was 1 month of transition between Option A and B+ for each clinic. A 26% increase in maternal retention was demonstrated after the transition to Option B+. During the study, 54% of infants were traced and 53% received a Polymerase Chain Reaction (PCR) test. We therefore decided to focus cost-effectiveness analyses on maternal retention and exclude effectiveness outcomes for infants as they may not be representative of the entire study cohort (5).

3.2.1 Study design

The economic evaluation was retrospectively undertaken from a health services perspective. The cost estimates include both the financial and economic costs. The economic costs differ from the financial costs, as they include training and training materials that were provided through the main study. A full rather than an incremental costing was undertaken.

3.2.2 Study facilities

Five clinics providing PMTCT, HIV care and ART and baby wellness services (among others) were purposively chosen to encompass various factors, which could describe variation in characteristics between health facilities (see Appendix S1). The clinics were visited by a health economist to observe clinic process, measure clinic space, inventory

equipment and furniture and assist staff in completing time sheets at three points in time; once while still under Option A, and twice after transition to Option B+. This method was used to assess changes in resource use and staff time, and to familiarise the health economist with the context and study setting.

3.2.3 Costing

Using an ingredients-based approach, the overall clinic costs and the total costs of providing PMTCT services under Option A and B+ were assessed from August 2013 to October 2015. All costs are presented in 2015 United States Dollars (US $). Costs collected in other years were inflated to 2015 US $ using the consumer price index (124, 125). Costs that were collected in Swazi Lilangeni (SZL) have been converted to US $ using the average exchange rate over the period January 2015 to December 2015 of 12.77 SZL for 1 US $ (126). The cost per woman receiving prophylaxis per month includes capital costs and recurrent costs.

3.2.4 Capital costs

Equipment and furniture were audited and costed based on current replacement value sourced through medical, hospital equipment and furniture suppliers in South Africa. Building space was costed using current replacement value sourced from Council for Scientific and Industrial Research (CSIR) in South Africa. For logistical and resource reasons we used South African prices.

Start-up costs comprised study-specific training for Option B+ per clinic and toolkits for each clinic. The toolkit is a desktop flipchart, which aids the staff when educating the patients about how to take their medication correctly. Initial costs for training at the clinics are presented separately from the start-up costs. Study records provided the cost of developing, updating and printing the toolkit. Study-specific and initial training included the cost of the venue used, catering, the facilitators' time and any transport provided. Data on initial training on PMTCT under Option A was collected through discussion with the staff providing PMTCT services.

These capital costs were annualised using a discount rate of 3%, with the assumption that the useful lifespan will be 30 years for buildings, 10 years for equipment and furniture, and 5 years each for the toolkit, initial and study-specific training.

3.2.5 Recurrent costs

Salaries of staff at the clinics were obtained from human resources and finance departments in the MoH, non-government organisation (NGO) and a faith-based organisation (FBO) that run the respective clinics. The overhead costs of running and maintaining the clinics were estimated using the expenditure reports from the same finance departments.

The prices of medication were collected from Central Medical Stores Swaziland. The cost per month of medication was calculated by multiplying the price of one pill of the respective medication (taken daily) for ART and cotrimoxazole (CTX) and the price of two pills of AZT (taken daily) by 30 days. All women were given daily CTX (under

Option A and B+). If a woman made a visit to the clinic it was assumed that she had received 1 month's worth of medication.

The prices of diagnostic tests (CD4, point of care PIMA CD4, haemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine and rapid HIV tests) were obtained from the National Health Laboratory Services South Africa. The cost of receiving the tests at first visit, 6 and 12 months later, was distributed over the time in care, 15 months (the gestation period (9 months) plus 6 months postpartum) to give a per-month diagnostic test cost (per guideline).

3.2.6 Cost allocation

Two unit costs were estimated, a 'cost per visit' and a 'cost per woman treated per month'. The total cost of providing Option A and B+ services was divided by the number of PMTCT visits made in the same period to get the unit 'cost per visit', which does not include diagnostic tests or medication costs.

A 'cost per woman treated per month' was calculated separately for those on AZT and ART under Option A and Option B+, respectively. This was performed by adding the 'cost per visit' to the monthly medication cost and the monthly diagnostic tests cost (which were the same for Option A and B+).

The weighted average cost per woman treated was estimated by multiplying the 'cost per woman treated per month' by the average number of visits made under the two different approaches, respectively, until 6 months postpartum (4.34 for Option A and

4.52 for B+). For Option A and B+, the proportion of those on ART in the study, (36% in Option A and 94% in Option B+) and AZT (64% in Option A and 6% of women who did not initiate ART under the B+ and received AZT) was used to weight the costs, respectively. In addition, the total costs were estimated by multiplying the total number of women enrolled in the study under Option A and B+, respectively, by the weighted average cost per women for Option A and Option B+, respectively.

3.2.7 Cost-effectiveness

Using the weighted average cost per woman treated for each approach, and the effectiveness data from the trial – the maternal loss to follow-up at 6 months postpartum – the incremental cost-effectiveness between the two approaches was estimated. The incremental cost-effective- ness ratios estimated reflect 'the additional cost per mother retained at 6 months postpartum'. These estimates are based on incremental costs and effects from Option A to B+, where Option A is the baseline.

3.2.8 Sensitivity analysis

To assess the uncertainty in the analysis, five univariate sensitivity analyses were performed. Firstly, as Swaziland was rolling out routine viral load monitoring in the post- study period, the cost of viral load testing was obtained from Swaziland Health Laboratory Services and was added to the primary analysis costs to assess the cost impact of adding viral load testing, to the Option B+ approach, as a monitoring test after 6 months and twelve months on treatment, respectively.

Secondly, TDF + FTC + EFV was donated to the study at a cost to the donor (Merck & Co). The cost of donated TDF + FTC + EFV was collected through study records and was used to assess the cost impact of using this medication on the ICER, rather than the less expensive generic medication (TDF + 3TC + EFV) under the Option B+ approach.

Thirdly, the effectiveness measure of maternal retention was varied by 15% above and below the proportion used in the primary analysis to consider the effect on the ICER. Fourthly, as Option B+ reduces the need for diagnostic testing, the impact of removing all diagnostic tests from the Option B+ approach was assessed.

Lastly, as less intensive training for transition to Option B+ may be provided in the future, the training cost under the primary analysis was reduced to one-third in the sensitivity analysis. This reduction was based on an interview with MoH around training they performed for transition.

3.2.9 Ethical considerations

Ethical clearance was provided by the National Scientific and Ethics Committee of the Ministry of Health in Swaziland (MH/599C/FWA 000 15267); the University of Cape Town (HREC REF: 418/2013); and Columbia University Medical Centre (IRB-AAAL0661). Throughout the study, anonymity of the women has been maintained using unique identifying numbers. Clinic sites have not been mentioned by name. The clinic personnel who filled in timesheets consented verbally, and remain anonymous. Study data were stored on password-protected computers. There were no direct benefits to those participants taking part in the study; however, their participation may positively

impact on others who may receive evidence- based PMTCT services in the future.

Results

3.2.10 Costs

Using medical record review, under Option A 1296 women (55%) were observed, while 1051 women (45%) were observed under Option B+. Of those, 353 (27%) were retained under Option A and 559 women (53%) were retained under Option B+ (see Table 3). A total of 3495 visits (ranging from 364 to 1218) were made under Option A and 2670 visits (ranging between 89 and 1518) were made under Option B+ for the five facilities.

The average cost per clinic visit under Option A was US $113.46 and US $169.65 under Option B+ (see Figure 2). The cost of medication per month was US $2.26 if a woman was on AZT (US $2.03) and CTX (US $0.23) and US $11.54 if a woman was taking TDF + 3TC + EFV (US $11.31) and CTX (US $0.23) (Table 2). The per guideline diagnostic test cost was US $2.06 under both Option A and B+ (Table 2). The cost per woman treated per month, which includes recurrent and capital costs was US $118 for a woman on AZT under Option A (US $127 if on ART) and US $183 for a woman on ART under Option B+.

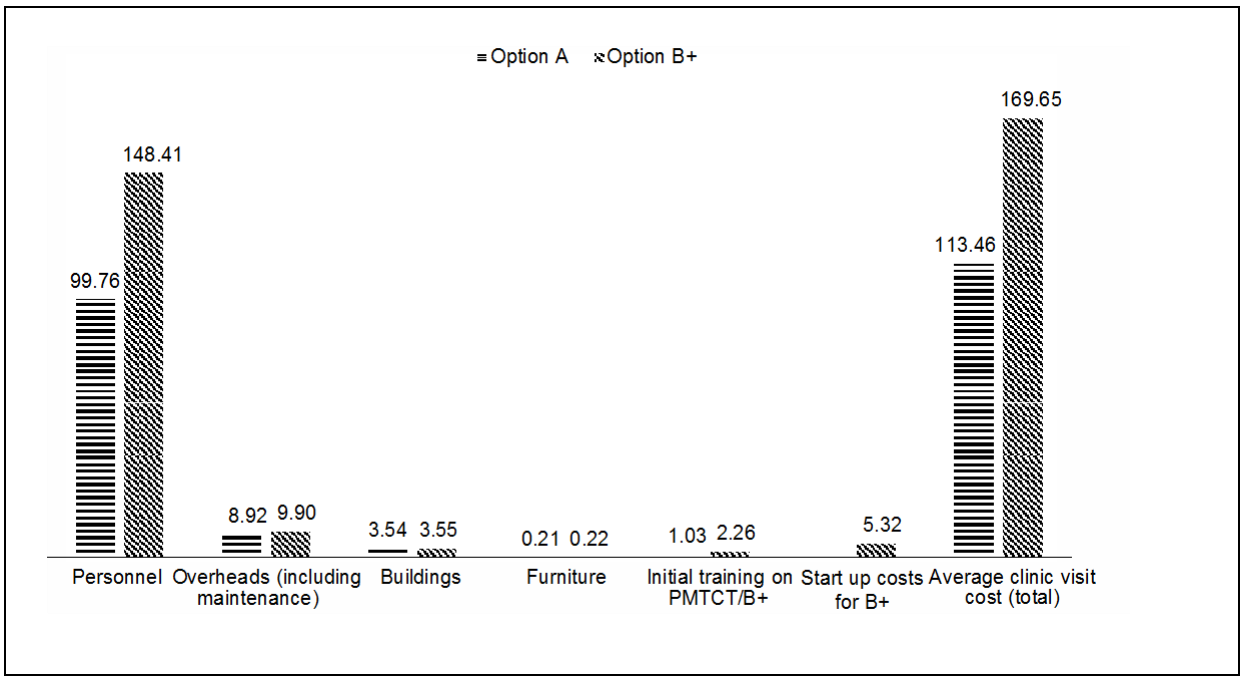

Figure 2: Average clinic visit cost for Option A and Option B+ in 2015 US $

The weighted average cost per woman treated under Option A was US $525 compared to US $826 under Option B+. The main cost drivers were the start-up costs (study specific training for Option B+ per clinic and toolkits for each clinic), increased training and staff time spent on PMTCT tasks under Option B+ (Figure 2). Staff time relates to the MoH, NGO and FBO time staff spent on PMTCT tasks under Option A and B+ (separately), with time apportioned through timesheets as described above, which has been costed using the graded salaries as provided by the three organisations (MoH, NGO and FBO).

Table 1 Cost per woman in care per month for Option A and Option B+ in 2015 US $

	Option A (women taking AZT)			Option A (women taking ART)			Weighted average cost per woman treated under Option A
	Costs	Average number of visits per woman for both antenatal and postnatal care until 6 months postpartum	Weighted average cost per woman treated	Costs	Average number of visits per woman for both antenatal and postnatal care until 6 months postpartum	Weighted average cost per woman treated	36% on ART, 64% on AZT (proportions from the study data)
Cost per visit	113.46	4.34	491.87	113.46	4.34	491.87	
Cost of drugs per month	2.03 (AZT) 0.23 (CTX)		8.81 1.00	11.31 (ART) 0.23 (CTX)		49.02 1.00	
Cost of diagnostic tests per month	2.06		8.93	2.06		8.93	
Cost per woman treated per month	117.78			127.06			
Weighted average cost per woman treated			510.61			550.82	525.08

	Option B+ (women using AZT)			Option B+ (women taking ART)			Weighted average cost per woman treated under Option B+
	Costs	Average number of visits per woman for both antenatal and postnatal care until 6 months postpartum	Weighted average cost per woman treated	Costs	Average number of visits per woman for both antenatal and postnatal care until 6 months postpartum	Weighted average cost per woman treated	94% on ART, 6% on AZT (proportions from the study data)
Cost per visit	169.65	4.52	767.30	169.65	4.52	767.30	
Cost of drugs per month	2.03 (AZT) 0.23 (CTX)		9.19 1.04	11.31 (ART) 0.23 (CTX)		51.14 1.04	
Cost of diagnostic tests per month	2.06		9.32	2.06		9.32	
Cost per woman treated per month	173.97			183.25			
Weighted average cost per woman treated			786.85			828.80	826.29

Table 2: Cost per woman in care per month for Option A and Option B+ in 2015 US $

For the five sites, the total cost for PMTCT during the study period was US $868,426 under Option B+ and US $680 508 under Option A. The difference in cost between the two approaches was US $187 918 (Table 3). Considering the 26% difference in maternal retention between the two approaches in favour of Option B+, the incremental cost-effectiveness ratio was estimated at US $912 (see Table 3).

3.2.11 Sensitivity analysis

Findings were sensitive to viral load testing, removing all tests, reduced training, medications and retention rates. Introducing viral load testing at 6 and 12 months after initial visits, using more expensive medication or decreasing the maternal retention under Option B+ increased the ICER, thereby reducing the approach's cost-effectiveness. Removing all diagnostic testing, increasing maternal retention and reducing the intensity of training under Option B+ decreased the ICER and made Option B+ more cost-effective (Table 4).

3.3 Discussion

The cost and cost-effectiveness outcomes from this study indicate that there is a robust economic case for pursuing the Option B+ approach in Swaziland and similar settings such as South Africa. This is one of the first studies to present an empirical economic evaluation using primary patient level data as opposed to modelled data as has been done in the recent past (46, 66, 98, 99, 127-131).

Table 3 Total costs of Option A and Option B+ and incremental cost-effectiveness ratio

Table 2 Total costs of Option A and Option B+ and incremental cost-effectiveness ratio

	Option A	Option B+	Difference in cost between Options A and Option B+	Difference in retention between Options A and Option B+	Incremental cost-effectiveness ratio
Total cost for PMTCT	US $680 508	US $868 426	US $187 918		US $912
Number of women enrolled	1296	1051			
Number of women retained at 6 months postpartum	353	559		206	
Maternal retention at 6 months postpartum	27%	53%		26%	

Option B+ is a costlier, but also a more effective approach in terms of maternal retention. The incremental cost-effectiveness ratio was US $912. This means that, under the Option B+ approach, it costs US $912 for every additional mother retained to 6 months postpartum. This is well below Swaziland's 2015 per capita gross domestic profit (GDP) of US $3 068 (132), and falls within the cost-effective range for the country (US $288- US $1 559) (133), which suggests that Option B+ is highly cost-effective in this setting.

In this study, personnel costs were the key cost driver, which is similar to other studies (123, 134), and can be attributed to the increased staff time spent on PMTCT tasks under Option B+. Start-up costs and increased training provided under Option B+ also impacted on the cost of the Option B+ programme.

Consistent cost results were found in this study to that of Zulliger et al. (96), who explored the cost-effectiveness of accelerating the initiation of ART among pregnant women, finding it cost US $880 per women for 1 year, compared to standard of care, which cost US $220. This is similar to the weighted average cost per woman treated

under Option B+ in this study of US $826, and may be comparable as the settings are alike and the costs were empirically collected.

Divergent results were found between this study, where weighted average cost per woman treated under the Option A approach was US $525 (and US $826 under Option B+), and the higher estimates in empirical work by Bautista-Arredondo et al. (123). They estimated the costs per woman under the Option A approach receiving medication in Kenya, South Africa and Zambia as ranging from US $704 to US $1 385 (in 2013 US $), while in Rwanda the cost of Option B+ was estimated to be US $2 214 per woman (123).

Table 4: The impact of alternative assumptions for diagnostic testing, medication, maternal retention and training

Table 3 The impact of alternative assumptions for diagnostic testing, medication, maternal retention and training

Parameter for sensitivity analysis	ICER in US $	Percentage increase/decrease in ICER
Diagnostic testing		
With viral load monitoring tests (at 6 months and 12 months)	960	+5%
As per primary analysis for Option A and removing all diagnostic tests for Option B+	865	−5%
Donated medication for Option B+		
As per primary analysis for Option A and replacing TDF + 3TC + EFV with donated TDF + FTC + EFV for Option B+	1765	+93%
Maternal retention		
If maternal retention under Option B+ decreased by 15% (in comparison with the study findings)	4085	+348%
If maternal retention under Option B+ increased by 15% (in comparison with the study findings)	519	−43%
Reduced training		
If training for transition to Option B+ was decreased to one-third (in comparison with the study findings)	890	−2%

Results from Malawi (127), Rwanda (135) and Cameroon (136) differ from our study findings as they modelled estimates, are from settings other than Swaziland and have differing time horizons. In the five papers reviewed by Karnon and Orji, cost inputs in the models for Option A ranged from US $16 to 76, while costs for Option B+ varied

from US $114 to 470 per year (122), which are lower than our estimates. In this study, the total cost for PMTCT in the five sites during the study period was US $680 508 under Option A and US $868 426 under Option B+. In comparison, the total programme costs for Option B+ as simulated by Tweya et al., (127) in Malawi were US $431 910 for a first pregnancy and US $662 074 for a woman's second pregnancy.

The intermediate outcome of retention in care is an important aspect in the continuum of HIV care as being diagnosed and starting ART are vulnerable areas of the HIV programme (137). Retention in care is an important precursor to a final outcome of prevention of mother-to- child transmission of HIV, as retention increases the potential time of patients being in care and on treatment. Improved retention could also be linked to increased staff training, improved staff skills and the increased patient- provider time. Hence providing additional staff training on PMTCT may result in higher retention rates. Attention needs to be paid to continuing the support and training of healthcare workers so that retention can be maintained and improved (138). In Cameroon (Option B+), retention rates of 88% were noted at 6 months, with decreases in retention over time (136) which are much higher than the retention rates found in this study.

Under the Option B+ approach, more women were placed on ART, requiring more follow-up and more time with providers. However, no major changes in infrastructure or staffing structure were needed to implement Option B+. This could speak to an increase in efficiency, and use of spare capacity, which may not be available in all settings. Once Option B+ is established and with scale, we may find that costs stabilise and plateau at a level that is lower than those found in this study (139).

There is a shift towards universal lifelong access to ART for all individuals with HIV (a test and treat strategy, not just pregnant women) regardless of their CD4 count (Joint United Nations Programme on HIV/AIDS (UNAIDS), (20, 140). Assessing the impact of Option B+ for pregnant women with HIV will help policymakers highlight areas that need to be addressed as general access to ART improves and more individuals are placed on ART. Even with the introduction of Option B+, the rate of retention was still suboptimal, which emphasises that focus needs to be placed on improving and maintaining retention. Better retention rates may put additional stress on the health system as there would be more women on ART. The unit costs in this study could be used to inform a budget for universal lifelong access to ART for all individuals with HIV, taking into consideration that there may be slight differences in the population group. A transition to universal lifelong treatment would impact on the budget due to scale up of services, as there would not be a differentiation by CD4 count and treatment would be maintained throughout the life of the individual. In addition, other strategies such as community-based approaches may be helpful in supporting those on universal lifelong treatment (141, 142).

3.3.1 Limitations

There are several study limitations. The cost of running the Option B+ approach over a longer period was not estimated. Personnel may behave differently due to the nature of being involved in a study, which may impact on both the resources used (i.e. costs) and the effective- ness of the intervention (i.e. retention).

Difficulties in infant tracing meant that mother-to-child transmission of HIV was not included as an effectiveness measure and cost-effectiveness outcome. Future studies should be aware of the challenges of tracing these infants, ensuring that medical file numbers and other linkages are maintained. In this analysis, we have not considered how the presumed health benefits of mothers being on ART and the loss to follow-up of patients may impact on the overall estimation of the cost-effectiveness. Due to the nature of the step wedge design, health economic researchers did not collect data at the same post-transition time points for all clinics. This may mean some variability in the information collected in timesheets over time. There is currently no willingness to pay (WTP) threshold for Swaziland and therefore GDP per capita and the cost- effective range for Swaziland were used as thresholds. This limits comparability with studies in countries with WTP thresholds. In addition, dolutegravir-based regimens are expected to be introduced more widely and updated estimates of cost and cost-effectiveness will be needed. Finally, there is a limit to the generalisability of the results as the data was collected specifically in the context of Swaziland transitioning from Option A to Option B+. However, in settings such as South Africa, where there is no empirical evidence regarding cost-effectiveness of Option B+, this study may help inform decision making.

3.4 Conclusions

Overall, findings from this economic evaluation suggest that there is a strong economic case for pursuing the Option B+ approach in Swaziland. Increased staff time and providing additional staff training as was the case in this study, may result in higher retention rates in other settings, which in turn may positively impact on the health of women in such programmes. As universal HIV treatment programmes are implemented,

providing Option B+ for women who are pregnant and HIV-positive is a good platform for initiating this expansion. Cost findings from this study could inform budgeting for countries moving to the test and treat strategy for all individuals living with HIV. Based on this study, there may be optimistic implications in terms of retention to care as all those individuals with HIV are offered lifelong treatment.

4 Chapter Four: Provider- and patient-level costs associated with providing antiretroviral therapy during the postpartum phase to women living with HIV in South Africa: A cost comparison of three postpartum models of care

This manuscript has been accepted in Tropical Medicine and International Health in 2020 and was completed to fulfil Objective 2) To estimate the costs of three models of care for mother-infant pairs during the postpartum phase (at 12 months postpartum) from a provider and patient's perspective. Formal permission was obtained by the publisher John Wiley and sons (license number: 4927670170025). An unpublished section on the costs of the pregnancy phase costs follows after which fulfils Objective 2b.) to estimate the costs of the pregnancy phase for mothers from a provider's perspective. Lucy Cunnama was the first author with input from all co-authors, in particular Edina Sinanovic, Caitlin Dugdale, Elaine Abrams and Landon Myer. The citation is as follows (143):

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Abstract

Background

Innovative models of care to deliver antiretroviral therapy (ART) during the postpartum period may aid engagement in care among women living with HIV (WLH), but there are few data on the costs of different approaches to delivering these services.

Objectives

We conducted two studies implementing three novel models of postpartum ART care for WLH: (I) - local standard of care with women in general ART services and infants at well-baby clinics; (II) - women and infants continue to receive care through an integrated maternal and child care approach during the postpartum breastfeeding period; and (III) - referral of women directly to community adherence clubs with their infants receiving care at well-baby clinics. We aimed to compare the unit and total costs of these three models of care for mother-infant pairs during the postpartum phase from provider and patient's perspectives. The effects found in the MCH-ART study were that Model I had 56% of mother-infant pairs retained and virally suppressed (which was defined as HIV ribonucleic acid (RNA) <50 copies/mL) at 12 months postpartum; Model II had a 77% proportion; and Model III as part of the PACER study, was the most effective in terms of these measures, with 84% of mother-infant pairs retained and virally suppressed (in comparison to Model I).

Methods

Capital and recurrent cost data (relating to buildings, furniture, equipment, personnel, overheads, maintenance, medication, diagnostic tests and immunisations) were collected from a provider's perspective at six sites in Cape Town, South Africa. Patient time, collected via time-and-motion observation and questionnaires, was used to estimate patient perspective costs, and are comprised of lost productivity time, time spent traveling and the direct cost of travelling.

Results

The cost of postpartum ART visits under Models I, II and III were US $13, US $10 and US $7 per visit for a mother-infant pair, respectively, in 2018 US $. The annual costs for the mother-infant pair utilising the average visit frequencies (a mean of 4.5, 6.9 and 6.7 visits postpartum for Models I, II and III respectively) including costs for infant immunisations, visits, medication and diagnostic tests for both mothers and infants were: I- US $222, II- US $335 and III- US $249. Sensitivity analysis to assess the impact of visit frequency on visit cost showed that Model I annual costs would be most costly if visit frequency was equalised.

Conclusions

This comparative analysis of three models of care provides novel data on unit costs and insight into the costs to provide ART and care to mother-infant pairs during the delicate postpartum phase. These costs may be used to help make decisions around integrated services models and differentiated service delivery for postpartum WLH and their children.

4.1 Introduction

The last 20 years have witnessed substantial increases in the coverage of antiretroviral therapy (ART) among women living with HIV (WLH) who are pregnant and breastfeeding, with consequent declines in mother-to-child-transmission (MTCT) of HIV (144). However there are widespread concerns about the ability of existing health services to retain postpartum WLH in care and maintain the high levels of treatment adherence required to maximise the benefits of ART for maternal and child health (145).

There is a need for innovative models of care to address these challenges. Since 2016 the WHO has suggested the use of alternative models to deliver ART ('differentiated care') to cater for patient's needs, promote retention, unload clinics and promote accessibility for patients such as stable postpartum mothers (68, 146, 147). The International AIDS (acquired immunodeficiency syndrome) Society categorises ART service delivery into four main types: 'facility-based individual models'; 'out-of-facility individual models'; 'healthcare worker-managed groups'; and 'client-managed groups' (69, 148). Some examples of specific ART delivery models within these four broad categories are: fast track systems for ART collection within clinics such as in Malawi; community pharmacy collection in Nigeria; pick up points outside of healthcare facilities in the Democratic Republic of the Congo; collection by family members in Zimbabwe; teen ART clubs in Malawi and Eswatini; community adherence clubs in South Africa; and ART care integrated with other healthcare services such as for depression as is being studied in Malawi and Zimbabwe (148-155). The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) particularly recommend supporting the adherence of mothers during the postpartum period as part of the third and fourth part, of four component strategic approach to the prevention of mother to-child-transmission of HIV (PMTCT) (16, 20). Explicitly these components of the strategic approach are to prevent: "HIV transmission from a woman living with HIV to her infant" and to provide "appropriate treatment, care and support to mothers living with HIV and their children and families" (16).

Multiple limiting and enabling factors have been found to assist successful delivery of ART. Identified enablers from a qualitative study in South Africa include care being

focused on the patient, as well as clear support and guidance from the National Department of Health which has been found to aid the adoption of context specific models of care which in turn facilitate flexibility for patients (149). Barriers include stigma and discrimination, as well as a lack of resources (such as physical space and personnel capacity due to their high workload and staff turnover) (70, 149).

Although several models have been put forward, including the approaches used in this paper; the costs of these different approaches have received little attention. Two trials were conducted in the same population to examine the impact of models of care on retention and viral suppression and collect associated cost data for each model from the provider and patient's perspectives. The three models in the postpartum period were the local standard of care of referral of women to general ART services and infants to well-baby clinics (Model I - Routine Care); women and infants continue to receive care through an integrated maternal and child care approach during the postpartum breastfeeding period (Model II - Integrated Care); and referral of women directly to a community-based adherence club (CAC) and infants to well-baby clinics (Model III - Community Care). The effectiveness of these three models of care are reported in detail elsewhere (2, 4, 156, 157). Furthermore the costs from this study were utilised to update the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International and CEPAC-Pediatrics Models and inform the cost-effectiveness analysis that was undertaken and published (158). Briefly Model III was found to be the most effective in terms of retention of mother-infant pairs and maternal viral suppression (which was defined as HIV ribonucleic acid (RNA) <50 copies/mL) at 12 months postpartum with 84% of mother-infant pairs meeting this criteria (2, 4, 156, 157). Model I had a 56% and Model II had a 77% proportion of mother-infant pairs retained and virally suppressed

at the 12 month mark (2, 156, 157). Dugdale et al. 2019, found Model II to be cost-effective in comparison to Model I with an ICER of US $599 per year of life saved with the threshold being an ICER below US $903 per year of life saved (158). Our detailed cost analysis fed into the study by Dugdale et al. 2019 and will lead into two separate upcoming papers (159, 160) and for these reasons as well as the valuable content of this analysis we felt this work necessitated a separate manuscript.

In this work we aimed to compare the unit and total costs of three models of care for mother-infant pairs during the postpartum phase from the provider and patient's perspective

4.2 Methods

Throughout the methodology section both the Methods for the Economic Evaluation of Health Care Programmes textbook and the Reference Case for Estimating the Costs of Global Health Services and Interventions have been extensively consulted (83, 87).

4.2.1 Parent studies

Three locally developed and policy relevant postpartum models of care, were compared through two studies in South Africa: 1- Strategies to Optimize ART Services for Maternal and Child Health (MCH-ART) study (NCT01933477; April 2013-December 2016) and 2- Postpartum CACs to Enhance Support (PACER) study (NCT02417675; February 2015-October 2016) (156, 157). All institutions approved protocols and there was individual written informed consent.

The MCH-ART study was a randomised controlled trial conducted in a subdistrict of Cape Town that evaluated two approaches to postpartum care for WLH who initiated ART antenatally and their breastfed children (2). The trial enrolled women from an observational cohort (where all WLH seeking antenatal care services who were at least 18 years of age and eligible for ART initiation, were studied from their second antenatal care visit at Site A, located in a community with a high prevalence of HIV, until their first postpartum clinic visit further details in the supplementary appendix and cited papers) who were less than 6 weeks postpartum (median of 5 days postpartum) and who had started ART during their recently completed pregnancy (2, 156, 161). In order to be eligible for trial enrolment, women had to be breastfeeding their infants at the time of screening. Mother-infant pairs (n=471) enrolled in the trial were randomised to one of two arms. The control arm (n=238), referred to here as Model I, consisted of immediate postnatal referral to local ART services after delivery, as per standard of care and paediatric care for infants at well-baby clinics (where they would receive routine immunizations and growth monitoring as well as HIV services including early infant diagnosis using polymerase chain reaction (PCR) testing and infant antiretroviral prophylaxis with nevirapine). In the intervention arm, referred to here as Model II (n=233), women and infants continued to receive care in co-located maternal/paediatric care integrated in Maternal and Child Health (MCH) services through the postpartum breastfeeding period at Site A. The infants in Model II received the same care at Site A that they would in the well-baby clinic. Once breastfeeding ceased, women and infants were referred to local clinics for routine care (as per Model I). We selected five referral clinics nearest to Site A, where the majority of women were referred due to proximity to their homes, for cost data collection. Guidance on preferred

ART regimens and routine monitoring was equivalent for Models I and II. The primary objective of the MCH-ART study was to evaluate the composite endpoint of maternal retention in ART services and viral suppression at 12 months postpartum by trial arm (2). These women were followed for 12 months postpartum with study measurements at 6 weeks and then at 3, 6, 9 and 12 months postpartum (2).

The PACER study enrolled 129 postpartum breastfeeding WLH who initiated ART during their recently completed pregnancy, who met local criteria for CAC membership (4, 157, 162). Eligible women were offered a choice for postpartum ART care: Model I (as described above) or Model III - referral directly to a CAC with their infants receiving care at well-baby clinics. These women were followed for 12 months postpartum with study measurement visits that paralleled the MCH-ART study methods. As in the MCH-ART study, the primary objective of the PACER study was to assess the composite endpoint of maternal retention in ART services and viral suppression at 12 months postpartum. The work presented here is a detailed costing study using bottom-up methodology performed alongside the MCH-ART and PACER studies. See Table 5 for a comparison of the three models of care.

4.2.2 Study setting

All study activities took place in a low-income area in Cape Town with high levels of poverty and HIV prevalence (163, 164). All women received antenatal care at the same large primary care antenatal clinic (Site A). Women referred out from Site A attended sites including Sites B-F. Women in Model III (n=84) who chose to be referred to CACs received their care at a nearby Community Centre (Site G). Facility level cost data were

collected at Sites A-F and site level costs at Site G (Table 6). We purposively selected the five clinics that were near to Site A and that were chosen by a large proportion of women.

4.2.3 Utilisation

Data regarding the mean number of visits was drawn from the study data, through medical record abstraction at the facilities. All women were seen in Site A in the postpartum phase before forming part of the Model I, II or III cohorts. Those under Model II were transferred out to general ART services at the end of breastfeeding or at 12 months (if breastfeeding was continued for longer than a year) for routine care (as per Model I).

4.2.4 Cost analysis

4.2.4.1 Cost data

When referring to costs in this paper we are referring to the economic costs collected through the quantification of the items (for instance the amount of time spent on a task) and assigning a value (price) to these items (87). Economic costs differ from financial costs in that they include goods that may have been donated or services that have been volunteered (83). A unit cost refers here to the average cost of a service i.e. the 'cost per visit per mother-infant pair', is the average cost of a single visit for postnatal care for both the mother-infant pair (87). We have costed the entire postpartum healthcare service, rather than using an incremental costing approach, using both a provider and a patient perspective (83, 87). A mixture of top-down (i.e. gross costing, allocative

method for overheads and maintenance) and bottom-up (i.e. micro-costing, ingredients based methods for buildings, furniture, equipment, personnel, medication, diagnostic tests and immunisations) costing methodology was utilised (87, 165).

Provider costs comprised an estimation of total and unit costs based on collection of capital and recurrent costs for postpartum WLH and their infants (Table 7). Direct non-medical patient cost data was collected in questionnaire form to assess the travel costs (transport time and out of pocket payment for transport) for Models I-III from Sites A (Model I), B (Model II) and G (Model III). All of the seven sites (see Table 6) are near Site A and so travel time collected for Sites A (Model I), B (Model II) and G (Model III) were representative. Time-and-motion studies were performed to evaluate the indirect patient costs in terms of loss of productive time by patients at all 7 sites (Sites A to G, for Models I-III see Table 6). Time-and-motion studies refer to a researcher observing workflow and keeping track of the time that the patients spent in the facility including the waiting time (166). This was done through the use of small sheets of paper attached to the patient file on which the researcher recorded the time that the patient arrived at the facility (through asking the patient), the time the folder was drawn (observed) and the time of exiting the facility (when the folder was returned by the patient on leaving the facility). Costs are presented in 2018 United States dollars (US $) and were inflated where necessary using the South African Consumer Price Index (167). The exchange rate of 1:13.24 United States dollars to South African Rands was used for 2018 (the average exchange rate for the 2018 year). Capital costs were annuitized using a standard discount rate of 3% (83, 87) and an expected number of years of useful life of 30 years for buildings and 10 years for equipment (168).

Table 5: Comparison of key features of the three models of care (2, 162, 169, 170)

Category	Model I - Routine Care	Model II - Integrated Care	Model III - Community Care
Setting	Clinic-based general ART services at Primary Care Clinics (PHC) and well-baby clinics	Clinic-based services at Midwife Obstetric Unit (MOU)	Community Adherence Club (CAC) and infants at well-baby clinics
Sites	B, C, D, E, F	A (Clinic-based)	G (Community-based [clinic-based for infants])
Units of care	Individual patient	Mother-infant pairs	Groups of 25–30 patients
Patient profile	Mother-infant pairs seen together in Sites C, D, E, F. In Site B, only mothers are seen	Mother-infant pairs	Mothers
Infants	Infants seen separately in well-baby clinics for mothers attending services in Site B		Infants seen separately in at well-baby clinics for mothers attending the CAC
Key personnel	Professional nurse/staff nurse (Site F only)/ counsellors	Professional nurse who is trained as a midwife as well as in PMTCT, HIV and paediatrics/ counsellors	Lay counselors
Frequency of visits	1-2 monthly	1-2 monthly	2-4 monthly
Frequency of clinical consultations	1-2 monthly (every visit)	1-2 monthly (every visit)	12-monthly
Emphasis of patient contacts	Detecting clinical complications	Detecting clinical complications	Treatment adherence, patient wellness
Services offered to mothers	ART adherence counselling ART dispensed Breastfeeding and infant feeding advice Family planning (contraception)	ART adherence counselling ART dispensed Breastfeeding and infant feeding advice Family planning (contraception)	ART adherence counselling ART dispensed Peer support
Services offered to infants	Infant weighing Immunisations as per the National Childhood Immunisation Schedule Nevirapine refills PCR testing Anthropometry	Infant weighing Immunisations as per the National Childhood Immunisation Schedule Nevirapine refills PCR testing Anthropometry	Infants must attend separate well-baby clinic (as with Site B)
Peer-based support	No emphasis	No emphasis	Strong emphasis
Patient self-management	Minimal emphasis	Minimal emphasis	Strong emphasis
Frequency of laboratory monitoring for stable patients	3-monthly	3-monthly	12-monthly
Management of clinical complications	On-site	On-site	Up-referral to PHC
ART packing and dispensing	Packed at the clinic pharmacy, dispensed from pharmacy or during consultations. Patients collect ART themselves.	Packed at the clinic pharmacy, dispensed during consultations. Patients collect ART themselves.	Pre-packed by central dispensing unit, dispensed at CAC visit. ART can be collected by a treatment "buddy"

Table 6: Sites A-G

	Site A	Site B	Site C	Site D	Site E	Site F	Site G
Predominant model of care	Model I	Model II	Model II	Model II	Model II	Model II	Model III
	Midwife Obstetric Unit - MOU (Provincial)	Clinic 1 (Non-Governmental Organisation on same grounds as MOU)	Clinic 2 (City of Cape Town)	Clinic 3 (City of Cape Town)	Clinic 4 (City of Cape Town)	Clinic 5 (City of Cape Town)	Community Centre (Community Adherence Club - CAC)
MCH-ART study	✓	✓					
PACER study	✓						✓
Provider's perspective postpartum phase costs	✓	✓	✓	✓	✓	✓	✓
Patient perspective postpartum phase non-medical direct and direct costs	✓	✓					✓
Patient perspective postpartum phase indirect costs	✓	✓	✓	✓	✓	✓	✓
Provider's perspective infant costs	✓		✓	✓	✓	✓	
Example of staff complement directly involved in postpartum care*	2 nursing assistants, 3 professional nurses (including a focal nurse), 2 counsellors	2 professional nurses, 1 counsellor	2 professional nurses, 1 counsellor, 1 administration officer	3 professional nurses, 1 counsellor	2 professional nurses, 2 clerks	1 professional nurses, 2 enrolled nurses, 1 counsellor, 2 clerks	1 professional nurse, 4 counselors, 1 coordinator, 3 data clerks

* Those involved directly in postpartum services who complete timesheets for the study. These staff members spend more than 0% and less than 100% of their time on postpartum services. This list excludes support staff who did not fill in timesheets, but whose time was accounted for through allocation.

4.2.4.2 Cost measures

Capital (buildings, furniture and equipment) and recurrent (personnel, overheads and maintenance) costs were estimated separately and summed to give the total cost at the health facility. The total costs were then apportioned using the total number of postnatal visits divided by the total clinic headcount for each input to value the total postpartum phase cost under each model. For the postpartum phase, the unit cost was defined as the 'cost per visit per mother-infant pair' from delivery to cessation of breastfeeding or 12 months postpartum. We multiplied the average number of visits made by mothers by the unit 'cost per visit' to calculate a 'cost per woman', with average medication and diagnostic costs added subsequently. The postpartum unit costs used the mother-infant pair to calculate an annual 'cost per mother-infant pair', with other per person costs of the average medication (for mothers and infants), diagnostic (for mothers and infants) and infant immunisation being added subsequently.

Postnatally the PCR for early infant diagnosis, was done at birth, 10 and 18 weeks and 9 months was added together and divided by 12 months. For postpartum diagnostic costs under Model I and II, initial CD4, haemoglobin and creatinine, and viral load testing at 3, 6, 9 and 12 months were added together and divided by 12 months. Under Model III, once yearly haemoglobin, creatinine and viral load testing were added and divided by 12.

Medication included ART for mothers (tenofovir/emtricitabine/efavirenz) and nevirapine syrup for infants. The daily unit cost for medication was multiplied by 30

days to get the per month cost for mother and infants separately. Immunisations as per the National Department of Health's Expanded Programme on Immunisation – EPI (SA) Revised Childhood Immunisation Schedule, included the prices of Bacillus Calmette-Guérin (BCG); oral polio vaccine (OPV); rotavirus vaccine (RV); diphtheria, tetanus, acellular pertussis, inactivated polio vaccine, haemophilus influenzae type B and hepatitis B combined (DTaP-IPV-Hib-HBV); pneumococcal conjugated vaccine (PCV); and the measles vaccine according to the schedule (up to 12 months), added together and divided by 12 months.

4.2.4.3 Cost data collection

As part of this undertaking, the sites were mapped and measured (in metres squared), and an inventory of furniture and equipment was made. All the staff that provided services during the postpartum phase under the three models completed timesheets to ascertain the percentage of their time dedicated to the various tasks for women in the postpartum phase, as well as for infants. For instance, these tasks included consulting, adherence training and educating, dispensing medication, management of services, record keeping and administration.

Salary information, patient utilisation and overhead costs, were provided by Site G, City of Cape Town and Western Cape Government Health administrators. The prices of equipment and furniture were sought from local medical equipment and furniture suppliers. Some utilisation data was sourced through the project records. The Council for Scientific and Industrial Research (CSIR) supplied building replacement costs. Diagnostic cost data was furnished by the South African National Health Laboratory

Services, while immunisation and medication costs were provided by Pharmacy Services in Western Cape Government Health (171, 172).

4.2.4.4 Patient costs

Patient level data was collected in terms of direct costs, which relate to the transport costs incurred by the patients. In addition, indirect costs were collected which cover lost productivity time and transport time. These costs were collected during the MCH-ART and PACER Studies through questionnaires administered at 6 months postpartum. The questionnaires provided information that could be separated easily into the three models of care as the control arm of MCH-ART represented postpartum mother-infant pairs in Model I, the intervention arm represented postpartum mother-infant pairs in Model II and the intervention arm of PACER represented postpartum mother-infant pairs in Model III. A convenience sample of 355 consecutive women had additional information collected using a time-in-motion tool. The time-and-motion tool was used to document the time that patients spent at the seven sites in terms of productive time lost. These time-in-motion studies followed three separate postpartum mother-infant pairs, i.e. postpartum mother-infant pairs in Model I, II and III respectively. A minimum wage of US $1.52 per hour (for 2018) was used to calculate the cost of transport and productive time lost (173). Income information was collected through the resource questionnaires, however the information received was very sparse and may have biased the valuation of productivity losses and so the choice was made to use minimum wage.

Sensitivity analyses assessed the change in cost if the number of visits was equalised between the models of care, using the scenario where mother-infant pairs attended

sites on a monthly basis for the year (i.e. 12 times) during the postpartum phase. In addition, we assumed that the cost for infants seen in well-baby clinics was the same whether a mother was seen in Model I or III.

4.3 Results

4.3.1 Costs for postpartum phase

During the postpartum phase the mother-infant pair received care in either Model I, II or III. The unit cost of a visit for a mother-infant pair from a provider perspective was US $13, US $10 and US $7 in Models I, II and III, respectively. The average annual total costs for visits for the mother-infant pair from a provider perspective were US $222, US $335, US $249 when medication, diagnostic tests (for infants and mothers) and infant immunisations were included for Models I, II and III respectively or US $54, US $75 and US $48 for the mother-infant visit only (indicated in the yellow bars of Figure 3). Visit costs accounted for 24% (average of 4.5 visits), 22% (average of 6.9 visits) and 19% (average of 6.7 visits) of the average annual postpartum care costs per mother-infant pair in each model (see Figure 4). Unit costs per visit from the patient perspective (to and from their residence) were US $7 for Model I, US $4 for Model II and US $5 for Model III respectively (see Table 9 - For the direct and indirect cost of transport time, there were 462 responses). Annually this amounted to between US $29-54, US $23-44, and US $75 from a patient perspective for Models I, II and III respectively (Figure 3).

Table 7: Impact Inventory (adapted from the Second Panel on Cost Effectiveness in Health and Medicine(174))

Sector	Type of impact	Perspective		Notes
		Provider	Patient	
	Formal healthcare sector			
Health	*Medical costs*			
	Paid for by healthcare sector	Costs of visits were collected as well as diagnostic, immunisation and medication costs. This was done through collection of utilisation data/ quantities as well as prices	Not collected	Timesheets were used to quantify healthcare provider time spent on tasks
	Informal healthcare sector			
Health	Patient time costs	N/A	Patient time for waiting was collected through time-in-motion	
	Unpaid caregiver time costs	N/A	Not collected	
	Transport costs	N/A	Direct transport costs collected through questionnaires Indirect transport costs linked to time traveling to and from the clinic was also included	
	Non-healthcare sectors			
Productivity	Labour market earnings lost	N/A	Attempt to collect via a questionnaire however very sparsely completed	
	Cost of unpaid lost productivity due to illness/ inability to work	N/A	Calculated using the minimum wage (US $1.52 per hour) (173)	This method has the draw-back in that the women attending are likely to earn less income on average than the minimum wage, however their time is important for other reasons and so it can be argued that this monetary evaluation of time does not do the valuation justice
	Cost of uncompensated household production	N/A	Not collected	

Table 8: Unit and total costs for the postpartum phase in 2018 US $

Postpartum phase unit costs	Visit cost (mother and infant)	Cost of medication per month (infant)	Cost of medication per month (mother)	Cost of diagnostic tests per month (mother and infant)	Immunisation costs per month (infants)	Total number mothers enrolled	Assumed number infants enrolled	Mean number of visits	Total clinic visit costs	**Average annual total cost per mother-infant pair**	**Total cost for annual postpartum care cost**
Model I – Routine Care	***US $13***	US $1	US $9	US $9	US $10	238	238	4.49[a]	*US $12 808*	**US $222**	**US $52 940**
Model II – Integrated Care	***US $10***	US $1	US $9	US $9	US $10	233	233	6.94[b]	*US $17 396*	**US $335**	**US $78 124**
Model III – Community Care	***US $7***	US $1	US $9	US $10	US $10	84	84	6.73[c]	*US $4 019*	**US $249**	**US $20 933**

a Women were retained for an average of 1.04 visits in Site A, before being transferred to Model I where they attended 3.45 visits on average
b Women attended an average of 5.5 visits in Model II, once they ceased breastfeeding, they were transferred to Routine Care (Model I) for an average of 1.44 visits
c Women were retained for an average of 1.04 visits in Site A, before being transferred to Model III where they attended 5.69 visits on average

4.3.2 Sensitivity analysis

In order to look at the impact of different visit loads, we assessed what the cost would be if the mother-infant pair received the same number of visits (12 visits) under each of the models (holding the initial number of visits constant (1.44 Routine Care visits after transferring out for Model II; 1.04 visits in Site A for Model I and III; see Table 10 and Figure 3 (light blue dotted bars)). The percentage increase for Model I would be 180% from the provider's perspective, making it the most costly model of care when assessing annual postpartum care visit costs per mother-infant pair (increasing from US $54 to US $151).

4.3.3 Patient time

Patient time at the facility/community centre from arriving to exiting across the three models (n=355 patients) was 3 hours on average (standard deviation 1 hour 34 minutes). For Model I (n= 250) the average time at the facility was 3 hours 33 minutes (standard deviation (SD) 1 hour and 28 minutes); the average time for Model II (n=52) was 1 hour 27 minutes (SD 60 minutes); the average time for Model III (n=53) was 2 hours 1 minute (SD 53 minutes).

4.3.4 Input proportions

The two main recurrent inputs in visit costs were personnel and overheads (including maintenance). Personnel made up the largest proportion of visit costs for all three models: Model I - 80%; Model II - 69%; and Model III - 78%. Overheads and

maintenance accounted for: I - 18%; II- 27%; and III - 20%. While the capital inputs for buildings accounted for less than 4% (I - 2%; II - 4%; and III - 2%,) across the three models and equipment and furniture less than 1%.

4.4 Discussion

Understanding the costs of care for postpartum WLH and their children is critical for program planning and optimization of ART services during the postnatal period. We took the approach of considering the costs for the mother-infant pair with the trialled models of care specifically assessing maternal (and infant) outcomes. In the PACER and MCH-ART studies Model III was found to be the most effective in terms of retention of mother-infant pairs and maternal viral suppression at 12 months postpartum with 84% of mother-infant pairs meeting this criteria (2, 4, 156, 157); Model I had a 56% and Model II had a 77% proportion (2, 156, 157). As the population of adults living with HIV is not homogeneous, there is a need to consider having a combination of different models depending on the characteristics of the population or individual's phase of life.

A large proportion of HIV care costs are attributable to service delivery. As ART services expand to achieve population-level coverage, building costs are unlikely to substantially increase, unless they reach capacity. However, healthcare provider time costs may go up significantly as larger numbers of patients receive care in the clinic or community. Initially there are economies of scale at play, where staff can care for more patients with the same resources, however when the capacity of the healthcare workers is reached additional staff (and other resources) will be needed (87). As the costs of ART medications continue to come down, the relative contribution of service delivery

related costs (e.g., provider time, clinic building costs/overheads, etc.) increase. With costs driven by service delivery elements, detailed costing data such as provided in this study are key to understanding the costs of different models of care.

Mother-infant pairs may have different needs in terms of the care they require. The clinical presentation of mothers may be that they are well or not well; this could be the first time that they are starting ART or they could have experience in taking ART (175). Prior ART experience could mean that mothers access to care was previously negatively impacted, for instance that they were lost to follow up at some point in the treatment cascade or defaulted. Further to this different patient needs can be addressed by the distinctive models, a crucial underpinning of the idea of differentiated care (37, 68). For instance, not all patients will be eligible for CACs and may be better suited to care under Model I or II. CAC inclusion criteria being that patients should be adults, who have been on ART for 6-12 months, be stable with a suppressed viral load, not be pregnant and should not require frequent clinical management for adherence issues or comorbidities (4). For those eligible and attending a CAC, the less frequent visit requirement of CACs (see Table 5) and ability to send a treatment 'buddy' to collect ART may aid WLH who are working or who would be unable to come to the clinic as regularly (176). This flexibility is appreciated by those in CACs (149, 176). Integrated Care has the benefit of prolonging the time that the mother-infant pair are kept together which may limit (at least initially) the loss to follow up during transfer to another model (177). Postpartum WLH were also found to breastfeed for a longer time in Model II, which in turn could positively impact their infant's health (2). Further evolution of these models may include combining ideas such as integrating peer support into facility-based models such as Mother to Mothers (M2M) which has been done elsewhere in South Africa and

extending ART refill times decreasing the visit frequency limiting face-to-face interaction especially in a time of COVID-19 (37, 70).

In assessing these three models of care, we were interested in considering whether community-based care can be a desirable alternative to facility-based care from a cost perspective, given the potential increase in patient numbers with expanded ART services. The provider's perspective annual costs are the highest for Model II - Integrated Care (women and infants continue to receive care through an integrated maternal and child care approach during the postpartum breastfeeding period), then Model III - Community Care (referral of women directly to CACs and Model I - Routine Care (local standard of care of referral of women to general ART services and infants to well-baby clinics). Both the costs from the provider and patient's perspectives are affected by the structure of the services provided. The important differences from a costing standpoint between the models are that: under Model II mother-infant pairs are seen together during the breastfeeding period (before transferring out to routine care (as per Model I); under Model I, mothers and infants are seen separately, but depending on the facility this may be within the same site or even in the same consultation as we observed in four facilities; and for Model III, mothers and infants are seen separately at separate sites. This has impact particularly on the patient costs, because one integrated visit as opposed to two visits reduces the productive time lost, time spent on transport and the direct transport costs. In Model II we saw a positive impact on travel costs, with the lowest mother-infant pair patient visit cost (see Figure 3) as only one visit is required for the pair. The observed waiting time for patients in Model III is relatively long as patients still arrive well before their medication is dispensed (or even before the community centre is opened), first listening to wellness talks given by the counsellors.

This is counter to the rationale of a CAC which aims to minimise the time spent by patients collecting medication (157).

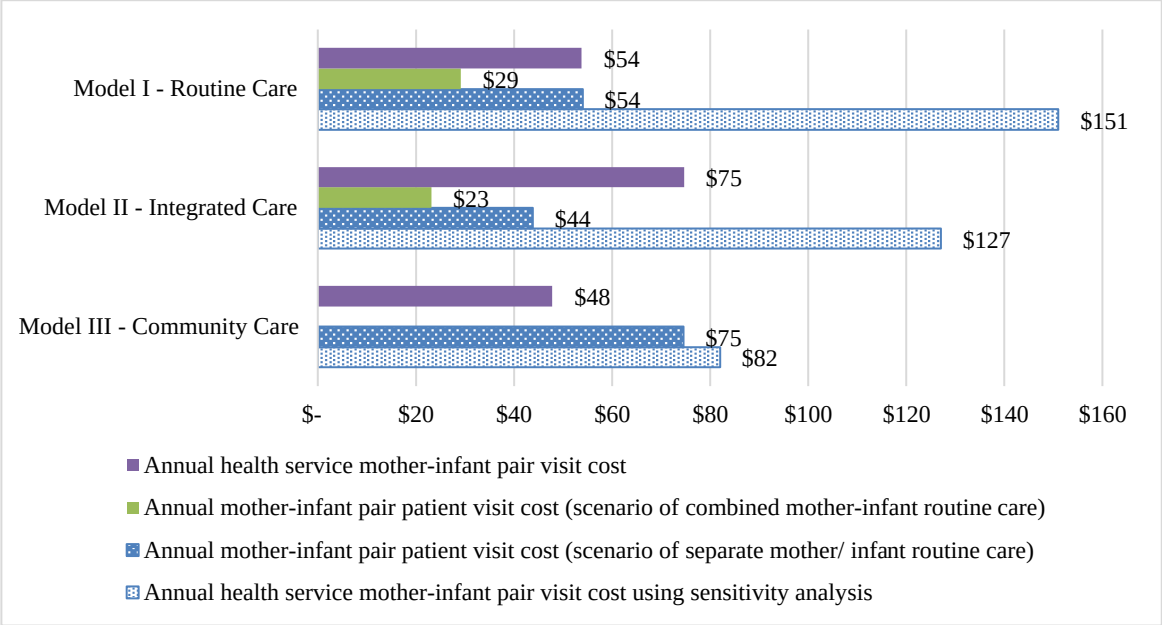

Figure 3: Annual provider and patient visit costs (including costs from the sensitivity analysis) per mother-infant pair in the postpartum phase in 2018 US $

The x-axis in the figure is the cost in 2018 US $, while the y-axis shows the the three models. The yellow bars show the annual provider cost for a mother-infant pair for visits only. A range is provided for Model I and II, where the lower amount, is shown in grey bars and the upper amount is shown in dark blue dotted bars. The grey bar, shows the annual patient cost for a mother-infant pair visit under the scenario of combined routine care for mothers and infants (both mother and infant in the same consultation). The dark blue dotted bars display the annual patient cost for a mother-infant pair for visits only, where routine care is provided under the scenario of mother and infants being seen in separate consultations i.e. not at the same site or on separate days. The costs from the sensitivity analysis for the annual provider for a mother-infant pair visit, shown here in light blue dotted bars are described in more detail in Table 10 – they show the cost of equalising the number of visits between models for the annum.

Immunisations costs per infant and diagnostic cost per mother-infant pair are the highest drivers of cost for Model III. However, the proportion of the annual cost for Model III specifically for mother's diagnostic testing accounts for only 3%, whereas it represents 17% and 18% in Model I and II. These higher proportions in Model I and II can be attributed to the extra monitoring performed in these models, specifically more frequent viral load testing. For Models I and II diagnostic cost per mother-infant pair is the main cost driver (35% and 36% of the annual costs). Personnel costs which relate to

time of healthcare professionals were the major cost driver in the visit costs for each of the three models, more so in Model I (19% of the annual cost) and less so in Model II and III (15% of the annual cost in each model respectively). Care in Model I, is delivered by a mix of professional nurses, nursing assistants and counsellors; Model II is mainly delivered by a focal nurse in conjunction with counsellors; while Model III is delivered primarily by a counsellor. The profession of the staff and by implication the salary level, as well as the time staff spent on postpartum care tasks all influence the personnel cost. In addition, there may be other value added such as in information exchange between counsellors and patients as this cadre of staff may help to de-medicalise information and reduce use of jargon (Model III), and more holistic care of the mother-infant pair when treated together (Model II). In the PACER study 78% of WLH who chose to stay in the control arm, reported a preference for attending a health facility (4). Zerbe et al. 2020, also note a movement of WLH from CACs back into health facilities with these WLH showing poorer outcomes (4). Hence there are nuances to the three models of care and many factors to weigh up aside from costs and outcomes.

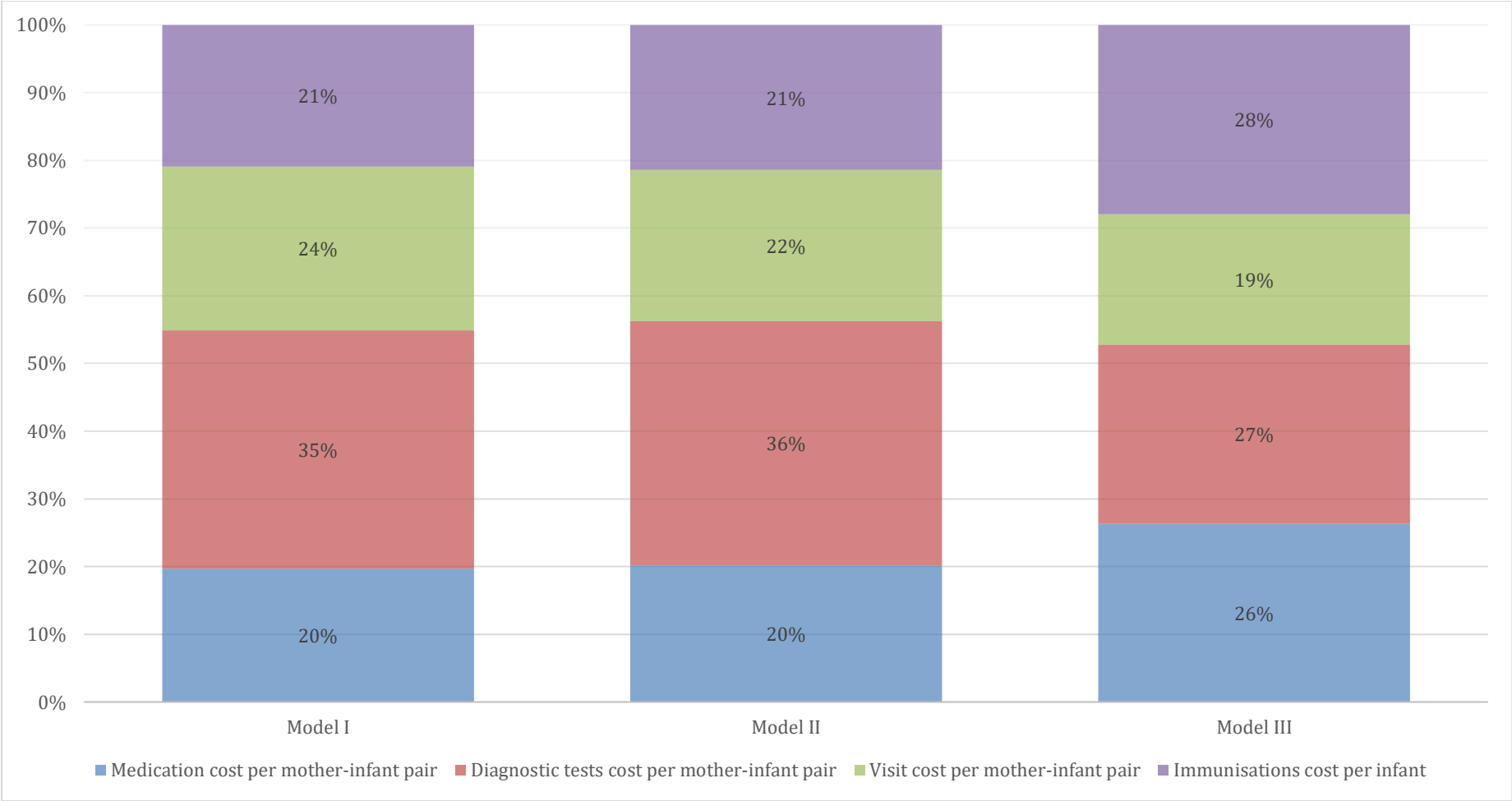

Figure 4: Proportion of average annual cost for postpartum care per mother-infant pair by category (medication, diagnostics, immunisation and visit cost

Table 9: Direct and indirect patient costs for the three models of care in 2018 US $

		Indirect patient cost	**Non-medical indirect patient cost**	**Non-medical direct patient cost**	**Total per patient visit cost**	**Total per patient visit cost**
		Mean waiting time/ lost productivity cost using time-in-motion	Cost of transport time/ time to clinic (at 6 months)	Out of pocket payment for transport to the clinic (at 6 months)	**Total indirect and direct (including transport to the clinic)**	**Total indirect and direct (including transport to and from the clinic)**
Model I – Routine Care	**Number of observations**	n=250	n=175	n=175		
	Mean (SD)	*US $5.41 (2.23*)	*US $0.49 (0.35)*	*US $*0.40 (0.29)	*US $***6.3**	*US $***7.19**
Model II – Integrated Care	**Number of observations**	n=52	n=178	n=178		
	Mean (SD)	*US $2.21 (1.51*)	*US $0.54 (*0.47)	*US $*0.46 (0.36)	*US $***3.21**	*US $***4.21**
Model III – Community Care	**Number of observations**	n=53	n=109	n=109		
	Mean (SD)	*US $3.07 (1.34)*	*US $0.50 (0.35)*	*US $*0.54 (1.05)	*US $***3.11**	*US $***5.15**

In an evaluation of CAC costs (comparable to those used in the Model III) in a similar setting in South Africa, Bango et al. (152) (costs have been inflated from 2011 to 2018 US$ for comparison using US $ Consumer Price Index (178)) found higher annual costs of US $418 for standard of care (compared to Model I - US $114 for mothers' care only) and US $335 for the CACs (compared to Model III - US $90 for mothers' care only). One of the factors that has affected the difference in values in the current study compared to the study by Bango et al. (152) is the reduction in ART medication cost by approximately one third. Another is the utilisation rate, which is higher in the study by Bango et al. (152) than for Model I in this work (10.3 versus 4.5 visits per year in the current study). The average number of clinic visits is an integral part of the annual cost and varies between the three models in this paper from 4.6 and 6.9.

Although these three models have been presented separately, there is a level of interdependence between the models and need for thought as to how patients flow through these models in order to ensure mothers and infants are retained in suitable care. For instance, as the models currently function, all mother-infant pairs continue to receive care in Site A for approximately one visit (or while breastfeeding in Model II) before either moving to routine clinic-based ART care or community-based care in the form of a CAC, where infants transfer to being cared for in well-baby clinics. To this end, we do not suggest that one model is superior to another. We also found that in reality four of the five clinics in Model I were consulting with mothers and infants in the same visit and in two of the facilities were also dispensing medication during that consultation. The total unit costs are also affected by assessing only the mother in isolation or by ignoring the patient costs, hence our approach of assessing the mother-infant pairs.

Table 10: Sensitivity analysis, normalising the number of visits between models of care (2018 US $)

	Provider's perspective (as per study visits)	Provider's perspective (12 visits)	Percentage increase
Model I: 12 visits Mean of 1.04 visits at Site A (in Model II - Integrated Care) remains constant; Model I visits increased to 10.96	*US $54*	US $151	180%
Model II: 12 visits Model II visits increased to 10.56; mean of 1.44 visits in the general ART clinic for routine care (as per Model I) after referral out from Model II - Integrated Care, stays the same	*US $75*	US $127	70%
Model III: 12 visits Mean of 1.04 visits at Site A (in Model II - Integrated Care) remains constant; Model III visits increased to 10.96*	*US $48*	US $82	72%

*An important part of CACs service delivery is that stable patients in the CACs can collect medication less frequently than in a standard of care setting, so in reality we would not want to increase the number of visits; however this is being done to be able to compare cost equally across the three model

The unit costs from this study could be generalised to the wider population in South Africa, taking note of the specific peri-urban setting and way the services are offered. Further work is needed to look into the outcomes and cost-effectiveness of the different models of care to make judgments on which model of care or mix of models of care are best suited to the healthcare system and to inform what these models would cost at scale. In low- and middle-income countries where unit cost estimates are not available these costs could assist in planning similar programmes or models.

4.4.1 Limitations

One limitation of this study could be the comparison of Model III, as the CAC is intended only for women who are already stable on ART, whereas Models I and II have no requirements for inclusion. In the case of the PACER study, all women enrolled had the prerequisite of having started ART during pregnancy, currently breastfeeding their

infant, with evidence of viral suppression after three months of ART (VL< 1000 copies/ mL) and no comorbidities that require frequent clinical review (4). As one of the goals of CACs service delivery model is that visits are less frequent for stable patients, we are not suggesting that the number of visits be increased as we have done in our sensitivity analysis, but rather are looking at the effect on cost when we equalise the number of visits. This is particularly relevant in light of the World Health Organization's recommendation to extend refills for clinically stable patients to between three and six months (21). An ongoing South African clinical trial is aiming to assess the impact of less frequent refills within the CAC setting which will aid policy going forward (179). It is important to note that these costs are most applicable to the population of women who started ART in pregnancy and may differ for those who have been stable on ART prior to conception. Another limitation is that the cost of care may vary from clinic to clinic, though our sample is representative and we present average unit costs. Also for Site A we used the average number of visits in the study per woman to inform the number of visits for postnatal care as the facility did not have utilisation data for this. The largest number of time-and-motion studies were completed for Model I across different clinics, this may have biased the time data as Models II and III had fewer time-and-motion studies.

4.5 Conclusions

Novel data on unit costs to provide ART to mother-infant pairs during the postpartum phase and insight into the cost drivers has been provided through this comparative analysis of three models of care. The unit costs of the two new models of care, using Integrated Care (Model II) and Community Care approaches (Model III) respectively,

are more expensive, however they are also more effective in terms of retention of mother-infant pairs and viral suppression at 12 months postpartum as shown by the MCH-ART and PACER studies . These costs may be used to help make decisions around integrated services models and differentiated service delivery for postpartum WLH and their children. Importantly these costs will be useful for informing budgeting for postpartum care and have already fed into a cost-effectiveness analysis comparing Integrated Care (Model II) to Routine Care (Model I). This work will feed into another cost-effectiveness analysis comparing all three models of care and a budget impact analysis for the South African setting.

4.6 Pregnancy costs unpublished supplementary information

There are widespread concerns about the ability of existing health services to retain pregnant women living with HIV (WLH) in care and maintain the high levels of treatment adherence required to maximise the benefits of ART for maternal and child health (145).

All pregnant WLH received integrated antenatal care, HIV care and antiretroviral treatment (ART) (including prevention of mother-to-child transmission of HIV (PMTCT)) services within a Midwife Obstetric Unit (MOU) (Site A). We aimed to estimate the costs of the pregnancy phase for women, combined across all three models, from health service perspective.

4.7 Methods

4.7.1 Parent study

The MCH-ART study was a multiphase longitudinal cohort study where women were enrolled within Site A (2). This is a single, large primary care antenatal care and obstetric service, located in a community with a high prevalence of HIV within Cape Town, South Africa. During the observational component (Phase 2) approximately 600 women seeking antenatal care services (from Phase 1), who were at least 18 years of age and were eligible for ART initiation, were studied from their second antenatal clinic visit until their first postpartum clinic visit and this data was used for the costing of the pregnancy phase (2, 156).

Pregnant women known or testing HIV positive but not on ART were started on ART on the day of testing (or at a maximum within one week). Antenatal care included palpation, blood pressure testing, weighing, education about pregnancy, breastfeeding and infant care. Routine blood work was done at the first antenatal care visit, as well as pre-test counselling for HIV testing and a rapid HIV test was performed. For these pregnant WLH, PMTCT services, including distributing ART, adherence counselling and pill counts were also provided within Site A during antenatal care visits. Routine infant deliveries were performed at Site A, and more complicated deliveries took place at a secondary level referral hospital.

4.7.2 Study setting

All study activities took place in a low socioeconomic community in Cape Town with high levels if HIV and poverty (8). All women received antenatal care at the same large primary care antenatal clinic (Site A).

4.7.3 Utilisation

Data regarding the mean number of visits was drawn from the study data, through medical record abstraction at the facilities. All women were seen at Site A during the pregnancy phase.

4.7.4 Cost analysis

4.7.4.1 Cost data

Health service costs comprised an estimation of total and unit costs based on collection of capital and recurrent costs for pregnant WLH (Table 11). Costs are presented in 2018 United States dollars (US $) and were inflated where necessary using the South African Consumer Price Index (167). Capital costs were annuitized using a standard discount rate of 3% (83, 87) and an expected number of years of useful life of 30 years for buildings and 10 years for equipment (168).

4.7.4.2 Cost measures

For the pregnancy phase in Site A, capital (buildings, furniture and equipment) and recurrent (personnel, overheads and maintenance) costs were estimated separately and summed to give the total cost at the health facility. The total costs were then apportioned using the total number of antenatal visits divided by the total clinic headcount for each input to value the total pregnancy phase cost.

We defined the pregnancy phase unit cost as the 'cost per visit' from the start of antenatal care through to just prior to delivery. We divided the total cost of providing services during the pregnancy phase by the number of visits made in the same period to get the unit 'cost per visit'. We multiplied the average number of visits made by mothers by the unit 'cost per visit' to calculate a 'cost per woman', with average medication and diagnostic costs added subsequently.

Antenatal diagnostic tests included initial Pima™ CD4 and rapid HIV test done at point of care; haemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine, as well as HIV viral load testing at 3, 6 and 9 months, performed at the South African National Health Laboratory Services (NHLS). These test costs were added together and divided by 6 months to give the per month value.

Medication included ART for mothers (tenofovir/emtricitabine/efavirenz) The daily cost per medication was multiplied by 30 days to get the per month cost.

4.7.4.3 Cost data collection

As part of this undertaking, the sites were mapped and measured (in metres squared), and an inventory of furniture and equipment was made. All the staff that provided services during the pregnancy phase completed timesheets to ascertain the percentage of their time dedicated to the various tasks for women in the pregnancy phase. For instance, these tasks included consulting, adherence training and educating, dispensing medication, management of services, record keeping and administration.

Salary information, patient utilisation and overhead costs, were provided by Western Cape Government Health administrators. The prices of equipment and furniture were sought from local medical equipment and furniture suppliers. Some utilisation data was sourced through the project records. The Council for Scientific and Industrial Research (CSIR) supplied building replacement costs. Diagnostic cost data was furnished by the South African National Health Laboratory Services, while medication costs were provided by Pharmacy Services in Western Cape Government Health (171, 172).

Table 11: Impact Inventory (adapted from the Second Panel on Cost Effectiveness in Health and Medicine(174))

Sector	Type of impact	Perspective		Notes
		Health service	Patient	
Health	*Formal healthcare sector*			
	Medical costs			
	Paid for by healthcare sector	Costs of visits were collected as well as diagnostic and medication costs. This was done through collection of utilisation data/ quantities as well as prices	Not collected	Timesheets were used to quantify healthcare provider time spent on tasks

Table 12: Unit and total costs for pregnancy phase in 2018 US $

Cost of a visit in Site A	Cost of medication per month	Cost of diagnostic tests per month	Total number pregnant women enrolled	Mean number visits in Site A	Total clinic visit costs	**Average 6-month total pregnancy care cost per woman**	**Total cost for 6-month pregnancy care cost for the cohort of 471 women**
US $12	US $9	US $15	471	3	US $17 090	**US $109***	**US $51 240**

*25% medication; 41% diagnostic tests; 33% pregnancy visit cost

4.8 Results

4.8.1 Costs for pregnancy phase

We present here a set of unit and total costs for the pregnancy phase from a health service perspective. The pregnancy cost was the same for all women as they received the same pregnancy care (regardless of which of the three postpartum models they entered). The unit cost per visit at Site A during the pregnancy phase was US $12 (Table 12) from a health service perspective. The cost per woman during the pregnancy phase was US $36 from a health service perspective, considering that there are on average 3 visits made (based on medical record abstraction). If one includes the health service costs of both medication and diagnostic test costs, the average cost per woman during pregnancy was US $109 (25% medication; 41% diagnostic tests; 33% pregnancy visit cost).

4.8.2 Input proportions

The two main recurrent inputs in visit costs were personnel and overheads (including maintenance). Personnel made up the largest proportion of costs, 74%. Overheads and maintenance accounted for 23% of the pregnancy phase costs, while the capital inputs for buildings accounted for less than 3% and furniture less than 1%.

4.9 Discussion

Understanding the costs of care for pregnant WLH is critical for program planning and optimization of ART services during the pregnancy period.

A large proportion of HIV care costs are attributable to service delivery. As ART services expand to achieve population-level coverage, building costs are unlikely to substantially increase, unless they reach capacity. However, healthcare provider time costs may go up significantly as larger numbers of patients receive care in the clinic or community. As the costs of ART medications continue to come down, the relative contribution of service delivery related costs (e.g., provider time, clinic building costs/overheads, etc.) increase. With costs driven by service delivery elements, detailed costing data such as that provided in this study are key to understanding the costs of different models of care.

4.10 Conclusion

This cost analysis provides insight into the costs to provide ART to pregnant women living with HIV.

5 Chapter Five: Cost-effectiveness analysis of three postpartum models of care for women living with HIV in Cape Town, South Africa

This manuscript was prepared with the journal BMC Cost Effectiveness and Resource Allocation in mind to fulfil Objective 3.) To compare the costs and effects of three models of care for mother-infant pairs during the postpartum phase (12 months postpartum) from a provider and patient's perspective in a cost-effectiveness analysis; and will be submitted later in 2020. Lucy Cunnama is the first author and has had input from Edina Sinanovic and Landon Myer.

Abstract

Background

Great strides have been made to prevent mother-to-child transmission of HIV (PMTCT). Focus is now being placed on how best to serve women during the sensitive postpartum phase so as to optimise maternal and child healthcare. The purpose of this study was to establish the cost-effectiveness of two models of care (Model II and III) relative to Model I – Routine Care where women are seen in general antiretroviral therapy (ART) services and infants in well-baby clinics. The two novel models of care were: Model II – Integrated Care where women and infants are retained in an integrated maternal and childcare approach during the postpartum breastfeeding period; and Model III – Community Care where women directly referred to community adherence clubs with their infants receive care at well-baby clinics.

Methods

The annual cost per mother-infant pair for each model of care in 2019 US $ and the effectiveness in terms of mother-infant pairs retained and mothers virally suppressed at 12 months postpartum were collected during two studies in Cape Town, South Africa, namely Strategies to Optimize ART Services for Maternal and Child Health (MCH-ART) Study and Postpartum Community Adherence Clubs to Enhance Support (PACER) Study. The incremental costs and effects of Models II and III were compared to that of Model I and plotted on a cost-effectiveness plane. A sensitivity analysis in the form of a univariate analysis using a tornado diagramme was performed to assess the robustness of the results.

Results

Model III is dominant to Model II with incremental cost-effectiveness ratios (ICERs) of US $97 and US $548 respectively, which fall below a revealed willingness to pay threshold of US $929 per life year saved for HIV investment in South Africa, however this threshold cannot be used for meaningful comparison given the difference in outcome measures among other reasons. A sensitivity analysis demonstrated that the results were robust to changes in the costs and effects.

Conclusions

The two innovative models of care have been shown to be cost-effective in comparison to Model I given the threshold 'indicators' for the setting. The implications are that there is evidence that can be used to provide an approach of different types of care dependant on the preference of women living with HIV in the postpartum period which may in turn

enhance outcomes for the mother-infant pair. Further research is needed to assess the affordability of these models at a national scale.

5.1 Background

With the roll out of lifelong triple antiretroviral therapy (ART) initiated during pregnancy, huge strides have been made in terms of the reduction of mother to child transmission of human immunodeficiency virus (HIV) and improving maternal and child health (180). For those women starting ART before conception with an undetectable viral load, it has been proven in a cohort of thousands that transmission rates are negligible rising to 0.9% in the third trimester (180, 181) which emphasises the need to screen and start treatment as early as possible. However screening and uptake of services is more complex than it seems with potential fallout of the treatment cascade at every step (180). In Sub-Saharan Africa, there are an estimated one million women a year who are pregnant and living with HIV, which accounts for nearly all cases globally. Between 2010 and 2019, the percentage of women living with HIV who access ART has risen from 71% to 97% in South Africa (182). Which in turn impacted on the vertical transmission decreasing the overall transmission from 16% to 3% in the same time period (182).

For those women living with HIV whose ART started during pregnancy, the transition from antenatal to postpartum care is an important yet precarious time. ART should continue for maternal health as well as during breastfeeding to reduce the chance of transmission to the newborn (180, 181, 183, 184). Therefore, different models of care that are context specific and locally tailored should be evaluated in order to increase or maintain coverage and effectiveness, decrease or maintain cost, and improve the quality of care (185). Four main alterations to create models of care have been identified by Bulstra et al. 2019 (185): an integrated model combining health services; a modified

model where, for instance, there is task shifting of health care professionals; a simplified model such as one where steps are removed and ART treatment is administered less frequently; and a change in the place of delivery such as from the health sector into the community. These can be compared to the standard of care (i.e. an unaltered model). Bulstra et al. 2019 (185) recommend piloting models of care to assess their impact.

This study is a cost-effectiveness analysis which assessed different models of care in an attempt to keep women retained in care and virally suppressed during the postpartum breastfeeding period. The data were collected during two studies conducted in a subdistrict of Cape Town, *Strategies to Optimize ART Services for Maternal and Child Health* (MCH-ART) and *Postpartum Community Adherence Clubs to Enhance Support* (PACER). MCH-ART was a randomised controlled trial that evaluated two approaches to postpartum care for women initiating ART antenatally and their breastfed children: standard care of referral of women to general ART services and infants to well-baby clinics (Model I - Routine Care) or retaining women and infants in care during the postpartum breastfeeding period under an integrated maternal and child care approach (Model II - Integrated Care) (2, 156). PACER, a supplementary study to MCH-ART, offered postpartum breastfeeding women living with HIV the choice between Model I - Routine Care (as described above) or referral of women directly to a community-based adherence club (CAC) and infants to well-baby clinics (Model III - Community Care) (157).

We aimed to assess the cost-effectiveness of the three models of care in terms of cost per mother retained and virally suppressed at 12 months postpartum. In doing so we

intend to contribute a comparative assessment of these models of care to inform postpartum care going forward.

5.2 Methods

5.2.1 Study aim

The aim of this study was to assess the cost-effectiveness of three novel postpartum models of care for mother-infant pairs.

5.2.2 Study design

A cost-effectiveness analysis was undertaken using costs and natural units for the outcome measures to calculate the incremental cost required to improve patient outcomes for mother-infant pairs. Empirical economic costs from a patient and provider's perspective had already been collected through the two projects MCH-ART and PACER (186) between 2013 and 2017. The annual cost per mother-infant pair for each of the three models of care were inflated and are presented in 2019 US $ (187). The effectiveness measures, also collected during the two studies, related to retention in care at 12 months postpartum combined with viral suppression, which was defined as HIV ribonucleic acid (RNA) <50 copies/mL (2, 156, 157).

5.2.3 Data analysis

A cost-effectiveness analysis was performed in a purpose built Microsoft Excel spreadsheet.

To assess the cost-effectiveness of the three models of care, the annual cost per mother-infant pair were ranked from low to high (least to most costly). Then the incremental costs were calculated for the second most costly model in comparison to the model with the lowest annual cost, and the most costly in comparison to the model with the lowest annual cost. The costs and effects were plotted in a cost-effectiveness plane with R software (R Project, Vienna, Austria) using the user interface of RStudio.

5.2.4 Sensitivity analysis

A sensitivity analysis was performed to assess uncertainties in both the costs and outcomes. The annual costs for Model II and III were altered by 5%, 10%, 15% and 20% above and below the figures established in the cost analysis (186) to determine the impact on incremental cost-effectiveness ratio (ICER). The same was done for the effectiveness measure. Maternal retention and viral suppression at 12 months postpartum, was also altered by 5%, 10%, 15% and 20% above and below the figures established in the effectiveness studies PACER (4, 157) and MCH-ART (2, 156), to determine the impact on ICER. Plausible ranges in which to vary the parameters were chosen in response to reviewing current literature and are displayed in tornado diagrammes.

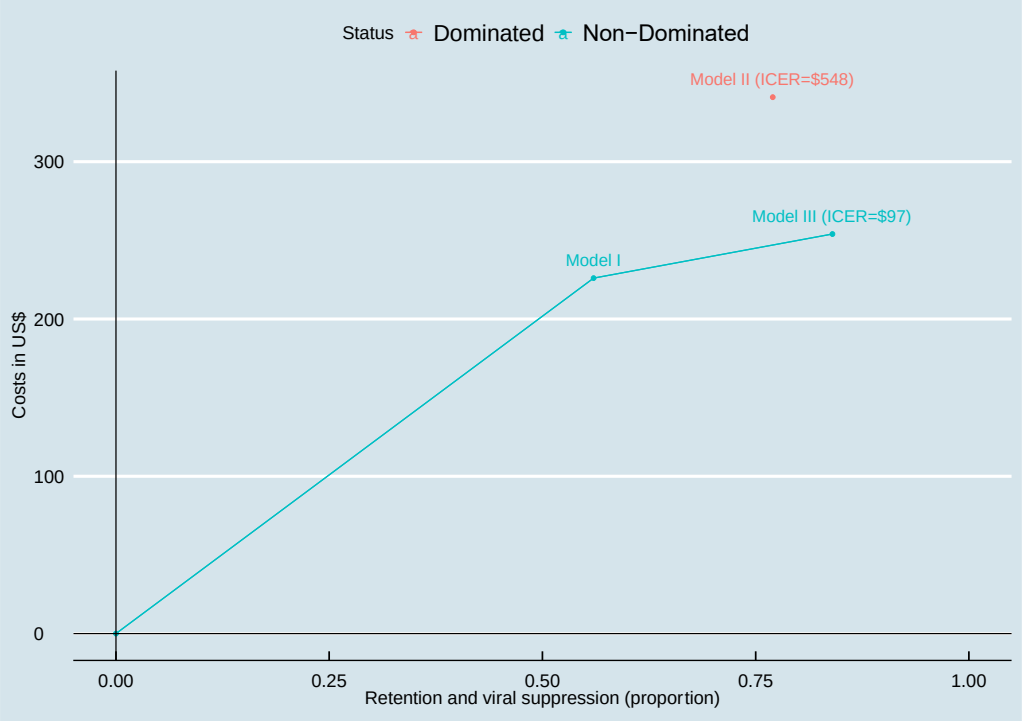

Figure 5: Cost-effectiveness plane with incremental cost per retained and virally suppressed mother (provider's perspective costs)

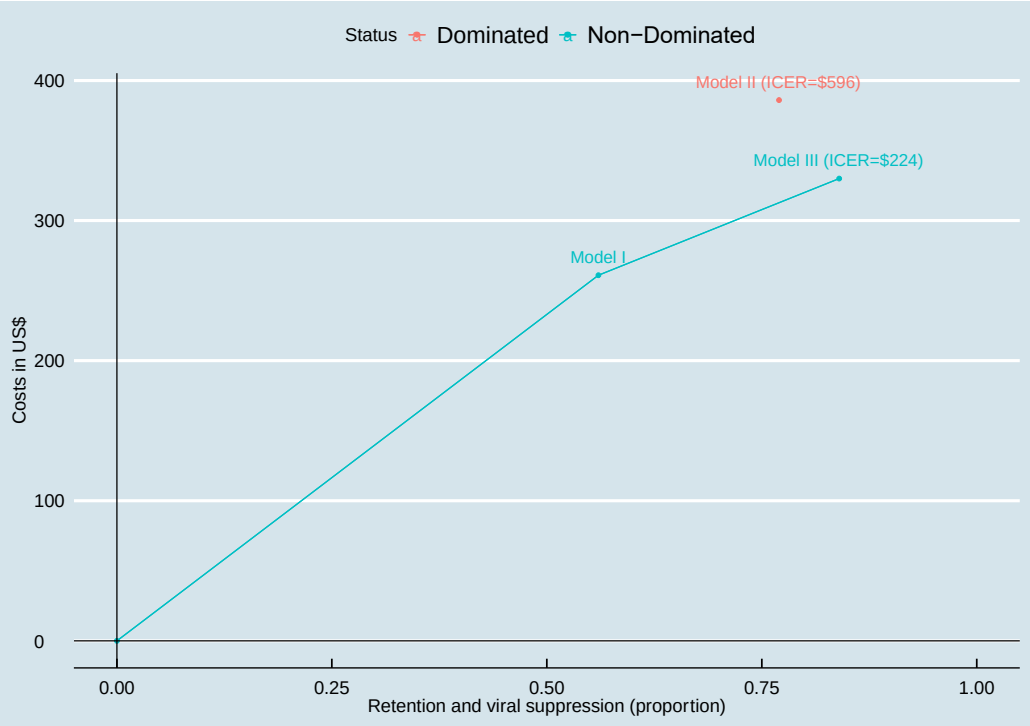

Figure 6: Cost-effectiveness plane with incremental cost per retained and virally suppressed mother (patient and provider's perspective costs combined)

5.3 Results

Model III – Community Care dominated Model II – Integrated Care in terms of cost-effectiveness. Model III cost slightly more, but was more effective in comparison to Model I – Routine Care (Tables 1 and 2). When plotted on a cost-effectiveness plane, both Model II and III are found in the North-East quadrant whether the costs utilised are from a provider's or patient and provider's perspective (Figure 5 and 6). The ICER for Model III was US $97 (Figure 5).

Table 13: Annual and incremental costs per mother-infant pair from a provider's perspective; and patient and provider's perspective in 2019 US $ for each model of care

	Annual cost Per mother-infant pair provider's perspective	*Incremental cost* **(Per mother-infant provider's perspective)**	**Annual cost Per mother-infant pair patient and provider's and perspective**	*Incremental cost* **(Per mother-infant pair patient and provider's perspective)**
Model I - Routine Care	US $226	-	US $261	-
Model III - Community Care	US $254	US $27	US $330	US $69
Model II - Integrated Care	$341	$115	$386	$125

Table 14: Effectiveness and incremental effectiveness, in terms of proportion of mothers retained in care and viral suppressed at 12 months postpartum, for each model of care

	Effectiveness: maternal retention in care and viral suppression (%)	*Incremental effectiveness*
Model I - Routine Care	56%	-
Model III - Community Care	84%	28%*
Model II - Integrated Care	77%	21%

* Dominated

The tornado diagramme visually displays which of the input variables, namely clinical effect and annual cost, have the biggest impact on the ICER (which is the output). They are displayed in decreasing importance where clinical effect altered by 20% has the most impact on ICER for Model II (Figure 7) and the annual cost being changed by 20% (Figure 8) for Model III.

5.4 Discussion

Cost-effectiveness aims to assess the opportunity cost of implementing a new programme in place. Some countries, such as the United Kingdom, have a threshold for cost-effectiveness analysis (CEA), and if an ICER for a programme falls below that threshold then it is considered good value (188). In South Africa, we do not have a cost-effectiveness threshold, but instead assess each CEA relative to those previously done as well as looking at the relative cost-effectiveness of programmes. Leech et al. 2018 (189) analysed the CEAs (using a disability adjusted life year (DALY) as an output so

technically a cost utility analysis (CUA) in our definition) performed between 2010 and 2015 in low- and middle- income countries to assess practice going forward. They found that the majority that report the use of a threshold used a now unsupported technique of comparison to gross domestic product per capita (188, 189). Their advice from the analysis was that, where possible, locally developed thresholds should be utilised. A study by Edoka and colleagues (190) estimated the value of a DALY averted in South Africa to be US $3 250 (inflated to 2019 US $) (190-192).

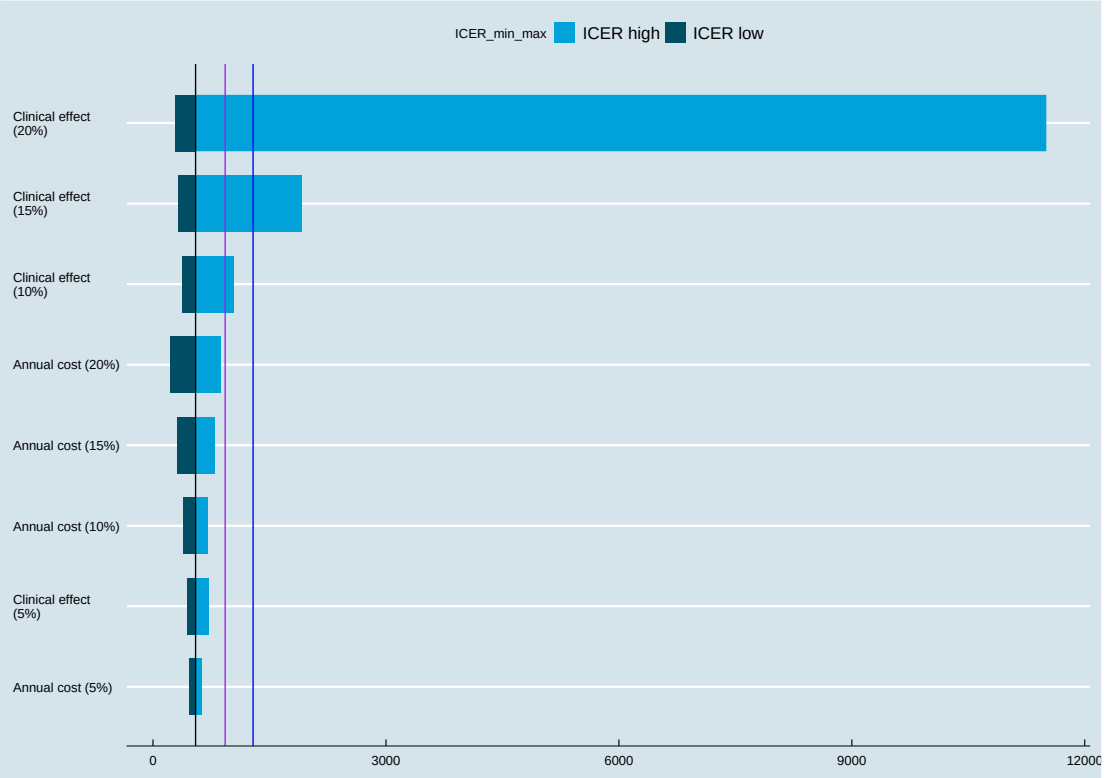

Figure 7: Tornado diagramme of univariate sensitivity analysis for Model II, base value ICER US $548

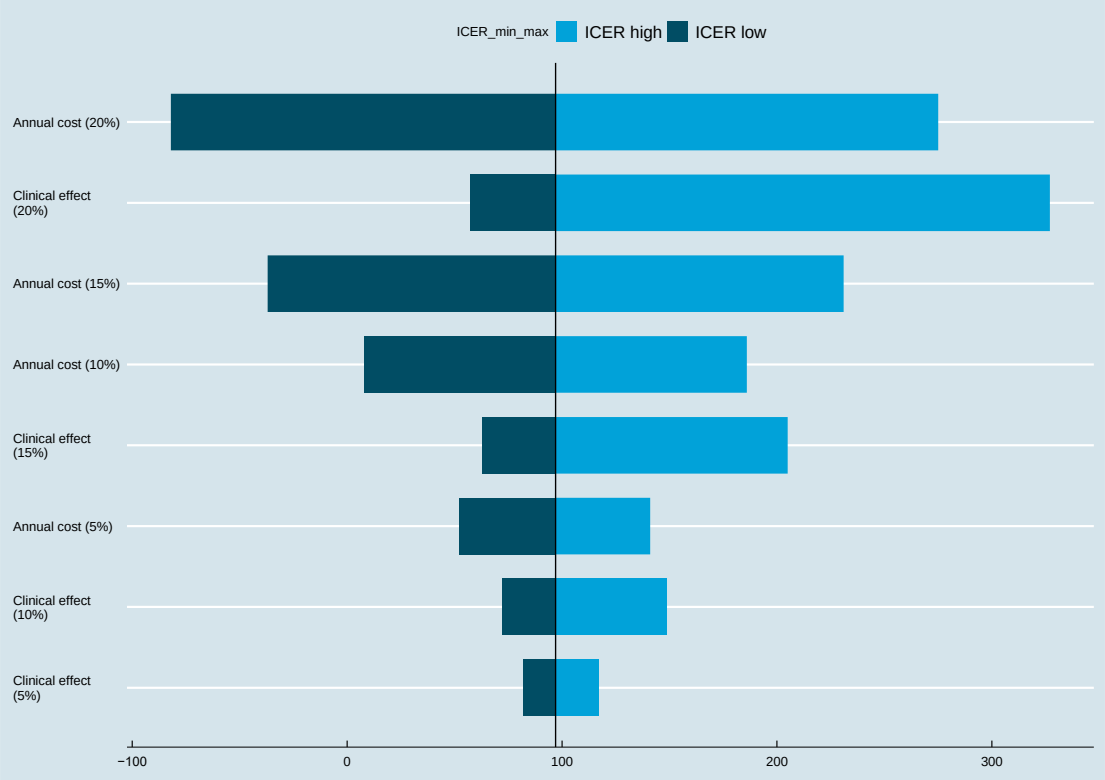

Figure 8: Tornado diagramme of univariate sensitivity analysis for Model III, base value ICER US $97

The purple and blue vertical 'threshold lines' in Figure 7 are US $929 (193) and US $1 289 (133) below which an intervention could be considered cost-effective (inflated to 2019 US $)) (187). The lower threshold of US $929 per life year saved (the purple line in the tornado diagramme, Figure 7) is the revealed willingness to pay threshold for South Africa which was established as part of the HIV investment case (193) however as the outcomes are different (retention and viral suppression versus life years saved) this does not lead to meaningful comparison and is not recommended as an indication of cost-effectiveness by the authors. The 'opportunity-cost-based' cost-effectiveness threshold of US $1 289 (133) is the recommended lower bound (US $5 173 is the upper bound) for South Africa as indicated by Woods et al. 2016. Using all of these threshold 'indicators', both Model II and Model III can be considered cost effective in the South African setting.

As Bulstra et al. (185) appropriately state, a mix of models of delivery may be the most acceptable to the population that is being served and may indeed reach the goals of maintaining cost, effectiveness, quality and coverage or better still decreasing cost, increasing effectiveness, improving quality and increasing coverage. Fox et al. assessed retention in adherence clubs and standard of care for individuals with HIV, not specifically postpartum women, and found there to be a benefit to adherence clubs in terms of retention (194).

Dugdale et al. performed a similar cost-effectiveness analysis limited to a comparison between Model I and II for postpartum care, utilising the visit unit costs and effectiveness from the MCH-ART Study and the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International and CEPAC-Pediatrics Models which are components of a long established complex HIV simulation model. They found Model II to be cost-effective in comparison to Model I with an ICER of US $599 per year of life saved with the threshold being an ICER below US $903 per year of life saved (158). The finding of this study was that Model II had an ICER of US $548 per mother-infant pair retained and virally suppressed at 12 months postpartum which is expectedly in line with the results of the model simulation by Dugdale et al. considering that the cost and effectiveness data was generated from the same study (158), despite the differencing effectiveness measures.. The main differences between this work and the work by Dugdale et al. are that we have added the comparison of a third model of care which was also empirically costed and effectiveness measures were captured through a parallel substudy which maintained the same measures; and unlike the work by Dugdale et al. this work comprised a focus on the comprehensive empirical costing of

these three models using simple methods without complex modelling and the implicit assumptions of a complex model.

In a the province of Yunnan in China, another modelling study found that Option B+ was cost-effective in their setting with the high ICER of US $5 485 per life year gained in mothers in comparison to Option B and the very low ICER of US $35 per quality adjusted life year (QALY) gained in infants (when inflated to 2019 US $) (187, 195). A recent systematic review located 15 economic evaluation studies for prevention of mother-to-child transmission of HIV (PMTCT) specifically in the Sub-Saharan African region with reference years between 2009-2016 (42). The revealed median values from these studies were US $1 447 per HIV infection averted and US $194 per DALY averted or QALY gained (when inflated to 2019 US $), noting that PMTCT in the region can be considered very cost-effective (42, 187). Our findings are similar in that both Models II and III can be considered cost-effective relative to Model I. The sensitivity analysis demonstrates the changes in ICER when either the effects or costs are altered. Apart from changes larger than 10% for the effectiveness of Model II (Figure 7), the ICER for both Models II and III (Figure 6) remain below the threshold indicators.

This study findings are generalisable to the rest of South Africa as well as other low- and middle-income settings with similarities to South Africa. However, it should be noted that for this study the setting was peri-urban and there may be factors, such as champion healthcare workers (in particular for the integrated approach of Model II) and well established and numerous CACs, which may have impacted the findings.

The main limitation of this study is that the outcomes are expressed in natural units making it difficult to make comparisons with other healthcare programmes. However, these measures are useful as they express important measures of HIV care, specifically retention in care - an important aspect of treatment allowing for a viral suppression which is a good indication of adherence to treatment and the model working to achieve its aims of maternal and child health. It is encouraging to see models of care that are locally relevant and which can be considered cost-effective relative to these threshold 'indicators'. Further research is needed to establish the affordability of scaling up these models of care in the South African context.

5.5 Conclusions

Model III – Community Care, which involved postpartum care for mothers at CACs and infants at well-baby clinics, is the most cost-effective model relative to the other models of care, whether costs were utilised from a provider's perspective or patient and providers' perspective. Model II - Integrated Care approach for mother-infant pairs was also found to be cost-effective relative to the threshold 'indictors' for the country. These findings are particularly notable for policy going forward as they could allow for a mix of models of care that are cost-effective, acceptable to mother-infant pairs, provide highly effective care in terms of retention and viral suppression, and have known costs for planning and budgeting purposes.

6 Chapter Six: Scaling-up postpartum models of care for mother-infant pairs in South Africa: A budget impact analysis

This manuscript was prepared with the journal BMC Cost Effectiveness and Resource Allocation in mind to fulfil Objective 4.) To estimate the budget impact of nationally scaling-up models of care for the postpartum period; and will be submitted later in 2020. Lucy Cunnama is the first author and has had input from co-authors Edina Sinanovic and Landon Myer.

Abstract

Background

In the age of universal antiretroviral therapy (ART), three postpartum models of care for mother-infant pairs in the Western Cape, South Africa, were assessed in terms of their relative cost-effectiveness. The three models were Routine Care (Model I) with women being cared for in general ART services and infants in well-baby clinics; an integrated maternal and child approach (Integrated Care - Model II) with women and infants being retained together during the postpartum breastfeeding period; and Community Care (Model III) where women are directly referred to community adherence clubs, with their infants receiving care at well-baby clinics. The purpose of this study was to assess the budget impact of nationally scaling up a more cost-effective postpartum model of care than current routine care.

Methods

The annual cost per mother-infant pair of the three models of care which were empirically collected, were inflated to 2019 US $. The target population of women living

with HIV in the reproductive age group of 15-49 years, who had delivered a baby in the last year in the public sector, was estimated through a series of steps using publicly available data. The cost of implementing the most cost-effective model of care (Model III) was compared to the cost of routine care at scale (Model I). In order to assess the robustness of results, four additional scenario analyses were performed (Alternate Scenarios A-D). This was compared to the National Healthcare Budget for South Africa for, the National Strategic Plan (NSP) summary of the anticipated budget for HIV, TB and STIS and the HIV and AIDS Component of the HIV, TB, Malaria and Community Outreach Grant, all for the period 2020/21.

Results

Implementing a relatively more cost-effective model of care, Model III at scale (100% coverage), resulted in an increased budget requirement of US $5 720 096, in comparison to Model I at scale. The total budget requirement of US $52 751 995 for Model III, represents an additional 0.2% of the total health budget, 0.3% of the NSP anticipated budget and an additional 0.5% of the HIV and AIDS Component of the Community Outreach Grant for 2020/21. In the scenario analyses a coverage of 12%, 23%, 65% for the three models respectively, Alternate Scenario A, an additional US $9 303 763 (in comparison to Model I) is required. If an equal weighting (Alternate Scenario B) between the three models of care is used (i.e. 33.3% of the target population is covered under each) then an additional US $9 886 016 is required (in comparison to Model I). Alternate Scenario C found the extra budgetary need for Model II at 100% scale was US $23 939 660, which is a 51% increase compared to Model I at scale. The fourth scenario, Alternative Scenario D, would only require an additional US $3 260 455

to implement Model III (in place of Model I), but would only cover 57% of those in need of care.

Conclusions

The net budget impact to introduce a more cost-effective model than the current standard of care represents an increase of 0.9 - 2.2% of the national healthcare budget. However as the different models are designed to suit different women's preferences, for instance facility based care (Models I and II) or non-facility based care (Model III) one of the alternate scenarios providing differentiated care although more expensive may be more acceptable to mothers. The potential implications are that more cost-effective novel options for postpartum maternal and child health have been established in the Western Cape which if scaled up countrywide could have particular impact on the health of the next generation as well the mothers of our country.

6.1 Background

Prevention of mother-to-child transmission (PMTCT) of the human immunodeficiency virus (HIV) has been a global success, however at every point in the HIV treatment cascade, there is a risk that mothers will disengage from care (144). There is hope for the complete elimination of transmission of HIV from mother-to child which seemed impossible in the past (144, 180) and this aim is supported by the Sustainable Development Goals which states that progress in combating HIV/AIDS needs to be increased (196). In the eastern and southern region of Africa, 60% of new infections are in females of reproductive age 15-49 (182). In South Africa, pregnant women living with HIV are often diagnosed and initiate treatment during the pregnancy phase, and

continue to receive care and antiretroviral therapy (ART) in combination with their antenatal care (144, 197). As they transition to the postpartum period there is a chance that women will be lost to follow up (LTFU). In some cases the lost to follow up rate has been found to be as high 49% in the first 6 months (164) however in another study 37% of women who were considered LTFU were found to be seeking HIV care in another facility sometimes in a different province (198). In order to retain women in care, different models of care are needed according to patient preference, for instance at different locations: facility-based or community-based; drug collection at differing intervals: monthly or multi-monthly; individual or peer group adherence counselling; and fast tracking or making use of a 'buddy' system for picking up medication (199).

Prior research assessed the costs and effectiveness of two models of postpartum care compared to the standard of care. A detailed costing study with a bottom-up methodology was undertaken (186) and then subsequently a cost-effectiveness analysis (CEA) was performed utilising 'the cost per mother-infant pair virally suppressed and retained in care' as the outcome measure for each model of care (159). The first of the two studies was *Strategies to Optimize ART Services for Maternal and Child Health* (MCH-ART) a randomised controlled trial conducted in a subdistrict of Cape Town that evaluated two approaches to postpartum care for women initiating ART antenatally and their breastfed children: standard care of referral of women to general ART services and infants to well-baby clinics (Model I - Routine Care) or retaining women and infants in care during the postpartum breastfeeding period under an integrated maternal and child care approach (Model II - Integrated Care) (2, 156). And the second study was *Postpartum Community Adherence Clubs to Enhance Support* (PACER) a supplementary study to MCH-ART where postpartum breastfeeding women living with HIV were

offered the choice between Model I - Routine Care (as described above) or referral of women directly to a community-based adherence club (CAC) and infants to well-baby clinics (Model III - Community Care) (157). The purpose of this analysis is to assess the budgetary impact of scaling up these complementary models of care nationally

Budget impact analysis (BIA) can provide evidence for decision making as it looks at the cost of scaling up a programme and estimates the funding needed to implement the programme. Which importantly is an assessment of the economic impact and hence uses information including economic costs (110, 200). When a programme is scaled up, then we need to assess what it will displace in term of cost within the budget and what the resultant opportunity cost will be. BIA considers the scale of the displacement within a budget or the amount that the budget will need to be adjusted so that all programmes can be funded (110). Whereas a CEA considers the relative costs and effects of a programme in combination, a BIA evaluates the budgetary need of a programme.

We identified the need for a BIA to be able to adequately judge the affordability of implementing postpartum models of care at scale. In light of estimating the budget needed, the national budget for healthcare in South Africa for 2020/21 is R56.7 billion or US $3.2 billion, while the Medium Term Expenditure Framework for the HIV and AIDS Component of the 'HIV, TB, Malaria and Community Outreach Grant' for the same financial year (2020/2021) is R22.2 billion or US $1.3 billion (114-116). In total the National Strategic Plan details that the anticipated budget for HIV, TB and STI is R37.5 billion or US $2.1 billion for the 2020/21 period which includes funding from the South

African Government, PEPFAR and USAID, Global Fund and estimated private sector ART funding (17).

This BIA aimed to assess how the introduction of novel postpartum models of care, in particular how the scale up of integrated care and community care would affect the healthcare budget for South Africa and the opportunity cost of implementation in terms of its impact on the HIV component of the conditional grant. Importantly the preferences and needs of women lead us to explore differing mixed strategies as well as the impact of coverage levels. The contribution that this BIA will add is in terms of data which can then be used for informed decision making with regard to the national scale up of postpartum models of care.

6.2 Methods

6.2.1 Study aim

The aim of this study was to assess the budget impact of national scale-up in terms of implementing these new postpartum models of care (Models II and III) in South Africa.

6.2.2 Study design

A BIA which assesses the net budget impact when adding a new approach or combination of approaches was utilised for this work. The economic unit costs of the three models of care were estimated from a provider perspective and have been discussed elsewhere (186). The costs for the three models of care were inflated and are presented in 2019 US $ (201) (see Table 15). These costs comprise apportioned capital

(building costs, furniture) and recurrent costs (healthcare worker costs, overheads, immunisations for infants, medication, diagnostic costs) for postpartum care annually, per mother-infant pair.

Table 15: Annual unit cost per mother-infant pair for each of the three models of care in 2019 US $

Model of care	**Annual unit cost per mother-infant pair in US $**
Model I – Routine Care	226
Model II – Integrated Care	341
Model III – Community Care	254

These unit cost estimates were combined with the effectiveness measures (retention in care at 12 months postpartum combined with viral suppression, HIV ribonucleic acid (RNA) <50 copies/mL) to assess the cost-effectiveness of the three models of care (159). These unit cost estimates were then used in this study to analyse the budget impact of nationally scaling up (to 100%) the most cost-effective model of care , Model III - Community Care, relative to the other two models, Model I - Routine Care and Model II – Integrated Care. The scaling up of Model III to 100%, to replace Model I, is the base case scenario where the resulting displacement of funds and budget requirements are calculated.

6.2.3 Data analysis

We have utilized the National Institute for Health and Care Excellence (NICE) Budget Impact Template in Microsoft Excel which provides a framework for estimating the BIA, in order to standardize the BIA process (202). It is a generic tool which can be adapted

to any country (202).The first step was to adapt the population by entering the South African national population of 58.8 million for 2019 (203). The national target population for this BIA, of the number of women living with HIV for reproductive ages (15-49), who had a baby in last year (2019) was then estimated and the cost of scaling up the base case scenario, Model III at 100% scale (in comparison to Model I at 100% scale), using the annual unit costs (Table 15) was calculated. In terms of effects, Model III, 84% of women were virally suppressed and retained at 12 months postpartum in the PACER study (4). Model III was also found to be the dominantly cost-effective model of care (159).

6.2.4 Sensitivity analysis

Sensitivity analysis took the form of scenario analysis to look at the structural uncertainty, where four alternate scenarios were modelled in addition to the base case of 100% coverage of Model III nationally. The first scenario (Alternate Scenario A), makes use of the preference of women in the PACER study, in which 65% chose Model III – Community Care, rather than Model I - Routine Care. The remaining proportion of the women (35%) were divided in a ratio of 1:2 to Model I (12%) and Model II (23%), with the rationale that Model II has a higher effectiveness (in terms of viral suppression and retention in care (77% of women were virally suppressed and retained at 12 months postpartum in Model II in the MCH-ART study)) than Model I (where 56% were virally suppressed and retained), but also a higher annual cost per mother-infant pair (2). The second scenario (Alternate Scenario B) uses equal weighting between the three models of care (Model I, II and III each accounting 33.33% coverage) acknowledging that there are merits to each of the models and potentially different characteristics that

would work for some mother-infant pairs and not for others. The third scenario (Alternate Scenario C), assesses Model II at scale, displacing Model I. The fourth scenario (Alternate Scenario D) is where Model III replaces Model I, but only at 57% coverage (for both Models I and II), which relates to the reported 118 608 antenatal clients initiated on ART in the 2017/8 financial year (115). In addition we used the Thembisa Model (a large mathematical model for HIV in South Africa) to consider the differences in estimated numbers of women living with HIV for reproductive ages (15-49), who had a baby in last year (2019).

6.2.5 Assumptions

We have assumed that the reproductive ages for women in South Africa are between 15-49 years, and that all reported births come from this age group. We have subtracted the infant deaths from the nationally reported birth figure based on the infant mortality rate for 2019 of 22.1 per 1000 live births. This assumes that the reported birth figure does not account for infant mortality. We have also assumed that the number of women that would be in the postpartum phase are equal to the number of live births (which does not take into account the birth of multiples but factors in infant mortality as described above). Models I-III, were specifically designed for the postpartum period where mothers started ART in pregnancy, this BIA however uses National HIV prevalence so treatment may already be well established in these women living with HIV. The proportion used to calculate the number of (births) postpartum women in the public sector (80%) (204, 205).

6.3 Results

6.3.1 Estimating the target population

We estimated the eligible population in a series of steps shown in Table 16. Almost one in every four women of reproductive age is HIV positive. Essentially the target population, of 208 084 mother-infant pairs, for the BIA was calculated using the number of births in the public sector and HIV prevalence (Step 8 in Table 16).

Table 16: Steps to estimate the target population

Step 1	Total population of South Africa (male and female)	58 800 000	Source: (203)	58 075 532	Source: Thembisa Model Version 4.4 (206)
Step 2	National numbers of women for reproductive ages (15-49)	15 850 574	Source: (203) Table 6	15 757 455	Source: (206)
Step 3	% HIV prevalence for women for reproductive ages (15-49)	23%	Source: (203) Figure 5	20%	Source: (206)
Step 4	Number of women for reproductive ages (15-49) living with HIV	3 599 665	Calculation: 15 850 574*23%	3 091 565	Calculation: 15 757 455*20%
Step 5	All recorded births nationally	1 171 219	Source: (203) Table 4	1 171 219	Source: (203) Table 4
Step 6	All recorded births nationally minus infant deaths (infant mortality 22.1 per 1000 live births)	1 145 335	Calculation: 1 171 219 - (1 171 219*2%)	1 145 335	Calculation: 1 171 219 - (1 171 219*2%)
Step 7	All live births in public health sector	916 268	Calculation: 1 145 335*80% Source: (205)	916 268	Calculation: 1 145 335*80% Source: (205)
Step 8	Number of women living with HIV for reproductive ages (15-49), who had a baby in last year (2019)	**208 084**	Calculation: 916 268*23%	**179 769**	Calculation: 916 268*20%

6.3.2 Scaling up

Model III – Community Care was found to be the most cost-effective model relative to Models I and II (159). It was found that if Model III was implemented at 100% coverage in South Africa, it would cost US $52 751 995 (see Table 17). Model I – Routine Care, which is the current practice, nationally has a budget requirement of US $47 031 899 when at 100% coverage. This means that the net budget impact or addition to the budget for Model III at scale is US $5 720 096 for the annum, a 12% increase from Model I, at scale.

As a proportion of the HIV, TB, Malaria and Community Outreach Grant, Model I currently consumes approximately 1.5%, while a change to 100% care on Model III, which was relatively the most cost-effective model, would require an additional 0.2% of this grant.

6.3.3 Sensitivity analysis

One can visually see the Alternate Scenarios A-D in Figure 9 below. An additional US $9 303 763 is required for Alternate Scenario A, an additional US $9 886 016 for Alternate Scenario B and an additional US $23 939 660 for Alternate Scenario C, all in comparison to Model I at scale. Alternate Scenario D, uses a more modest coverage level of 57% which results in an increased budget need of only US $3 260 455 in comparison to Model I (also at 57% coverage). When using the prevalence as portrayed in the Thembisa Model one can see that the difference between the two estimates for the number of women living with HIV for reproductive ages (15-49), who had a baby in last year (2019), is relatively small at 14% (see Table 16).

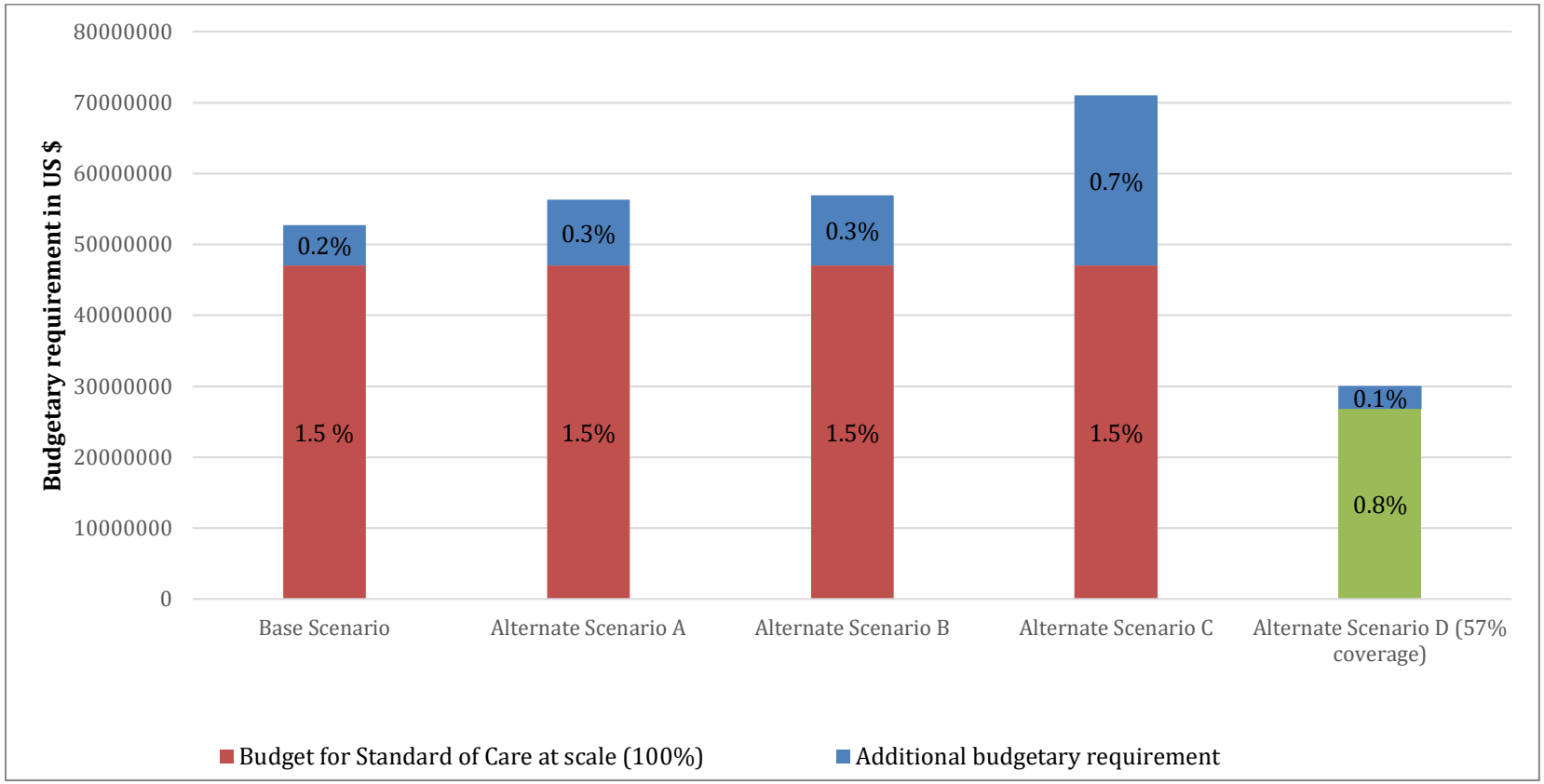

Figure 9: Budget impact for Base and Alternate Scenarios with percentage of the Healthcare Budget (2020/21) required displayed on the bars

Table 17: Budget impact and scenario analysis (all in 2019 US $)

Scenario	**Eligible population**	**Total budget at scale**	**Net budget impact (relative to Model I at scale)**	**Percentage of healthcare budget 2020/21**	**Percentage of NSP anticipated funding for HIV, TB and STIS 2020/21**	**Percentage of HIV and AIDS Component***
Standard of Care: ***Model I - Routine Care at scale - 100%***	*208 084*	*US $47 031 899*		*1.5%*	*2.2%*	*3.7%*
Base Scenario: **Model III – Community Care at scale – 100%**	208 084	US $52 751 995	US $5 720 096	0.2% (1.6%)	0.3% (2.5%)	0.5% (4.2%)
Alternate Scenario A: **Model I – 12% coverage** **Model II – 23% coverage** **Model III – 65% coverage**	208 084 Model I: 24 276 Model II: 48 553 Model III: 135 255	US $56 335 662	US $9 303 763	0.3% (1.8%)	0.4% (2.6%)	0.7% (4.5%)
Alternate Scenario B: **Equal weighting between models**	208 084 Model I: 69 361	US $56 917 915	US $9 886 016	0.3% (1.8%)	0.5% (2.7%)	0.8% (4.5%)

Model I – 33.3% coverage **Model II – 33.3% coverage** **Model III – 33.3% coverage**	Model II: 69 361 Model III: 69 361					
Alternate Scenario C: **Model II – Integrated Care at scale – 100%**	208 084	US $70 971 560	US $23 939 660	0.7% (2.2%)	1.1% (3.3%)	1.9% (5.6%)
Alternate Scenario D:	**Eligible population**	**Total budget at 57% implementation**	**Net budget impact (relative to Model I at 57% implementation)**	**Percentage of healthcare budget 2020/21**	**Percentage of NSP anticipated funding for HIV, TB and STIS 2020/21**	**Percentage of HIV and AIDS Component ***
Standard of Care: ***Model I - Routine Care at scale - 57%***	*118 608*	*US $26 808 183*		*0.8%*	*1.3%*	*2.1%*
Alternate Scenario D: **Model III – Community Care at scale – 57%**	118 608	US $30 068 637	US $3 260 455	0.1% (0.9%)	0.2% (1.4%)	0.3% (2.4%)

* HIV and AIDS Component of the 'Community Outreach Grant' 2020/21

6.4 Discussion

The annual cost of scaling up these postpartum models of care countrywide were between US $3 260 455 and US $23 939 660. One aspect mentioned in the National Strategic Plan on HIV, TB and STIs, is the need to continue care for the mother-infant pair through breastfeeding with the aim of sustaining mothers' adherence to medication and keeping mother-to-child transmission risk low (17). The hope is that through addressing adherence and retention, mother-to-child transmission can be eliminated as transmission is linked to maternal replication of the virus (180). However different models of care suited to mother-infant pairs are needed to enhance adherence and retention and achieve this aim.

Dugdale et al. 2019 (158) assessed the budget impact of implementing Model II in place of Model I using an estimated 250 000 women in need of HIV care during the postpartum phase which is similar but slightly higher (17%) than the estimate used in this BIA. The amount quoted for Model I in this BIA is almost a quarter (23%) of what was estimated (when inflated from 2016 to 2019 US $) in the Dugdale et al. study (158), and 34% of the amount estimated for Model II at scale (Alternative Scenario C) due to a much higher annual mother-infant pair cost under both models (US $550 and US $570 respectively) used in the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model utilised by Dugdale et al (158, 201). As the Dugdale et al. study (158) used the same unit cost for visits, the difference in cost can be attributed to differences in the medication, immunisation, diagnostic costs and frequency of visits.

In the 2017/8 financial year 118 608 antenatal clients were initiated on ART (115) which is 57% coverage when using the target population of 208 084. If we use this number as a proxy for mother-infant pairs currently in postpartum care as we have done in the Alternate Scenario D, then we see that the increased budget needed to change to a more cost-effective model of care only requires 0.9% of the National Healthcare Budget.

Model II - Integrated Care, was particularly successful in the MCH-ART study due to a champion professional nurse who provided services which would often be delivered by a whole team of individuals namely: the services of a midwife, specifically antenatal and postnatal care, as well as ART and HIV care and paediatric services. The implementation of Model II would need adequately trained staff who are able to deliver these services as an individual or multidisciplinary team in an integrated manor. Model III could be easily 'scaled up' for postpartum women within the Western Cape where there are already in the region of 1300 CACs and approximately a quarter of all ART patients are attended to through this community-based approach (207, 208). Women in the postpartum phase are already attending CACs as standard adult clients.

Published work by MacGregor and colleagues (209) assessing the scaling-up of CACs cautions that once adherence clubs reached the critical point where more than one meeting was provided per day (over 40 clubs) in the Western Cape, a system failure was noted which then impacted on the quality delivered by the clubs provided prior to this point. This was due to capacity and logistical reasons such as provision of large quantities of medication (209). This is a crucial finding which in part guides our

recommendation that although Model III was the most cost-effective of the three models assessed in this dissertation, we do not recommend its exclusive use.

The main limitation of this study is that we are unsure what the particular mother-infant pair preference would be nationally in terms of models of care. Therefore we suggest that a discrete choice experiment would be beneficial further research. In addition in the current climate of a pandemic (COVID-19), healthcare budgets will be under huge pressure and expansion for current services, whether cost-effective or not may not be seen as a priority and may not be affordable. Modelling efforts suggest that due to COVID-19, we may see negative effects such as an estimated 10% increase in deaths for those living with HIV in high burden settings such as South Africa, over the next five years (36). The suggestion for keeping HIV programmes impactful is by ensuring continued access to ART during this time of increased strain on health systems (36). It is important to note that these costs are most applicable to the population of women who started ART in pregnancy and may differ for those who have been stable on ART prior to conception. In this work we have not evaluated the impact of scale on unit costs as it was difficult given the scope of the work, however we recommend that future research assesses this important aspect.

In order to cater for individual's preferences we have provided Alternate Scenario analyses with varying combinations. For instance CACs have been found to be welcomed by patients for their flexibility (176). The essential message from this BIA however is that in order to have a more cost-effective model in place whether at 100% or in combination with other cost-effective models of care, there will be increased budgetary needs ranging from 12% to 51%. This BIA relates to affordability of scaling

up more cost-effective models and displacing the standard of care which should be decided by policy-makers. If an increase of 0.9-2.2% can be accommodated in the current healthcare budget then more cost-effective models can be put in place or alternatively additional funds can be raised to facilitate the inclusion of more cost-effective models of care.

Model II and III have been shown to be effective in terms of maternal retention and viral suppression (2, 4). If mother-infant pairs are retained and virally suppressed then potentially there may be upstream effects that are also mitigated, such as reduced LTFU, decreased transmission and fewer opportunistic infections. These long term savings from the implementation of cost-effective interventions for HIV, promote the increased need for spending by the South African government now (210).

The findings of this BIA, namely the evidence for scale up, are directly applicable to South Africa and could be generalised to other Sub-Saharan African settings or similar low- and middle-income settings. These models would be most beneficial and relevant to settings where there is a need for differentiated care and improved retention and viral suppression in mothers. In order to secure the necessary budget there will have to be opportunity costs in other less pressing areas of the health budget (i.e. budget cuts) or preferably an injection of funding committed by the South African Government perhaps through the minimisation of administration costs or additional funding secured through international donors. This is especially important given the goal of ending AIDS by 2030 linked to the Sustainable Development Goals (27) as well as HIV/AIDS being a key priority in South Africa (115).

6.5 Conclusions

Evidence of the amount of funding needed to scale up innovative models of care for South Africa has been provided. Tangible figures have been presented for different structures of provision and differing levels of scale up to better protect and support the postpartum phase for women living with HIV going forward. The net budget impact to introduce a more cost-effective model than the standard of care represents an increase of 0.9 - 2.2% of the national healthcare budget and 2.4 - 5.6% of the committed HIV and AIDS Component of the 'Community Outreach Grant'. Differentiated care is needed to suit different women's preferences, for instance facility based care (Models I and II) or non-facility based care (Model III) and therefore one of the alternate scenarios providing differentiated care although more expensive may be more acceptable to mothers.

The HIV burden among pregnant women is large with almost a quarter of women of reproductive age being HIV positive (23%). The potential implications of this BIA are that more cost-effective novel options for postpartum maternal and child health have been established in the Western Cape which if scaled up countrywide could have particular impact on the health the mothers of our country as well as the next generation.

7 Chapter Seven: Discussion and conclusion

This chapter brings together the contents of the four results chapters summarizing the key messages for policy makers in South Africa, Eswatini and similar settings. This chapter also highlights the unique contributions of this thesis to the literature generally. Costs in this section have been inflated to 2019 US $ using CPI for comparability (201)

7.1 Summary of thesis findings

7.1.1 Aim of the research

As described in Chapter One, the overall aim of this work was to evaluate the cost and cost-effectiveness of different models of PMTCT for women living with HIV and their infants, in order to estimate the national budget for large scale implementation, taking into consideration the change to the lifelong ART (Option B+) approach.

7.1.2 Specific objectives were

1. To compare the costs and effects of the Option B+ approach to the Option A approach to PMTCT from a provider's perspective in a cost-effectiveness analysis

2. To estimate the costs of three models of care for mother-infant pairs during the postpartum phase (at 12 months postpartum) from a provider and patient's perspective and b.) to estimate the costs of the pregnancy phase for mothers from a provider's perspective

3. To compare the costs and effects of three models of care for mother-infant pairs during the postpartum phase (12 months postpartum) from a provider and patient's perspective in a cost-effectiveness analysis

4. To estimate the budget impact of nationally scaling-up models of care for the postpartum period

We accomplished this aim and these objectives through three parent studies, SG, MCH-ART and PACER. This dissertation assessed the cost and cost-effectiveness of Option A in comparison to the Option B+ approach to PMTCT in Eswatini as well as the cost of transitioning, using a step wedge design in the SG implementation science study. The costs and cost-effectiveness of three models of care for postpartum WLH, as well as the costs of the preceding pregnancy phase, were assessed through another implementation science project MCH-ART where women were randomised into two models of care, Model I – Routine Care (mothers in general ART clinics and infants in well-baby clinics) and Model II – Integrated Care (mothers-infant pairs seen together in integrated care in the MOU (Site A)); and PACER a supplementary study to MCH-ART in the same geographical area without randomisation, but rather determined by the choice of the postpartum WLH in the study, allowing for the evaluation of an additional model of care, Model III – Community Care (mothers in CACs and infants in well-baby clinics) in comparison to Model I – Routine Care (as provided in MCH-ART).

7.1.3 Summary of chapter contents

Outlined by results Chapters Three to Six, in this dissertation we have found the following:

Chapter Three - Cost and cost-effectiveness of transitioning to universal initiation of lifelong antiretroviral therapy for all HIV-positive pregnant and breastfeeding women in Swaziland includes a paper which was published in Tropical Medicine and International Health in 2018 (117). This chapter found that universal/ lifelong ART (Option B+) can be considered cost-effective in Eswatini using the intermediate outcome of retention with an incremental cost effectiveness ratio (ICER) of US $984 per mother retained to six months postpartum (inflated to 2019 US $) in comparison to ART initiation based on CD4 cell count and WHO clinical staging (Option A). The total cost of PMTCT was US $936 724 for universal ART and US $734 027 for ART initiation based on CD4 cell count and clinical staging. Under universal ART the cost per woman treated per month was US $197 while the weighted average cost per woman treated was US $891 in 2019 US $ (201). The main cost drivers were the start-up costs, additional training provided, and staff time spent on PMTCT tasks.

Chapter Four - Provider- and patient-level costs associated with providing antiretroviral therapy during the postpartum phase to women living with HIV in South Africa: A cost comparison of three postpartum models of care includes a paper which has been accepted for publication in Tropical Medicine and International Health in 2020, which is available online ahead of print (143). When inflated to 2019 US $ (201), Routine Care (Model I) cost US $226 per mother-infant pair per annum; Integrated Care cost US $341 (Model II); and Community Care cost US $254 (Model III). Annual patient costs for Models I-III, were US $30-55, US $23-45 and US $76 per mother-infant pair respectively (in 2019 US $). Average visit frequencies were 4.5, 6.9 and 6.7 visits postpartum for Models I, II and III respectively.

From a health service perspective, the unit cost per visit during the pregnancy phase was US $12 in 2019 US $ (201), of which personnel was the biggest cost driver, accounting for 74% of the costs. Through medical record abstraction we were able to establish that there are on average three visits made during the pregnancy phase resulting in a cost per woman of US $37 from a health service perspective. If one includes the health service costs of both medication and diagnostic test costs, the average cost per woman during pregnancy was US $111 (25% medication; 41% diagnostic tests; 33% pregnancy visit cost).

Chapter Five - Cost-effectiveness analysis of three postpartum models of care for women living with HIV in Cape Town, South Africa includes a paper which has been prepared for submission later in 2020. Comparatively Community Care (Model III) was found to be the most cost-effective model with an ICER of US $97 per mother-infant pair retained and virally suppressed which was defined as HIV RNA <50 copies/mL at 12 months postpartum (in 2019 US $). The ICER falls below a revealed willingness to pay threshold of US $872 for HIV investment in South Africa indicating that Community Care (Model III) can be considered cost-effective in comparison to the other two evaluated models of care (193).

Chapter Six: Scaling-up postpartum models of care for mother-infant pairs in South Africa: A budget impact analysis includes a paper which has been prepared for submission later in 2020. Scaling-up Community Care (Model III) nationally in South Africa to 100% coverage would require US $5 720 096 more than Routine Care (Model I) at scale, which would comprise 0.2% of the total health budget for 2020/21 or an

additional 0.5% of the HIV and AIDS Component of the HIV, TB, Malaria and Community Outreach Grant for 2020/21. Using a scenario analyses, Alternate Scenario A, where Routine Care (Model I) is at a coverage of 12%, Integrated Care (Model II) is 23%, and Community Care (Model III) is at 65% coverage, an additional US $9 303 763 (in comparison to Routine Care only, at scale (100% coverage)) is required. Alternate Scenario B demonstrated that if an equal weighting between the three models of care is used (i.e. 33.3% of the target population is covered under each) then an additional US $9 886 016 is required (in comparison to Routine Care only, at scale (100% coverage)).

7.2 Generalisability

Broadly speaking the results of this dissertation will be useful for informing HIV budget formation and planning the prioritisation of model implementation in South Africa, Eswatini and similar LMIC settings especially in Sub-Saharan Africa. In Chapter Three, the data was collected specifically in the context of Eswatini transitioning from the Option A approach to lifelong ART (Option B+), which may limit the generalisability of the results due to the small size of Swaziland as a country, the high level of donor partnerships in health and the MoH's strong participation in healthcare programmes. To aid generalisability we have presented average unit costs, have included a mix of urban and rural facilities of differing sizes and have presented economic costs including volunteered time and donated goods. In settings such as South Africa, where there was no empirical evidence regarding cost-effectiveness of Option B+, this study may have helped inform decision making for expanding lifelong ART (Option B+) countrywide, which has been the recommendation since 2015, and may assist as universal ART becomes the standard of care for PLWHA. It may also serve neighbouring countries with

similar settings, where costs for PMTCT programmes are lacking and will provide a reliable comparison for LMICs when countries assess the costs of lifelong ART starting in pregnancy in literature.

The study findings from Chapters Four to Six are generalisable to the rest of South Africa as well as other LMIC settings with similarities to South Africa in particular landlocked Eswatini. However, it should be noted that for this study the setting was peri-urban with well-established and numerous CACs. There may be factors which could have impacted the findings, such urbanicity of placement of clinics and CACs, and champion healthcare workers, which make this work hard to generalise to rural areas or settings with staff that are less trained or motivated. However with these factors in mind one could utilise these costs to inform budgetary processes and planning for HIV in particular for PMTCT programmes.

This dissertation generated evidence that is directly applicable to South Africa, regarding the affordable scale up of models of care which could be generalised to other Sub-Saharan African settings or similar LMIC settings. These models would be most beneficial and relevant to settings where there is a need for differentiated care and improved retention and viral suppression in mothers.

7.3 Limitations

There are several study limitations within this dissertation. As is always a concern, there may have been a Hawthorne effect, where personnel observed and involved in discussion may behaved differently due to the nature of being involved in a study, which may impact on both the costs and the effectiveness of the interventions, either

positively or negatively. In order to minimise this, the researcher observed over several sessions, and verified information with the facility managers, other staff and research staff. Another limitation is that the costs and effectiveness were not estimated over a period of more than 18 months and so the long-term cost-effectiveness has not been established in this work. We opted not to model longer than the duration of retention in care, nor did we make use of a multidimensional outcome measure (QALY or DALY) in the cost-effectiveness analyses. The rationale being that the focus was on empirical data collection and analysis of this data, which is where a substantial data gap was identified in the literature. The use of natural units does of course limit comparability with other studies, but are useful as they express important measures of HIV care in the treatment cascade, specifically retention in care.

In SG, there were some challenges in tracing infants which meant that MTCT (measured through a positive infant PCR result) was not included as an effectiveness measure or in the cost-effectiveness outcome. CACs are intended only for women who are already stable on ART, however Routine and Integrated Care (Models I and II) do not have this limiting factor.

It is important to note that these costs are most applicable to the population of women who started ART in pregnancy and may differ for those who have been stable on ART prior to conception. Another limitation is that the cost of care may vary from clinic to clinic, though our samples are small (but relatively normal for costing work) it is representative of different sized facilities and we present average unit costs which should mitigate this concern.

One of main limitations of the BIA is that we are unsure what the particular mother-infant pair preference would be nationally in terms of models of care or what the capacity would be for hosting multiple models of care in different provinces. In addition COVID-19 is placing healthcare budgets under huge pressure and expansion for current services, whether cost-effective or not may not be seen as a priority and may not be affordable.

7.4 Summary of thesis contributions

The findings of this dissertation have the following implications. During the Safe Generations study, the Eswatini MoH made the decision to implement lifelong ART in PMTCT programmes nationwide based on interim results and discussion with research staff. Costs from this work on lifelong/ universal ART could also be used for budgeting and planning for decision makers in Eswatini and similar settings. In Uganda the change to Option B+ for mother-infant pairs (when inflated to 2019 US $) cost US $239 per annum with ART for mothers being the biggest cost driver at 63% of the cost (54, 201). Similarly, in Ethiopia the cost of ART for PMTCT for mother-infant pairs comprised the largest proportion of the annual cost. The range of unit cost per mother-infant pairs per year was US $355-1 224 (when inflated to 2019 US $) (55, 201). Although this dissertation did not find ART to be the biggest cost driver, the overall annual costs for the studies in Uganda and Ethiopia were similar to our findings.

Community care (Model III), which involved postpartum care for mothers at CACs and infants at well-baby clinics, was found to be the most cost-effective model of care

relative to the other models assessed, whether costs were utilised from a provider's perspective or patient and providers' perspective. However, we recommend that a mixture of the three models of care would be most ideal, given the needs and expectations of the mother-infant pairs (211). Published work by MacGregor and colleagues (209) assessing the scaling-up of CACs cautions that once adherence clubs reached the critical point where more than one meeting was provided per day (over 40 clubs) in the Western Cape, a system failure was noted which then impacted on the quality delivered by the clubs provided prior to this point. This was due to capacity and logistical reasons such as provision of large quantities of medication (209). This is a crucial finding which in part guided our recommendation that although Model III was the most cost-effective of the three models assessed in this dissertation, we do not recommend its exclusive use.

In a systematic review investigating the literature on the cost-effectiveness of preventative interventions in Sub-Saharan Africa, PMTCT had the lowest median cost-effectiveness rations of US $1 144 per HIV infection averted and US $191 per DALY averted. This provides evidence that most PMTCT interventions that have been assessed are cost-effective in the African setting (42). Although we have not used a multidimensional outcome unit such DALYs averted, our findings that Option B+ and Community Care are cost-effective are in line with current literature which showed these interventions to be cost-effective.

The HIV burden among pregnant women in South Africa is large with almost a quarter of women of reproductive age being HIV positive (23%). The potential implications of this dissertation are that more cost-effective novel options for postpartum maternal and

child health have been established in the Western Cape which if scaled up countrywide could have particular impact on the health of the mothers of our country as well as the next generation.

It has been made evident in this work that innovative models of care may be affordable in the South African context as decided by budgeters and policy makers. Evidence of the amount of funding needed to scale up these models has been provided. Tangible figures have been presented for different structures of provision and differing levels of scale up to better protect and support the postpartum phase for women living with HIV going forward. The data generated in this study can be used for informed decision making in South Africa, Eswatini as well as other similar LMIC settings.

7.5 Key messages for policy makers:

- Lifelong ART was found to be cost-effective in the Eswatini setting with an ICER of US $984 (2019 US $) for every additional mother retained in care through six months postpartum

- Community Care, provided through community adherence clubs was found to be cost-effective in the South African setting, with an ICER of US $97 per mother-infant pair retained and virally suppressed which was defined as HIV RNA <50 copies/mL at 12 months postpartum (in 2019 US $), below the revealed willingness to pay threshold of US $872 for HIV investment in South Africa

- The financial requirement to implemented Community Care at scale (100% coverage) may be considered affordable depending on the decisions made by budgeters and decision-makers, entailing US $5 720 096 more than Routine Care at scale, which would comprise 0.2% of the total health budget for 2020/21 or an additional 0.5% of the HIV and AIDS Component of the HIV, TB, Malaria and Community Outreach Grant for 2020/21. However we recommend the utilisation of one of our scenario analyses as a combination of care is strongly suggested to cater for mother-infant pair preferences and needs

- Implementation science studies (such as Safe Generations) are able to assess changes as they happen, allowing for careful evaluation and involvement of stakeholders such as MoH and Departments of Health

- Now in the era of universal ART, a mix of care in the postpartum period may be more acceptable for mother-infant pairs, and be more apt and feasible for sustainable management, not overloading the healthcare system or the exceeding capacity of models of care

7.6 Future directions

As donors continue to withdraw funding generally and from HIV/AIDS in particular, it becomes even more crucial that HIV programmes are well and efficiently run, with thought as to what patients need from models of care (185). Differentiated care should take into consideration the context such as urbanicity and HIV burden; the specific population in need for example postpartum WLH; and clinical characteristics namely

are the individuals stable or unstable on their ART which can inform the level of healthcare provider involvement in their care (68). The findings of this dissertation have provided evidence for three models of care in a high HIV burden peri-urban context for postpartum WLH who are both stable and unstable on treatment as well as providing several different combinations for how these models could be scaled-up in South Africa. However, to establish the preferences of the mother-infant pairs in terms of the model of care that best suits their needs a discrete choice experiment would be beneficial further research. Additional work on quality of care of scaled-up models of care will be needed particularly to assess if further investment and resources are required to prevent capacity being surpassed leading to system failure. Also understanding the differential pattern of service needs or preferences across different regions and areas should be added to the future research agenda.

Models of care which improve access and adherence of ART allow for better outcomes, but in turn changes the focus to providing more support for non-communicable diseases which are more prominent as people live longer (185). This points to further integration of programmes for instance of postpartum HIV care with non-communicable diseases such as through CACs. Hence in the South African setting additional work is needed to tailor new models of care that integrate HIV and non-communicable diseases. And broadly further research is required to assess ways of retaining mothers in care, ensuring adherence, and reaching the goal of eliminating paediatric HIV is necessary in the southern African context.

In terms of strengthening the health system work should be done to ensure that medical file numbers and other linkages are maintained, so that infants are not lost to follow up,

which would also assist future studies. The assessment of the economic impact of loss to follow up would be of interest going forward. As HIV regimens and models change, updated estimates of cost and cost-effectiveness will be needed. And in terms of HIV prevention for pregnant women, as encouraging work emerges on the safety of pre-exposure prophylaxis (PrEP) for women during pregnancy and postpartum while breastfeeding (212, 213) more research will be needed to assess the acceptability, affordability, outcomes and ability of the health system to provide PrEP for this vulnerable portion of the population (212, 213).

7.7 Conclusion

The findings from this dissertation are particularly notable for policy going forward as they could allow for a mix of postpartum models of care as part of universal/ lifelong ART, that are cost-effective, acceptable to mother-infant pairs, provide highly effective care in terms of retention and viral suppression, and have known costs for planning and budgeting purposes.

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9 Appendices

9.1 Appendix 1: Supplemental information linked to Chapter Three

Supplementary appendix from Cost and cost-effectiveness of transitioning to universal initiation of lifelong antiretroviral therapy for all HIV-positive pregnant and breastfeeding women in Swaziland

A secondary aim of this research is to estimate the cost of transitioning to Option B+ from Option A in Swaziland, as is described below.

9.1.1 Additional methodological details

Swaziland is a LMIC, with a population of 1.2 million and an HIV prevalence of 31% (for individuals aged between 18 and 49 years) (214). Globally, it has the most severe countrywide HIV epidemic (215).

The transition from Option A to B+ under SG resulted in a more than two-fold increase in the number of women initiating ART and a decrease in median days from first ANC visit to ART initiation of 40 to 0 days. An advantage of the study design was that study staff did not alter clinical care, providing a true snapshot of services and health worker time unlike many other economic evaluations relying on studies where participants are enrolled and studied. Very few of the retained infants tested PCR positive and reported rates of early transmission are reported in Swaziland (5).

9.1.2 Patient management process

9.1.2.1 Option A

Pregnant women, under Option A, who received positive rapid HIV test results, in the antenatal care departments of the clinics, were given a series of tests (CD4, haemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine) during their first antenatal visit. These women were differentiated by CD4 count into receiving either lifelong ART (TDF+3TC+EFV) if their CD4 count was below 350 cells/µl or prophylactic AZT. Women spent time with providers during consultations, going through adherence training and education, and receiving medication.

9.1.2.2 Option B+

Pregnant women, under Option B+, in the antenatal care departments of the clinics, were given the same series of tests (CD4, haemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine) during their first antenatal visit if their rapid HIV test was positive. These women started lifelong ART (TDF+3TC+EFV) on the same day as HIV testing occurred. A desktop flipchart, aided the staff when educating the patients about how to take their medication correctly. As with women under Option A, under Option B+ women spent time with a variety of providers during consultations, going through adherence training and education, and
having medication dispensed to them.

9.1.3 Study design

The economic costs include capital as well as recurrent costs such as the time of the study staff involved in training, mentoring and facilitating clinical work. The costing uses real world costs (except for diagnostic tests (CD4, point of care PIMA CD4, haemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine and rapid HIV tests) which are costed per guideline) and estimates the costs incurred.

All costs were estimated using bottom-up methods, except the category of overheads, which was estimated using top-down methods (165). Above service level costs (such as running costs within the MoH, NGO and FBO, information technology and human resources support) were excluded.

The prices of performing diagnostic tests were obtained from the National Health Laboratory Services South Africa rather than from Swaziland, as only the actual test prices were available in Swaziland, and not the cost of performing the tests (for instance the inclusion of personnel time, equipment use, running and building costs). Further work is needed in Swaziland to cost the diagnostic tests performed at the Swaziland Health Laboratory Service. Using South African prices is a limitation given the two countries' differing GDPs and the percentage allocated to healthcare expenditure. Additionally, the higher numbers of individuals seeking care in South Africa means that economies of scale come into play.

The five purposively chosen clinics were a mix of three urban and two rural sites, variably sized ranging from total clinic headcount of ~3,800-48,000 per year and had different funding structures: three MoH, a NGO and a FBO (see Supplementary Table 1).

9.1.3.1 Recurrent costs

The overhead costs of running the clinics include use of electricity, water, sewage, cleaning, laundry, security, phone, internet and stationery (subscriptions, photocopying and printing, packaging if any). In addition, maintenance costs of the buildings and equipment were included at an annual rate of 7% of the total cost (216).

9.1.3.2 Cost allocation

The capital items were apportioned to PMTCT services using the percentage of the PMTCT visits out of total clinic visits in a year, as were the recurrent components of overheads and personnel at the clinics who were not directly involved in PMTCT services. Initial training on PMTCT under Option A, start-up costs under Option B+, medication and diagnostics costs were directly allocated to the PMTCT services. Staff involved in providing PMTCT services filled out timesheets to provide a sample of the usual tasks performed in one week during the three study visits (to minimise recall bias). This was done together with a health economist to assess distribution of time for the various PMTCT and non-PMTCT tasks. Salary costs were then allocated using the ratio of the time spent on different PMTCT activities divided by the total time spent working in the week.

9.1.3.3 Transitioning costs

The transitioning costs involved in moving from the Option A to Option B+ approach were estimated by incorporating the additional costs of the resources needed to implement the Option B+ approach. These costs are presented separately, but incorporate elements of the start-up costs of Option B+. These costs include more staff being involved in services (SG nurse site coordinator, data clerk, adherence and psychosocial counselling officer), the toolkit (mentioned above under start-up costs), training and additional equipment (a new filing cabinet and adult weighing scale for each clinic).

The annualised cost of transitioning from Option A to Option B+ including additional human resources, equipment, training related to the study, toolkit development and reproduction as well as Option B+ training was US $21 425. The main cost related to staff time (92%), with the toolkit (4%), study specific training (2%) and Option B+ training (2%) making up the remainder of the cost.

Supplementary Table 1: Description of selected clinics by characteristics of rural or urban placement, region, total clinic headcount and funding

Clinic	Rural/ urban placement, region	Total clinic headcount 2013	Total clinic headcount 2014	Funding
Clinic 1	Urban/semi-urban in Manzini Matshapa corridor	47988	39319	Government supported
Clinic 2	Urban/semi-urban in Manzini Matshapa corridor	3926	3864	Non-governmental organization supported
Clinic 3	Urban/semi-urban in Manzini Matshapa corridor	10823	11511	Faith based organization
Clinic 4	Rural clinic, South-west of Manzini	37208	34081	Government supported
Clinic 5	Rural clinic, South-west of Manzini	4543	4601	Government supported

Supplementary Table 2: Medication and diagnostic tests for Option A and Option B+ as costing in Swaziland

	Treatment (eligible if CD4 count below or equal to 350 cells/µl)	Prophylaxis (ineligible if CD4 count above 350 cells/µl)	Diagnostic tests
Antepartum Option A	Lifelong ART (TDF+3TC+EFV) and CTX	Zidovudine (AZT) and CTX	CD4, Haemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine and rapid HIV test
Postpartum Option A			CD4
Antepartum Option B+	Lifelong ART (TDF+3TC+EFV) and CTX regardless of CD4 count		CD4, Haemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine and rapid HIV test
Postpartum Option B+			CD4

9.2 Appendix 2: Supplemental information linked to Chapter Four

Supplemental appendix from 'Provider- and patient-level costs associated with providing antiretroviral therapy during the postpartum phase to women living with HIV in South Africa: A cost comparison of three postpartum models of care'

9.2.1 Parent studies

The MCH-ART study was a multiphase longitudinal cohort study where women were enrolled within Site A in order to evaluate a novel platform of integrated postpartum care in South Africa (2). For the observational component women were enrolled when they booked for antenatal care, prior to ART initiation (eligible for ART), and were followed through until shortly after delivery of their infants. Those women who continued to breastfeed when seen within a month of delivery, were enrolled into a randomised trial of two different ART delivery models.

The current standard of care was compared to the MCH-ART intervention of integrating concurrent and co-located maternal ART and paediatric care into the MCH clinic through the end of breastfeeding. The MCH-ART intervention increased the primary endpoint of combined maternal retention and virologic suppression (HIV RNA <50 copies/mL) at 12 months postpartum and extended breastfeeding duration (2).

In Phase 1, approximately 1600 women who were infected with HIV, seeking antenatal care were part of a cross-sectional evaluation. During Phase 2 approximately 600 women from Phase 1, who were eligible for ART initiation, were studied from their second antenatal clinic visit until their first postpartum clinic visit.

In Phase 3, approximately 440 postpartum breastfeeding WLH were randomised into receiving ART in two different ways, either in Model I or II. Model I entailed referral to their nearest general adult ART services between 4-8 weeks postpartum and infants to their local well-baby clinic for early infant diagnosis (using (PCR testing) as well as nevirapine refills, immunisations and other services. Model II entails continued ART receipt and care for mothers in the antenatal clinic, where mothers were only referred to general adult ART services at the end of breastfeeding and once the final infant HIV status was determined. The infants in Model II also continued to receive the same care they would in the well-baby clinic (such as early infant diagnosis (using PCR testing) as well as nevirapine refills, immunisations and other services) in Site A. The medications used as well as the routine monitoring was standard for Model I and II.

The third postpartum model of care, Model III – Community Care, was assessed under the PACER study. There is a concern that patients spend large amounts of time waiting in the clinic in order to receive medication (217). CACs were designed to unload the clinic as well as provide care to people living with HIV/AIDS (PLWHA), which is less time intensive for patients. CAC members attend counselling in a group of peers (15-30 individuals) facilitated by a community healthcare worker and collect medication (which is pre-packed) every eight weeks outside of the clinic setting (218). They are assessed annually by a nurse and can be referred back to the clinic if necessary. The outcomes of the CACs have been assessed in terms of loss to follow-up and have been found to show a reduced loss to follow-up rate in comparison to the community health centre (169). For PLWHA, such as mothers in the PACER study, medication is just one aspect of their lives, and by reducing the need to access clinics as frequently, individuals are able to focus on other areas of their lives.

9.3 Appendix 3: UCT PhD Ethical approval and renewal (HREC 461/2016)

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

21 July 2016

HREC REF: 461/2016

A/Prof E Sinanovic
Division of Health Economic Unit
School of Public Health & Family Medicine
FHS

Dear A/Prof Sinanovic

PROJECT TITLE: ECONOMIC EVALUATION OF MODELS OF PMTCT INTERVENTION FOR LARGE SCALE IMPLEMENTATION (PhD-candidate-L Cunnama)

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

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

Approval is granted for one year until the 30 July 2017.

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/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Lucy Cunnama 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 note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

pp T.J.Burgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.8.2018
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	10/8/2017

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	26/07/2017		
HREC REF Number	461/2016	Current Ethics Approval was granted until	30 July 2017
Protocol title	Economic evaluation of models of PMTCT intervention for large scale implementation		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	✓☐ Yes ☐ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.	418/2013 451/2012 775/2014		
Principal Investigator	Assoc. Prof. Edina Sinanovic		
Department / Office Internal Mail Address	Division of Health Economics, School of Public Health and Family Medicine		

9.4 Appendix 4: Safe Generations Ethical approval

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

25 July 2013

HREC REF: 418/2013

A/Prof L Myer
Public Health & Family Medicine

Dear A/Prof Myer

PROJECT TITLE: SITUKULWANE LESIPHEPHILE-SAFE GENERATIONS: IMPROVING APPROACHES TO ANTIRETROVIRAL THERAPY FOR HIV-POSITIVE PREGNANT WOMEN

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.

Approval is granted for one year till the 30th July 2014

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)

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely

pp TuBurgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
03 JUL 2015
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001697; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.7.2016
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	3/7/15

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	19 June 2015		
HREC REF Number	418/2013	Current Ethics Approval was granted until	
Protocol title	SITUKULWANE LESIPHEPHILE-SAFE GENERATIONS: Improving Approaches to Antiretroviral Therapy for HIV-Positive Pregnant Women		
Protocol number (if applicable)	N/A		
Are there any sub-studies linked to this study?	☐ Yes x No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study			
Principal Investigator	Professor Landon Myer		
Department / Office Internal Mail Address	CIDER SPH &FM		

1.1 Does this protocol receive US Federal funding?	x Yes	☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	x No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget	☐ Yes	x No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

July 22, 2013

COLUMBIA UNIVERSITY MEDICAL CENTER

Institutional Review Board
(CU IRB)
722 W. 168th Street, 4th floor
New York, NY 10032
212.305.5883 Tel
212.305.1316 Fax

www.cumc.columbia.edu/dept/irb

Elaine Abrams
ICP ICAP - 823100X
Mailman School of Public Health/ICAP
722 West 168th Street
MSPH

Protocol Number: IRB-AAAL0661
Title: Situkulwane Lesiphephile-Safe Generations: Improving Approaches to Antiretroviral Therapy for HIV-Positive Pregnant Women
Approval Date: 07/10/2013
Expiration Date: 04/24/2014

Grant #: AID-OAA-A-12-00020

Dear Dr. Abrams,

On July 10, 2013, a modification to the above-mentioned protocol was reviewed and approved under an expedited review procedure by the Chair or Designee of Columbia University Medical Center Institutional Review Board (IRB) Exp. You may now implement the following.

Modification:
- Addition of the MOH waiver of consent letter dated June 11, 2013
- Revised Protocol version 3.0 dated 6/25/2013
- Locator form and questionnaires updated to correctly reflect the names of the study sites.
- Decrease of interviews from 3 to 2.
- Interviews to now occur at 1 month after women initiate PMTCT services and at approximately 3-6 months postpartum.
- Revised PP PMTCT Client Acceptability Questionnaire- updated 14May2013; attached 7/1/2013
- Revised PCR Consent Form_6.25.2013; attached 7/1/2013
- Revised HCW Consent Form, 06.25.2013; attached 6/25/2013
- Revised PMTCT Client Accept Consent, 06.25.2013; attached 6/26/2013
- Revised SG Locator Form, 05.14.2013; attached 6/25/2013
- Revised HCW Accept. F/U Questionnaire, 05.14.2013; attached 6/25/2013
- Revised HCW Baseline Questionnaire, 05.14.2013; attached 6/25/2013
- Revised ANC PMTCT Client Accept. Questionnaire, 05.14.2013; attached 6/25/2013

Reminders:
- Please be reminded that approval from University of Cape Town Ethics committee must be obtained and submitted to the CUMC IRB prior to the initiation of procedures at that site. Please include documentation of University of Cape Town Ethics Committee approval with your next submission to the IRB.
- Please archive/remove the obsolete/inactive documents associated with your project when preparing your next submission to the IRB. If you need assistance removing the documents please contact the RASCAL help team at (212) 851.0213

During the approval period, all subjects enrolled not only must provide voluntary informed consent to participate in the study, but also must sign a copy of the appropriate stamped consent document(s). A copy of the consent document(s) must be given to the subjects for their record.

The requirement to obtain informed consent from the subjects will be waived by the IRB in accordance with 45 C.F.R. § 46.116(d) for the PMTCT Options Evaluation.

The following study-related materials were approved:
- Protocol version 3.0 dated June 25, 2013, attached 06/26/2013
- MOH Waiver of Consent Letter, attached 06/25/2013
- SG Locator Form, 05.14.2013, clean, attached 06/25/2013
- Consent Form PCR Consent Form, 06.25.2013, clean, attached 06/26/2013

Telegrams:
Telex:
Telephone: (1268 404 2431)
Fax: (1268 404 2092

MINISTRY OF HEALTH
P.O. BOX 5
MBABANE
SWAZILAND

THE KINGDOM OF SWAZILAND

FROM: The Chairman
Scientific and Ethics Committee
Ministry of Health
P. O. Box 5
Mbabane

RECEIVED
11 JUN 2013

TO: Ms. Elaine Abrams
PI Safe Generations
ICAP Columbia University

DATE: 10th June 2013

REF: MH/599C/FWA 000 15267

RE: Situkulwane Lesiphephile – Safe Generations: Improving Approaches to Antiretroviral Therapy for HIV – Positive Pregnant Women version 2.0 dated 18th March 2013

The committee thanks you for your submission on a request by the CUMC IRB to this research protocol, which had been approved by the SEC on December 2012.
The Committee also notes that a waiver of consent was submitted in the original version of the protocol, and approved by the Swaziland SEC. The full details of this waiver are found on pages 28 and 52 of the above mentioned protocol.
May it be noted that the Swaziland SEC is the final point of approval for a study that will be conducted in Swaziland and therefore included the waiver approval in the original letter.
The committee further requests that you add the SEC Secretariat as a point of contact if there are any questions about the study on 24047712/24045469.
The committee wishes you the best and is eagerly awaiting findings of the study to inform proper planning and programming to use for analysis

DIRECTOR OF HEALTH SERVICES
MINISTRY OF HEALTH
10 JUN 2013
P.O. BOX 5, MBABANE
SWAZILAND

Yours Sincerely,

Dr S.M.Zwane
DIRECTOR OF HEALTH SERVICES
(THE CHAIRMAN)
cc: SEC members

9.5 Appendix 5: MCH-ART Ethical approval (renewal)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
6 OCT 2015
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.10.2016
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	7/10/2015

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	23 SEP 2015		
HREC REF Number	451/2012	Current Ethics Approval was granted until	30 OCT 2014
Protocol title	Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study		
Protocol number (if applicable)	N/A		
Are there any sub-studies linked to this study?	✓ YES		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.	**HREC REF 194/2013** Estimation of delivery dates using obstetric ultrasound in the MCH-ART study **HREC REF 550/2015** Childbearing, family planning and relationships among women living with HIV in Gugulethu, Cape Town.		
Principal Investigator	Prof Landon Myer		
Department / Office Internal Mail Address	CIDER, School of Public Health and Family Medicine, Faculty of Health Sciences		

1.1 Does this protocol receive US Federal funding?	✓ Yes	☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	✓ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857: fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: RP 167/2012
ENQUIRIES: Ms Charlene Roderick

School of Public Health & Family Medicine
University of Cape Town
Faculty of Health Sciences
Falmouth Building
Anzio Road
Observatory

For attention: **Prof Landon Myer**

Re: Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

Gugulethu CHC	**Dr Katy Murie**	**Contact No. 021- 633 0020**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR NT Naledi
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 20/5/2013
CC **MS P OLCKERS** **DIRECTOR: KLIPFONTEIN / MITCHELLS PLAIN**

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857; fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_2016RP16_842
ENQUIRIES: Ms Charlene Roderick

University of Cape Town

Anzio Road

Observatory

7705

For attention: Prof Landon Myer, Ms Tammy Phillips

Re: Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study (current provincial approval RP 167/2012).

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact following people to assist you with any further enquiries in accessing the following sites:

Gugulethu CHC	**Lunga Makamba**	**021 633 0020**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.

2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of

CITY OF CAPE TOWN
ISIXEKO SASEKAPA
STAD KAAPSTAD

CITY HEALTH

Dr Hélène Visser
Manager: Specialised Health

T: 021 400 3981 F: 021 421 4894 M: 083 298 8718
E: Helene.Visser@capetown.gov.za

2015-11-04

Re: Research Request: Strategies to optimize anti-retroviral therapy services for maternal and child health: the MCH-ART study. (6560) (ID No: 10524)

Dear Dr van de Venter,

Your research has been approved for access to records at the following facilities as per your request, except for Khayelitsha Site B and Crossroads 2 which are under MDHS authority so please approach WCG for approval for those sites. **NB** Kasselsvlei and Nolungile are combined facilities with MDHS so approval is needed from WCG as well as CCT. Hanover Park and Heideveld permission is given for the clinics; the CHCs are under MDHS so please ensure you have approval for the right facilities. Also to note Phumlani is in Mitchells Plain.

Northern Sub District: Contact people	**Wallacedene Clinic** Dr A Zimba (Sub District Manager) Tel/Cell: (021) 980-1230 / 084 627 2425 Mrs J Coetzee (Head: PHC & Programmes) Tel/Cell: (021) 980-1211
Mitchells Plain Sub District: Contact People	**Crossroads1, Mzamomhle and Weltevreden Valley, Phumlani Clinics** Mrs S Elloker (Sub District Manager) Tel: (021) 391-5012/ 084 222 1478 Mrs N Nqana (Head: PHC & Programmes) Tel: (021) 391-0175/ 084 2221489
Southern Sub District: Contact People	**Retreat Clinic** Dr M Osman (Sub District Manager) Tel: (021) 444-3258/ 083 556 9838 Mrs K Shuping (Head: PHC & Programmes) Tel: (021) 444-3260 / 082 728 4531
Klipfontein Sub District: Contact People	**Hanover Park, Heideveld, Masincedane and Vuyani Clinics** Mr K Nkoko (Sub District Manager) Tel: (021) 630-1667/ 082 433 1332 Mrs T Nojaholo (Head: PHC & Programmes) Tel: (021) 630-1626/ 084 220 0133
Khayelitsha Sub District: Contact People	**Kuyasa, Luvuyo, Nolungile, Matthew Goniwe and Town Two Clinics** Dr V de Azevedo (Sub District Manager) Tel: (021) 360-1258/ 083 629 3344 Mrs S Patel Abrahams (Head: PHC & Programmes) Tel: (021) 360-1153/ 084 405 6065

9.6 Appendix 6: PACER Ethical approval (renewal)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30 JAN 2017
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	22/12/2015

Comments to PI from the HREC	HUMAN RESEARCH ETHICS COMMITTEE 22 DEC 2015 HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	14 Dec 2015		
HREC REF Number	775/2014	Current Ethics Approval was granted until	30 January 2016
Protocol title	Postpartum Adherence Clubs to Enhance Support: the PACER study		
Protocol number (if applicable)	N/A		
Are there any sub-studies linked to this study?	☐ Yes		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.	This study is linked to REC REF 451/2012 Strategies to optimize antiretroviral therapy services for maternal & child health: the MCH-ART study		
Principal Investigator	Prof Landon Myer		
Department / Office Internal Mail Address	Center for Infectious Disease Epidemiology and Research (CIDER),School of Public Health and Family Medicine ,Faculty of Health Sciences. Landon.myer@uct.ac.za		

1.1 Does this protocol receive US Federal funding?	✓ Yes	☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	✓ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	✓ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

9.7 Appendix 7: MCH-ART Time Sheet Tools

MCH-ART: Time motion tool version 2.0
08 May 2015

Weekly Timesheet: MCH-ART Study – MOU Antenatal and Focused care
Name of clinic: _____
Position/post: _____
Date: _____
Shift (times) _____

Please estimate the time spent on each activity for a standard week (average time spent on a task).

	Consulting with antenatal mothers	Consulting with postnatal mothers	Adherence training and educating antenatal mothers	Adherence training and educating postnatal mothers	Dispensing medication to antenatal mothers	Dispensing medication to postnatal mothers	Record keeping and administration for antenatal mothers (e.g. filling forms)	Record keeping and administration for postnatal mothers (e.g. filling forms)	Management of services for antenatal mothers (e.g. meetings at the District level)	Management of services for postnatal mothers (e.g. meetings at the District level)	Other activities NOT related to antenatal or postnatal mothers	Breaks (e.g. tea and lunch)
Monday 8:00 – 16:00												
Tuesday 8:00 – 16:00												
Wednesday 8:00 – 16:00												
Thursday 8:00 – 16:00												
Friday 8:00 – 16:00												

Weekly Timesheet: MCH-ART Study – General ART

Name of clinic: _____
Position/post: _____
Date: _____
Shift (times) _____

Please estimate the time spent on each activity for a standard week (average time spent on a task).

	Consulting with postpartum mothers	**Adherence training and educating postpartum mothers**	**Dispensing medication to postpartum mothers**	**Record keeping and administration for postpartum mothers (e.g. filling forms)**	**Management of services for postpartum mothers (e.g. meetings at the District level)**	**Other activities NOT related to postpartum mothers**	**Breaks (e.g. tea and lunch)**
Monday 8:00 – 16:00							
Tuesday 8:00 – 16:00							
Wednesday 8:00 – 16:00							
Thursday 8:00 – 16:00							
Friday 8:00 – 16:00							

Weekly Timesheet: MCH-ART Study – Infants

Name of clinic: _____
Position/post: _____
Date: _____
Shift (times) _____

Please estimate the time spent on each activity for a standard week (average time spent on a task).

	Consulting with mother about HIV exposed infant, infant check up etc.	Consulting with mother about HIV unexposed infant, infant check up etc.	Adherence training and educating HIV exposed infant's mother	Adherence training and educating HIV unexposed infant's mother	Dispensing medication for HIV exposed infant	Dispensing medication for HIV unexposed infant	Record keeping and administration for HIV exposed infant (e.g. filling forms)	Record keeping and administration for HIV unexposed infant (e.g. filling forms)	Management of services for HIV exposed infant (e.g. meetings at the District level)	Management of services for HIV exposed infant (e.g. meetings at the District level)	Other activities NOT related to HIV exposed or unexposed infants	Breaks (e.g. tea and lunch)
Monday 8:00 – 16:00												
Tuesday 8:00 – 16:00												
Wednesday 8:00 – 16:00												
Thursday 8:00 – 16:00												
Friday 8:00 – 16:00												

9.8 Appendix 8: MCH-ART Time Motion Tool

MCH-ART: Time motion tool version 2.0
08 May 2015

MCH-ART: TIME MOTION TOOL	
Facility:	MOU/Hannan Crusaid/NY1/ Other: ____________
Fieldworker initials:	____________ (e.g. LS)
Date:	___/___/_____ (DD/MM/YYYY)
Patient folder number:	____________
Time of arrival at facility:	____________ (e.g. 06:22)
Time folder drawn:	____________ (e.g. 08:22)
Time of exiting facility:	____________ (e.g. 08:37)

MCH-ART: TIME MOTION TOOL	
Facility:	MOU/Hannan Crusaid/NY1/ Other: ____________
Fieldworker initials:	____________ (e.g. LS)
Date:	___/___/_____ (DD/MM/YYYY)
Patient folder number:	____________
Time of arrival at facility:	____________ (e.g. 06:22)
Time folder drawn:	____________ (e.g. 08:22)
Time of exiting facility:	____________ (e.g. 08:37)

MCH-ART: TIME MOTION TOOL	
Facility:	MOU/Hannan Crusaid/NY1/ Other: ____________
Fieldworker initials:	____________ (e.g. LS)
Date:	___/___/_____ (DD/MM/YYYY)
Patient folder number:	____________
Time of arrival at facility:	____________ (e.g. 06:22)
Time folder drawn:	____________ (e.g. 08:22)
Time of exiting facility:	____________ (e.g. 08:37)

MCH-ART: TIME MOTION TOOL	
Facility:	MOU/Hannan Crusaid/NY1/ Other: ____________
Fieldworker initials:	____________ (e.g. LS)
Date:	___/___/_____ (DD/MM/YYYY)
Patient folder number:	____________
Time of arrival at facility:	____________ (e.g. 06:22)
Time folder drawn:	____________ (e.g. 08:22)
Time of exiting facility:	____________ (e.g. 08:37)

9.9 Appendix 9: Example of MCH-ART Demographics & Medical History Interview

MCH-ART: Demographics & Medical History, Phase 3 12mo pp PID: 3 - __ __ __ __ - __ __
Xhosa-English Version 3.3, 29 September2013

		Visit Date: __ __/__ __ __/__ __ __ __	
Sokubeleka sicela ukujonga ukuba zisemi ngendlela owawusinike yona iinkcukacha zakho: ***Please can we update your locator information:***			
1.	Usahlala okanye ufudukile kula ndlu ubukade uhlala kuyo ukugqibela sithetha? *Have you moved to a different home since we last spoke to you?*	Hayi/*No* =0 Ewe/*Yes* =1	*If YES, updated LOCATOR FORM.*
2.	Uzitshintshile inombolo zakho zomnxeba ukugqibela kwethuukuthetha? *Have you changed your cell phone number(s) since we last spoke to you?*	Hayi/*No* =0 Ewe/*Yes* =1	*If YES, updated LOCATOR FORM.*
3.	Ukhona omnye umntu esinoqhakamishelana naye xa kukho imfuneko? *Is there anyone else that we can contact if we are looking for you in the event of an emergency?*	Hayi/*No* =0 Ewe/*Yes* =1	*If YES, updated LOCATOR FORM.*
Siza kubuza imibuzo embalwa: *We are now going to ask you a few questions:*			
4.	Uze njani ekliniki namhlanje? *How did you get to the clinic today?*	Uqeshe imoto = 1 *Hired car* Uze ngemoto yakho=2 *My own car* Uze ngetaxi=3 *Taxi* Ngebhasi=4 *Bus* Ngenyawo=5 *Walk* Olunye =6,cacisa:_____ *Other, specify*	
5.	Uthathe ixesha elingakanani ukuza ekliniki namhlanje? *How long did it take you to get to the clinic today?*	Imizuzu*/Minutes:* _____ Iyure*/Hours:* _____	
6.	Uhlawule malini ngesithuthi? *How much did you pay for transport?*	*Rand:* _____	
7.	Uthathe ixesha emsebenzini ukuza apha? *Did you take time off of work to come here?*	Hayi/*No* =0 Ewe/*Yes* =1	
8.	Kuye kwafuneka wenze isivumelwano nabantu bajonge umntwana/abantwana? *Did you have to make special arrangements for people to watch your child/children?*	Hayi *No* = 0 → Gqithela ku Q10 *SKIP to Q10* Ewe *Yes* = 1 Andinabantwana = 2 → Gqithela ku Q10 *Don't have any children SKIP to Q10*	
9.	Kuye kwafuneka uhlawule umntu oza kujonga usana ngelixesha uze ekliniki? *Did you pay someone to watch your child so you could come to the clinic?*	Hayi/*No* =0 Ewe/*Yes* =1	
10.	Ukugqibela kwethu ukuthethanawe uye wathunyelwa kwesinye isibhedlele ngenxayokugula(Jooste,Groote Schuur) *Since we last spoke to you, have you been referred to any other health facility for <u>other medical care</u> (eg, GF Jooste or Groote Schuur)?*	Hayi *No* = 0 → Gqithela ku Q11 *SKIP to Q11* Ewe *Yes* = 1	
a.	Ubuthunyelwe phi? *Where were you referred?*	Igama lendawo*:* _____ *Location*	
b.	Wawusithini umhla wokuthunyelwa kwakho? *What was the date of the referral?*	Umhla:____ Inyanga:_____ Unyaka:_____ *Day Month Year*	

c.	Yintoni isizathu sokuthunyelwa kwakho? *What was the reason for the referral?*		Isizathu: *Reason*	
d.	Ingaba wafumana unyango olutsha/ amayeza? *Did you receive any new treatment or medications as a result of this referral?*		Hayi/*No* =0 Ewe/*Yes* =1 Ukuba nguEwe, cacisa:_____ *If Yes, specify*	
11.	Oku ulubelekile usana lwakho, selukhe lwathunyelwa kwamanye amacandeo empilo kuba lugula zizifo zabantwana? *Since delivery, has your new baby been referred to any other health facility for infant-related care?*		Hayi *No* = 0 → Gqithela ku Q12 *SKIP to Q12* Ewe *Yes* = 1	
a.	Ubuthunyelwe phi? *Where were you referred?*		Igama lendawo*:* _____ *Location*	
b.	Wawusithini umhla wokuthunyelwa kwakho? *What was the date of the referral?*		Umhla:____ Inyanga:_____ Unyaka:_____ *Day Month Year*	
c.	Yintoni isizathu sokuthunyelwa kwakho? *What was the reason for the referral?*		Isizathu: *Reason*	
d.	Ingaba wafumana unyango olutsha/ amayeza? *Did you receive any new treatment or medications as a result of this referral?*		Hayi/*No* =0 Ewe/*Yes* =1 Ukuba nguEwe, cacisa:_____ *If Yes, specify*	
12.	Ukugqibela kwethu ukuthetha ugqira okanye unesi bakhe bathi une-TB? *Since we last spoke to you, has a doctor or nurse told you that you have TB?*		Hayi *No* = 0 → Gqithela ku Q17 *SKIP to Q17* Ewe *Yes* = 1	
13.	Uxelelwe nini ngoku kugula? *When did you receive this diagnosis?*		Umhla:____ Inyanga:_____ Unyaka:_____ *Day Month Year*	
14.	Uxelelwe phi ngoku kugula? *Where did you receive this diagnosis?*		Igama lekliniki *:* _____ *Name of clinic*	
15.	Iphi emzimbeni wakho le TB? *Where in your body was the TB (eg, lungs, other location)?*		Indawo emzimbeni *:* _____ *Place in body*	
16.	Uye wafumana unyango lwayo? *Did you receive treatment for TB?*		Hayi/*No* =0 Ewe/*Yes* =1	
17.	Ukugqibela kwethu ukuthetha nawe ukhona omnye umntu osele umxelele ukuba uphila nentshologwae ongakhange umxelele kuqala? *Since we last spoke to you have you told anyone about your HIV-status who you had not told before?*		Hayi *No* = 0 → Gqithela ku Q20 *SKIP to Q20* Ewe *Yes* = 1	
18.	Nceda phendula lombuzo ngelungu ngalinye losapho oludweliswe ngezantsi. *Please answer this question for each of the family members listed below.*	i. Bahlala nawe ? *Do they live with you?* *If NA selected, do not answer i and ii for that person*	ii. Bayazi uphila nentsholongwane ? *Do they know you are HIV positive?*	iii. Bayazi utya iART? *Do they know if you are taking ART?*
a.	Umyeni/iqabane *Husband/partner/boyfriend*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
b.	Umama *Mother*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1

c.	Utata *Father*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
d.	Udade *Sister*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
e.	Umtakwenu *Brother*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
f.	Intombi *Daughter*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
g.	Unyana *Son*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
h.	Umalume *Uncle*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
i.	U-anti *Aunt*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
j.	Umzala wesikhomo *Male cousin*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
k.	Umzala wesikhomokazi *Female cousin*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
l.	Enye indoda yalapha efemelini *Other male family member*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
m.	Esinye isikhomokazi se femeli *Other female family member*	Hayi/*No* = 0 Ewe/*Yes* = 1 N/A = 9	Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
19.	Ngaphandle kwabantu bakho bekhaya abasentla ,ngubani omnye umntu omxelele ngokuphila nentsholongwane ongazange umxelele ngaphambili? *Aside from family members listed above, who else have you told about your HIV status who you had not told before? (read and answer for all)*		i. Bayazi uphila nentsholongwane? *Do they know you are HIV positive?*	ii. Bayazi utya iART? *Do they know if you are taking ART?*
a.	Amanesi/ogqira *Health professionals*		Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
b.	Iqumru lenxaso labantu abaphila nentsholongwane *Support group*		Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
c.	Umntu owabelana naye ngesondo ongahlali naye *A sexual partner who does not live with you*		Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
d.	Isihlobo *Friends*		Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
e.	Inkokheli ngokwa kwamoya *Spiritual leader*		Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
f.	Umntu okuqashileyo/wayekuqashile *Current or former employer*		Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
g.	Ukuchaza esidlangalaleni *Public disclosure/ community*		Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1
h.	Abanye, chaza: _____ *Other, specify*		Hayi/*No* = 0 Ewe/*Yes* = 1	Hayi/*No* = 0 Ewe/*Yes* = 1

Initials of counsellor: _____

20.	Ukugqibela kwethu ukuthetha kuye kwakho utshintsho phakathi kwakho nomyeni/iqabane? *Since we last spoke to you, have there been any changes in your relationship with your husband or partner?*	Hayi *No* = 0 → Gqithela ku Q26 *SKIP to Q26* Ewe *Yes* = 1
21.	Ukuba nguEwe, yintoni ethe yatshintsha kokuthandana *If Yes, what has changed in your relationship since we last spoke?*	
	If participant reports that there have been changes in relationship, complete the following questions (Q22-25) with updated information.	
22.	Unomntu omtsha othandana naye? *Are you currently in a new relationship?*	Hayi/*No* = 0 → Gqithela ku Q26 *SKIP to Q26* Ewe/*Yes* = 1
23.	Loo mntu umtsha uthandana naye uhlala nawe *Is your new partner living with you?*	Hayi/*No* = 0 Ewe/*Yes* = 1
24.	Uyathandana /wabelana ngesondo nabanye abantu ngaphandle kwalo mntu mtsha? *Do you have relationships/sexual partners with people other than this new partner?*	Hayi/*No* = 0 → Gqithela ku Q26 *SKIP to Q26* Ewe/*Yes* = 1
25.	Sinjani isimo sobunye ubuhlobo bakho? *What is the nature of your other relationship(s)?* Rhangqa konke okungqamene nawe. *Mark all that apply.*	a. Umlingane/nditshatile *Spouse/ married* b. Iqabane lam *Boyfriend* c. Iqabane lethutyana *Casual Partner/One Night Stands* d. Omnye ,cacisa:_____ *Other, specify*
26.	Loluphi usuku ukugqibela kwakho ukutya iART? *When was the last day you took ART?*	Umhla:____ Inyanga:_____ Unyaka:_____ *Day Month Year*
a.	Ukhe wawatya iART akho kwezi ntsuku zi-7 zidlulileyo? *Have you taken ART at all in the last 7days?*	Hayi/*No* = 0 Ewe/*Yes* = 1→ Gqithela ku Q27 *SKIP to Q27*
b.	Ukuba hayi, kutheni? *If No, why not?*	Isizathu: *Reason*
27.	Ekugqibeleni kwethu ukuthetha,ubukhe wathetha nekhawunsela ekliniki ngokutya iART? *Regardless of whether or not you have taken ART:* *Since we last spoke to you have you spoken to a counsellor at the clinic/ hospital about taking ART?*	Hayi/*No* = 0 →*SKIP to Q28* Ewe/*Yes* = 1
a.	Ukuba ewe,uye phi? *If Yes, where did you go?*	Igama lekliniki: _____ *Clinic name*
b.	Emva kokuba sithethile nawe,ukhawunselwe kangaphi? *Since we last spoke to you how many times have you been counselled?*	Amaxesha: _____ # of times
c.	Uye wathetha nabani ngoku ubukhawunselwa? *Who did you speak to during this counselling?*	
d.	Ngoku ubukhanselwa niye nathetha ngantono? *What did you talk about during this counselling?*	
28.	Ugqibele nini ukuya exesheni? When was your last menstrual period?	Umhla:____ Inyanga:_____ Unyaka:_____ *Day Month Year* Andiqinisekanga/*Unsure = 9*

Initials of counsellor

29.	Ukhulelwa ngoku? Are you pregnant at the moment?	Hayi/*No* = 0 →*Phela apha/END* Ewe/*Yes* = 1 Not sure = 2
30.	Ingaba oku kukhelelwa kuqinisekisiwe? Has the pregnancy been confirmed?	Hayi/*No* = 0 →*DO PREGNANCY TEST NOW* Ewe/*Yes* = 1

Date completed: __ __ /__ __ __ / __ __ __ __ Signed counsellor completing CRF: _____

Date of QC: __ __ /__ __ __ / __ __ __ __ Signed measurement nurse: _____

Initials of counsellor:

9.10 Appendix 10: Example of MCH-ART Resource Interview

MCH-ART Resource Interview
Xhosa of English V2.0, 25 April 2014

VISIT	3.3 6 months	3.5 12 months
Visit date	__ __/__ __ __/__ __ __ __	

IMIGAQO: Gqibezela olu dliwano-ndlebe nomthathi nxaxheba wophando uze ufake iimpendulo zomthathi nxaxheba zombuzo ngamnye. Umbuzo ngamnye mawuphendulwe ngumthathi nxaxheba, Hayi umbuzi-mibuzo. Bhala kuphela iimpendulo zomthathi nxaxheba wophando ngokurhangqa inani elililo nkgqo. Nceda khetha impendulo ibenye qha kumbuzo ngamnye.

INSTRUCTIONS: Complete this interview with the study participant and enter the participant's response for each question. Each question is to be answered by the participant, not the interviewer. Record only the participant's response by circling the appropriate number. Please choose only one answer for each question.

NOTE: All these questions are referring to routine health care services and NOT study measurement visits.

A) Maternal Interview

Nceda ucinge ngobom bakho kwezinyanga zintathu zidlulileyo. Kangangoko ukhumbula, phendula le mibuzo ilandelayo malunga nendlela ezahlukeneyo enokuthi impilo yakho ibe ibuchapazele ubom bakho kwezinyanga zintathu zidlulileyo.
Please think about your life over the past 3 months. As well as you can remember, answer the following questions about the different ways your health may have affected your life during these past 3 months.

	NONE 0	1-2	3-5	6-10	11-16	If >16, indicate number
1. KWINYANGA EZINTATHU EZIDLULILEYO, zintsuku ezingaphi uhleli ebhedini ubuninzi bemini kuba ubungaziva mnandi? *DURING THE PAST 3 MONTHS, HOW MANY DAYS did you stay in bed most of the day because you were not feeling well?*	0	1	2	3	4	5 :_____
2. KWINYANGA EZINTATHU EZIDLULILEYO, zintsuku ezingaphi ucutha imisebenzi yakho yesiqhelo, nje ngomsebenzi wakho, umsebenzi wasendlini, okanye isikolo kuba ubungaziva mnandi? *DURING THE PAST 3 MONTHS, HOW MANY DAYS did you reduce your usual daily activities, such as your work, housework, or school because you were not feeling well?*	0	1	2	3	4	5 :_____
3. KWINYANGA EZINTATHU EZIDLULILEYO, zintsuku ezingaphi kusiza omnye umntu endlini/ekhayeni lakho ukuza kunceda kuba ubungaziva mnandi? *DURING THE PAST 3 MONTHS, HOW MANY DAYS did someone come to your home/household to help you because you were not feeling well?*	0	1	2	3	4	5 :_____

Initials of counsellor: _____

4. KWINYANGA EZINTATHU EZIDLULILEYO, zintsuku ezingaphi uchithe ubusuku esibhedlele, ekliniki okanye iwadi lehospisi ngenxa yempilo yakho? *DURING THE PAST 3 MONTHS, HOW MANY NIGHTS did you stay in a hospital ward, clinic, or hospice ward for your own health?*	0	1	2	3	4	5 :_____
5. KWINYANGA EZINTATHU EZIDLULILEYO, utyelele kangaphi ekliniki okanye kwi-wadi labagula behamba (ingozi okanye indawo yezimo eziphuthumayo) ngenxa yempilo yakho? *DURING THE PAST 3 MONTHS, HOW MANY VISITS did you make to a health clinic or casualty ward (accident or emergency facility) for your own health?*	0	1	2	3	4	5 :_____
6. KWINYANGA EZINTATHU EZIDLULILEYO, utyelele kangaphi kugqirha wesintu ngenxa yempilo yakho? *DURING THE PAST 3 MONTHS, HOW MANY VISITS did you make to a traditional healer for your own health?*	0	1	2	3	4	5 :_____
7. KWINYANGA EZINTATHU EZIDLULILEYO, ukhe wamkela umvuzo ngenxa yohlobo oluthile lomsebenzi okanye ingqesho? *DURING THE PAST 3 MONTHS, did you earn any income through some kind of work or occupation?*	No=0 → SKIP to Section B			Yes=1 →continue to 7a)		
7a) **UKUBA EWE**, xa ubusenza lomsebenzi/ingqesho, ingaba ubukhulu becala ubusebenza isigxina okanye manqapha-nqapha? ***If yes**, when you did this work/occupation, did you mostly work full time or part time?*	Isigxina/ Full time = 0			manqapha-nqapha/ Part time =1		

B) Infant Interview

Nceda ucinge ngempilo yosana lwakho kwezi nyanga zinthathu zidlulileyo. Kangangoko unako ukukhumbula, phendula le mibuzo ilandelayo ngendlela ezahlukeneyo ezichaphazela ngayo impilo kwezinyanga zinthathu zidlulileyo.
Please think about your child's life over the past 3 months. As well as you can remember, answer the following questions about the different ways your child's health may have affected their life during these past 3 months.

NOTE: These questions pertain to your youngest child, the one that you had most recently.

	NONE 0	**1-2**	**3-5**	**6-10**	**11-16**	**If >16, indicate number**
8. KWEZINYANGA ZINTHATHU ZIDLULILEYO, zintsuku ezingaphi umntwana engadlali ngesiqhelo, njengokutya, ukulala kuba engaziva mnandi? *DURING THE PAST 3 MONTHS, HOW MANY DAYS did your child reduce their usual daily activities, such as eat, sleep, because they were not feeling well?*	0	1	2	3	4	5 :_____

Initials of counsellor: ____

9. KWEZINYANGA ZINTHATHU ZIDLULILEYO, zintsuku ezingaphi umntwana achithe ubusuku esibhedlele ngenxa yempilo yakhe? *DURING THE PAST 3 MONTHS, HOW MANY NIGHTS did your child stay overnight in a hospital for their own health?*	0	1	2	3	4	5 :_____
10. KWEZINYANGA ZINTHATHU ZIDLULILEYO, utyelele kangaphi umntwana wakho ekliniki, okanye kwincandelo le trauma (ingozi, unyango olukhawulezileyo) ngenxa yempilo yakhe, kodwa akalaliswa? *DURING THE PAST 3 MONTHS, HOW MANY VISITS did your child make to a health clinic or trauma unit (accident or emergency facility) for their own health but did not stay overnight?*	0	1	2	3	4	5 :_____
11. KWEZINYANGA ZINTHATHU ZIDLULILEYO, kubekangaphi umntwana wakho etyelela kugqirha wesintu? *DURING THE PAST 3 MONTHS, HOW MANY VISITS did your child make to a traditional healer for their own health?*	0	1	2	3	4	5 :_____

C) Health clinic visits

Le mibuzo ilandelayo inxulumene namava akho ngokuya eklinik (ekuhlukuhleni, kumaziko amachiza okuthomalalisa intsholongwane kagawulayo) malunga nempilo yakho
The following questions are related to your experiences going to a health clinic (ANC, ART) for your own health.
QAPHELA: le mibuzo ayinxulumenanga nokuza kutyelelo lophando
NOTE: These questions are not related to attending study visits.

Ukusuka kumbuzo 16-24- cinga into oqhele ukuyenza xa kufuneka uye eklinik ukuya kufumana ukhathalelo lwempilo.
For Questions 16-24- Think of what you typically do when you have had to go to the health clinic to receive medical care .

12. Uye njani eklinik? *How did you get to the clinic?*	Imoto eqeshiweyo/*Hired Car*=1 Imoto yam/*My own car* = 2 Itaxi/*Taxi* = 3 Ibhasi/*Bus* = 4 Ngenyawo/*Walk* = 5 Enye/*Other* = 6, Chaza/*specify*: _____
13. Kuthatha ixesha elingakanani ukuza kufika eklinik? *How long did it take for you to get to the clinic?*	Imizuzu/*Minutes*: _____ Iiyure/ *Hours*: _____
14. Uhlawula malini kwisithuthi ukuya eklinik? *How much did you pay for transport to the clinic?*	Rand: _____

Initials of counsellor _____

15. Kuye kwafuneka ungapha ngeli ukuze uze kutyelelo ekliniki? *Did you have to take time off of work to attend clinic visits?*	Hayi/ *No* = 0 Ewe/ *Yes* = 1
16. Ukuba kunjalo, ingaba uphulukene nomvuzo kuba uze kutyelelo eklinik? *If yes, did you miss income because of having to attend these clinic visits?*	Hayi/ *No* = 0 Ewe/ *Yes* = 1 Khange ndithathe xesha emsebenzini, ndiphinde ndaya emsebenzini/*Did not have to take time off/sick leave* = 3 Ngale mini yotyelelo lwam eklinik/*I still went to work on the day of my clinic visit* =4
17. Ukuba kunjalo, qikelela ixabiso lomvuzo ophulukene? *If yes, estimate amount of missed wages.*	Rand: _____
18. Ingaba kuye kwafuneka wenze amalungiselelo akhethekileyo nabantu ukujonua umntwana/abantwana ukuze ukwazi ukuza? *Did you have to make special arrangements for people to watch your child/children so that you can attend these clinic visits?*	Hayi/ *No* = 0 Ewe/ *Yes* = 1 Andina bantwana/*Don't have any children* = 2
19. Kuye kwafuneka uhlawule umntu ozakugcinela umntwana ukuze eze eklinik? *Did you have to pay someone to watch your child so that you could attend these clinic visits?*	Hayi/ *No* = 0 Ewe/ *Yes* = 1 Andina bantwana/*Don't have any children* = 2
20. Ukuba kunjalo, umhlawule malini? *If yes, how much did you pay?*	Rand: _____ Andina bantwana/ *Don't have any children* = 0 Bekungeyomfu-neko yomgcini mntwana/ *Didn't need childcare* = 1
D) Infant Feeding	
21. Oko wazalwa umntwana wakho wakhe wamthengela ubisi olungumgubo lwabantwana? *Since your child's birth have you purchased any formula milk for your infant?*	Hayi/ *No* = 0 Ewe/ *Yes* = 1
22. Ukuba kunjalo, uchitha malini ukuthenga ubisi elingumgubo wabantwana? *If yes, how much did you spend per week on formula?*	Rand: _____ Andiluthengi ubisi/*Did not purchase formula* = 0

Date completed: __ __ /__ __ __ / __ __ __ __ Signed counsellor completing CRF: _____

Date of QC: __ __ /__ __ __ / __ __ __ __ Signed measurement nurse: _____

Initials of counsellor: _____

9.11 Appendix 11: Co-authors' affiliations

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9.12 Appendix 12: Permission for inclusion of publications

ICAP Empowering Health
Columbia University
Mailman School
of Public Health

21 September 2020

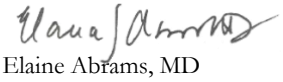
Doctoral Degrees Board
University of Cape Town

RE: Permission to include publications in PhD thesis of Lucy Cunnama entitled: Economic evaluation of models of PMTCT intervention for large scale implementation

1. Cunnama L, Abrams EJ, Myer L, Gachuhi A, Dlamini N, Hlophe T, Kikuvi J, Langwenya N, Mthethwa S, Mudonhi D, Nhlabatsi B, Nuwagaba-Biribonwoha H, Okello V, Sahabo R, Zerbe A, Sinanovic E. Cost and cost-effectiveness of transitioning to universal initiation of lifelong antiretroviral therapy for all HIV-positive pregnant and breastfeeding women in Swaziland. Tropical Medicine & International Health. 2018;23(9):950-9.
2. Cunnama L, Abrams EJ, Myer L, Phillips TK, Dugdale CM, Ciaranello AL, Zerbe A, Iyun V, MacQuilkan K, Daries V, Sinanovic E. Provider- and patient-level costs associated with providing antiretroviral therapy to women living with HIV in South Africa: A cost comparison of three models of care. In press. 2020.
3. Cunnama L, Abrams EJ, Myer L, Phillips TK, Zerbe A, Iyun V, Sinanovic E. Cost-effectiveness analysis of three postpartum models of care for women living with HIV in Cape Town, South Africa. Being prepared for submission.
4. Cunnama L, Abrams EJ, Myer L, Sinanovic E. Scaling up postpartum models of care for mother-infant pairs in South Africa: A budget impact analysis. Being prepared for submission.

I, Professor Elaine Abrams, the lead investigator, and co-author of the publications listed above, on behalf of myself and my team, do hereby give Lucy Cunnama (Student number: SHLLUC001) permission to include these publications in her PhD thesis. The status of each publication (published, submitted, being prepared for submission) is correct at the time of writing.

Yours sincerely,



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21 September 2020

Doctoral Degrees Board
University of Cape Town

Dear colleagues

Permission to include publications in PhD thesis of Lucy Cunnama entitled: "Economic evaluation of models of PMTCT intervention for large scale implementation"

I, Landon Myer, the lead investigator, and co-author of the publications listed below, on behalf of myself and my team, do hereby give Lucy Cunnama (Student number: SHLLUC001) permission to include these publications in her PhD thesis. The status of each publication (published, submitted, being prepared for submission) is correct at the time of writing.

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Yours sincerely

Landon Myer