An evaluation of the effectiveness of task-shifting health systems approaches, including community-based and pharmaceutical care models, for HIV treatment and prevention programs in South Africa

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Dissertation presented for the degree of Doctor of Philosophy (Epidemiology) in the Faculty of Medicine and Health Sciences at Stellenbosch University

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Date: December 2020

DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: September 2020

SUMMARY

Southern Africa is the epicentre of the human immunodeficiency virus (HIV) pandemic having the highest burden of HIV globally. Although South Africa has made great strides with the roll-out of its antiretroviral treatment (ART) program, ongoing challenges include high attrition of patients from ART care and ongoing elevated HIV incidence. There is also a severe shortage of professional health workers in the region, which impacts HIV program delivery. Task-shifting health systems approaches have been developed in order for the health system to provide large-scale HIV program delivery with limited numbers of professional health workers. This thesis evaluates the effectiveness of task-shifting health systems interventions in HIV prevention and treatment programs in South Africa, including community-based programs utilizing community healthcare workers (CHWs), and pharmaceutical care models. Data were collected in cohort studies conducted between 2004 and 2015/2016 in four provinces of South Africa.

The results chapters of the thesis are presented in the form of published papers. The first paper evaluates the effectiveness of a community-based support (CBS) program amongst a large cohort of adults living with HIV receiving ART up to five years after ART initiation. Adults who received CBS had improved ART outcomes, including improved patient retention with lower loss to follow-up and lower mortality, both of which were reduced by one third. The second paper evaluates the effectiveness of a community-based combination HIV prevention intervention delivered by CHWs for pregnant and postpartum women in a high HIV incidence district in KwaZulu-Natal. Maternal HIV incidence amongst participants who received the intervention was considerably lower compared to other studies from the region. The paper further

recommends expanded roll-out of home-based couples HIV counselling and testing, and initiating oral pre-exposure prophylaxis for HIV particularly for pregnant women within serodiscordant couples, in order to reduce maternal HIV incidence. The third paper compares the effectiveness and cost of two task-shifting pharmaceutical care models for ART delivery in South Africa, namely the indirectly supervised pharmacist assistant (ISPA) model and the nurse-managed model. The ISPA model was found to have a higher quality of pharmaceutical care, was less costly to implement and was possibly associated with improved patient clinical outcomes. The fourth paper evaluates the effectiveness and cost-effectiveness of CBS for adolescents and youth receiving ART at 47 health facilities in South Africa. CBS was found to substantially reduce patient attrition from ART care in adolescents and youth, and was a low cost intervention with reasonable cost-effectiveness. Lastly, a published scientific letter is included as an appendix, which is a critique of findings from a cluster-randomized trial investigating the effectiveness of two interventions as part of the current South African National Adherence guidelines (AGL). The letter recommends the inclusion of long-term CBS for ART patients utilizing CHWs in a revised version of the AGL.

The thesis concludes that task-shifting healthcare models including community-based and pharmaceutical care models are effective and cost-efficient for HIV program delivery in South Africa, and can aid the greater Southern African regions' progress toward several of the interrelated UNAIDS Sustainable Development Goals by 2030.

OPSOMMING

Suider-Afrika is die episentrum van die menslike immuniteitsgebreksvirus (MIV) pandemie, en het wêreldwyd die grootste las van MIV. Alhoewel Suid-Afrika groot vordering gemaak het met die instelling van sy antiretrovirale behandelingsprogram (ARB), is daar voortdurende uitdagings insluitende 'n hoë verlies van pasiënte vanuit ARB-sorg en 'n verhoogde insidensie van MIV. Daar is ook 'n ernstige tekort aan professionele gesondheidswerkers in die streek, wat die lewering van MIV-programme beïnvloed. Taakverskuiwende benaderings vir gesondheidstelsels is ontwikkel sodat die gesondheid sisteem MIV-programme op groot skaal kan verskaf met beperkte aantal professionele gesondheidswerkers kan aanbied. Hierdie tesis evalueer die doeltreffendheid van intervensies van gesondheidstelsels in MIV-voorkomings- en behandelings programme in Suid-Afrika, insluitend gemeenskapsgebaseerde programme wat gebruik maak van gemeenskap gesondheidswerkers (CHW's) en farmaseutiese sorg modelle. Data is versamel in kohort studies tussen 2004 en 2015/2016 in vier provinsies van Suid-Afrika.

Die resultate van die tesis word aangebied in die vorm van gepubliseerde artikels. Die eerste artikel evalueer die doeltreffendheid van 'n gemeenskap-gebaseerde steun program (CBS) onder 'n groot groep volwassenes wat met MIV leef, wat ARB tot vyf jaar na ARB inisiëring ontvang. Volwassenes wat CBS ontvang het, het verbeterde ARB-uitkomste insluitend verbeterde pasiëntretensie, en verminderde verlies aan opvolg en verminderde mortaliteit; albei is met een derde verminder. Die tweede artikel evalueer die doeltreffendheid van 'n gemeenskap-gebaseerde kombinasie MIV-voorkomings program wat deur CHW's gelewer word vir swanger en postpartum vroue in 'n distrik met 'n hoë MIV-voorkoms in KwaZulu-Natal. MIV-

voorkoms van moeders wat die intervensie ontvang het was aansienlik laer in vergelyking met ander studies uit die streek. Die artikel beveel verder aan dat huis-gebaseerde paartjies MIV-berading en -toetsing uitgebrei moet word, en om mondelinge voorkomings-behandeling vir MIV in te stel, veral vir swanger vroue binne serodiscordant paartjies, om MIV-voorkoms in moeders te verminder. Die derde artikel vergelyk die effektiwiteit en koste van twee taakverskuiwende farmaseutiese sorg modelle vir ARB-voorsorg in Suid-Afrika, naamlik die indirekte toesighoudende aptekerassistent (ISPA) -model en die verpleegsterbestuurde MIV inledings model. Die ISPA-model het 'n hoër gehalte farmaseutiese sorg gehad, was goedkoper om te implementeer en was moontlik geassosieer met verbeterde kliniese uitkomste van pasiënte. Die vierde artikel evalueer die doeltreffendheid en koste-effektiwiteit van CBS vir adolessente en jeugdiges wat ARB by 47 gesondheidsfasiliteite in Suid-Afrika ontvang. Daar is gevind dat CBS die verlies van ARB-sorg onder adolessente en jeugdiges aansienlik verminder, en dat CBS 'n lae koste-intervensie was met redelike kostedoeltreffendheid. Laastens word 'n gepubliseerde wetenskaplike brief as 'n bylaag ingesluit, wat 'n kritiek is op bevindings van 'n groep-gerandomiseerde proef wat die doeltreffendheid van twee intervensies ondersoek as deel van die huidige Suid-Afrikaanse riglyne vir nasionale nakoming (AGL). Die brief beveel aan dat langtermyn CBS met die gebruik van CHWs vir ARB-pasiënte in 'n hersiende weergawe van die AGL ingesluit moet word.

Die tesis kom tot die gevolgtrekking dat taakverskuiwende gesondheidsorg modelle, insluitend gemeenskapsgebaseerde en farmaseutiese sorg modelle effektief en kostedoeltreffend is vir die verskaffing van MIV-programme in Suid-Afrika, en ook

kan bydra tot vordering van die groter Suider-Afrikaanse gebied na die interafhanklike UNAIDS volhoubare ontwikkelingsdoelwitte vir 2030.

ACKNOWLEDGEMENTS

I wish to acknowledge:

- My supervisors, Professor U. Chikte and Professor J. Nachega for their ongoing encouragement and support.
- Dr Ashraf Grimwood for his support and mentorship.
- The funders of the programs that were evaluated as part of this thesis: US President's Emergency Plan for AIDS Relief/US Agency for International Development; Global Fund to fight AIDS, TB and Malaria; Elton John AIDS Foundation; Positive Action for Children Fund, Absolute Return for Kids.
- Kheth'Impilo colleagues who implemented and monitored the programs that were evaluated as part of the thesis, in particular colleagues in the Monitoring and Evaluation unit.
- Healthcare workers in the field that were part of the programs evaluated, particularly community health workers and pharmacist assistants.
- Participants that were included as part of the studies.
- The Provincial Departments of Health of the Western Cape, KwaZulu-Natal, Eastern Cape and Mpumalanga.
- Cape Town City Health.
- The eThekwini district health department and the KwaZulu-Natal Health Research and Knowledge Unit.
- Professor Peter Bock for encouragement and inspiration to pursue PhD studies.
- Dr. Chanelle Windvogel and Dr. Jyothi Chabilall for their helpful support regarding registration and the university regulations.
- I, Geoffrey Fatti acknowledge the support of the South African DSI-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA) towards this research. Opinions expressed and conclusions arrived at, are those of the authors and do not represent the official views of SACEMA.
- Finally, my family for their ongoing support during this time.

Disclaimer: This thesis is the work of the candidate and does not reflect the official opinions of any funders related to any aspect of the work.

PREFACE

This thesis includes published papers, as per provision 6.9.5.2 of the Stellenbosch University General Calendar Part 1 (2020), and the Faculty Of Medicine And Health Sciences General Information on Doctoral Studies. The following four first-authored published papers are formally included as part of the thesis, and in addition one published scientific letter related to the other published articles is included as an appendix.

1. Fatti G, Meintjes G, Shea J, Eley B, Grimwood A. Improved Survival and Antiretroviral Treatment Outcomes in Adults Receiving Community-Based Adherence Support: 5-Year Results From a Multicentre Cohort Study in South Africa. J Acquir Immune Def Syndr. 2012;61(4):e50-e8

2. Fatti G, Shaikh N, Jackson D, Goga A, Nachega JB, Eley B, Grimwood A. Low HIV incidence in pregnant and postpartum women receiving a community-based combination HIV prevention intervention in a high HIV incidence setting in South Africa. PloS One. 2017;12(7):e0181691

3. Fatti G, Monteith L, Shaikh N, Kapp E, Foster N, Grimwood A. Implementation and Operational Research: A Comparison of Two Task-Shifting Models of Pharmaceutical Care in Antiretroviral Treatment Programs in South Africa. J Acquir Immune Def Syndr. 2016;71(4):e107-13.

4. Fatti G, Jackson D, Goga AE, Shaikh N, Eley B, Nachega JB, Grimwood A. The effectiveness and cost-effectiveness of community-based support for adolescents receiving antiretroviral treatment: an operational research study in South Africa. Journal of the International AIDS Society. 2018;21(Suppl 1): e25041

5. Fatti G, Shaikh N, Bock P, Nachega JB, Grimwood A. South African National Adherence Guidelines: need for revision? Tropical Medicine & International Health: 2019;24(10):1260-2

Statement of the candidates contribution to research studies included in this thesis

“This thesis includes four original papers, and one scientific letter published in peer-reviewed academic journals and nil unpublished publications. The development and writing of the papers were the principal responsibility of the candidate and for each of the cases where this is not the case, a declaration is included in the dissertation indicating the nature and extent of the contribution of co-authors.”

The contribution of the candidate is stated as part of an introduction to each paper (pages 30, 64-65, 81, 112 and 155). In summary, the candidate wrote all four study protocols, performed the data management, personally performed all of the data analyses, wrote and managed all drafts of the manuscripts, and was the corresponding author with all of the journals. The candidate was also closely involved with data collection procedures for the four studies, which included data systems development and support, merging of databases, performing data quality checks, generating data queries, and support of data collection personnel. All co-authors critically reviewed and approved the submitted manuscripts, and any comments were assessed by and where appropriate integrated by the candidate. The senior author for each of the published papers has certified separately that the included publications overwhelmingly reflect the candidate’s own scientific work.

ABBREVIATIONS

3TC	lamivudine
AC	adherence club
AGL	South African National Adherence Guidelines
aHR	adjusted hazard ratio
AIDS	Acquired Immune Deficiency Syndrome
aOR	adjusted odds ratio
aRR	adjusted relative risk
ART	antiretroviral treatment
asHR	adjusted subhazard ratio
CBAS	community-based adherence support
CBS	community-based support
CD4	cluster of differentiation 4 T lymphocyte
CHW	community health worker
CI	confidence interval
COVID-19	coronavirus disease of 2019
d4T	stavudine
DoH	Department of Health
DSD	differentiated service delivery
DSP	district supervisory pharmacist
EAC	enhanced adherence counselling
EFV	efavirenz
FTE	full-time equivalent
GPS	global positioning system
HIV	human immunodeficiency virus
HTC	HIV testing and counselling
HR	hazard ratio
HREC	health research ethics committee
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ISPA	indirectly supervised pharmacist assistant
ITT	intention-to-treat
LTFU	loss to follow-up

mHealth	mobile health
MMD	multimonth dispensing
MPR	medication possession ratio
MTCT	mother-to-child transmission of HIV
NGO	nongovernmental organization
NIMART	nurse initiated and managed antiretroviral treatment
NNT	number needed to treat
NVP	nevirapine
OR	odds ratio
PA	patient advocate
PEPFAR	US Presidents Emergency Plan for AIDS Relief
PHC	primary healthcare
PLHIV	people living with HIV
PrEP	pre-exposure prophylaxis
PY	person-year
RR	relative risk
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SDGs	United Nations Sustainable Development Goals
sHR	subhazard ratio
SSA	sub-Saharan Africa
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
TRIC	early Tracing and Retention in Care
TB	tuberculosis
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV and AIDS
VMMC	voluntary male medical circumcision
VS	virological suppression
WBOTs	ward-based outreach teams
WHO	World Health Organization
ZDV	zidovudine

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CHAPTER 1: INTRODUCTION

Background and literature review

Southern Africa is the epicentre of the human immunodeficiency virus (HIV) pandemic having the highest burden of HIV globally (1), and HIV prevention in the region is an important public health imperative (2-4). The scale-up of antiretroviral treatment (ART) has been the most sweeping change in healthcare delivery in the region in recent years (5). Although there has been significant progress in the number of people living with HIV (PLHIV) receiving ART in Southern Africa (1), a number of challenges in the region remain evident: Very high HIV incidence amongst young women, particularly during pregnancy and postpartum, continues despite HIV prevention efforts (4,6-8). As ART patient numbers have expanded, increasing ART patient loss to follow-up (LTFU) has occurred (9-13) and higher levels of virologic failure and drug resistant mutations have been reported (12,14,15). The South African Department of Health (DoH) has acknowledged that “retention in care and adherence to ART in South Africa are suboptimal and pose a serious threat to the long-term success of the national HIV response” (16), a statement substantiated by a number of studies (17-19). As ART is a lifelong treatment, long term adherence is crucial. However, the effect of interventions improving adherence tends to wane over time (20), barriers to adherence change over time (21) and LTFU increases with longer-term treatment (9,22). A demographic group having particular risk are adolescents and youth receiving ART as they have reduced ART adherence, lower viral suppression, and increased risks of LTFU (23-28). Pregnant adolescent girls are at particularly high risk of poor ART outcomes and poor maternal and infant outcomes (29-31).

In September 2016, South Africa adopted the World Health Organization (WHO) recommendation that all PLHIV are eligible to receive ART irrespective of clinical or immunological status (32), allowing a substantially increased number of people to be eligible to initiate ART in the country. The ambitious UNAIDS 90-90-90 goals for HIV treatment are that by December 2020: 1) 90% of PLHIV will know their HIV status; 2) 90% of those with diagnosed HIV infection will receive sustained ART, and 3) 90% of all people receiving ART will have viral suppression (33). By mid-2018, South Africa had achieved 90%-68%-88% for each of these indicators, with total viral suppression amongst all PLHIV of 55%, being 18% percentage points lower than the target of 73% (34). Poor retention in ART care is an important reason for the low ART coverage that the country currently has, being the most important deficiency in the country's progress in achieving the UNAIDS goals.

Sub-Saharan Africa has 25% of the world's disease burden but only 1.3% of the world's health workers (35), and there is a severe shortage of professional health workers in the region (36-39). The health workforce underpins every aspect of the health system, and is the rate-limiting step in achieving universal health (40). Shortages of each cadre of health workers at primary health centres critically impact service delivery (41). This shortage of human resources for health is a critical limitation to the provision of ART to those in need of it. An assessment of the South African National DoH National Adherence guidelines for Chronic Diseases (AGL) has indicated that a lack of human resources is the primary barrier to the introduction of adherence interventions (16). Patient adherence counselling brings an additional burden to health workers time, and cannot always be implemented due to staff shortages. Staff shortages also limit the ability of services to trace patients who

default appointments. In addition, from a patient perspective, routine facility-based ART adherence counselling may frequently be unsatisfactory, and poor professional staff attitude and time spent waiting at clinics for adherence counselling are seen as important deterrents to patients and are reasons for defaulting from care (42).

As a response to professional health worker shortages, the WHO has recommended task-shifting to scale up healthcare services in resource-poor areas (43). The WHO describes task shifting as the redistribution of tasks amongst members of the healthcare team. Certain tasks are transferred, as appropriate, from more highly qualified health workers to workers with less training and fewer qualifications. This process utilizes the health workforce more efficiently, as there are a greater number of less qualified health workers available in the health workforce, their training is of shorter duration, and remuneration is lower than that of more highly trained health workers. Task-shifting is seen as a pragmatic response to health worker shortages in low and middle-income countries, and is a method to extend access to quality health care to greater numbers of people.

Task-shifting programs utilizing non-physician healthcare workers in low and middle income countries have been implemented in a variety of health fields including tuberculosis and malaria treatment, non-communicable diseases (NCDs), and neglected tropical diseases, and have been found to be potentially effective and affordable (44,45). In higher-income countries, transferring the care of urgent physical complaints and chronic conditions from primary care physicians to trained nurse practitioners results in an equal or possibly higher quality of care (46). More recently, task-shifting has been successfully used for the management of common

mental disorders including anxiety and depression, whereby lay health workers deliver psychological therapies in lieu of more highly trained mental health professionals (47). The majority of task-shifting procedures have occurred in primary healthcare; however, in hospital-based settings, task-shifting surgical care from fully qualified surgeons to non-surgeon physicians and non-physician clinicians has also been accomplished (48).

In HIV programs, task shifting procedures initially primarily involved delegating tasks (particularly initiation and monitoring of ART care) from doctors to nurses and other non-physician clinicians. This was found to result in non-inferior clinical patient outcomes, increased access to ART through expanded clinical capacity, and was cost-effective (49,50). However, implementation challenges included the provision of suitable training for staff taking on new tasks, provision of sustainable support and mentoring of workers, and adequate integration of new members into the interdisciplinary healthcare teams (50). Integrating lay workers in HIV program delivery has received increasing attention in low-income settings in the last decade (39,51,52). Community-based support (CBS) programs are task-shifting models involving lay community healthcare workers (CHWs) that have been developed in sub-Saharan Africa (53,54). CHWs have been drafted as a priority workforce in South Africa's approach to the re-engineering of primary healthcare (55). Amongst others, CBS programs aim to prevent HIV in HIV-susceptible populations, and to provide adherence support for HIV-infected adults and adolescents receiving ART to attempt to improve patient virological suppression and reduce LTFU. Excellent adherence to ART producing sustained virological suppression is crucial both for the individual's benefit as well as for public health benefit to reduce community HIV viral

load and to reduce subsequent horizontal transmission. It has been suggested that CHWs can have an important role in South Africa achieving its UNAIDS 90-90-90 goals (56). CHWs have also been deployed in a number of roles including HIV counselling and testing programs (57), community-based HIV prevention interventions, programs for maternal and infant health, as well as NCDs (58). Previous evaluations of lay health workers in HIV programs sub-Saharan Africa have suggested that they are potentially effective strategies to address health worker shortages, expand access to HIV-related prevention and care (51), and reduce inefficiency in program services (39). A small study in the Free State province found community support to be a determinant of ART treatment success (52). Community-based support provides a link between traditional clinic-based services, promotes patient empowerment, improves comprehensive patient care, and helps with defaulter tracing (51). However, challenges have included concerns regarding the quality and safety of care provided by lay health workers, resistance from institutions and professional health workers, the need to sustain motivation and performance, and concerns regarding the fidelity of certain aspects of lay worker task performance (59-61). Quality of care may decrease particularly where CHWs are expected to perform multiple or complex tasks (62). To expand the evidence base, task-shifting innovations need to be evaluated with rigorous research designs to estimate effects on health outcomes, quality of care delivered, and cost-effectiveness (45,59)

Pharmaceutical services also experience staff shortages, particularly as the ART program has expanded so rapidly during the last decade (63,64). The African region has the lowest density of pharmaceutical staff worldwide (0.8 per 10,000 population, almost five-fold lower than the region with the next-lowest density) (65).

Pharmaceutical care is an important component of the ART program, and addresses potential pharmaceutical-related problems and promotes patient adherence (66). Factors contributing to the shortage of pharmacists include a shortage of training institutions, migration of pharmacists to developed countries, an urban/rural maldistribution of pharmacists and the majority of pharmacists working in the private sector serving a small proportion of the population (64,66). In light of the shortage of pharmacists in in sub-Saharan Africa, training lower cadres of pharmacy workers has been recommended to promote pharmaceutical care for ART patients (66). Such task-shifting models include nurses who dispense ART to patients they consult (67,68), and indirectly supervised pharmacist assistants (ISPAs) who are pharmacist assistants who work at facilities that are supervised by a roving pharmacist (64,69).

Research rationale and motivation

Evaluations of the effectiveness of task-shifting health systems interventions are an important part of their implementation (43). To justify further resource allocation for CBS interventions in HIV prevention and treatment programs, evidence of their effectiveness is required. Further significant gaps in the knowledge base include: I) An important paucity of data exists regarding the effectiveness of combination HIV prevention interventions for women during pregnancy and postpartum (4,70,71). II) Evaluations of community-based support programs for ART patients have mostly involved small sample sizes with limited durations of patient follow-up, and there is little data available regarding the large-scale implementation of CBS programs with longer participant follow-up durations (51). III) Systematic reviews have indicated that the evidence base for interventions that enhance ART adherence amongst HIV-infected adolescents and youth is sparse and underdeveloped, and that the

identification of effective interventions that enhance ART adherence in this group is overdue (23,24,72,73). As adolescents are a particularly vulnerable group with poorer ART outcomes and reduced adherence, thus this group is particularly in need of evidence-based interventions to enhance adherence and retention in ART care (74). The effectiveness of CBS programs for adolescents receiving ART also requires evaluation (75). IV) Few evaluations have been conducted regarding task-shifting pharmaceutical health systems models, despite pharmaceutical care being an important component of the ART program. Particularly, little data regarding the clinicial effectiveness and quality of pharmaceautical task-shifting health systems interventions are available (64,76).

Research aim and objectives

Aim:

To evaluate the effectiveness of community-based support programs and pharmaceutical care task-shifting health systems interventions for HIV prevention and treatment in South Africa.

Objectives

Four objectives are evaluated as follows:

- **Objective 1**: To evaluate the effectiveness of a large-scale CBS program for adults living with HIV up to five years after starting ART in four South African provinces.

- **Objective 2**: To evaluate the effectiveness of a community-based combination HIV prevention intervention for pregnant and postpartum HIV-uninfected women a high HIV incidence district in KwaZulu-Natal.

- **Objective 3**: To compare the effectiveness and cost of two task-shifting pharmaceutical care models for ART delivery in South Africa.

- **Objective 4:** To evaluate the effectiveness and cost-effectiveness of CBS for adolescents and youth receiving ART in South Africa.

The studies included in this thesis have been conducted to provide important evidence regarding the effectiveness of task-shifting health systems interventions for HIV prevention and treatment in South Africa and the greater Southern African region. Study results are anticipated to inform policy regarding the value of further expansion of similar interventions.

Methods

The objectives were evaluated as four separate studies, with each study having its own set of methods. A brief overview of the methods for each study is provided here, with greater detail included within each of the following chapters (each objective/study forms one chapter of this thesis).

Methods for objective 1: To evaluate the effectiveness of a large-scale CBS program for adults living with HIV up to five years after starting ART in four South Africa provinces.

A retrospective multicentre cohort study utilizing routinely collected electronic data of adults initiating ART was conducted at 57 health facilities in four South African provinces. The intervention evaluated (CBS for ART patients) involved CHWs who provided regular home-based adherence and psychosocial support for ART patients, who undertook home visits to ascertain and address household challenges potentially impacting ART adherence (77). Issues assessed included education regarding HIV and adherence, nutrition security, substance abuse, domestic violence, non-disclosure of HIV status, tuberculosis and sexually transmitted infections (STI) symptom screening, and HIV testing status of the household.

Prospectively collected clinical data of ART-naive adults who initiated triple-drug combination ART were included in analyses. Clinical, virological and immunological outcomes of patients were analysed up to a maximum of five years after starting ART, comparing outcomes between patients who did and who did not receive CBAS from ART initiation, in order to measure the effectiveness of the intervention. The hypothesis was that adults who received CBS from the start of ART would have improved ART outcomes compared to adults who did not receive CBS.

Methods for objective 2; To evaluate the effectiveness of a community-based combination HIV prevention intervention for pregnant and postpartum HIV-uninfected women in a high HIV incidence district in KwaZulu-Natal.

A prospective cohort study was performed at a primary healthcare centre in eThekwini, a high HIV incidence district (78) in KwaZulu-Natal. HIV incidence amongst HIV-uninfected pregnant and postpartum women who participated in the CBS combination HIV prevention intervention was measured, and factors associated with HIV acquisition were assessed. Women were followed-up with their infants until a maximum of 18 months postpartum. HIV incidence was compared to previously published estimates of HIV incidence amongst pregnant and postpartum women in the same district and region (78,79). The hypothesis was that, compared to previous studies of HIV incidence amongst pregnant and postnatal women in the same district and region, pregnant women who received the community-based HIV prevention intervention would have reduced HIV incidence.

The component interventions of CBS for HIV-uninfected women and their male partners included behavioural education and psychosocial counselling; biomedical interventions included three-monthly home-based HIV counselling and testing, facilitated linkage to HIV care facilities for either partner testing HIV positive with subsequent ART adherence counselling, referral of eligible men for voluntary male medical circumcision (VMMC), and symptom screening of women and partners for STIs with referral for treatment if symptomatic.

The primary outcome was the HIV incidence rate and cumulative HIV incidence amongst HIV-uninfected pregnant and postpartum women. Secondary outcomes (other measures of program effectiveness and process evaluations) were: I) HIV incidence during pregnancy; II) Postpartum HIV incidence; III) Socio-demographic

factors associated with incident HIV infection; IV) Mother-to-child transmission at 6 weeks postpartum amongst women with incident HIV infection prior to 6 weeks postpartum (proportion of HIV-tested infants testing HIV positive); V) Time from diagnosis until ART initiation amongst women with incident HIV; VI) Proportion of women with incident antenatal HIV infection who initiated ART antenatally; VII) Maternal mortality rate; VIII) Cumulative probability of LTFU of enrolled women; IX) Socio-demographic factors associated with LTFU; X) Proportion of male partners who received HIV counselling and testing (with recorded test results). XI) Proportion of partners testing HIV positive successfully linked with HIV care facilities; XII) Time from HIV diagnosis till ART initiation amongst partners eligible to initiate ART; XIII) Proportion of eligible partners referred for VMMC.

Sample size estimate: In order to detect a 35% reduction in maternal HIV incidence (combined antenatal and postnatal) compared to the results of a systematic review of maternal HIV incidence in Southern Africa (79) (incidence rate 4.8 per 100 person-years), using the test of the Poisson rate statistic with alpha=0.05 and power=90%, at least 1202 participants were required. Assuming 10% LTFU, the sample size requirement was inflated to 1322 enrolled participants. The average rate of enrolment in the program was anticipated to be ~60 pregnant women per month, thus sufficient sample size was expected to be available from a recruitment period of approximately 22 months duration.

Methods, objective 3: To compare the effectiveness and cost of two task-shifting models of pharmaceutical care in ART programs in South Africa.

A retrospective cohort study was conducted at 15 primary healthcare clinics to compare the effectiveness and cost of two task-shifting health systems models for pharmaceutical care, namely: 1) indirectly supervised pharmacist assistant (ISPA) model; and 2) nurse-dispensing model. Three aspects of the models were compared, namely: A) The quality of pharmaceutical care; B) patient clinical outcomes and C) provider costs to implement each model. The hypothesis was that the ISPA model would be associated with improved quality of pharmaceutical care; patients who attend ISPA sites would have clinical outcomes that are not significantly worse than patients attending nurse-dispensing facilities; and that provider costs of the ISPA model would be lower than those of the nurse-dispensing model.

Pharmaceutical quality audit data, patient clinical data and staff costing data collected from 15 primary healthcare facilities in KwaZulu-Natal province and Cape Town, Western Cape province were analysed.

A. Pharmaceutical care data

Standardized audit tools were developed to assess the quality of pharmaceutical care at ART sites. The audit form assessed four components of pharmaceutical care, namely 1) Good Pharmacy Practice; 2) stock control; 3) evaluation of prescription and patient folders; 4) patient exit interviews.

B. Clinical data

Prospectively collected clinical data of all ART-naive adults ≥ 16 years of age who commenced triple ART at the 15 clinics were included in analyses. The outcomes were patient attrition (through death or loss to follow-up) after starting ART, and

proportions of patients achieving virological suppression on ART up to 24 months after starting ART.

C. Cost data

An incremental ingredients costing method was used to estimate the mean human resource costs per patient visit and per item dispensed, which was compared between the two pharmaceutical models of care. Human resources costs pertaining to pharmaceutical-related activities only were considered. Pharmaceutical-related activities were defined as any staff activity pertaining to ordering and management of pharmaceutical stock, maintenance of medicine rooms and time spent issuing medication and counselling patients regarding correct use of medication.

Methods, objective 4: To evaluate the effectiveness of CBS for adolescents and youth receiving ART in four South African provinces.

A retrospective cohort study using routinely collected electronic clinical data at 61 ART sites in South Africa was conducted. ART outcomes, ART adherence and implementation costs were compared between adolescents and youth who did, and who did not receive CBS from the start of ART, in order to evaluate the effectiveness of the intervention. The hypothesis was that adolescents and youth who received CBS would have improved ART program outcomes compared to those who did not receive CBS.

The primary outcomes were retention in ART care, mortality, and LTFU analysed to a maximum of five years after ART initiation. The secondary outcomes were

adherence to ART derived from pharmacy refill data (the medication possession ratio [MPR]); CD4 cell count slope after ART initiation; and proportions of patients with unsuppressed viral loads.

All ART-naïve adolescents and youth (ages 10-24) who started ART at the sites with documented date of birth, gender, date of starting ART, who initiated ART at least 6 months before site database closure, and in whom it was documented whether the patient received CBS support from the start of ART were included in analyses (data was collected prospectively).

Sample size estimate: For the primary outcome of retention in care, using the superiority by a margin statistical test for two survival curves using Cox's proportional hazards model according to Schoenfeld's method: Assuming 40% of participants are enrolled in the intervention (CBS) group; and that the probability of overall patient attrition is 20% and 23% in the intervention and control (non-CBS) groups, respectively; specifying a superiority hazard ratio of 0.85 and assuming an actual hazard ratio of 0.74; specifying $\alpha=0.05$ and power=85%, 4293 participants were required in the control group and 2862 participants in the intervention group, with a total sample size of approximately 7155.

Brief chapter overview

Each chapter (chapters 2–5) is a published peer-reviewed article for each of objectives 1–4, as described above. Chapter 6 is the conclusion chapter. Appendix 1 is a published scientific letter that relates to the thesis, particularly to chapters 2 and

5. Appendix 2 is a list of other peer-reviewed research output authored by the candidate which relates to, and are cited in this thesis.

Ethical Approval

1. Ethical approval for the first study (regarding adults receiving antiretroviral treatment) was obtained from the University of Cape Town Health Research Ethics committee (HREC Ref 494/2009) and the Stellenbosch University Health Research Ethics committee (Ref. N17/01/012_RECIP_UCT 494/2009).

2. Ethical approval for the second study (evaluation of an HIV prevention intervention for pregnant and postpartum women) was obtained from the University of Cape Town Health Research Ethics committee (HREC Ref 223/2016) and the Stellenbosch University Health Research Ethics committee (Ref. N17/01/012_RECIP_UCT 223/2016).

3. Ethical approval for the third study (comparison of pharmaceutical care models) was obtained from the University of Cape Town Health Research Ethics Committee (HREC Ref 312/2015).

4. Ethical approval for the fourth study regarding adolescents receiving ART was obtained from the University of Cape Town Health Research Ethics Committee (HREC Ref 368/2008) and the Stellenbosch University Health Research Ethics committee (Ref. N17/01/012_RECIP_UCT 368/2008).

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CHAPTER 2: Survival and Antiretroviral Treatment Outcomes in Adults Receiving Community-Based Adherence Support: Five-Year Results from a Multicentre Cohort Study in South Africa

Citation: Fatti G, Meintjes G, Shea J, Eley B, Grimwood A. Improved Survival and Antiretroviral Treatment Outcomes in Adults Receiving Community-Based Adherence Support: 5-Year Results From a Multicentre Cohort Study in South Africa. J Acquir Immune Def Syndr. 2012;61(4):e50-e8

This study is published in final format in the *Journal of Acquired Immune Deficiency Syndromes* (Journal Impact Factor 4.65 at time of publication). This article has been cited 100 times (Google scholar, April 2020).

Article URL:

https://journals.lww.com/jaids/fulltext/2012/12010/Improved_Survival_and_Antiretroviral_Treatment.13.aspx

Overview

This study evaluated the effectiveness of the large-scale implementation of a community-based adherence program for HIV-infected adults in four South African provinces at 57 ART sites, with up to five years of patient follow-up after starting ART. Clinical, immunological and virological outcomes were compared between adults who received community-based adherence support from the start of ART, in order to evaluate the effectiveness of the intervention.

Contribution to the thesis and novelty

This study forms objective 1 of the thesis. At the time of publication, no studies had evaluated the effectiveness of community-based support for ART patients during large-scale implementation. Prior studies of community-based support had a

maximum follow-up duration of 26 months; in contrast this study followed patients up to 60 months. In addition, this study included one of the largest sample sizes (66,953) of patients receiving ART at the time of publication, globally.

Contributions of candidate

The candidate was the Principal Investigator for this study, designed the study, wrote the study protocol, performed the data management, personally analysed the data, wrote and managed all drafts of the manuscript, and was the corresponding author with the journal. The candidate was also closely involved with data collection procedures for the study including data systems development and support, merging of databases, performing data quality checks, generating data queries, and support of data systems personnel. Co-authors critically reviewed and approved the submitted manuscripts, and any comments were assessed by and where appropriate integrated by the candidate. All authors read and approved the published version.

“This is a non-final version of an article published in final form in J Acquir Immune Def Syndr. 2012;61(4):e50-e8”

Improved Survival and Antiretroviral Treatment Outcomes in Adults Receiving Community-Based Adherence Support: Five-Year Results from a Multicentre Cohort Study in South Africa

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Presented (in part) at the 19th Conference on Retroviruses and Opportunistic Infections, March 5-8, Seattle, USA.

Sources of support: President's Emergency Plan for AIDS Relief, Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Western Cape Department of Health.

ABSTRACT

Introduction

A large increase in lay healthcare workers has occurred in response to shortages of professional healthcare staff in sub-Saharan African antiretroviral treatment (ART) programs. However, little effectiveness data of the large-scale implementation of these programs is available. We evaluated the effect of a community-based adherence-support (CBAS) program on ART outcomes across 57 South African sites.

Methods

CBAS workers provide adherence and psychosocial support for patients and undertake home visits to address household challenges affecting adherence. An observational multicohort study of adults enrolling for ART between 2004 and 2010 was performed. Mortality, loss to follow-up (LTFU) and virological suppression were compared by intention-to-treat between patients who received and did not receive CBAS until five years of ART, using multiple imputation of missing covariate values.

Results

66,953 patients were included, of whom 19,668 (29.4%) received CBAS and 47,285 (70.6%) did not. Complete-case covariate data were available for 54.3% patients. After five years, patient retention was 79.1% (95% CI: 77.7%-80.4%) in CBAS patients vs. 73.6% (95% CI: 72.6%-74.5%) in non CBAS patients; crude hazard ratio (HR) for attrition 0.68 (95% CI: 0.65-0.72). Mortality and LTFU were independently lower in CBAS patients, adjusted HR 0.65 (95% CI: 0.59-0.72) and aHR 0.63 (95%

CI: 0.59-0.68), respectively. After six months of ART, virological suppression was 76.6% (95% CI: 75.8%-77.5%) in CBAS patients vs. 72.0% (95% CI: 71.3%-72.5%) in non-CBAS patients (*P*<0.0001), adjusted odds ratio (aOR) 1.22 (95% CI: 1.14-1.30). Improvement in virological suppression occurred progressively for longer durations of ART (aOR 2.66 [95% CI: 1.61-4.40] by 5 years).

Conclusions

Patients receiving CBAS had considerably better ART outcomes. Further scale-up of these programs should be considered in low-income settings.

Key Words: Antiretroviral treatment; community-based adherence support; outcomes; South Africa; resource-limited settings; health workers

INTRODUCTION

In patients receiving antiretroviral treatment (ART), adherence is a critical predictor of HIV viral suppression, disease progression and mortality.(1,2) In sub-Saharan Africa, ART adherence has been equal or superior to adherence in developed countries.(3) However, adherence tends to wane with increasing duration of treatment, and sustained efforts to ensure high levels of long-term adherence to ART are vital.(1) As sub-Saharan African ART program patient numbers have expanded, increasing patient attrition has occurred (4-6) and higher levels of virologic failure and drug resistant mutations have been reported.(5,7) There is a severe shortage of professional health workers in sub-Saharan African countries.(8-11) As a response to this, the number of lay health workers in ART programs has been substantially increased during the last half-decade,(12,13) and there have been calls to further strengthen community-based adherence support (CBAS) initiatives for patients receiving ART.(14,15) To justify further resource allocation to such interventions, evidence of their effectiveness is required.

CBAS has been associated with reduced mortality and loss to follow-up (LTFU) as well as improved virological outcomes in low-income settings.(16-19) Limitations of these studies, however, include small sample size,(16) lack of adjustment for potential confounding,(17,20) control arm contamination,(21) and these studies followed patients for a maximum of 26 months. Data is not yet available on the long term effectiveness of large-scale implementation of CBAS programs for ART patients in low-income settings.

The aim of this study was to assess the effectiveness of a large CBAS program for ART patients enrolled between 2004 and 2010 in four South African provinces. Clinical, virological and immunological outcomes after starting ART were compared between patients who received and did not receive CBAS at government-sector ART facilities using routinely collected data.

METHODS

Study design and setting

A multicentre cohort study of adults starting ART was conducted at 57 public healthcare facilities supported by Kheth'Impilo (KI) (previously Absolute Return for Kids), a South African non-governmental organization (NGO). The government-implemented rollout of ART, initiated in 2004, follows the World Health Organization's (WHO) public health approach with the provision of standardised first and second-line regimens. At the end of 2010, almost 1.4 million South Africans had been initiated on ART in the public sector, with ART coverage being 55%.(22) KI provides clinical staff, infrastructure, capacity development, electronic data collection systems and utilises a CBAS program employing patient advocates (PAs). PAs are lay community health workers who provide adherence and psychosocial support for ART patients, and undertake home visits to ascertain and address household challenges potentially impacting on adherence. PA-support starts from the time of pre-ART preparation and continues throughout long-term patient care.

PAs are community members chosen through a transparent process involving community representatives, clinic staff members and NGO line managers. PAs are

generally unemployed prior to working as a PA, and positions for PAs are advertised in local media. They have to have completed high school, be numerate and literate in English, be fluent in the local language and have good community standing. They are trained (in a three-week intensive course) regarding HIV and tuberculosis (TB) infection and treatment, including psychosocial issues impacting on adherence and how to address these. PAs receive a 5 day refresher course a year after starting as well as monthly one day training and debriefing workshops.

During a patient's initial home assessment by a PA, family and other household members are also evaluated. Issues assessed (using a standardised form) include TB and HIV testing status of the household, nutrition security, substance abuse, domestic violence, non-disclosure, current household recipients and those eligible to receive government social grants (as poverty relief), and vital documentation including birth certification. All psychosocial issues are discussed at clinic multi-disciplinary team meetings (comprising doctors, nurses, clinic adherence counsellors, PAs and social workers), and interventions agreed by the team are implemented by the PA or social worker. PAs also offer group educational sessions to all patients at the clinic about HIV/TB, the importance of adherence and nutrition.

Following the psychosocial screening visit, home visits occur weekly for a month. PAs supervise taking of medication, advise on medication storage and do adherence checks using self-reported adherence and, in certain situations, ART pill counts. They provide one-on-one counselling with patients regarding adherence and psychosocial problems, and follow-up on progress made regarding referrals to social workers. Health promotion education, symptom screening for TB and other

opportunistic infections is performed, with referral to clinics if indicated. Patients who are clinically ill, pregnant, or are on TB treatment are regarded as 'very important patients', and subsequent visit frequency remains high, being at least monthly. Stable patients are visited on at least a three-monthly basis. If clinic visits are delayed, home visit frequency increases. Site-based patient facilitators link patients to PAs and community-based area coordinators manage approximately 20 PAs each in the community. Each PA is assigned 80-120 ART patients, and tracks patients with a paper diary. Visit details, including interventions, are recorded and captured electronically by site-based data capturers.

Patients from all NGO-supported ART sites at which PAs were active that had electronic clinical data collection systems were eligible for inclusion during the study period. Facilities are distributed across four provinces (Western Cape, KwaZulu-Natal, Eastern Cape and Mpumalanga), and included hospitals and primary healthcare clinics in urban and rural areas.

Adults with CD4 cell counts <200 cells/µl and/or a WHO stage IV defining illness were eligible to start treatment as per the 2004 South African national treatment guidelines.(23) From April 2010, ART eligibility criteria were expanded to include adults who were pregnant or diagnosed with active TB with CD4 cell counts ≤350 cells/µl.(24) Standardised first-line regimens consisted of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor. Fixed-dose combinations were not used (except for combined zidovudine/lamivudine).

All adults (≥16 years of age) not previously enrolled for ART starting triple-drug combination ART between 1 January 2004 and 30 September 2010 with documented date of birth, gender, date of starting ART, who initiated ART at least six months before site database closure, who had at least one day of follow-up time on ART, and in whom it was documented whether the patient received CBAS support from the start of ART were included in analyses. Patients were followed up from the start of ART until the earliest of last clinic follow-up visit (for patients dying, transferring out or LTFU), five years from starting ART, NGO exit from a site (7 sites), or 31 March 2011.

Patients were allocated to receive CBAS during the pre-treatment preparation period by the community area co-ordinator if a PA was active in the area of the patients home, PA capacity was available, and if patient consent was obtained. As the development of the CBAS program at individual sites was progressive, few patients were initially allocated to PAs but this increased as the program expanded. Clinical and socioeconomic criteria were not used in deciding the initial allocation status of patients to receive CBAS (although clinical severity would affect subsequent visit frequency of CBAS patients). For analyses, patients were assigned to the CBAS group if allocated to receive support from a named PA since the start of ART. All patients (CBAS and non-CBAS) received three group training sessions regarding HIV education and adherence prior to starting ART. Certain clinics had site-based adherence counsellors who provided individual and/or group adherence counselling to both CBAS and non-CBAS patients referred to them by clinical staff if there were concerns about non-adherence.

Analyses were by intention-to-treat (ITT) ignoring subsequent changes in exposure status. Outcome measures were: death, LTFU, virological suppression (VS), and changes in CD4 cell count after starting ART. Patient attrition was defined as a combined endpoint of mortality or LTFU. A patient was defined as LTFU if no visits to the clinic occurred for 180 days or more.(25) Patients who did not receive CBAS who missed appointments would be traced by telephone, or where available, a district tracing team would visit the home. CD4 cell count was measured at ART initiation and at six-monthly intervals, and viral load was measured six-monthly on treatment. Virological suppression was defined as a viral load <400 copies/ml. Laboratory measurements were performed by the South African National Health Laboratory Service.

Data collection and statistical analyses

Individual-level patient data were collected prospectively for routine monitoring purposes by designated site-based data capturers at each patient visit using standardised custom-designed databases, which were pooled to a central data warehouse using standard operating procedures. The site databases were designed by the NGO using Microsoft Access ®, and were used for routine clinical data collection as well as patient and clinic management. Regular data cleaning and quality control procedures were implemented.

Baseline characteristics between groups were compared with relative risks (RR) and 95% confidence intervals. Kaplan-Meier estimates were used to calculate crude estimates of time to death or LTFU from starting ART. The logrank test was used to compare groups.

Multivariable Cox proportional hazards models were used to analyse the association of CBAS with mortality and LTFU. All models were adjusted for gender, age, baseline CD4 cell count, and additional *a priori* specified baseline patient and site-related covariates that were plausible confounders which produced a variation in the point estimate. Additionally, models were controlled for unmeasured heterogeneity between site cohorts. To avoid potential bias from excluding patients with missing covariate values, multiple imputation of missing values by chained equations were performed using 10 imputed datasets.(26) Multivariable analyses were run on each of the datasets that included the imputed values, and the results combined using Rubin's rules.(27) As a sensitivity analysis, models were also run using a complete-subjects approach (including only subjects with all data for all variables). Modification of the effect of CBAS on mortality and LTFU was assessed by stratifying effect measures by plausible modifiers. The number needed to treat (NNT) to prevent a case of death or LTFU were calculated as appropriate for time-to-event outcomes.(28)

Virological outcomes were analysed primarily by ITT,(29) including all patients in the denominator for each group as allocated but censoring observations for patients in care with missing viral load results at that time point. Log-binomial regression with generalised estimating equations was used to calculate crude associations of CBAS with virologic suppression between months 6 to 60 after starting ART, using robust variance estimates.(30) For multivariable analyses using the imputed datasets a logit link function was employed to estimate adjusted odds ratios (aOR). Additionally, estimates were calculated for each six-monthly measurement interval. A sensitivity

analysis was conducted to determine the effect of the distribution of missing viral load test results for patients in care (and eligible for testing) by firstly considering all missing test results as unsuppressed, and secondly as suppressed.(29) An on-treatment analysis was also performed, including only patients in the denominator who had an available viral load result for each particular six-monthly interval. (All available viral load results for a particular patient were used for both the ITT and on-treatment analyses).

As an additional sensitivity analysis, multivariable models of all outcomes were run restricted to patients enrolled at primary health care (PHC) clinics. Analyses were performed with Stata version 11.1 (College Station, TX, USA). The study was approved by the University of Cape Town Research Ethics Committee.

RESULTS

Database records for 136,524 patients were reviewed for inclusion in analyses. Patients excluded were 5271 from four sites that did not collect baseline demographic or outcome data, 22,096 patients who were transferred-in to sites already receiving ART, 6686 who were <16 years of age, 15,525 from sites at which no patients received CBAS, 15,421 who started ART during the six months prior to site database closure, 2537 who had zero observation time, and 2035 patients with unknown group allocation at the start of ART. A total of 66,953 of 136,524 (49.0%) patients from 57 sites were thus included; of whom 19,668 (29.4%) received CBAS and 47,285 (70.6%) did not.

Table 1 shows patients' baseline characteristics. CBAS patients had more advanced WHO clinical stage disease, more concurrent TB, a slightly higher baseline CD4 cell count, were enrolled on ART during the more recent study period, and were more likely to be enrolled at PHC facilities. Compared to the Western Cape, CBAS patients were approximately two-fold more likely to be enrolled in the Eastern Cape and Mpumalanga, provinces in which higher ART patient mortality is reported,(31) and which reflects the relative distribution of adherence support across the network of sites.

The total observation time was 100,295 person-years with a median follow-up duration of 14.8 months (IQR: 7.7-25.5), being equivalent between patients with and without CBAS (*P*=0.39). During the study period, 970 (4.9%) CBAS patients and 2,968 (6.3%) non-CBAS patients died. A total of 1,185 (6.0%) CBAS patients and 4,498 (9.5%) non-CBAS patients became LTFU.

After five years of treatment, the Kaplan-Meier estimates of patient retention were 79.1% (95% CI: 77.7%-80.4%) in CBAS patients vs. 73.6% (95% CI: 72.6%-74.5%) in non CBAS patients; crude hazard ratio (HR) for attrition 0.68 (95% CI: 0.65-0.72; *P* <0.0001). After five years, LTFU was 13.2% (95% CI: 12.0%-14.4%) in CBAS patients vs. 17.7% (95% CI: 16.8%-18.6%) in non-CBAS patients; crude HR 0.62 (95% CI: 0.59-0.67; *P* <0.0001); and mortality was 9.0% (95% CI: 8.0%-10.0%) in CBAS patients vs. 10.6% (95% CI: 10.0%-11.3%) in non-CBAS patients; crude HR 0.77 (95% CI: 0.72-0.83; *P* <0.0001) (Figure 1). During the first three months of treatment, the rate of attrition in CBAS patients was 15.1 persons/100 person-years

(95% CI: 14.1-16.3) vs. 25.0 persons/100 person-years (95% CI: 24.1-26.0) in non CBAS patients, incidence rate ratio 0.61 (95% CI: 0.56-0.66).

In multivariable analyses using the imputed datasets, (table 2) patients who received CBAS had independently reduced mortality after starting ART, adjusted hazard ratio (aHR) 0.65 (95% CI: 0.59-0.72). The NNT to prevent one death at one and three years were 10.2 (95% CI: 7.8-14.2) and 8.4 (95% CI: 6.6-11.6), respectively. Low baseline CD4 cell count was strongly predictive of mortality, and mortality was increased by two to three-fold in Mpumalanga and Eastern Cape provinces compared to the Western Cape. The proportion of imputed baseline covariate values were as follows: CD4 cell count-16.1%, pregnancy status 6.8%, tuberculosis treatment-10.1%, WHO clinical stage-31.6%, initial regimen 14.4%. In a sensitivity model using complete-subjects analysis, the adjusted effect measure for mortality in CBAS patients was similar (table 2). When stratifying models of mortality by baseline CD4 cell count (complete-subjects), the association of CBAS with reduced mortality was more pronounced amongst patients with baseline CD4 cell counts of 0-200 cells/µl (aHR 0.59 [95% CI: 0.53-0.64] than in patients with baseline CD4 cell counts greater than 200 cells/µl (aHR 0.88 [95% CI: 0.64-1.23]).

LTFU was reduced in CBAS patients in multivariable analyses, aHR 0.63 (95% CI: 0.59-0.68), (table 2). The NNT to prevent one case of LTFU at one and three years were 8.3 (95% CI: 7.0-10.3) and 6.5 (95% CI: 5.7-8.0), respectively. The complete-subjects analysis adjusted HR for LTFU was similar: 0.70 (95% CI: 0.64-0.76). The association of CBAS with reduced LTFU did not vary significantly in magnitude across categories of other covariates.

In total, 62,611 viral load results were available for analyses. Figure 2 shows proportions of patients achieving virological suppression (VS) according to duration of ART. In ITT analyses (figure 2a), VS was 76.6% (95% CI: 75.8%-77.5%) in CBAS patients vs. 72.0% (95% CI: 71.3%-72.5%) in non-CBAS patients after six months of ART (*P* <0.0001). Table 3 indicates effect measures of VS at six monthly intervals after starting ART. VS was greater in patients who received CBAS, and increased in magnitude for longer durations of ART: After one and five years of ART the adjusted estimates were aOR 1.33 (95% CI: 1.24-1.43) and aOR 2.66 (95% CI: 1.61-4.40), respectively. In a summary model of VS over five years adjusted for all measured baseline characteristics and duration of ART, the aOR associated with CBAS was 1.49 (95% CI: 1.40-1.58). Patients with lower baseline CD4 cell counts had a progressively decreased probability of achieving VS (<50 cells/µl aOR 0.50 [CI: 0.45-0.56]; 50-100 cells/µl aOR 0.68 [CI: 0.61-0.76] compared to >200 cells/µl).

Overall, 52.1% and 50.9% of viral load results were unavailable for patients in care and eligible for testing amongst CBAS and non CBAS patients, respectively (RR 1.02 [95% CI: 1.02-1.03]). As illustrated in figures 2b and 2c, improved virological suppression in CBAS patients remained evident in sensitivity analyses when considering all missing test results as either suppressed (aOR 1.44 [95% CI: 1.37-1.52]) or else as unsuppressed (aOR 1.15 [95% CI: 1.11-1.19]). In on-treatment analyses, virologic suppression was equivalent (months 36-60), to marginally poorer (months 6-30) in patients receiving CBAS, overall RR 0.97 (95% CI: 0.96-0.97) (Figure 2d).

Median increases in CD4 cells after one and three years of ART were 159 cells/µl (IQR: 81-253; n=10,955) and 277 cells/µl (IQR: 157-423; n=2267) respectively, and were equivalent between groups (*P*=0.56 and *P*=0.51, respectively).

When restricting analyses to patients enrolled at PHC clinics, adjusted effect measures for CBAS vs. non-CBAS patients were similar to those for the full cohort: mortality aHR 0.64 (95% CI: 0.58-0.70); LTFU aHR 0.63 (95% CI: 0.58-0.68) and virological suppression (ITT summary model over 5 years) aOR 1.44 (95% CI: 1.35-1.54).

DISCUSSION

This study provides data on the effectiveness of the large-scale implementation of CBAS programs in four South African provinces with up to five years of patient follow-up. Patients receiving CBAS had a 35% reduction in mortality and a 37% reduction in LTFU when compared to those without.

Virological suppression was also superior in CBAS patients, the magnitude of which increased for longer durations of therapy. Patients on long-term ART are at risk of "treatment fatigue" (i.e. patients tiring after taking ART over long periods of time),(1,19) which may be mitigated by community adherence support. In Uganda, greater improvement in virologic outcomes were also described with increasing durations of treatment amongst patients supported by peer health workers compared to controls.(19)

The reduction in LTFU associated with CBAS did not vary across categories of baseline CD4 cell count. Mortality, in contrast, was reduced to a greater extent in CBAS patients with lower baseline CD4 cell counts (<200 cells/ µl). Low baseline CD4 cell count itself was strongly predictive of both mortality and reduced virologic suppression, as demonstrated in previous studies.(5,32,33) Patients with low baseline CD4 cell counts in the CBAS group in whom mortality may have been averted through improved adherence would, nevertheless, remain at increased risk of having a subsequently unsuppressed viral load, i.e. CBAS would retain a larger pool of patients at increased risk of having unsuppressed viral loads. This may be the reason that no improvement in virological suppression was seen amongst CBAS patients in on-treatment analyses. The ITT approach is, however, a preferable analytic method for the pragmatic assessment of the effect of an intervention,(29,34) and demonstrated improved virologic suppression in CBAS patients. LTFU was higher in the non-CBAS group, and patients who are truly LTFU would have unsuppressed viral loads.(35)

Improved outcomes in patients receiving CBAS are likely due to overcoming of denial, improved knowledge of HIV/AIDS, understanding the importance of adherence, and improvement in psychosocial problems which in turn lead to improved behaviour skills related to adherence.(36) CBAS also likely reduces stigmatization due to HIV/AIDS and leads to greater social capital (community relationships).(37) CBAS is expected to widen the “community safety net”(38) and heighten social responsibility, with positive effects on adherence and clinic attendance, as adherence to ART in Africa is not merely an individual activity but a community effort.(39)

In addition to adherence support and health education, PAs assist with access to social pensions and grants. This is expected to improve the households' economic status and reduce food insecurity, which can improve survival.(40)

The company cost per PA (including support services costs in January 2012) is USD 225-275 per PA per month, with an approximate cost of USD 1.88-3.43 per patient per month and an approximate cost of USD 1.98 per patient visit (average of 6 patients visited per day per PA). Low-cost interventions that reduce LFTU substantially improve both program effectiveness and cost-effectiveness in low-income settings.(41) The PA program is a low-cost intervention which can be introduced in low-income settings. In addition, this intervention is a source of job creation and provides a potential for further career development for PAs.(42)

The strengths of this study include the large sample size from a number of different sites, which has allowed precise estimation of effect measures. Prospective, individual-level data were collected enabling controlling for patient factors associated with outcomes. Effect measures from multivariable analyses using imputed datasets, complete-subjects methods and sensitivity analyses showed the same direction of effect and were of similar magnitude. Missing viral load results and the lack of effect seen in on-treatment virological analyses does, nevertheless, reduce the strength of the conclusion of improved virological suppression due to CBAS.

Other limitations relate to the use of routine data and the non-randomised allocation of patients to groups, with the potential for information bias and unmeasured

confounding. However, the pre-study probability of these findings was high, as the results concur with previous smaller studies.(43) As CBAS workers were more active in geographic areas closer to local clinics, non-CBAS patients may have lived at greater distances from ART facilities. Living further from the clinic may slightly increase the risk of LTFU, and may have been an unmeasured confounder in the relationship between CBAS and LTFU. However, similar to our results, LTFU was substantially reduced in CBAS patients in a randomised trial in Uganda,(19) suggesting that CBAS truly reduces LTFU. Baseline socioeconomic factors may be associated with mortality and were potential unmeasured confounders. Previous South African analyses showed that CBAS patients were not more socioeconomically advantaged than non-CBAS patients,(17) thus socioeconomic differences are unlikely to have confounded effect measures in favour of CBAS. Although measured baseline characteristics between the groups were dissimilar, the large dataset may produce statistically significant baseline differences between groups that may not necessarily be clinically meaningful. In addition, residual confounding is unlikely to have confounded effect measures in favour of CBAS as the majority of potential confounders associated with poor outcome were more prevalent in CBAS patients (advanced clinical stage,(44) concurrent TB,(45) more recent year of starting ART,(4,5) provincial distribution). Missing viral load results may bias virologic outcomes; however, effect measures from extreme-case sensitivity analyses pointed in the same direction as the primary analyses. Missing data values from routine ART programs in sub-Saharan Africa are common.(4,46,47) Reasons for this include a lack of data capturers, overwhelmed administrative systems, a low return of laboratory results, poor clerical support at clinical sites leaving results unfiled as well as inadequate training of clinical staff regarding data

collection. Attempts are underway to improve data completeness through improving clinical and data staff training and improving systems for capturing relevant data and laboratory results. In addition, the South African government is rolling out Tier.net, a national system for data collection for ART patients.

All sites were supported by an NGO, and it is possible that outcomes may not be well generalizable to non-NGO supported government health facilities; however, the large number of sites included raises the likelihood that subjects were well-representative of South African public sector ART patients. It is possible that patients who declined consent for PA support had increased psychosocial issues (such as denial) that may have been adversely associated with retention. Due to the large size of the cohort, patients LTFU were not tracked and linkage with the national death registry was not performed. Adherence determination data were not analysed as there are no standard government protocols or tools to measure patient-level adherence.

In conclusion, the large-scale implementation of low-cost community-based adherence support programs is shown to improve survival, retention in care and virological outcomes for adults receiving ART, with benefit sustained or increasing up to five years after starting ART. Further scale-up of these programs should be considered for the increasing number of patients receiving ART in low-income settings where the professional healthcare workforce is limited.

Acknowledgements

The authors acknowledge Kheth'Impilo colleagues, PEPFAR, the Global Fund to fight AIDS, Tuberculosis and Malaria, the Health Departments of the Western Cape, KwaZulu-Natal, Eastern Cape and Mpumalanga, and Absolute Return for Kids.

Tables, chapter 2:

Table 1: Characteristics of patients at the start of ART receiving and not receiving community-based adherence support.

	Patients received CBAS (n= 19,668)	**Patients without CBAS (n= 47,285)**	**Relative Risk (95% CI)**
Median age, y (IQR) (n=66,953)	35.1 (29.4-42.3)	34.6 (29.3-41.4)	
Male gender, n (%) (n=66,953)	5955 (30.3%)	15,154 (32.1%)	0.94 (0.92-0.97)
WHO clinical stage, n (%)[a], (n=45,785)			
I/II	3268 (26.0%)	9810 (29.5%)	0.89 (0.86-0.92)
III	7874 (62.7%)	20,250 (60.9%)	Reference
IV	1412 (11.3%)	3173 (9.6%)	1.10 (1.05-1.15)
CD4 cell count; median (IQR), (cells/µl), (n=56,206)	132 (73-181)	122 (63-173)	
CD4 cell categories, n (%)[a]			
< 100	5902 (36.3%)	16,351 (40.9%)	0.91 (0.88-0.94)
101-200	7952 (48.9)	19,312 (48.3%)	Reference
> 200	2394 (14.7%)	4295 (10.8%)	1.23 (1.18-1.27)
Tuberculosis treatment, n (%)[a] (n=60,158)	2762 (14.3%)	5170 (12.6%)	1.10 (1.07-1.14)
Pregnancy, n (%)[a] (n=62,412)	928 (4.8%)	1713 (4.0)	1.14 (1.08-1.20)
Initial ART regimen, n (%)[a], (n=57,338)			
d4T-3TC-EFV	11,437 (62.6%)	25,828 (66.1%)	Reference

d4T-3TC-NVP	3686 (20.2%)	9540 (24.4%)	0.91 (0.88-0.94)
ZDV-3TC-EFV	295 (1.6%)	371 (1.0%)	1.44 (1.32-1.57)
ZDV-3TC-NVP	322 (1.8%)	245 (0.6%)	1.84 (1.71-1.99)
TDF-3TC-EFV	1857 (10.2%)	2061 (5.3%)	1.54 (1.48-1.60)
TDF-3TC-NVP	660 (3.6%)	1036 (2.7%)	1.27 (1.19-1.35)
Year of starting ART, median (IQR) (n=66,953)	2009 (2008-2010)	2008 (2007-2010)	
Categories of year of starting ART, n (%)			
2004-2006	2123 (10.8%)	7310 (15.5%)	Reference
2007-2008	5763 (29.3%)	18,981 (40.1%)	1.03 (0.99-1.08)
2009-2010	11,782 (59.9%)	20,994 (44.4%)	1.59 (1.53-1.66)
PHC based care, n (%) (n=66,953)	17,198 (87.4%)	30,796 (65.1%)	2.75 (2.64-2.86)
Rural ART facility, n (%) (n=66,953)	996 (5.1%)	3089 (6.5%)	0.82 (0.78-0.87)
Province, n (%) (n=66,953)			
Western Cape	2381 (12.1%)	6273 (13.3%)	Reference
Eastern Cape	6013 (30.6%)	5874 (12.4%)	1.84 (1.78-1.91)
Kwazulu-Natal	7670 (39.0%)	32,741 (69.2%)	0.69 (0.66-0.72)
Mpumalanga	3604 (18.3%)	2397 (5.1%)	2.18 (2.10-2.27)

[a] Proportions of available values

CBAS-community-based adherence support, ART-antiretroviral treatment, WHO-World Health Organization, PHC-primary health care, IQR-interquartile range, d4T-stavudine, 3TC-lamivudine, EFV-efavirenz, NVP-nevirapine, ZDV-zidovudine, TDF-tenofovir

Table 2: Crude and adjusted hazard ratios of mortality and loss to follow-up after starting antiretroviral treatment

	Mortality			Loss to follow-up		
Predictor of mortality or LTFU	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**		**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	
		Multiple imputation [a]	**Complete-subjects** [b]		**Multiple imputation** [a]	**Complete-subjects** [b]
Patients received CBAS						
Yes	**0.77 (0.72-0.83)**	**0.65 (0.59-0.72)**	**0.63 (0.56-0.70)**	**0.62 (0.59-0.67)**	**0.63 (0.59-0.68)**	**0.70 (0.64-0.76)**
No	Reference	Reference	Reference	Reference	Reference	Reference
Gender						
Male	1.60 (1.51-1.71)	1.38 (1.30-1.48)	1.38 (1.26-1.50)	1.23 (1.16-1.30)	1.30 (1.23-1.38)	1.34 (1.24-1.44)
Female	Reference	Reference	Reference	Reference	Reference	Reference
Age (continuous)	1.01 (1.01-1.02)	1.01 (1.01-1.01)	1.01 (1.01-1.02)	0.98 (0.98-0.98)	0.98 (0.98-0.98)	0.98 (0.97-0.98)
Baseline CD4 cell count category						
< 50 cells/µl	3.89 (3.31-4.56)	3.28 (2.78-3.86)	3.17 (2.58-3.89)	1.48 (1.31-1.66)	1.36 (1.20-1.53)	1.34 (1.16-1.55)
50-100 cells/µl	2.29 (1.93-2.70)	2.04 (1.71-2.43)	1.90 (1.53-2.35)	1.22 (1.08-1.38)	1.21 (1.06-1.37)	1.19 (1.02-1.37)
101-200 cells/µl	1.23 (1.05-1.45)	1.18 (1.00-1.40)	1.15 (0.94-1.42)	1.03 (0.92-1.15)	1.06 (0.94-1.19)	1.03 (0.90-1.18)
201-350 cells/µl	Reference	Reference	Reference	Reference	Reference	Reference
> 350 cells/µl	0.80 (0.54-1.18)	0.69 (0.47-1.01)	0.45 (0.25-0.80)	1.07 (0.85-1.34)	0.98 (0.77-1.23)	0.62 (0.43-0.88)
Baseline WHO clinical stage						
I-II	Reference	Reference	Reference	Reference	Reference	Reference
III-IV	1.92 (1.74-2.13)	1.58 (1.41-1.75)	1.42 (1.27-1.60)	1.20 (1.11-1.28)	1.14 (1.06-1.23)	1.13 (1.03-1.22)
Baseline TB treatment	1.12 (1.02-1.23)	0.97 (0.86-1.10)	0.98 (0.88-1.12)	0.98 (0.90-1.07)	1.06 (0.96-1.17)	1.07 (0.97-1.19)
Pregnancy status						
Pregnant women	0.35 (0.26-0.47)	0.52 (0.39-0.70)	0.50 (0.34-0.74)	1.35 (1.19-1.53)	1.30 (1.13-1.49)	1.42 (1.21-1.67)
Non-pregnant women	Reference	Reference	Reference	Reference	Reference	Reference

Year of starting ART (per annual increase)	0.85 (0.83-0.87)	0.82 (0.80-0.84)	0.76 (0.74-0.79)	1.01 (0.99-1.03)	1.08 (1.06-1.10)	1.07 (1.04-1.10)
Initial regimen NRTI						
ZDV	0.83 (0.63-1.10)	1.22 (0.84-1.78)	1.13 (0.74-1.73)	0.99 (0.80-1.23)	1.02 (0.82-1.27)	1.18 (0.88-1.60)
d4T	Reference	Reference	Reference	Reference	Reference	Reference
TDF	0.49 (0.41-0.59)	0.82 (0.64-1.04)	0.87 (0.67-1.13)	0.49 (0.42-0.58)	0.58 (0.49-0.70)	0.61 (0.49-0.77)
Initial regimen NNRTI						
EFV	Reference	Reference	Reference	Reference	Reference	Reference
NVP	0.58 (0.53-0.63)	0.94 (0.83-1.06)	0.95 (0.84-1.07)	1.01 (0.95-1.08)	0.98 (0.92-1.05)	1.02 (0.94-1.12)
Level of Care						
PHC clinics	0.85 (0.79-0.91)	1.00 (0.92-1.08)	1.06 (0.96-1.17)	0.78 (0.74-0.82)	0.86 (0.80-0.92)	0.92 (0.84-1.00)
Hospitals	Reference	Reference	Reference	Reference	Reference	Reference
Rural/Urban site						
Rural	1.83 (1.65-2.03)	2.07 (1.84-2.31)	1.56 (1.28-1.89)	0.78 (0.74-0.82)	0.62 (0.53-0.71)	0.49 (0.39-0.63)
Urban	Reference	Reference	Reference	Reference	Reference	Reference
Province						
Western Cape	Reference	Reference	Reference	Reference	Reference	Reference
KwaZulu-Natal	1.31 (1.17-1.46)	1.41 (1.25-1.59)	1.42 (1.20-1.67)	1.00 (0.93-1.08)	1.00 (0.92-1.09)	0.95 (0.85-1.07)
Eastern Cape	1.78 (1.58-2.01)	2.78 (2.42-3.19)	3.00 (2.47-3.62)	1.04 (0.95-1.15)	1.27 (1.14-1.41)	1.24 (1.07-1.44)
Mpumalanga	1.37 (1.18-1.60)	2.24 (1.89-2.65)	1.69 (1.27-2.24)	0.71 (0.62-0.81)	0.99 (0.86-1.14)	0.59 (0.46-0.76)

Hazard Ratios (HR) are from Cox proportional hazards regression models. Crude models analysed each variable by itself. Adjusted models were adjusted for all variables appearing in the table.

[a] Multivariable models derived from multiple imputation of missing covariate values by chained equations using 10 imputed datasets (n=66,953).

[b] Multivariable models derived using complete-subjects analysis (n=36,344).

CBAS-community based adherence support, LTFU-loss to follow-up, WHO-World Health Organisation, CI-confidence interval, PHC-primary health care, TB-tuberculosis, ART-antiretroviral treatment, NRTI-nucleoside reverse transcriptase inhibitor, NNRTI-non-nucleoside reverse transcriptase inhibitor, d4T-stavudine, ZDV-zidovudine, TDF-tenofovir , EFV-efavirenz, NVP-nevirapine.

Table 3: Virological suppression in patients who received and did not receive community-based adherence support at six monthly intervals on ART.[1]

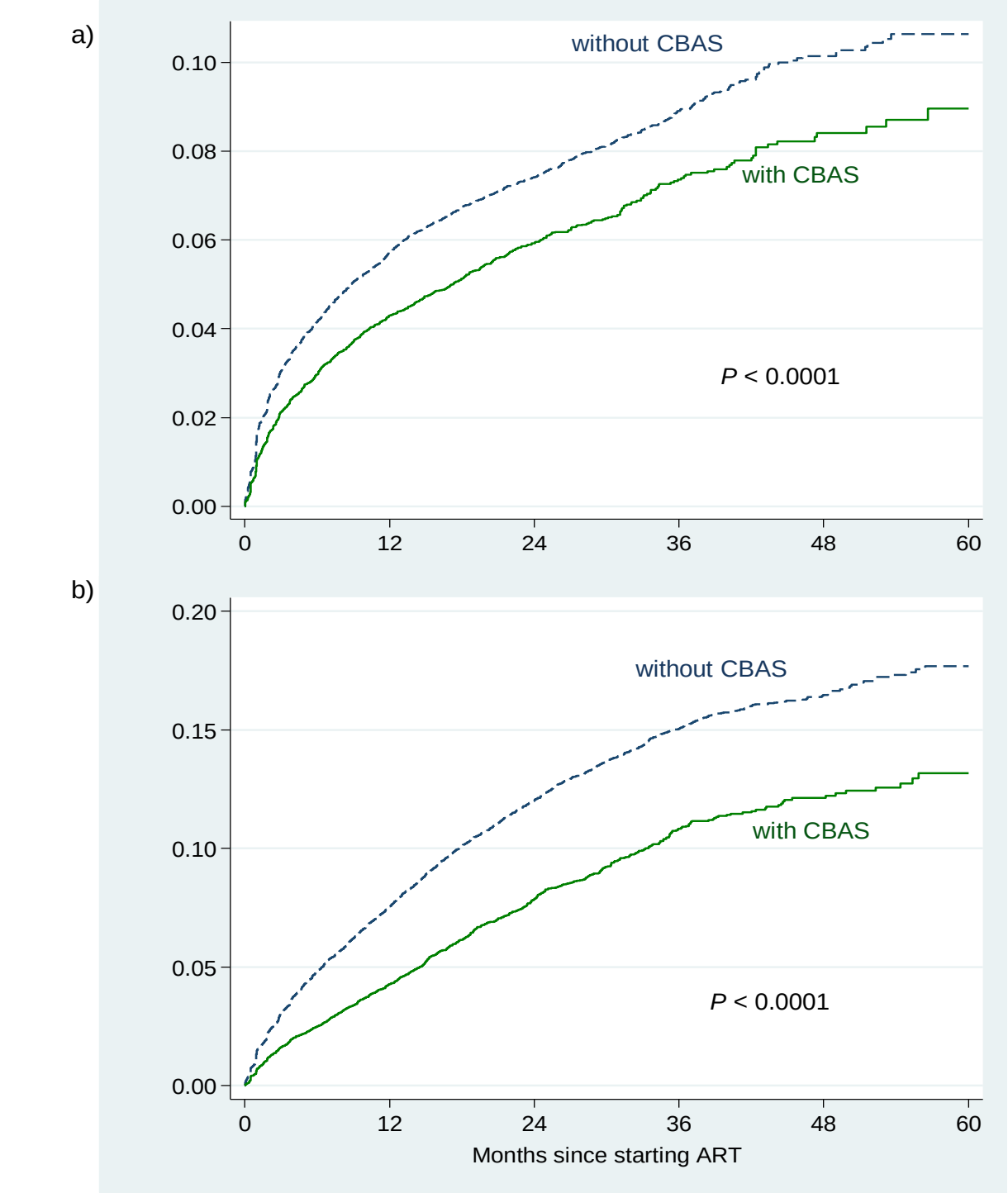
	Patients received CBAS	Patients without CBAS		
Months of ART	**n suppressed/N (%)**	**n suppressed/N (%)**	**Crude RR (95% CI)**	**Adjusted OR[2] (95% CI)**
6	7266/9481 (76.6)	15,458/21,478 (72.0)	1.06 (1.05-1.08)	1.22 (1.14-1.30)
12	4004/6087 (65.8)	8,271/14,813 (55.8)	1.18 (1.15-1.21)	1.33 (1.24-1.43)
18	2291/4068 (56.3)	4725/11,183 (42.3)	1.33 (1.29-1.38)	1.46 (1.34-1.59)
24	1724/3248 (53.1)	3143/8954 (35.1)	1.51 (1.45-1.58)	1.57 (1.42-1.72)
30	918/2100 (43.7)	1719/6507 (26.4)	1.65 (1.55-1.76)	1.80 (1.58-2.06)
36	714/1681 (42.5)	1088/4709 (23.1)	1.84 (1.70-1.98)	2.20 (1.87-2.59)
42	378/1057 (35.8)	600/3169 (18.9)	1.89 (1.70-2.10)	2.27 (1.79-2.88)
48	216/649 (33.4)	317/2157 (14.7)	2.26 (1.95-2.62)	2.50(1.79-3.49)
54	124/371 (33.7)	220/1405 (15.7)	2.13 (1.77-2.57)	2.61 (1.72-3.98)
60	75/192 (39.1)	110/791 (13.9)	2.80 (2.19-3.60)	2.66 (1.61-4.40)

[1] Analyses were by intention-to-treat (denominator includes all patients allocated to each group with follow-up till each respective time interval, excluding patients with missing values).

[2] Odds ratios were derived from logistic regression of CBAS vs non-CBAS patients adjusting for age, gender, baseline CD4 cell count, baseline WHO clinical stage, initial regimen, baseline pregnancy and tuberculosis status, rural/urban nature of site, province and level of care. Models used imputed data for missing covariate values and were adjusted for clustering by site.

CBAS-Community based adherence support, ART-antiretroviral treatment, RR-relative risk, OR-odds ratio, CI-confidence interval

Figures, chapter 2:



No. in care						
with CBAS	19,668	11,160	5520	2593	940	226
without CBAS	47,285	28,069	13,448	4870	1541	392

Figure 1: Cumulative incidences of (a) mortality and (b) loss to follow-up after starting ART in patients who received and did not receive community-based adherence support.

CBAS-community-based adherence support, ART-antiretroviral treatment

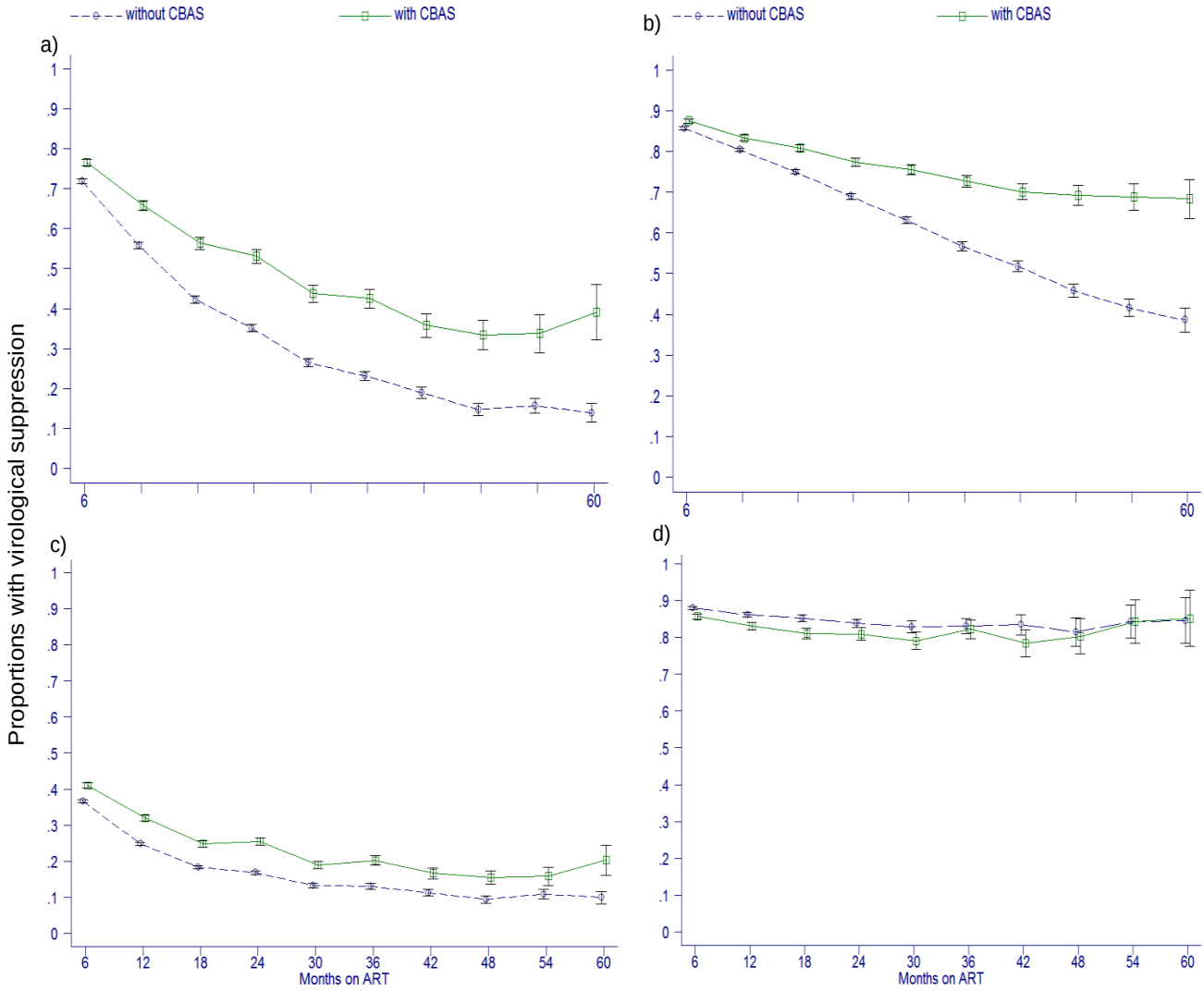


Figure 2: Proportions of patients achieving virological suppression in (a) intention to treat (ITT) analyses censoring missing values, (b) ITT analyses regarding missing values as suppressed, (c) ITT analyses regarding missing values as unsuppressed and (d) on-treatment analyses.

Error bars are 95% confidence intervals. CBAS-community-based adherence support

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CHAPTER 3: HIV Incidence in Pregnant and Postpartum Women Receiving a Community-Based Combination HIV Prevention Intervention in a High HIV Incidence Setting in South Africa

Citation: Fatti G, Shaikh N, Jackson D, Goga A, Nachega JB, Eley B, Grimwood A. Low HIV incidence in pregnant and postpartum women receiving a community-based combination HIV prevention intervention in a high HIV incidence setting in South Africa. PloS One. 2017;12(7):e0181691

This article is published in final format in *PLoS One* (Journal Impact Factor 2.80 at time of publication).

Article URL: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0181691

Overview

This study evaluated the effectiveness of a community-based combination HIV prevention intervention for pregnant and postpartum women and their children in a high HIV-incidence setting in South Africa. HIV incidence amongst HIV-uninfected pregnant and postpartum women who received the intervention was measured, and factors associated with HIV acquisition were assessed.

Contribution to thesis and novelty

This study forms objective 2 of the thesis. This study addresses an important knowledge gap regarding the effectiveness of combination HIV prevention interventions during pregnancy and postpartum. Evaluations of community-level interventions for maternal and neonatal health are also a research priority, and this study yields valuable evidence regarding the effectiveness of one such intervention.

Contributions of candidate

The candidate designed the study, wrote the study protocol, obtained relevant permissions from the Department of Health, performed the data management, personally analysed the data, wrote and managed all drafts of the manuscript, and was the corresponding author with the journal. The candidate also contributed to data collection procedures for the study including data systems support, merging of databases, performing data quality checks, generating data queries, and support of data collection personnel. Co-authors critically reviewed and approved the submitted manuscripts, and any comments were assessed by and where appropriate integrated by the candidate. All authors read and approved the published version.

PLOS ONE

RESEARCH ARTICLE

Low HIV incidence in pregnant and postpartum women receiving a community-based combination HIV prevention intervention in a high HIV incidence setting in South Africa

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Citation: Fatti G, Shaikh N, Jackson D, Goga A, Nachega JB, Eley B, et al. (2017) Low HIV incidence in pregnant and postpartum women receiving a community-based combination HIV prevention intervention in a high HIV incidence setting in South Africa. PLoS ONE 12(7): e0181691. https://doi.org/10.1371/journal.pone.0181691

Editor: Dimitrios Paraskevis, National and Kapodistrian University of Athens, GREECE

Received: January 20, 2017

Accepted: July 4, 2017

Published: July 27, 2017

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The Positive Action for Children's Fund, ViiV Healthcare, funded the implementation of the program that was evaluated in this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background

Young Southern African women have the highest HIV incidence globally. Pregnancy doubles the risk of HIV acquisition further, and maternal HIV acquisition contributes significantly to the paediatric HIV burden. Little data on combination HIV prevention interventions during pregnancy and lactation are available. We measured HIV incidence amongst pregnant and postpartum women receiving a community-based combination HIV prevention intervention in a high HIV incidence setting in South Africa.

Methods

A cohort study that included HIV-uninfected pregnant women was performed. Lay community-based workers provided individualized HIV prevention counselling and performed three-monthly home and clinic-based individual and couples HIV testing. Male partners were referred for circumcision, sexually transmitted infections or HIV treatment as appropriate. Kaplan-Meier analyses and Cox's regression were used to estimate HIV incidence and factors associated with HIV acquisition.

Competing interests: The Positive Action for Children's Fund, ViiV Healthcare, funded the implementation of the program that was evaluated in this study. ViiV Healthcare did not provide employment or consultancy for any of the investigators. Neither the program nor the study involved any patents, products in development, or marketed products related to ViiV Healthcare. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

Results

The 1356 women included (median age 22.5 years) received 5289 HIV tests. Eleven new HIV infections were detected over 828.3 person-years (PY) of follow-up, with an HIV incidence rate of 1.33 infections/100 PY (95% CI: 0.74–2.40). Antenatally, the HIV incidence rate was 1.49 infections/100 PY (95% CI: 0.64–2.93) and postnatally the HIV incidence rate was 1.03 infections/100 PY (95% CI: 0.33–3.19). 53% of male partners received HIV testing and 66% of eligible partners received referral for circumcision. Women within known serodiscordant couples, and women with newly diagnosed HIV-infected partners, adjusted hazard ratio (aHR) = 32.7 (95% CI: 3.8–282.2) and aHR = 126.4 (95% CI: 33.8–472.2) had substantially increased HIV acquisition, respectively. Women with circumcised partners had a reduced risk of incident HIV infection, aHR = 0.22 (95% CI: 0.03–1.86).

Conclusions

Maternal HIV incidence was substantially lower than previous regional studies. Community-based combination HIV prevention interventions may reduce high maternal HIV incidence in resource-poor settings. Expanded roll-out of home-based couples HIV testing and initiating pre-exposure prophylaxis for pregnant women within serodiscordant couples is needed in Southern Africa.

Background

Southern Africa is the epicentre of the HIV pandemic having the highest burden of HIV globally [1]. Young women and adolescent girls are the demographic group having the highest HIV incidence, up to eight-fold higher than their male peers, attributed to complex social, behavioural, biologic and structural factors [2–4].

HIV acquisition is further increased two to four-fold during pregnancy, due to biological and behavioural factors including immunological changes, hormonal changes affecting the genital tract mucosa, higher frequency of unprotected sex and incident sexually transmitted infections (STIs) during pregnancy [5–9]. HIV incidence remains increased during the postnatal period [10,11]. In addition, mother-to-child transmission (MTCT) amongst women who acquire HIV during pregnancy/lactation is double to triple compared to women who acquire HIV prior to pregnancy [11,12], and contributes significantly to the Southern African pediatric HIV burden [13,14].

HIV prevention in young women in sub-Saharan Africa is a public health imperative [15], and prevention efforts during pregnancy and postpartum should be particularly prioritized due to the increased risk of HIV acquisition in both women and infants [10,11]. Prevention efforts have included structural, biomedical and behavioural interventions [16]. Behavioural interventions have reported modest impact on self-reported HIV-preventive behaviours but little impact on HIV incidence [3,17]. Biomedical prevention for pregnant and breastfeeding women in South Africa is limited due to oral pre-exposure prophylaxis (PrEP) being contraindicated in current guidelines because of limited safety data regarding the developing fetus and infant [18,19], despite the World Health Organization's (WHO) guidelines indicating that PrEP "can be used during pregnancy" [20]. As HIV epidemics are complex due to a variety of contextual risk factors, programs that incorporate comprehensive combination interventions are important [3,4].

Health systems interventions involving community-based workers have become increasingly important in sub-Saharan Africa due to severe professional health worker shortages and the WHOs recommendations regarding task-shifting [21,22]. Lay health worker interventions have shown successes in HIV treatment programs [23,24], and the South African Department of Health's strategy to re-engineer primary healthcare emphasizes the critical role of community health workers [25].

An important current knowledge gap is the lack of data regarding the effectiveness of combination HIV prevention interventions during pregnancy and postpartum [4,26]. Evaluating community-level interventions for maternal and neonatal health is also a current research priority [27].

A combination HIV prevention intervention for pregnant and postpartum women utilizing community-based health workers has recently been established in KwaZulu-Natal province, South Africa, a region having high HIV incidence [6,28]. This study aimed to measure this interventions effectiveness in preventing incident HIV infection in this vulnerable key population, and to investigate factors associated with HIV acquisition, and were aims that were achieved.

Methods

Study design, setting and inclusion criteria

A cohort study utilizing enhanced routine clinical data was performed at an urban primary healthcare facility north of Durban in eThekwini district. The district antenatal HIV prevalence in 2013 was 41.1% having increased from 38.0% in 2011 [29], with HIV incidence in nonpregnant women being 6.4 infections/100 person-years (PY) [28].

All pregnant women who presented for antenatal care between 01 March 2013 and 31 May 2015 who tested HIV-negative at the first antenatal visit, who gave informed consent to enrol in the community-based program, and who had one or more follow-up HIV tests at least 8 weeks after the initial HIV test were included in analyses. Women were followed-up with their infants until the earliest of 18 months postpartum, transfer to another clinic, loss to follow-up (LTFU), mortality, or 28 February 2016. For HIV-infected pregnant and breastfeeding women, national guidelines recommended WHO option B (immediate triple ART until the end of breastfeeding or lifelong if CD4 cell count $<$ 350 cells/μL) prior to January 2015 [30], and lifelong ART irrespective of CD4 cell count thereafter [31].

Community-based combination HIV prevention intervention

The intervention aimed to reduce HIV incidence in pregnancy and postpartum, thus to reduce the number of infants being HIV-exposed. Behavioural and psychosocial component interventions included individual counselling and education for women and their male household partners regarding HIV risk and safe sex practices (including promotion of condom use), education regarding multiple and concurrent sexual partnerships, couples counselling, counselling regarding HIV serodiscordant couples, addressing alcohol and substance abuse, assessing and addressing mental health needs, and group HIV prevention education at the clinic. Biomedical interventions involved provision of male and female condoms, home and clinic-based three-monthly individual and couples HIV testing and counselling (HTC) by community workers throughout pregnancy until 18 months postpartum, facilitated linkage to HIV care facilities for either partner testing HIV positive with subsequent antiretroviral treatment (ART) adherence counselling, referral of eligible men for voluntary male medical circumcision (VMMC), and symptom screening of women and male partners for sexually transmitted infections (STIs) with referral for treatment if symptomatic. A structural component of the intervention

involved assessment and counselling and referral for gender-based violence as required, and discussion regarding gender identities and roles.

All women were assigned a community-based healthcare worker, named a Patient Advocate (PA), who provided home and clinic-based support two to three-weekly until six weeks postpartum, and monthly thereafter. PAs also provided education regarding contraception and reproductive health, infant health and feeding practices, encouraged women to attend all antenatal and infant immunization clinic visits, and supported women to access government social security grants. Non-household male partners were invited to receive HTC at the facility through word of mouth messages, invitation cards and telephonic invitations, but were not physically traced to their homes.

Disclosure of HIV serostatus was addressed by PAs at enrolment and during HIV test counselling. HIV test results were kept confidential by PAs (including in the case of minors with regards to caregivers). PAs discussed possible disclosure of positive HIV status of participants to others (including partners and caregivers); however, the decision whether to disclose HIV status resided with the participant. An anonymized key was used to identify study participants for data analyses.

The intervention was instituted by Kheth'Impilo, a nonprofit organization supporting the Department of Health with public health systems innovations. PAs originally provided community-based adherence support to ART patients [24,32], and have more recently been utilized for HIV prevention.

Outcomes and definitions

The primary outcome was the HIV incidence rate and cumulative HIV incidence amongst HIV-uninfected pregnant and postpartum women. Secondary outcomes (other program effectiveness and process measures) were: I) HIV incidence during pregnancy; II) Postpartum HIV incidence (until 18 months); III) Socio-demographic factors associated with incident HIV infection; IV) MTCT at 6 weeks postpartum amongst women with incident HIV infection prior to 6 weeks postpartum (proportion of HIV-tested infants testing HIV positive); V) Time from diagnosis until ART initiation amongst women with incident HIV; VI) Proportion of women with incident antenatal HIV infection who initiated ART antenatally; VII) Maternal mortality rate; VIII) Cumulative probability of LTFU of enrolled women; IX) Socio-demographic factors associated with LTFU; X) Proportion of male partners who received HTC (with recorded test results); XI) Proportion of partners testing HIV positive successfully linked with HIV care facilities; XII) Time from HIV diagnosis till ART initiation amongst partners eligible to initiate ART; XIII) Proportion of eligible partners referred for VMMC.

Adult HIV testing was performed using the Advanced Quality$^{(TM)}$ Rapid Anti-HIV (1&2) test, and positive tests were confirmed with the Abon$^{(TM)}$ HIV 1/2/O Tri-line Rapid test device. Infant HIV testing was performed with HIV deoxyribosenucleic acid polymerase chain reaction (PCR) testing. Maternal deaths were recorded as per professional healthcare worker or PA report and defined as deaths during pregnancy or until 42 days of termination of pregnancy related to or aggravated by the pregnancy. LTFU was defined as no contact with clinic staff or PA for at least 120 days from last recorded visit, or if reported as LTFU by the PA. Men eligible to be referred for VMMC were uncircumcised males (by self-report) or who had unknown circumcision status who tested HIV negative or who had unknown HIV status.

Data collection and statistical analyses

Enhanced routine clinical data were prospectively collected by site-based data capturers from clinical records in a custom-designed electronic database following participant clinic visits.

PAs collected home visit data with paper forms. Data accuracy were reviewed by the district data co-ordinator and data queries resolved by site and community-based staff.

For HIV incidence, person-time was calculated from the first negative HIV test to the last negative HIV test or the midpoint of the first positive test and the preceding negative test for those who tested positive [33]. Person-time was also calculated using the first positive HIV test date for those who tested positive; results were only insignificantly changed and results are presented using the midpoint as the time of infection. Participants transferring to other facilities were censored at the last visit date. Cumulative HIV incidence and the cumulative probability of LTFU were estimated using Kaplan-Meier analyses, and the logrank test used to compare exposure categories. Cox's proportional hazards regression was used to estimate univariable and multivariable hazard ratios (HR) for associations of exposures with incident HIV infection and LTFU. Variables associated with the outcomes were included in multivariable models where their *P*-value in univariable models were ≤ 0.1. The Efron method was used to approximate the exact conditional probability of tied failure times [34]. Proportional hazards assumptions were assessed by comparing Kaplan-Meier observed survival curves and Cox predicted curves for each variable, and statistical testing for nonzero slope of scaled Schoenfeld residuals on functions of time. Model overall goodness-of-fit was assessed by plotting Cox-Snell residuals vs. the Nelson-Aalen cumulative hazard estimator. Data were analysed with Stata version 13.1 (College Station, TX, USA)$^{(TM)}$. The University of Cape Town Human Research Ethics Committee granted ethical approval for the study.

Results

3480 pregnant women presented for antenatal care during the enrolment period. The following were excluded (S1 Fig): 1583 women known or found to be HIV-infected at the first antenatal visit; 135 who declined consent to participate in the program; 329 who received no follow-up HIV tests (short-term visitors to the area who transferred-out of the program); and 77 whose final HIV test result was < 8 weeks after the initial test. Thus, 1356 women were included in analyses.

At baseline, the median age was 22.5 years (IQR: 19.4–27.0 years) and 30% were adolescents (aged ≤ 19 years) (Table 1). The median gestational age at presentation was 16 weeks (IQR: 12–16 weeks). Almost two-thirds of women requested contraception counselling; 70% required support to access government grants, and 7% requested counselling regarding gender-based violence.

HIV incidence

Included women received 5289 HIV tests with a median of 4 HIV tests per woman. During 828.3 person-years of follow up, 11 new HIV infections were detected, yielding an HIV incidence rate of 1.33 infections/100 PY (95% CI: 0.74–2.40). Cumulative HIV incidence after 12 months of follow-up was 0.92% (95% CI: 0.51%-1.66%).

Antenatally (i.e. between the first negative antenatal HIV test and delivery), eight new HIV infections were detected during 537 person-years of follow-up, with an antenatal HIV incidence rate of 1.49 infections/100 PY (95% CI: 0.64 to 2.93) and cumulative HIV incidence during pregnancy of 0.68% (95% CI: 0.29%-1.33%). Postnatally, three new cases of HIV were detected over 291 person-years, with an incidence rate of 1.03 infections/100 PY (95% CI: 0.33–3.19).

Table 1 shows HIV incidence according to socio-demographic characteristics of women and their partners. Women with known HIV-infected partners at enrolment had an HIV incidence rate of 40.3 infections/100 PY (95% CI: 5.67–286.0). Women whose partners had newly

Table 1. Baseline characteristics and HIV incidence according to characteristics of pregnant women and their partners in South Africa.

	Total, N (%)	Infections/ 100 PY	Incidence rate per 100 PY (95% CI)	*P*-value*
Overall	1356 (100.0)	11/828.3	1.33 (0.74–2.40)	-
Age at baseline				0.0303[$]
14–19 years	410 (30.2)	0/248.9	0 (0–1.48)	
20–24 years	488 (36.0)	5/305.4	1.63 (0.68–3.93)	
≥ 25 years	458 (33.8)	6/273.9	2.19 (0.98–4.88)	
Gestational age at first visit				
< 14 weeks	427 (31.5)	4/278.2	1.44 (0.54–3.83)	0.853
14–27 weeks	882 (65.0)	7/526.1	1.33 (0.63–2.78)	
≥ 28 weeks	47 (3.5)	0/24.0	0 (0–15.3)	
Requested contraception counselling?				0.72
Yes	892 (65.8)	9/631.7	1.42 (0.74–2.73)	
No	464 (34.2)	2/196.5	1.01 (0.25–4.06)	
Support to access social security grant				0.748
Support given	954 (70.4)	9/693.7	1.30 (0.67–2.49)	
Support not given	402 (29.7)	2/134.5	1.49 (0.37–5.94)	
Required gender-based violence counselling or referral				0.368
No	1264 (93.2)	11/769.5	1.43 (0.79–2.58)	
Yes	92 (6.8)	0/58.7	0 (0–6.2)	
Initial circumcision status of partner				0.011
circumcised	625 (46.1)	1/393.0	0.25 (0.04–1.80)	
not circumcised	484 (35.7)	7/303.9	2.30 (1.10–4.83)	
not recorded	247 (18.2)	3/131.4	2.28 (0.73–7.07)	
Partners HIV status				<0.0001
HIV uninfected	717 (52.9)	0/544.1	0 (0–0.7)	
Known HIV infected at enrolment	4 (0.3)	1/2.48	40.3 (5.67–286.0)	
Newly diagnosed HIV-infected	5 (0.4)	4/1.81	221.4 (83.1–590)	
not HIV tested/unknown status	630 (46.5)	6/279.9	2.1 (0.96–4.77)	

*P-values estimated by the log-rank test comparing HIV incidence.

[$]log-rank test for trend.

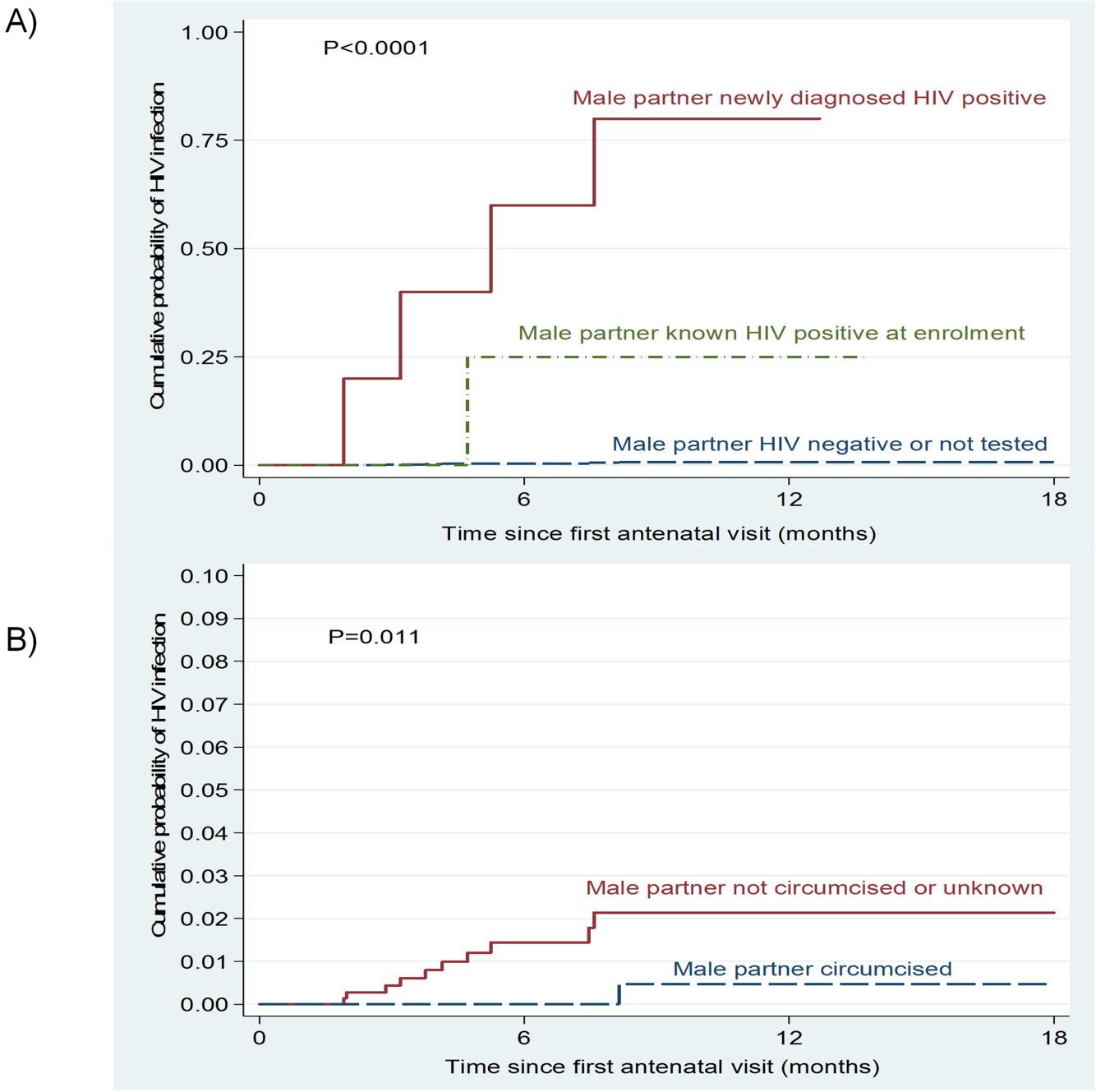
PY-person years.

https://doi.org/10.1371/journal.pone.0181691.t001

diagnosed HIV infection had very high HIV incidence, being 221.4 infections/100 PY (95% CI: 83.1–590) with a cumulative probability of acquiring HIV twelve months after the first visit of 80.0% (95% CI: 41.8%-99.1%) (Fig 1A). In contrast, women whose partners were HIV-uninfected or who had unknown HIV serostatus had an incidence rate of 0.73 infections/100 PY (95% CI: 0.33–1.62) and a cumulative probability of acquiring HIV of 0.8% (95% CI: 0.3%-1.8%) twelve months after the first visit (logrank P <0.0001). Amongst women with incident HIV infection (n = 11), 45.5% had HIV-infected male partners and the remaining partners had unknown HIV serostatus.

HIV incidence in women was higher where the male partner was uncircumcised (2.30 infections/100 PY [95% CI: 1.10–4.83] vs. 0.25 infections/100 PY [95 CI: 0.04–1.80] where male partner circumcised; P = 0.011) (Fig 1B).

Table 2 shows univariable and multivariable analyses of factors associated with incident HIV infection (n = 1356). Women with known HIV-infected male partners, adjusted hazard ratio (aHR) = 32.7 (95% CI: 3.8–282.2), and women whose partners were newly diagnosed with HIV infection, aHR = 126.4 (95% CI: 33.8–472.2) had substantially increased HIV



N at risk at beginning of interval (events) according to partner status:

Newly HIV +ve	5	(3)	3	(1)	2	(0)	1
known HIV +ve	4	(1)	4	(0)	2	(0)	1
HIV –ve/untested	1347	(4)	723	(2)	211	(0)	61
Not circumcised /UNK	731	(8)	375	(2)	119	(0)	25
Circumcised	625	(0)	353	(1)	95	(0)	36

Fig 1. Kaplan-Meier failure estimates of time till HIV infection amongst HIV-negative pregnant women. A) According to male partner's HIV serostatus, B) According to male partner's circumcision status.

https://doi.org/10.1371/journal.pone.0181691.g001

Table 2. Univariable and multivariable Cox regression of factors associated with incident maternal HIV infection (n = 1356).

	Univariable Hazard Ratio (HR)	Univariable 95% CI for HR	*P*	Multivariable HR	95% CI for multivariable HR	*P*
Age at baseline						
< 25 years	1.0 (Ref)	-				
≥ 25 years	2.42	0.73–7.94	0.14	-		
Gestational age at first visit						
< 14 weeks	1.0 (Ref)	-				
≥ 14 weeks	0.92	0.26–3.15	0.90	-		
Required contraception counselling	1.32	0.28–6.21	0.73	-		
Received support to access social security grant	0.77	0.15–3.79	0.75	-		
Male partner's initial circumcision status						
not circumcised or unknown	1.0 (Ref)	-		1.0 (Ref)	-	
circumcised	0.11	0.01–0.86	0.035	0.22	0.03–1.86	0.16
Male Partner's HIV status						
uninfected or not tested	1.0 (Ref)	-		1.0 (Ref)	-	
known HIV-infected	52.4	6.3–438.3	<0.0001	32.7	3.8–282.2	0.001
newly diagnosed HIV infection	202.3	56.9–719.0	<0.0001	126.4	33.8–472.2	<0.0001

https://doi.org/10.1371/journal.pone.0181691.t002

acquisition. Women with circumcised partners at baseline had a reduced risk of incident HIV infection, although this did not reach statistical significance at the 95% level in the multivariable model, aHR = 0.22 (95% CI: 0.03–1.86).

Secondary outcomes

Table 3 lists the secondary study outcomes. Women with incident HIV infection initiated ART on the same day as HIV diagnosis in most cases, and all women with antenatal incident HIV infection initiated ART antenatally. Amongst women with incident HIV infection, MTCT at 6 weeks postpartum was 22.2%.

One (0.07%) maternal death was recorded, with a maternal mortality rate of 0.12 deaths/100 PY (95% CI: 0.02 to 0.85). During the study period, 122 (9.0%) women become LTFU. The cumulative probability of LTFU twelve months after the first antenatal visit was 10.8% (95% CI: 9.1%-12.8%). Table 4 shows the multivariable model of factors associated with LTFU (n = 1356; 122 events). Women who first attended antenatal facilities in late pregnancy and women aged ≥ 25 years had increased risks of LTFU. Women who received support to access social security grants, women whose partners received HTC, and women who received family planning counselling had reduced LTFU.

Amongst male partners, 722 (53.4%) received HTC and had a recorded HIV test result, of whom 60.0% received home-based HTC. Five (0.7%) partners were newly diagnosed with HIV infection. Amongst those women who acquired HIV and who had male partners with newly diagnosed HIV infection (n = 4), all the partners first accepted HTC only after the women tested HIV-positive (median 4.5 days). All the newly diagnosed HIV-infected male partners were successfully linked with HIV care facilities; however, only 1/5 (20%) initiated ART (seven days after HIV diagnosis), as the remainder had CD4 cell counts greater than 500 cells/μL and were not eligible to initiate ART according to prevailing South African ART guidelines. Amongst partners with recorded HIV serostatus and recorded baseline circumcision status, HIV prevalence was considerably higher in uncircumcised males (3.3%) vs. 0.0% in

Table 3. Secondary study outcomes evaluating a combination HIV prevention intervention amongst pregnant and postpartum women in South Africa.

	Point estimate	95% Confidence interval (or IQR)
Antenatal HIV incidence, infections/100 person-years	1.48	0.64 to 2.92
Postnatal HIV incidence, infections/100 person-years	1.03	0.33 to 3.19
Vertical HIV transmission amongst infants (at age six weeks) amongst women with incidence HIV infection, n/N (%)	2/9* (22.2%)	2.8% to 60%
Time since diagnosis until initiating ART amongst women with incident HIV infection, days	0	IQR: 0–0
Proportion of women with incident antenatal HIV infection who initiated ART antenatally, n/N (%)	8/8 (100%)	63.1% to 100%
Maternal mortality rate, deaths/person-years (deaths/100 person-years) [& #]	1/832.7 (0.12)	0.02 to 0.85
Cumulative probability of loss to follow-up 12 months after the first antenatal visit, %[#]	10.8%	9.1% to 12.8%
Proportion of eligible male partners received HTC with recorded test results, n/N (%)	722/1352 (53.4%)	50.7% to 56.1%
Proportion of male partners who received HTC with newly diagnosed HIV infection, n/N (%)	5/722 (0.7%)	0.2% to 1.6%
Proportion of newly diagnosed HIV-infected male partners linked to HIV care facilities, n/N (%)	5/5 (100%)	47.8% to 100.0%
Time from HIV diagnosis till ART initiation amongst males partners eligible to initiate ART, days	7	-
Proportion of eligible male partners referred for VMMC, n/N (%)**	476/722 (65.9%)	68.9% to 76.1%

* Two women tested HIV positive more than six weeks after birth, thus their infants did not receive HIV testing at the six week immunization visit.

[#] From Kaplan-Meier analyses.

** Eligible males were uncircumcised males (or who had unknown circumcision status) who tested HIV negative or who had unknown HIV status.

[&] Deaths during pregnancy or until 42 days of termination of pregnancy related to or aggravated by the pregnancy

ART-antiretroviral treatment; IQR-interquartile range; VMMC-voluntary male medical circumcision; HTC-HIV testing and counselling.

https://doi.org/10.1371/journal.pone.0181691.t003

Table 4. Factors associated with loss to follow-up amongst pregnant and postpartum women enrolled in a combination HIV prevention intervention in South Africa.

	Univariable Hazard Ratio (HR)	Univariable 95% CI for HR	*P*	Multivariable HR	95% CI for multivariable HR	*P*
Age at baseline						
< 20 years	1.0 (Ref)	-		1.0 (Ref)	-	
20–24 years	1.11	0.69–1.78	0.66	1.08	0.67–1.73	0.75
≥ 25 years	1.58	1.00–2.47	0.047	1.57	1.00–2.47	0.048
Gestational age at first visit						
< 14 weeks	1.0 (Ref)	-		1.0 (Ref)	-	
14–27 weeks	1.14	0.77–1.69	0.50	1.63	1.07–2.42	0.015
≥ 28 weeks	1.99	0.83–4.71	0.10	3.63	1.52–8.70	0.004
Required gender-based violence counselling or referral	1.64	0.93–2.92	0.090	1.52	0.78–2.96	0.21
Received contraception counselling	0.22	0.16–0.32	<0.001	0.58	0.35–0.97	0.036
Received support to access social security grant	0.14	0.09–0.20	<0.001	0.31	0.18–0.53	<0.001
Male partner received HTC						
No	1.0 (Ref)	-			1.0 (Ref)	-
Yes	0.16	0.10–0.24	<0.001	0.30	0.18–0.51	<0.001

HTC-HIV testing and counselling.

https://doi.org/10.1371/journal.pone.0181691.t004

circumcised males (P <0.0001). Amongst partners eligible for VMMC, 65.9% accepted referral for VMMC.

Discussion

In a high HIV incidence area of South Africa, HIV incidence was found to be low amongst pregnant and postpartum women who received a community-based combination individual and couple's HIV prevention intervention. Previous studies have found HIV incidence amongst nonpregnant female adolescents in the same district to be 17.2 infections/100 PY [28]; 10.7 infections/100 PY during pregnancy (all ages) in South Africa [6]; and 16.8 infections/100 PY during pregnancy in neighbouring Swaziland [35]. A recent systematic review and meta-analysis of HIV incidence during pregnancy/postpartum in Southern Africa indicated HIV incidence of 4.8 infections/100 PY (95% CI: 3.5–6.4) [11]. Recent South African data from a national survey estimated cumulative HIV incidence during pregnancy to be 3.3% (95% CI: 2.8%-3.8%) [14]. The maternal HIV incidence rate measured in our study thus represents a decrease of 73%–86% compared to previously published Southern African studies.

One of South Africa's strategic health objectives is to reduce HIV incidence by 50% by the end of 2016 [36]. However, to decrease HIV incidence and prevalence over a 50-year timescale, it has recently been shown that substantial scale-up of combination HIV prevention programs will be required [37]. Community health workers have been drafted as a priority workforce in South Africa's approach to re-engineering primary healthcare [25]. This community-based intervention shows promise in reducing high HIV incidence amongst pregnant and postpartum women.

MTCT amongst women acquiring HIV during pregnancy was high, similar to previous studies [12,13], and is due to high maternal HIV viral load and reduced transfer of protective immunity to the child during acute maternal infection [38].

Male involvement and uptake of partner HTC in antenatal settings in sub-Saharan African is low [39–41]. Partner HTC uptake in this intervention was considerably higher than in a previous South African trial (11%-32%) [42]. Most previous studies investigating incident HIV infection during pregnancy/lactation did not attempt to record male partner's HIV serostatus [6,10,35,43,44]. One Kenyan study recorded partner's HIV status as reported by women [9]. Our study is unusual in that it attempted to directly measure partner's HIV serostatus; and found that almost half of incident infections in women were associated with the main partner being HIV-infected. It is notable that amongst woman who acquired HIV and whose partners tested HIV-positive, partners first accepted HTC only after the woman seroconverted. The serostatus of the partner was thus initially unknown, and the couple may not have taken precautions to minimize transmission. Prioritizing HTC of partners (and initiating ART if required) as early as possible during pregnancy is thus important to detect serodiscordant couples and to minimize transmission risk.

Circumcision does not decrease the risk of HIV transmission from HIV-infected men to uninfected women [45]. The protective effect of partner circumcision in our study is likely an indirect effect related to lower HIV prevalence amongst circumcised partners who had unknown HIV status, as amongst males with known HIV status, uncircumcised males had considerably higher HIV prevalence.

Concerns and uncertainty about the safety of tenofovir disoproxil fumarate (TDF)-based PrEP during pregnancy and lactation have prevented large-scale PrEP implementation amongst women of child-bearing age. Indeed, current South African public sector HIV guidelines consider PrEP use for commercial sex workers only [46,47], while private sector guidelines consider PrEP contraindicated during pregnancy and breastfeeding and do not address

the issue of PrEP for HIV-uninfected pregnant and breastfeeding women within serodiscordant couples [18]. Given the efficacy of PrEP in preventing HIV acquisition amongst adherent women (up to 75% risk reduction in heterosexual African couples) [48], and balanced with potential concerns of the effect of PrEP on the fetus/infant, it has recently been suggested that studies should identify subgroups of pregnant/postpartum women at high risk of acquiring HIV, and limit provision of PrEP to these subgroups [9,49]. Notably, studies involving breastfeeding HIV-infected women and their infants showed very low exposure to TDF from breast milk [50,51]. Also, duration of in-utero exposure to TDF was not associated with infant early linear growth [52]. There are few studies of TDF in HIV-uninfected women. However, data from hepatitis B virus (HBV) mono-infected pregnant women showed foetal/infant exposure to TDF was not associated with any adverse outcomes, and TDF reduced perinatal HBV transmission [53–55]. Data from two PrEP studies in HIV-uninfected women are similarly reassuring [19,56]. Given the limited available safety data, ongoing surveillance is needed, but the benefits of PrEP use for pregnant/lactating women at high risk of HIV acquisition (and associated increased risk of MTCT) appears to far outweigh the potential risks of foetal, infant and maternal TDF exposure [57]. Therefore, strong consideration should be given to revising South African guidelines to include initiation and maintenance of PrEP for HIV-uninfected women within serodiscordant couples during pregnancy and breastfeeding. Recent cost-effectiveness modelling has shown that provision of PrEP to pregnant/breastfeeding women in sub-Saharan Africa would likely be cost-effective [49].

Challenges to the program included women not always being available for home visits or clinic groups because of work commitments; broaching issues regarding age-disparate and concurrent sexual relationships during individual counselling; and inconsistent uptake of HTC amongst men.

The strengths of the study include that prospective cohort data were collected that enabled detection of incident HIV throughout pregnancy and postpartum. The routine urban setting with high HIV incidence indicates that results would likely be generalizable to other high HIV incidence Southern African settings. LTFU was reasonable, considering that LTFU of pregnant women from health programs in Southern Africa may be substantial [58,59].

The study limitations include the lack of a comparison cohort who did not receive the intervention to directly measure the effect of the intervention. Due to the data's routine nature, a relatively small number of potential predictors of HIV acquisition were available for analysis. Although the few incident HIV infections was encouraging, low case numbers resulted in imprecise effect measures of factors associated with incident HIV infection. Partner HIV testing frequently post-dated that of the female partner due to slower uptake of male HIV testing, thus for those partners who tested HIV-positive at initial testing, we could not distinguish prevalent male partner HIV infection at baseline (i.e. the pregnant women's first antenatal clinic visit) from incident male HIV infection during the woman's follow-up. The proportion of referred men who received VMMC was also unavailable in the routine dataset.

In conclusion, low HIV incidence amongst pregnant and postpartum women in a high HIV incidence setting was observed amongst women who received a community-based combination HIV prevention intervention for women and couples. Incident HIV cases were highly associated with serodiscordant couples and new HIV diagnoses in male partners. Expanded roll-out of combination HIV prevention interventions incorporating home-based couples HTC for pregnant women and partners in high HIV prevalence settings should be considered, attempting early uptake of HTC amongst males and referral for VMMC or ART initiation as indicated. Together with ART for HIV-infected partners, initiating PrEP for HIV-uninfected pregnant and breastfeeding women within serodiscordant couples should be considered to decrease both maternal HIV incidence and pediatric HIV. Increased frequency of HIV testing

of pregnant women (4–6 weekly) should be considered, and further research is needed regarding innovative and feasible strategies to enhance early HTC uptake for partners.

Supporting information

S1 Fig. Flow chart of women included and excluded from analyses.
(PDF)

Acknowledgments

The authors thank and acknowledge study participants and the KwaZulu-Natal Department of Health.

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Investigation: Geoffrey Fatti.

Methodology: Geoffrey Fatti.

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Visualization: Geoffrey Fatti.

Writing – original draft: Geoffrey Fatti.

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CHAPTER 4: A Comparison of Two Task-Shifting Models of Pharmaceutical Care in Antiretroviral Treatment Programs in South Africa

Citation: Fatti G, Monteith L, Shaikh N, Kapp E, Foster N, Grimwood A. Implementation and Operational Research: A Comparison of Two Task-Shifting Models of Pharmaceutical Care in Antiretroviral Treatment Programs in South Africa. J Acquir Immune Def Syndr. 2016;71(4):e107-13.

This article is published in final format in the *Journal of Acquired Immune Deficiency Syndromes* (Journal Impact Factor 3.93 at time of publication).

Article URL:

https://journals.lww.com/jaids/fulltext/2016/04010/Implementation_and_Operational_Research__A.13.aspx

Overview

This study compared two task-shifting pharmaceutical care models for ART delivery in high HIV prevalence settings in South Africa. The study compared the effectiveness and cost of the Indirectly Supervised Pharmacist Assistant (ISPA) model and the nurse-dispensing (NIMART) model and was conducted at 15 primary healthcare clinics. Three aspects of the models were compared, namely: A) the quality of pharmaceutical care; B) patient clinical outcomes and C) provider costs to implement each model.

Contribution to thesis and novelty

This study forms objective 3 of the thesis. At the time of publication, there were no

published data comparing the quality of pharmaceutical care or the clinical effectiveness of ART amongst patients who access sites that have adopted these task-shifting models.

Contributions of candidate

The candidate wrote the study protocol, obtained relevant permissions from the Department of Health, performed the data management, personally analysed the data, wrote and managed all drafts of the manuscript, and was the corresponding author with the journal. The candidate also contributed to data collection procedures for the study including data systems support, merging of databases, performing data quality checks, generating data queries, and support of data collection personnel. Co-authors critically reviewed and approved the submitted manuscripts, and any comments were assessed by and where appropriate integrated by the candidate. All authors read and approved the published version.

“This is a non-final version of an article published in final form in J Acquir Immune Def Syndr. 2016;71(4):e107-13”

A Comparison of Two Task-Shifting Models of Pharmaceutical Care in Antiretroviral Treatment Programs in South Africa

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Presented in part at the 7th South African AIDS conference, Durban, South Africa, 9-12 June 2015.

Sources of support: President's Emergency Plan for AIDS Relief, United States Agency for International Development

Running head: Task-Shifting ART Pharmaceutical Care Models

ABSTRACT

Background

The severe shortage of pharmacists is an important limitation to providing antiretroviral treatment (ART) in resource-limited countries. Two task-shifting pharmaceutical care models have been developed to address this in South Africa, namely Indirectly Supervised Pharmacist Assistant (ISPA) and nurse-managed models. This study compared pharmaceutical care quality, patient clinical outcomes, and provider staff costs between these models.

Methods

An analysis of pharmaceutical quality audits, patient clinical data and staff costing data collected at seven ISPA and eight nurse-managed facilities was undertaken. Pharmaceutical audits were conducted by pharmacists using a standardized tool. Routine clinical data were collected prospectively at patient visits, and staff human resources costs were analysed.

Results

Overall pharmaceutical care quality scores were higher at ISPA sites than nurse-managed sites; 88.8% vs. 79.9%, respectively; risk ratio (ISPA vs. nurse)=1.11 (95% CI: 1.09-1.13; P<0.0001). Mean provider pharmaceutical-related human resources costs per patient visit and per item dispensed were 29% and 49% lower, respectively, at ISPA facilities. At ISPA facilities, patient attrition was observed to be lower and viral suppression higher than at nurse-managed sites.

Conclusion

The ISPA model had a higher quality of pharmaceutical care and was less costly to implement. Further expansion of this model or integrating it with nurse-managed ART may enhance the cost-efficient scale-up of ART programs in Sub-Saharan Africa.

Key Words: antiretroviral treatment; pharmaceutical care; task-shifting; pharmacist assistant; South Africa; nurse initiated and managed ART

INTRODUCTION

Sub-Saharan Africa (SSA) has 25% of the world's disease burden but only 1.3% of the world's health workers.(1) This shortage of human resources for health is a critical limitation to the provision of antiretroviral treatment (ART) to those in need of it in SSA, the region having the highest burden of HIV globally.(2,3) The lack of qualified human resources is a major challenge to meeting the United Nations three 90% targets for testing, treatment coverage and viral suppression by 2020.(4)

Pharmaceutical services also experience staff shortages and workload pressure, particularly as the ART program has expanded so rapidly during the last decade.(5,6) The African region has the lowest density of pharmaceutical staff worldwide (0.8 per 10,000 population, almost five-fold lower than the region with the next-lowest density).(7) Pharmaceutical care is an important component of the ART program, and addresses potential pharmaceutical-related problems and promotes patient adherence.(8) Excellent adherence is critical to individual patient's wellbeing and to prevent the development of viral resistance which may compromise the effectiveness of the ART program.(9) The shortage of pharmacists also deprives the population of vital expertise in the management of drug-related problems.(10) Factors contributing to the shortage of pharmacists include a shortage of training institutions, migration of pharmacists to developed countries, an urban/rural maldistribution of pharmacists and the majority of pharmacists working in the private sector serving a small proportion of the population.(6,8)

To address staff shortages and facilitate increased scale-up of the ART program, task-shifting for mid-level workers to perform the tasks of more highly trained health workers has been recommended by the World Health Organization.(11) Task-shifting the clinical management of ART patients from doctors to nurses has been shown to produce comparable patient ART outcomes.(12) Training lower cadres of pharmacy workers has also been recommended to promote pharmaceutical care for ART programs in SSA.(8)

South Africa has the world's largest ART program with over 2.6 million people who have started ART.(3) There remains, however, a great need to initiate people onto ART as only 42% of adults living with HIV receive ART.(3) Two pharmaceutical care models have recently developed in the country involving firstly, indirectly supervised pharmacist assistants (ISPAs), and secondly, clinical nurse practitioners who issue pharmaceuticals. A previous economic evaluation has found the ISPA model to be the least costly pharmaceutical model in the ART program, but did not include measures of quality of care or patient outcomes.(6) Evaluation of the quality of care is an important part of the quality assurance mechanism for task-shifting approaches.(11) There are no published data comparing the quality of pharmaceutical care or the clinical effectiveness of ART amongst patients who access sites that have adopted these two models. The aim of this study was to compare the ISPA and nurse-managed dispensing of ART models in terms of I. the quality of pharmaceutical care, II. clinical outcomes of ART patients accessing these services, and III. the cost of providing each of the approaches from a health services perspective.

METHODS

Study design and setting

A retrospective analysis of pharmaceutical care quality audits, patient clinical data and staff costing data collected from seven ISPA facilities and eight nurse-managed facilities was undertaken in South Africa. All the facilities were primary healthcare sites. The ISPA facilities were located in the Cape Town metropolitan district, Western Cape, and the nurse-managed facilities were located in KwaDukuza sub-district of Ilembe, KwaZulu-Natal province. All facilities were supported by Kheth'Impilo, a nonprofit organization that supports the South African Department of Health with health systems strengthening innovations and pharmaceutical services. The selected facilities were all of the ISPA facilities supported by Kheth'Impilo, and all the primary healthcare facilities supported by Kheth'Impilo in KwaDukuza sub-district. (There were no ISPA facilities located in KwaDukuza and no nurse-managed facilities in Cape Town).

Description of pharmaceutical care models

Indirectly Supervised Pharmacist Assistant model

ISPAs are post-basic pharmacist assistants who have received an additional 6-12 months of on-site training and mentoring by a registered pharmacist in order to work under the indirect supervision of a pharmacist. Post-basic pharmacist assistants are a cadre of mid-level workers, specifically trained to manage pharmaceutical stock control, issue medication, provide medication information to patients, advise on

adherence, and intervene where needed regarding the legality of prescriptions. They are registered with the South African Pharmacy Council after achieving competence in accredited course material and completing two years of in-service training in a pharmacy registered for training. The Pharmacy Act allows post-basic pharmacist assistants to work under the indirect supervision of a pharmacist in primary healthcare setting under certain specific conditions: Only patient-ready packs can be dispensed; all pharmacy-related standard operating procedures must be available, read and signed by the ISPA; and a pharmacist must visit the site at least once per month and document the visit. The ISPAs are expected to take responsibility for pharmaceutical services within their scope of practice at site level. Responsibilities include the dispensing of ART, management of the dispensary, and management of all orders and stock in the facility. The Designated Supervisory Pharmacists (DSPs) supervise up to five ISPAs (who work in clinics other than where the DSP is based), visit the clinics once per week to oversee the ISPA functions, and perform an audit of the site pharmaceutical service monthly. Additional training and mentoring of ISPAs is provided by the DSP to ensure continued quality of care while working under indirect supervision.

Nurse-managed sites

In order to expand the ART program, nurse initiated and managed ART (NIMART) was introduced in South Africa in 2010.(13) At certain sites, clinical nurse practitioners issue prescriptions which are dispensed by pharmacists or ISPAs at the pharmacy or dispensary. However, in the nurse-managed pharmaceutical model, nurses issue pharmaceuticals during patient consultations, which was the model adopted at the nurse-managed sites included in this study during 2012, and is a

model which has been widely implemented. Small supplies of pharmaceuticals are kept in the consultation rooms with additional medication fetched from the medicine room on a daily basis. Nurses also perform stock ordering, stock control and general management of the medicine rooms. At the two largest sites, post-basic pharmacist assistant's supported nurses in the medicine rooms being involved with stock ordering and stock control, but they were not trained in indirect supervision and did not dispense pharmaceuticals. A roving DSP oversaw pharmaceutical care within the district and performed a quality audit at the sites on a monthly basis.

Data collection and analysis

1. Pharmacy quality audits

Standardized audit tools were developed to routinely assess the quality of pharmaceutical care at sites where ART is offered. The audit form assessed four components of pharmaceutical care, namely 1) Good Pharmacy Practice (13 point score); 2) stock control (12 point score); 3) evaluation of prescription and patient folders (scores depended on the number of folders evaluated and ranged from 30-600, with six points per folder); 4) patient exit interview (checking of medication label and standardized questions posed to 10-20 patients after they had received medication. For folder evaluations, pharmacists randomly selected folders of existing ART patients to review, as well as all folders of new patients initiated on ART by nurses in the preceding month, thus the number of folders evaluated per month per site was variable. The pharmacists selected consecutive patients on the day that the pharmacist visited the clinic for exit interviews. Structured exit interview questions included assessing the patient's knowledge of the indication for the medication, knowledge of the use and storage of the medication, and rating the patient's

satisfaction with the dispensing process. The results of routine monthly audits conducted by DSPs between January 2013 and December 2013 were analysed. Scores for each section were calculated as a proportion, and proportions were compared using risk ratios (RRs) and 95% binomial exact confidence intervals. Overall weighted scores combining all four sections were calculated for each dispensing model such that the score from each section contributed an equal weight to the overall score.

2. Clinical data

All ART-naive adults ≥ 16 years of age who commenced triple ART at the 15 clinics between 01 January 2012 and six months prior to site database closure were included in analyses. Site database closure varied slightly between the sites (between December 2013 and October 2014). Prior to April 2013, HIV-positive adults and adolescents were eligible to start ART if they had a CD4 cell count ≤ 200 cells/μl and/or a World Health Organisation (WHO) stage IV defining illness; were pregnant or had tuberculosis with a CD4 cell count ≤350 cells/μl; or had multidrug resistant tuberculosis irrespective of CD4 cell count.(13) From April 2013, ART eligibility criteria were expanded to include all patients with CD4 cell counts ≤350 cells/μl and/or a WHO stage III or IV defining illness, and all pregnant women irrespective of CD4 cell count.(14) Standardized first-line regimens consisted of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor.

Routine, individual-level patient data were collected prospectively for patient monitoring purposes by designated site-based data capturers at each patient visit using standardized custom-designed electronic databases, with data being regularly pooled to a central data warehouse using standard operating procedures. Regular data cleaning and quality control procedures were implemented.

Patients were followed up from the start of ART until the earliest of loss to care (through mortality or loss to follow-up), transfer-out to another facility, or two years after starting ART. Patients transferring to other facilities were censored on the date of last clinic visit. The clinical outcomes analysed were patient attrition (through death or loss to follow-up) after starting ART and proportions of patients achieving virological suppression on ART. Patients were recorded as having died based on health care worker or community-health worker reports. A patient was defined as lost to follow-up if no visits to the clinic occurred for 180 days or more.(15) Virological suppression was defined as a viral load < 400 copies/ml.

Kaplan-Meier estimates were used to analyse time until patient attrition. For patients who did not return to the clinic after starting ART, one day of survival time was added in order to include them in survival analyses.

3. Cost data

An incremental ingredients costing method was used to estimate the mean human resource costs per patient visit and per item dispensed for the period January 2013

to December 2013, and then compared between the two pharmaceutical models of care. Salary unit costs were derived from staff salary records in Cape Town and estimated from Department of Public Service and Administration Circulars of Occupational Specific Dispensation salaries for KwaZulu-Natal with levels supplied by the Department of Health. Human resources costs pertaining to pharmaceutical-related activities only were considered. Pharmaceutical-related activities were defined as any staff activity pertaining to ordering and management of pharmaceutical stock, maintenance of medicine rooms and time spent issuing medication and counselling patients regarding correct use of medication. Costs related to clinical consultation and medication costs were not considered. In both models, the cost of pharmacist supervision was also included (above-service level cost). All costs are presented in 2013 prices and were converted to United States (US) dollars at the average exchange rate in 2013 of US$1 = ZAR 10.34.(16)

At nurse-managed sites, professional nurses worked in the medicine room doing stock control and ordering, and also consulted patients and issued medicine. The Full Time Equivalent (FTE) of nurses doing stock control and ordering at sites were estimated based on interviews with facility managers. The average proportion of time that consulting nurses spent on pharmaceutical-related activities was assumed to be 32%, derived from a previous time and motion study.(6) A sensitivity analysis was also performed assuming lesser and greater proportions of 28% and 36%, respectively.(6) At ISPA facilities, ISPAs spent the majority of their time managing and dispensing medication for ART patients, and cost calculations were limited to estimated expenditure related to ART patient visits. A proportion of their time (and that of the DSPs) was related to stock control and stock ordering for general primary

healthcare pharmaceuticals. The FTE spent for ART patient related activities was derived from interviews with DSPs and the district program manager, and was assumed to be 80% for ISPAs and 62.5% for DSPs.

Population and health services characteristics of the provinces and districts in which the two pharmaceutical models were located were compared using Pearson's χ^2 test where numeric data were available. Data were analysed using Microsoft Excel(R) and Stata version 13 (College Station, TX, USA). Ethical permission for the study was provided by the University of Cape Town Human Research Ethics Committee. Permission for the study was also granted by the City of Cape Town health and the KwaZulu-Natal department of health research committee.

RESULTS

Key characteristics of the population and health services of the districts in which the two pharmaceutical models were located are tabulated in Table 1. The region in which the nurse-managed clinics were located had a higher antenatal HIV prevalence rate, higher HIV testing coverage, a lower provincial rate of loss to follow-up amongst ART patients and equivalent viral suppression amongst ART patients, compared to the region in which the ISPA clinics were located.

1. Quality of Pharmaceutical care

The results of the pharmaceutical care audits are shown in table 2. Good Pharmacy Practice scores were 15% higher (relatively) at ISPA compared to the nurse-

managed clinics (overall 84.0% at ISPA sites vs. 73.3% at nurse clinics; RR= 1.15 [95% CI: 1.09-1.20]; P<0.0001). Stock control scores were 12% higher at ISPA sites (90.2% at ISPA sites vs. 80.4% at nurse clinics; RR=1.12 [95% CI: 1.08-1.17]; P<0.0001). Evaluation of prescription and patient folder scores were similar between models, RR=1.01 [95% CI: 1.00-1.03]; P=0.071). Standardized patient exit interview scores were 17% higher at ISPA sites (89.1% at ISPA sites and 75.9% at nurse clinics; RR= 1.17 [95% CI: 1.16-1.19]; P<0.0001). The overall weighted score was 11% higher at ISPA sites (88.8% at ISPA and 79.9% at nurse clinics; RR=1.11 [95% CI: 1.09-1.13]; P<0.0001). Figure 1 shows patient exit interview scores according to month during 2013.

2. Clinical outcomes

10,751 patients were included in clinical analyses, of whom 5406 (50.3%) attended ISPA sites. Characteristics at the start of ART were similar between patients at ISPA and nurse sites: The median age was 32.9 years at ISPA sites and 33.4 years at nurse sites; men accounted for 37.5% of patients at ISPA sites and 39.6% at nurse sites; the median CD4 cell count was 220 cell/µL (IQR: 121-300) at ISPA sites and 226 cells/µL (IQR: 129-303) at nurse sites; and in both groups 47% of patients were in World Health Organization clinical stages 3 or 4.

During 11,514 patient-years of follow-up, 217 deaths were recorded and an additional 1965 patients became lost to follow-up. Figure 2 shows the Kaplan-Meier cumulative probabilities of patient attrition according to duration of ART. After two years, cumulative attrition at ISPA and nurse-managed sites was 20.7% (95% CI:

19.4%-22.0%) and 31.5% (30.0%-33.2%), respectively. After two years, the Kaplan-Meier cumulative probabilities of reported mortality were 1.7% (95% CI: 1.3%-2.1%) and 3.8% (95% CI: 3.2%-4.6%) at ISPA and nurse-managed sites, respectively; and the cumulative probabilities of loss to follow-up were 19.3% (95% CI: 18.0%-20.6%) and 28.8% (95% CI: 27.2%-30.4%) at ISPA and nurse-managed sites, respectively.

A total of 8897 viral load results were available to analyze. After one year of ART, the proportion of patients in the cohort achieving virological suppression at ISPA and nurse-managed sites was 89.6% (95% CI: 87.9%-91.1%) and 85.9% (95% CI: 83.7%-88.0%), respectively.

3. Costing results

Table 3 shows the human resources involved with pharmaceutical related activities and mean provider staff costs per patient visit and per item dispensed. The mean cost per patient visit was US$ 1.35 at ISPA and US$ 1.89 at nurse-managed facilities, i.e. 29% lower at ISPA facilities. The mean cost per item dispensed was US$ 0.43 at ISPA and US$ 0.84 at nurse-managed facilities, i.e. 49% lower at ISPA facilities.

Table 4 shows the sensitivity analysis when using low and high assumptions regarding the proportion of time that dispensing nurses spent on dispensing-related activities. The proportionate savings at ISPA facilities per patient visit varied between 21% and 35%, and per item dispensed varied between 44% and 54%, i.e. they were reasonably stable using the differing assumptions.

DISCUSSION

Pharmaceutical care is an important determinant of the success of the ART program,(8,17) and will play an important role for Sub-Saharan Africa achieving the UNAIDS goal of 90% of diagnosed HIV-positive people receiving ART and 90% being virologically suppressed by 2020.(4) In light of the shortage of pharmacists in Sub-Saharan Africa, task-shifting pharmaceutical care from pharmacists to lower cadres of workers has become essential to address the human resources required for the ART program. This is the first study to our knowledge that has compared the quality of pharmaceutical care and patient clinical outcomes between two task-shifting approaches to pharmaceutical care in Sub-Saharan Africa.

Pharmaceutical quality of care was found to be higher at ISPA sites than at nurse-managed sites. There have been anecdotal reports of possible compromised quality of pharmaceutical care at nurse-managed sites,(6) as well as a lack of maintenance of pharmacy records.(18) Quality may be reduced where the prescriber and the dispenser are the same person, due to a lack of quality control. The focussed training, support and mentoring regarding pharmaceutical care which ISPAs receive likely enhances the quality of pharmaceutical management and dispensing at ISPA sites. Although in a previous study qualitative exit interviews found patients preferred the anonymity of receiving ART in the consultation room at nurse-managed sites instead of at the dispensary at ISPA sites,(6) quantitative patient exit interview scores in this study (which included client satisfaction) were 17% higher at ISPA

sites. It may be that patients are more comfortable receiving medication at dispensaries in more recent years as a result of reduced stigma.

Patient clinical outcomes were observed to be better at ISPA managed sites. A previous study found that patient clinical outcomes were equivalent between patients at ISPA sites and patients accessing sites having a full-time pharmacist.(19) As the clinics utilizing the two pharmaceutical care models in the current study were located in different provinces, local differences in health systems and population differences may have influenced clinical ART outcomes. HIV prevalence was higher in the province in which the nurse-managed clinics were located; however, provincial ART outcomes during the study period were not inferior in the province in which the nurse-managed sites were situated.(20) Geographic differences may, nevertheless, have contributed to differences in the clinical ART outcomes observed in this study, and it was not possible to quantify the effect of the pharmaceutical care model attributable to observed differences in clinical outcomes independently from other health systems and population level factors.

Provider staff costs for pharmaceutical-related activities were lower for the ISPA model per patient visit and per item dispensed. The ISPA model was also considerably less expensive in an economic evaluation conducted in 2009/2010.(6) Cost differences between the models may be explained due to the considerably lower salaries of ISPAs than professional nurses. Compared to the evaluation in 2009/2010, costs per patient visit were considerably lower for both models. This is likely related to the doubling and tripling of patient to staff ratios between the evaluations as the number of patients on ART has increased considerably.(5) The

33% depreciation of the South African Rand to the USD between the two evaluations further contributed to this difference.

Nurses who manage ART patients in South Africa have high workloads and have much work pressure.(18,21) A vacancy rate of 40% amongst nurses has been reported in South Africa,(22) with estimates that up to 50% of nurses time may be required for ART program data collection and management.(23) The importance of supporting nurses who manage ART patients with other lower staff cadres has previously been highlighted.(18) The two pharmaceutical models are not mutually exclusive, and considering that the salary of an ISPA is lower than that of a professional nurse, nurse-managed sites should be able to cost-effectively employ ISPAs to take over the role of pharmaceutical care to ease the workload burden of nursing staff, which may result in improvements in both pharmaceutical care and patient clinical care. A dispensing ISPA employed at nurse managed sites would free up nurse time which may allow a greater number of patients to receive clinical consultations, thus expanding the capacity of the overburdened ART program. The ISPA model could thus compliment the NIMART program which has been extensively rolled out in South Africa.

The strengths of the study include that three aspects of the pharmaceutical models were compared, that data were drawn from a relatively large number of sites, and that clinical data from a large patient cohort were collected prospectively. The limitations of the study include that sites adopting the two pharmaceutical models were situated in different provinces of South Africa, and that routine data were utilised to calculate patient clinical outcomes. For the cost analysis, assumptions had

to be made regarding the proportion of time that ISPAs and DSPs spend on non-ART related activities as accurate measurements were not available.

Conclusions

The ART program in Sub-Saharan Africa requires considerable expansion using cost-effective interventions to reach those in need of treatment and achieve the targets set by UNAIDS for 2020 and 2030, while simultaneously sustaining a high quality of care for patients currently receiving treatment. Expansion of pharmaceutical care capacity is a necessary component of scaling-up this program. This study has found that facilities that adopted the ISPA model had a better quality of pharmaceutical care, were less costly to manage, and were possibly associated with improved clinical outcomes. Further research comparing facility characteristics such as patient waiting times and investigating the ease of scale-up and sustainability of the models is warranted. Further qualitative research utilizing interviews with nursing staff may be helpful to assess the burden on nurses regarding consulting and dispensing medication simultaneously. In the interim, further expansion of the ISPA pharmaceutical model and integrating it with NIMART care would likely enhance the cost-efficient scale-up of the ART program in Sub-Saharan Africa and other regions where expansion of treatment access is urgently needed.

Acknowledgements

The authors wish to acknowledge participants included in the study, the departments of Health of the Western Cape and KwaZulu-Natal, the City of Cape Town Health,

the Elton John AIDS Foundation, the United States Agency for International Development and the President's Emergency Plan for AIDS Relief.

Tables, chapter 4:

Table 1: Characteristics of the population and health services of the clinics and districts in which the two pharmaceutical models were located

	Characteristic	Indirectly Supervised Pharmacist Assistant clinics	Nurse-managed clinics	P-value
Population characteristics	**District population size, 2011**	2,361,000[1]	231,000[2]	
	District antenatal clinic HIV prevalence, 2012[3]	18.6%	37.4%	< 0.0001
	Estimated provincial proportion of HIV-positive population receiving ART, 2011[4]	35.4%	39.2%	
	District HIV testing coverage, 2013/2014[5]	6.0%	30.4%	
Health services provision characteristics	**Number of persons receiving ART at included clinics, 2013**	11,694	14,679	
	Provincial proportion of patients who started ART lost to follow-up after 12 months (patients started 2012/2013)[6]	20.9%	18.7%	<0.001
	Provincial proportion of patients achieving viral load suppression after 48 months of ART[6]	84.2%	84.8%	0.42
	Method of tracing defaulting patients	Clinic-linked community health workers	Clinic-linked community health workers	
	Nongovernmental organization support	Kheth'Impilo provided pharmaceutical	Kheth'Impilo provided	

		services support and community-based services support. Yabonga supported one clinic with community care services.	pharmaceutical services support and community-based services support. SACTWU supported voluntary male medical circumcision services.
	Initial ART regimen used	Two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor	Two nucleoside reverse tran-scriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor

1. Population of the five sub-districts in Cape Town in which the ISPA clinics were located. Note that numerous other clinics also served this population

2. Population of KwaDukuza sub-district. The clinics included are eight of the nine clinics serving this population.

3. Source: South African National Department of Health. The 2012 National antenatal sentinel HIV and herpes simplex type 2 prevalence survey in South Africa. Pretoria, 2013.

4. Sources: Johnson, L. Access to Antiretroviral Treatment in South Africa, 2004-2011. *The Southern African Journal of HIV Medicine.* 2012;13(1):22-27 and Actuarial Society of South Africa AIDS and Demographic model 2008. March 2011.

5. Number of people aged 15 to 49 years tested for HIV as a percentage of the total population in this age group. Source: Massyn N, Day C, Peer N, Padarath A, Barron P, English R, editors. District Health Barometer 2013/14. Durban: Health Systems Trust; October 2014.

6. Source: South African National Department of Health. ART Programme analysis: Reviewing the ART Programme from April 2004 to March 2014., Pretoria, 2014.

ART-antiretroviral treatment

Table 2: Pharmaceutical care audit scores at indirectly supervised pharmacist assistant (ISPA) and nurse-managed facilities in South Africa

Audit section	Clinic Type	Score Percent	Binomial 95% CI	Risk ratio (ISPA vs. nurse)	95% CI for the risk ratio	P-value
Good Pharmacy Practice	ISPA	84.0%	81.7%-86.1%	1.15	1.09-1.20	<0.0001
	Nurse	73.3%	70.0%-76.2%			
Stock control	ISPA	90.2%	88.2%-91.2%	1.12	1.08-1.17	<0.0001
	Nurse	80.4%	77.3%-83.1%			
Evaluation of prescriptions and folders	ISPA	91.3%	90.0%-92.3%	1.01	1.00-1.03	0.071
	Nurse	90.2%	89.8%-90.5%			
Patient exit interview	ISPA	89.1%	88.6%-89.6%	1.17	1.16-1.19	<0.0001
	Nurse	75.9%	75.1%-76.6%			
Weighted total score	ISPA	88.8%	87.9%-89.7%	1.11	1.09-1.13	<0.0001
	Nurse	79.9%	78.6%-81.1%			

Table 3: Facility human resources involved with pharmaceutical related activities and average provider costs

	ISPA facilities[1]	Nurse managed facilities
Number of sites	7	8
Staff FTE assisting in pharmaceutical related activities		
Pharmacists	0.9	0.6
Indirectly Supervised Pharmacist Assistants	9.3	-
Post-Basic Pharmacist Assistants	-	5
Professional nurses[2]	0	23.5
Annual number of items dispensed	420 332	1 121 537
Annual number of patient visits	132 834	497 488
Ratio FTE pharmacy related staff to monthly patient visits	1:1085	1:1423
Provider staff cost per patient visit (US$), mean	1.35	1.89
Provider staff cost per item dispensed (US$), mean	0.43	0.84

[1] Values refer to staff and activities limited to HIV-related care.

[2] Nurses who consulted patients and issued medicines were assumed to spend an average of 32% of their time with pharmaceutical related activities.

ISPA, indirectly supervised pharmacist assistant; FTE, full time equivalent

Table 4: Sensitivity analysis of average provider costs using alternate assumptions of nurse time related to pharmaceutical care

	Assumed proportion of nurse time related to pharmaceutical care (nurse sites only)	ISPA facilities	Nurse managed facilities	Proportionate savings at ISPA facilities
Provider staff cost per patient visit, mean	28%	US$ 1.35	US$ 1.71	21.0%
	36%	US$ 1.35	US$ 2.07	34.8%
Provider staff cost per item dispensed, mean	28%	US$ 0.43	US$ 0.76	43.7%
	36%	US$ 0.43	US$ 0.92	53.5%

Figures, chapter 4:

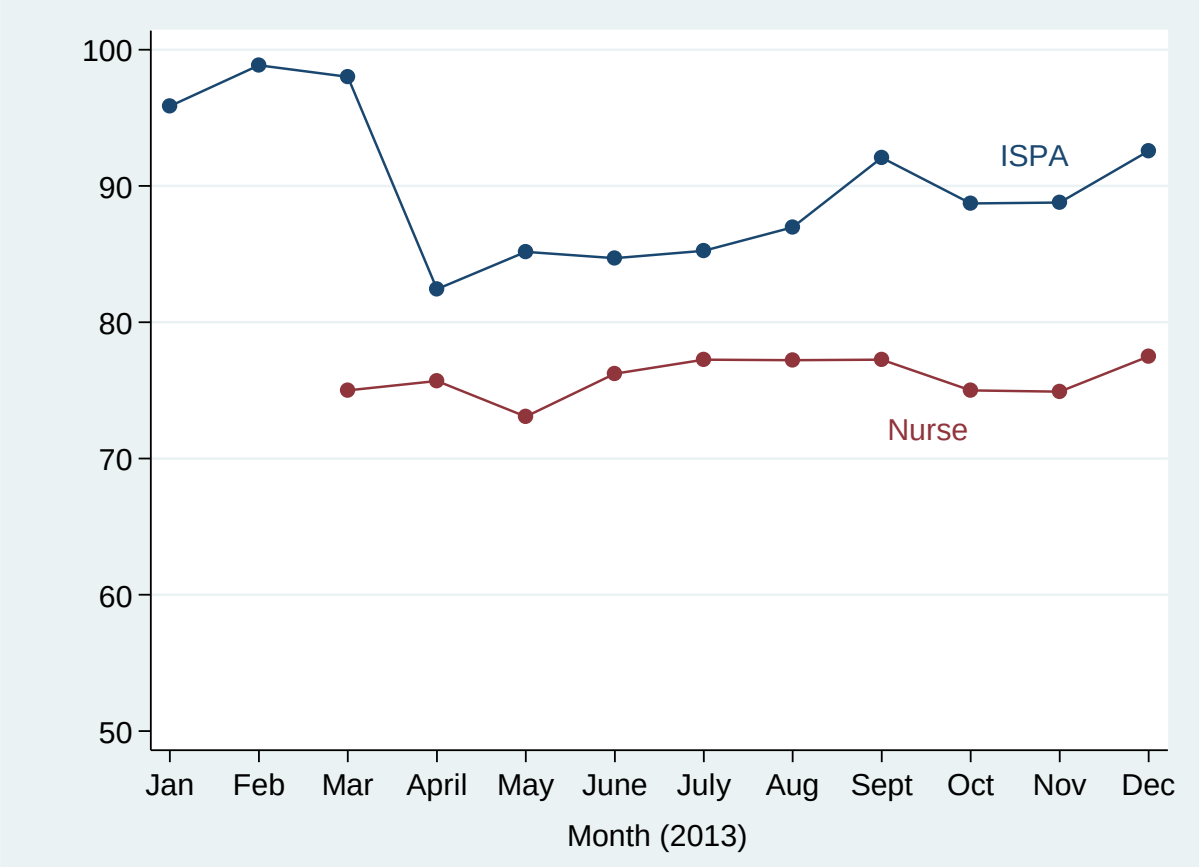

Figure 1: Pharmaceutical care exit interview scores amongst patients who attended indirectly supervised pharmacist assistant (ISPA) and nurse-managed facilities according to month in 2013.

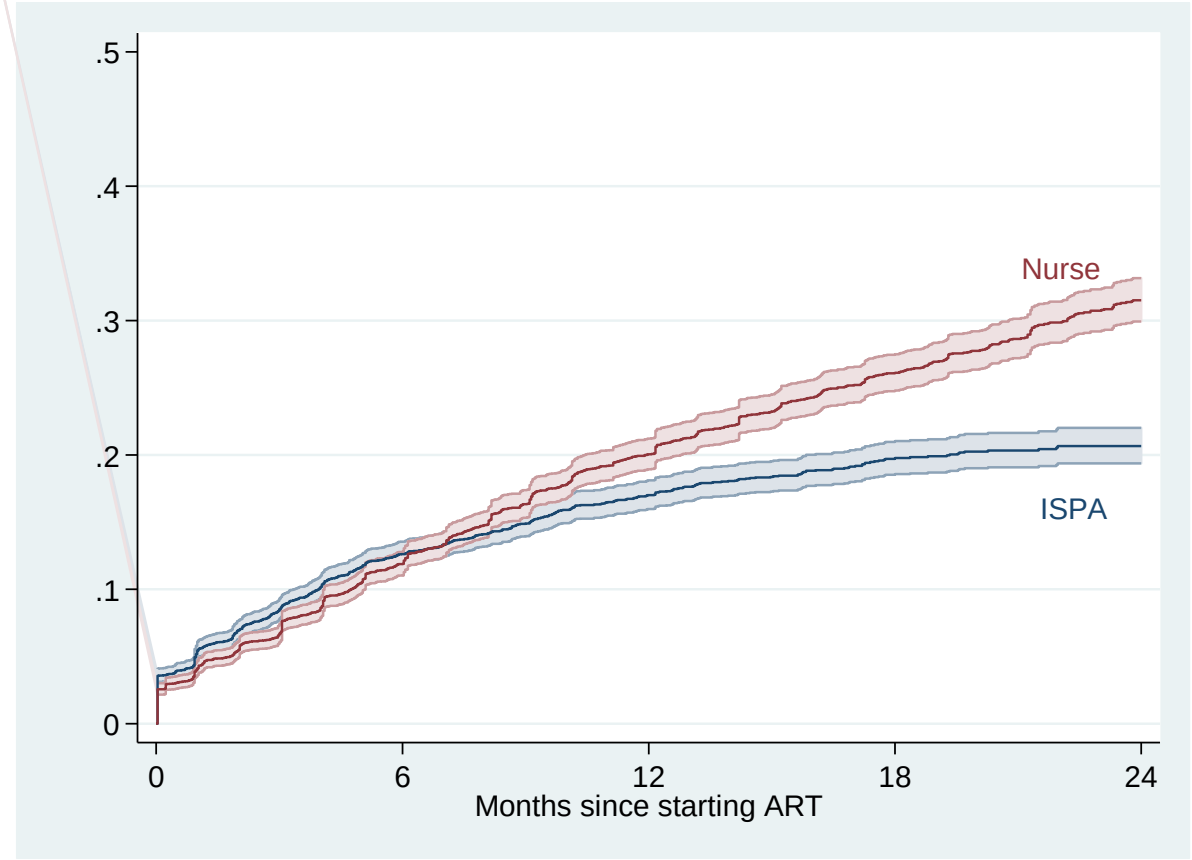

Figure 2: Kaplan-Meier curves of patient attrition at ISPA and nurse-managed facilities in South Africa

Shaded areas are 95% confidence intervals

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CHAPTER 5: The Effectiveness and Cost-Effectiveness of Community-Based Support for Adolescents Receiving Antiretroviral Treatment: an Operational Research Study in South Africa

Citation: Fatti G, Jackson D, Goga AE, Shaikh N, Eley B, Nachega JB, Grimwood A. The effectiveness and cost-effectiveness of community-based support for adolescents receiving antiretroviral treatment: an operational research study in South Africa. Journal of the International AIDS Society. 2018;21(Suppl 1): e25041

This article is published in final format in the *Journal of the International AIDS Society* (Journal Impact Factor 5.19).

Article URL: https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25041

Overview

This study evaluated the effectiveness and cost-effectiveness of community-based support for adolescents and youth receiving ART at 61 facilities in four provinces of South Africa. Clinical outcomes, immunological and virological outcomes, ART adherence, and implementation costs were compared between adolescents and youth who did, and who did not receive community-based support from ART initiation in order to evaluate the effectiveness of the intervention. The manuscript was submitted and successfully selected for a special edition of the Journal of the International AIDS Society/Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) entitled "*Paediatric and Adolescent HIV and the Sustainable Development Goals: the road ahead to 2030."* The manuscript was written in such a way to indicate the contribution and relevance of task-shifting interventions (particularly community-based support) for adolescent HIV care in progress toward achieving the interlinked United Nations Sustainable Development Goals (SDGs) by 2030.

Contribution to thesis and novelty

This study forms objective 4 of the thesis. The evidence base for interventions that enhance retention and adherence amongst adolescents in high HIV-burden settings is sparse. This study is one of the first to evaluate both the effectiveness and cost-effectiveness of community-based support for adolescent and youth receiving ART, and which included a substantial sample size (6706 participants). In addition, the importance and relevance of community-based support for adolescent HIV care in producing progress toward achieving the United Nations SDGs has not been previously delineated.

Contributions of candidate

The candidate was the Principal Investigator for the study, conceptualized the study, designed the study, wrote the study protocol, performed the data management, personally analysed the data, wrote and managed all drafts of the manuscript, and was the corresponding author with the journal. The candidate was also closely involved with data collection procedures for the study including data systems development and support, merging of databases, performing data quality checks, generating data queries, and support of data collection personnel. Co-authors critically reviewed and approved the submitted manuscripts, and any comments were assessed by and where appropriate integrated by the candidate. All authors read and approved the published version.

Fatti G et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25041
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25041/full | https://doi.org/10.1002/jia2.25041

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

The effectiveness and cost-effectiveness of community-based support for adolescents receiving antiretroviral treatment: an operational research study in South Africa

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Abstract

Introduction: Adolescents and youth receiving antiretroviral treatment (ART) in sub-Saharan Africa have high attrition and inadequate ART outcomes, and evaluations of interventions improving ART outcomes amongst adolescents are very limited. Sustainable Development Goal (SDG) target 3c is to substantially increase the health workforce in developing countries. We measured the effectiveness and cost-effectiveness of community-based support (CBS) provided by lay health workers for adolescents and youth receiving ART in South Africa.

Methods: A retrospective cohort study including adolescents and youth who initiated ART at 47 facilities. Previously unemployed CBS-workers provided home-based ART-related education, psychosocial support, symptom screening for opportunistic infections and support to access government grants. Outcomes were compared between participants who received CBS plus standard clinic-based care versus participants who received standard care only. Cumulative incidences of all-cause mortality and loss to follow-up (LTFU), adherence measured using medication possession ratios (MPRs), CD4 count slope, and virological suppression were analysed using multivariable Cox, competing-risks regression, generalized estimating equations and mixed-effects models over five years of ART. An expenditure approach was used to determine the incremental cost of CBS to usual care from a provider perspective. Incremental cost-effectiveness ratios were calculated as annual cost per patient-loss (through death or LTFU) averted.

Results: Amongst 6706 participants included, 2100 (31.3%) received CBS. Participants who received CBS had reduced mortality, adjusted hazard ratio (aHR) = 0.52 (95% CI: 0.37 to 0.73; $p < 0.0001$). Cumulative LTFU was 40% lower amongst participants receiving CBS (29.9%) compared to participants without CBS (38.9%), aHR = 0.60 (95% CI: 0.51 to 0.71); $p < 0.0001$). The effectiveness of CBS in reducing attrition ranged from 42.2% after one year to 35.9% after five years. Virological suppression was similar after three years, but after five years 18.8% CBS participants versus 37.2% non-CBS participants failed to achieve viral suppression, adjusted odds ratio = 0.24 (95% CI: 0.06 to 1.03). There were no significant differences in MPR or CD4 slope. The cost of CBS was US$49.5/patient/year. The incremental cost per patient-loss averted was US$600 and US$776 after one and two years, respectively.

Conclusions: CBS for adolescents and youth receiving ART was associated with substantially reduced patient attrition, and is a low-cost intervention with reasonable cost-effectiveness that can aid progress towards several health, economic and equality-related SDG targets.

Keywords: HIV; antiretroviral treatment; adolescents; United Nations Sustainable Development Goals; community-based support; cost-effectiveness

Received 8 May 2017; **Accepted** 11 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

The UN Sustainable Development Goals (SDGs) are 17 universal, ambitious and interrelated goals established to guide the development policy and agenda of member states till 2030 [1]. UNAIDS has also set ambitious HIV treatment targets to help end the AIDS epidemic by 2030 (SDG 3.3) [2]. For the SDGs to be achievable, evidence-based interventions need to be implemented [3], and to reach the UNAIDS treatment goals, innovative and efficient healthcare service delivery models are required [4].

Amongst adolescents in sub-Saharan Africa (SSA), progress towards the SDGs and HIV prevention and care goals are particularly lagging [5,6]. Adolescents in SSA have the highest HIV incidence globally [7,8], and adolescents are the only demographic group in whom AIDS-related mortality is

increasing, having tripled since 2000 [9,10]. Adolescents and youth receiving antiretroviral treatment (ART) have poorer patient retention and treatment outcomes than adults [11-15]. Ensuring high retention is a crucial aspect of the ART programme to maximize treatment outcomes [16], as well as to reduce community viral load to prevent horizontal transmission [17,18]. ART programmes retention in SSA is poor, being only 56% after five years [19]. The barriers to retention amongst adolescents and youth are numerous and diverse, and include the burden of multiple vulnerabilities, barriers to healthcare access, mental health needs, a lack of psychosocial support, a lack of trained healthcare workers focusing on adolescent-specific care, and lack of support during the transition from paediatric to adult care [20-23]. Appropriate, individualized, holistic and durable interventions that support adolescent's clinical, psychosocial and nutritional care have been suggested [20,21,23].

In SSA, adolescents and youth form the greatest proportion of the population (over 33%), and SSA is the only region in which this group continues to grow substantially [24]. The health of adolescents is crucial that they may meaningfully contribute to the economy [25,26]. Their economic potential will support progress towards SDGs 1, 2, 8 and 9 to reduce poverty and hunger, promote economic growth and build industry. As SSA has very high HIV prevalence amongst adolescents and youth [27], promoting the health of adolescents and youth living with HIV is essential for the region to make meaningful progress towards the SDGs over and beyond health-related SDGs.

HIV-infected adolescents are a neglected group [28]. Recent systematic reviews indicate that the evidence base for adherence and retention-enhancing interventions amongst HIV-infected adolescents and youth is very sparse, and that most studies focussed on high-income countries and had low participant numbers [23,28,29]. These reviews conclude that identifying effective interventions that improve ART outcomes amongst adolescents is overdue. Evidence of the longer-term effectiveness and cost-effectiveness of adherence and retention-enhancing interventions are particularly lacking [30]. The limited evidence that exists suggests that interventions that include individualized psychosocial support, counselling and education, and the provision of specific adolescent-tailored services are promising and require further investigation [23,28,29].

SSA also has critical shortages of professional healthcare workers–particularly aggravated due to the HIV/AIDS epidemic–and needs to substantially increase its health workforce to attain its development goals [31,32]. SDG target 3c is to substantially increase the recruitment, development and training of the health workforce in developing countries [1]. Community-based support (CBS) programmes are task-shifting healthcare interventions involving lay healthcare workers that have been developed to increase the health workforce at limited cost in developing countries [33,34]. Amongst others, CBS programmes have aimed to support HIV-infected adults receiving ART [35]. The effectiveness of CBS for adolescents receiving ART requires evaluation, and cost-effectiveness evaluations of CBS are lacking [36].

South Africa has the greatest number of people living with HIV globally, and is showing poor performance regarding its HIV-related SDG target [3,37]. South Africa also has one of the most unequal societies worldwide [38]. South Africa's unemployment rate (27%) is amongst the ten highest national unemployment rates globally, [39,40] with youth unemployment being approximately 50% [41]. Almost two-thirds of young South African children live in poverty, and 20% of the population live in extreme poverty [38,42].

This study aimed to evaluate the effectiveness and cost-effectiveness of a large CBS programme for HIV-infected adolescents and youth receiving ART (with five years of patient outcomes) in four South African provinces.

2 | METHODS

A retrospective cohort study was performed at 47 public ART facilities, using routinely collected clinical data. The facilities were located in KwaZulu-Natal, Western Cape, Eastern Cape and Mpumalanga provinces, in both urban (33 facilities) and rural areas (14 facilities). Included facilities were all facilities supported by Kheth'Impilo, a non-profit organization, which had a CBS programme for adolescents and youth. Kheth'Impilo supports the South African Department of Health with public health systems strengthening. The majority were primary healthcare facilities, and six were secondary-level hospitals. Antenatal HIV prevalence in these provinces varied between 18.2% and 37.4% [43]. Co-infection with tuberculosis amongst adolescents and youth starting ART in South Africa is high (9% to 13%) [13].

Antiretroviral-naive adolescents and youth aged 10 to 24 years who initiated ART between 01 January 2004 and 30 September 2010 were included. Follow-up was until mortality, loss to follow-up (LTFU), documented transfer-out to other sites, 30 September 2011 (database closure) or five years on ART (whichever occurred first). To evaluate the effectiveness of CBS, ART outcomes were compared between adolescents and youth who received CBS plus standard clinic-based care versus adolescents and youth who received standard care only. During the pre-ART preparation period, patients initiating ART were evaluated by a facility-based community co-ordinator (named a "site-facilitator"), who assigned patients in a non-randomized manner to receive CBS in addition to usual care if the following criteria were fulfilled: CBS-workers were active in the area of the patient's home, CBS-worker capacity was available, and patient consent was obtained. As the development of the CBS programme was progressive, few patients initially received CBS but this increased as the programme expanded. Clinical and socioeconomic factors were not criteria in the allocation of patients to receive CBS. For analyses, patients were assigned to the CBS group if they were allocated to and received support from a named CBS-worker from ART initiation.

2.1 | CBS intervention

CBS-workers are clinic-linked, lay community health workers who provided ART patient support by undertaking home visits to ascertain and address household challenges impacting on clinic attendance and adherence. CBS-workers resided in low socioeconomic, high HIV-prevalence areas. Preference was given to employing previously unemployed people as CBS-workers. They were trained regarding HIV and tuberculosis

(TB) infection and treatment, including addressing psychosocial issues impacting adherence. Support started from the time of pre-ART preparation and continued throughout long-term care. Patient, family and household issues assessed by CBS-workers included nutrition security, substance abuse, mental health including depression, domestic violence, non-disclosure, and HIV-related stigma and discrimination. Issues were discussed at clinic multidisciplinary team meetings and interventions agreed by the team were implemented by the CBS-worker as appropriate. CBS included providing one-on-one counselling regarding adherence, and support and referral for psychosocial problems and nutrition security. Participants were provided with information and education regarding sexual and reproductive health and family planning. Adolescents' carers were offered educational sessions regarding HIV/TB information, medication adherence, and nutrition. Adolescents and youth who defaulted clinic visits were traced by CBS-workers. Eligibility for government social assistance grants (for poverty relief) was assessed and support provided to obtain these where eligible.

Participants were scheduled for weekly visits during the first months following ART initiation, then monthly for at least six months. Once stable, home visits were performed at least quarterly, but if clinic visits were delayed, home visit frequency increased. Health promotion education and symptom screening for TB, opportunistic infections and sexually transmitted infections (STIs) were performed, with referral to clinics for further management if indicated.

CBS-workers had a specific geographic area which they supported and were assigned 80 to 120 patients each. Career development of CBS-workers was encouraged, with certain CBS-workers subsequently employed as social auxiliary workers or home-based care co-ordinators [44].

2.2 | Outcomes and definitions

The primary outcomes were as follows: time to all-cause mortality after starting ART, and time till LTFU after starting ART. Attrition was defined as a combined endpoint due to patient losses due to either mortality or LTFU. The secondary outcomes were as follows: (i) Adherence to ART measured using Medication Possession Ratios (MPRs)–an adherence measure derived from pharmacy refill data (number of days of dispensed medication divided by the number of days between the first and last pharmacy refill during the study period) [45,46]; (ii) CD4 cell count increases between months 0 and 36 after starting ART; (iii) CD4 count slope (mean change in CD4 count per month) between months 0 to 6 and 6 to 60; and (iv) the proportion of patients not achieving virological suppression after three years and during the fifth year of ART. We were primarily interested in longer-term immunological reconstitution and virological outcomes and not the initial rapid rise in CD4 count following ART initiation [47].

Deaths were recorded as reported by professional healthcare workers or family members. Patients were defined as LTFU if they were not known to have died or to have transferred out (as documented in site databases), and had no visit to the site for six months or more prior to database closure [48,49]. Patients who returned to care after treatment interruptions were considered remaining in care. The date of last contact was assigned for the outcome of mortality or LTFU in time-to event analyses, with one day of follow-up added for patients who did not return after initiating ART to include them in analyses. Patients documented as transferring to other facilities were censored on the last clinic visit date. Patients who did not receive CBS who missed appointments were traced by telephone or a district tracing team would visit the home where available. All patients visited the clinic at a frequency determined by clinic professional staff (generally monthly). Virological suppression was defined as viral load <400 copies/ml. Laboratory measurements were performed by the South African National Health Laboratory Service.

Individual-level patient data were collected prospectively for programme monitoring purposes by designated site-based data capturers at each visit using standardized custom-designed databases, which were regularly pooled to a data warehouse, using standardized operating procedures. Site databases were designed in Microsoft Access®, and were used for clinical data collection and patient and clinic management. Regular data cleaning and quality control procedures were implemented.

Participant baseline characteristics were compared with medians, interquartile ranges and percentages, and binary variables were compared with risk ratios and 95% confidence intervals. Outcomes were by intention-to-treat ignoring changes in exposure status after ART initiation. Cumulative incidence functions were used to calculate time till mortality or LTFU, using a competing-risks approach. Multivariable Cox regression and Fine and Grey competing-risks regression were used to compare mortality and LTFU between patients who received and did not receive CBS, controlling for demographic, clinical and site-related confounding. To account for clustering of observations within sites, stratified Cox regression was conducted allowing the baseline hazard for each site to vary [50], and for the competing-risks models site was included as a fixed effect. Incidence rate ratios of attrition were calculated stratified by site, with the combined estimate calculated using Mantel–Haenszel weights.

Mean MPR was analysed using generalized estimating equations specifying for clustering within sites and using Huber–White (robust) variance estimates. MPR was also analysed as a binary variable with mixed-effects logistic regression including site as a random intercept, using a threshold MPR of ≥95% to indicate high adherence. CD4 count increases were analysed with linear regression, and CD4 cell slopes were analysed with multilevel mixed-effects linear regression including site and patient as random effects to account for the longitudinal nature of the data and clustering within sites. Models were adjusted for ART duration and baseline variables were included as fixed effects. Proportions of patients not achieving viral suppression were analysed using mixed-effects logistic regression.

To impute missing baseline covariate data, multiple imputations by chained equations were conducted using 20 imputed datasets, under the assumption that missing data were likely missing at random. Multivariable analyses were run on each data set that included the imputed values and the results combined, using Rubin rules [51].

All available plausible demographic, clinical and site-related variables were considered as potential confounders and were included in multivariable models when their inclusion altered

the association between CBS and the outcomes or were significantly associated with the outcomes with $p < 0.05$. Modification of the effect of CBS on outcomes was assessed by stratifying effect measures by plausible modifiers. The number needed to treat (NNT) to prevent a case of death or LTFU were calculated as appropriate for time-to-event outcomes [52].

2.3 | Cost-effectiveness analyses

A top-down expenditure approach was used to determine the incremental cost of CBS to usual ART care from a provider perspective. Expenditure of the CBS programme according to the financial records of the programme were collected, which included costs of human resources, training, management and administration, infrastructure and equipment, and monitoring and evaluation over a two-year period between 01 April 2011 and 31 March 2013. The cost of usual ART patient care was not considered and was assumed to be equal between patients with and without CBS. The number of patient-years of CBS during this period was calculated from programme monitoring data.

The cost outcomes were: (i) average cost of CBS per patient-year of support, and (ii) cost-effectiveness defined as cost per patient-loss (through death or LTFU) averted. The effectiveness of CBS in preventing patient attrition at annual intervals after starting ART (compared to usual care) was calculated as the difference in patient attrition between patients who did and who did not receive CBS (estimated from a stratified Cox model) divided by attrition amongst patients who did not receive CBS [53]. Incremental cost-effectiveness ratios (ICERs) were calculated from one through five years of treatment. For cost calculations, patients lost to care were considered lost at the mid-point of each year. Costs were converted to United States dollars at the average exchange rate of ZAR 1 = US$0.1219 in 2012 [54]. For ICERs, costs and patient losses averted were discounted at 3% per annum [55]. Analyses were conducted with Stata® version 13.1 (College Station, TX, USA), and Microsoft Excel®. The University of Cape Town Human Research Ethics Committee provided the studies ethical approval, and the study conformed to the Declaration of Helsinki ethical principles.

3 | RESULTS

Database records of 85,997 patients who initiated ART were screened for inclusion, with the following excluded: 3756 patients aged <10 years when starting ART; 74,123 aged ≥25 years; and 1412 who started ART after the study enrolment period. Thus 6706 participants were included, of whom 2100 (31.3%) received CBS and 4606 (68.7%) who received standard care only. Most (82.4%) participants were female and 1810 (27.0%) were aged 10 to 19 years. At ART initiation, participants who received CBS had: a higher proportion with advanced clinical stage disease (World Health Organization (WHO) stages III/IV), a slightly higher median CD4 count, a higher proportion who received concomitant TB treatment, a higher proportion who were pregnant, a higher proportion who attended rural facilities and a higher proportion who attended primary healthcare clinics (Table 1). The proportion of patients who received CBS increased from 19.3% to 33.5% during the study period.

During 9215 person-years of follow-up, 87 (4.1%) and 256 (5.6%) of participants who received and did not receive CBS were reported as having died, respectively ($p = 0.015$). A further 286 (13.6%) and 885 (19.2%) became LTFU amongst those who received and did not receive CBS, respectively ($p < 0.0001$). 375 (8.5%) participants transferred out. After five years of ART, the cumulative incidence of mortality amongst adolescents and youth who received and did not receive CBS was 8.3% and 10.8%, respectively ($p = 0.027$), and the cumulative incidence of LTFU was 29.9% and 38.9%, respectively ($p < 0.0001$) (Figure 1).

For multivariable analyses, the proportions of imputed baseline values were: TB treatment status-5.6%; pregnancy status-5.3%; CD4 count-17.1%; initial regimen-15.6%; WHO stage-34.0%. After controlling for confounding using multivariable Cox regression, participants who received CBS had a significantly reduced probability of mortality, adjusted hazard ratio (aHR) = 0.52 (95% CI: 0.37 to 0.73; $p < 0.0001$) (Table 2). Estimates from the competing-risks regression models were similar. Adolescents and youth who received CBS had a 40% reduced probability of becoming LTFU, aHR = 0.60 (95% CI: 0.51 to 0.71; $p < 0.0001$). The effect of CBS on LTFU was more pronounced at rural facilities, aHR = 0.43 (95% CI: 0.30 to 0.62) and slightly more pronounced amongst pregnant women, aHR = 0.53 (95% CI: 0.31 to 0.92).

The NNT to prevent one case of mortality after one and three years was 6.4 (95% CI: 3.6 to 16.7) and 5.3 (3.2 to 13.0), respectively, and the NNT to prevent one case of LTFU after one and three years was 6.0 (95% CI: 4.4 to 9.4) and 5.4 (4.2 to 8.0), respectively.

Considering the combined endpoint of attrition, the incidence rate of attrition was 12.9 cases/100 person-years (95% CI: 11.7 to 14.3) amongst adolescents and youth who received CBS, and 18.0 cases/100 person-years (95% CI: 17.0 to 19.1) amongst adolescents and youth without CBS, incidence rate ratio (stratified by site) = 0.55 (95% CI: 0.48 to 0.64; $p < 0.0001$).

Mean MPR was similar between patients with and without CBS; 82.5% and 83.0%, respectively, adjusted mean difference = −1.0 % (95% CI: −2.6% to 0.5%), $p = 0.20$ (Table 3). There was no difference in the proportion of patients who achieved high adherence (MPR ≥95%), viz. 35.4% and 35.8% amongst patients with and without CBS, respectively, adjusted odds ratio (aOR) = 1.00 (95% CI: 0.86 to 1.19; $p = 0.92$).

CD4 count increases were 384.5 cells/μl and 366 cells/μl amongst adolescents and youth with and without CBS, respectively, after 36 months. CD4 count slope between months 6 to 60 in adolescents and youth with and without CBS was 6.7 cells/μl/month and 7.1 cells/μl/month, respectively, with no difference in multivariable analyses; coefficient = 1.28 cells/μl/month (95% CI: −1.12 to 3.68; $p = 0.30$).

The proportions of adolescents with and without CBS who failed to achieve virological suppression after three years were similar, aOR = 0.96 (95% CI: 0.41 to 2.28), $p = 0.93$. During the fifth year of ART, the proportions with and without CBS who failed to achieve virological suppression were 18.8% and 37.2%, respectively, with the adjusted effect measure approaching a significant difference in favour of CBS, aOR = 0.24 (95% CI: 0.06 to 1.03), $p = 0.055$.

Table 1. Characteristics of adolescents and youth at antiretroviral treatment initiation who received and did not receive CBS in South Africa

	Total (n = 6706)	Did not received CBS (n = 4606)	Received CBS (n = 2100)	Risk ratio (CBS vs. no CBS) (95% CI)[a]
Female, n (%) (n = 6706)	5523 (82.4)	3752 (81.5)	1771 (84.3)	1.04 (1.01 to 1.06)
Median age, years, (IQR) (n = 6706)	22.4 (19.6 to 23.9)	22.4 (19.5 to 23.9)	22.5 (19.9 to 23.9)	
Age categories, n (%) (n = 6706)				
Ages 10 to 19 years	1810 (27.0)	1268 (27.5)	542 (25.8)	0.93 (0.86 to 1.02)
Ages 20 to 24 years	4896 (73.0)	3338 (72.5)	1558 (74.2)	
WHO clinical stage, n (%) (n = 4424)				
I/II	1564 (35.4)	1171 (37.5)	393 (30.1)	
III/IV	2860 (64.7)	1949 (62.5)	911 (69.9)	1.12 (1.06 to 1.17)
CD4 cell count, cells/μl, median (IQR) (n = 5560)	136 (70 to 187)	131 (65 to 182)	145 (82 to 195)	
Pregnancy amongst females, n (%) (n = 5166)				
Not pregnant	4512 (87.3)	3031 (88.4)	1481 (85.3)	
Pregnant	654 (12.7)	399 (11.6)	255 (14.7)	1.26 (1.09 to 1.46)
Received tuberculosis treatment, n (%) (n = 6332)				
No	5623 (88.8)	3831 (89.6)	1792 (87.1)	
Yes	709 (11.2)	443 (10.4)	266 (12.9)	1.25 (1.08 to 1.44)
Initial regimen, n (%) (n = 5657)				
d4T-3TC-EFV	2792 (49.4)	1961 (52.5)	831 (43.2)	
d4T-3TC-NVP	2006 (1342)	1342 (36.0)	664 (34.5)	
ZDV-3TC-EFV	38 (0.7)	19 (0.5)	19 (1.0)	
ZDV-3TC-NVP	106 (1.9)	37 (1.0)	69 (3.6)	
TDF-3TC-EFV	339 (6.0)	163 (4.4)	176 (9.2)	
TDF-3TC-NVP	322 (5.7)	184 (4.9)	138 (7.2)	
Other	54 (1.0)	27 (0.7)	27 (1.4)	
Year of starting ART, n (%)(n = 6706)				
2004 to 2005	218 (3.3)	176 (3.8)	42 (2.0)	
2006 to 2007	1384 (20.6)	1038 (22.5)	346 (16.5)	
2008 to 2010	5104 (76.1)	3392 (73.6)	1712 (81.5)	
Location of site attended, n (%) (n = 6706)				
Urban	5238 (78.1)	3784 (82.2)	1454 (69.2)	
Rural	1468 (21.9)	822 (17.9)	646 (30.8)	1.72 (1.58 to 1.88)
Hospital-based clinic/primary healthcare clinic attended, n (%) (n = 6706)				
Hospital	1612 (24.0)	1407 (30.6)	205 (9.8)	
Primary healthcare clinic	5094 (76.0)	3199 (69.5)	1895 (90.2)	1.30 (1.27 to 1.33)
Province, n (%) (n = 6706)				
Western Cape	803 (12.0)	523 (11.4)	280 (13.3)	
Eastern Cape	1259 (18.8)	587 (12.7)	672 (32.0)	
KwaZulu-Natal	4035 (60.2)	3243 (70.4)	792 (37.7)	
Mpumalanga	609 (9.1)	253 (5.5)	356 (17.0)	

ART, antiretroviral treatment; CBS; community-based support; WHO, World Health Organization; IQR, interquartile range; CI, confidence interval; d4T, stavudine; 3TC, lamivudine; EFV, efavirenz; NVP, nevirapine; ZDV, zidovudine; TDF, tenofovir.
[a]For binary variables.

3.1 | Cost-effectiveness results

The average cost of CBS was US$49.5/patient/year, with 84% spent on human resources (Table 4). The entire programme employed 576 CBS-workers. The effectiveness of CBS in reducing patient attrition ranged from 42.2% after one year to 35.9% after five years. The incremental cost of CBS per patient-loss averted after one, two and five years was US $600, US$776 and US$1149, respectively (Table 5).

4 | DISCUSSION

The SDGs are opportune to improve the health and wellbeing of disadvantaged groups globally. Government commitment to the SDGs needs to be translated into programmes that can deliver on the wide-ranging goals and accompanying targets. The SDG targets are interrelated and overlap; notably 28 targets across 11 goals are health-related [3,26]. To reach the SDGs for adolescents by 2030, the importance of innovations

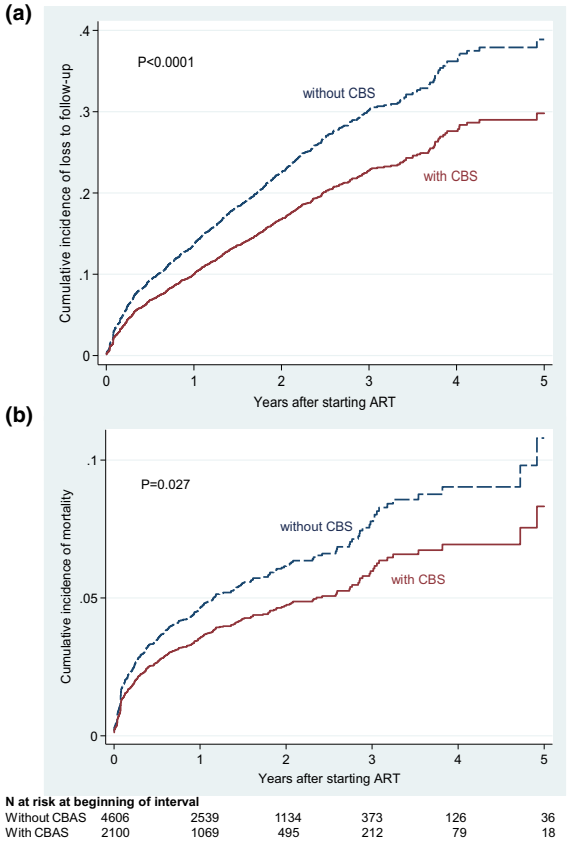

Figure 1. Cumulative incidence of (A) Loss to follow-up and (B) mortality amongst adolescents and youth starting antiretroviral treatment in South Africa.

in adolescent health involving biomedical and behavioural interventions delivered together has recently been highlighted [56].

Adolescents are a key group for targeting of the UNAIDS 90-90-90 HIV treatment goals [57]. In view of their poorer ART outcomes, there have previously been calls for adolescents and youth to receive specific additional support [11-13,15]. This study has found that CBS was associated with substantially improved retention in adolescents and youth receiving ART, and is a low-cost intervention with reasonable cost-effectiveness. Cost-effectiveness of CBS was greatest during the first two years of treatment.

Improved programme retention increases the number of HIV-infected adolescents and youth receiving ART, which would lead to greater numbers potentially being able to achieve viral suppression due to ART use. In turn, this can potentially decrease sexual transmission due to ART [58,59] and aid progress towards SDG target 3.3 to reduce HIV incidence.

Community support has previously been found to reduce ART programme attrition amongst adults and children [35,60]. Mechanisms underlying these improvements include defaulter tracing, psychosocial support offered by CBS workers, improved patient links with clinics, decreased treatment fatigue, improved self-management skills regarding HIV/AIDS, greater disclosure, greater social capital and a widened community safety net [35,61,62]. The primary driver of decreased attrition associated with CBS in this study was reduced LTFU, with reduced mortality accounting for a small component only. Except for a trend towards improved viral suppression at five years amongst those who received CBS, significant differences in immunological restitution or the adherence measure utilized were not observed. In the absence of these, the reasons for the difference in mortality observed are unclear and require further research. It is plausible that CBS was associated with health aspects not measured in this study, such as earlier referral and treatment for incident opportunistic infections, improvements in nutritional status or mental health, or improved socioeconomic status through access to grants. Future research should also incorporate more accurate measures of adherence.

In adults, the cost-effectiveness of strategies to reduce ART patient attrition have been evaluated in two previous studies. A hypothetical study found that interventions costing up to US$120/person/annum with effectiveness ≥40% in reducing attrition would be cost-effective with high degrees of regional ART coverage [63]. A Cote d'Ivoire study found that interventions preventing LTFU would result in a substantial saving of life-years, and an intervention costing US$53 per person/annum would be cost-effective by international criteria (<3 times gross domestic product per capita) if ≥28% effective [53]. Although we did not model cost-effectiveness based on disability-adjusted life years averted, CBS was found to cost US $50/person/annum and have effectiveness between 42% to

Table 2. Univariable and multivariable models of factors associated with loss to follow-up and mortality amongst adolescents initiating ART in South Africa

Predictor (baseline)	Loss to follow-up						Mortality					
	Univariable Cox		Multivariable Cox		Multivariable competing risks		Univariable Cox		Multivariable Cox		Multivariable competing risks	
	HR (95% CI)	*p*-value	aHR (95% CI)	*p*-value	asHR (95% CI)	*p*-value	HR (95% CI)	*p*-value	aHR (95% CI)	*p*-value	asHR (95% CI)	*p*-value
Received CBS												
Yes	0.59 (0.50 to 0.70)	<0.0001	0.60 (0.51 to 0.71)	<0.0001	0.61 (0.52 to 0.73)	<0.0001	0.45 (0.32 to 0.63)	<0.0001	0.52 (0.37 to 0.73)	<0.0001	0.56 (0.41 to 0.76)	<0.0001
No	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Age (years)	1.03 (1.02 to 1.05)	<0.0001	1.03 (1.02 to 1.05)	<0.0001	1.04 (1.02 to 1.05)	<0.0001	1.00 (0.98 to 1.03)	0.88	0.99 (0.96 to 1.01)	0.29	0.98 (0.96 to 1.01)	0.28
Gender												
Female	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Male	0.86 (0.73 to 1.00)	0.048	0.97 (0.82 to 1.15)	0.71	0.97 (0.82 to 1.15)	0.70	1.02 (0.78 to 1.35)	0.84	0.91 (0.67 to 1.22)	0.52	0.90 (0.33 to 1.21)	0.48
WHO stage												
I/II	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
III	1.10 (0.94 to 1.29)	0.22	1.18 (1.00 to 1.39)	0.049	1.18 (1.02 to 1.37)	0.028	2.19 (1.54 to 3.11)	<0.0001	1.84 (1.29 to 2.64)	0.001	1.86 (1.30 to 2.66)	0.001
IV	1.12 (0.86 to 1.48)	0.38	1.20 (0.91 to 1.60)	0.19	1.21 (0.93 to 1.57)	0.16	4.5 (2.79 to 7.27)	<0.0001	3.48 (2.15 to 5.62)	<0.0001	3.4 (2.12 to 5.51)	<0.0001
CD4 count, cells/μl												
0 to 99	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
100 to 199	1.06 (0.92 to 1.22)	0.40	1.04 (0.90 to 1.20)	0.63	1.09 (0.94 to 1.27)	0.25	0.36 (0.28 to 0.47)	<0.0001	0.42 (0.31 to 0.54)	<0.0001	0.42 (0.32 to 0.55)	<0.0001
200 to 349	1.11 (0.91 to 1.36)	0.30	1.11 (0.90 to 1.37)	0.32	1.17 (0.94 to 1.45)	0.17	0.27 (0.17 to 0.42)	<0.0001	0.36 (0.22 to 0.58)	<0.0001	0.35 (0.21 to 0.56)	<0.0001
≥350	1.03 (0.86 to 1.23)	0.72	1.33 (0.93 to 1.92)	0.12	1.47 (1.02 to 2.10)	0.036	0.16 (0.05 to 0.51)	0.002	0.18 (0.05 to 0.57)	0.004	0.18 (0.05 to 0.60)	0.005
Pregnancy												
Yes	1.42 (1.17 to 1.72)	<0.0001	1.43 (1.17 to 1.74)	<0.0001	1.45 (1.19 to 1.77)	<0.0001	0.25 (0.12 to 0.52)	<0.0001	0.38 (0.19 to 0.79)	0.010	0.38 (0.19 to 0.79)	0.009
No	Reference	-	Reference	-			Reference	-	Reference	-	Reference	-
TB treatment												
Yes	0.95 (0.79 to 1.15)	0.61	0.98 (0.80 to 1.19)	0.82	0.98 (0.81 to 1.19)	0.87	1.10 (0.77 to 1.55)	0.61	0.88 (0.61 to 1.29)	0.48	0.90 (0.63 to 1.30)	0.57
No	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Year of starting ART (continuous)	1.12 (1.05 to 1.19)	<0.0001	1.17 (1.10 to 1.25)	<0.0001	1.15 (1.08 to 1.22)	<0.0001	0.71 (0.64 to 0.79)	<0.0001	0.77 (0.69 to 0.86)	<0.0001	0.74 (0.67 to 0.82)	<0.0001
Site location												
Urban	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Rural	1.01 (0.27 to 3.75)	0.98	1.15 (0.31 to 4.27)	0.83	0.65 (0.17 to 2.50)	0.54	1.46 (0.16 to 12.60)	0.73	1.19 (0.13 to 11.03)	0.88	1.31 (0.15 to 11.7)	0.81
PHC clinic /hospital												
Hospital	0.68 (0.51 to 0.90)	0.007	0.71 (0.53 to 0.96)	0.025	0.57 (0.25 to 1.30)	0.19	1.35 (0.77 to 2.37)	0.30	0.88 (0.47 to 1.64)	0.69	3.42 (0.40 to 28.9)	0.26
PHC clinic	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-

Regression results using models with multiple imputation of missing covariate data, using 20 imputed datasets. To account for clustering within sites, Cox models were stratified by site, and a fixed-effects approach was used for the competing risks models. Multivariable models were also adjusted for initial antiretroviral regimen. HR, hazard ratio; aHR, adjusted hazard ratio; asHR, adjusted subhazard ratio; CBS, community-based support; ART, antiretroviral treatment; TB, tuberculosis; WHO, World Health Organization; PHC, primary healthcare; CI, confidence interval.

Fatti G et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25041
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25041/full | https://doi.org/10.1002/jia2.25041

Table 3. Secondary outcomes of CBS for adolescents and youth receiving antiretroviral treatment in South Africa

Outcome	Received CBS	Did not receive CBS	Crude effect measure (95% CI) (CBS vs. no CBS)	Crude *p*-value	Adjusted effect measure (95% CI)[a]	Adjusted *p*-value
Mean MPR, % (95% CI)	82.5% (81.6% to 83.4%)	83.0% (82.3% to 83.7%)	−0.6% (−1.7% to 0.6%)[b]	0.33	−1.0% (−2.6% to 0.5%)[c]	0.20
Proportion with MPR ≥95%, % (95% CI)	35.4% (33.2% to 37.6%)	35.8% (34.1% to 37.5%)	0.99 (0.92 to 1.07)[d]	0.79	1.00 (0.86 to 1.19)[e]	0.92
CD4 count increases after three years of ART, cells/μl (IQR)	384.5 (152 to 521)	366 (208 to 485)	11.9 (−67.6 to 91.6)[f]	0.76	21.8 (−60.2 to 103.9)[f]	0.60
CD4 cell slope between months 0 and 6 after ART initiation, cells/μl/month, median (IQR)	27.0 (12.9 to 43.4)	25.6 (11.9 to 42.0)	1.31 (−1.92 to 4.55)[g]	0.43	2.10 (−1.21 to 5.39)[g]	0.22
CD4 cell slope between months 6 and 60 after ART initiation, cells/μl/month, median (IQR)	6.7 (−2.0 to 16.4)	7.1 (−0.6 to 16.1)	1.09 (−1.34 to 3.51)[g]	0.38	1.28 (−1.12 to 3.68)[g]	0.30
Proportions not achieving viral suppression after three years of ART, % (95% CI)	28.2% (19.7% to 37.9%)	32.7% (26.1% to 39.7%)	0.81 (0.48 to 1.36)[e]	0.43	0.96 (0.41 to 2.28)[e]	0.93
Proportions not achieving viral suppression during fifth year of ART, % (95% CI)	18.8% (7.2% to 36.4%)	37.2% (24.1% to 51.9%)	0.39 (0.14 to 1.11)[e]	0.079	0.24 (0.06 to 1.03)[e]	0.055

[a]Adjusted for baseline confounding using 20 multiple imputed datasets.
[b]Mean absolute difference.
[c]Coefficient from generalized estimating equation specifying for clustering within sites.
[d]Risk ratio.
[e]Odds ratios using mixed-effects logistic regression including site as a random intercept.
[f]Coefficient from linear regression.
[g]Coefficient from mixed-effects linear regression (cells/μl/month) including site and individual as random effects, and adjusted for duration of ART.
CBS, community-based support; MPR, medication possession ratios; IQR, interquartile range.

Table 4. Costs of CBS for antiretroviral treatment patients in South Africa

Total patient-years supported	126,485
No. community workers employed	576
Item	**Average costs per patient year supported, US$ (%)[a]**
Human resources	41.83 (84.4)
Training	5.97 (12.1)
Infrastructure and equipment	0.02 (0.05)
Clothing for CBS-workers	0.15 (0.3)
Management and administration	0.48 (1.0)
Monitoring and evaluation	0.10 (0.2)
Overhead costs	0.99 (2.0)
Total cost per patient supported/year	49.5 (100.0)

[a]Values in parentheses are percentages of the total cost.

36%, and would thus be expected to cost-effectively reduce high attrition amongst SSA adolescents and youth.

The health workforce underpins every aspect of the health system, and is the rate-limiting step in achieving universal health coverage by 2030 [64]. There is pronounced inequity in the distribution of health workers globally, with Africa carrying 25% of the world's disease burden but only 1.3% of the world's health workers, with little progress being evident in this regard [65,66]. To achieve health-related SDGs, task-shifting to maximize the use of available funds and health workers in the region will be essential. Efficiency and value for money will be important priorities. Amongst children, UNICEF is promoting task-shifting from professional to community health workers to improve access to health interventions, in order to achieve SDG target 3.2 to prevent common causes of child mortality [67]. The CBS programme evaluated in this study extends this model for the care of HIV-infected adolescents and youth.

Community health workers can play a key role in attaining a number of SDGs, including health, ending poverty and hunger, equality, clean water and sanitation, and partnerships for global health (SDG 17), as highlighted in the recent Kampala statement [68,69]. Important actions to support the role of community health workers in this regard include financial and political support, partnerships with a range of healthcare providers, and disseminating cross-country learnings. Rigorous research to expand the evidence base for policy and practice to maximize the contribution and potential of community health workers in progress towards these SDGs is vital [70]. Research priorities include the roles of cross-cutting enabling factors such as education and accreditation of community health workers, management, effective linkage with other professional staff cadres, remuneration, and motivation and performance [64,68]. Translating evidence to investment decisions will also be required to enable sustainable health solutions in pursuit of the SDGs. Including community engagement as an additional aspect of the SDG health targets has also been suggested [26].

Innovations in health worker training will be important in attaining the SDGs. CBS involves training previously unemployed persons living in impoverished areas and employing them as lay health workers, and assisting their further career development [44]. As CBS is labour-intensive, large CBS programmes will aid progress towards SDG targets 4.4, 8.5 and 8.6 (provision of skills to facilitate employment and job creation). Job-creation further impacts other health-related targets, as access to gainful employment improves the mental and physical well-being of families and young people [26]. Provision of jobs for CBS-workers also increases income to the lowest 40% income group (SDG target 10.1) which can support the targets to reduce poverty and food insecurity amongst CBS-workers and their families (SDG targets 1.1, 1.2 and 2.1).

HIV-related interventions that have cross-sectoral benefits produce development synergies and will accelerate progress across development goals [71]. CBS-workers provided counselling regarding mental health, sexual and reproductive health (particularly for adolescent girls), nutrition counselling, and support to access social grants. These interventions can aid progress towards SDG target 3.4 (promotion of mental health and wellbeing), SDG target 3.7 (universal access to sexual and reproductive healthcare services), as well as reduce poverty

Table 5. Cost-effectiveness of CBS for ART patients in South Africa

Duration of ART (years)	Proportion of patients retained in care (%)[a]		Effectiveness of intervention in reducing patient attrition (%)[b]	No. patient losses averted due to CBS (per 100 patients initiating ART)[c]	Cumulative cost of CBS (per 100 patients initiating ART), US$[c,d]	Cost-effectiveness ratio (US$/patient-loss averted)
	With CBS	Without CBS				
1	89.3	81.5	42.2	7.6	4549	600.7
2	82.7	71.0	40.3	11.0	8561	776.3
3	76.4	61.5	38.7	13.6	12,165	892.1
4	70.7	53.5	37	15.3	15,400	1007.7
5	66.9	48.4	35.9	16.0	18,337	1149.1

[a]Estimated from the survivor function of a stratified Cox model.
[b]The effectiveness of the CBS programme in preventing attrition (through death or loss to follow-up) was calculated as the difference in patient attrition between patients who did and who did not receive CBS divided by attrition amongst patients who did not receive CBS.
[c]Costs and no. of patient losses averted were discounted at 3% per annum.
[d]Patients lost to the programme were considered lost at the mid-point of each year.
CBS, community-based support; ART, antiretroviral treatment.

and hunger. As almost 85% of CBS-supported participants were female, gender-equality progress (SDG target 5.6) is also supported. The impact of these services was not assessed in this evaluation; however, future economic analyses may incorporate the potential cross-sectoral benefits of CBS.

South Africa has recently introduced and is scaling-up implementation of new national adherence guidelines [72]. In line with this, CBS workers currently provide home and clinic-based support for the initial 12 months after starting ART and for patients who are unstable. This study's results provide evidence of the effectiveness of an individualized approach to support adolescents and youth, and encourage scale-up of implementation of these guidelines. Individual and group counselling and education for adolescents have shown promise in previous smaller studies conducted mostly in developed countries [28,29]. The role of CBS workers is currently expanding to include facilitation of community and clinic-based adherence clubs for stable, virologically suppressed adults from 12 months of ART and beyond.

Challenges faced by the CBS programme include the rural context of many patients' homes with long travel distances and inadequate transport, and inconsistent availability of some adolescents for follow-up counselling sessions. CBS is not a panacea, and other important facets of comprehensive care include youth-friendly clinical management, peer-support groups, and integrated management of the transition from child to adult care services [20,21].

The strengths of this study include the large sample size drawn from many sites situated in low-income, high HIV prevalence areas, with results thus likely being generalizable to other SSA areas. Prospectively collected individual-level data were collected with up to five years of patient follow-up. Additionally, clinical as well as cost outcomes were analysed.

The study limitations include the non-random allocation of patients to groups, with the potential for selection bias and unmeasured or residual confounding. Effect measures were, however, adjusted for site-related and individual-level confounding using multiple imputation of missing covariate values. Differences in measured baseline characteristics were observed between CBS and non-CBS patients; however, most confounders associated with increased attrition were more prevalent amongst CBS patients (advanced clinical stage disease [73], concurrent TB [74], pregnancy [75], more recent year of starting ART [14,76], and attending rural facilities [77]). Residual confounding is thus unlikely to have confounded effect measures in favour of CBS. The routine nature of the data may have produced information bias. Mortality was likely underestimated in both CBS and non-CBS patients, as misclassification of patients who have died as being LTFU is common in SSA routine ART data [78]. Patients who were classified as LTFU may have been undocumented transfers to other treatment sites outside the study facilities.

5 | CONCLUSIONS

The SDG process reinforces the central importance of health in sustainable development. Greater attention to adolescent health, particular regarding HIV/AIDS, will be critical to achieve universal and sustainable development [56]. This study found CBS to be a low-cost intervention associated with substantially improved retention in adolescents and youth receiving ART, which had reasonable cost-effectiveness. CBS for adolescents and youth can potentially aid progress towards twelve targets from eight health, economic, equality and education-related SDGs. Future qualitative research may shed greater light on mechanisms that may improve outcomes and how community-support may be further tailored specifically for adolescents.

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COMPETING INTERESTS

The authors all declare that they have no conflicts of interests.

AUTHORS' CONTRIBUTIONS

GF and AG conceived the study. GF designed the study. GF contributed to data collection and managed the data. GF analysed the data. GF drafted the manuscript. All authors interpreted the data and contributed to writing the manuscript. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS AND FUNDING

The authors gratefully acknowledge the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Departments of Health of KwaZulu-Natal, Eastern Cape, Western Cape and Mpumalanga. Funding for the study was provided by the US President's Emergency Plan for AIDS Relief, USAID. This research has been supported by the U.S. Presidents' Emergency Plan for AIDS Relief (PEPFAR, grant number U51HA02522) through Centers for Disease Control and Prevention under the terms of grant 5U2GPS001966.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the United States Agency for International Development or the President's Emergency Plan for AIDS Relief. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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CHAPTER 6: CONCLUSION

Summary of main findings

The four studies included in this thesis have each addressed one of the main objectives of the thesis. The main findings are as follows:

1. LTFU and mortality were independently lower amongst adults on ART who received CBAS, with outcomes sustained till five years after starting ART.
2. HIV incidence amongst pregnant and postpartum women who received a combination community-based HIV prevention intervention in a high HIV incidence setting in KwaZulu-Natal was substantially lower compared to previous studies in the region. Women within known serodiscordant partnerships and women with newly diagnosed HIV-infected partners were at substantially increased risk of HIV acquisition.
3. The ISPA model had a higher quality of pharmaceutical care and was less costly to implement than the nurse-managed model, and the ISPA model may be associated with improved retention and viral suppression of ART patients.
4. Community-based support for adolescents and youth receiving ART was associated with substantially reduced patient attrition, and is a low-cost intervention with reasonable cost-effectiveness.

Primary strengths of the research

1. The relatively large sample sizes for most of the studies allowed reasonably precise estimation of effect measures.
2. Participants from facilities in low-income, high HIV-prevalence settings in both rural and urban areas were included, which increases the generalizability of

the findings to other Southern African provinces and countries (excepting for objective 2 which was urban only).

3. The sites were routine government public health facilities and likely reflective of other routine public facilities.
4. The studies were all longitudinal in nature with prospectively collected individual-level participant electronic data.
5. Participants had significant follow-up durations (maximum of five years).

Primary limitations of the research

1. The studies were observational nonrandomized studies, with the potential for selection bias and unmeasured confounding. Adjustment for measured confounders was, however, conducted using multivariable analyses.
2. Selection bias may have occurred as patients who declined to receive support from community workers may have had increased risks of adverse outcomes associated with e.g. denial or non-disclosure of HIV status.
3. The use of routine data may have produced information bias, and missing values for certain variables were evident (e.g. baseline WHO stage, CD4 cell count and viral load results). Missing covariate values were, however, imputed using multiple imputation of missing data.
4. As participants that became LTFU were not cross-checked with the national death registry, misclassification of patients as LTFU who had in fact died may have occurred, as is common in routine ART programs (1).
5. For objective 2, a direct measure the effect of the intervention was not possible due to the lack of a concurrent control group in the study. Comparison of HIV incidence from this study with HIV incidence from

previously conducted studies may be affected by a temporal decrease in HIV incidence in the region, thus the effect of the intervention may be over-estimated by direct comparisons with previously conducted studies. However, other studies of HIV incidence conducted during a similar time period as the study for objective 2 of this thesis in the same province (KwaZulu-Natal) that were published at the same time or later also showed significantly higher HIV incidence in comparison to our study: (HIV incidence rate 7.45 per 100 PY for non-pregnant women aged 20-24 years, Chimbindi et. al (2); and incidence rate of 4.5 per 100 PY for pregnant women, Chetty et. al (3), compared to our study with HIV incidence of 1.3 per 100 PY).

6. For the study comparing pharmaceutical models (objective 3), all the sites for each model evaluated were located in different provinces. Provincial-level variation in patient clinical outcomes (due to health systems and population differences) could thus not be controlled for in the multivariable analyses, and direct comparisons in patient clinical outcomes between the two models should thus be interpreted cautiously. However, comparisons of pharmaceutical care quality and costs were unlikely to be significantly affected by interprovincial variation.

The most important limitation across all the studies are that the interventions were not randomly allocated to participants, with selection bias thus being an important consideration. Participants who accepted receiving the interventions may have had greater commitment to improve their health, may have had less fear of stigma associated with HIV-status, or may have been more willing to engage with healthcare service provision in general. In addition, some of the studies had

retrospective designs (protocol developed after implementation of the intervention), with the potential for misclassification of intervention and exposure due to information bias. Future prospective studies with an individual or cluster-randomized design, as has recently been performed for evaluations of Differentiated Service Delivery models of ART patients (4,5), would more accurately assess causality due to the interventions and the strength of these effects. However, randomized study designs are costly, results would not be available for a number of years, participant follow-up durations would likely need to be limited due to cost considerations (1-2 years), and these studies may not be a priority for current funders of health research. In contrast, the retrospective evaluations included in the dissertation were less costly to implement and allowed longer-term participant outcome assessments (up to 5 years of follow-up).

Participants and health facilities in the studies originated from up to four different provinces in South Africa, and were located in both urban and rural areas. Heterogeneity in socio-economic indices and health systems between the provinces and urban/rural settings were apparent, as some provinces (e.g. Eastern Cape) were associated with greater levels of deprivation and weaker health systems. The effectiveness of task-shifting implementation is sensitive to local factors, and may perform better or worse depending on the strength of the underlying health system and local and contextual factors. Future analyses may investigate and compare the effectiveness and cost-effectiveness of task-shifting interventions within more specific geographic locations in South Africa, and evaluate to what extent local factors are predictive of outcomes of task-shifting implementation. Results of the studies included in the dissertation may also not necessarily be generalizable to

other sub-Saharan African countries with weaker health systems than South Africa, as poorer underlying health systems may not necessarily efficiently adapt to the changes involved with task-shifting procedures. It is important that task-shifting models be adapted to local contexts and health systems (6).

Evolution of ART program delivery and task-shifting in South Africa (including international policy changes resulting from articles included in this thesis and related peer-reviewed publications authored by the candidate)

At the start of the ART program in South Africa, delivery of ART care was principally centred at hospital-based facilities and usually associated with long travel distances for ART clients. In its 2013 consolidated ART guidelines, the WHO made an important recommendation to decentralize HIV care and treatment to peripheral primary health care facilities away from hospitals (7), citing, amongst others, a widely referenced study showing improved ART outcomes at primary healthcare facilities compared to hospitals in South Africa (8). This recommendation has since been widely implemented in low-income settings and has substantially facilitated the scale-up of ART access, with ART services delivered closer to patients' homes. In September 2016, South Africa adopted the WHO recommendation that all PLHIV are eligible to receive ART irrespective of clinical or immunological status (9), with a substantially increased number of people thus being eligible to initiate ART in the country. Virological outcomes of those initiating early ART (CD4 counts > 500 cells/µL) have been favourable; however, higher LTFU from ART programs has been observed amongst those who initiate early ART (who are frequently asymptomatic) (10,11). Increasing LTFU has also been observed as clinic patient loads have increased and with longer durations of patient ART receipt (12,13). Improving

retention of patients within the ART program has thus become a top priority in order for the country to reach the UNAIDS 90-90-90 targets.

In recent years, community-based service delivery models have been rising to greater prominence with greater decentralization of aspects of service delivery from the clinic into the community to allow the health system to manage the increasing number of ART patients (4,5,14-22) and which can facilitate adherence and retention as part of the “treat all” strategy (23). Systematic reviews and meta-analyses (which included the publication of objective 1 of this thesis) have found that community-based ART delivery models are at least as effective as facility-based delivery models, with two primary studies showing community-based models to be cost-saving or cost-effective (24,25). CHWs increased the quality and reach of HIV care and treatment programs, and enhanced the life quality, dignity, and retention amongst people included in the programs. The South African National DoH has recommended that health systems address and reduce the significant shortages in CHWs and lay adherence counsellors, and that links with communities need to be further leveraged to promote retention and adherence to treatment services (26).

The WHO and UNAIDS have also made a number of recommendations regarding CBS for ART patients. Citing the article from objective 1 of this thesis and an evaluation of CBS for children receiving ART (27), the WHO in 2013 recommended that “Community-based approaches can improve treatment adherence and retention in care of adolescents living with HIV” (28). In its 2016 consolidated ART guidelines, the WHO made a further recommendation that “Programmes should provide community support for PLHIV to improve retention in HIV care” (29), citing an

evaluation of the PA/CBS model. UNAIDS in its 2016 “HIV care and support document” (30) highlighted the importance of social support for retention in ART programmes, citing a further evaluation of CBS for ART patients (31).

In 2018, citing a study led by the candidate evaluating the long-term effectiveness of CBS for ART patients (until 8 years after starting ART) (32), UNAIDS stated that “Community-health workers are vital for managing the increasing numbers of people on ART in low-resource settings” (33). Also, citing the candidates and others’ work, UNAIDS in its 2018 Global AIDS update stated that “Community-based or community-supported models of care are among the most effective ways of improving retention in care and adherence to treatment, while at the same time reducing the burden on formal health systems. Task shifting to community health workers is vital for managing the increasing numbers of people on HIV treatment in low-resource settings” (34).

In 2019, UNAIDS recommended community-based support for adolescents receiving ART as being an example of “differentiated, family-centred, age-sensitive HIV treatment and care”, and that “adolescents are less likely to drop out of care if they receive peer support” (citing the article from objective 4 of this thesis in two UNAIDS publications) (35,36).

As ART is a lifelong treatment, long term adherence is crucial. The effect of interventions improving adherence tends to wane over time (37), barriers to adherence change over time (38) and LTFU increases with long-term treatment (13,39). The PA model for adherence has the advantage that it would be a long-term

or even lifelong intervention. In contrast, the current South African National Adherence guidelines (AGL), released in 2016, recommend only 1-2 facility-based adherence counselling sessions (Enhanced Adherence Counselling; EAC) for ART patients who develop elevated viral loads. However, a randomized evaluation of this intervention has found it to be non-effective (40) (see Appendix 1). The Early Tracing and Retention in Care (TRIC) intervention as part of the AGL was also non-effective in this evaluation. The TRIC intervention differs from the PA model of care in that CHWs would only trace patients after they became LTFU, and there was not a long-term relationship that developed between the PA and each patient since the ART initiation/pre-ART initiation period (as was the case with the PA model). The EAC intervention also apparently does not provide the tools for the fundamental and long-lasting behaviour changes that are required for ART patients who have become unstable to develop the adherence skills necessary to successfully empower them to adhere to ART, in order to translate to long-term health benefits. Interventions that promote long-term adherence are vital given the large number of patients who require lifelong ART in sub-Saharan Africa, and inclusion of long-term home-based community adherence support for ART patients should be considered for a revised version of the South African AGL (Appendix 1). ART patients may benefit more from a continuum of care based on support and a longer-term relationship with a CHW who provides ongoing psychosocial support, can respond to the emerging needs of patients during long-term treatment, enables greater self-management skills regarding ART adherence and HIV/AIDS, and who can use social capital and widen the community safety net, all of which contribute to reducing treatment fatigue and improve retention and ART outcomes (41-43).

Evaluations of other components of the AGL have also found no benefit of Decentralized Medication Delivery and no benefit of Fast Track Initiation Counselling (FTIC) at 12 months after ART initiation vs. standard of care (44,45). The FTIC intervention provides only four in-clinic counselling sessions for those initiating ART, and no community-based support and no longer-term adherence support. Adherence clubs (ACs) as part of the AGL did show benefit in terms of improved retention after 12 months (45). The South African DoH has adopted ACs as the intervention of choice for longer-term adherence support for stable ART patients, as it is relatively inexpensive to implement as it deals with large groups of ART patients simultaneously (up to 40 people). Effectiveness and cost-effectiveness comparisons between ACs and CBS for ART patients have not yet been conducted, and these evaluations would shed valuable light on the comparative benefits of each intervention.

Regarding CBS for pregnant women living with HIV, UNAIDS in 2018 stated that "To maximize the benefits of lifelong antiretroviral therapy, more effective counselling and preparation of [pregnant] women is needed before they start ART; appropriate support, especially community-based and peer support, is needed to help them adhere to treatment" (34), citing further research led by the candidate (46). In 2019, UNAIDS stated that "Women living with HIV who are receiving ART require support, especially partner and peer support, to assist them in remaining in care and adhering to effective treatment" (47). Other studies have found that vertical HIV transmission was reduced amongst HIV-positive pregnant women who received CBS (48) and that lay health workers increase access to prevention of MTCT services and reduce MTCT (49).

A roving nurse-mentoring healthcare model for prevention of MTCT programs at PHC clinics (also evaluated by the candidate) is a further example of a task-shifting intervention that has shown positive outcomes for maternal and child health in South Africa (50). Late gestational HIV test receipt, antenatal CD4 cell count testing uptake, maternal antiretroviral receipt, and early infant HIV testing receipt improved with a corresponding decrease in vertical HIV transmission being observed following implementation of the intervention, as evaluated in a before-after study.

Regarding pharmaceutical care services, provision of pharmaceutical services by NIMART nurses has been found to be inadequate in another study from South Africa (51). The burden of ART dispensing may hinder the quality of care provided by nurses who consult patients, potentially compromising both clinical care and medicines control at these facilities. This study recommended that the training and placement of pharmacy support staff is of the utmost importance to ensure that pharmaceutical care is maintained for the increasing number of ART patients at PHC clinics (51). The ISPA model for pharmaceutical care has been found to be less costly than the NIMART dispensing model in a previous evaluation (52). A systematic review and meta-analysis of ART delivery by non-pharmacy personnel vs. pharmacy personnel that included only three randomized trials had inconclusive results due to the small amount of published data (53). Further robust studies are required in a variety of settings to evaluate pharmaceutical care provided by non-pharmacy staff.

Regarding task-shifting in HIV counselling and testing services, the WHO has recommended implementation of community-based "index case testing" (54) (citing research authored by the candidate) (55,56). This intervention utilizes lay health workers for community-based HIV testing of contacts of known HIV positive clients. This is a high-yield testing strategy to identify previously undiagnosed HIV-infected individuals, and which has high linkage to care amongst those newly testing HIV positive. In the (cross-sectional) evaluation of the intervention, 59,500 household contacts of HIV-positive index clients consented to receive home-based HIV testing, of whom 15% were found to HIV-positive, with 94% of those found positive successfully linked to HIV treatment services (55). PEPFAR has also recently been actively encouraging index-case testing in resource-poor settings including South Africa (57).

Other community-based models of ART delivery involving health worker task-shifting

A number of other forms of community-based ART delivery models have developed in recent years, in which ART delivery is devolved to the community and which are frequently facilitated by lay CHWs. These models include differentiated service delivery (DSD) models which are developed to better serve the needs of PLHIV and to reduce unnecessary burdens on the healthcare system (4,58). DSD models include community ART groups, developed in Mozambique and also implemented in Lesotho (5,14-16,21,22,59), and community ART refill groups in Zimbabwe (4,60). These are small groups of stable ART patients (usually 6-12 people) who meet in the community and receive regular ART supplies at the group meetings. Visits to the clinic for clinical consultations and viral load measurement of these stable patients

may be extended to annually, thus decongesting clinics so that facility-based clinical staff are better able to focus on ART initiation and managing clinically ill patients. Multimonth dispensing (MMD) of ART at up to six-monthly intervals within these community-based delivery models has recently been shown to be noninferior to ART provided three-monthly at the clinic in two cluster-randomized studies in Zimbabwe and Lesotho (both authored by the candidate) (4,5,60,61). Expanded implementation of MMD within community-based distribution models is expected to further decrease daily facility patient volumes, reduce costs of access to care for patients (62) and is also an important intervention to promote social distancing amongst ART patients to prevent spread of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) amongst PLHIV, who may potentially be at risk of more severe coronavirus disease complications.

Clinic and community-based ACs for stable ART patients, which are facilitated by lay CHWs, is a decentralized DSD model using task-shifting which has been developed in South Africa and has shown good patient clinical outcomes with high patient acceptability (17-20,63). The model is currently being further rolled-out throughout South Africa. A cluster-randomized trial of six-monthly provision of ART within these ACs has recently reported noninferior outcomes vs. two-monthly ART provision (19).

Lay health workers have also provided group support psychotherapy for PLHIV, which has recently been shown to be effective and very cost-effective for treating depression in rural Uganda in a cluster-randomized trial (64).

Regarding task-shifting in health systems for a variety of diseases, a systematic review of task-shifting models in middle and low-income countries (which also cited the publication from objective 3 of this thesis) has concluded that task-shifting models produce cost-savings and efficiency improvements for health systems in the care of a wide range of illnesses including HIV/AIDS, TB, malaria, NCDs, and childhood illnesses (6). Furthermore, CHW's are able to play key roles in progress towards achieving a number of the interrelated SDGs by 2030, including health (SDG 3), ending poverty and hunger (SDG 1 and 2), reducing inequality (SDG 10), clean water and sanitation (SDG 6), decent work (SDG 8) and partnerships for global health (SDG 17), as highlighted in the Kampala statement (65,66).

Learnings from community-based task-shifting initiatives in HIV programs can inform task-shifting in other health areas, particularly regarding health promotion, primary curative health services and care for NCDs. As HIV is a chronic disease and ART adherence needs to be maintained for life, adherence counselling as provided by CHWs can also be provided in the community for patients with reasonably stable NCDs such as hypertension and diabetes mellitus. Home visits for adherence counselling can be leveraged to also provide multiple other household health promotion activities including HIV prevention messaging for the household, screening for TB, STIs and SARS-CoV-2, household HIV testing, provision of infant and maternal health services, screening for NCDs, and screening for substance abuse, gender-based violence and common mental disorders including anxiety and depression. Household nutrition security status and access to potential government social security grants may further be assessed. Referrals to clinic-based health services or social services may then be effected as appropriate. Community-based

support can be a vital link between health clinics and the community not only for HIV care but also for multiple aspects of health.

Qualitative enquiry regarding community-based HIV programs and evaluations of the fidelity of CHWs work

The studies included in the dissertation focus on quantitative effectiveness outcomes and cost outcomes. However, qualitative enquiry regarding clients' and CHWs experience of the CHW-client interaction, enablers and barriers to CHW-client interactions, and barriers and enablers of CHW efficiency are also important to provide a holistic picture of CHW task-shifting implementation. Other qualitative studies have indicated that CHWs in HIV programs are viewed positively by community members (67). Patients see contact with CHWs as beneficial regarding retention in care, and that they appreciate home tracing (26). CHWs have expressed that they are passionate about their work, and that in some instances, this work has been a stepping stone to more advanced cadres of healthcare work including careers as auxiliary social workers, grant officers, data capturers or administrative clerks (68). The importance of the relationship between CHWs and community members is vital and contributes to higher levels of social capital, which has been found to be associated with improved ART adherence and protective against poor ART outcomes (43,69).

The community health program implemented by the South African National DoH is delivered by ward-based outreach teams (WBOTs), which comprises a professional nurse and up to five CHWs (70). The team of five CHWs is designed to support 7660 people in the ward and provide general health education, health status monitoring,

and referral to the PHC facility where indicated. There is an important focus on vulnerable populations and chronic non-communicable and communicable diseases including HIV and TB. Evaluations of the fidelity of the work of CHWs regarding HIV program implementation as part of the WBOTs have found that the duration of program delivery and content of program delivery were adequate, individuals in the community reporting a CHW visit were more likely to know their HIV status, and that the community showed high appreciation for CHW visits (71). However, the proportion of the targeted community that received services (coverage) and the frequency of household visits by CHWs were suboptimal, identification of appropriate people for referral and systems for referral to PHC clinics were inadequate, and the success of tracing of ART patients who were LTFU was suboptimal (71,72). Implementation of human resource management strategies are needed to improve CHW performance. CHWs have expressed the need for better support from management, greater recognition, increased flexibility to allow their own decision making, a need for further training, and increased remuneration (25,49,67,73). Crucial elements for CHWs to perform their duties effectively and for optimal functioning of CHW programs include adequate infrastructure and resources, continuous training of CHWs and their supervisors, the availability and implementation of appropriate human resource policies, CHW performance evaluations and supervisory mechanisms, as well as clinical and managerial integration of the CHW program with the formal health system (71,72). As the cost-savings produced by CHW programs is significant and CHWs reduce the workload of clinicians allowing them to spend additional time with patients, adequate compensation for CHWs is vital (74), particularly as higher remuneration is a

frequent need expressed by CHWs and is a motivating factor for improved work performance.

CHWs and the Coronavirus Disease of 2019 (COVID-19) pandemic

In April 2020 a large number of CHWs working in HIV and TB programs were leveraged by the National DoH to be at the forefront of South Africa's community-based response to the recent and rapidly evolving COVID-19 pandemic. Over 28,000 CHWs have been tasked with going door-to-door in predominantly informal settlement areas to perform symptom screening with referral to formal health services for SARS-CoV-2 testing if symptom positive, as well as to perform data capture with geographic information system-enabled software. By the end of April 2020, over six million people were screened and over 42,0000 people had been referred for SARS-CoV-2 testing.

Early implementation experiences in the Western Cape have included CHWs requesting additional remuneration for screening activities ("danger pay"), apprehension amongst CHWs of exposing themselves and their families to the virus, shortages of personal protective equipment, lack of policing associated with household screening and security issues in informal settlements, certain communities ignoring lockdown regulations and not being available for screening during home visits, some households not accepting screening as they are reluctant to be exposed to CHWs, community members not accepting screening without receiving concurrent SARS-CoV-2 testing, instability of mobile-device applications for collection of household data, difficulty in obtaining global positioning system (GPS) data from

home visits, parallel data collection system requirements for the Department of Health and external funders, as well as long daily walking distances for CHWs.

Although CHWs are stretched with the massive COVID-19 screening effort, screening efforts should maximize this opportunity to also include screening and point-of-care testing for other morbidities including HIV, TB and NCDs (75). Particularly, people with undiagnosed HIV infection in Southern Africa are urgently needing to start ART in light of the COVID-19 pandemic. More visible policing as part of community screening, integration and simplification of mobile screening data collection systems that include GPS data collection without needing parallel data collection systems, and community education regarding the benefits of screening (in the mass media or at shopping centres) are likely to enhance screening efforts.

With the development of the COVID-19 pandemic, a greater scope for task-shifting and evolution of task-roles is developing as COVID-19 increases the burden on the already overburdened health system in Southern Africa. For CHW programs, there is great scope to provide a combined package of home-based screening for SARS-CoV-2, TB and NCDs, provide HIV self-testing kits for household members, and provide adherence counselling for those receiving ART and chronic medication while incorporating social distancing during interactions. ART services should urgently expand and leverage the provision of DSD so that stable ART patients can receive ART in the community with provision of up six months of ART at a time, thus limiting the need for frequent health facility visits (60,76). Implementation challenges for CHW programs include developing guidelines regarding social distancing while

conducting HIV testing and counselling and facilitating ART ACs, and the provision of ongoing adequate supplies of personal protective equipment.

Future directions

Reducing future HIV incidence in South Africa is the overarching challenge for all HIV programs. A modelling analysis which evaluated the comparative efficacy of the various component health systems interventions for reducing future HIV transmission in South Africa found that "the most important epidemiological parameter to target will be **the infectiousness of patients receiving ART.** This will mean **promoting adherence interventions** such as adherence clubs… and **community-supported models of care to improve retention**" (77). ART policy debates should focus on interventions that maximise viral suppression in order to decrease HIV transmission in the region, and interventions employing task-shifting can play a critical role in these programs.

In the broader context, task-shifting interventions have taken a variety of forms for different health systems contexts, a number of new task-shifting efforts are underway worldwide, and task-shifting can be moved in future from lower cadres of health work to more advanced settings including hospitals and speciality settings, as well as sectors such as supply-chain management and monitoring and evaluation (6).

Many community-based health programs currently have inadequate data collection systems, and CHW process indicators and daily work outputs are infrequently measured. Advanced, real-time data collection systems using mobile health (mHealth) solutions that include GPS data collection have recently been developed

for CHWs. mHealth systems can also provide decision support tools for CHWs, support client education, assist with CHW supervision and provide communication between clients and CHWs. However, mHealth systems for CHWs have not been extensively rolled out in low-income settings. Challenges regarding sustainable implementation of these interventions include variable internet connectivity in remote areas, suboptimal technical support, high initial investment cost, ongoing equipment maintenance costs, administrative-related challenges (78), and mHealth systems may decrease the quality of personal interaction between CHWs and beneficiaries (79). Research regarding the utility of these systems for CHWs is needed to assess if they are implementable, practical, provide accurate data collection for process, output and outcome indicators, whether data from these systems are utilized adequately by program managers to adapt CHW programs to improve outcomes and impact of the program, and are cost-effective. Qualitative research should also be conducted to understand how mHealth software and implementation of mHealth interventions can be adapted to improve CHW program performance to maximize program impact. mHealth data systems were not used by CHWs in the studies included in this dissertation; however, they are an attractive alternative for data collection that may be used in ongoing CHW routine programs or for future evaluations of community-based task-shifting interventions. mHealth solutions may be particularly useful for providing real-time data for program managers to be able to act on and adapt and improve programs in response to varying program performance.

Further research is also required to evaluate the optimal number of functions and optimal scope of work of CHWs, and to define the optimal coverage area and

number of people to be covered per CHW so that CHWs may perform their duties efficiently and effectively and are not overburdened. Also, further quantitative and qualitative evaluations of barriers and facilitators of CHW efficiency and community-health program implementation fidelity are required (71). Evaluations of the potential of task-overload due to task-shifting and assessments of options to mitigate risks of task-overload are needed. Further detailed cost-effectiveness evaluations of community-based ART program delivery that include e.g. measuring cost per disability-adjusted life years averted are required. Rigorous research to further expand the evidence base for policy and practice to maximise the potential of CHWs in progress towards achieving the SDGs is also important.

Long-acting injectable ART regiments are currently under investigation and may be a future option to simplify therapy and reduce the burden of long-term pill adherence. Phase III trials have recently reported non-inferior maintenance of viral suppression with monthly injectable ART vs. standard oral therapy; however, injection-related adverse events were common (80,81). If approved for use in sub-Saharan Africa, injectable ART regiments offer an exciting new treatment paradigm; however, significant individual-level and systems-related barriers to implementation are also anticipated (82), which may be a focus for future implementation research in low-income settings.

Conclusion

In conclusion, task-shifting health systems models including community-based and pharmaceutical care models are shown to be effective and cost-efficient in improving HIV treatment and prevention program outcomes in South Africa. Specifically,

community-based support programs improve retention in ART programs, the ISPA model improves the quality of pharmaceutical care in ART programs and may improve patient clinical outcomes, and community-based combination HIV prevention programs likely reduce HIV incidence amongst pregnant and postpartum women. CBS for ART patients is a low-cost intervention and the ISPA pharmaceutical care model results in cost-savings compared to the nurse-managed model. Incorporation of long-term home-based community support for ART patients should be considered for inclusion in a revised version of the AGL. Additional recommendations are to expand the roll-out of home-based couples HIV counselling and testing, and to initiate oral pre-exposure prophylaxis particularly for pregnant women within serodiscordant couples, in order to reduce ongoing high maternal HIV incidence.

Task-shifting healthcare models are able to aid the greater Southern African regions' progress toward several of the interrelated UNAIDS Sustainable Development Goals by 2030. For CHW programs, there is furthermore great scope to provide a combined package of home-based screening for SARS-CoV-2, TB and NCDs, provide HIV testing for household members (currently focussing on providing HIV self-testing kits in view of the COVID-19 pandemic), and provide adherence counselling for those receiving ART and chronic medication.

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APPENDIX 1: South African National Adherence Guidelines: Need for Revision?

Citation

The following is the peer-reviewed version of the article: Fatti G, Shaikh N, Bock P, Nachega JB, Grimwood A. South African National Adherence Guidelines: need for revision? Tropical Medicine & International Health: 2019;24(10):1260-2, which has been published in final form at
https://onlinelibrary.wiley.com/doi/abs/10.1111/tmi.13298

Published in Tropical Medicine and International Health (Journal Impact Factor 2.42).

Overview

This is a published scientific letter and is a critique of findings from a cluster-randomized trial investigating the effectiveness of two interventions as part of the current South African National Adherence guidelines (AGL), i.e. Enhanced Adherence Counselling (EAC) and early Tracing and Retention in Care (TRIC). The letter concludes with a recommendation to include long-term home-based ART adherence support utilizing lay community-based staff as part of the AGL.

Novelty

EAC and TRIC as part of the AGL have not previously received a critique in a peer-reviewed scientific journal.

Contributions of candidate: The candidate developed the outline for this scientific letter, wrote and managed all drafts of the manuscript, and was the corresponding author with the journal. Co-authors critically reviewed and approved the submitted manuscripts, and any comments were assessed by and where appropriate integrated by the candidate. All authors read and approved the published version.

South African National Adherence Guidelines: Need for Revision?

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The Editor,

Fox *et. al.* recently reported a cluster-randomized evaluation of two interventions forming part of the South African National Adherence Guidelines (AGL) at 24 facilities in four South African provinces (1). As the authors note, South Africa has the greatest number of people living with HIV and the largest HIV care and treatment program globally. However, suboptimal patient retention and viral suppression put patients receiving antiretroviral treatment (ART) at risk of poor health outcomes, the development of viral resistance, a heightened risk of transmitting HIV, as well as threaten the country achieving the UNAIDS 2nd and 3rd 90-90-90 HIV treatment targets (2). Thus, an important national and international health priority is to improve patient retention and viral suppression amongst this large number of ART patients, and the AGL have been implemented to attempt to improve both. However, in the most rigorous evaluation of the AGL to date, enhanced adherence counselling (EAC) for patients with an elevated viral loads and Early Tracing and Retention in Care (TRIC) for those who missed a facility visit showed no benefit over control after 12 months.

In an unplanned secondary analysis using a difference-in-differences approach which included people excluded according to the protocol, the author's document higher viral re-suppression at EAC intervention facilities after three months. It is notable that amongst patients eligible for EAC and who received viral load testing at three months, the proportion who achieved viral suppression did not increase during the intervention period at intervention sites (compared to the pre-intervention period) but rather decreased (from 31% to 28%). The treatment effect thus found was due to the fact that re-suppression worsened to a lesser degree during the intervention

period in the intervention sites, whereas at control sites re-suppression dropped to a greater extent (from 35% pre-intervention to 25% during intervention). Also, for the primary analysis of EAC, it is noteworthy that in the EAC study population the proportion of participants with suppressed viral loads after three months (amongst those with available viral load results) was 15.5% compared to 35.3% in the control group, being statistically significantly worse in the intervention group. This data, together with the absence of any effect at 12 months, suggests that a single (or possibly two) in-facility counselling sessions as implemented under AGL have no effect in improving viral suppression amongst those with elevated viral loads.

The authors postulate that some form of counselling for those with elevated viral loads in the control arm may have masked any benefit of EAC; that EAC is not effective, at least as implemented; or the lack of benefit of EAC may be due to delays in administering the intervention rather than the intervention itself. To take this further, it is plausible that one or two in-facility counselling sessions with a clinic counsellor in routine settings is insufficient to affect the adherence behaviour of those with elevated viral loads, and more intensive or aptly designed interventions may be required to have a measurably beneficial effect. The TRIC model also showed no benefit when compared to the standard of care tracing procedures for returning patients to care, and the author's state that it has been a difficult intervention to roll out and monitor.

In the face of this randomized evaluation which fails to show any benefit of EAC and TRIC as part of the AGL, the AGL would benefit from a re-examination to include evidence-based and cost-effective interventions that improve retention and viral

suppression amongst ART patients. One or two in-clinic counselling sessions for patients receiving ART as implemented under EAC seems unable to provide the tools for fundamental and long-lasting behaviour changes that are required for ART patients who have become unstable to develop the adherence skills necessary to successfully empower them to adhere to ART, in order to translate to long-term health benefits.

A more intensive intervention that has shown promise in improving both retention and viral suppression in large-scale implementation (albeit in non-randomized studies that included both unstable and stable participants) is home-based adherence support, which utilizes lay health workers who perform regular visits at the patients home to support ART adherence and retention (3-6). Amongst ART patients with elevated viral loads, home-based visits and adherence counselling provided by lay counsellors also resulted in a high proportion who achieved virological re-suppression (7). Longer-term community-based support enables ART patients to develop relationships and build trust with the community health workers (CHWs) who provide a link between the facility and the community, who are able to identify and assist in addressing household and psychosocial barriers to adherence, and who are more easily able to respond to the emerging needs of patients during long-term treatment.

Implementation of interventions according to whether ART patients are either stable or unstable may benefit the health system to relatively easily classify a large body of patients. However, this may not necessarily benefit the individual patient who passes through both stable and unstable periods during long-term ART. The patient may

benefit more from a continuum of care based on support and a longer-term relationship with a CHW who provides ongoing psychosocial support, enables greater self-management skills regarding ART adherence and HIV/AIDS, and who can utilize social capital and widen the community safety net, all of which may contribute to decreasing treatment fatigue and improving retention and ART outcomes (8-10). Adherence and retention in ART care in the sub-Saharan Africa context is not merely an individual activity but rather a community effort.

The results of this evaluation of the AGL have important implications for adherence and retention enhancing programs in South Africa. There exists a paucity of high-quality studies from resource-poor settings on interventions that improve adherence to ART, particularly amongst unstable patients and regarding the cost-effectiveness of interventions (11). Further research that allows large-scale implementation in this critical area is required. Adapting the AGL to promote long-term ART adherence and retention support, bearing in mind the changing needs of individual patients during life-long treatment, and addressing the complex interplay of psychosocial and community factors that enhance adherence and retention in high-burden settings, will likely have value for the region in its quest to achieve the ambitious UNAIDS HIV treatment goals by 2030 (12).

There is increasing global support for the community-based care components of primary healthcare services (PHC) including household services and ART adherence support (13,14). There is vast scope to effectively expand PHC services at the community level whilst maintaining quality of care, and simultaneously reap the

benefits of closer collaboration between health services and communities when delivering PHC.

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APPENDIX 2: Additional related research output authored by the candidate and cited in this thesis

1. **Fatti G**, Ngorima-Mabhena N, Mothibi E, Muzenda T, Choto R, et al. Outcomes of Three versus Six-Monthly Dispensing of Antiretroviral Treatment (ART) for Stable HIV Patients in Community ART Refill Groups: A Cluster-Randomized Trial in Zimbabwe. J Acquir Immune Defic. 2020. Epub ahead of print, 21 Feb.

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