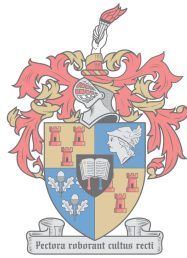


# **The impact of the HPTN 071 (PopART) intervention on mortality and AIDS related morbidity amongst HIV positive adults in South Africa**

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and Health Sciences at Stellenbosch University

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**This dissertation is dedicated to all the individuals and health care staff living and working in communities affected by HIV and TB**

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### **Statement on my contribution to research studies included in this dissertation**

I am co-principal investigator on the HPTN 071 (PopART) trial in South Africa, and I have been intimately involved with the implementation and management of all aspects of HPTN 071 (PopART) reported on in the studies presented in chapters 3 - 6. For the clinic-based studies, presented in chapters 4 - 6, I developed the idea of establishing a cohort and was responsible for establishing the clinic cohort supported by colleagues working for the Western Cape Government and City of Cape Town departments of health. For the systematic review and meta-analysis, presented in chapter 7, I completed the primary review of the literature and the analysis and led the completion and publication of the study.

This dissertation includes 3 original studies published or accepted for publication in peer-reviewed journals and 2 unpublished papers. The development and writing of the studies (published and unpublished) were the principal responsibility of myself and for each of the cases where this is not the case, a declaration is included in the dissertation indicating the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.



## Summary

In 2015 WHO recommended antiretroviral treatment (ART) for all HIV-positive individuals regardless of CD4 count and set a target for Universal Access to ART, that >80% of HIV-positive individuals should be on ART. The HPTN 071 (PopART) trial, a community randomized trial in 21 communities in South Africa and Zambia, aims to determine the impact of two community-level combination prevention packages on population-level HIV incidence. HPTN 071 (PopART) has implemented household-based HIV point of care testing (POCT) and provided ART regardless of CD4 count at department of health clinics (DOH) in the trial communities from January 2014. This was ahead of recent changes to WHO and South African ART guidelines, which now provide ART regardless of CD4 count. The primary outcome of HIV incidence was evaluated in a randomly selected research cohort, the Population Cohort (PC), which aims to recruit 44,500 HIV-positive and negative participants aged 18 to 45, approximately 2000 from each of the 21 communities.

The aim of this PhD dissertation was to evaluate the outcomes of clinical activities key to effective provision of HIV treatment services in high burden settings. PhD objectives were to evaluate: i) the accuracy of household HIV POCT and the impact of routine initiation of ART at baseline CD4 counts > 500cells/mL on ii) attrition during early ART, iii) TB incidence during early ART, iv) the incidence of renal dysfunction during early ART and iv) adherence to ART. These objectives were addressed through the completion of five studies.

Four of the five studies presented were embedded within the HPTN 071 (PopART) trial. The fifth study, evaluating ART adherence, was a systematic review and meta-analysis. The study presented in chapter 3, evaluated the accuracy of household-based HIV POCT between January 2014 and August 2016 across all 21 PopART sites in both South Africa and Zambia, through a series of cross-sectional analyses. This study showed initial low HIV POCT sensitivity in South Africa (45-54%). HIV POCT sensitivity in Zambia, which implemented more extensive quality assurance (QA) and quality control (QC) and used different HIV POCT kits, during the same time period, was significantly better (95.8%). HIV POCT sensitivity in South Africa improved over time to rates comparable to the Zambian sites when implementing rigorous HIV POCT QA/QC.

The studies presented in chapters 4 to 6 analysed data on a cohort of adults ( $\geq 18$  years of age) initiating ART regardless CD4 count at three department of health (DOH) clinics in the Western Cape, South Africa; between January 2014 and November 2015. Cohort follow-up was completed at the end of May 2016. The cohort studies evaluated the impact of routine initiation of ART at baseline CD4 counts  $>500$  cells/ $\mu\text{L}$  on i) attrition ii) TB incidence and ii) incidence of renal dysfunction during early ART.

A total of 2423 adults with a median baseline CD4 count of 328 (IQR 195-468) cells/ $\mu\text{L}$  were included in the clinic cohort. Attrition included individuals no longer retained in ART care due to loss to follow up or death (chapter 4). A total of 636 (26.2%) adults in the cohort experienced attrition during the follow-up period. Attrition was higher amongst individuals with baseline CD4 counts  $>500$  cells/ $\mu\text{L}$  compared to individuals with baseline CD4 counts 0-500 cells/ $\mu\text{L}$  (aHR 1.28, 95%CI 1.07 -1.55). This finding raised concerns about the potential for increased attrition from ART care when providing ART regardless of CD4 count.

The overall TB incidence in the cohort was 4.4 cases/100PY (chapter 5). TB incidence was lower amongst individuals with baseline CD4 counts  $>500$  cells/ $\mu\text{L}$  compared to those with baseline CD4 counts 0-500 cells/ $\mu\text{L}$  (aHR=0.27; 95% CI 0.12 to 0.62). There were no incident TB cases in the first three months of ART amongst individuals with baseline CD4 counts  $>500$  cells/ $\mu\text{L}$ . These findings were promising, highly suggestive that routine provision of ART at baseline CD4 counts  $>500$  cells/ $\mu\text{L}$  will lead to a significant reduction in TB amongst individuals starting ART.

The prevalence of baseline moderate or severe renal dysfunction (Estimated Glomerular Filtration Rate (EGFR)  $< 60$ ml/min) in the cohort was low (1.9%) (chapter 6), as was the rate of incident moderate or severe renal dysfunction after initiation of ART (1.9cases/100PY). The study showed no significant association between baseline CD4 count and incident moderate or severe renal dysfunction occurring after initiation of ART. Analysis restricted to individuals with normal baseline renal function, showed no cases of incident moderate or severe renal dysfunction amongst individuals with baseline CD4 counts  $>500$ cells/ $\mu\text{L}$ . This is also a promising finding that needs to be confirmed by completion of further studies.

The fifth study (chapter 7), was a systematic review and meta-analysis of studies published between 2004 and 2015, which evaluated the association between baseline CD4 count and ART adherence. This systematic review showed lower ART adherence amongst individuals starting ART at higher baseline CD4 counts categories (pooled OR 0.90; 95%CI 0.84-0.96). Baseline CD4 count categories used in the included studies varied. The most commonly used comparison was between individuals initiating ART at CD4 counts > 200 cells/ $\mu$ L and at CD4 counts 0-200 cells/ $\mu$ L. In the two included studies that reported on individuals with baseline CD4 counts > 500 cells/ $\mu$ L, there was no difference in ART adherence between individuals with baseline CD4 counts > 500 cells/ $\mu$ L and those with baseline CD4 counts 0-500 cells/ $\mu$ L.

Overall the studies presented for this PhD dissertation demonstrated both benefits and challenges when conducting household-based HIV POCT and routinely initiating ART in HIV-positive individuals at baseline CD4 counts >500cells/ $\mu$ L. The studies presented in chapters 5 and 6 suggest potential reduction in incidence of TB and renal dysfunction with routine provision of ART at baseline CD4 counts >500cell/ $\mu$ L; providing a strong motivation for striving to attain universal access to ART in high burden settings. At the same time, the reported low HIV POCT sensitivity and the need for rigorous QA/QC when implementing household-based HIV POCT was concerning. As were the study findings showing higher attrition and poorer ART adherence when initiating ART at higher CD4 counts. Strategies to improve HIV POCT sensitivity, retention in ART care and ART adherence, in these contexts, should therefore be a priority for programme implementers in high-burden settings.

## **Opsomming**

Die Wêreldgesondheidsorganisasie (WGO) het in 2015 antiretrovirale behandeling (ART) aanbeveel vir alle MIV-positiewe individue, ongeag hulle CD4-telling. Wat universele toegang tot ART betref, het die WGO die mikpunt gestel dat ten minste 80% van MIV-positiewe individue op ART behoort te wees. Die doel van die HPTN 071 (PopART) proef, 'n verewekansigde proef in 21 gemeenskappe in Suid-Afrika en Zambië, is om te bepaal hoe twee kombinasievoorkomingspakkette op gemeenskapsvlak MIV-insidensie op bevolkingsvlak beïnvloed. HPTN 071 (PopART) het sedert Januarie 2014 tuisgebaseerde MIV-sorgpunttoetsing ("POCT") van stapel gestuur en, ongeag CD4-telling, ART by staatsklinieke in die proefgemeenskappe voorsien. Dit was vóór die onlangse veranderinge aan WGO- en Suid-Afrikaanse riglyne oor ART, wat nou vir ART-behandeling ongeag CD4-telling voorsiening maak. Die hoofuitkoms van MIV-insidensie is beoordeel in 'n ewekansig-gekose navorsingskohort, die populasiecohort ("PC"), wat beoog om uiteindelik 44 500 MIV-positiewe en -negatiewe deelnemers tussen die ouderdom van 18 en 45 – sowat 2 000 uit elk van die 21 gemeenskappe – te werf.

Die doel van hierdie PhD-proefskrif was om die uitkomst te bepaal van kliniese aktiwiteite wat die kern uitmaak van die doeltreffende voorsiening van MIV-behandelingsdienste in omgewings met 'n hoë siektelas. Die doelwitte van die PhD-studie was om te evalueer i) hoe akkuraat tuisgebaseerde MIV POCT is en watter impak die roetineaanvang van ART by individue met CD4-basislyntellings bo 500 selle/ $\mu$ L het op ii) attrisie in die vroeë fases van ARV-behandeling, iii) TB-insidensie in die vroeë fases van ARV-behandeling, iv) die insidensie van nierdisfunksie in die vroeë fases van ARV-behandeling, en v) ARV-getrouheid. In die strewe na hierdie doelwitte is vyf studies uitgevoer.

Vier van die vyf studies is binne die HPTN 071 (PopART) proef uitgevoer. Die vyfde studie, wat ARV-getrouheid beoordeel, was 'n stelselmatige oorsig en metaontleding. Die studie wat in hoofstuk 3 beskryf word, het 'n aantal deursneeontledings gebruik om die akkuraatheid van tuisgebaseerde MIV POCT tussen Januarie 2014 en Augustus 2016 by al 21 PopART-terreine in Suid-Afrika sowel as Zambië te beoordeel. Hierdie studie het op aanvanklik lae MIV POCT-sensitiwiteit in Suid-Afrika gedui (45-54%). MIV POCT-sensitiwiteit in Zambië, wat meer omvattende gehalteversekering en -beheer toegepas en ander MIV POCT-toestelle gebruik het, was beduidend beter vir dieselfde tydperk (95,8%). MIV POCT-sensitiwiteit in Suid-Afrika het mettertyd verbeter tot soortgelyke syfers as in Zambië deur die toepassing van streng gehalteversekering en -beheer.

Die studies wat in hoofstuk 4 tot 6 gemeld word, het die data ontleed van 'n kohort volwassenes (18 jaar of ouer) wat tussen Januarie 2014 en November 2015 by drie staatsklinieke in die Wes-Kaap, Suid-Afrika, met ART begin het. Kohortnasorg is teen die einde van Mei 2016 voltooi. Die kohortstudies het bepaal watter impak die roetineaanvang van ART by individue met CD4-basislyntellings bo 500 selle/ $\mu$ L het op i) attrisie, ii) TB-insidensie, en iii) die insidensie van nierdisfunksie in die vroeë fases van ARV-behandeling.

Altesaam 2 423 volwassenes met 'n gemiddelde CD4-basislyntelling van 328 (IQR 195-468) selle/ $\mu$ L is by die kliniekkohort ingesluit. Attrisie het individue ingesluit wat verlore was vir ARV-sorg weens hetsy verlies uit die nasorgstelsel of sterfte (hoofstuk 4). 'n Totaal van 636 (26,2%) volwassenes in die kohort het in die loop van die nasorgtydperk attrisie ervaar. Attrisie was hoër onder individue met CD4-basislyntellings bo 500 selle/ $\mu$ L vergeleke met diegene met CD4-basislyntellings van 0-500 selle/ $\mu$ L (aHR 1,28, 95% CI 1,07-1,55). Hierdie bevinding wek kommer oor 'n moontlike toename in attrisie uit ARV-sorg wanneer ART ongeag CD4-tellings voorsien sal word.

Die algehele TB-insidensie in die kohort was 4,4 gevalle/100 PJ (hoofstuk 5). TB-insidensie was laer onder individue met CD4-basislyntellings bo 500 selle/ $\mu$ L vergeleke met diegene met CD4-basislyntellings van 0-500 selle/ $\mu$ L (aHR = 0,27; 95% CI 0,12-0,62). Daar was geen voortvloeiende TB-gevalle in die eerste drie maande van ARV-behandeling onder individue met CD4-basislyntellings bo 500 selle/ $\mu$ L nie. Hierdie bevindinge is belowend en 'n sterk

aanduiding dat die roetinevoorsiening van ART op CD4-basislyntellings bo 500 selle/ $\mu$ L tot 'n beduidende afname in TB sal lei onder individue wat met ARV-behandeling begin.

Die prevalensie van matige of ernstige basislynnierdisfunksie (geskatte glomerulêre filtreertempo ("EGFR") van minder as 60 ml/min) in die kohort was laag (1,9%) (hoofstuk 6), en so ook die insidensiesyfer van matige of ernstige nierdisfunksie ná die aanvang van ART (1,9 gevalle/100 PJ). Die studie dui op geen beduidende verband tussen CD4-basislyntellings en voortvloeiende matige of ernstige nierdisfunksie ná die aanvang van ARV-behandeling nie. Ontleding van slegs daardie individue met normale basislynnierfunksie bring geen gevalle van voortvloeiende matige of ernstige nierdisfunksie aan die lig onder diegene met CD4-basislyntellings bo 500 selle/ $\mu$ L nie. Ook dít is 'n belowende bevinding, wat met verdere studies bevestig moet word.

Die vyfde studie (hoofstuk 7) was 'n stelselmatige oorsig en metaontleding van studies wat tussen 2004 en 2015 gepubliseer is en wat die verband tussen CD4-basislyntellings en ARV-getrouheid beoordeel. Hierdie stelselmatige oorsig dui op laer ARV-getrouheid onder individue wat in hoër CD4-basislyntellingkategorieë met ARV-behandeling begin (saamgevoeg OF 0,90; 95% CI 0,84-0,96). Voormelde gepubliseerde studies het van verskillende CD4-basislyntellingkategorieë gebruik gemaak. Die algemeenste vergelyking was dié tussen individue wat op CD4-tellings bo 200 selle/ $\mu$ L en CD4-tellings van 0-200 selle/ $\mu$ L met ARV-behandeling begin. In die twee gepubliseerde studies wat oor individue met CD4-basislyntellings bo 500 selle/ $\mu$ L verslag gedoen het, was daar geen verskil in ARV-getrouheid tussen individue met CD4-basislyntellings bo 500 selle/ $\mu$ L en dié met CD4-basislyntellings van 0-500 selle/ $\mu$ L nie.

Die studies wat vir hierdie PhD-proefskrif onderneem is, bring oor die algemeen bepaalde voordele sowel as uitdagings aan die lig wat tuisgebaseerde MIV POCT en die roetine voorsiening van ART by MIV-positiewe individue met CD4-basislyntellings bo 500 selle/ $\mu$ L betref. Die studies in hoofstukke 5 en 6 dui op 'n moontlike afname in die insidensie van TB en nierdisfunksie met die roetine voorsiening van ART op CD4-basislyntellings bo 500 selle/ $\mu$ L, wat as sterk motivering dien vir die strewe na universele toegang tot ART in omgewings met 'n hoë siektelas. Terselfdertyd is die aangemelde lae MIV POCT-sensitiwiteit

en die behoefte aan streng gehalteversekering en -beheer in die implementering van tuisgebaseerde MIV POCT kommerwekkend, soos ook die bevindinge wat dui op hoër attrisie en swakker ARV-getrouheid onder diegene wat op hoër CD4-tellings met ARV-behandeling begin. Strategieë om MIV POCT-sensitiwiteit, behoud in ARV-sorg sowel as ARV-getrouheid in hierdie konteks te verbeter, behoort dus 'n voorrangsaak te wees vir program implementeerders in omgewings met 'n hoë siektelas.

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## List of abbreviations

**3TC** lamivudine

**ART** antiretroviral therapy

**CHiPs** community HIV care providers

**DOH** Department of Health

**DTG** dolutegravir

**EFV** efavirenz

**FTC** emtricitabine

**HIV** human immunodeficiency virus

**HIVDR** HIV drug resistance

**HTS** HIV testing services

**HPTN** HIV prevention trials network

**NNRTI** non-nucleoside reverse-transcriptase inhibitor

**NRTI** nucleoside reverse-transcriptase inhibitor

**NVP** nevirapine

**PI** protease inhibitor

**PC** population cohort

**POCT** point of care test

**PopART** Population Effects of Antiretroviral Therapy to Reduce HIV Transmission trial

**PEPFAR** President's Emergency Plan For AIDS Relief

**QA** quality assurance

**QC** quality control

**SSA** sub-Saharan Africa

**STI** sexually transmitted infection

**SU** Stellenbosch University

**TB** Tuberculosis

**TDF** tenofovir disoproxil fumarate

**TAF** tenofovir alafenamide

**TEE** fixed dose combination of tenofovir disoproxil, emtricitabine and efavirenz

**TFO** transfer out

**UNAIDS** Joint United Nations Programme on HIV/AIDS

**VMMC** voluntary male medical circumcision

**WHO** World Health Organization

## **Chapter 1: Introduction**

This PhD dissertation evaluated clinical outcomes key to achieving universal access to antiretroviral treatment (ART) in settings with an human immune deficiency virus (HIV) prevalence rate  $\geq 1\%$  (high-burden settings). (1) The introductory chapter describes the burden of HIV, pathogenesis of HIV infection, approaches to ART and the effectiveness of ART in reducing morbidity and mortality in HIV-positive individuals in high-burden settings. This chapter also provides an overview of the methodology and layout of the dissertation and how the research objectives address existing gaps in the research evidence for best practice in implementation of HIV treatment services in high-burden settings.

### **1.1 HIV burden of disease**

More than 30 years after the HIV virus was first identified, (2) there remains no effective preventative vaccine or cure and the illness continues to affect millions of individuals. In 2016, there were an estimated 36.7 million HIV-positive individuals and a million HIV-related deaths globally, with an HIV prevalence rate in 18 to 45 year olds of 0.8%. (3) The burden of HIV is heavily focused in poorer developing regions. In 2016 there were 19.4 million HIV-positive individuals, more than half the global total, living in Eastern and Southern Africa. (3) In the same year there were 420 000 HIV-related deaths in the region, with an HIV prevalence amongst 18 to 45 year olds of 7.0%. (3) In Zambia, in 2016, there were a reported 1.2 million HIV-positive individuals and 21 000 HIV-related deaths, with an HIV prevalence amongst 18 to 45 year olds of 12.4%. (3) South Africa has one of the largest HIV-positive populations globally, with 6.9–7.03 million HIV-positive individuals, and a high number of HIV-related deaths (110 000) in 2016. This massive burden of HIV in South Africa is emphasised by the HIV prevalence rate amongst 18 to 45 year olds of 18.9%, as estimated by UNAIDS, in 2016. (3, 4) This HIV prevalence rate is higher than that reported by Statistics South Africa for 2015 (16.6%), (3, 4) and very similar to that reported by the Human Sciences Research Council (HSRC) Survey for 2012 (18.8%) for the same age group. (5) The HSRC also reported wide variation in HIV prevalence in 18 to 45 year olds across South Africa, ranging from 7.8% in the Western Cape to 27.9% in KwaZulu-Natal. (5)

### **1.2 HIV pathogenesis**

HIV is transmitted through exposure of mucosal surfaces to infected body fluids, including blood, semen, vaginal fluids, rectal fluids and breast milk. (6) Transmission occurs typically

during sexual intercourse, by percutaneous inoculation as in a needle-stick injury, needle-sharing by intravenous drug users or by transmission from mother to child during pregnancy, childbirth and breast-feeding. (6) There are two main HIV strains, HIV 1 and HIV 2, which are similar with respect to genetic structure, modes of transmission and replication within cells. HIV 2, however, shows lower transmissibility and rates of progression to acquired immune deficiency syndrome (AIDS) and is more resistant to some antiretrovirals commonly used in high-burden settings. HIV 1 is responsible for the vast majority of HIV infections worldwide, with HIV 2 infection largely restricted to West Africa. (7, 8)

Once the HIV virus is introduced into an individual's bloodstream, the typical sequence of infection includes the following steps (9):

- i) HIV in the bloodstream enters T lymphocyte cells by way of the CD4 and either CC-chemokine 5 (CCR5) or CXC chemokine receptor 4 (CXCR4) through interaction with envelope (Env) glycoprotein;
- ii) after fusion and un-coating within the cell, the viral RNA is reverse transcribed into DNA by the action of the **reverse transcriptase enzyme**;
- iii) integration of viral DNA into host DNA within the lymphocyte through the action of the **viral enzyme integrase**. This integrated viral DNA is called 'pro virus';
- iv) transcription of pro virus into multiple RNA copies through cleavage of DNA polypeptide sequences by viral **protease enzyme** activation to produce new viral RNA;
- v) assembly and budding and release from the lymphocyte of viral RNA into the bloodstream where it may infect other lymphocytes.

The natural course of untreated HIV infection is increasing serum viral load, with an associated decline in T lymphocytes exhibiting the CD4 antigen (CD4 cells) leading to immunosuppression. (10, 11) Stages in the progression of HIV infection to AIDS include:

- i) primary infection, during which the HIV RNA is present at very high levels in the host bloodstream; however, HIV antibodies are not yet detectable. The high serum viral load during this period is associated with high risk of development of viral reservoirs, where CD4 cells, in areas such as the brain and lymphoid tissue, are infected with replicable HIV virus. The high rates of viral load during this

- period are also associated with increased risk of onward transmission of HIV;
- (12, 13) ii) seroconversion, with the development of a host antibody response;
- iii) progression through a period of absence of clinical symptoms or limited symptoms; and
- iv) decline in CD4 cells and occurrence of AIDS, a symptom-based diagnosis made on occurrence of opportunistic infections or HIV-related cancers. (10, 14)

The WHO has developed clinical criteria for the staging of AIDs, with stages 1 to 4 based on the diagnosis of HIV-related illnesses. (14)

### **1.3 HIV diagnosis**

Diagnosis of HIV in high-burden setting is primarily completed using HIV point of care tests that measure HIV serum antibodies on whole blood obtained through finger pricking. Sequential with confirmation of the HIV status amongst individuals testing HIV positive on the first HIV POCT by a second HIV POCT using a different test kit is recommended as standard care for high-burden settings. (15) Provision of HIV testing services at both clinic and community, including household settings is recommended and there has been a steady expansion of community based HTS over the last decade. (15) Sensitivity of commonly used HIV POCT kits is high in controlled laboratory settings (>98%); (16) however there are limited high quality data from field settings (both community and clinic) and available data show varying sensitivity in these contexts. Effective scale up of HTS in high-burden settings is challenged by poor uptake amongst high risk population groups and commonly reported. HIV POCT false negative and HIV false positive results in both clinic and community settings. (15)

### **1.4 Mechanisms of action of antiretrovirals**

ART inhibits viral replication with associated decline in serum viral load and increase in CD4 cell count. (9) (17) ART drugs commonly used in high-burden settings inhibit HIV reverse transcriptase enzyme and can be categorised primarily in two groups: non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs). Based on available evidence from randomised controlled trials (RCTs) and programmatic studies, the WHO recommends a limited number of first-line ART regimens

for adult treatment in high-burden settings which commonly include two NRTIs, tenofovir (TDF) plus lamivudine (3TC) or emtricitabine (FTC) and an NNRTI, such as efavirenz (EFV) or nevirapine (NVP). (18) A fixed-dose combination of TDF, 3TC/FTC and EFV remains the preferred first-line option in many high-burden settings. Use of protease enzyme inhibitors and integrase enzyme inhibitors in high-burden settings is largely restricted to second- and third-line treatment. (18)

Routine viral load monitoring is recommended for high-burden settings and is implemented in selected countries such as South Africa. (18) Continued viral replication, while individuals are on ART, can promote the selection of HIV virus with drug-resistant mutations (DRMs) during viral replication. Drug-resistant HIV virus can then be transmitted to other individuals, limiting ART effectiveness. The number of DRMs required to cause resistance varies between different ART drugs. (19) In response to increasing rates of HIV drug resistance (HIVDR), particularly to NNRTIs, there is a push toward strengthening HIVDR monitoring in high-burden settings through completion of sentinel HIVDR surveys. (18) In contrast, individuals starting ART in more developed countries, such as the United States, have routine access to individualised genotypic screening for HIVDR, the results of which are used to inform the choice of first-line ART; this may include a wider range of first-line ART drugs, including protease inhibitors (PIs), ritonavir-boosted PIs and integrase inhibitors such as dolutegravir (DTG), which are less susceptible to HIVDR. (20, 21)

### **1.5 HIV treatment coverage in high-burden settings**

In 2014, UNAIDS published the 90-90-90 targets: that by the end of 2020, 90% of people living with HIV know their HIV status; 90% of individuals diagnosed with HIV are on ART; and 90% of individuals on ART are virally suppressed. (22) In addition, in 2016, the WHO recommended 'Universal Access to ART', defined as >80% of HIV-positive individuals on ART. (18) Responding to the need for rapid scale-up of HIV treatment services required to achieve these targets, (3, 18, 22) while maintaining quality of care in high-burden settings, is extremely challenging, (23) with poor uptake at all stages of the HIV treatment cascade, namely, HIV diagnosis, linkage to care, ART uptake, retention on ART and viral load suppression. (3, 18, 22)

Strengthening community-based HIV testing service (HTS) strategies is critical to increasing HTS coverage. (15, 18) Published studies show community-based HTS to be highly acceptable and effective in identifying HIV-positive individuals in high-burden settings, including certain high-risk groups such as men. (24-26) Good progress has been made over recent years in increasing HTS coverage, with an estimated 76% of HIV-positive individuals in Eastern and Southern Africa and 86% in South Africa knowing their HIV status; however, challenges in delivery of HTS remain. (3) In addition to low HTS coverage in many high-burden settings, there is concern over accuracy of HIV point of care (POCT) kits, commonly used in high-burden settings. These kits measure HIV antibodies in whole blood attained by finger prick, (15) and show decreased sensitivity during HIV seroconversion and in advanced HIV disease when positive individuals may be antigen-positive with low antibody titres. (27-29)

There are also challenges with linkage to ART care and ART initiation after HIV diagnosis. Overall rates of linkage to ART care are low compared to global targets, with only 60% of HIV-positive individuals in Eastern and Southern Africa and 56% of HIV-positive individuals in South Africa who know their HIV status on ART (3). Delays in the time between HIV diagnosis and ART initiation are also common, and delay in initiation of ART is further exacerbated by high rates of loss to follow-up from clinic care prior to ART initiation (pre-ART care). (24, 30)

After ART initiation, there are high rates of attrition from ART care and non-adherence to ART amongst individuals remaining in care, both of which are associated with increased viral load and increased rates of HIVDR. (31-33) To illustrate, a recent systematic review reported 40% attrition from ART care (defined as no longer retained in ART care due to loss to follow-up or death) in sub-Saharan African (SSA) countries after 24 months ART duration. (34) There is also a worrying trend toward deteriorating clinical outcomes as health facilities become overburdened by increasing numbers of ART patients, (35, 36) as well as concerns about low rates of viral load suppression and increasing rates of HIVDR amongst individuals retained in ART care. A multi-centre programmatic study from Africa showed variable HIV viral suppression during the first 24 months of ART, ranging from 2.6 to 20.6%, with high levels of HIVDR. (37) Although viral load monitoring is recommended in all settings, it is not routinely provided in many high-burden settings, due to lack of the necessary laboratory

infrastructure. (38) In settings where viral load monitoring is available, there are reports of poor implementation, (38) with <60% of scheduled viral load tests completed, as per ART guidelines, at PHC clinics in the Western Cape. (39)

ART adherence is defined as the extent to which an individual's taking of prescribed medication corresponds with healthcare provider recommendations. (1) Poor ART adherence is strongly associated with increased viral load and development of HIVDR amongst HIV-positive individuals on ART. (31, 40, 41) ART adherence support is extremely challenging in busy primary healthcare (PHC) clinics, and there is marked heterogeneity in methodologies used for promoting and monitoring adherence between programmes. (42, 43) A systematic review of published studies from Africa, showed overall poor ART adherence, with study participants taking <60% of prescribed ART drugs. (44) In this context, there is growing concern about HIVDR in high-burden settings. National HIVDR surveillance estimates in high-burden settings showed that in six out of ten countries surveyed, more than 10% of individuals initiating ART had NNRTI resistance, with increased HIVDR among individuals with previous ART exposure. (33) In response to these findings, the WHO has published recommendations for management of pre-ART HIVDR. (41) These recommendations included substitution of EFV and NVP in first-line ART regimens with DTG or ritonavir-boosted PIs; however, these new guidelines are not fully implemented in high-burden settings. (41)

## **1.6 Morbidity and mortality in HIV-positive individuals**

AIDs-related mortality is defined as mortality as the result of an HIV-related illness (HIV-related morbidity). (45) In countries in high-burden settings, including Zambia and South Africa, AIDS-related mortality caused by HIV-related illnesses continue to be the most common cause of mortality amongst HIV-positive individuals. (46, 47) This is in contrast to more developed countries, such as the United States, where non-HIV-related illnesses, including cardiovascular disease and non-AIDS-defining cancers, are increasingly common. (47)

In 2015, there was an estimated annual TB incidence of 142/100 000 population and 195/100 000 population globally and in high-burden settings, respectively. (48) In the same



year, South Africa had the highest estimated annual TB incidence worldwide (834/100 000 population), with 57% of TB cases occurring in individuals co-infected with HIV. (48) TB in HIV-positive individuals initiating ART is more common amongst those with lower CD4 cell counts at the time of ART initiation (baseline CD4 count). A study from Cape Town, South Africa, reported TB incidence rates among HIV-positive individuals starting ART that ranged from 25 cases/100 person years at baseline CD4 counts <100 cells/ $\mu$ L to five cases/100 person years at baseline CD4 counts >350 cells/ $\mu$ L. The study had limited data on individuals with baseline CD4 counts >500cell/ $\mu$ L. (49) Amongst HIV-positive individuals initiated on ART, published data show higher TB incidence during the first four months of ART and approximately double in the first year of ART compared to subsequent years. (50-53). These increased TB incidence rates during initial months on ART may, in part, be attributable to restored immune response in individuals initiated on ART, leading to immune reconstitution inflammatory syndrome (IRIS) with clinical presentation of previously asymptomatic TB. (51)

Renal dysfunction occurs through a variety of mechanisms, including HIV-related nephropathy (HIVAN), HIV immune complex kidney disease, thrombotic microangiopathy and toxicity to some ART drugs such as tenofovir. (54, 55) Routine monitoring of renal function through measurement of serum estimated glomerular filtration rate (EGFR) is recommended for individuals started on tenofovir-containing regimens. (18, 56) American National Kidney Foundation recommendations for the classification of renal dysfunction are based on serum EGFR as follows; mild renal dysfunction (EGFR 60 - 89 mL/min), moderate renal dysfunction (EGFR 30 - 59 mL/min) or severe renal dysfunction (EGFR <30mL/min). (57)

Renal dysfunction is a common HIV-related illness, diagnosed in approximately 20% of HIV-positive individuals initiating ART in South Africa, (58) and is associated with increased mortality amongst individuals initiating ART. (59) The reported association between baseline CD4 count and baseline renal dysfunction varies, with some studies showing higher baseline renal dysfunction at lower CD4 counts, (59, 60) and other studies showing no association. (58, 61) Programmatic studies, with median baseline CD4 counts ranging from 154 to 209 cells/ $\mu$ L, show decreased renal dysfunction after ART initiation amongst individuals with baseline CD4 counts >200 cells/ $\mu$ L compared to lower values. (62, 63) With respect to the impact of initiating ART at baseline CD4 counts >500 cells/ $\mu$ L, results from a recently

published randomised control trial (RCT) showed higher average EGFR after ART initiation amongst individuals starting ART at baseline CD4 counts >500 cells/ $\mu$ L when compared to those with baseline CD4 350 to 500 cells/ $\mu$ L. (64).

### **1.7 ART impact on morbidity and mortality in HIV-positive individuals**

Published data from programmatic cohorts and RCTs clearly demonstrate the effectiveness of ART in reducing the occurrence of HIV-related illnesses (AIDS-related morbidity) and all-cause mortality in HIV-positive individuals when initiating ART at baseline CD4 counts <200 cells/ $\mu$ L. [16-18] Published data also show further reductions in AIDS-related morbidity and all-cause mortality when initiating ART at baseline CD4 counts 200 to 350 cells/ $\mu$ L compared to baseline CD4 counts <200 cells/ $\mu$ L. Further reductions are seen when initiating ART at baseline CD4 counts 351 to 500 cells/ $\mu$ L when compared to initiating ART at baseline CD4 counts <350 cells/ $\mu$ L. [19, 20]

Two recent RCTs that describe the impact of ART started at CD4 counts >500 cells/ $\mu$ L have greatly influenced debate on when to routinely start ART: The Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis against Tuberculosis in HIV-positive Adults (ANRS 12136 TEMPRANO) and the Strategic Timing of Antiretroviral Treatment (START) trials. [21, 22] TEMPRANO showed a 44% reduction in severe AIDS-related morbidity, including TB and all-cause mortality, when ART was initiated at baseline CD4 counts 500 to 800 cells/ $\mu$ L, compared to cases when ART was started according to pertinent ART guidelines, which changed, in the trial sites, from a CD4 cut-off for ART initiation from 350 cells/ $\mu$ L to 500 cells/ $\mu$ L part way through the trial. [21] In addition, the trial showed a 35% reduction in severe morbidity when six months isoniazid (INH) prophylaxis (IPT) was added at the start of ART. [21] Results from the START trial, first released in May 2015, supported these findings, showing a 57% reduction in a composite primary end point of any serious AIDS-related event or serious non-AIDS-related event or death from any cause amongst participants starting ART at CD4 counts >500 cells/ $\mu$ L, compared to between 351 and 500 cells/ $\mu$ L. [22] START also showed a reduction in occurrence of specific diseases in the intervention arm, including TB and renal dysfunction. (64, 65)

## **1.8 ART access in HIV high-burden settings**

There has been a steady broadening in eligibility criteria for access to ART in high-burden settings since 2002. The first WHO ART guidelines for high-burden settings, published in 2002, used a CD4 cut-off of 200 cells/ $\mu$ L for ART initiation. (66) In 2010, the CD4 cut-off was changed from 200 to 350 cells/ $\mu$ L, (67) and in 2013 from 350 cells/ $\mu$ L to 500 cells/ $\mu$ L. (1) Further updated WHO HIV treatment guidelines, first published in 2015, (11) based primarily on the results of the TEMPRANO and START trials, recommended ART for all HIV-positive individuals regardless of CD4 count. ART access criteria in South Africa, including in the Western Cape Province, have changed in line with WHO recommendations. In January 2015, South African and Western Cape ART guidelines changed the CD4 cut-off for ART from 350 to 500 cells/ $\mu$ L, (68) and in October 2016 ART guidelines changed to recommending ART regardless of CD4 count. (69)

## **1.9 Gaps in research evidence for HIV treatment**

RCTs, such as TEMPRANO and START, remain the gold standard for clinical evidence, with random allocation of individuals to treatment and comparison arms, along with accurate standardisation of interventions and outcome measurements. (70) However, given that RCTs are undertaken under rigid research conditions, which often do not reflect real-life programmatic conditions, there is also a need for data from operational research studies, defined as studies completed in programmatic settings, (71) when developing clinical guidelines. (71) There are good data from both RCTs and operational research studies of additional reductions in HIV-related morbidity and all-cause mortality as a result of initiation of ART at higher baseline CD4 counts, up to baseline CD4 counts  $\leq$ 500 cells/ $\mu$ L. However, there remains a dearth of data from high-burden programmatic settings evaluating the impact on HIV-related morbidity and all-cause mortality of routine initiation of ART at CD4 counts  $>$ 500 cells/ $\mu$ L.

In this context, the overall aim of this PhD dissertation was to evaluate the accuracy of household HIV testing and the impact of routine provision of ART  $>$ 500 cells/ $\mu$ L in HIV-positive adults on rates of attrition from ART care, on TB incidence and on renal dysfunction. In addition, a systematic review of published literature evaluating the association between baseline CD4 count and ART adherence was conducted.

## **1.10 PhD dissertation outline**

### **1.10.1 PhD dissertation context**

The original studies in this PhD dissertation research were embedded within the HPTN 071 (PopART) trial in South Africa. The HPTN 071/Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) trial is a community randomised trial currently in 21 communities in South Africa and Zambia. PopART field activities began in January 2014 and are scheduled to be completed in June 2018. The aim of the trial is to determine the impact of two community-level combination prevention packages on population-level HIV incidence. (72) PopART communities were randomly allocated to Arms A, B or C. The PopART household intervention was delivered to all individuals in Arm A and B communities by a cadre of community HIV care providers (CHiPs). DOH clinics in communities allocated to Arm A provided ART regardless of CD4 count from January 2014, 18 to 24 months ahead of recent changes to South African and Western Cape ART guidelines. (68) Clinics allocated to Arms B and C provided ART as per local standard care. (11, 68) The primary outcome of HIV incidence is evaluated in a randomly selected research cohort, the Population Cohort (PC), which aims to recruit 52,500 HIV-positive and negative participants aged 18 to 45, 2500 from each of the 21 communities. A full description of the PopART trial is provided in chapter 2.

### **1.10.2 PhD aim and objectives**

#### Overall PhD aim

The aim of this PhD dissertation was to evaluate the outcomes of clinical activities key to effective provision of HIV treatment services in high-burden settings.

#### PhD objectives

##### To evaluate within the PopART PC

1. The accuracy of household HIV POCT

##### To evaluate the impact of routine initiation of ART at baseline CD4 counts >500cells/ $\mu$ L at

##### DOH ART clinics on

2. Attrition during early ART
3. TB incidence during early ART

4. The incidence of renal dysfunction during early ART

To evaluate through completion of a systematic review and meta-analysis of published literature:

5. The association between baseline CD4 count and adherence to ART.

### **1.10.3 Overview of PhD dissertation chapters**

In chapter 2, I give a brief summary of the outline of the HPTN 071/ Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) trial in which the work for this thesis is embedded.

Chapters 3 to 7 present the studies completed for this PhD. In each chapter the study is prefaced by an introduction that provides: i) the citation for the study presented in the chapter where relevant. ii) a brief overview of the study design and how the study was positioned with the PopART trial iii) an outline of which data were used for the completion of the study and iv) an outline of my contribution and the contribution of the co-authors to the completion of the study presented in the chapter.

The study presented in chapter 3, 'Understanding low sensitivity of community-based HIV rapid testing: experiences from the HPTN 071 (PopART) trial in Zambia and South Africa', evaluated the accuracy of household-based HIV POCT. In addition, I present the activities we put in place to improve the accuracy and the lessons that can be learnt from this for the roll-out of community-based HIV POCT.

For the work presented in chapters 4-6, I set up a cohort of HIV-positive individuals who initiated ART regardless of CD4 count at DOH clinics. This cohort offered the opportunity to evaluate clinical outcomes during the routine provision of ART regardless CD4 count in HIV positive adults and provide early information on these outcomes at CD4 counts >500cells/ $\mu$ L. The results from these studies might be of benefit to DOH as the new policy of ART regardless CD4 is rolled out in South Africa.

The study presented in chapter 4, 'Attrition when providing antiretroviral treatment at CD4 counts >500cells/ $\mu$ L at three government clinics included in the HPTN 071 (PopART) trial in

South Africa', evaluated the impact of routine initiation of ART at baseline CD4 counts >500cells/ $\mu$ L at DOH clinics on attrition during early ART.

The study presented in chapter 5, 'Incidence of Tuberculosis amongst HIV-positive individuals initiating antiretroviral treatment at higher CD4 counts in the HPTN 071 (PopART) trial in South Africa', evaluated the impact of routine initiation of ART at baseline CD4 counts >500cells/ $\mu$ L at DOH clinics on TB incidence during early ART.

The study presented in chapter 6, 'Renal dysfunction in a cohort of adults starting antiretroviral treatment at baseline CD4 counts > 500cells/ $\mu$ L in the HPTN 071 (PopART) study in South Africa', evaluated the impact of routine initiation of ART at baseline CD4 counts >500cells/ $\mu$ L on the incidence of renal dysfunction during early ART.

The study presented in chapter 7, 'Baseline CD4 Count and Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis', evaluated the association between baseline CD4 and ART adherence in studies published between January 2004 and September 2015.

Chapter 8, the discussion chapter, summarises the key findings of this research and discusses how these findings can contribute toward improving HIV treatment services in high-burden settings. The chapter also highlights operational gaps identified through completion of the studies that may be of importance to health care providers.

Chapter 9 lists additional publications I contributed to since January 2014, referenced in this PhD dissertation.

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## **Chapter 2: Outline of the HPTN 071/Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) trial**

This chapter provides an overview of the HPTN 071 (PopART) trial in both Zambia and South Africa. Additional information on clinic activities in South Africa relevant to the completion of the studies presented in chapters 4 to 6 is also provided.

The HPTN071 (PopART) trial is a three-armed community randomised study set in Zambia and South Africa, which aims to determine the impact of two community-level combination prevention packages on population-level HIV incidence. PopART is funded by the United States National Institutes for Health (NIH), the President's Emergency Plan For AIDS Relief (PEPFAR) and the Bill & Melinda Gates Foundation. PopART is implemented in close partnership between study partners in the United Kingdom, United States, Zambia and South Africa; with extensive collaboration with Zambian and South African DOH and PEPFAR implementing partners. PopART implementation of field activities started in January 2014 and is scheduled to end in June 2018.

### **2.1 HPTN 071 (PopART trial) overview**

For PopART, a community is defined as the catchment population of a DOH primary healthcare (PHC) clinic. (1, 2) The total population per PopART community averages 55,000 individuals. Within each country, communities were matched based on the best available estimates of HIV prevalence and ART coverage. The 21 PopART communities were divided into seven matched triplets, with three triplets in South Africa and four in Zambia. Sites in South Africa were selected based on the criteria listed below.

- Burden of HIV/TB
- Drainage population of the clinic > 25 000 adults
- A functioning ART service
- Clinic must have capacity for expansion to meet scale up demands
- Perceived low mobility of population
- Compatibility with other sites to form triplet
- Proximity to Cape Town
- Existing knowledge of site from the Zamstar study

In each matched triplet, one community was randomly allocated to Arm A, B or C (Table 1). The PopART intervention targeted all individuals in the Arm A and B study communities and was delivered jointly in the community by a cadre of community HIV care providers (CHiPs) and at DOH PHC clinics. From October 2016, ART guidelines, in South Africa and Zambia recommended ART regardless of CD4 count, (3, 4) and from that time Arms A and B therefore offered the same intervention. Despite these changes, PopART remained well powered to evaluate the primary outcome. The primary outcome of HIV incidence is evaluated in a randomly selected research cohort, the Population Cohort (PC), which aims to recruit 44,500 HIV-positive and negative participants aged 18 to 45, approximately 2000 from each of the 21 communities (Table 1). (5)

**Table 1: Outline of PopART trial**

<b>ARM A</b>	<b>ARM B</b>	<b>ARM C</b>
<b>CHiPs*</b>	<b>CHiPs</b>	<b>Standard of care (No CHiPs)</b>
<b>ART irrespective of CD4 Count at DOH clinics</b>	<b>ART as per country guidelines at DOH clinics **</b>	
<b>PC</b>	<b>PC</b>	<b>PC</b>

\*CHiPs will visit all households in the PopART communities allocated to Arms A and B.

\*\* From October 2016 ART guidelines recommended ART regardless of CD4 count and from that time Arm A and B therefore offered the same intervention.

Extensive community consultation was completed during the development and implementation of the PopART trial. Study-specific community advisory boards were established in both Zambia and South Africa. Ongoing study progress is discussed at regular monthly community advisory board (CAB) meetings. Additional ad hoc meetings are scheduled to discuss any specific challenges that arise during study implementation. (1, 2)

### **2.1.2 PopART trial objectives**

Analysis of trial objectives is completed by comparison across Arms A, B and C of the trial.

Primary Objective:

To measure the impact of the two intervention packages delivered to Arms A and B on HIV incidence by enrolling and following a random sample of adults (the *Population Cohort*) in the trial communities over four annual rounds. (2)

Secondary objectives evaluated using PC data:

1. To measure the impact of the two intervention packages on:
  - community viral load
  - HSV-2 incidence
  - uptake of HIV testing and retesting over the entire study period
  - ART screening and uptake
  - sexual risk behaviour
  - uptake of male circumcision
  - HIV-related stigma
  - ART adherence and viral suppression (if funding is identified)
  - ART drug resistance (funding is identified).

Secondary objectives evaluated using ChiPs and DOH clinic data

2. To measure the impact of the two intervention packages on:
  - Time between HIV diagnosis and initiation of care
  - Retention in HIV care
  - HIV disease progression and death
  - ART toxicity based on clinic records
  - Case notification rate of tuberculosis
  - Uptake of PMTCT
  - Uptake of male circumcision.

(Additional secondary objectives, including costing evaluations, will be evaluated through a number of nested ancillary studies.)

## **2.2 PopART interventions in Zambia and South Africa**

Arm A communities received the full intervention package, which included HIV prevention services delivered by community HIV care providers (ChiPs) through door-to-door visits throughout the whole community. As well as ART regardless of CD4 count for all HIV-positive

individuals at DOH clinics (Table 1). (1, 2) Arm B was provided the same community interventions as Arm A, but with provision of ART according to prevailing South African and Zambian DOH guidelines. In the control arm (Arm C) there are no CHiPs workers and HIV, TB and sexually transmitted infections (STIs) services are conducted as per DOH guidelines.

### **2.2.1 CHiPs interventions in Zambia and South Africa**

The CHiPs teams routinely visit each household in the communities, at least annually for four years (2013 to 2017) with field work ending in December 2017. Included in the CHiPs visits were:

- Household HIV counselling and testing (HTS) using HIV POCT in line with DOH guidelines
- Counselling on sexual risk reduction
- Condom provision
- STIs and TB, including collection of sputum for TB diagnostics if symptomatic
- Promotion of voluntary male medical circumcision (VMMC) among HIV-negative men (VMMC was also provided to any HIV-positive men who requested it.)
- Active linkage to care for HIV, TB and VMMC.

Activities of the CHiPs workers in the houses were guided by standardised questions presented on an electronic data capture (EDC) device. All individuals screened positive for HIV and/or TB were referred to the local clinic and followed up to confirm linkage to care through review of clinic data and repeat household visits. Data from the CHiPs EDC was uploaded to a central database in at the Desmond Tutu TB Centre daily using 3G internet connectivity and subsequently shared with the London School of Hygiene and Tropical Medicine (LSHTM) where it was integrated with data from Zambian sites for development of monitoring reports and evaluation of secondary outcomes.

### **2.2.2 Clinic interventions in Zambia and South Africa**

HIV-positive individuals referred by CHiPs teams were fully assimilated into DOH care at the clinics and managed the same as individuals testing HIV-positive with other service providers. All services at clinics included in the PopART trial were delivered according to DOH standard care, with one exception; at clinics allocated to Arm A, all HIV-positive individuals were eligible for ART regardless of CD4 count from January 2014, ahead of

recent changes to WHO and in-country ART guidelines. (3, 4, 6) Both countries recommended a triple therapy first-line ART regimen with two NRTIs, tenofovir plus either lamivudine (3TC) or emtricitabine (FTC), along with an NNRTI (EFV or NVP) for first-line ART. (3, 4) With the exception of validation of linkage to care, there is currently no linkage of CHiPs and DOH clinic data. Toward the end of the trial, a folder review process of clinic folders on individuals included in the PC who have given consent will be conducted to extract data to address secondary outcomes. A more detailed description of activities at the South African clinics, relevant to the studies presented in chapters 4 to 6 of this dissertation, is provided below.

### **2.2.3 Detailed description of clinic interventions in the Western Cape, South Africa**

A fixed-dose combination of tenofovir, emtricitabine and efavirenz (TEE) was the first-choice ART regimen for first-line treatment at all clinics participating in PopART in the Western Cape. According to Western Cape ART guidelines, (7) tenofovir was contraindicated in clients with baseline estimated glomerular filtration rate (EGFR) <50 mL/min, in which case tenofovir was substituted with an alternative NRTI (zidovudine or abacavir), as part of a triple therapy regimen. Second-line treatment, for individuals failing first-line, included protease inhibitors and ritonavir-boosted protease inhibitors combined with two NNRTIs. There was no standard third-line regimen. Individuals failing second-line treatment were referred for genotypic resistance testing and further ART that might also have included integrase inhibitors, such as DTG. ART pharmacy pick-up dates were initially scheduled monthly, and then up to once every three months, once clients were assessed as stable on ART.

Routine laboratory monitoring in South Africa was completed by the National Health Laboratory Services (NHLS), and included routine measurement of CD4 cell count at four and 12 months of ART and of viral load at four months, 12 months and then annually. (4) DOH standard adherence and retention interventions were retained throughout PopART to ensure sustainability and strengthened through CHiPs activities. Stable ART clients meeting standardised criteria were routinely referred to clinic or community-based adherence clubs. (8) The work of clinic and community-based staff was integrated by their attendance at joint clinic operational meetings, (1, 4) and discussed at regular partnership meetings attended

by DOH, DTTC and PEPFAR implementing agency staff. PopART support for clinics included in the trial will end in June 2018.

All individuals starting ART and TB treatment in South Africa were registered on the DOH routine HIV monitoring system, Tier.net, (9) and the electronic TB register (ETR.net), (10) respectively. Aggregate Tier.net data, detailing the numbers of clients starting ART, are collected for PopART and included in the PopART intervention quarterly monitoring reports.

### **2.3 The population cohort (PC) in Zambia and South Africa**

PC participants, aged 18 to 45, were randomly selected from randomly selected households in each of the 21 PopART trial communities in Zambia and South Africa. (1, 2) All households within the defined trial community boundaries were initially enumerated through a census in 2013, prior to the study commencing. If the selected individual in a household declined to participate in the PC cohort, another adult in the household was randomly selected for trial inclusion. If there were no eligible adults willing to consent to the study, the household was replaced with another sample from the household list.

PC participants were visited annually for three rounds, between 2013 and 2016, namely, PC0, PC12 and PC24. PC36 began in September 2017 and will end in June 2018. At each annual round visit, participants were requested to complete a questionnaire and give blood for measurement of trial endpoints, including HIV. Laboratory-based HIV testing was first completed in-country using Abbott Architect HIV Ag/Ab Combo assay. A subsequent confirmatory HIV test was completed by the Network Laboratory (NL) in the United States using the 4th-generation Architect HIV test. These laboratory HIV results were not made available to the participant. All PC participants who do not know their HIV status or were reported as HIV-negative were offered an HIV point of care test (POCT). The HIV POCT kits used by PopART PC teams in South Africa varied. Between January and June 2014, First Response™ HIV 1-2-0 Card Test was used for screening and Alere Determine™ HIV-1/2 for confirmation, between July and December 2014, SD Bioline HIV-1/2 3.0 was used for screening and Alere Determine™ HIV-1/2 test for confirmation, and from January to June 2015, ADVANCED QUALITY™ Rapid Anti-HIV (1&2) Test and Abon HIV 1/2/O Tri-line test were used for screening and confirmation respectively. In Zambia, Alere Determine™ HIV-



1/2 test and Uni-Gold HIV were used for screening and confirmatory tests respectively, consistently from January 2014. In August 2015, PopART sites in South Africa changed to Alere Determine™ HIV-1/2 test and Uni-Gold HIV test in line with the Zambian sites.

Data on HIV POCT results were initially recorded on a paper form and subsequently entered into the PC database. All PC questionnaire data were captured on an EDC during the household visit and, together with laboratory test results, uploaded to a central database accessible from South Africa, Zambia, the United Kingdom and the United States.

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## Chapter 3: Understanding low sensitivity of community-based HIV rapid testing: experiences from the HPTN 071 (PopART) trial in Zambia and South Africa.

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### Study design overview

For this study a series of cross sectional analyses, completed quarterly between January 2014 and June 2016, were used to evaluate HIV POCT sensitivity amongst PC participants who accepted both HIV POCT and HIV serum testing at the PC0 and/or PC12 annual visits. The study also described quality assurance (QA) of HIV POCT activities and quality control (QC) of HIV POCT kits and QA/QC results over the same time period. Data for this study were accessed primarily from the PC database and integrated with additional data from PC QA/QC activities. These data were further integrated with additional data on PC participants who had a discordant HIV POCT result collected either when they were re-visited by the PC teams to follow up on their incorrect HIV POCT result, or from their DOH clinics records. This study addressed the following PhD objective:

To evaluate within the PopART PC the accuracy of household-based HIV POCT.

**Table 2: HTS study outline**

Primary outcome	Study site	Study period	Inclusion criteria	Data sources
HIV POCT sensitivity	PC0 and PC12 Zambia and South Africa	1 January 2014 to end June 2016	PC participants who accepted both laboratory and POCT HIV tests during PC0 and or PC12	PC database, PC process data and DOH clinic records

**Author contributions to study:** I am co-principal investigator in the HPTN 071 PopART trial in South Africa and have been intimately involved in implementation of the PopART PC. For this study I worked closely with the senior authors to develop the study design. I also

worked closely with the HPTN statistical centre (AY and DD) to develop the statistical analyses. I was the corresponding author in submission and publication of the study and jointly with the senior author coordinated development, submission, edits to reviewer comments and finalisation of the manuscript. All authors contributed towards development of the manuscript and reviewed drafts. All the authors read and approved the published version.

## Research article

# Understanding low sensitivity of community-based HIV rapid testing: experiences from the HPTN 071 (PopART) trial in Zambia and South Africa

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## Abstract

**Introduction:** Population-wide HIV testing services (HTS) must be delivered in order to achieve universal antiretroviral treatment (ART) coverage. To accurately deliver HTS at such scale, non-facility-based HIV point-of-care testing (HIV-POCT) is necessary but requires rigorous quality assurance (QA). This study assessed the performance of community-wide HTS in Zambia and South Africa (SA) as part of the HPTN 071 (PopART) study and explores the impact of quality improvement interventions on HTS performance.

**Methods:** Between 2014 and 2016, HIV-POCT was undertaken within households both as part of the randomly selected HPTN 071 research cohort (Population Cohort [PC]) and as part of the intervention provided by community HIV-care providers. HIV-POCT followed national algorithms in both countries. Consenting PC participants provided a venous blood sample in addition to being offered HIV-POCT. We compared results obtained in the PC using a laboratory-based gold standard (GS) testing algorithm and HIV-POCT. Comprehensive QA mechanisms were put in place to support the community-wide testing. Participants who were identified as having a false negative or false positive HIV rapid test were revisited and offered retesting.

**Results:** We initially observed poor sensitivity (45–54%, 95% confidence interval [CI] 31–69) of HIV-POCT in the PC in SA compared to sensitivity in Zambia for the same time period of 95.8% (95% CI 93–98). In both countries, specificity of HIV-POCT was >98%. With enhanced QA interventions and adoption of the same HIV-POCT algorithm, sensitivity in SA improved to a similar level as in Zambia.

**Conclusions:** This is one of the first reports of HIV-POCT performance during wide-scale delivery of HTS compared to a GS laboratory algorithm. HIV-POCT in a real-world setting had a lower sensitivity than anticipated. Appropriate choice of HIV-POCT algorithms, intensive training and supervision, and robust QA mechanisms are necessary to optimize HIV-POCT test performance when testing is delivered at a community level. HIV-POCT in clients who did not disclose that they were on ART may have contributed to false negative HIV-POCT results and should be the topic of future research.

**KEYWORDS:** HIV rapid test; community; household; sensitivity; quality control; HPTN 071 (PopART)

To access the supplementary material to this article please see [Supplementary Files](#) under Article Tools online.

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## Introduction

Globally, 37 million people are estimated to be living with HIV [1]. In 2014, UNAIDS announced a global target of 90% of HIV-positive individuals knowing their HIV status in order to deliver universal access to antiretroviral treatment (ART) for all people living with HIV (PLWH) [2]. However, there remains a considerable HIV testing gap, with only 54% of PLWH aware of their HIV status in 2014 [3]. Reaching the UNAIDS 90-90-90 targets will require a massive scale-up of

HIV testing and will necessitate innovative strategies to achieve this goal.

Whilst HIV testing services (HTS) are usually provided at healthcare facilities, multiple barriers prevent wide-scale access and acceptance of testing through this approach [4]. To improve knowledge of HIV status, non-facility-based HIV testing approaches have been explored [5,6] and many are now integrated into community testing programmes [5,7–9]. Previous studies have shown high levels



of competency in HIV testing amongst counsellors in household settings [10,11], and high levels of acceptance for community-based HIV testing are reported [5]. However, the quality assurance (QA) of this mode of HIV testing may be more challenging. The sensitivity and specificity of HIV point-of care testing (HIV-POCT) may be affected by user training and competency, testing environments, the algorithm used, test kit handling and storage as well as test kit performance [12–14]. Sensitivity and specificity of commonly used HIV-POCT in laboratory conditions are high (consistently 97–99%) [5,15,16]. However, there are limited and varied data on the performance of HIV-POCT in field settings, and comparison to a laboratory-based gold standard (GS) is uncommon [15,16]. The World Health Organization (WHO) pre-qualifies certain HIV testing strategies [7], but countries may utilize algorithms based on price and availability of test kits.

HIV-POCT QA guidelines vary across settings. The WHO emphasizes the importance of QA supported by well-structured quality management services and has recently updated its guidance for establishing HIV testing QA. The WHO recommends using a combination of quality control (QC) of HIV test kits and monitoring of proficiency of the staff conducting tests using both internally and externally generated plasma panels [7]. Effective implementation of these guidelines is resource-intensive and requires basic equipment and laboratory infrastructure that may be difficult to access in many high-burden settings [7].

HPTN 071 (PopART) is a community-randomized trial investigating the impact of a combination HIV prevention package on HIV incidence. The design of the study has been reported previously [17]. A key component of the combination prevention package is community-wide HIV testing offered by a novel cadre of community HIV-care providers (CHiPs) within the households of consenting individuals using HIV-POCT. CHiPs workers are “lay counsellors” who have a minimum of grade 11 or 12 high school education prior to employment and received basic accredited HIV counselling and testing training prior to conducting HIV-POCT in the field. In parallel with the CHiPs HIV testing, a randomly selected research Population Cohort (PC) of participants consented to provide an annual blood sample to determine HIV status in study laboratories for the study’s primary endpoint; many of these individuals also accept optional HIV-POCT delivered by research nurses in their households. This cohort provides an opportunity to assess performance of community-wide HIV-POCT compared to a laboratory-based GS. This manuscript describes the performance of community-wide HIV-POCT in Zambia and South Africa (SA) as part of the HPTN 071 (PopART) study.

## Methods

Within each of the 21 communities in Zambia and SA included in the HPTN 071 (PopART) study, a random sample of approximately 2000 participants aged between 18 and 44 years were selected to join the PC. Consenting participants were visited in their households and asked to provide

a venous sample of blood for laboratory-based HIV testing (blinded for study arm) to inform the study primary endpoint (HIV incidence). Results of this laboratory HIV testing were not routinely returned to study participants. All participants were encouraged to undergo HIV-POCT using the current nationally approved test algorithm. The results of this testing were given directly to the participant. Not all PC participants chose to have a HIV-POCT; some may already have been tested by the CHiPs or have previously known their status. For this paper, data from the baseline survey of the PC (PC0) and the 12-month follow-up survey (PC12) were analysed.

## HIV-POCT testing algorithms

In both Zambia and SA, HIV-POCT was undertaken by both trained CHiPs (lay counsellors) for the community combination prevention intervention and research nurses for the PC. In both cases, two HIV-POCT tests performed in series were used, in line with national and local guidelines. In Zambia, the Alere Determine™ HIV-1/2 test (Alere inc., CA, USA) was used for screening and the Uni-Gold HIV test (Trinity Biotech, Bray, Co.Wicklow, Ireland) was used for confirmation throughout the study period.

In SA testing followed the national algorithm which varied during the study period. From January to June 2014, the First Response™ HIV 1-2-0 Card Test (Real Relief India Private Limited, Tamil Nadu, India) was used for screening and the Alere Determine™ HIV-1/2 for confirmation; from July to December 2014, SD Bioline HIV-1/2 3.0 (Alere, CA, USA) for screening and Alere Determine™ HIV-1/2 test was used for confirmation; from January to June 2015, the ADVANCED QUALITY™ Rapid Anti-HIV (1&2) Test (InTec Products Inc., Haicang, Xiamen, China) was used for screening and the Abon HIV 1/2/O Tri-line test (Alere Inc., CA, USA) was used for confirmation. These changes in tests kits matched those of the SA Department of Health (SADOH) which provided the study with test kits during that period.

Following the analysis of the performance of these HIV-POCT algorithms, the study team chose to provide kits for SA HIV-POCT from July 2015 onwards such that Alere Determine™ HIV-1/2 test was used for screening and the Uni-Gold™ Recombigen® HIV-1/2 test was used for confirmation, to be consistent with the algorithm used in Zambia.

## HIV-POCT quality management

A system of quality management for the HIV-POCT was developed which included both QC for the test kits and QA of the testing procedure (QA/QC). This system used nationally available guidelines, but was expanded by the study team to include internal quality control (IQC) panel testing of test kits, temperature monitoring of test kits and proficiency testing of all staff conducting HIV testing. In Zambia, additional procedures were established earlier than in SA, as initially the SA test kits were provided by the DOH and QC systems used by DOH were assumed to be adequate. The timing of the implementation of additional procedures by the study team is shown in Table 1. Details of the additional procedures are as follow:



**Table 1. Performance, test kits used and quality measures in Zambia (Z) and South Africa (SA)**

	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016
<b>Zambia</b>										
N (total test)	1317	2038	2346	2318	2103	0 <sup>a</sup>	822	2002	2194	1140
Correctly identified HIV-positive (HIV-POCT+/GS +)	229/238	231/248	197/221	213/235	146/157		48/51	125/130	124/130	70/74
Correctly identified HIV-negative (HIV-POCT-/GS-)	1077/1079	1788/1790	2121/2125	2081/2083	1944/1946		767/771	1871/1872	2063/2064	1065/1066
Sensitivity % (95% CI)	96.2 (93–98)	93.1 (89–96)	89.1 (84–93)	90.6 (86–94)	93.0 (88–96)		94.1 (84–99)	89.9 (84–94)	95.4 (90–98)	94.6 (87–98)
Specificity % (95% CI)	99.8 (99.3–100)	99.9 (99.6–100)	99.8 (99.5–100)	99.9 (99.7–100)	99.9 (99.6–100)		99.5 (98.6–100)	99.9 (99.6–100)	100 (99.7–100)	99.9 (99.5–100)
Zambia first-line POCT	Determine	Determine	Determine	Determine	Determine		Determine	Determine	Determine	Determine
Zambia second-line POCT	Uni-Gold	Uni-Gold	Uni-Gold	Uni-Gold	Uni-Gold		Uni-Gold	Uni-Gold	Uni-Gold	Uni-Gold
IQC test strips/devices (pass/tested)	67/67	95/95	615/615	752/752	423/423	1164/1164	2840/2840	2874/2874	3543/3543	2528/2528
Panel proficiency testing (pass/total)		96/99	79/82	143/151	98/100	108/110	141/144	120/124	55/55	102/106
<b>South Africa</b>										
N (total test)	429	672	395	90	453	0 <sup>a</sup>	1029	911	973	436
Correctly identified HIV-positive (HIV-POCT +/GS +)	13/24	21/43	9/20	3/3	16/23		38/52	33/42	16/21	13/13
Correctly identified HIV-negative (HIV-POCT-/GS-)	405/405	629/629	375/375	87/87	430/430		977/977	868/869	952/952	423/423
Sensitivity % (95% CI)	54.2 (33–74)	48.8 (33–65)	45.0 (23–68)	<sup>b</sup>	69.6 (47–87)		73.1 (59–84)	78.6 (63–90)	76.2 (53–92)	100 (75–100)
Specificity % (95%CI)	100 (99–100)	100 (99–100)	100 (99–100)	100 (96–100)	100 (99–100)		100 (99.6, 100)	99.9 (99–100)	100 (99.6, 100)	100 (99–100)
SA first-line POCT	First response	First response	SD Bioline	SD Bioline	Advance quality		Advance quality	Determine	Determine	Determine
SA second-line POCT	Determine	Determine	Determine	Determine	Abon		Abon	Uni-Gold	Uni-Gold	Uni-Gold
IQC test strips/devices (pass/tested)					1482/1482	556/556	718/718	2297/2297	2131/2131	3090/3090
Panel proficiency testing (pass/total)					4/4	119/122	129/130	43/43	32/34	0

HIV-POCT+: final result of HIV-POCT algorithm is positive; HIV-POCT-: final result of HIV-POCT algorithm is negative; GS+: final result of laboratory algorithm is positive; GS-: final result of laboratory algorithm is negative.

HIV-POCT: HIV point-of-care testing; IQC: internal quality control; GS: gold standard; QA: quality assurance; PC: Population Cohort.

<sup>a</sup>No PC activity this quarter but QA continued.

<sup>b</sup>Sensitivity not calculated due to small number of positive results.



IQC panel testing of test kits was performed (i) when new tests kits were delivered to study head office, (ii) after transport of test kits to site offices within the communities and (iii) monthly for test kits that had been stored at site offices and transported in the field. Due to the large number of test kits used, panels used for IQC testing were generated by each in-country study laboratory. In Zambia, IQC activities described in this paper were initiated at the beginning of the study whilst in SA QC of test kits was conducted by the SADOH initially but was undertaken by the study team from Q1 2015 onwards.

Temperature monitoring during test kit storage was conducted in each country at the in-country study head office, at field offices and in cooler boxes that were used to transport HIV-POCT kits in the field. In instances where out-of-range temperatures were reported (>27°C for three consecutive days), IQC was performed for the affected test kits as described above.

User proficiency to perform the HIV-POCT kit procedures according to the manufacturers' specifications was assessed among all PC research staff and among CHiPs. In both countries, PC research nurses and CHiPs completed regular internal and external proficiency testing (EQA).

A checklist was developed to be used for observation of all staff performing HIV-POCT. This checklist covered all aspects of home-based testing, including: preparing the testing environment, obtaining a finger stick sample, carrying out testing and interpreting results (see Appendix). In addition, in both countries, internal proficiency panel testing was done with blinded plasma panels of HIV-positive and HIV-negative samples at least once per year for all testers. EQA with samples provided by the National Health Laboratory Service (NHLS) in SA and the National Virology Reference Laboratory (NVRL) in Zambia was also conducted on an annual basis from 2015 when these panels were made available.

If an individual staff member failed internal- or external proficiency testing, the individual underwent re-training and repeat proficiency testing before being allowed to resume HIV testing.

### Laboratory-based HIV testing

In this large clinical trial, special algorithms were developed for laboratory-based HIV testing in the PC. In addition to HIV-POCT described above which was part of the study intervention, venous blood was collected from each PC study participant for laboratory-based testing to provide data for the primary study endpoint of HIV incidence. This testing was done in two stages. In the first step, a single HIV screening assay (Abbott Architect Combo) was performed in-country. The results of that test dictated the algorithm that was used at the HPTN Laboratory Center (HPTN-LC, Johns Hopkins Univ. School of Medicine, Baltimore, MD, USA) for QA and HIV confirmation. For 10% of the samples where the in-country test was non-reactive, testing was repeated at the HPTN-LC with the same 4th generation test (the Abbott Architect Combo). If the results of the two tests were discrepant, samples were tested with the 4th generation Bio-Rad HIV 1/2 Combo (Bio-Rad Combo test) and the Bio-Rad Geenius discriminatory assay. For all

samples that had a reactive in-country test, testing was performed at the HPTN-LC with a different 4th generation test (the Bio-Rad 4th generation assay). If the in-country and HPTN-LC test results were discrepant, samples were tested at the HPTN-LC with Abbott Architect assay, the Bio-Rad Geenius discriminatory assay and HIV viral load testing. The final HIV status determined at the HPTN-LC is defined in this paper as the GS. Results of HIV tests performed in the in-country laboratories and at the HPTN-LC were not reported to study participants, unless discrepancies were identified between HIV-POCT among those who accepted the testing and final laboratory test results.

### Management of discrepant results between laboratory test and HIV-POCT

In both countries, PC participants who had discrepant results for the laboratory-based test and HIV-POCT were revisited by the research staff and offered the opportunity for repeat HIV testing using HIV-POCT; this was followed by collection of an additional venous blood sample in cases where the HIV-POCT was still discrepant with the laboratory result. Information was also collected regarding prior knowledge of HIV status, engagement in care if aware of HIV-positive status and ART at the time of initial HIV-POCT.

### Data management and statistical analysis

Data for all PC participants were collected electronically using a specially designed database. All participants were identified by a unique barcode. HIV-POCT results were recorded first on a barcoded paper-based results form by the nurse, and this information was entered into the electronic data capture device at the end of each day by the research assistant. All blood samples were labelled using the participant barcode and sent to laboratories for processing within 6 h of blood draw. Aliquots of plasma were stored at -80°C until laboratory testing. All laboratory data were entered into a laboratory data management system. In the case of discrepant results between laboratory test and HIV-POCT, data entry errors were excluded by retrieval of the source document HIV-POCT form and comparison and correction on the electronic data base.

This analysis of performance of HIV-POCT compared to a laboratory reference standard was limited to those PC participants with both an HIV-POCT result and a laboratory HIV test result corresponding to PC visits taking place between January 2014 and June 2016. Estimates of sensitivity and specificity of HIV-POCT over time, with exact binomial 95% confidence intervals (95% CI), were calculated in order to assess the possible effects of test kit choice and improvement in quality management.

### Ethical approval

Ethical approval for the HPTN 071 study was obtained from the University of Zambia research ethics committee, Stellenbosch University health research ethics committee and the London School of Hygiene and Tropical Medicine ethics committee.



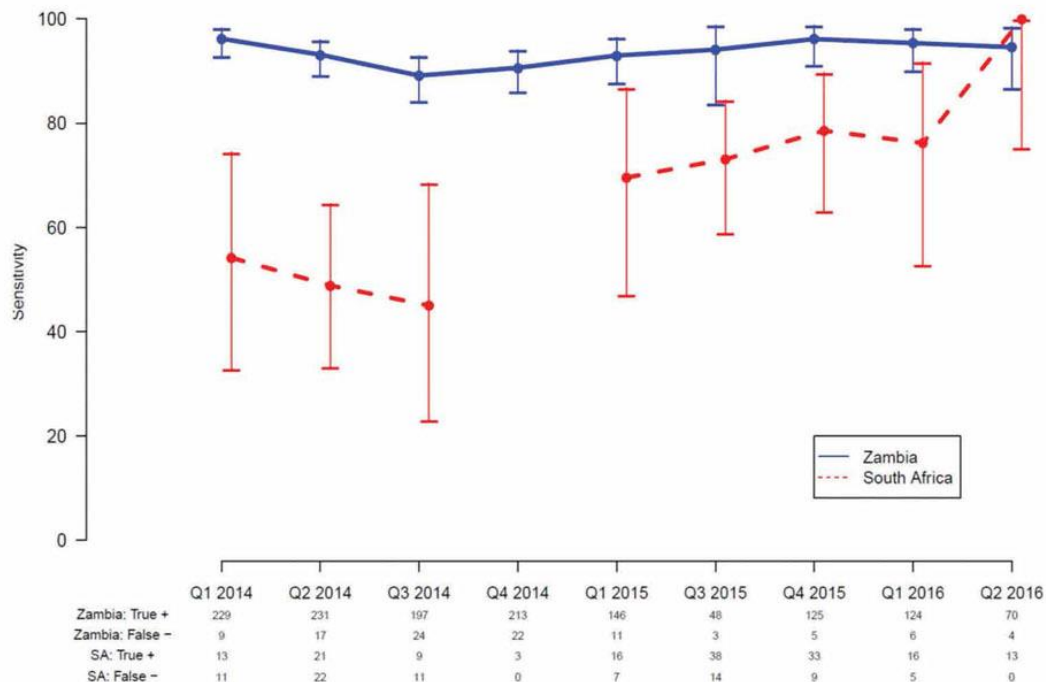


Figure 1. Sensitivity of HIV-POCT in Zambia and South Africa by quarter. HIV-POCT: HIV point-of-care testing.

## Results

### Study population

Data analysed in this paper include 21,668 paired HIV-POCT and laboratory GS results obtained from 17,680 PC participants at the PC enrolment and/or 12-month follow-up surveys (16,280, 75.1% Zambia, 5388, 24.9% SA).

### HIV-POCT performance

Using data from PC participants who had both HIV-POCT and laboratory results available, we examined HIV-POCT performance over time by quarter. Figure 1 summarizes HIV-POCT sensitivity for each country. Table 1 shows sensitivity and specificity by country over time alongside the test kit algorithms and other quality management activities.

Data from Zambia for the entire period showed a sensitivity of 89–96%, with the lower limit of the 95% CI remaining above 84% throughout. However, the sensitivity of HIV-POCT in SA was very different, with observed sensitivity as low as 45%.

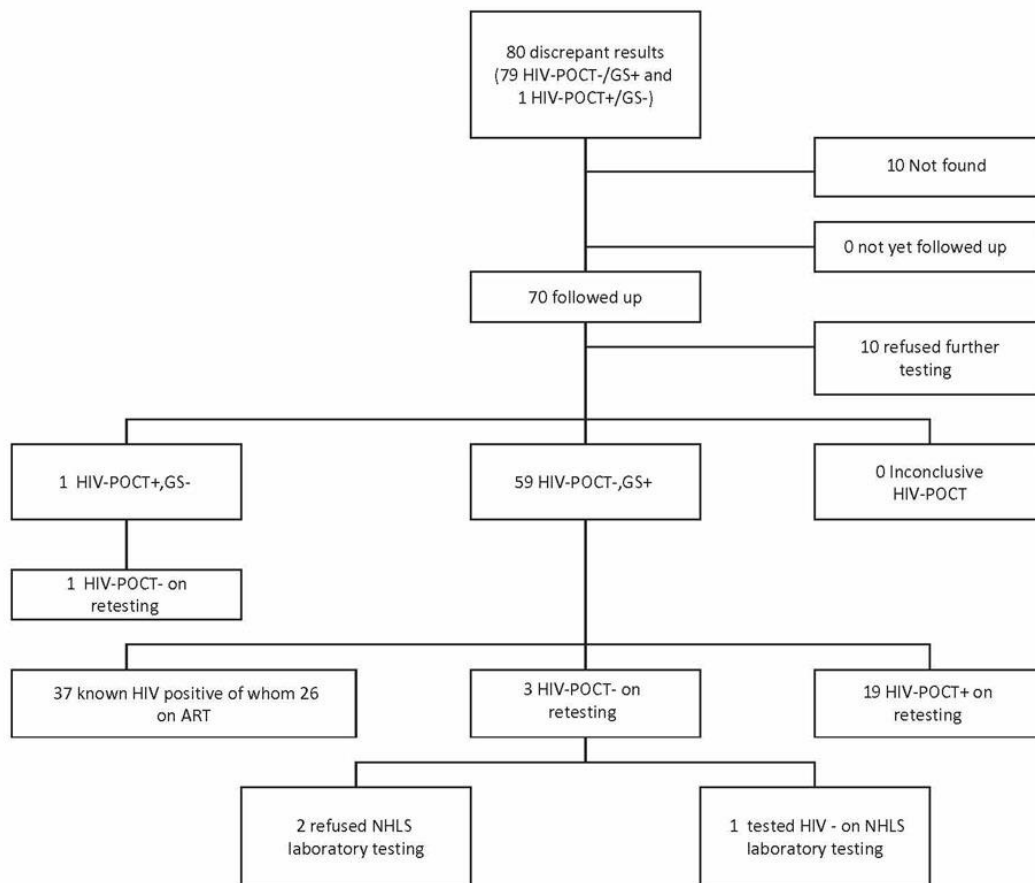
In SA the test kit algorithm changed first in Q3 2014 in line with SA national guideline change and again in Q1 2015. Neither of these changes in HIV-POCT algorithm appeared to significantly change the performance of the testing process. As a consequence of continuing poor performance in SA, HIV-POCT algorithm was changed in Q4 2015 to be consistent with that used in Zambia (Alere Determine™ HIV-1/2 followed by Uni-Gold™ Recombigen® HIV-1/2). Additional quality management procedures were also employed to monitor HIV-POCT performance, similar to what was being implemented in Zambia. These included re-training of all staff and more frequent staff supervision. Proficiency testing using approved plasma panels was introduced.

### Quality assurance

IQC testing was performed on a total of 25,175 test strips/devices overall at central storage and field sites, as well as when temperature monitoring showed deviations from the recommended storage temperatures in storage sites or field cooler boxes. On all occasions, the test strips/devices tested, passed (IQC) (Table 1).

Internal proficiency panel testing was conducted annually so that during this period individual testers may have been tested more than once. A total of 971 proficiency panels were used (934 for CHiPs and 37 for PC nurses) in Zambia with an overall pass rate of 96% (Table 1). External proficiency panel testing was conducted once during the period of this report and 419/444 testers (94%) passed (20 PC nurses were tested with 100% pass rate). In SA, internal proficiency panel testing started later and a total of 333 proficiency panels being used (271 for CHiPs and 62 for PC nurses) with an overall pass rate of 98%. All individuals failing proficiency panel testing were re-trained and had to pass a further proficiency panel test before being allowed to resume testing. External panel proficiency testing was conducted in the six HPTN 071 intervention sites with one panel per site being tested rather than individual testers. All six sites were tested on four occasions with one site failing on one occasion. This site received additional re-training.

Observation of all steps in the HIV-POCT process using the supervision checklist started in 2015, and observations using this revealed that most errors were made in the finger stick and correct use of the sample collection device (capillary tube or pipette according to test used). Errors were also made in the timing and amount of chase buffer added.



**Figure 2a. Flow chart of follow up of participants with discrepant HIV results South Africa.**

HIV-POCT: HIV point-of-care testing. HIV-POCT-: original HIV-POCT algorithm negative; HIV-POCT+: original HIV-POCT algorithm positive; inconclusive HIV-POCT-: original HIV-POCT algorithm discordant; GS+: laboratory algorithm (gold standard) HIV positive; GS-: laboratory algorithm negative; GS confirmed: after retesting the HIV-POCT agreed with the laboratory gold standard; HIV-POCT confirmed: after retesting the results of the repeat HIV-POCT algorithm agreed with the original HIV-POCT algorithm.

#### Follow-up of individuals with discrepant HIV-POCT and laboratory tests

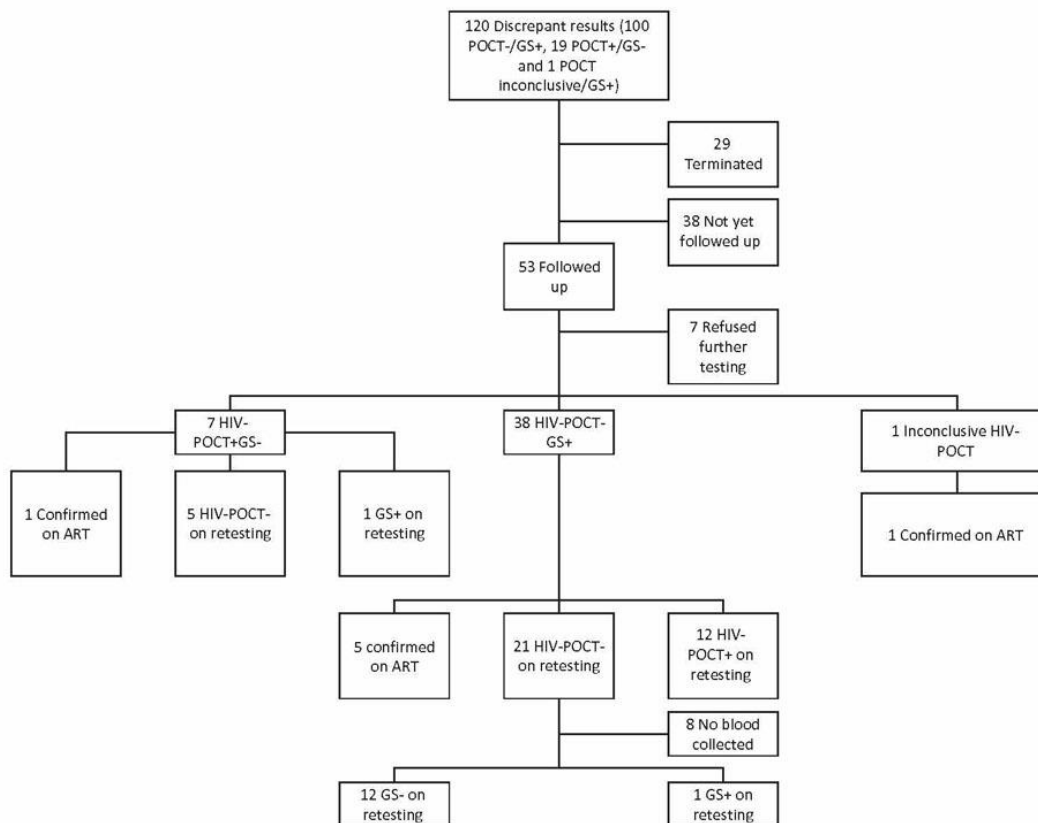
Overall, 199 participants had 200 discrepant HIV results (participants were seen annually so it was possible for them to receive discrepant results in both years). Figure 2 summarizes for each country the follow-up of participants with test results that were discrepant between the HIV-POCT and the laboratory GS. In Zambia 120 and in SA 80 participants were identified with discrepant results. Multiple attempts to revisit all these participants were made by the research teams in both countries, according to a standardized algorithm, during which these participants were offered a repeat HIV-POCT and laboratory test. There were some differences in the procedures for conducting re-test visits between Zambia and SA.

In SA, re-test visits have been attempted for all 80 participants with confirmed discrepant results. PC staff were unable to locate 10 participants, and a further 10 declined a re-test visit, for the remaining 60 participants, 59 appeared to have initial false negative results (HIV-POCT-negative but GS-positive) and 1 an initial false positive result (HIV-POCT-positive but GS-negative). Of the 59 individuals with false negative results, 37 (63%) were found to already know their HIV-positive status and 26 (44%) were

confirmed to be on ART at the time of the false negative POCT. Re-testing was not performed on known HIV-positives; however, they were given adherence counselling and advised to attend the clinic. For the remaining 22 individuals, HIV-POCT was repeated using the algorithm of Alere Determine™ HIV-1/2 and Uni-Gold™ Recombigen® HIV-1/2. Three of these participants again tested HIV-negative on HIV-POCT. Of these, two did not consent to further blood draw for plasma HIV testing and one tested HIV-negative on further in-country laboratory testing. Investigation of this participant was terminated after the participant was lost to follow-up due to relocation out of the study area. Including individuals known to be HIV-positive, a total of 56/59 (95%) were confirmed to have been prior false negative HIV-POCT results. One participant had a false positive HIV rapid test; this participant was re-visited and on re-testing with HIV-POCT tested HIV-negative.

In Zambia, the picture was different. Of the 120 participants with discrepant results, 29 terminated participation at a subsequent PC visit (moved out, not found or refused further participation). Due to delays in laboratory results and receipt of source data from remote sites, the follow-up results of a further 38 participants could not be included. Of the remaining 53 participants followed up, 7 participants





**Figure 2b. Flow chart of follow up of participants with discrepant HIV results Zambia.**

declined further testing, leaving 46 of whom 38 initially appeared to have false negative HIV-POCT results (HIV-POCT-negative but GS-positive), 7 false positive results (HIV-POCT-positive but GS-negative) and 1 an inconclusive HIV-POCT result (discordant results between the two rapid tests used as the HIV-POCT algorithm, GS-positive). Of the 38 individuals with false negative results, 5 (13%) were already known to be HIV-positive and taking ART. The majority, 21 (55%), had repeat HIV-POCT results consistent with the original negative HIV-POCT, demonstrating some inherent differences between the laboratory and HIV-POCT and some possible laboratory errors. For the remaining 12 (32%), repeat HIV-POCT confirmed the positive laboratory result. For five out of seven apparent false positives, the repeat HIV-POCT was negative, the other two participants were confirmed to be HIV-positive, one participant confirmed that they were on ART and for the other repeat HIV-POCT and laboratory testing confirmed a positive result. Finally, the participant with an inconclusive HIV-POCT stated they were on ART at the follow-up visit.

## Discussion

Expanding high-quality community-based HIV-POCT is critical if high burden communities are to achieve the UNAIDS 90-90-90 targets. The HPTN 071 (PopART) study offered a unique opportunity to assess the performance of HIV-POCT conducted in the homes of over 17,000 participants in urban and peri-urban high HIV-burden communities in Zambia and

SA. Through comparison of results from field (household) HIV-POCT testing with laboratory-based testing on venous blood samples, we noted that despite careful and repeated user training and assessment and monitoring of cold chain storage of HIV-POCT kits, the sensitivity of field HIV-POCT is less than that reported for laboratory-based HIV testing [16].

The situation in the SA sites demonstrated a “perfect storm” of poor choice of HIV-POCT algorithms, inadequate QA and user error. It is impossible to identify which contributed most to the poor performance. The requirement for staff re-training to accommodate frequent changes in the type of HIV-POCT kits procured by SADOH is likely to have contributed to user error in this setting. Change in HIV-POCT kits to consistent use of a well-established algorithm in combination with strengthened training, supervision and quality management all played a part in improving the performance.

One critical stage in the performance of HIV-POCT is sample collection. This involves the use of different manufacturer-provided sample collection tools some of which are challenging for non-laboratory staff to use, for example, the capillary tube device. Additionally, some manufacturers offer complete kits but also sell the components individually which may result in HIV-POCT being conducted without the correct sample collection device. Panel proficiency testing does not test this step and whilst the use of dried samples, as is currently recommended by WHO for QA, allows for easier shipment of QA materials, it requires different skills in rehydration



and testing which do not reflect the real-life situation [7]. In the proficiency panel testing for this study with over 700 nurses and lay counsellors, the pass rate was consistently high (>95%), but user errors were detected when we implemented our increased supervision and use of a checklist (Appendix) which ensures that testers are assessed for proficiency in all stages of testing, including sample collection as well as counselling.

IQC of test kits after exposure to out-of-range temperatures in both countries did not reveal any functional abnormalities, suggesting that in this study, this factor did not contribute to the observed poor test kit performance. The number of test kits tested during internal QA was very large necessitating large quantities of positive and negative controls to be produced at a significant cost.

The laboratory GS used in this study included combined antigen–antibody 4th generation tests and viral load testing and so 3rd generation HIV-POCT will never be able to perform as well. However, it is unlikely that even with the anticipated differences in sensitivity between HIV-POCT 3rd generation antibody testing and laboratory testing, failure to identify acute infection was the primary driver of decreased sensitivity. Accounting for missed acute infections, which can be assumed to account for only a small proportion of the observed false negative HIV-POCT results, the performance of community-wide HIV-POCT was still not ideal. Laboratory testing, which was conducted during this study, is extremely labour-intensive and time-consuming and so it is not being recommended as an alternative to HIV-POCT. There is, however, a need to balance the widespread scale-up of HTS with quality of the results. Our results from the re-visits to participants with discrepant results in Zambia also show that laboratory testing may also have errors, possibly due to sample mislabelling.

The finding of increased false negative results in those individuals taking ART warrants further investigation. There is a paucity of evidence for decreased sensitivity of POCT in HIV-positive clients who are taking ART in the adult population; however, there is emerging evidence of this in children and adolescents [18,19]. HIV-POCT was not intended for use among individuals on ART, and this was an unexpected scenario in our study. In a “real-world” setting, this is a potentially important finding which requires further research and emphasizes the importance of appropriate messaging when offering community-based HIV testing, particularly with reference to limitation of HIV-POCT for individuals on ART. Further investigation of the association between ART exposure and false negative results and the possible immunological mechanisms underpinning this effect are outside the scope of this paper but should be a priority.

Few studies have been conducted comparing HIV-POCT using finger stick whole blood in field conditions with a laboratory GS. Specificity in data from the current study was high; we found very low levels of false positive rapid test results, in contrast to some studies [20]. Published data on sensitivity of HIV rapid tests in the field vary. One study from SA nested within the *Good Start Trial* showed sensitivity of 98% when comparing HIV-POCT tests with

laboratory-based HIV tests [10], whereas another South African study measured accuracy of HIV-POCT testing in a clinic setting and found high rates of false negative HIV tests (sensitivity 69%, 95% CI: 41–89%) which was improved by introduction of a different testing algorithm and QA measures [13]. The authors concluded that user error was the most significant contributor to inaccuracy.

Throughout the study period, the same HIV-POCT kits and QA/QC procedures were used for the CHiPs intervention as in the PC research cohort. Whilst parallel laboratory testing was not undertaken for the community members tested by CHiPs, we assume that similar challenges of HIV-POCT sensitivity are likely to have occurred in that context. Thus, it was critical to communicate the observed poor HIV-POCT performance to the community. Throughout the conduct of the HPTN 071 (PopART) study, the study team reported the findings of HIV-POCT performance to in-country ethics committees, study communities and international advisory boards, the study sponsor and Department of Health partners. In partnership with all stakeholders, community messaging was developed and delivered. This messaging focused on encouragement of repeat HIV testing for all at-risk individuals to avoid missed HIV diagnoses and consequently compromising individual health as well as risk of onward transmission and included reference to the fact that HIV rapid tests, like other diagnostic tests, are not 100% accurate.

### Strengths and limitations

This study was conducted in the real-world setting using HIV-POCT as used in national algorithms and nationally approved QA procedures. The study setting offered a unique opportunity to compare HIV-POCT results to laboratory-based 4th generation testing completed in parallel on the same individuals. The study does, however, have limitations. It is difficult to attribute improvements in HIV-POCT sensitivity to specific factors, as multiple components of QA intervention were implemented concurrently with changes in test kits in SA. However, this is exactly how these changes would be implemented by national health systems. In the data shown here, the testing was conducted by nurses and we have assumed that similar results were seen in the HIV-POCT being done by lay counsellors at the same time using the same test algorithms and QA systems.

### Conclusions

In conclusion, this is one of the first reports of wide-scale delivery of HIV-POCT in high-burden real-world settings compared to a laboratory GS. In this study, we demonstrate that detection of HIV infection can be improved significantly with enhanced user training, implementation of frequent and vigilant QA and QC monitoring and consistent use of an approved HIV-POCT algorithm. HIV RNA testing is more sensitive for detecting HIV infection than 4th generation assays but may not be feasible or affordable in some settings.

In order to reach our goals of universal knowledge of HIV status using large-scale non-facility-based HIV testing programmes, appropriate QA procedures must be carefully established and users must be adequately trained and



supervised in conducting all testing procedures. Programmes should also pay specific attention to advances in HIV-POCT technology and new evidence evaluating HIV-POCT in field settings, ensuring that they are using the best option for their setting.

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#### Competing interests

No authors declare a conflict of interests.

#### Authors' contribution

PB, HA SF, RH, NB, DD, WES and EPW conceptualized the manuscript. MS, CP, KS, BK, NM, AJ, AB, AY and DD worked closely to develop the data set. All authors contributed towards development of the manuscript and reviewed drafts. All the authors have read and approved the final version.

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## Chapter 4: Attrition when providing antiretroviral treatment at CD4 counts >500 cells/ $\mu$ L at three government clinics included in the HPTN 071 (PopART) trial in South Africa

Unpublished: Under review with Plos One.

### Study design overview

For this study, a cohort study design was used to evaluate the impact of baseline CD4 count >500 cells/ $\mu$ L on attrition from ART care during early ART amongst adults ( $\geq 18$  years) starting ART at the three PopART Arm A clinics in South Africa. A detailed description of relevant clinic activities was provided in chapter 2. All adults starting ART at the three study clinics between January 2014 and End November 2015 were screened for inclusion in the study sample (Table 3). Having a reported baseline CD4 count was an inclusion criterion for the study. A total of 2423 adults, with a reported baseline CD4 count, were included in the study sample. Attrition included individuals no longer retained in ART care due to loss to follow-up or death. Individuals were defined as experiencing attrition if they were more than three months late for a pharmacy pick-up appointment. All individuals were followed up until the date of attrition, elective transfer to another facility (TFO) or end May 2016; whichever occurred first. Data were extracted from the following sources; i) the routine HIV monitoring system (Tier.net) ii) the electronic TB register (ETR.net) and iii) from NHLS routine reports. This study addressed the following PhD objective:

To evaluate the impact of routine initiation of ART at baseline CD4 counts >500 cells/ $\mu$ L at DOH clinics on attrition during early ART

**Table 3: Attrition study outline**

Primary outcome	Study site	Recruitment period	Exclusion criteria	Follow-up	Data sources
Attrition	Three SA PopART Arm A clinics	1 January 2014 to end November 2015	Missing baseline CD4 count	Until attrition TFO or end May 2016	Tier.net, ETR.net and NHLS reports

**Author contribution:** I was responsible for setting up this study cohort in partnership with DOH and PEPFAR implementing partners. Along with co-authors (GF, NF, SF and NB), I

conceptualised this study and completed the statistical analysis with support from SF and GF. All authors contributed toward development of the manuscript and reviewed drafts including the version included in this dissertation. I was the corresponding author in submission of the study to the journal.

**Attrition when providing antiretroviral treatment at CD4 counts >500cells/ $\mu$ L at three government clinics included in the HPTN 071 (PopART) trial in South Africa.**

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## **Abstract**

### **Introduction**

WHO recommends antiretroviral treatment (ART) for all HIV-positive individuals. This study evaluated the association between baseline CD4 count and attrition in a cohort of HIV positive adults initiating ART at three department of health (DOH) clinics routinely providing ART at baseline CD4 counts >500cells/ $\mu$ L for the HPTN 071 (PopART) trial.

### **Methods**

All clients attending the DOH clinics were managed according to standard care guidelines with the exception that those starting ART outside of pertinent local guidelines signed research informed consent. DOH data on all HIV-positive adult clients recorded as having initiated ART between January 2014 and November 2015 at the three study clinics was analysed. Attrition, included clients lost to follow up or died, and was defined as 'being three or more months late for an antiretroviral pharmacy pick-up appointment'. All clients were followed until attrition, transfer out or end May 2016.

### **Results**

A total of 2423 clients with a median baseline CD4 count of 328 cells/ $\mu$ L (IQR 195-468) were included of whom 631 (26.0%) experienced attrition and 140 (5.8%) were TFO. Attrition was highest during the first six months of ART (IR 38.3/100 PY; 95% CI 34.8-42.1). Higher attrition was found amongst those with baseline CD4 counts > 500 cells/ $\mu$ L compared to those with baseline CD4 counts of 0-500 cells/ $\mu$ L (aHR 1.26, 95%CI 1.05 to 1.52) This finding was confirmed on subset analyses when restricted to individuals non-pregnant at baseline and when restricted to individuals with follow up of > 12months.

### **Conclusions**

Attrition in this study was high, particularly during the first six months of treatment. Attrition was highest amongst clients starting ART at baseline CD4 counts > 500 cells/ $\mu$ L. Strategies to improve retention amongst ART clients, particularly those starting ART at baseline CD4 counts >500cells/ $\mu$ L, need strengthening. Improved monitoring of clients moving in and out of ART care and between clinics will assist in better understanding attrition and ART coverage in high burden countries.

### **Introduction**

There are 36.7 million HIV positive individuals and 19.5 million people on antiretroviral treatment (ART) worldwide (1). UNAIDS has set global HIV treatment targets of 90:90:90; 90% of HIV positive individuals knowing their HIV status, of which 90% are on ART, of which 90% are virally suppressed (2). To achieve the sustained viral suppression required to prevent progression to AIDS disease in HIV positive individuals and to limit onward viral transmission of HIV, high levels of retention in ART care and adherence to medication are required (3, 4).

Retention in ART programmes in high burden settings is extremely challenging. A recent systematic review, which included 1.5 million participants from African and Asian programmatic studies (75% from Africa), the majority of whom started ART at baseline CD4 counts  $< 200\text{cells}/\mu\text{L}$ , found 17% and 26% of individuals on ART lost to follow up or died (attrition) at 12 months and at 24 months respectively (5). The association between baseline CD4 count and attrition varies, with some programmatic studies having reported decreased (6) and some showing increased attrition at higher CD4 counts (7-9). The median baseline CD4 counts in these published studies, however, was low with a high proportion of individuals starting ART at CD4 counts  $< 200\text{cells}/\mu\text{L}$  and mortality may have contributed extensively to attrition amongst individuals with lower CD4 counts.

Following results of the START and TEMPRANO randomised control trials (RCTs) in 2015 (10, 11), WHO guidelines have recommended ART for all PLHIV regardless of CD4 count (12). There are, however, very limited published data evaluating the impact of routine provision of ART at CD4 counts  $> 500\text{cells}/\mu\text{L}$  on attrition from ART programmes in high burden settings. Concerns also remain that increased numbers of clients starting ART at baseline CD4 counts  $> 500\text{cell}/\mu\text{L}$ , when clinically well, may be associated with increased attrition (13). This study evaluated the association between baseline CD4 count  $> 500\text{cells}/\mu\text{L}$  and attrition in a cohort of adults initiating ART regardless at three department of health (DOH) clinics in the Western Cape Province, South Africa.

## **Methods**

### ***Study setting***

This study was conducted at three DOH primary health care (PHC) clinics included in the 'Population effect of antiretroviral therapy to reduce HIV incidence' HPTN 071 (PopART) trial

in the Western Cape (WC), South Africa. A full description of the HPTN 071 (PopART) trial design has been published (14). The communities surrounding the three study clinics received the full HPTN 071 (PopART) intervention which consisted of household delivery of an HIV combination prevention package, including HIV rapid testing in the house by community HIV care providers (CHiPs), referral to the clinics and active linkage to ART care. CHiPs routinely visited clients annually with more intensive follow up when clinically indicated e.g. after HIV diagnosis (14).

Two clinics were located in the metro district (Metro 1 and 2) and one in a rural district (Rural 1). These study clinics offered ART regardless of CD4 count for all HIV positive clients aged 18 or older. During the study period for standard care at other clinics DOH ART guidelines recommended ART initiation at baseline CD4 count  $\leq 350$  cells/ $\mu\text{L}$  until January 2015 and thereafter at baseline CD4 count  $\leq 500$  cells/ $\mu\text{L}$  (15). All clients attending the study clinics received standard care as per DOH ART guidelines with the exception that ART was provided to all HIV positive individuals and individuals starting ART outside of pertinent DOH guidelines signed informed consent.

A fixed-dose combination of tenofovir, emtricitabine and efavirenz (TEE) was used for first line treatment. Pharmacy pick up dates for collection of TEE were initially scheduled monthly, then every two to three months once clients were assessed as stable on ART by a clinician. CD4 count was routinely measured at four months and 12 months of ART and viral load at 4 months, 12 months and then annually (15). All routine laboratory services were provided by the National Health Laboratory Service (NHLS). All ART clients start ART were registered on the ART routine monitoring system, Tier.net (16). For sustainability, standard adherence and retention interventions provided by DOH facilities were continued throughout HPTN 071 (PopART), complimented by the work of the CHiPs teams. As per ART guidelines and HPTN 071 (PopART) standard operating procedures, all ART clients should have been supported by clinic-based adherence counsellors, community-based adherence workers (CCWs) and CHiPs teams. The work of the clinic adherence counsellors, CCWs and CHiPs was integrated through joint attendance of clinic operational meetings (14, 15). Stable ART clients were routinely referred to adherence clubs, either at the facility or in the community, according to DOH adherence club guidelines (17).

## **Cohort overview and definitions**

This study included data on all clients 18 years and older recorded in Tier.net as initiating ART at the three study clinics, between 1 January 2014 and 30 November 2015 (14, 16). Follow up continued until 30 May 2016 the time of administrative data censor. Clients with previous ART exposure but no longer on ART, restarting ART at the study clinics were eligible for inclusion in the study sample. Clients transferred into the study clinics from another ART clinic, already on ART, during this period were excluded from the study sample. Baseline CD4 was defined as the most recent CD4 count within the six months prior to starting ART. Baseline TB treatment was defined as having started TB treatment within the 6 months prior to starting ART. Clients were routinely dispensed between 1 and 3 months ART medication at their last recorded clinic visit. The date of their next scheduled visit was calculated based on the number of days medication dispensed. The primary outcome, attrition, was defined as 'being three months or more late for this calculated next scheduled visit. All clients were followed up for a minimum of six months. Death was not analysed separately due to significant under-recording in Tier.net. Clients electively transferred to another facility were, in line with Tier.net definitions, defined as transfer outs (TFOs).

## **Data management**

All data were initially extracted from Tier.net except the data on baseline TB treatment which were extracted from the electronic TB register (ETR.net). If the baseline CD4 count results were missing from Tier.net, these were extracted from the National Health Laboratory Services (NHLS) databases. Data from Tier.net were linked to ETR.net data through a matching algorithm utilising name, surname and date of birth in Microsoft SQL Server™. CD4 count data, extracted from the NHLS database, were linked to data in Tier.net using the WC DOH 'Clinicom number' as unique clinic identifier in Stata13™. Pharmacy pick up data recorded in Tier.net was used to calculate the date for next scheduled clinic appointment. Data cleaning and validation included cross-referencing data fields within Tier.net and across Tier.net, NHLS and ETR.net databases. Data elements in Tier.net that were adjudged to have with high rates of missing or incorrect data, e.g. baseline WHO stage and data on adherence club attendance were excluded from analysis.

## **Analysis**

Baseline characteristics were described for continuous and categorical variables and distribution across CD4 strata was assessed using Chi Squared tests and Kruskal-Wallis tests. Incidence rates were estimated and time-to-event analyses were conducted using Kaplan Meier survival and smoothed hazard estimates. Clients were censored on either the date of attrition, TFO, or on 30<sup>th</sup> May 2016 (end of the study); whichever was the earliest. Unadjusted and adjusted comparisons of the hazard of attrition at different baseline CD4 count strata were carried out using Cox regression. Potential confounding baseline characteristics for inclusion in the adjusted analysis were selected a priori based on clinical relevance; these included: age, sex, pregnancy status, TB treatment, clinic, previous ART exposure of more than 3 months and year of ART start. Baseline CD4 count strata were chosen to align with previous ART guideline cut offs. (18) Proportional hazards assumptions were checked with scaled Schoenfeld residuals. Likelihood ratio tests were used to estimate P values in regression models where categorical variables had more than two strata. For each variable included in the model, the category chosen as baseline for comparison (HR=1) was based on sample size and clinical significance. Multivariate logistic regression, including the same baseline characteristics, with the exception of baseline CD4 count was used to compare baseline characteristics of clients excluded from analysis due to missing baseline CD4 count and those included in the study sample. All analyses were performed using Stata version 13 (StataCorp LP, College Station, TX, USA).

## **Ethics statement**

The HPTN 071 (PopART) trial was approved by the Stellenbosch University Health Research Ethics Committee (SU HREC) (Ref. No. N12/11/074) and the London School of Hygiene and Tropical Medicine Research Ethics Committee (Reference number 6362). All clients initiating ART outside local DOH guidelines for HPTN 071 (PopART) gave written informed consent. Further permission for this study and the use of individual level data from the WC DOH sources (Tier.net, ETR.net and NHLS) with a waiver for informed consent has also been received from SU HREC (reference number N12/11/074A), the Western Cape Government (Reference no. WC\_2015RP51\_715) and City of Cape Town (Reference no. 10529).

## Results

A total of 2593 clients who started ART at the study clinics between 1 January 2014 and end November 2015 were screened for inclusion in the study, of whom 170 (6.6%) were excluded due to missing baseline CD4 counts. This left a sample of 2423 clients included in the analysis. The distribution of clients by baseline CD4 count strata was 631 (26.0%) at CD4 0-200 cells/ $\mu$ L, 708 (29.2%) at CD4 201-350 cells/ $\mu$ L, 582 (24.0%) at CD4 351-500 cells/ $\mu$ L and 502 (20.7%) at CD4 >500 cells/ $\mu$ L (Table 1). Median baseline CD4 count was 328 cells/ $\mu$ L (IQR 195-468 cells/ $\mu$ L). Most clients were women, 1643 (67.8%), and median age was 31 (IQR 26-38) years. One hundred and forty two (8.6% of women) clients were confirmed pregnant at ART initiation. A total of 285 (11.8%) clients were on TB treatment at baseline, this proportion ranged from 25.7% among those with CD4 counts  $\leq$ 200 cells/ $\mu$ L down to 5.2% among those with counts >500 cells/ $\mu$ L. More clients were treated at metro clinics; 1022 (42.2%) and 947 (39.1%) at Metro 1 and 2 respectively with 454 (18.7%) treated at the rural clinic. A small number of clients, 49 (2.0%) had previous ART exposure of more than three months. The majority of clients started ART in 2015; 1733 (71.5%) compared to 690 (28.5%) in 2014.

Overall, 631 (26.0%) clients experienced attrition during 2389 person years (PY) of follow up (Incidence Rate (IR): 26.4/100 PY) and 140 (5.8%) were TFO. Amongst individuals experiencing attrition, 11 (1.7%) were documented in Tier.net as having died. Median baseline CD4 count amongst those individuals who died was 34 cells/ $\mu$ L (IQR: 63-155). Median follow up time was 11.2 (IQR 7.2-16.1) months. Cumulative numbers of clients experiencing attrition was 418 (17.3%), 561 (23.2%), 613 (25.3%), 631 (26.0%) at 6, 12, 18 and 24 months on ART respectively). Kaplan Meier estimates showed higher attrition amongst clients with baseline CD4 counts > 500cells/ $\mu$ L compared to  $\leq$  500cells/ $\mu$ L ( $P < 0.02$ ) (Figure 1) Attrition peaked at three months across all CD4 count strata and was higher during the first 6 months of ART compared to longer treatment durations; IR: 38.6/100 PY (95% CI 35.1-42.4) from 0 to 6 months ART, 19.2/100 PY (95% CI 16.3-22.6) from 7 to 12 months ART, 14.3 /100 PY (95% CI 10.9-18.7) from 13 to 18 months ART and 11.8 /100 PY (95% CI 7.4-18.7) from 19 to 24 months ART (Table 2).

Adjusted Cox regression analysis using the full model showed higher attrition amongst clients with baseline CD4 counts > 500 cells/ $\mu$ L (aHR 1.26, 95%CI 1.05 to 1.52; ( $P = 0.014$ ))

compared to 0-500cells/ $\mu$ L (Table 3) There was higher attrition amongst clients aged 18-25 years when compared to those aged 26-35 years (aHR 1.30, 95% CI 1.07-1.58). The hazard of attrition was lower amongst clients starting ART in 2014 compared to 2015 (aHR 0.81, 95% CI 0.66--1.00; P=0.051). There were no significant differences in attrition between men and women or between study clinics in adjusted analysis.

Additional multivariate analysis that further stratified baseline CD4 count showed higher attrition in individuals with baseline CD4 >500cells/ $\mu$ L when compared to those with baseline CD4 counts 350-500 cells/ $\mu$ L (aHR 1.42, 95%CI 1.12-1.79) (Supplementary data file 1). There was no significant difference in attrition when comparing clients with baseline CD4 counts 350-500 cells/ $\mu$ L to those with baseline CD4 counts 201-350 cells/ $\mu$ L or 0-200 cells/ $\mu$ L. The higher attrition in individuals with baseline CD4 counts >500 cells/ $\mu$ L persisted in subset analyses restricted to 2281 individuals who were non-pregnant at the time of ART initiation (aHR 1.29, 95%CI 1.07-1.57) (Supplementary data file 2) and in subset analysis restricted to 1100 individuals with follow up of more than 12 months (aHR 1.29, 95%CI 1.07-1.57) (Supplementary data file 3).

Multivariate logistic regression of factors associated with missing baseline CD4 counts showed increased rates of missing baseline CD4 counts amongst clients who were pregnant at baseline (aOR 2.40, 95% CI 1.35-4.26) and amongst those starting ART in 2014 (aOR 20.2, 95% CI 8.83-46.54) compared to 2015. Being treated at Metro 2 (aOR 0.29, 95% CI 0.12-0.69) and the rural clinic (aOR 0.01, 95% CI 0.00-0.04) were associated with decreased rates of missing baseline CD4 counts.

## Discussion

In this study we found, in a cohort of clients receiving ART regardless of CD4 count at three DOH clinics, we found high rates of attrition, higher amongst clients who started ART with baseline CD4 counts > 500cells/ $\mu$ L compared to those with baseline CD4 count 0-500 cells/ $\mu$ L. This finding was confirmed in subset analyses restricted to individuals non-pregnant at baseline and when restricted to individuals with follow up time of > 12 months. When dividing baseline CD4 count to four strata, attrition was higher amongst clients with baseline CD4 counts > 500 cells/ $\mu$ L compared to those with baseline CD4 counts of 350-500 cells/ $\mu$ L.

The cumulative proportion of clients experiencing attrition in this paper was comparable to that reported by DOH for the corresponding health districts during the same time period (19); as well as with data from a large systematic review of programmatic data from Africa and Asia (26% at 24 months ART) (20).

This finding of higher attrition amongst individuals with higher baseline CD4 counts, who may be more likely to be clinically well when starting ART, supports findings from previous studies. (7-9). The underlying reasons for the higher attrition in this group in this study is not clear and may have been driven by psychosocial and health systems factors not measured in the study. The extent to which mortality contributed to attrition was not accurately documented in Tier.net. Although mortality as a cause of attrition is decreasing in Africa (21), it remains a significant contributor; particularly during the initial six months on ART (22, 23). Published studies, with lower median baseline CD4 counts, where clients experiencing attrition were actively followed up with extraction of data from additional sources such as death registries, showed that approximately 40% of clients documented as lost to follow up from ART programmes have in fact died (21). The START and Temprano RCTs showed significantly lower mortality amongst ART clients with baseline CD4 counts >500 cells/ $\mu$ L (10, 11), and it is therefore plausible that higher attrition amongst those with baseline CD4 counts > 500 cells/ $\mu$ L in this study was driven more by individual choice than by mortality.

The peak in attrition during the first six months on ART across all CD4 strata emphasises the need for additional retention strategies at clinics during early ART. The higher attrition amongst younger clients (18 to 25 years) is in keeping with previously published data and highlights the need to continue to strengthen interventions and support focused on this age group (24, 25). Attrition was also higher amongst clients starting ART in 2015 compared to 2014. This may be associated with overburdening of study clinic resources as a result of increased numbers of clients on ART over time (26, 27). The WC DOH has a well-established adherence club programme (17) and further development this model of care may be effective in decongesting clinics and improving outcomes (28, 29).

Despite a well-established ART service in the Western Cape since 2004 and provision of ART regardless of CD4 count for HPTN 071 (PopART) since January 2014 a high proportion of



clients (26.0%) in this study initiated ART at baseline CD4 counts < 200 cells/ $\mu$ L. This persistence of low baseline CD4, even in the context of ART regardless of CD4 count, is a serious concern. Interventions aimed at promoting earlier ART uptake should therefore continue to be a priority and further strengthened. A recent systematic review of community and clinic based interventions aimed at increasing uptake of ART in sub-Saharan Africa found home based HIV testing and improved efficiencies and structure at clinics to be effective in improving ART uptake (20). The evidence was, however, reported to be of low quality and the authors identified an urgent need for well-structured studies on the topic. The review also raised concerns about a lack of focus on retention on ART in the literature (20).

### **Strengths and weaknesses**

The study has a number of key strengths. Data used in the analysis was part of a high quality routine dataset, strengthened by prospective data quality improvement for HPTN 071 (PopART) and clients were provided ART regardless of CD4 count ahead of recent changes to WHO and local guidelines. There were high rates of completeness in key data fields with only a small proportion (6.6%) of eligible clients excluded from the analysis due to missing baseline CD4 count results. There was also high similarity in baseline characteristics associated with attrition between clients excluded due to missing baseline CD4 counts and those included in the study. The three study clinics were typical of metro and rural clinics in the Western Cape and clinic activities were closely aligned to standard care during the study period, supporting generalisability of study findings. Another major strength was the use of an objective measure for determination of attrition (pharmacy pick up date).

There are, however, a number of limitations to consider. Factors not measured by the available data set including psychosocial and health systems factors may have confounded the association between baseline CD4 count and attrition. In this regard; although activities at clinics included in this study were closely aligned for PopART and choice of clinic was not associated with attrition on multivariate analysis it is possible that clinic-related factors not measured in this paper may have confounded the primary analysis. Data and resources required for active follow up of individuals experiencing attrition to determine whether they had died or transferred to another facility without informing their current facility (silent transfers) were not available for this study. Published data show high rates of silent transfer

to other ART clinics amongst individuals documented lost to follow up at PHC clinics in the Western Cape. (30) The extent to which silent transfers, contributed to attrition in this study, as in many studies in high burden regions, is unknown. These silent transfers are likely to have led to overestimation of attrition. Silent transfer may also have been higher amongst clients starting ART at baseline CD4 counts  $> 500\text{cells}/\mu\text{L}$ , as ART regardless of CD4 counts was not available at neighboring clinics during the study period and clients may have come to the study clinic to initiate treatment and then returned to their 'usual' clinic.

Throughout HPTN 071 (PopART) additional support was provided through staff and health systems support at clinics and in the community by CHiPs workers. This support was likely to have reduced overall attrition. Although all ART clients were meant to have received community-based support from both DOH CCWs and/or CHiPs teams, it was not known what proportion of clients received community-based support or whether the community based support differentially impacted clients with baseline CD4 counts  $> 500\text{cells}/\mu\text{L}$ .

There are further limitations affecting the generalisability of these results. Clients starting ART outside of pertinent DOH guidelines received additional counselling during the signing of research informed consent and which may have in turn reduced their risk of attrition amongst individuals with baseline CD4  $>500\text{cells}/\mu\text{L}$ . In addition, CD4 count is often used in community narratives around ART and it is likely that community perception of the benefits of starting ART at baseline CD4 counts  $> 500\text{ cells}/\mu\text{L}$  will further develop over time as ART regardless CD4 count becomes standard care. This change in community perception may in turn be associated with decreased attrition amongst clients initiating ART at higher CD4 counts (31).

## **Conclusions**

We documented higher attrition amongst clients initiating ART at baseline CD4 counts  $> 500\text{cells}/\mu\text{L}$ , highlighting an urgent need for retention with a focus on clients initiating ART at higher baseline CD4 counts. At the same time, strategies to improve earlier uptake of ART before their CD4 counts fall below  $200\text{cell}/\mu\text{L}$  need to be strengthened. Monitoring systems that more accurately measure the contribution of death and silent transfers to attrition from ART programmes will assist in a better understanding of retention in ART programmes and ART coverage in high burden areas.

**Conflict of interest:** No authors declare a conflict of interest.

**Author contribution:** PB, GF, NF, S Floyd, S Fidler and NB conceptualised the manuscript. PB, GF, NB and S Floyd developed the data and completed the analysis. All authors contributed toward development of the manuscript and reviewed drafts including the final draft in this submission.

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## Tables

Table 1: Baseline characteristics

Baseline factor		Units	0 - 200 cells/ $\mu$ l*	201-350 cells/ $\mu$ l	351-500 cells/ $\mu$ l	>500 cells/ $\mu$ l	Total	P value**
All		N (%)	631 (26.0)	708 (29.2)	582 (24.0)	502 (20.7)	2423	
Gender	Female	N (%)	355 (56.3)	463(65.4)	421 (72.3)	404 (80.5)	1643 (67.8)	P<0.0001
	Male	N (%)	276 (43.7)	245 (34.6)	161 (27.7)	98 (19.5)	780 (32.1)	
Age		Median (IQR)	33(29.0-40.0)	31(25.0-37.0)	31(26.0-37.0)	30(25.0-37.0)	31(26.0-38.0)	P=0.0001
	18-25 years	N%	79 (12.5)	179 (25.3)	142 (24.4)	134 (26.7)	534 (22.0)	P<0.0001
	26-35 years	N	312 (49.6)	311 (43.9)	272 (46.7)	227 (45.2)	1122 (46.3)	
	36-45 years	N	167 (26.5)	138 (19.5)	109 (18.7)	87 (17.3)	501 (20.7)	
	46-55 years	N	57 (9.0)	63(8.9)	46(7.9)	44(8.8)	210(8.7)	
	>55 years	N	17 (2.7)	17(2.4)	13(2.2)	10(2.0)	57(2.3)	
Pregnant at ART start	Yes	N	14 (3.9)	39(8.4)	41 (9.7)	48 (11.9)	142 (8.6%)	P<0.0001
Baseline TB treatment	Yes	N	162 (25.7)	56 (7.9)	41 (6.7)	26 (5.2)	285 (11.8)	P<0.0001
Clinic	Rural 1	N	88 (13.9)	113(15.9)	126(21.7)	127(25.3)	454 (18.7)	P<0.0001
	Metro 1	N	299 (47.4)	301 (42.5)	231 (39.7)	191 (38.1)	1022 (42.2)	
	Metro 2	N	244 (38.7)	294 (41.5)	225 (38.7)	184 (36.7)	947 (39.1)	
Previous ART of > 3mths	Yes	N	27 (4.3)	10 (1.4)	7 (1.2)	5 (1.0)	49 (2.0)	P<0.0001
ART start year	2014	N	161 (25.5)	208 (29.4)	160 (27.5)	161 (32.1)	690 (28.5)	P=0.091
	2015	N	470 (74.2)	500 (70.6)	422 (72.5)	341 (67.9)	1733 (71.5)	

Baseline CD4 count categories were chosen to align with ART previous ART guideline cut-offs. \*\*The denominator for all %'s is the total sample for that CD4 count category with the exception of pregnancy where the denominator is limited to females in that CD4 count category. \*\*Chi squared tests were used to evaluate differences across baseline CD4 strata for all categorical variables and the *Kruskal-Wallis test* for numerical variables (age).

**Table 2: Summary of incidence rates of attrition by baseline CD4 count strata and time on ART**

Time on ART	0 to 6 months			7 to 12 months			13 to 18 months			19 to 24 months		
Baseline CD4 strata	PY*	No. LTF U	LTFU/100 PY*	PY	No. LTF U	LTFU/100 PY*	PY	No. LTF U	LTFU/100 PY*	PY	No. LTF U	LTFU/100 PY*
0 - 200 cells/ $\mu$ l	283	108	38,2 (95%CI:31.1-46.1)	194	33	17,1 (95%CI:12.1-23.9)	86	13	15,1 (95%CI:8.8-26.0)	36	5	13,8 (95%CI:5.7-33.1)
201 - 350 cells/ $\mu$ l	323	119	36,9 (95%CI:30.1-44.0)	223	52	23,3 (95%CI:17.8-30.6)	109	11	10,1 (95%CI:5.6-18.3)	50	8	16,0 (95%CI:8.0-32.2)
351 - 500 cells/ $\mu$ l	263	96	36,50 (95%CI: 29.9-44.6)	184	22	11,9 (95%CI:7.9-18.2)	87	9	10,3 (95%CI:5.4-19.8)	38	2	5,30 (95%CI:1.3-21.0)
>500 cells/ $\mu$ l	223	95	42,7 (95%CI:34.9-52.2)	156	36	23,1 (95%CI:16.7-32.0)	80	19	23,8 (95%CI:15.2-37.3)	28	3	10,6 (95%CI:3.4-33.0)
<b>Total</b>	1092	418	38,30 (95%CI:34.8-42.1)	756	143	18,9 (95%CI:16.1-22.3)	362	52	14,4 (95%CI:10.9-18.9)	152	18	11,8 (95%CI:7.5-18.8)

\*PY: Person Years \*\*Incidence rates were calculated using the stptime command in Stata 13™

**Table 3: Cox regression modelling of baseline characteristics and attrition comparing baseline CD4 categories > 500 cells/ $\mu$ L and 0-500 cells/ $\mu$ L.**

		Crude hazard ratio (95% CI)	P	Adjusted hazard ratio (95% CI)	P
<b>Baseline CD4 (cells/<math>\mu</math>L)</b>	<b>&gt; 500</b>	1,24(1,03-1,48)	0,022	1,26(1,05-1,52)	0,014
	<b>0-500</b>	1		1	
<b>Gender</b>	<b>Male</b>	1,06(0,9-1,25)	0,483	1,23(1,03-1,47)	0,025
	<b>Female</b>	1		1	
<b>Age category</b>	<b>18-25</b>	1,29(1,07-1,56)	<0.001	1,3(1,07-1,58)	0,002
	<b>26-35</b>	1		1	
	<b>36-45</b>	0,91(0,73-1,12)		0,9(0,72-1,11)	
	<b>46-55</b>	0,7(0,5-0,97)		0,69(0,49-0,96)	
	<b>&gt;55</b>	0,82(0,46-1,46)		0,8(0,45-1,44)	
<b>Pregnant at baseline</b>	<b>Yes</b>	1,36(1,01-1,82)	0,045	1,27(0,93-1,72)	0,134
<b>Clinic</b>	<b>Metro 1</b>	1	0,279	1	0,137
	<b>Metro 2</b>	1,05(0,88-1,26)		1,16(0,95-1,43)	
	<b>Rural 1</b>	0,89(0,71-1,11)		0,96(0,75-1,23)	
<b>Baseline TB</b>	<b>Yes</b>	0,91(0,51-1,61)	0,744	0,94(0,53-1,68)	0,841
<b>Previous ART of &gt; 3 months</b>	<b>Yes</b>	0,88(0,5-1,56)	0,667	0,91(0,51-1,61)	0,739
<b>Year ART start</b>	<b>2014</b>	0,86(0,72-1,02)	0,088	0,81(0,66-1)	0,051
	<b>2015</b>	1		1	

Proportional hazards assumptions were checked with scaled Schoenfeld residuals. Likelihood ratios were used to estimate P values in regression models where categorical variables had more than two strata. Model fits were assessed as good based on the likelihood ratio test statistic. Selection of baseline variable category for comparison (HR=1) was based on sample size and clinical significance.



## Supplementary data

## Supplementary data file 1: Cox regression modelling of baseline characteristics and attrition comparing all baseline CD4 categories.

		Crude hazard ratio (95% CI)	P	Adjusted hazard ratio (95% CI)	P
<b>Baseline CD4 (cells/<math>\mu</math>L)</b>	<b>&gt; 500</b>	1.39(1.1-1.76)	0.049	1.42(1.13-1.8)	0.033
	<b>351-500</b>	1		1	
	<b>201-350</b>	1.2(0.96-1.5)		1.19(0.95-1.48)	
	<b>0-200</b>	1.16(0.92-1.47)		1.2(0.94-1.52)	
<b>Gender</b>	<b>Male</b>	1.06(0.9-1.25)	0.483	1.22(1.02-1.45)	0.031
	<b>Female</b>	1		1	
<b>Age category</b>	<b>18-25</b>	1.29(1.07-1.56)	<0.001	1.31(1.08-1.59)	<0.001
	<b>26-35</b>	1		1	
	<b>36-45</b>	0.91(0.73-1.12)		0.89(0.72-1.11)	
	<b>46-55</b>	0.7(0.5-0.97)		0.69(0.49-0.96)	
	<b>&gt;55</b>	0.82(0.46-1.46)		0.81(0.45-1.44)	
<b>Pregnant at baseline</b>	<b>Yes</b>	1.36(1.01-1.82)	0.045	1.27(0.93-1.73)	0.125
<b>Clinic</b>	<b>Metro 1</b>	1		1	0.149
	<b>Metro 2</b>	1.05(0.88-1.26)		1.17(0.95-1.43)	
	<b>Rural 1</b>	0.89(0.71-1.11)		0.97(0.76-1.25)	
<b>Baseline TB</b>	<b>Yes</b>	0.91(0.51-1.61)	0.744	0.92(0.51-1.64)	0.77
<b>Previous ART of &gt; 3 months</b>	<b>Yes</b>	0.88(0.5-1.56)	0.667	0.89(0.5-1.58)	0.687
<b>Year ART start</b>	<b>2014</b>	0.86(0.72-1.02)	0.088	0.81(0.66-1)	0.046
	<b>2015</b>	1		1	

Likelihood ratios were used to estimate P values in regression models where categorical variables had more than two strata. Model fits were assessed as good based on the likelihood ratio test statistic. Selection of baseline variable category for comparison (HR=1) was based on sample size and clinical significance.

**Supplementary data file 2: Cox regression modelling of baseline characteristics and attrition comparing baseline CD4 categories > 500 cells/ $\mu$ L and 0-500 cells/ $\mu$ L restricted to individuals non-pregnant at baseline.**

		Crude hazard ratio (95% CI)	P	Adjusted hazard ratio (95% CI)	P
Baseline CD4 (cells/ $\mu$ L)	> 500	1.24(1.02-1.5)	0.029	1.29(1.07-1.57)	0.009
	0-500	1		1	
Gender	Male	1.1(0.93-1.3)	0.287	1.24(1.04-1.48)	0.017
	Female	1		1	
Age category	18-25	1.3(1.06-1.59)	0.003	1.33(1.09-1.64)	0.001
	26-35	1		1	
	36-45	0.92(0.74-1.15)		0.91(0.73-1.13)	
	46-55	0.69(0.5-0.97)		0.68(0.49-0.95)	
	>55	0.83(0.47-1.49)		0.81(0.45-1.44)	
Clinic	Metro 1	1	0.225	1	0.076
	Metro 2	1.05(0.88-1.26)		1.23(0.98-1.55)	
	Rural 1	0.86(0.68-1.1)		1.01(0.77-1.31)	
Baseline TB	Yes	0.95(0.54-1.68)	0.86	0.97(0.54-1.72)	0.913
Previous ART of > 3 months	Yes	0.97(0.55-1.72)	0.921	1(0.56-1.77)	0.997
Year ART start	2014	0.81(0.67-0.97)	0.024	0.75(0.6-0.94)	0.011
	2015	1		1	

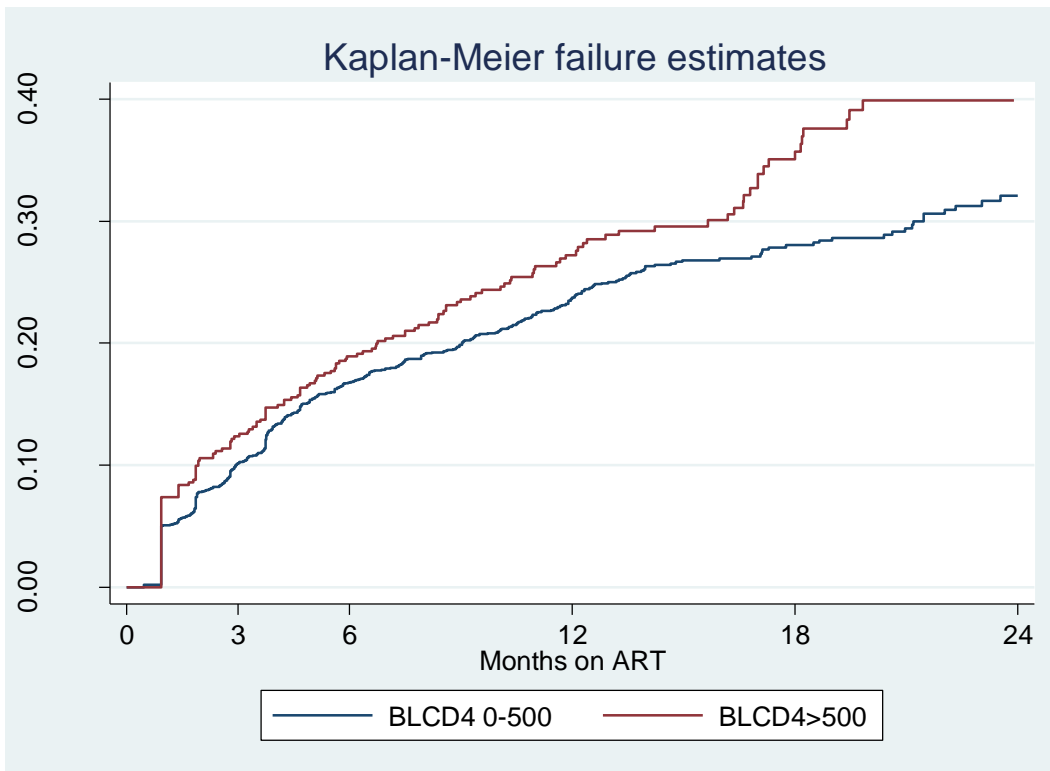
Analysis restricted to 2281 individuals non-pregnant at baseline. Likelihood ratios were used to estimate P values in regression models where categorical variables had more than two strata. Model fits were assessed as good based on the likelihood ratio test statistic. Selection of baseline variable category for comparison (HR=1) was based on sample size and clinical significance.

**Supplementary data file 3: Cox regression modelling of baseline characteristics and attrition comparing baseline CD4 categories > 500 cells/ $\mu$ L and 0-500 cells/ $\mu$ L restricted to individuals with follow up of >12months.**

		Crude hazard ratio (95% CI)	P	Adjusted hazard ratio (95% CI)	P
Baseline CD4 (cells/ $\mu$ L)	> 500	1.24(1.02-1.5)	0.029	1.29(1.07-1.57)	0.009
	0-500	1		1	
Gender	Male	1.1(0.93-1.3)	0.287	1.24(1.04-1.48)	0.017
	Female	1		1	
Age category	18-25	1.3(1.06-1.59)	0.003	1.33(1.09-1.64)	0.001
	26-35	1		1	
	36-45	0.92(0.74-1.15)		0.91(0.73-1.13)	
	46-55	0.69(0.5-0.97)		0.68(0.49-0.95)	
	>55	0.83(0.47-1.49)		0.81(0.45-1.44)	
Clinic	Metro 1	1	0.225	1	0.076
	Metro 2	1.05(0.88-1.26)		1.23(0.98-1.55)	
	Rural 1	0.86(0.68-1.1)		1.01(0.77-1.31)	
Baseline TB	Yes	0.95(0.54-1.68)	0.860	0.97(0.54-1.72)	0.913
Previous ART of > 3 months	Yes	0.97(0.55-1.72)	0.921	1(0.56-1.77)	0.997
Year ART start	2014	0.81(0.67-0.97)	0.024	0.75(0.6-0.94)	0.011
	2015	1		1	

Analysis restricted to 1100 individuals with follow up >12months. Likelihood ratios were used to estimate P values in regression models where categorical variables had more than two strata. Model fits were assessed as good based on the likelihood ratio test statistic. Selection of baseline variable category for comparison (HR=1) was based on sample size and clinical significance.

Figure1: Kaplan Meir failure estimates for attrition stratified by baseline CD4 cell count.



BLCD4: Baseline CD4 cell count in cells/ $\mu$ L. Log-rank test for equality of survivor functions:  $P=0.02$

## Chapter 5: Incidence of Tuberculosis amongst HIV-positive individuals initiating antiretroviral treatment at higher CD4 counts in the HPTN 071 (PopART) trial in South Africa

**Citation:** Bock P, Jennings K, Vermaak R, Cox H, Meintjes G, Fatti G, et al. Incidence of Tuberculosis Among HIV-Positive Individuals Initiating Antiretroviral Treatment at Higher CD4 Counts in the HPTN 071 (PopART) Trial in South Africa. *J Acquir Immune Defic Syndr.* 2018 Jan 1;77(1):93-101.

### Study design overview

This study used the same cohort of 2423 individuals used in chapter 4 to evaluate the impact of HIV-positive individuals initiating ART a baseline CD4 count >500 cells/ $\mu$ L on TB incidence during early ART (Table 4). TB incidence, the primary endpoint, was defined as having been recorded as starting TB treatment after ART initiation in ETR.net. All individuals were followed up until the date of attrition, elective transfer to another facility (TFO), incident TB or end May 2016, whichever occurred first. Data was from the same sources as the study evaluating attrition presented in chapter 4 was used. This study addressed the following PhD objective:

To evaluate the impact of routine initiation of ART at baseline CD4 counts >500 cells/ $\mu$ L at DOH ART clinics on TB incidence during early ART.

**Table 4: TB study outline**

Primary outcome	Study site	Recruitment period	Exclusion criteria	Follow-up	Data sources
Incident TB	Three SA PopART Arm A clinics	1 Jan 2014 to end Nov 2015	Missing baseline CD4 count	Until attrition, TFO, Incident TB or end May 2016	Tier.net, ETR.net and NHLS reports

**Author contribution:** I was responsible for setting up the study cohort used for this study in partnership with DOH and PEPFAR implementing partners. I conceptualised this study with the senior authors (PB, GF, HC, NB) and completed the statistical analysis with support from SF and GF. All authors contributed toward development of the manuscript and reviewed

drafts, including the final version accepted by the journal. I was the corresponding author in submission and publication of the study.

# Incidence of Tuberculosis Among HIV-Positive Individuals Initiating Antiretroviral Treatment at Higher CD4 Counts in the HPTN 071 (PopART) Trial in South Africa

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**Introduction:** Antiretroviral treatment (ART) guidelines recommend life-long ART for all HIV-positive individuals. This study evaluated tuberculosis (TB) incidence on ART in a cohort of HIV-positive individuals starting ART regardless of CD4 count in a programmatic setting at 3 clinics included in the HPTN 071 (PopART) trial in South Africa.

**Methods:** A retrospective cohort analysis of HIV-positive individuals aged  $\geq 18$  years starting ART, between January 2014 and November 2015, was conducted. Follow-up was continued until 30 May 2016 or censored on the date of (1) incident TB, (2) loss to follow-up from HIV care or death, or (3) elective transfer out; whichever occurred first.

**Results:** The study included 2423 individuals. Median baseline CD4 count was 328 cells/ $\mu\text{L}$  (interquartile range 195–468); TB

incidence rate was 4.41/100 person-years (95% confidence interval [CI]: 3.62 to 5.39). The adjusted hazard ratio of incident TB was 0.27 (95% CI: 0.12 to 0.62) when comparing individuals with baseline CD4  $>500$  and  $\leq 500$  cells/ $\mu\text{L}$ . Among individuals with baseline CD4 count  $>500$  cells/ $\mu\text{L}$ , there were no incident TB cases in the first 3 months of follow-up. Adjusted hazard of incident TB was also higher among men (adjusted hazard ratio 2.16; 95% CI: 1.41 to 3.30).

**Conclusions:** TB incidence after ART initiation was significantly lower among individuals starting ART at CD4 counts above 500 cells/ $\mu\text{L}$ . Scale-up of ART, regardless of CD4 count, has the potential to significantly reduce TB incidence among HIV-positive individuals. However, this needs to be combined with strengthening of other TB prevention strategies that target both HIV-positive and HIV-negative individuals.

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**Key Words:** HIV, antiretroviral treatment, CD4 count, TB

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## INTRODUCTION

Tuberculosis (TB) remains the leading cause of morbidity and mortality among HIV-positive individuals.<sup>1</sup> Recent antiretroviral treatment (ART) World Health Organization (WHO) guidelines recommend life-long ART for all HIV-positive individuals regardless of CD4 count.<sup>2</sup> This expanded ART access should lead to a reduction of TB and other WHO-defining illnesses and mortality among HIV-positive individuals initiating ART.<sup>3–6</sup>

TB at the time of ART initiation (baseline TB) is significantly higher at lower baseline CD4 counts among HIV-positive individuals.<sup>4</sup> Two South African programmatic studies completed between 2002 and 2008, in patients with low median baseline CD4 counts, reported high baseline TB prevalence, between 20% and 30%,<sup>7,8</sup> and baseline TB prevalence continues to be underestimated because of the difficulties in diagnosing among individuals starting ART in routine settings.<sup>9</sup>

Published TB incidence rates (IRs) in the first 12 months on ART range from 7.3/100 person-years (PY) to 10.9/100PY and are particularly high when pre-ART (baseline) CD4 counts are below 100 cells/ $\mu$ L.<sup>8,10</sup> TB IRs have been reported to be highest during the first 4 months on ART and approximately double in the first year of ART compared with subsequent years.<sup>9</sup> When measuring the association between CD4 count measured after a period of immune reconstitution on ART (“on ART” CD4 counts) and TB incidence, TB incidence is significantly lower among individuals with higher “on ART” CD4 counts.<sup>7,10</sup>

Although randomized controlled trials have shown lower TB incidence among HIV-positive individuals initiating ART at baseline CD4 counts  $>500$  cells/ $\mu$ L compared with CD4  $\leq 500$  cells/ $\mu$ L and CD4 351 to 500 cells/ $\mu$ L,<sup>11,12</sup> there are very few published studies from programmatic settings on the impact of routine ART initiation at CD4 counts  $>500$  cells/ $\mu$ L on TB incidence. This study, embedded in the HPTN 071 (PopART) trial, assessed the association between baseline CD4 count and TB incidence after ART initiation in a cohort of HIV-positive individuals starting ART regardless of CD4 count under programmatic conditions in the Western Cape, South Africa.

## STUDY SETTING

The study was conducted at 3 primary health care (PHC) Department Of Health (DOH) clinics that offered ART regardless of CD4 count (arm A) for the “Population Effect of ART to Reduce HIV Incidence,” HPTN 071 (PopART) study. Study clinics were in 2 subdistricts in the Cape Metro district (metro 1 and metro 2 clinics) and in 1 subdistrict in the Cape Winelands district (Rural clinic). Antenatal HIV prevalence in the Cape Metro and Cape Winelands districts is 20.3% and 14.3%, respectively, and routine DOH data show that annual TB IRs are 596/100,000 and 880/100,000 population, respectively.<sup>13,14</sup>

A full description of the HPTN 071 (PopART) study design has been previously published.<sup>15</sup> Communities randomly allocated to arm A of the HPTN 071 (PopART) trial received, from January 1, 2014, a combination HIV prevention package including HIV education, HIV testing, screening for TB symptoms, and active linkage to care for individuals diagnosed with HIV, TB, and sexually transmitted infections. Clinics allocated to arm A of the HPTN 071 (PopART) trial provided ART regardless of CD4 count to all HIV-positive individuals aged  $\geq 18$  years. Clients initiating ART outside prevailing ART guidelines signed research informed consent before ART initiation. All HIV-positive individuals on ART were otherwise managed according to DOH ART guidelines. Routine assessment before ART initiation included TB symptom and pregnancy screening.<sup>16</sup>

HIV and TB services were integrated at all 3 study clinics. Isoniazid TB prophylaxis (IPT) was recommended for individuals with a positive tuberculin skin test (TST) at ART initiation, to be continued for 36 months. If TST was unavailable or negative, then a 12-month IPT was advised for individuals starting ART.<sup>16</sup> HIV-positive individuals with TB symptoms were investigated according to a standardized diagnostic algorithm that used GeneXpert MTB/RIF (Xpert) for first-line diagnostic investigation, followed by culture if Xpert was negative. HIV-positive individuals, diagnosed with TB at ART initiation and started on TB treatment, were recorded in the routine DOH electronic TB monitoring system (ETR.net) and stabilized on TB treatment for 2 to 8 weeks before ART initiation.<sup>17</sup> The same TB diagnostic algorithm was used for diagnosis of TB in individuals already initiated on ART.<sup>18</sup>

## COHORT OVERVIEW, DATA SOURCES, AND DEFINITIONS

A retrospective cohort study design was used. All data were obtained from routine DOH systems including the routine HIV monitoring system, Tier.net,<sup>19</sup> ETR.net, and routine laboratory reports from the National Health Laboratory Services. All HIV-positive individuals aged  $\geq 18$  years, recorded in Tier.net as having started ART at the 3 study clinics between January 1, 2014 and November 30, 2015 with a recorded baseline CD4 count, were included in the study sample. Individuals were followed up until May 30, 2016 or until the date of (1) incident TB, (2) loss to follow-up (LTFU) from HIV care or death, or (3) elective transfer out (TFO); whichever occurred first.

Data linkage between Tier.net and ETR.net was conducted using an automated linkage algorithm in Microsoft SQL Server previously validated in other studies, which used the first name, surname, and date of birth as individual identifiers, and linkages were validated manually. CD4 data missing from Tier.net were, where available, extracted directly from the National Health Laboratory Services database and linked to Tier.net data using the DOH unique identifier. Data cleaning and validation included manual checking of automated linkages and cross referencing data of key across data elements within Tier.net and within ETR.net.



The following standardized definitions were used; (1) baseline CD4 as the most recent CD4 count completed within 6 months before starting ART. Baseline CD4 categories were chosen to align with previous guideline ART criteria,<sup>20</sup> (2) baseline TB as recorded in ETR.net as having started on TB treatment in the 6 months before ART initiation, (3) bacteriologically confirmed TB as confirmed with TB on smear microscopy, Xpert, or culture on one of sputum, lymph node tissue, pleural effusion, or cerebrospinal fluid, (4) incident TB as recorded in ETR.net as starting TB treatment after ART initiation; this included individuals on TB treatment at baseline who, after stopping TB treatment while on ART, were subsequently recorded in ETR.net as restarting TB treatment for a new TB episode, (5) LTFU as 3 months late for an antiretroviral pharmacy pickup appointment. LTFU was reported in combination with death because of significant underreporting of death in Tier.net, (6) TFO as electively transferred to another health facility.

Baseline characteristics were described using standard descriptive statistics for continuous and categorical variables. Heterogeneity of baseline characteristics across baseline CD4 count categories was assessed using  $\chi^2$  and Kruskal–Wallis tests. Binomial confidence intervals (CIs) were generated for baseline TB prevalence by baseline CD4 count category. Person time was measured from ART initiation or from the estimated date of stopping baseline TB treatment. Recording of the outcome date of baseline TB episodes in ETR.net was of poor quality; therefore, the outcome date for baseline TB cases was assumed to be 6 months after the start of TB treatment in all cases. The date for incident TB was the date an individual started TB treatment recorded in ETR.net. Individuals were permanently censored at the first occurrence of either incident TB, LTFU, TFO, or May 30, 2016.

Time-to-event analyses were completed using Kaplan–Meier survival estimates. Cox regression was used for crude and adjusted modeling of the association of baseline characteristics with incident TB. Proportional hazard assumptions were tested using Schoenfeld residuals. Baseline variables for inclusion in regression analysis were selected a priori, based on clinical significance. Selection of the baseline variable category used for comparison (hazard ratio [HR] = 1) was based on sample size and clinical significance. All adjusted models included the following baseline characteristics unless otherwise stated: baseline CD4 count, age, sex, pregnancy status, baseline TB, previous ART exposure of more than 3 months, and clinic and year of ART initiation. Likelihood ratios were used to calculate *P* values in regression models for categorical independent variables with more than 2 strata. A subset analysis was conducted excluding individuals with baseline TB. A sensitivity analysis was also conducted in which incident cases of TB were restricted to bacteriologically confirmed cases. Logistic regression was used to compare baseline characteristics of individuals retained in the study sample and those combined LTFU and TFO. All analyses were performed using Stata version 13 (StataCorp LP, College Station, TX).

## ETHICS STATEMENT

The HPTN 071 (PopART) study was approved by the Stellenbosch University Health Research Ethics Committee (SU HREC) (Ref. No. N12/11/074) and the London School of Hygiene and Tropical Medicine research ethics committee (Ref no. 6326). All individuals starting ART outside prevailing routine guidelines signed informed consent. Further approvals for this study, including for the use of

**TABLE 1.** Baseline Characteristics of Study Cohort

		Baseline CD4 Cell Count (Cells/ $\mu$ L)					All 2423	<i>P</i> *
		N (%)†	0–200 631 (26.0)	201–350 708 (29.2)	351–500 582 (24.0)	>500 502 (20.7)		
Sex	Female	N (%)	355 (56.3)	463 (65.4)	421 (72.3)	404 (80.5)	1643 (67.8)	<0.001
	Male	N (%)	276 (43.7)	245 (34.6)	161 (27.7)	98 (19.5)	780 (32.1)	
Age (yr)		Median (IQR)	33 (29.0–40.0)	31 (25.0–37.0)	31 (26.0–37.0)	30 (25.0–37.0)	31 (26.0–38.0)	<0.001
	18–25	N (%)	79 (12.5)	179 (25.3)	142 (24.4)	134 (26.7)	534 (22.0)	<0.001
	26–35	N	312 (49.6)	311 (43.9)	272 (46.7)	227 (45.2)	1122 (46.3)	
	36–45	N	167 (26.5)	138 (19.5)	109 (18.7)	87 (17.3)	501 (20.7)	
	46–55	N	57 (9.0)	63 (8.9)	46 (7.9)	44 (8.8)	210 (8.7)	
	>55	N	17 (2.7)	17 (2.4)	13 (2.2)	10 (2.0)	57 (2.3)	
Pregnant at ART start	Yes	N	14 (3.9)	39 (8.4)	41 (9.7)	48 (11.9)	142 (8.6%)	<0.001
Baseline TB	Yes	N	162 (25.7)	56 (7.9)	41 (6.7)	26 (5.2)	285 (11.8)	<0.001
Clinic	Rural clinic	N	88 (13.9)	113 (15.9)	126 (21.7)	127 (25.3)	454 (18.7)	<0.001
	Metro clinic 1	N	299 (47.4)	301 (42.5)	231 (39.7)	191 (38.1)	1022 (42.2)	
	Metro clinic 2	N	244 (38.7)	294 (41.5)	225 (38.7)	184 (36.7)	947 (39.1)	
ART exposed‡	Yes	N	27 (4.3)	10 (1.4)	7 (1.2)	5 (1.0)	49 (2.0)	0.005
Year of ART start	2014	N	161 (25.5)	208 (29.4)	160 (27.5)	161 (32.1)	690 (28.5)	0.091
	2015	N	470 (74.2)	500 (70.6)	422 (72.5)	341 (67.9)	1733 (71.5)	

\*The *P* value measures heterogeneity across baseline CD4 categories. Chi-square and Kruskal–Wallis tests were used—measure heterogeneity of baseline characteristics.

†For the first row of the table, the % refers to the % across CD4 categories. For all other rows, the % refers to the % within the CD4 category.

‡ART exposed is defined as previous ART exposure of >3 months.

**TABLE 2.** Incidence of TB and Characteristics of Incident TB Cases by Baseline CD4 Count

Baseline CD4 Categories (Cells/ $\mu$ L)	TB Incidence		Bacteriologically Confirmed TB		Site of TB Disease		Treatment Type		
	PY*	TB Cases	IR (95% CI)	Yes	No	Pulmonary	Extrapulmonary	New TB	Retreatment TB
	N	N	TB Cases/100PY	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
0–200	509	49	9.62 (7.27 to 12.73)	29 (59.2)	20 (40.8)	39 (79.6)	10 (20.4)	31 (63.3)	18 (36.7)
201–350	667	21	3.15 (2.05 to 4.83)	14 (66.7)	7 (33.3)	18 (85.7)	3 (14.3)	15 (71.4)	6 (28.6)
351–500	545	21	3.85 (2.51 to 5.91)	14 (66.7)	7 (33.3)	18 (85.7)	3 (14.3)	17 (80.9)	4 (19.1)
>500	475	6	1.26 (0.57 to 2.81)	5 (83.3)	1 (16.7)	6 (100.0)	0 (0.0)	5 (83.3)	1 (16.7)
Total	2196	97	4.41 (3.62 to 5.39)	62 (63.9)	35 (36.1)	81 (83.5)	16 (16.5)	68 (70.1)	29 (29.9)

This table includes all individuals in the study sample including those with baseline TB.

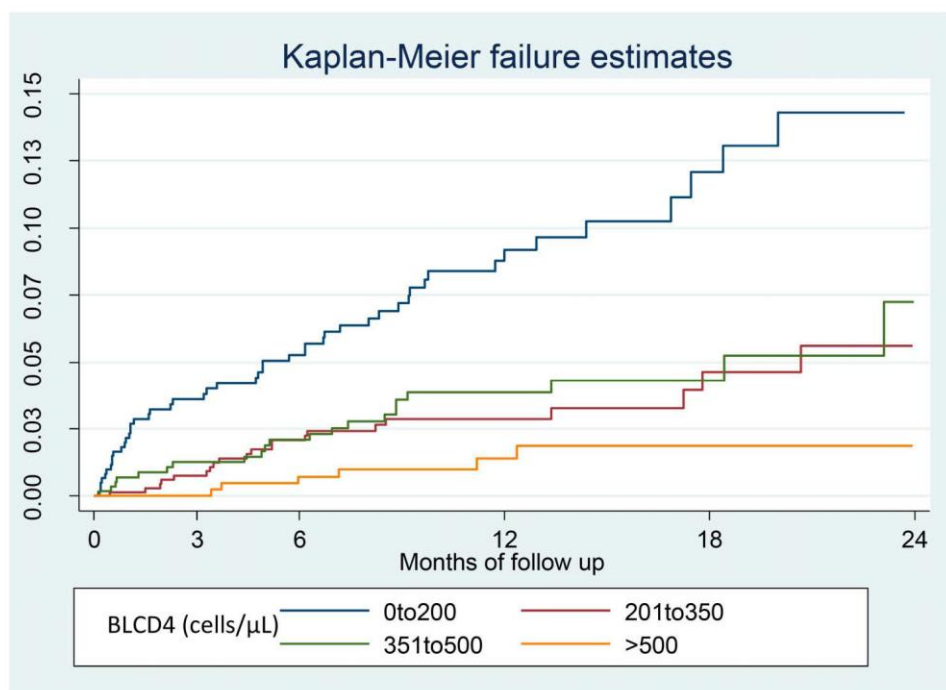
\*PY person time was measured from the estimated time of the end of TB treatment in individuals on TB treatment at baseline. In all other participants, person time was measured from the date of ART start.

individual level routine data with a waiver of informed consent, were received from SU HREC (reference number N12/11/074A), the Western Cape Government (Ref no. WC\_2015RP51\_715), and the City of Cape Town (Ref no 10529) research committees.

**RESULTS**

A total of 2593 individuals started ART during the study enrollment period. Baseline CD4 counts were missing for 170 individuals (6.6%) who were excluded leaving 2423 (93.4%) individuals in the analysis (Table 1). Median follow-up time was 10.4 months (interquartile range [IQR]: 6.4–15.6). In total, 600 (24.7%) individuals were defined LTFU with a median follow-up of 3.4 (IQR: 0.9–7.2) months among those LTFU. There were 134 (5.5%) individuals with TFO recorded during the follow-up period.

Median baseline CD4 count was 328 cells/ $\mu$ L (IQR: 195–468), median age 31 years (IQR: 26–38), and 1643 (67.8%) individuals were women. The numbers of individuals initiating ART in different baseline CD4 count categories varied from 631 (26.0%) at CD4 0–200 cells/ $\mu$ L to 502 (20.7%) at CD4 >500 cells/ $\mu$ L (Table 1). Baseline TB was recorded in 285 individuals (11.8% 95% CI: 10.5% to 13.1%). Baseline TB prevalence ranged from 25.7% (95% CI: 22.3% to 29.3%) at baseline CD4 counts <200 cells/ $\mu$ L to 5.2% (95% CI: 3.4% to 7.5%) at CD4 >500 cells/ $\mu$ L. A small number of individuals, 49 (2.0%), were recorded as having previous ART exposure of more than 3 months duration at baseline, the majority (33, 67.5%) of whom presented with a baseline CD4 count <200 cells/ $\mu$ L. More individuals attended metro 1 (1022, 42.2%) and metro 2 clinics (947, 39.1%) compared with the rural clinic (454, 18.7%).



**FIGURE 1.** Kaplan–Meir failure estimates for incident TB stratified by baseline CD4 cell count categories. BLCD4: Baseline CD4 cell count. Log-rank test for equality of survivor functions:  $P < 0.001$ .



There were 97 incident TB cases during 2196 PY of follow-up [IR: 4.41/100 PY (95% CI: 3.62 to 5.39) (Table 2)]. Eleven (11.3%) of these incident cases occurred in individuals with baseline TB. Kaplan–Meier estimates showed lower rates of incident TB in individuals with baseline CD4 counts >500 cells/ $\mu$ L when compared with those with CD4 <500 cells/ $\mu$ L and across all CD4 categories ( $P < 0.001$ ) (Fig. 1). TB IRs in different baseline CD4 count categories ranged from 9.62/100 PY (95% CI: 7.27 to 12.73) at CD4 0–200 cells/ $\mu$ L to 1.26/100 PY (95% CI: 0.57 to 2.81) at CD4 >500 cells/ $\mu$ L (Table 2). There was a nonsignificant trend toward a decrease in TB incidence at longer follow-up duration; IRs were 5.96/100PY (95% CI: 4.24 to 8.38) from 0 to 3 months, 4.73/100PY (95% CI: 3.14 to 7.12) from 4 to 6 months, 4.73/100PY (95% CI: 3.14 to 7.12) from 4 to 6 months, and 3.04/100PY (95% CI: 1.79 to 5.13) from 13 to 24 months. When analyzing TB incidence by baseline CD4 category and follow-up duration, there were, notably, no recorded incident TB cases during the first 3 months of follow-up among

individuals with baseline CD4 counts >500 cells/ $\mu$ L. Subset analysis excluding individuals with baseline TB showed similar TB IRs and with IRs ranging from 6.6/100PY (95% CI: 4.69 to 9.29) from 0 to 3 months to 2.97/100PY (95% CI: 1.72 to 5.12) from 13 to 24 months.

Of 97 incident TB cases, 81 (83.5%) cases were pulmonary and 16 (16.5%) extrapulmonary. (Table 2). Sixty-eight (70.1%) cases were recorded as new (not previously treated) and 29 (39.9%) as having been previously treated but were not on TB treatment at initiation of ART.

Sixty-two (63.9%) incident TB cases were bacteriologically confirmed, most commonly on sputum using Xpert (54, 86.0%). Of the 35 (36.1%) incident TB cases not bacteriologically confirmed, diagnosis was based on x-ray for 21 (60.0%). There were no significant differences across baseline CD4 count categories in the proportions of TB cases that were pulmonary or extrapulmonary, new or retreatment cases, or bacteriologically confirmed.

**TABLE 3.** Cox Regression Modeling of Baseline Characteristics and Incident TB

	Unadjusted Analyses		Adjusted Analyses	
	HR (95% CI)	<i>P</i>	AHR (95% CI)	<i>P</i>
Baseline CD4* (Cells/ $\mu$ L)				
>500	0.13 (0.06 to 0.32)	<0.001	0.15 (0.06 to 0.36)	<0.001
350–500	0.41 (0.24 to 0.68)		0.45 (0.27 to 0.77)	
200–350	0.33 (0.20 to 0.56)		0.36 (0.21 to 0.60)	
0–200	1.00		1.00	
Gender				
Male	2.58 (1.73 to 3.85)	<0.001	2.16 (1.41 to 3.30)	<0.001
Female	1.00		1.00	
Clinic				
Metro 1	1.00	0.212	1.00	0.047
Metro 2	1.26 (0.77 to 2.05)		1.54 (0.89 to 2.66)	
Rural 1	1.63 (0.95 to 2.79)		2.17 (1.19 to 3.97)	
Age category, yrs				
15–25	0.84 (0.47 to 1.49)	0.465	1.18 (0.66 to 2.13)	0.951
26–35	1.00			
36–45	1.38 (0.84 to 2.27)		1.28 (0.68 to 1.87)	
46–55	1.34 (0.69 to 2.61)		1.22 (0.62 to 2.38)	
>55	1.52 (0.47 to 4.89)		1.34 (0.41 to 4.38)	
Pregnant at baseline†				
Yes	0.51 (0.16 to 1.62)	0.207	0.79 (0.23 to 2.46)	0.727
Baseline TB‡				
Yes	1.50 (0.80 to 2.82)	0.155	0.83 (0.41 to 1.53)	0.487
Previous ART exposure of >3 mo				
Yes	3.94 (1.82 to 8.52)	0.001	3.28 (1.49 to 7.2)	0.003
Year ART start				
2014	0.97 (0.62 to 1.53)	0.906	0.75 (0.45 to 1.26)	0.272
2015	1.00		1.00	

All individuals were included in this analysis regardless of baseline TB status. Follow-up time is therefore not equal; time on ART as follow-up for individuals on TB treatment at ART initiation was delayed until the estimated end of TB treatment (6 months after TB treatment initiation).

Baseline characteristics for inclusion in multivariate modeling were chosen based on clinical significance. For baseline characteristics with more than 2 categories, likelihood ratios were used—estimate *P* values for hazard of incident TB.

\*Baseline CD4 count was the most recent CD4 count completed in the 6 months before ART initiation.

†All individuals initiating ART are screened for pregnancy at baseline.

‡Baseline TB was defined as having started TB treatment within the 6 months before ART initiation.

Multivariate Cox regression showed a lower hazard of incident TB (adjusted HR [aHR] 0.27; 95% CI: 0.12 to 0.62) among individuals with baseline CD4 count >500 cells/ $\mu$ L when compared with CD4  $\leq$ 500 cells/ $\mu$ L. When stratifying by all baseline CD4 count categories, aHR for incident TB were as follows: aHR 0.15 (95% CI: 0.06 to 0.36) at CD4 >500 cells/ $\mu$ L; aHR 0.45 (95% CI: 0.27 to 0.77) at CD4 351–500 cells/ $\mu$ L; and aHR 0.36 (95% CI: 0.21 to 0.60) at CD4 201–350 cells/ $\mu$ L compared with CD4 0–200 cells/ $\mu$ L (Table 3). The aHR of incident TB was higher among men (aHR 2.16; 95% CI: 1.41 to 3.30), individuals with previous ART exposure more than 3 months (aHR 3.28; 95% CI: 1.49 to 7.2), and individuals attending the rural clinic (aHR 2.17; 95% CI: 1.19 to 3.97).

A subset analysis that excluded the 285 individuals with baseline TB showed similar results (Table 4). Hazard of TB remained lower at higher baseline CD4 counts; aHR = 0.13 (95% CI: 0.05 to 0.33) at CD4 >500 cells/ $\mu$ L; aHR = 0.42 (95% CI: 0.24 to 0.74) at CD4 351–500 cells/ $\mu$ L; and aHR 0.35 (95% CI: 0.20 to 0.60) at CD4 201–350 cells/ $\mu$ L compared with CD4 0–200 cells/ $\mu$ L. Hazard of incident TB remained higher in men (aHR 2.31; 95% CI: 1.48 to 3.60), individuals with previous ART exposure more than 3 months (aHR 2.71; 95% CI: 1.08 to 6.81), and among individuals

attending the rural clinic (aHR 2.16; 95% CI: 1.13 to 4.13) on subset analysis.

Sensitivity analysis using bacteriologically confirmed incident TB as the primary outcome showed similar results with a lower hazard of bacteriologically confirmed incident TB in individuals starting ART at baseline CD4 counts >500 cells/ $\mu$ L compared with CD4  $\leq$ 500 cells/ $\mu$ L (aHR 0.35; 95% CI: 0.14 to 0.89). Sensitivity analyses also confirmed reduced hazard of bacteriologically confirmed incident TB at higher baseline CD4 counts when comparing across all baseline CD4 count categories; aHR: 0.21 (95% CI: 0.08 to 0.57) at CD4 >500 cells/ $\mu$ L; aHR: 0.51 (95% CI: 0.26 to 0.98) at 350–500 cells/ $\mu$ L; aHR: 0.41 (95% CI: 0.22 to 0.79) at 201–350 cells/ $\mu$ L compared with CD4 <200 cells/ $\mu$ L.

Logistic regression analysis of the association of baseline characteristics with an end point that combined LTFU and TFO showed that adjusted odds ratios (aORs) of LTFU and TFO at different baseline CD4 categories were 1.23 (95% CI: 0.95 to 1.61), 0.74 (95% CI: 0.56 to 0.96), and 1.05 (95% CI: 0.82 to 1.33) among individuals with baseline CD4 counts >500, 351–500, and 201–350 cells/ $\mu$ L, respectively when compared with those with baseline CD4 counts  $\leq$ 200 cells/ $\mu$ L. Other baseline characteristics associated with combined LTFU and TFO included age 18 to 25 (aOR = 1.36;

**TABLE 4.** Subset Cox Regression Modeling of Baseline Characteristics and Incident TB Excluding Individuals With Baseline TB

	Crude Hazard Ratio (95% CI)	P	aHR (95% CI)	P
Baseline CD4 (Cells/ $\mu$ L)				
>500	0.11 (0.04 to 0.28)	<0.001	0.13 (0.05 to 0.33)	<0.001
351–500	0.37 (0.22 to 0.64)		0.42 (0.24 to 0.74)	
201–350	0.32 (0.19 to 0.55)		0.35 (0.20 to 0.60)	
0–200	1.0		1.0	
Sex				
Male	2.75 (1.8 to 4.19)	<0.001	2.31 (1.48 to 3.60)	<0.001
Female	1.0		1.0	
Clinic				
Metro 1	1.0	0.286	1.0	0.059
Metro 2	1.35 (0.8 to 2.26)		1.73 (0.98 to 3.07)	
Rural 1	1.58 (0.88 to 2.84)		2.16 (1.13 to 4.13)	
Age category, yrs				
15–25	0.91 (0.5 to 1.63)	0.416	1.28 (0.7 to 2.32)	0.762
26–35	1		1	
36–45	1.55 (0.92 to 2.61)		1.30 (0.77 to 2.21)	
46–55	1.27 (0.61 to 2.63)		1.17 (0.56 to 2.44)	
>55	0.65 (0.09 to 4.71)		0.57 (0.08 to 4.16)	
Pregnant at baseline*				
Yes	0.53 (0.17 to 1.69)	0.285	0.85 (0.26 to 2.77)	0.785
Previous ART exposure of >3 months				
Yes	3.46 (1.4 to 8.55)	0.007	2.71 (1.08 to 6.81)	0.785
Year ART start				
2014	0.93 (0.57 to 1.52)	0.780	1.36 (0.79 to 2.36)	0.271
2015	1.0		1.0	

Individuals (285) with baseline TB were excluded. In this analysis, follow-up time equals time on ART. Baseline characteristics for inclusion in multivariate modeling were chosen based on clinical significance. For baseline characteristics with more than 2 categories, likelihood ratios were used—estimate P values for hazard of incident TB. Baseline CD4 count was the most recent CD4 count completed in the 6 months before ART initiation.

\*All individuals initiating ART are screened for pregnancy at baseline. Baseline TB was defined as having started TB treatment within the 6 months before ART initiation.



95% CI: 1.09 to 1.70) and age 46 to 55 (aOR 0.65; 95% CI: 0.46 to 0.93) compared with age 26 to 35, being treated at metro 2 (aOR: 1.31; 95% CI: 1.05 to 1.66) compared with metro 1 and baseline TB treatment (aOR: 1.44; 95% CI: 1.09 to 1.91). Male sex was not associated with increased LTFU and TFO (aOR 1.11; 95% CI: 0.90 to 1.36) when compared with female sex.

## DISCUSSION

Life-long ART is now recommended for all HIV-positive individuals regardless of CD4 count.<sup>2</sup> In addition to improving individual level clinical outcomes and potentially reducing community HIV transmission, earlier ART initiation has the potential to reduce population level TB incidence.<sup>3,5</sup> The impact of starting ART at baseline CD4 counts >500 cells/ $\mu$ L on subsequent TB incidence has been demonstrated in randomized controlled trials; however, there are very limited data from programmatic settings. This study has demonstrated significantly lower TB incidence for individuals starting ART at CD4 counts >500 cells/ $\mu$ L (1.26/100 PY (95% CI: 0.57 to 2.81) compared with those starting at lower CD4 counts. This rate is, however, higher than previously reported TB case notification rates for the HIV-negative population, aged 15–60 years, in the Cape Town area (0.48/100PY).<sup>21</sup> A direct comparison cannot be made because these were different studies with different methodologies, and interpretation of this comparison is limited by the relatively small sample size of our study and should be the subject of further evaluation.

In contrast to previous studies among HIV-positive individuals,<sup>7,8,10</sup> the hazard of incident TB on ART in this study was higher among men, reasons for which are not clear from these data. This may, however, be due to lower ART adherence among men, with associated greater immunosuppression, as reported in other studies.<sup>22</sup> There is a reported trend toward recurrent episodes of ART nonadherence among individuals on ART, and it is therefore possible that individuals with previous ART exposure were more likely to be nonadherent to ART, which may account for the higher TB incidence in this group.<sup>23</sup> The higher TB incidence at the rural clinic is likely to, in part, reflect higher background annual TB incidence.<sup>17</sup> Previous studies have shown a strong trend toward decreasing TB incidence with increasing duration of follow-up after ART initiation.<sup>8,10</sup> By contrast, in this study, there was a trend toward decreased TB incidence at longer durations of ART; however, it was not statistically significant. This may be in part due to limited sample size; however, there were no recorded incident TB cases during the first 3 months on ART among individuals with baseline CD4 counts starting >500 cells/ $\mu$ L, which would have reduced overall cohort incidence during early ART.

Unmasking of TB is known to contribute to TB incidence during the first 3 months on ART.<sup>24,25</sup> The absence of incident TB cases during this period of ART in HIV-positive individuals who have not spent time pre-ART at CD4 counts lower than 500 cells/ $\mu$ L in this high-TB burden setting is promising and should be the subject of future research.

Effective management of HIV and TB at PHC clinics is critical in reducing associated morbidity and mortality in high-burden settings.<sup>26,27</sup> Integration of HIV and TB services in PHC clinics is increasingly recommended,<sup>26,27</sup> but has not always been shown to lead to improved clinical outcomes. The best way to integrate services may be highly context specific,<sup>28,29</sup> and there remains the need for high quality data evaluating best practices for HIV and TB integration.<sup>2</sup> Differentiated models of care, which provide intensified care for high-risk individuals in PHC clinics, may be a successful strategy for improving integrated HIV and TB care.<sup>30,31</sup> To this end, studies such as this one, which have identified key baseline risk factors for TB incidence on ART, could be used to develop risk matrices for incorporation into differentiated models of care for improving clinical outcomes in HIV and TB co-infected individuals.

The HPTN 071 (PopART) trial has provided a unique opportunity to evaluate, under programmatic conditions, a cohort of HIV-positive individuals routinely starting ART at baseline CD4 counts >500 cells/ $\mu$ L, before ART regardless of CD4 count being recommended by WHO and South African guidelines. The primary outcome of this study, TB incidence, is a topic of great public health importance, and the analysis of an objective primary end point was strengthened by sensitivity analyses of microbiologically confirmed TB. Data included in this analysis were representative of the planned study cohort with only 170 (6.6%) of eligible individuals excluded because of missing baseline CD4 count. The prospective health systems support provided by HPTN 071 (PopART) to the study clinics was likely to have improved the accuracy with which TB was diagnosed and reported in ETR.net.

There were, however, limitations that require consideration. ETR.net captures only individuals starting TB treatment. Individuals diagnosed with TB but not started on TB treatment were, therefore, excluded along with individuals starting TB treatment who were erroneously not recorded in ETR.net. Similarly, the majority of the estimated 4%–5% of individuals diagnosed with drug-resistant TB at the time of TB treatment start<sup>32</sup> were not captured in ETR.net, but into a separate database [Electronic Drug-Resistant TB register (EDR.net)] and were therefore excluded in this analysis. The authors were, therefore, not able to report the contribution of MDR to incident TB cases. The omission of MDR TB cases in this study may have reduced the overall reported TB incidence, but given that CD4 count has not been shown to be associated with the risk of MDR TB versus drug susceptible TB,<sup>33</sup> there is no evidence that the missing MDR data differentially affected TB incidence across different baseline CD4 categories in this study. Despite these missing data, baseline TB prevalence stratified by baseline CD4 count category in this study was similar to that reported for corresponding baseline CD4 count categories by another South African study, from a comparable area in the Cape Metro, in which data were limited to individuals with baseline CD4 counts  $\leq$  500 cells/ $\mu$ L.<sup>4</sup>

Furthermore, there was marked heterogeneity of baseline characteristics across baseline CD4 categories, and although we adjusted for some of these characteristics in



the Cox regression analysis, we cannot rule out that there may be residual confounding. There were also high rates of LTFU (24.7%) and TFO (5.5%), which are likely to have reduced the overall reported TB incidence. When analyzing LTFU and TFO across baseline CD4 categories, although there was reduced LTFU and TFO among individuals with baseline CD4 counts of 351–500 cells/ $\mu$ L. However, LTFU and TFO amongst individuals with baseline CD4 counts of >500 cells/ $\mu$ L, and 201–350 cells/ $\mu$ L was not different from LTFU and TFO among individuals with baseline CD4 counts  $\leq$ 200 cells/ $\mu$ L, and it is therefore not evident that LTFU and TFO differentially affected TB incidence across baseline CD4 categories. LTFU and TFO were similar with respect to other baseline characteristics associated with TB incidence. Non-availability of viral load data after ART initiation is a further limitation of this study. Increased viral load after ART initiation is associated with increased incidence of TB on ART,<sup>8</sup> and inclusion of these data would have assisted in interpreting the association of key baseline characteristics with TB incidence, such as the increased hazard of TB in men who are also associated with decreased ART adherence and increased risk of increased viral load on ART.<sup>22</sup>

IPT has been shown to decrease the risk of TB among individuals starting ART.<sup>11</sup> The nonreporting of IPT provision in this study due to missing data in ETR.net and Tier.net is a limitation. It was not apparent whether IPT uptake in this study differed across baseline CD4 categories and the non-availability of IPT data may therefore have biased the primary outcomes. Anecdotally, the use of IPT was low and inconsistent in PHC clinics in the Western Cape at the time of this study. IPT has been shown to be effective in reducing TB incidence in HIV-positive individuals testing TST positive.<sup>11,34,35</sup> The need for TST testing and concerns about isoniazid resistance are thought to have contributed to low uptake of IPT.<sup>36,37</sup> The need for TST testing before IPT is debated, and recent changes to ART guidelines, with more individuals starting ART at higher CD4 counts, when TST testing is more sensitive,<sup>35</sup> should be a critical consideration in this debate going forward.

## CONCLUSIONS

The HPTN 071 (PopART) trial has provided a unique opportunity to evaluate TB incidence in the setting of universal offer of ART through programmatic clinic data. This study showed a significantly lower TB prevalence and on ART incidence among HIV-positive individuals initiating ART at CD4 counts >500 cells/ $\mu$ L, suggesting that the scale-up of ART regardless of CD4 count has the potential to significantly reduce TB burden among HIV-positive individuals. At the same time, scale-up of other TB prevention strategies that target both HIV-positive and HIV-negative individuals is urgently required to contribute substantially to TB elimination in high-HIV prevalence settings.

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## Chapter 6: Renal dysfunction in a cohort of adults starting antiretroviral treatment at baseline CD4 counts >500 cells/ $\mu$ L in the HPTN 071 (PopART) study in South Africa.

Unpublished: This study will be submitted to the HPTN 071 (PopART) publication review process in October/November 2017.

### Study design overview

This study evaluated the impact of starting ART at baseline CD4 counts >500 cells/ $\mu$ L on incidence of renal dysfunction during early ART. Routine NHLS laboratory creatinine results were used to calculate EGFR levels which were used for measurement of the primary endpoint, incident renal dysfunction. Incident renal dysfunction was defined as an EGFR <60ml/min after ART initiation. The study used the same cohort of adults used in chapters 3 and 4. All individuals were followed up until the date of attrition, elective transfer to another facility (TFO), incident renal dysfunction or end May 2016, whichever occurred first. In addition to the data sources used in chapters 3 and 4, missing EGFR data were extracted from clinic folders. This study addressed the following PhD objective:

To evaluate the impact of routine initiation of ART at baseline CD4 counts >500 cells/ $\mu$ L at DOH ART clinics on the incidence of renal dysfunction during early ART

**Table 5: Renal dysfunction study outline**

Primary outcome	Study site	Recruitment period	Exclusion criteria	Follow-up	Data sources
Incident renal dysfunction	Three SA PopART Arm A clinics	1 January 2014 to end November 2015	Missing baseline CD4 count	Until attrition, TFO, incident renal dysfunction or end May 2016.	Tier.net, ETR.net, NHLS reports and clinic folders

**Author contribution:** I was responsible for setting up the study cohort used for this study in partnership with DOH and PEPFAR implementing partners. I, with support from senior authors (GF, NF, NB and SF), conceptualised this study. I completed the statistical analysis with



support from Sian Floyd (SF), Rosa Sloot (RS) and Geoffrey Fatti (GF). All authors contributed toward development of the manuscript and reviewed drafts including the final version included in this dissertation.

**Renal dysfunction in a cohort of adults starting antiretroviral treatment at baseline CD4 counts >500 cells/ $\mu$ L in the HPTN 071 (PopART) study in South Africa.**

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## Abstract

### Introduction

Renal dysfunction is a significant cause of morbidity and mortality amongst HIV-positive individuals. This paper evaluates renal dysfunction in a cohort of adults starting antiretroviral treatment (ART) regardless of CD4 count at three department of health (DOH) clinics included in the HPTN071 (PopART) trial.

### Methods

A retrospective cohort analysis of routine data of HIV-positive individuals starting ART between January 2014 and November 2015 was completed. Incident renal dysfunction was defined as an estimated glomerular filtration rate (EGFR)  $<60\text{mL}/\text{min}$  after ART initiation amongst individuals with a baseline EGFR  $\geq 60\text{mL}/\text{min}$ . All participants were followed up from ART initiation until loss to follow-up, death, transfer out to another clinic or incident renal dysfunction, or until end May 2016; whichever occurred first.

### Results

Overall 2423 individuals with a median baseline CD4 count of 328 cells/ $\mu\text{L}$  (IQR 195-468) were included in the analysis. Regression analysis showed lower odds of baseline EGFR  $<60\text{mL}/\text{min}$  at baseline CD4 counts of  $>500$  cells/ $\mu\text{L}$  (aOR 0.29; 95% CI 0.11-0.80), 351-500 cells/ $\mu\text{L}$  (aOR 0.22; 95% CI 0.08-0.59) and 201 to 350 (aOR 0.48; 95% CI: 0.24-0.97) when compared to baseline CD4 counts CD4  $<200$  cells/ $\mu\text{L}$ . Amongst individuals with baseline EGFR  $>60\text{mL}/\text{min}$ , there was no association between baseline CD4 count and incident EGFR  $<60\text{mL}/\text{min}$ . Analysis restricted to individuals with baseline EGFR  $\geq 90\text{mL}/\text{min}$  showed no incident cases of EGFR  $<60\text{mL}/\text{min}$  amongst individuals with baseline CD4 counts  $>500$  cells/ $\mu\text{L}$ .

### Conclusion

This study showed lower rates of renal dysfunction amongst individuals with baseline CD4  $>200$  cell/ $\mu\text{L}$  at the time of starting ART. The study also, promisingly, showed no incident renal dysfunction amongst individuals with normal baseline EGFR and baseline CD4 counts  $>500$  cells/ $\mu\text{L}$ , although larger studies are required to confirm this finding. Strategies that incorporate risk matrices to guide more focused implementation of EGFR monitoring as part

of differentiated models of care may enhance EGFR monitoring and should be the subject of implementation research.

## Introduction

The number of individuals on antiretroviral therapy (ART) continues to increase annually. (1) Implementation of recent WHO recommendations of ART regardless of CD4 count in high-burden settings will lead to an increased number of HIV-positive individuals starting ART at baseline CD4 counts  $>500$  cells/ $\mu$ L. (2)

Renal dysfunction is a well-recognised cause of morbidity and mortality amongst HIV-positive individuals starting ART. (3, 4) Although immune reconstitution after ART initiation is overall associated with improved renal function, it may, conversely, be negatively impacted by toxicity of commonly used antiretrovirals, such as tenofovir. (3, 4) In the absence of accessible alternative antiretrovirals, with superior renal toxicity profiles, tenofovir remains a drug of choice for first line ART in high burden settings. (2, 5, 6) Routine monitoring of renal function in individuals starting tenofovir, by measurement of serum estimated glomerular filtration rate (EGFR), is recommended, and tenofovir is contraindicated in individuals with EGFR  $<50$  mL/min at the time of ART initiation.

Programmatic studies from high-burden settings show varying baseline prevalence of renal dysfunction amongst individuals starting ART. (7-11). (7, 10). The reported association between baseline CD4 count and baseline renal dysfunction varies; with some studies showing higher baseline renal dysfunction at lower CD4 counts, (9, 10) and other studies showing no association. (7, 11)

With respect to renal function after ART initiation, programmatic studies, with median baseline CD4 counts ranging from 154 to 209 cells/ $\mu$ L, show decreased renal dysfunction after ART initiation amongst individuals with baseline CD4 counts  $>200$  cells/ $\mu$ L compared to lower values. (12, 13) Recently published results from the START trial showed higher mean EGFR after ART initiation amongst individuals starting ART at baseline CD4 counts  $>500$  cells/ $\mu$ L when compared to those with baseline CD4 350 to 500 cells/ $\mu$ L. (14) There are, however, limited data from programmatic studies to confirm these findings. In this context, the primary aim of this study was to evaluate the impact of routine initiation of ART at CD4 counts  $>500$  cells/ $\mu$ L on the incidence of renal dysfunction during early ART in a cohort of

adults starting ART regardless of CD4 at three Department of Health (DOH) clinics included in the HPTN 071 (PopART) trial, in South Africa.

### **Study setting**

The HPTN 071 Population Effect of Antiretroviral Therapy to Reduce HIV Transmission (PopART) study is a community randomised trial currently being implemented in South Africa and Zambia. A full description of the PopART trial design is previously published. (15) For PopART, a community was defined as the catchment population of a DOH primary healthcare (PHC) clinic. PopART communities were randomly allocated to one of three arms: A, B or C. Arm A communities received the full intervention including community HIV prevention services delivered by a cadre of community workers named 'CHiPs' ('Community HIV Care Providers') and ART regardless of CD4 count at the local DOH clinic. Arm B communities received the CHiPs intervention with ART as per in-country guidelines, while Arm C communities received standard care interventions only.

ART services at the three study clinics were provided according to provincial department of health (DOH) ART guidelines; (5) with the exception that all three study clinics provided ART regardless of CD4 count from 1 January 2014, before the provincial DOH ART guidelines changed to ART regardless of CD4 count in October 2016. (5) Routinely, all individuals starting ART are recorded in the electronic HIV program monitoring system, Tier.net, (16) A fixed-dose combination tablet of tenofovir, emtricitabine and efavirenz (TEE) was used as the first-line ART regimen of choice. All laboratory services were provided by the centralised regional National Health Laboratory Services (NHLS) with daily pick up of specimens from all PHC clinics. Tenofovir was contraindicated in clients with baseline EGFR <50 mL/min in whom zidovudine (AZT), stavudine (D4T) or abacavir (ABC) were recommended first-line alternatives. For individuals starting tenofovir, serum creatinine used for EGFR estimation was measured prior to ART initiation at 4 and 12 months after initiating therapy, and annually thereafter. (17)



## **Cohort overview and definitions**

A retrospective cohort study design was utilised. All HIV-positive adults ( $\geq 18$  years) recorded in Tier.net, (16) as having started ART at the three study clinics between 1 Jan 2014 and end November 2015 were screened for inclusion. Individuals were excluded from analysis if they did not have a recorded baseline CD4 count. All individuals were followed up for a minimum of six months until end May 2016 (the date of administrative censor) or until the date of attrition or transfer out (TFO), if that occurred earlier. For the analysis of incident renal dysfunction, as a binary variable, individuals were censored after the first episode of  $\text{EGFR} < 60 \text{ mL/min}$ .

Baseline CD4 was defined as the most recent CD4 completed in the six months prior to starting ART. Baseline EGFR was estimated from the most recent serum creatinine (SCR) completed in the six months prior to starting ART. American National Kidney Foundation criteria were used to define levels of renal dysfunction; mild ( $\text{EGFR} 60 - 89 \text{ mL/min}$ ), moderate ( $\text{EGFR} 30 - 59 \text{ mL/min}$ ) or severe ( $\text{EGFR} < 30 \text{ mL/min}$ ) to best align with other published data. (18) Moderate and severe renal dysfunction were combined ( $\text{EGFR} < 60 \text{ mL/min}$ ) for analysis of both baseline renal dysfunction ( $\text{EGFR} < 60 \text{ mL/min}$ ) and incident renal dysfunction ( $\text{EGFR} < 60 \text{ mL/min}$ ). Baseline TB was defined as being on TB treatment at the time of ART start. Attrition included all individuals no longer in care as a result of loss to follow-up (LTFU) or death. Attrition was defined as being three months late for a scheduled clinic appointment. Death and LTFU was not analysed separately in this study as death was not consistently recorded in Tier.net. Transfer out (TFO) was defined as elective transfer of an individual to another ART clinic documented in Tier.net.

## **Data sources and management**

Routine DOH and National Health Laboratory Services (NHLS) data were used for this study. Unless otherwise stated all data were extracted from Tier.net. (16) Data on SCR results were extracted from the NHLS database and linked to Tier.net data using the DOH unique identifier. EGFR was calculated from SCR age and sex using the MDRD Study equation ( $\text{EGFR} = 175 \times \text{standardized SCR}^{-1.154} \times \text{age}^{-0.203} \times 1.212$  [if black]  $\times 0.742$  [if female]), (19) with omission of the racial categorisation factor as recommended in previous publications. (13, 20) Additional creatinine data, missing from the NHLS data extracts were, where available,

extracted from clinic folders. Data from the DOH electronic TB monitoring system, ETR.net, was used to identify individuals with baseline TB. All data fields and data linkages were reviewed for completeness and accuracy.

## **Analysis**

Standard descriptive analyses including absolute numbers and proportions were used to describe baseline characteristics. Similarity of baseline characteristics across baseline CD4 count categories was analysed using Chi-Square and Kruskal-Wallis tests. Logistic regression was used to model the association of other baseline characteristics with baseline renal dysfunction. Two way scatter and fitted line graphs were used to illustrate trends in EGFR over time on ART. Mixed effects linear regression was used to model the association of baseline characteristics with mean EGFR over time on ART. Time-to-event analyses of incident EGFR<60mL/min as a binary variable were completed using Kaplan-Meier survival estimates amongst individuals with baseline EGFR  $\geq$ 60mL/min. Cox regression was used in analysis of baseline characteristics associated with hazard of EGFR<60mL/min on ART amongst individuals with baseline EGFR  $\geq$ 60mL/min. Women pregnant at the time of starting ART were excluded from the analysis of baseline and on ART EGFR<60mL/min due to increases in EGFR levels during pregnancy of up to 50%. (21)

The same baseline characteristics namely age, sex, CD4 count, EGFR, TB status, clinic where treatment was received, year when ART started, pregnancy at baseline and previous ART exposure of more than three months, were included in all multivariate models unless otherwise stated. Baseline characteristics for inclusion in multivariate modelling were selected based on clinical significance of available data. The reference category for categorical variables was selected by using the category with the largest sample size or on clinical significance. Comparison of baseline characteristics between individuals excluded from analysis due to missing results of baseline EGFR or EGFR after ART initiation and those retained in the analysis were completed using logistic regression. Logistic regression was also used to compare baseline characteristics of individuals retained in the study cohort and those experiencing attrition or TFO. Analyses were performed using Stata™ version 13 (StataCorp LP, College Station, TX, USA).

## Ethics

The HPTN 071 (PopART) trial has been approved by the Stellenbosch University Health Research Ethics Committee (HREC) (Ref. No. N12/11/074) and the London School of Hygiene and Tropical Medicine research ethics committee (Ref no. 6326). All HIV-positive individuals starting ART outside of provincial ART guidelines signed informed consent. Additional HREC approval for the use of individual-level DOH data, including a waiver for informed consent, for the completion of this study was received from SU HREC (Ref no. N12/11/074A) as well as from the Western Cape Government (Ref no. WC\_2015RP51\_715) and City of Cape Town (Ref no 10529) research committees.

## Results

### Baseline characteristics

Overall 2593 individuals were screened for study inclusion, 170 (6.6%) were excluded due to missing baseline CD4 cell counts leaving 2423 (93.4%) individuals included in the baseline analysis (Table 1). Median baseline CD4 count was 328 cells/ $\mu$ L (IQR 195-468). The proportion of individuals across baseline CD4 cell categories varied between 631 (26.0%) at CD4 0-200 cells/ $\mu$ L and 502 (20.7%) at CD4 >500 cells/ $\mu$ L. Median age was 31 years (IQR 26-38) and the majority (1661/67.9%) were women. Baseline EGFR was available for 2141 (88.4%) of individuals with a reported baseline CD4 count. Median baseline EGFR was 110.5 mL/min (IQR 93.5 - 131.9). A total of 47 (1.9%), 394 (16.3%) and 1700 (70.2%) individuals had baseline EGFRs <60 mL/min, 60-89 mL/min and  $\geq$ 90 mL/min respectively. The number with EGFR <60 mL/min ranged from 24 (3.8%) at baseline CD4 count 0-200 cells/ $\mu$ L to 5 (1.0%) at baseline CD4 counts >500 cells/ $\mu$ L ( $P < 0.001$ ).

### Analysis of baseline characteristics associated with baseline renal dysfunction.

Univariate and multivariate logistic regression analysis of the association between baseline characteristics and baseline EGFR <60 mL/min amongst the 2014 non-pregnant individuals with a reported baseline CD4 count are shown in table 2. The adjusted odds ratios (aORs) of baseline EGFR <60 mL/min across baseline CD4 categories were 0.29 (95% CI 0.11-0.80) for CD4 counts >500 cells/ $\mu$ L, 0.22 (95% CI 0.08-0.59) for CD4 counts 351-500 cells/ $\mu$ L and 0.48 (95% CI: 0.24-0.97) for CD4 counts 201 to 350 cells/mL when compared to CD4 0-200 cells/ $\mu$ L. Baseline EGFR <60 mL/min was also more common in individuals aged >35 years with

aORs of 3.38(95% CI: 1.64-6.95) for ages 36-45 years and 6.40 (95% CI: 3.06-13.37) for ages >45 years when compared to individuals aged  $\leq 35$  years. Baseline EGFR<60mL/min was also more common amongst males (aOR = 1.99; 95% CI: 1.08-3.66) than amongst women. There were no other baseline variables associated with baseline EGFR<60mL/min.

### **Analysis of renal function after ART initiation**

A total of 651 (26.9%) individuals were excluded from the analysis of EGFR after ART initiation for the following reasons: i) missing baseline EGFR (282 individuals/43.3%); ii) started on an ART regimen which did not contain tenofovir or unknown baseline ART regimen (53 individuals/ 8.1%) and iii) no reported EGFR after ART initiation (on ART EGFR) (316 individuals/48.5%). The remaining 1772 (73.1%) individuals were included in the analysis of EGFR after ART initiation (on ART EGFR) and were followed up for a median of 12.1 (IQR 7.9-16.9) months, during which time 329 (18.6%) experienced attrition and 85 (4.8%) experienced TFO.

The mean EGFR on ART was 114mL/min (95%CI 113 -115). Changes in on ART EGFR are shown in figures 1a to 1d. Multivariate mixed effects linear regression showed that compared to those with baseline EGFR  $\geq 90$ mL/min, mean on ART EGFR was 37.49 mL/min (95% CI 28.52-46.46) lower amongst individuals with baseline EGFR <60mL/min and 22.47mL/min (95%CI 19.34-25.60) lower amongst individuals with baseline EGFR 60 to 89 mL/min when. Mean on ART EGFR was 20.56mL/min (95%CI 15.57-25.55) greater amongst women pregnant at baseline and 6.80mL/min (95% CI 3.67-9.92) lower amongst individuals attending Metro 2 clinic compared to Metro 1. There was no difference in mean EGFR when comparing individuals treated at the rural clinic and Metro 1.

For analysis of incident EGFR<60ml/min, 107 women pregnant at baseline were excluded from analysis of incident EGFR<60ml/min leaving a sample size of 1665. Kaplan Meier estimates showed higher rates of on ART EGFR<60mL/min over time at lower baseline CD4 counts ( $P<0.05$ ) (Figure 2). There were 33 incident cases of EGFR<60mL/min during 1749 person years (PY), incidence rate (IR) 1.9/100PY (95%CI 1.3-2.6). The IR of EGFR<60mL/min amongst this group was highest during the first six months of ART (IR = 2.3/100PY (95% CI 1.99-2.66) compared to longer duration of ART; however this difference was not statistically significant. Additional analysis further restricted to 1651 non-pregnant individuals with

baseline EGFR  $\geq 60$  mL/min showed a lower IR of EGFR  $< 60$  mL/min (1.6/100PY; 95% CI 1.1-2.3) (Table 4). When further restricting analysis to 1333 non pregnant individuals with EGFR  $\geq 90$  mL/min, there were only 15 incident cases of EGFR  $< 60$  mL/min (IR = 1.1/100PY; 95% CI (0.6-1.8). Notably when limiting analysis to this group with normal baseline EGFR there were no incident cases of EGFR  $< 60$  mL/min amongst individuals with baseline CD4 counts  $> 500$  cells/ $\mu$ L.

Multivariate Cox regression which included all 1651 non-pregnant individuals with baseline EGFR  $\geq 60$  mL/min (Table 5) showed a lower hazard ratio of EGFR  $< 60$  mL/min at higher baseline CD4 categories compared to baseline CD4 count  $< 200$  cells/ $\mu$ L, but this finding was not statistically significant. There was a higher hazard of incident EGFR  $< 60$  mL/min amongst individuals with baseline EGFR 60 to 89 mL/min (aHR = 2.62; 95% CI 1.17-5.83) compared to those with baseline EGFR  $\geq 90$  mL/min and amongst individuals aged  $> 45$  years (aHR 3.25; 95% CI: 1.30-8.14) compared to individuals aged  $\leq 35$  years. No other baseline characteristics were associated with incident EGFR  $< 60$  mL/min.

### **Analysis of missing data**

Logistic regression using the full model showed increased rates of missing baseline EGFR results at higher baseline CD4 counts  $> 500$  cells/ $\mu$ L (aOR = 1.54; 95% CI 1.04-2.26) compared to baseline CD4 counts  $\leq 200$  cells/ $\mu$ L. Individuals with missing baseline EGFR results were less likely to be men (aOR = 0.71; 95% CI 0.55-0.93) and more likely to attend the rural clinic (aOR = 1.54 95% CI: 1.01 -2.33) rather than Metro 1. Individuals excluded from follow-up analysis due to missing on ART EGFR were more likely to have a baseline CD4 count of 201 to 350 cells/ $\mu$ L (aOR = 1.35; 95% CI 1.00-1.83). Individuals experiencing attrition or TFO were less likely to have started ART in 2015 (aOR = 0.60 95% CI: 0.46-0.79) as opposed to 2014; less likely to be aged 36-45 years (aOR = 0.72 95% CI: 0.55-0.97) or  $> 45$  years (aOR = 0.49 95% CI: 0.33 0.72) as opposed to  $\leq 35$  years and more likely to be treated at Metro 2 clinic (aOR = 1.46; 95% CIs 1.09-1.95) rather than at Metro 1.

### **Discussion**

This is one of the first papers to evaluate the association between baseline CD4 count and renal dysfunction in a cohort of individuals routinely starting ART regardless of CD4 count in a high-burden programmatic setting. This study showed low baseline prevalence rate of

EGFR <60mL/min (1.9%) similar to a large published study from Zambia (22) Also similar to previous studies, (10, 13, 23) this study showed lower baseline prevalence of renal dysfunction at baseline CD4 counts >200 cells/ $\mu$ L and amongst older individuals. Notably, this study showed no significant difference in prevalence rate of baseline EGFR <60mL/min between different categories in individuals with baseline CD4 counts >200 cells/ $\mu$ L. Comparison of both the prevalence rate of baseline EGFR <60mL/min and the incidence of EGFR <60mL/min after ART initiation between this study and other published studies was hampered by extensive heterogeneity of definition for renal dysfunction across studies.

The overall incidence rate of EGFR<60mL/min (1.9 cases/100PY) was lower than that reported in a previous study (5.9 cases/100PY) with a lower baseline median CD4 count that reported the same endpoint. (13) In contrast to previous studies, (7, 14) this study did not show an association between baseline CD4 count and average EGFR or renal dysfunction after ART initiation when adjusting for key baseline characteristics. Notably, analysis of incident EGFR <60mL/min -restricted to individuals with a normal baseline renal function- showed a low incidence rate of EGFR <60mL/min 1.1 cases/100PY (95% CI: 0.6-1.8) and no incident cases amongst individuals with baseline CD4 counts >500 cells/ $\mu$ L. As in previous studies, this study showed baseline renal dysfunction to be a very strong predictor of on ART renal dysfunction. (10, 13, 22)

Overall the results of this study show a small decline in EGFR after ART initiation with low baseline prevalence and on ART incidence of EGFR<60mL/min in a cohort of individuals started on tenofovir. Monitoring of renal function in high-burden settings is challenging. (10, 24) Tenofovir continues to be widely used for first line ART in high-burden regions and in the absence of an affordable alternative, strategies to improve EGFR monitoring in individuals on tenofovir are a priority (2, 17)

Tenofovir alafenamide (TAF) is a tenofovir prodrug, now available in the developed world, with reported lower risk of renal toxicity, (25, 26) and routine access to TAF in high-burden settings may greatly reduce the need for renal monitoring on ART. There are, however, concerns related to this approach, as TAF interacts with rifampicin used for TB treatment. Further research into its efficacy and safety in contexts with high rates of HIV and TB coinfection are required. (2, 27)



Despite a well-established ART service in the Western Cape since 2014, and the provision of ART regardless of CD4 count in the PopART intervention since January 2014, a significant proportion (26%) of this cohort presented with baseline CD4 counts  $<200$  cells/ $\mu$ L. These data suggest that ART regardless of CD4 count, with increased numbers of individuals starting ART at higher CD4 counts, will have a positive impact on baseline renal function amongst individuals starting ART, and interventions to reduce the number of individuals starting ART late at low CD4 counts should be further strengthened. Although these data did not show an association between baseline CD4 count and renal dysfunction in the primary analysis, the absence of incident renal dysfunction amongst individuals with baseline CD4  $>500$  cells in analysis restricted to individuals with normal baseline renal function, is promising and should be further evaluated in larger studies.

Management of renal function on ART is further challenged by limited access to laboratory services in resource-limited settings and further research to evaluate the potential of more accessible of point of care technology for monitoring renal function are urgently needed. (24) In settings where relevant laboratory services are available, non-adherence to EGFR monitoring is widely reported. (24) Development of risk matrices for renal dysfunction amongst individuals starting ART to guide more focused implementation of EGFR monitoring as part of differentiated models of care may be an effective approach to improving EGFR monitoring, (28) and should be the subject of implementation research.

### **Strengths and weaknesses**

This study presents high-quality routine data from three clinics providing ART regardless of CD4 count, ahead of recent changes in WHO and in-country ART guidelines. The routine data used also benefited from data quality improvement interventions during the PopART intervention. The study has been a joint undertaking between researchers and clinical staff ensuring that the analysis and interpretation of the data correctly reflect clinical activities. The study does, however, have a number of weaknesses for consideration. There were significant amounts of missing data and attrition from ART care. Individuals excluded because of missing baseline EGFR were more likely to have baseline higher CD4 counts and inclusion of these individuals in the study sample could have resulted in decreased rates of renal dysfunction being reported. Individuals experiencing attrition or TFO were more likely to be aged  $<35$  years which may have exaggerated the observed lower renal dysfunction in

these age groups seen in the multivariate analyses. Extrapolation of these findings is also decreased by limited follow-up person time with several findings, such as the association between baseline CD4 count and incident EGFR<60mL/min, of borderline statistical significance.

### **Conclusion**

In conclusion, this study showed lower prevalence of baseline EGFR<60mL/min at higher CD4 counts and no association between baseline CD4 count and incident on ART EGFR<60 mL/min. Overall incidence of EGFR<60ml/min on ART was low; analysis restricted to individuals with normal baseline EGFR, however, promisingly showed no incident on ART EGFR<60mL/min amongst individuals with baseline CD4 count >500 cells/ $\mu$ L. Differentiated models of care that identify individuals starting ART, who are at high risk of renal dysfunction, for enhanced EGFR monitoring and alternative ART regimens may be more effective than the current one size fits all approach. At the same time improved access to suitable affordable alternatives to tenofovir, should be further evaluated in high-burden settings.

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## Tables and figures

Table 1: Baseline characteristics

		cells / $\mu$ L	0 to 200	201 to 350	351 to 500	>500	Total	P value
Baseline CD4 category		N(%)	631 (26.0)	708 (29.2)	582 (24.0)	502 (20.7)	2423	
Age (Years)	Median	(IQR)	33 (29.0-40.0)	31 (25.0-37.0)	31 (26.0-37.0)	30 (25.0-37.0)	31 (26.0-38.0)	<0.001
Age category (years)	18-25	N(%)	79 (12.5)	179 (25.3)	142 (24.4)	134 (26.7)	534 (22.0)	<0.001
	26-35	N(%)	312 (49.6)	311 (43.9)	272 (46.7)	227 (45.2)	1122 (46.3)	
	36-45	N(%)	167 (26.5)	138 (19.5)	109 (18.7)	87 (17.3)	501 (20.7)	
	46-55	N(%)	57 (9.0)	63 (8.9)	46 (7.9)	44 (8.8)	210 (8.7)	
	>55	N(%)	17 (2.7)	17 (2.4)	13 (2.2)	10 (2.0)	57 (2.3)	
Gender	Female	N(%)	361 (56.4)	467 (65.4)	425 (72.5)	408 (80.5)	1661 (67.9)	P<0.001
	Male	N(%)	279 (43.6)	247 (34.6)	161 (27.5)	99 (19.5)	786 (32.1)	
Pregnant at ART start	Yes	N(%)	14 (3.9)	39 (8.4)	41 (9.7)	48 (11.9)	142 (8.6)	P<0.001
Baseline TB	Yes	N(%)	162 (25.7)	56 (7.9)	41 (6.7)	26 (5.2)	285 (11.8)	P<0.001
Clinic	Metro 1	N(%)	88 (13.9)	113(15.9)	126 (21.7)	127 (25.3)	454 (18.7)	P<0.001
	Metro 2	N(%)	299 (47.4)	301 (42.5)	231 (39.7)	191 (38.1)	1022 (42.2)	
	Rural 1	N(%)	244 (38.7)	294 (41.5)	225 (38.7)	184 (36.7)	947 (39.1)	
Previous ART>3mths	Yes	N(%)	27 (4.3)	10 (1.4)	7 (1.2)	5 (1.0)	49 (2.0)	P = 0.005
ART start year	2014	N(%)	161 (25.5)	208 (29.4)	160 (27.5)	161 (32.1)	690 (28.5)	P = 0.091
	2015	N(%)	470 (74.2)	500 (70.6)	422 (72.5)	341 (67.9)	1733 (71.5)	
Baseline EGFR (mL/min)	Median	(IQR)	106.7 (89.5-130.6)	110.6 (94.3-129.7)	111.1 (93.1-131.7)	112.9 (96.5-134.1)	110.5 (93.5-131.9)	P = 0.0186
	<60	N(%)	24 (3.8)	14 (1.9)	4 (0.7)	5 (1.0)	47 (1.9)	<0.001
	60 - 89	N(%)	114 (18.1)	106 (14.9)	100 (17.2)	74 (14.7)	394 (16.3)	
	>90	N(%)	399 (63.3)	56 (71.4)	418 (71.8)	377 (75.1)	1700 (70.2)	
	Missing	N(%)	93 (14.8)	83 (11.7)	60 (10.3)	46 (9.2)	282 (11.6)	

\*This table includes all 2423 participants included in the study sample. Chi squared and Kruskal Wallis tests were used to measure heterogeneity of baseline characteristics across the baseline CD4 categories Overall there is significant heterogeneity across baseline CD4 categories. \*\*\* American Kidney Foundation definitions were used for defining renal function by EGFR. EGFR <60 mL/min = Moderate and severe renal dysfunction) EGFR 60 to 89 mL/min= Mild renal dysfunction EGFR >90 mL/min = Normal renal function

**Table 2: Logistic regression of baseline characteristics association with baseline EGFR <60mL/min**

		<b>Crude odds ratio (95% CI)</b>	<b>Adjusted odds ratio (95% CI)</b>
<b>Baseline CD4 (cells/<math>\mu</math>L)</b>	>500	0.19 (0.07-0.56)	0.29 (0.11-0.8)
	351-500	0.17 (0.06-0.47)	0.22 (0.08-0.59)
	201-350	0.38 (0.18-0.83)	0.48 (0.24-0.97)
	101-200	1	1
<b>Gender</b>	Male	2.99 (1.68-5.34)	1.99 (1.08-3.66)
	Female	1	1
<b>Age at ART start (years)</b>	18-35	1	1
	36-45	4.14 (2.04-8.41)	3.38 (1.64-6.95)
	>45	7.39 (3.59-15.21)	6.40(3.06-13.37)
<b>Clinic</b>	Metro 1	1	1
	Metro 2	1.68 (0.87-3.25)	1.96 (0.93-4.11)
	Rural	1.68 (0.76-3.69)	1.84 (0.77-4.39)
<b>Baseline TB</b>	TB	1.55 (0.84-2.88)	0.97 (0.5-1.87)
<b>Previous ART&gt;3mths</b>	Yes	1.03 (0.14-7.64)	0.86 (0.11-6.68)
<b>Year of ART start</b>	ART2014		
	ART2015	1.08 (0.59-2.00)	1.21 (0.59-2.48)

Includes 2014 non-pregnant, individuals with recorded baseline CD4 count and baseline EGFR. Women pregnant at baseline were excluded due to changes in EGFR associated with pregnancy. Age category 18 to 25 and 26 to 35 were combined and age category 46 to 55 and >55 were combined for the regression analysis due to collinearity between age categories 18 to 25 and >55 years with the dependant variable.



**Figures 1a to 1d: Two way scatter plots of EGFR mL/min over time on ART**

(● Estimated EGFR — Fitted values)

Figure 1a: All participants

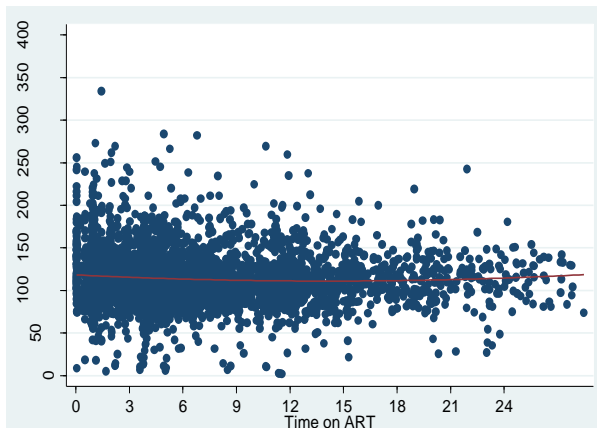


Figure 1b: Participants with baseline EGFR  $\geq 90$  mL/min

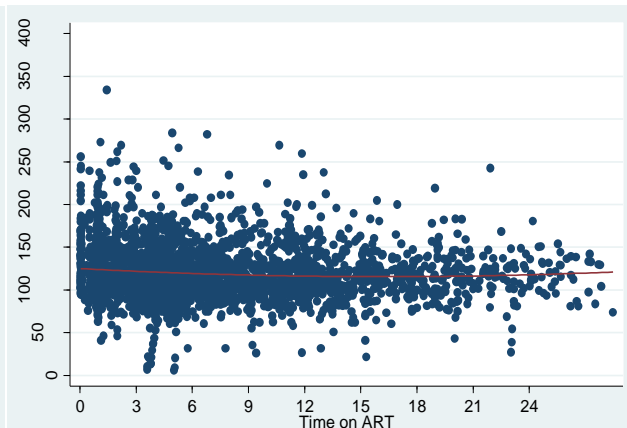


Figure 1c: Participants with baseline EGFR 60 to 89 mL/min

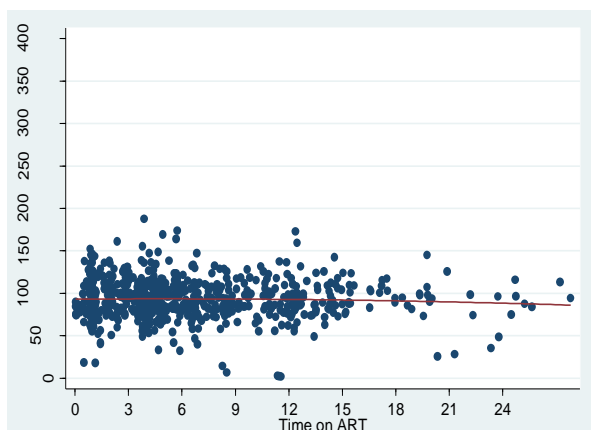
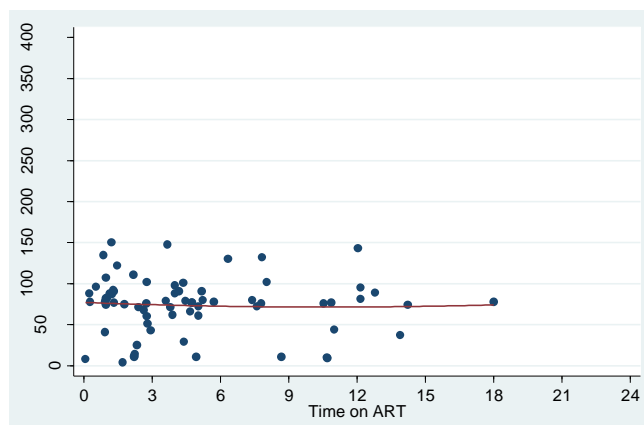


Figure 1d: Participants with baseline EGFR  $< 60$  mL/min

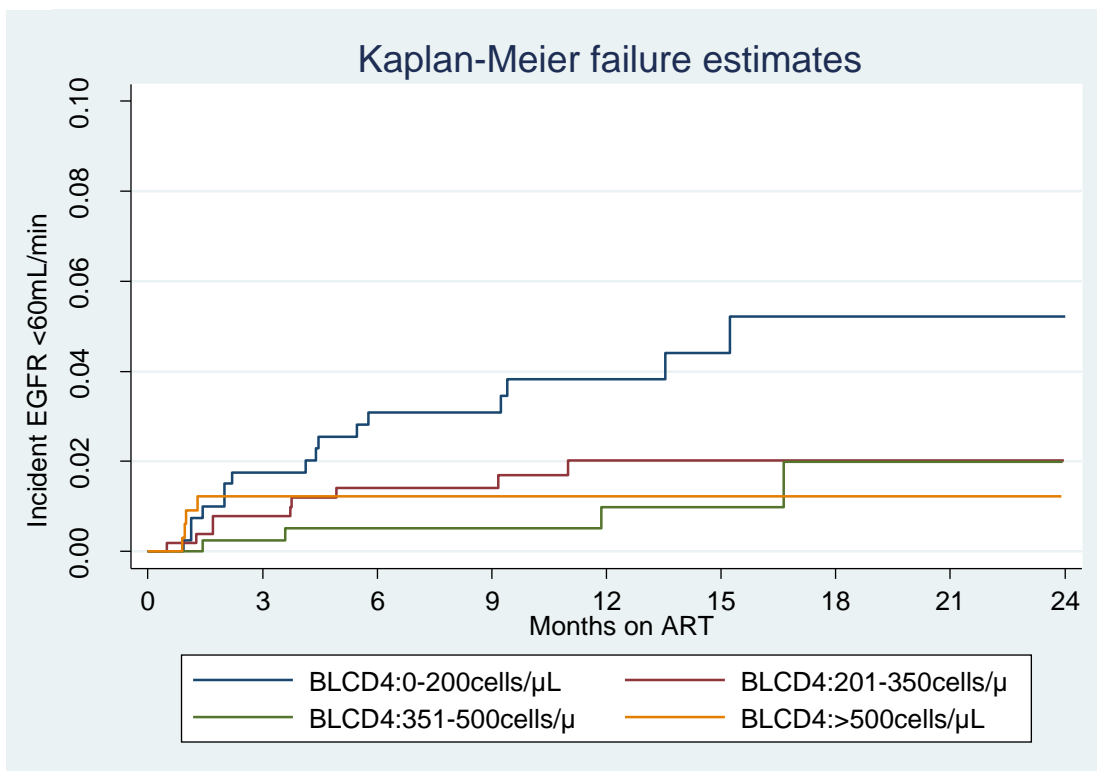


**Table 3: Mixed effects linear regression of mean on ART EGFR**

<b>Estimated EGFR</b>		<b>Crude coefficient (95% CI)</b>	<b>Adjusted coefficient (95% CI)</b>
<b>Baseline CD4 (cells/<math>\mu</math>L)</b>	>500	2.72(-1.3-6.74)	-0.79(-4.38-2.8)
	350 - 500	1.94(-1.93-5.81)	-0.13(-3.56-3.29)
	200 - 350	1.28(-2.4-4.97)	-0.17(-3.42-3.08)
	0 - 200	1	1
<b>Baseline EGFR (mL/min)</b>	<60	-27.08(-30.26 to-23.91)	-37.49(-46.46 to-28.52)
	60 - 90	-44.46(-53.74 to-35.17)	-22.47(-25.60 to-19.34)
	>90	1	1
<b>Gender</b>	Male	-4.65(-7.57 to-1.73)	1.27(-1.42-3.96)
	Female	1	1
<b>Age category (years)</b>	18-35	1	1
	36-45	-22.35(-26.48 to-18.22)	-10.3(-13.36 to-7.25)
	>45	25.99(20.51-31.47)	-13.3(-17.22 to-9.38)
<b>Pregnant at baseline</b>	Yes	25.99(20.51-31.47)	20.56(15.57-25.55)
<b>Clinic</b>	Metro 1	1	1
	Metro 2	-7.43(-10.45--4.4)	-6.80(-9.92 to-3.67)
	Rural 1	-2.15(-5.77-1.48)	-2.09(-5.69-1.52)
<b>Baseline TB</b>	Yes	1.67(-1.63-4.97)	-6.71(-17.38-3.96)
<b>Previous ART of &gt;3 months</b>	Yes	-10.44(-22.63-1.75)	2.45(-0.52-5.42)
<b>Year ART start</b>	2014	1	1
	2015	2.29(-0.56-5.13)	-1.67(-4.68-1.35)
<b>Months on ART</b>		-0.36(-0.51 to-0.21)	-0.36(-0.52 to-0.2)

Modelling includes 1772 individuals with reported baseline and on ART EGFR including pregnant women. The individual unique identifier was used as the panel variable. For categorical variables the coefficient represents the difference in mean EGFR in mL/min from baseline compared to the reference category.

**Figure 2: Kaplan Meier estimates of EGFR<60mL/min on ART in participants with baseline EGFR ≥ 60mL/min**



Includes 1651 individuals with baseline EGFR ≥60mL/min Log rank test for difference in KP estimates by CD4 category: P= 0.011

**Table 4: Incident EGFR<60mL/min on ART amongst by baseline EGFR category**

	Baseline CD4 count (cells/ $\mu$ L)	All baseline EGFR	Baseline EGFR $\geq$ 60mL/min	Baseline EGFR $\geq$ 90mL/min
<b>Sample size</b>	N	1665	1651	1401
<b>Number of incident cases</b>	N	33	27	15
<b>Person Years</b>	PY	1749	1722	1421
<b>IR</b>	0 to 200	3.8 (2.3-6.2)	3.2 (1.8-5.5)	2.5 (1.2-4.9)
	201 to 350	1.6 (0.9-3.1)	1.1 (0.5-2.5)	0.9 (0.3-2.4)
	301-500	0.9 (0.4-2.5)	0.9 (0.4-2.5)	0.9 (0.3-2.7)
	>500	1.1 (0.4-2.9)	1.1 (0.4-3)	0 (0-0)
	All	1.9 (1.3-2.6)	1.6 (1.1-2.3)	1.1 (0.6-1.8)

PY: Person Years. IR: Incidence rate. Baseline EGFR cut offs were selected to align to American Kidney Foundation definitions; EGFR $\geq$ 60mL/min= normal EGFR or mild renal impairment and EGFR $\geq$ 90mL/min = normal renal function.

**Table 5: Cox regression of baseline factors associated with incident EGFR <60mL/min on ART amongst individuals with baseline EGFR  $\geq$ 60 mL/min**

		<b>Crude hazard ratio (95%CI)</b>	<b>Adjusted hazard ratio (95% CI)</b>
<b>Baseline CD4</b>	>500	0.36(0.12-1.11)	0.41(0.13-1.3)
<b>Baseline EGFR (mL/min)</b>	351 - 500	0.3(0.1-0.92)	0.35(0.11-1.1)
	201 - 350	0.35(0.13-0.93)	0.38(0.14-1.03)
	0 - 200	1	1
	60 - 89	3.46(1.62-7.39)	2.62(1.17-5.83)
	>90	1	1
<b>Gender</b>	Male	1.46(0.68-3.15)	1.08(0.48-2.42)
	Female	1	1
<b>Age category(years)</b>	18 - 35	1	1
	36 - 45	1.63(0.61-4.35)	1.24(0.46-3.39)
	>45	4.33(1.83-10.29)	3.25(1.30-8.14)
<b>Clinic</b>	Metro 1	1	1
	Metro 2	0.86(0.37-2.01)	0.74(0.26-2.12)
	Rural 1	0.74(0.25-2.17)	0.68(0.19-2.39)
<b>Baseline TB</b>	Yes	1.61(0.7-3.67)	1.27(0.54-3.04)
<b>Previous ART of &gt;3 months</b>	Yes	3.2(0.43-23.61)	1.77(0.23-13.77)
<b>Year ART start</b>	2014	1	1
	2015	1.07(0.47-2.44)	0.89(0.31-2.57)

Non pregnant Individuals with baseline EGFR<60ml/min were excluded from analysis and the model includes 1651 individuals with reported baseline EGFR $\geq$  60 mL/min. Women pregnant at baseline were excluded due to changes in EGFR associated with pregnancy. The multivariate model showed good fit ( $P<0.001$ ). The baseline category with the largest sample size was used as the reference. There were no incident EGFR<60mL/min cases amongst individuals reported pregnant at baseline therefore this data variable was omitted from regression analysis. Age categories 46 to 55 years and >55 years were combined as >45 years due to limited sample size.

## Chapter 7: Baseline CD4 Count and Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis.

**Citation:** Bock P, James A, Nikuze A, Peton N, Sabapathy K, Mills E, et al. Baseline CD4 Count and Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *J Acquir Immune Defic Syndr.* 2016 Dec 15;73(5):514-21.

### Study design overview

This study was a systematic review and meta-analysis that evaluated the association between baseline CD4 count and ART adherence in published research studies. The study was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. For completion of the study we reviewed all English language journal articles, published between January 2004 and September 2015, listed in Medline, Web of Science, LILACS, AIM, IMEMR and WPIMR databases; as well as available conference presentations from key HIV conferences published between 2012 to 2015. The study addressed the following PhD objective:

To evaluate through completion of a systematic review and meta-analysis of published literature the association between baseline CD4 count and adherence to ART.

**Table 6: ART adherence systematic review outline**

Primary outcome	Study design	Review period	Primary inclusion criterion	Data sources
ART adherence	Systematic review of published literature	English language studies published between January 2004 and September 2015. Conference abstracts published from 2012 to 2015.	Studies that reported directly on the association between baseline CD4 count and ART adherence	Medline, Web of Science, LILACS, AIM, IMEMR and WPIMR databases as well as available conference presentations from key HIV conferences

### Author contribution

I conceptualised the design of this systematic review and meta-analysis in partnership with NF. I was responsible for the primary review of the literature which was then duplicated by AN, and/or AJ. I worked with NF to complete the statistical analysis. I coordinated development and finalisation of the manuscript for journal submission and publication. All



authors have contributed to development of the manuscript and have approved the version accepted for publication.

# Baseline CD4 Count and Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis

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**Background:** In light of recent changes to antiretroviral treatment (ART) guidelines of the World Health Organization and ongoing concerns about adherence with earlier initiation of ART, we conducted a systematic review of published literature to review the association between baseline (pre-ART initiation) CD4 count and ART adherence among adults enrolled in ART programs worldwide.

**Methods:** We performed a systematic search of English language original studies published between January 1, 2004 and September 30, 2015 using Medline, Web of Science, LILACS, AIM, IMEMR, and WPIMR databases. We calculated the odds of being adherent at higher CD4 count compared with lower CD4 count according to study definitions and pooled data using random effects models.

**Results:** Twenty-eight articles were included in the review and 18 in the meta-analysis. The odds of being adherent was marginally lower for patients in the higher CD4 count group (pooled odds ratio, 0.90; 95% confidence interval, 0.84 to 0.96); however, the majority of studies found no difference in the odds of adherence when comparing CD4 count strata. In analyses restricted to comparisons above and below a CD4 count of 500 cells per microliter, there was no difference in adherence (pooled odds ratio, 1.01; 95% confidence interval: 0.97 to 1.05).

**Conclusions:** This review was unable to find consistent evidence of differences in adherence according to baseline CD4 count. Although this is encouraging for the new recommendations to treat all HIV-positive individuals irrespective of CD4 count, there is a need for additional high-quality studies, particularly among adults initiating ART at higher CD4 cell counts.

**Key Words:** adherence, antiretroviral therapy, CD4 count, HIV

(*J Acquir Immune Defic Syndr* 2016;73:514–521)

## INTRODUCTION

There are 37 million people living with HIV (PLHIV) and more than 17 million people on antiretroviral treatment (ART) globally.<sup>1</sup> In 2015, after the publication of findings from 2 large randomized trials indicating the clinical benefit of starting ART at any CD4 cell count, the World Health Organization (WHO) issued updated guidelines recommending that ART should be started in all HIV-infected adults regardless of CD4 count or WHO stage.<sup>2–6</sup> Current UNAIDS targets for HIV treatment scale-up are for 90% of PLHIV to know their HIV status, 90% of those who know their status to be on ART, and 90% of those on ART to be virally suppressed.<sup>7</sup> Achieving these targets will require rapid further scale-up of testing and ART initiation and excellent adherence to treatment. Although many factors are known to influence adherence,<sup>8</sup> one frequently raised concern in the context of new WHO guidelines is the possibility that individuals starting ART at higher CD4 counts when generally clinically well may have lower adherence rates.<sup>9,10</sup>

Although there is strong evidence from individual-level, randomized, controlled trials for increased patient benefit when routinely initiating ART at CD4 counts greater than 500 cells per microliter, there is limited data informing how ART for all PLHIV will play out in programmatic settings, where the numbers of individuals receiving care and level of resources directed at retaining patients and maximizing adherence is likely to differ from well-resourced randomized trials. Concern has been expressed about potential increases in loss to follow-up, ART nonadherence, sexual disinhibition, and viral resistance among individuals starting treatment earlier, particularly in high-prevalence regions where health facilities are often overburdened.<sup>11,12</sup>

In light of steadily increasing number of adults starting ART at higher CD4 counts when clinically well and recent changes to WHO ART guidelines, we conducted a systematic

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P.B., A.N., and A.J. conducted searches. P.B. and N.F. completed the meta-analysis. All authors have contributed to design and development of the manuscript. All authors have approved the version submitted to the journal. Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site ([www.jaids.com](http://www.jaids.com)).

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review of the published literature that reported the association between baseline CD4 count and adherence among adult patients enrolled in ART programs worldwide.

## METHODS

### Eligibility

As we were interested in the relationship between baseline CD4 count and adherence in routine program settings, controlled trials were excluded from review. The age of 15 years was used for eligibility because this is the commonly used age cutoff for the management of ART patients at the “adult clinic” for clinical reasons, including drug formulation and dosage. Studies reporting on women starting ART for the prevention of mother-to-child transmission, and use of antiretrovirals for preexposure prophylaxis were also excluded because adherence trends in these populations are not representative of the general population initiating ART.<sup>13,14</sup>

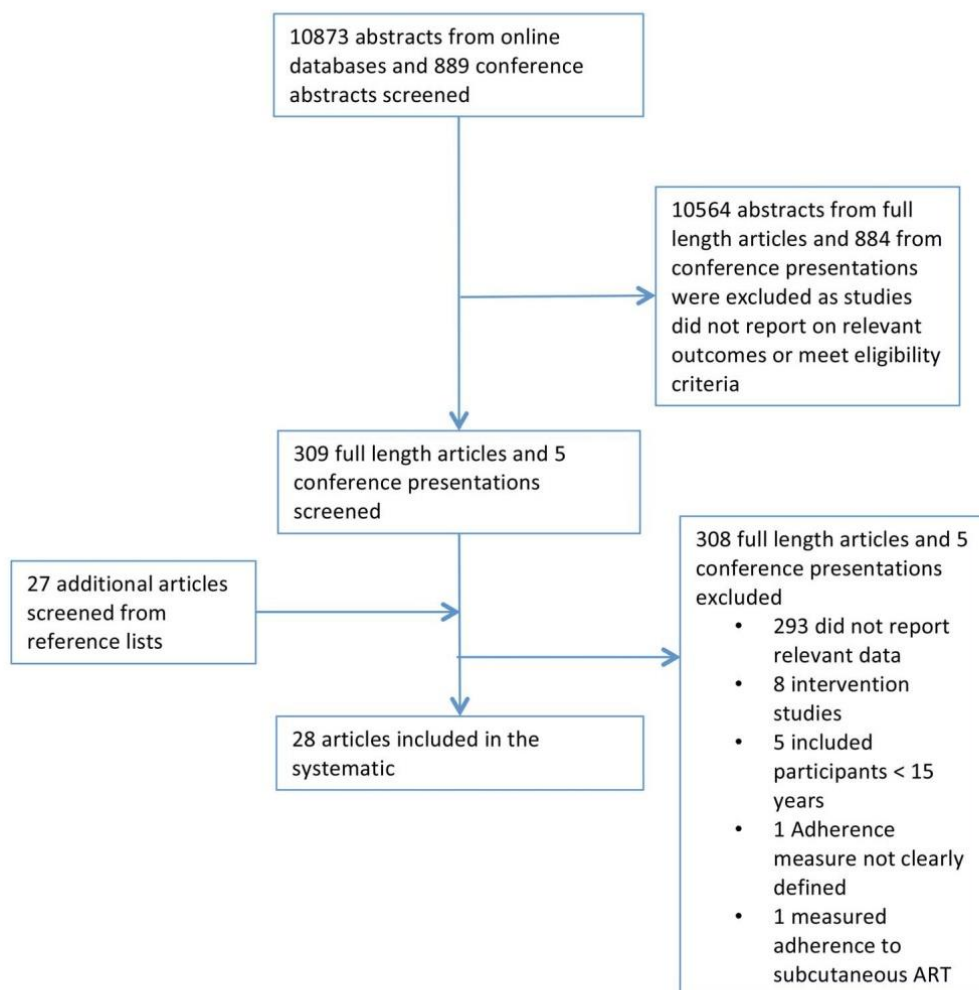
### Search Strategy and Study Selection

This study has been designed and reported according to the Preferred Reporting Items for Systematic Reviews

and Meta-Analysis (PRISMA) statement.<sup>15</sup> We performed a systematic search of English language, original studies published between January 1, 2004 and September 30, 2015 for studies reporting on ART adherence among adults aged  $\geq 15$  years according to baseline CD4 count. A limit of January 2004 was used to align with the start of the ART rollout in public health systems in many high-burden countries. Baseline CD4 count was defined as the most recent CD4 count reported before initiating ART and the publishing authors definition of adherence was used for each included study. Medline, Web of Science, LILACS, AIM IMEMR, and WPIMR databases were searched using a compound search strategy incorporating terms for antiretrovirals, adherence, and CD4 count defined in a study protocol (available from the corresponding author). Published abstracts from all Conferences of the International AIDS Society and the Conference on Retroviruses and Opportunistic Infections were searched from 2011 to 2015 to identify data that may have been presented but not yet published in full.

### Selection of Studies and Data Extraction

The primary investigator (P.B.) conducted all searches and reviewed all relevant abstracts, conference presentations,



**FIGURE 1.** Study selection process.

and full-length articles. All steps in the search process were verified by a second investigator (A.N. or A.J.) (Fig. 1). Disagreements were resolved through consensus. Data extraction followed the same verification procedure, and it included patient and program characteristics according to a predefined data extraction form. Where studies reported both subjective and objective measures of adherence, the objective measure was used based on the assumption that this was likely to be more accurate. Risk of bias was assessed by the assessment of the following criteria: (1) objective versus subjective adherence measure, (2) baseline differences (other than CD4 count) balanced or adjusted for at analysis, (3) prospective versus retrospective or cross-sectional study design, and (4) and nondifferential loss to follow-up with respect to likelihood of being adherent. We used GRADE to assess the overall quality of the evidence.<sup>16</sup>

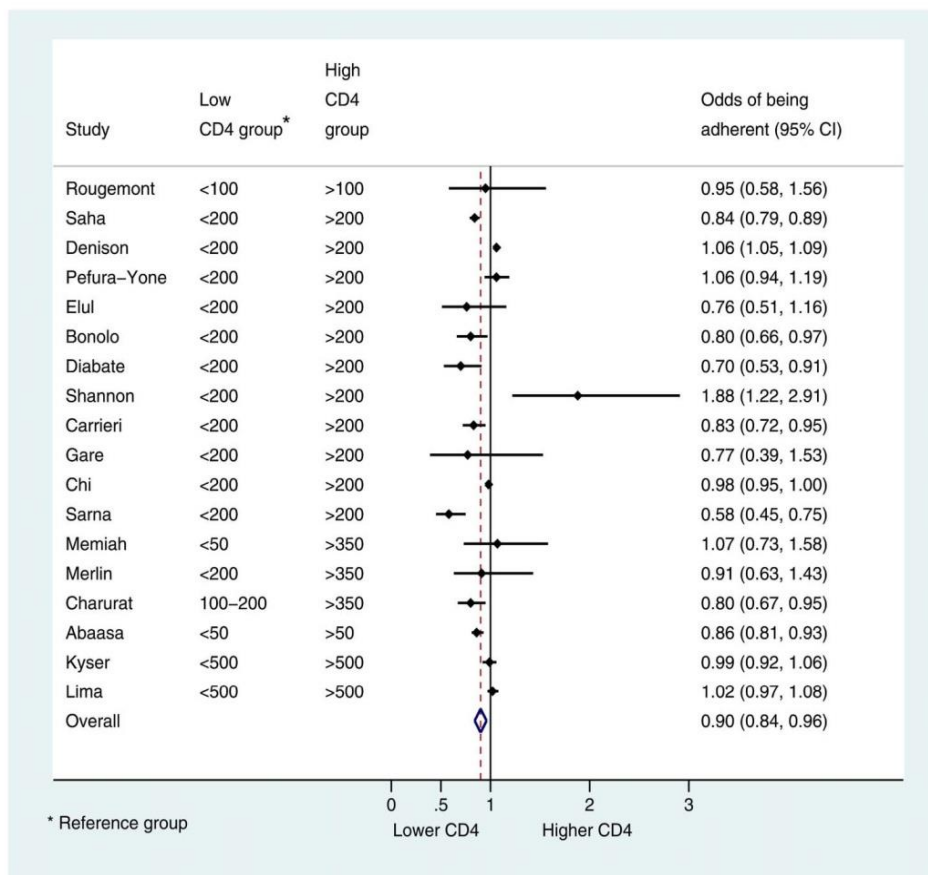
**Data Analysis**

Our primary effect measure was the odds of being adherent at higher CD4 count compared with lower CD4 count as defined by the studies. Studies that provided raw data on the number of adherent patients or odds ratios (ORs) for adherence by CD4-cell count strata were included in a meta-analysis that estimated ORs and corresponding 95% confidence intervals (CIs) comparing adherence at lower and higher CD4 counts at baseline; data were pooled using a DerSimonian and Laird<sup>17</sup> random effects model. Where studies reported multiple CD4 count group comparisons, we

included data from the comparison of the lowest and highest CD4 count groups. Where studies reported ORs adjusted for potential confounders, these estimates were used; otherwise, crude estimates were used as indicated in Figure 2. Because the *I*<sup>2</sup> statistic does not work well with observational studies,<sup>18</sup> heterogeneity was assessed by visual inspection of forest plots. Predefined subgroup analyses were run to explore potential differences by income status (as defined by World Bank Income Classification)<sup>19</sup>; we further undertook a post hoc subgroup analysis to assess the potential influence of the 2010 WHO guideline change in treatment eligibility (from CD4 200 cells/μL to 350 cells/μL) by assessing differences before and after 2010. We used STATA version 12.0 (StataCorp LP, College Station, TX) for all analysis. All *P* values were 2 sided, with a *P* value less than 0.05 regarded as statistically significant.

**RESULTS**

From an initial screen of more than 10,873 abstracts, 27 full-length articles met the inclusion criteria<sup>20-46</sup>; 1 additional article was identified from bibliography screen,<sup>47</sup> yielding 28 articles in total included in this review (Fig. 1 and Table 1). The majority of studies (18) were from low-income and middle-income countries.<sup>20-22,24,25,27-30,33-35,40-44,46</sup> Studies provided data for 72,119 participants, sample sizes ranged from 76 to 3700 adults, with 31,011 men and 40,669 women included (1 study did not disaggregate data by sex).<sup>46</sup> Median baseline CD4 count ranged from 104 to 486 cells per microliter and was



**FIGURE 2.** Forest plot of the odds of being adherence when comparing patients who started ART in the higher CD4 category with those who start ART in the lower baseline CD4 category.



**TABLE 1.** Overview of Review Studies

First Author	Publication Year	Country	Study Type	No. Participants	Period of Initiating ART
Abaasa <sup>20</sup>	2008	Uganda	Retrospective cohort	897	2004–2006
Bonolo Pde <sup>21</sup>	2005	Brazil	Prospective cohort	306	Not indicated
Byakika-Tusiime <sup>22</sup>	2013	Uganda	Prospective cohort	76	2002–2007
Carrieri <sup>23</sup>	2006	France	Prospective cohort	1110	1997–1999
Charurat <sup>24</sup>	2010	Nigeria	Retrospective cohort	5760	2005–2006
Chi <sup>25</sup>	2009	Zambia	Retrospective cohort	37,039	2004–2007
Conen <sup>26</sup>	2013	Switzerland	Retrospective cohort	2928	2005–2012
Deloria-Knoll <sup>47</sup>	2004	United States	Cross-sectional survey within cohort	255	March–Nov 1999
Denison <sup>27</sup>	2015	Tanzania, Uganda, and Zambia	Cross-sectional survey within cohort	4489	2004–2010
Diabate <sup>28</sup>	2007	Côte d'Ivoire	Prospective cohort	591	2005
Elul <sup>29</sup>	2013	Rwanda	Cross-sectional survey within cohort	1951	2002–2007
Gare <sup>30</sup>	2015	Papua New Guinea	Cross-sectional survey within cohort	102	2004–2011
Kyser <sup>31</sup>	2011	United States	Retrospective cohort	528	2004–2006
Lima <sup>32</sup>	2015	Canada	Retrospective cohort	4120	2000–2012
Maqutu <sup>33</sup>	2010	South Africa	Retrospective cohort	688	2004–2006
Maqutu <sup>34</sup>	2011	South Africa	Retrospective cohort	688	2004–2006
Memiah <sup>35</sup>	2013	Nigeria, Uganda, Zambia, and Tanzania	Cross-sectional survey within cohort	2344	2004–2005
Merlin <sup>36</sup>	2012	United States	Retrospective cohort	1521	2007–2011
Moore <sup>37</sup>	2010	Canada	Retrospective cohort	1707	2000–2006
Murphy <sup>38</sup>	2013	United States	Retrospective cohort	2090	1994–2002
Palepu <sup>39</sup>	2006	Canada	Retrospective cohort	276	1996–2003
Pefura-Yone <sup>40</sup>	2013	Cameroon	Cross-sectional survey within cohort	889	Before 2011
Ramadhani <sup>41</sup>	2007	Tanzania	Retrospective cohort	150	2005
Rougemont <sup>42</sup>	2009	Cameroon	Prospective cohort	312	2006
Saha <sup>43</sup>	2014	India	Cross-sectional survey within cohort	370	2005–2006
Sarna <sup>44</sup>	2008	India	Cross-sectional survey within cohort	310	2004
Shannon <sup>45</sup>	2006	Canada	Retrospective cohort	184	Before 2002
Weiser <sup>46</sup>	2014	Uganda	Prospective cohort	438	2005–2010

First Author	Minimum Age of Participant (yrs)	Median Age of Participant (yrs)	Median Baseline CD4 Cell Count (Cells/mL)	Adherence Measure	Adherence Cutoff (%)	Overall Reported Adherence (%)
Abaasa <sup>20</sup>	15	37	Not indicated	Self report: VAS and pill count	95	78
Bonolo Pde <sup>21</sup>	18	Not indicated	Not indicated	Self report: 3 d recall	95	Not indicated
Byakika-Tusiime <sup>22</sup>	15	36	56	Self report: VAS and number of doses missed	Linear	96
Carrieri <sup>23</sup>	Not indicated	37	Not indicated	Self report: 4 d recall	100	63
Charurat <sup>24</sup>	Not indicated	35	121	Pharmacy pill count	95	25
Chi <sup>25</sup>	15	Not indicated	132	MPR based on pharmacy pill count	100	63
Conen <sup>26</sup>	16	39	269	Unscheduled treatment interruption	No interruption ≥7 mo	85
Deloria-Knoll <sup>47</sup>	Not indicated	41	229 and 234	Self report: 3 d recall	Not indicated	NA
Denison <sup>27</sup>	18	40	Not indicated	Self report: treatment interruption	No interruption ≥48 h	96.8
Diabate <sup>28</sup>	Not indicated	36 to 39	124	Self report: 4 d recall	95	74
Elul <sup>29</sup>	18	38	130 to 221	Self report: 3 and 30 d recall	100	94 and 78 at 3 and 30 d
Gare <sup>30</sup>	20	Not indicated	264	Self report: 1 mo and pill count	100	82
Kyser <sup>31</sup>	18	41	486	Self report: 3 d recall	95	84
Lima <sup>32</sup>	19	42	Not indicated	Pharmacy pill count	95	70 to 80
Maqutu <sup>33</sup>	Not indicated	32.5	108	Pharmacy pill count	95	79

*(continued on next page)*



**TABLE 1.** (Continued) Overview of Review Studies

First Author	Minimum Age of Participant (yrs)	Median Age of Participant (yrs)	Median Baseline CD4 Cell Count (Cells/mL)	Adherence Measure	Adherence Cutoff (%)	Overall Reported Adherence (%)
Maqutu <sup>34</sup>	Not indicated	32.5	107	Pharmacy pill count	95	58 at 1 mo to 86 at 17 mo
Memiah <sup>35</sup>	16	38	227	Self report: 7 d recall	95	76
Merlin <sup>36</sup>	19	44	NA	Self report: 2 wk recall	100	71
Moore <sup>37</sup>	18	39 to 43	150 and 170	Unscheduled treatment interruption -3 mo	No interruption $\geq 3$ mo	61 to 81
Murphy <sup>38</sup>	18	39 to 41	206 to 221	Self report	95	73–80 across race groups
Palepu <sup>39</sup>	Not indicated	35.3 to 36.3	270 and 229	Pharmacy pill count	95	50
Pefura-Yone <sup>40</sup>	18	40	122	Self report: case index	Case index score $>10$	78
Ramadhani <sup>41</sup>	18	41	114	Self report: questionnaire	100	16
Rougemont <sup>42</sup>	18	37	104	Pharmacy pill count	100	85
Saha <sup>43</sup>	18	34	241	Self report: 4 d recall	100	88
Sarna <sup>44</sup>	18	36 to 39	Not indicated	Self report: 4 d recall	90	93
Shannon <sup>45</sup>	16	42	270	Pharmacy pill count	95	30
Weiser <sup>46</sup>	18	38	137	Self report: VAS	90	61

MPR, medicine possession ratio; VAS, visual analogue scale.

$<200$  cells per microliter for 12 studies.<sup>21,23,25,27 31,40,43 45</sup> Twenty-seven studies reported adherence as a binary outcome and one as a linear outcome, detail of which is presented in Table 1.<sup>22</sup> Twelve used  $<95\%$  adherence to antiretroviral doses as a threshold for poor adherence, 2 used  $<90\%$ , and 8 used  $<100\%$ . Three studies reported on unscheduled treatment interruption of 2 days, 7 days, and 3 months, respectively.<sup>26,27,37</sup> One cross-sectional study used a case index score generated by a questionnaire of greater than “10” to generate a binary definition of adherence versus nonadherence (case index score  $<10$ ).<sup>40</sup> None of the studies specifically assessed adherence by CD4 count as the primary outcome.

Studies varied in their reporting of adherence with respect to time on ART. The majority of studies in this review presented multiple pooled estimates of adherence measurements from individuals on ART for durations ranging from 0 to  $>7$  years. Two studies reported adherence from initiation to a cutoff time on ART (1 month and 6 months).<sup>33,42</sup> A further 9 studies excluded participants on ART for less than 3,<sup>24,30 6,<sup>27,29,41</sup> or 12<sup>23,25,28</sup> months of ART. Where studies reported adherence at multiple time points, the data at the measurement taken at the longest duration of ART was used for analysis.</sup>

Risk of bias was judged to be moderate based on the characteristics outlined below (see Supplemental Digital Content, <http://links.lww.com/QAI/A841>). Retrospective designs (21 studies) and subjective measures of adherence (16 studies) were used most commonly. In the majority (24 studies), baseline differences other than CD4 counts were balanced at baseline or adjusted for in analysis; loss to follow-up was judged to be nondifferential with respect to adherence in 5 of the 10 studies, where the relevant information was provided. Overall, the quality of the evidence was judged to be low.

Eighteen studies provided data on 62,823 participants that could be included in the meta-analysis,<sup>20,21,23,24,27 32,35,36,40,42,44,45,48,49</sup> among which 11 provided adjusted

estimates (Fig. 2).<sup>20,23 25,28,29,31,35,36,42,44</sup> Overall, the odds of being adherent was slightly lower for patients in the higher CD4 count group (pooled OR, 0.90; 95% CI: 0.84 to 0.96); however, the majority of studies found no difference in the odds of adherence comparing lower and higher CD4 count strata, and there was little evidence of heterogeneity (Fig. 2). Results were not different when studies were restricted to comparisons above and below a CD4 count of 200 cells per microliter (pooled OR, 0.88; 95% CI: 0.80 to 0.96) compared with higher thresholds. When restricting the analysis to studies reporting adherence above and below 350 cells per microliter, results were again similar to the overall result (3 studies; pooled OR, 0.85; 95% CI: 0.73 to 0.97)<sup>24,35,36</sup>; however, 2 of the 3 studies contributing to this analysis found no difference in adherence.<sup>35,36</sup> Two studies compared adherence above and below 500 cells per microliter and found no difference in adherence (pooled OR, 1.01; 95% CI: 0.97 to 1.05).<sup>31,32</sup> Subgroup analysis by income classification found decreased adherence at higher CD4 counts in low-income and middle-income countries (OR, 0.88; 95% CI: 0.80 to 0.96), whereas for high-income countries, there was no difference (OR, 0.97; 95% CI: 0.87 to 1.07). Studies published before 2010 found decreased adherence at higher CD4 counts (OR, 0.85; 95% CI: 0.76 to 0.93), whereas studies published after 2010 found no difference (OR, 0.97; 95% CI: 0.87 to 1.07).

Five studies from low-income and middle-income settings,<sup>22,33,34,41,46</sup> and 5 from high-income settings<sup>26,37 39,45</sup> provided insufficient data for inclusion in the meta-analysis. Of these, 7 studies presented adjusted ORs of the association between adherence and a numerical baseline CD4 count<sup>22,26,33,34,38,39,46</sup>, one presented adjusted ORs of adherence by median baseline CD4 count<sup>41</sup> and a further 2 studies<sup>37,47</sup> presented a crude comparison of median baseline CD4 between adherent and nonadherent



**TABLE 2.** Overview of Data From Studies Not Included in the Meta-Analysis

Author	Year	Country	Measure of Baseline CD4	Adjusted Analysis	Association With Adherence
Deloria-Knoll	2004	United States	Median CD4 count comparison between adherent and nonadherent groups	No	Mean baseline CD4: adherent group = 378 cells/mL. Nonadherent group = 336 cells/mL; <i>P</i> = 0.18
Byakika-Tusiime	2013	Uganda	Numerical baseline CD4 count	Yes	Adjusted OR, 0.99 (95% CI: 0.997 to 0.999)
Conen	2013	Switzerland	Baseline CD4 cell count per 100 cells/mL increase	Yes	Adjusted OR, 1.20 (95% CI: 1.14 to 1.26)
Maqutu	2010	South Africa	Numerical baseline CD4 count	Yes	Adjusted OR, 0.995 (95% CI: 0.992 to 0.999)
Maqutu	2011	South Africa	Numerical baseline CD4 count	Yes	Adjusted OR, 1.000 (95% CI: 0.998 to 1.001)
Moore	2010	Canada	Median CD4 count comparison between adherent and nonadherent groups	No	Median baseline CD4: adherent group = 150 cells/mL. Nonadherent group = 170 cells/mL; <i>P</i> < 0.001
Murphy	2013	United States	Baseline CD4 cell count per 100 cells/mL increase	Yes	Adjusted OR, 1.07 (95% CI: 1.01 to 1.14)
Palepu	2006	Canada	Baseline CD4 cell count per 100 cells/mL increase	Yes	Adjusted OR, 0.90 (95% CI: 0.83 to 0.99)
Ramadhani	2007	Tanzania	Baseline median CD4 count	Yes	Adjusted OR, 1.0 (95% CI: 1.0 to 1.0)
Weiser	2014	Uganda	Baseline CD4 cell count per 100 cells/mL increase	Yes	Adjusted OR, 0.90 (95% CI: 0.78 to 1.05)

groups. The results of these studies are presented in Table 2. Overall median baseline CD4 count ranged from 56 to 270 cells per microliter, and 6 studies reported a median CD4 count of <200 cells per microliter.<sup>22,33,34,37,41,46</sup> Two studies showed increased adherence with increased CD4 count (1.01 to 1.14 per 100 cells per microliter increase in baseline CD4 count),<sup>26,38</sup> 4 studies reported a decrease in adherence at higher CD4 count,<sup>22,33,37,39</sup> and 4 reported no difference.<sup>34,41,46,47</sup>

## DISCUSSION

Overall, the findings of this review showed decreased adherence at higher baseline CD4 count (OR, 0.90; 95% CI: 0.84 to 0.96), although results were inconsistent across studies. Of the 28 studies, 15 showed an individual difference with 11 reporting decreased adherence<sup>20, 24,28,33,37,39,43,44</sup> and 4<sup>26,27,38,45</sup> reporting increased adherence at higher baseline CD4 count. The odds of being adherent ranged from 0.58 (95% CI: 0.45 to 0.75)<sup>44</sup> to 1.8 (95% CI: 1.22 to 2.91).<sup>45</sup> Interpretation of these findings is limited by variability in the definition of higher and lower CD4 count categories between studies. When studies were restricted to a threshold of >500 vs ≤500 cells per microliter, no differences were observed.

Reported barriers to adherence are multifactorial. A recent systematic review of the predictors of adherence identified a number of factors associated with adherence, including self-efficacy, substance use, depressive symptoms, concerns about ART, beliefs about the utility of ART, satisfaction with the care provider, stigma, and social support.<sup>50</sup> Qualitative studies have identified a number of patient-reported barriers to adherence, including forgetfulness, limited understanding of the importance of treatment, drug side effects, pill burden, disruptions to daily routine, and competing priorities.<sup>51</sup> Some studies have reported that feeling sick is a more frequent barrier to adherence than feeling healthy<sup>52</sup>; this may in part be related to the higher pill

burden associated with the treatment of comorbidities.<sup>53</sup> The relationship between baseline CD4 count and adherence to ART is complex and contextual, and other factors are likely as important or more important in determining adherence, as suggested by the variability in adherence levels between studies included in this review. Although adherence counseling needs to be adapted to respond to the growing number of people starting ART without having experienced an illness event, focusing on any single factor as the cause of poor adherence is unlikely to lead to the necessary support for patients in a way that will lead to optimal health outcomes over time.

Strengths of this review include the comprehensive search of the available literature that allowed us to assess outcomes among over 72,000 adults initiating ART. Nevertheless, the findings of this review are judged to be based on low-quality evidence. This was driven in large part by differences in CD4 count thresholds and adherence definitions applied between studies, which to a degree reflect differences in ART initiation thresholds applied in different settings. We present forest plots to display between-study heterogeneity and used random effects models. Another limitation with respect to informing current ART guideline changes is that many of the studies included in this review were done at a time when ART was initiated at a low threshold of CD4 count 200 or 350 cells per microliter.<sup>2</sup> In such settings, patients initiating ART at higher CD4 counts represent specific patient populations (eg, pregnant women or tuberculosis-HIV coinfecting patients) who may not be representative of the broader patient population, and only 4 studies adjusted for the presence of WHO defining illness at ART initiation in the analysis of adherence.<sup>23,25,40,42</sup> Duration of ART may also be an important factor affecting adherence, although this relationship was inconsistent with some studies showing an increased adherence over time<sup>54</sup> and some showing a decreased adherence.<sup>24,32</sup> Therefore, a further



important limitation is the marked heterogeneity and the lack of reporting of the duration on ART at which adherence was measured.

In conclusion, this review was unable to find strong evidence supporting consistent differences in adherence according to baseline CD4 count, particularly at CD4 counts >500 cells per microliter. Although this may be encouraging for the implementation of the new WHO ART guidelines, the quality of the limited published evidence to date is variable. Further studies with improved standardization of methods for monitoring and reporting ART adherence are therefore encouraged as HIV programs shift toward starting treatment irrespective of immune status.

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## **Chapter 8: Discussion**

This chapter provides an overview of the results of the studies contributing to this PhD dissertation. For each study, the results are discussed in the context of the published literature; the strengths and limitations of the study are also discussed. This discussion chapter also highlights how study findings, when combined with the findings of other studies, can strengthen the evidence base for HIV treatment services in high-burden settings. The chapter further discusses possible steps to address gaps in knowledge, health systems infrastructure, access to drugs and technology and models for the delivery of PHC services identified during the completion of the research.

### **8.1 PhD dissertation overview**

The aim of this PhD dissertation was to evaluate the accuracy of household-based HIV point of care testing and the impact of routine provision of antiretroviral therapy (ART) on attrition, TB, renal dysfunction and ART adherence after ART initiation in HIV positive adults, at baseline CD4 counts  $>500$  cells/ $\mu$ L. Overall, the findings from the studies in this dissertation are likely to be of high relevance to programme implementers in high-burden settings.

### **8.2 Study evaluating HIV point of care testing (POCT) accuracy**

#### **8.2.1 HIV POCT study findings**

The study presented in chapter 3, 'Understanding low sensitivity of community-based HIV rapid testing: experiences from the HPTN 071 (PopART) trial in Zambia and South Africa', evaluated the accuracy of household HIV POCT within the PopART population cohort (PC).

Key findings of the study included low initial HIV POCT sensitivity in South Africa (45-54%), with improvement in sensitivity over time when implementing rigorous quality assurance (QA) of HIV POCT activities and quality control (QC) of HIV POCT kits. Sensitivity in Zambia during the same time period was significantly better (95.8%). There were some differences in the manner in which HIV POCT was conducted in Zambia and South Africa during the study period, to which this difference in sensitivity may be attributable. In Zambia, Alere Determine™ HIV-1/2 was used as the HIV screening test, during sequential HIV POCT,



throughout the study period. In South Africa, until September 2015, when sites also changed to using Alere Determine™ HIV-1/2 for screening as part of a sequential algorithm, First Response™ HIV 1-2-0 Card Test and SD Bioline HIV-1/2 3.0 were used for screening. The Zambian sites also conducted more rigorous QA/QC from the start of the study period, which included panel testing of HIV POCT test kits and proficiency testing of individuals conducting HIV POCT. In contrast, in South Africa, panel and proficiency testing were only introduced from January 2015. A further interesting finding in the study was a trend toward known HIV-positive individuals, some on ART, not disclosing their HIV status to PC staff and accepting HIV POCT: a scenario in which, the HIV POCT sensitivity might have been decreased by ART exposure. (1)

### **8.2.2 HIV POCT study findings in context**

Household-based HIV POCT services have been shown to be an effective component of community-based HIV testing strategies (HTS), increasing the identification of HIV-positive individuals, including amongst high-risk, difficult-to-access groups, such as men. (2-4) This study, however, highlighted the potential for low HIV POCT sensitivity in community settings and the need for rigorous HIV POCT QA/QC. Published HIV POCT sensitivity data from South African studies completed in both clinic and community settings ranges from 68 to 98%. (5, 6) Encouragingly, however, a recent systematic review found overall low rates of HIV POCT false negative results (0.4%) in community settings in comparable high-burden settings. (5) Furthermore, the systematic review identified 'remediable' factors, such as user error, as the most significant contributors to decreased test accuracy. (7) At the same time, new HIV POCT kits with increased sensitivity for HIV antigen, such as the Alere™ HIV Combo assay (not used in PopART), may increase HIV POCT sensitivity in community-based settings and need further evaluation. (8) There remains limited published data reporting on the accuracy of household-based HTS. Completion of further operational research on this topic should be a priority. The finding that some individuals on ART were not disclosing their treatment status and were being retested for HIV should be a specific focus area for research.

HTS coverage in high-burden settings remains well below global targets. (9, 10) In addition to strengthening existing HTS strategies, there remains an urgent need for new innovative strategies that target specific population groups that are at high risk of HIV infection and

difficult to access. In high-burden settings, these groups often include men, women aged 15 to 24 and sex workers. (11, 12) Routine provision of oral HIV self-testing (13, 14) may be effective in increasing HTS coverage in high-burden settings, and may assist in reaching the high HTS coverage targeted by global agencies. (9)

### **8.2.3 Strengths and limitations of the HIV POCT study**

The PopART trial provided a unique opportunity to evaluate the accuracy of HIV POCT in a field setting, through parallel HIV testing of individuals with HIV POCT and 4th-generation laboratory assays. There were, however, some limitations to the generalisability of these findings. Although the PopART sites were selected according to standardised criteria and we believe the sites included in PopART to be representative of the areas in which the trial is being completed, there was some non-adherence to these criteria in the ultimate selection of the PopART sites as the result of some eligible sites not being included in PopART. Reasons for this non- inclusion included being over burdened with prior research studies and relevant clinic management staff not wanting to be part of the trial. When data were stratified, by annual quarter and country, sample sizes were small with low precision of sensitivity estimates. The study also did not directly analyse the association between factors potentially associated with HIV POCT sensitivity. These factors included choice of HIV POCT kit, extent of QA/QC implementation, variation between individual PC staff members (user error) and ART exposure. Furthermore, testing by the PopART PC teams only included individuals aged 18 to 45 years and HIV POCT was conducted by professional nurses as a component of a complex research intervention. Household-based HIV POCT is not yet standard care in most high-burden settings, but it is likely that the manner in which it will be conducted will differ from that used for PopART. These differences may include using a different cadre of staff, such as lay counsellors, and targeting a wider population group.

### **8.3 Studies that evaluated the association between baseline CD4 count and attrition, TB incidence and renal dysfunction during early ART**

The studies presented in chapters 4 to 6 used routine data from a cohort of adults initiating ART at the three DOH PHC clinics included in Arm A of the PopART trial in South Africa.

### **8.3.1 Attrition during early ART study findings**

The study presented in chapter 4, 'Attrition when providing antiretroviral treatment at CD4 counts >500 cells/ $\mu$ L at three government clinics included in the HPTN 071 (PopART) trial in South Africa', evaluated the impact of routine initiation of ART at baseline CD4 counts >500 cells/ $\mu$ L at DOH clinics on attrition during early ART. Attrition included individuals no longer retained in care, due to both loss to follow-up or death, and was defined as being three months late for a pharmacy pick-up appointment. Overall, the study showed high cumulative attrition during the first 24 months on ART (26.2%), with increased attrition amongst individuals starting ART at CD4 counts >500 cells/ $\mu$ L, both when compared to individuals with baseline CD4 counts of 0-500 cells/ $\mu$ L (aHR 1.28, 95%CI 1.07 to 1.55) and when compared to individuals with baseline CD4 counts of 351-500 cells/ $\mu$ L (aHR 1.42, 95% CI 1.12-1.79).

### **8.3.2 Attrition study findings in context**

Attrition from ART care is strongly associated with subsequent increased viral load. (15) As high-burden countries strive to attain universal access to ART, rapidly increasing ART coverage, while maintaining quality of care, will become increasingly challenging. (16) A wide range of strategies have been shown to be effective in improving retention in ART programmes; (17) however, despite this, attrition from ART programmes in high-burden settings is high. (18) In addition, there is a reported trend toward increased attrition as the number of individuals treated at PHC clinics increases and clinics become more congested. (19, 20) This trend is particularly concerning when considered in the context of the rapid scale-up of ART required to reach global targets in high-burden settings.

Differentiated models of care that move away from the 'one size fits all' approach to ART service delivery, (21-23) may assist in improving retention in ART care. These differentiated models of care can include development of risk matrices used to identify individuals at high risk for attrition, such as the individuals with higher baseline CD4 counts identified in this study, for increased clinic and community support. At the same time, there can be referral of selected clinically stable individuals to clinic or community-based ART clubs, where they are managed in groups, helping to decongest overcrowded PHC clinics. (24) Early studies

have shown improved or comparable clinical outcomes when implementing clinic or community-based ART clubs compared to clinic care. (22, 23) There remains, however, a lack of research evidence on how best to structure and manage ART clubs, as well as the cost-effectiveness of this approach.

### **8.3.3 TB incidence during early ART study findings**

The study presented in chapter 5, 'Incidence of Tuberculosis amongst HIV-positive individuals initiating antiretroviral treatment at higher CD4 counts in the HPTN 071 (PopART) trial in South Africa', evaluated the impact of routine initiation of ART at baseline CD4 counts >500 cells/ $\mu$ L at DOH clinics on TB incidence during early ART. Incident TB was defined as being recorded in the electronic TB register (ETR.net) as starting TB treatment after ART initiation. The study showed significantly lower TB incidence among individuals with baseline CD4 counts >500 cells/ $\mu$ L compared to those with baseline CD4 counts 0 to 500 cells/ $\mu$ L (aHR = 0.27; 95% CI 0.12 to 0.62). These results were confirmed by a sensitivity analysis in a subset of individuals, which used bacteriologically confirmed TB as the primary endpoint. Furthermore, the study showed no incident TB in the first three months on ART among individuals with baseline CD4 counts >500 cells/ $\mu$ L; although the sample size in this group was relatively small, this finding may suggest a reduction in TB-associated IRIS, (25) among individuals whose CD4 count has never dropped below 500 cells/ $\mu$ L. The impact of isoniazid prophylaxis (IPT) on TB incidence was not reported in this study, as there were very high rates of missing data reporting on IPT provision in ETR.net.

### **8.3.4 TB study findings in context**

TB remains the most common cause of death among HIV-positive individuals in high-burden settings. (26) These findings confirm, in a programmatic setting, the potential for routine initiation of ART at CD4 counts >500 cells/ $\mu$ L to reduce TB incidence amongst individuals on ART, which was previously demonstrated in randomised controlled trials (RCTs). (27, 28) Differentiated models of care may also be used to improve TB-related outcomes on ART. (29) Known risk factors, such as baseline CD4 count as illustrated in this study, can be used to generate risk matrices that identify individuals at high risk of TB on ART for more intensive screening after ART initiation. Risk matrices can also be used to identify individuals at high risk of TB at the time of ART initiation, for more intensive TB diagnostic screening

prior to ART initiation; screening could contribute to improved TB diagnosis at the time of ART initiation and improved TB-related outcomes on ART. (29, 30)

Reductions in TB incidence among HIV-positive individuals on ART may also contribute to reductions in TB incidence at the population level. (31, 32) IPT has been shown to be effective in reducing TB incidence in HIV-positive individuals with positive tuberculin skin test (TST) results. (27, 33, 34) IPT implementation and monitoring in high-burden settings is, however, highly challenging, and to date, in South Africa, IPT has been poorly implemented. (27, 35) The need for TST prior to IPT provision and concerns about INH resistance are thought to have contributed to low uptake of IPT. (35, 36) The need for TST prior to IPT is debatable; (35) TST is more accurate in HIV-positive individuals with higher CD4 counts. (34) Recent changes to ART guidelines, with more individuals starting ART at higher CD4 counts, may strengthen the argument for TST before IPT provision and should be an important consideration in the ongoing debate on how best to improve IPT implementation.

### **8.3.5 Incidence of renal dysfunction during early ART study findings**

The study presented in chapter 6, 'Renal dysfunction in a cohort of adults starting antiretroviral treatment at baseline CD4 counts >500 cells/ $\mu$ L in the HPTN 071 (PopART) study in South Africa', evaluated the impact of routine initiation of ART at baseline CD4 counts >500 cells/ $\mu$ L on the incidence of renal dysfunction during early ART. Incident renal dysfunction was defined as an estimated glomerular filtration rate (EGFR <60mL/min) amongst individuals with baseline EGFR  $\geq$ 60mL/min. In this study, baseline CD4 was not associated with incident renal dysfunction or mean EGFR on ART. Other baseline factors, including age >45years and baseline mild renal dysfunction (EGFR 60 to 89mL/min) were, however, strongly associated with both higher average EGFR and higher incident renal dysfunction. When analysis of incident renal dysfunction on ART was restricted to individuals with normal baseline EGFR (EGFR  $\geq$ 90ml/min), there were no cases of incident renal dysfunction amongst individuals with baseline CD4 >500 cells/ $\mu$ L. Analysis of factors associated with baseline moderate or severe renal dysfunction (EGFR <60ml/min) was also completed. This analysis showed a decreased prevalence of baseline moderate or severe renal dysfunction amongst individuals with baseline CD4 counts >500 cells/ $\mu$ L (aOR 0.29; 95% CI 0.11-0.80), 351-500 cells/ $\mu$ L (aOR 0.22; 95% CI 0.08-0.59) and 201 to 350 (aOR 0.48;



95% CI: 0.24-0.97) when compared to baseline CD4 counts CD4 <200 cells/ $\mu$ L. The baseline analysis also showed significantly higher baseline moderate or severe renal dysfunction amongst individuals of 36 to 45 years (aOR = 3.30; 95% CI: 1.60-6.77 and >45 years (aOR = 6.32; 95% CI: 3.03-13.22) when compared to individuals  $\leq$ 35 years old.

### **8.3.6 Renal dysfunction study findings in context**

This programmatic study evaluating renal dysfunction after ART initiation, in the context of ART regardless of CD4 count, in high-burden regions, showed some important findings. The finding of no incident cases of renal dysfunction amongst individuals with normal baseline renal function, starting ART at baseline CD4 counts >500cel/ $\mu$ L, is novel and needs to be confirmed in other settings. The absence of an association between baseline CD4 >500cells/ $\mu$ L and mean 'on ART' EGFR contrasts with results from the START trial, which showed a modestly improved mean EGFR amongst individuals starting ART at baseline CD4 counts >500 cells/ $\mu$ L. (37) The lower prevalence of baseline renal dysfunction amongst individuals with higher CD4 counts at ART initiation reported in this study concurs with previously published data. (38) The higher rates of renal dysfunction amongst older individuals, both at the time of starting ART and while on ART, reported in this study are also supported by previous studies. (39-41) Comparison of the results of this study to other published data, however, was limited by heterogeneity in study methods, particularly in relation to the definitions of incident renal dysfunction on ART. (41, 42)

Laboratory-based EGFR monitoring is recommended for individuals receiving tenofovir, a drug commonly used for first-line ART in high-burden settings. (43, 44) EGFR monitoring is often challenging, particularly in settings where the necessary laboratory equipment may be permanently or intermittently unavailable. (45) Baseline characteristics, such as older age and low BMI amongst individuals starting ART, have consistently been identified as risk factors for renal dysfunction after ART initiation. (39, 40) These proven risk factors for renal dysfunction could be used to identify high-risk individuals for more focused renal monitoring at baseline and after ART initiation. In addition further research is required to evaluate the more effective use of more accessible POCT tests such as urine dipsticks for proteinuria into simplified, renal monitoring algorithms (45, 46.) Improved routine access in high-burden settings to tenofovir alafenamide (TAF), a tenofovir prodrug with lower risk of renal toxicity,

(47, 48) may reduce the need for renal monitoring on ART. There are, however, concerns regarding the use of TAF in settings with high rates of HIV and TB coinfection. TAF interacts with rifampicin used for first-line TB treatment, and further investigation into its efficacy and safety in these contexts is urgently required. (44, 49)

### **8.3.7 Strengths and limitations of the studies that evaluated the association between baseline CD4 count and attrition, TB incidence and renal dysfunction during early ART**

The studies presented in chapters 4 to 6 addressed topics of high public health importance and have resulted in some important findings. These were also some of the first studies to report on the provision of household-based HIV POCT and ART regardless of CD4 count in a programmatic setting. A further strength of these studies was the use of high-quality routine data, prospectively improved by health system strengthening activities linked to the PopART trial. As discussed with reference to the HTS study although there was some non-adherence to the site selection process, we believe the PopART sites in which these studies were completed to be representative of high burden urban and peri-urban areas in the Western Cape. The studies were also completed in close partnership with DOH and PEPFAR implementing partners, who were, directly, involved in the provision of clinic services and in the development and quality control of relevant routine data systems, which greatly enhanced the accurate understanding and interpretation of study findings.

There are, however, limitations to these three clinic-based studies that should be taken into consideration. The precision of estimates generated in the analyses of these studies was limited by small sample size and limited person time for follow-up. The study findings should, therefore, be confirmed by completion of further studies with increased recruitment and follow-up periods. Study validity was also reduced by missing data in reported data fields or non-availability of data for key outcomes. For example, in the attrition paper (chapter 4) there was apparent systematic under-recording of death in Tier.net and no available data from other sources, such as hospital records and death registries, to confirm vital status amongst individuals experiencing attrition. For the TB paper (chapter 5), in the absence of accurate recording of individuals diagnosed with TB, but not started on TB treatment in ETR.net, starting TB treatment was used as a proxy to define an incident TB case. Furthermore, the effect of IPT exposure was not analysed in the TB study due to

significant under-reporting of IPT exposure in ETR.net. IPT is a potential confounder in the relationship between baseline CD4 count and incident TB, and the availability of IPT data would have greatly strengthened the analysis. The validity of the renal paper (chapter 6) was similarly reduced by high rates of missing baseline EGFR and on ART EGFR results. While a systematic review of healthcare records from individuals with missing EGFR results was completed, this process was hampered by difficulties in locating records and accurately finding the EGFR results within records that were successfully accessed.

Although HIV-positive individuals starting ART at the three DOH Arm A clinics were managed according to standard DOH ART guidelines, there were some important differences in their management to that of the standard care scenario. During the study period, January 2014 to May 2016, individuals starting ART outside of pertinent local guidelines signed research informed consent. Signing research informed consent, an activity that would not be part of standard care, may have affected health-related behaviours such as retention in ART care and ART adherence. Furthermore, clinic- and community-based services, during the study period, were strengthened for PopART by additional clinic staff, community HIV care providers (CHiPs) and PC teams. These additional staff may also have positively impacted retention in ART care and ART adherence. In addition there may have been some selection biases as a result of this increased clinic and community support. After the introduction of PopART activities in January 2014 there was a rapid increase in ART uptake, of up to three times as many new ART initiations per month, at the three study clinics. This increase is likely to have been partly the result of CHiPs household activities, which may have resulted in individuals with certain characteristics linking to care. The baseline characteristics of these individuals may be different to those that would be found in a standard care scenario without the CHiPs support; this may, in turn, have affected ART outcomes in this cohort and limited the generalisability of the research findings.

The provision of ART regardless of CD4 count in this setting, ahead of universal access becoming standard care, may have further impacted the study results in several ways. A previous study showed that approximately one-third of individuals documented as lost to follow-up from ART care, in comparable settings, have in fact transferred to another clinic without informing staff (silent transfers). (50) In the context of PopART, this trend may have been greater amongst individuals with baseline CD4 counts  $>500$  cells/ $\mu$ L, who, eager to

start ART, would have come to the PopART clinic to start ART outside of local guidelines. After ART initiation, they may then have returned to their 'usual' clinic for ongoing treatment and consequently been documented as lost to follow-up. Furthermore, HIV treatment narratives in communities including those in the PopART trial have traditionally focused on starting ART when your CD4 count drops to a certain level. (51) This narrative made explaining the risks and benefits of routinely starting ART at higher CD4 counts, when an individual is more likely to be clinically well, challenging. (51) In this regard, it is possible that the lack of community familiarity with the risks and benefits of starting ART at baseline CD4 counts >500 cells/ $\mu$ L may have adversely affected retention in ART care in this group. Going forward, now that ART regardless of CD4 count is standard care, it is likely that there will be further transition of these community narratives about when is the best time to start ART. This transition may in turn positively influence retention in ART care amongst individuals initiating ART at baseline CD4 counts >500 cells/ $\mu$ L. (51)

## **8.4 Systematic review and meta-analysis of the association of baseline CD4 count with ART adherence**

### **8.4.1 ART adherence systematic review and meta-analysis findings**

This systematic review, which included 28 published research papers, 18 of which were included in the meta-analysis, showed lower ART adherence among HIV-positive adults starting ART in higher baseline CD4 count categories (pooled OR 0.90; 95% CI 0.84-0.96). These baseline CD4 count categories varied between studies; the most common comparison, reported by 11 studies, was between individuals with baseline CD4 counts above and below 200 cells/ $\mu$ L. Median baseline CD4 counts in the included studies were low overall, with only two studies reporting on HIV-positive individuals starting ART at baseline CD4 counts >500 cells/ $\mu$ L. In analysis restricted to these two studies, there was no difference in ART adherence between individuals with baseline CD4 counts above and below 500 cells/ $\mu$ L (pooled OR = 1.01; 95% CI 0.97-1.05).

### **8.4.2 ART adherence systematic review and meta-analysis strengths finding in context**

Published ART adherence levels in high-burden settings are generally low (<60%). (52) Poor adherence to ART in these settings is attributed to a wide range of factors, including stock-outs of ART medication, contrary health beliefs, pill burden and mental health issues. (53)

The varied nature of factors associated with poor adherence suggests that multiple interventions, addressing a wide range of causal factors, are needed to improve ART adherence. (53) Differentiated care models using standardised criteria for identifying individuals at high risk of poor adherence for increased support may again be an effective strategy for improving adherence to ART. (53) Furthermore, efavirenz (EFV) remains the NNTRI of choice for first-line ART in high-burden settings, and neuropsychiatric side effects, common in individuals taking EFV, (54) may adversely affect ART adherence. Access to alternative ART drugs with lower toxicity, such as dolutegravir (DTG), may be effective in improving adherence. (49) DTG is also associated with reduced risk of developing drug resistance (HIVDR), which may further improve ART outcomes. (49) Modelling studies suggest that rates of HIVDR, particularly to NNRTIs, will increase with universal access to ART. (55) This predicted increase in HIVDR further strengthens the argument for improved access to DTG in high-burden settings. (55, 56) At the same time, extensive focused research is needed to evaluate the potential routine use of parentally administered intermittent ART, such as intramuscular cabotegravir and rilpivirine administered every 4 to 8 weeks, to improve clinical outcomes with ART. (57)

#### **8.4.3 ART adherence systematic review and meta-analysis strengths and limitations**

This systematic review and meta-analysis evaluated an important topic. The study included data on a large number of individuals, more than 72,000 adults, and was rigorously completed according to the PRISMA guidelines. (58) However, there were key limitations for consideration. The study found the included studies to be of poor quality overall and comparison of results across included studies was limited by extensive heterogeneity in the methodologies used in different studies. This applied particularly to differences in baseline CD4 count categories in studies that reported baseline CD4 count as a categorical variable. There was also marked heterogeneity in the definitions of ART non-adherence between studies. This definition ranged from <95% self-reported ART adherence over the last three days to pharmacy records showing an unscheduled treatment interruption of more than three months.



## **8.5 How can the results of this PhD dissertation be used to improve clinical care in high-burden settings?**

### **8.5.1 PhD dissertation results**

There remains a significant HIV treatment gap in high-burden settings. Programme implementers in these settings will need to strengthen services at all steps in the HIV treatment continuum if they are to reach the 90-90-90 targets and fulfil the promise of universal access to ART. (44) The studies presented in this dissertation are some of the first to report on provision of household-based HIV POCT and ART regardless of CD4 count, in a programmatic setting, and highlight some important benefits of these approaches. These include the potential for a reduction in TB incidence and renal dysfunction amongst HIV-positive individuals when starting ART at CD4 counts  $>500\text{cell}/\mu\text{L}$ . The studies also identified areas of concern, including the need for rigorous HIV POCT QA/QC when conducting household-based HIV POCT, increased attrition amongst individuals starting ART at baseline CD4 counts  $>500\text{ cells}/\mu\text{L}$  and a trend toward decreased ART adherence amongst individuals starting ART at higher CD4 counts.

### **8.5.2 Contextual gaps highlighted in completion of the PhD dissertation**

In addition to the study results, through the conduct of the studies included in this dissertation, a number of important gaps were identified in the knowledge base, health systems, drugs and technologies and approach to the HIV-positive individual used for implementation of HIV treatment services.

### **Research evidence**

There are very limited published data on the outcomes evaluated in this dissertation, and further operational studies are urgently needed to confirm these results and address other evidence gaps. A further challenge to developing the required strong evidence base, to support HIV treatment services, is the marked heterogeneity in operational research methodologies and contextual factors between operational research studies. (59) This issue was clearly illustrated in the adherence systematic review (chapter 7), and increased efforts to standardise operational research methodologies are needed. The WHO has recently published guidelines to strengthen and standardise criteria and data collection for the

conduct of operational research studies. (59) Improved dissemination of these types of guidelines should be a priority.

### **Health systems**

Effective management of HIV and TB at the PHC level is critical for high-burden settings. (60) The number of HIV-positive individuals in these settings continues to increase. At the same time there is a steady decline in global HIV and TB funding support, further stretching health systems. As described above, differentiated models for integrated HIV and TB care, implemented according to context, may be an effective strategy. There is, however, limited research evaluating how best to implement these models and their cost-effectiveness.

Health systems challenges at busy PHC clinics are further exacerbated by limitations in routine data systems, such as those experienced with the use of Tier.net and ETR.net during completion of this dissertation. Further to high rates of missing data, integration of individual-level data across different health facilities and between clinic- and community-based services is severely restricted. (61) This limitation was clearly illustrated in the analysis of attrition (chapter 4), where the extent to which silent transfers contributed to attrition was not apparent in the routine data, in turn leading to possible under-estimation of the actual number of individuals remaining on ART. Loss to follow-up between the time of HIV diagnosis and starting ART is often high, (62) and integration of clinic and community databases has the potential to improve follow-up of individuals testing HIV-positive in the community and not linking to ART care.

### **Technologies and drugs**

The research presented for this dissertation also highlighted limitations of diagnostic technologies and ART regimens currently used by HIV treatment services in high-burden settings. There are concerns over the accuracy and acceptability of currently used HIV POCT kits; development and field testing of more accurate HIV POCT testing kits and self-testing strategies should be a priority. (7) Access to laboratory services in many high-burden settings is limited, and increased access to a range of affordable POCT tests, including CD4 count and viral load testing, may improve HIV treatment outcomes. (63, 64) In areas where laboratory services are available, more cost-effective strategies for aspects of laboratory-based ART monitoring are needed. These strategies may include pooling of viral load, which

can reduce the cost of viral load monitoring. (65) As well as the improved use of renal dipstick POCT for renal monitoring of individuals taking tenofovir, which can both improve access to renal monitoring and reduce cost. (45) Tenofovir and efavirenz, drugs which are strongly associated with renal toxicity and neuropsychiatric disturbances respectively, remain first-choice ART in high-burden settings. Improved access to newer, alternative ART drugs, such as TAF and DTG, may contribute to improved outcomes on ART. (49) However there are some uncertainties about their safety and effectiveness for routine use in high-burden settings that urgently need to be evaluated. (49) This further research needs to be combined with strong advocacy across the globe to increase affordable access to newer ART drugs in these regions.

### **Client-centeredness**

As outlined above, wide-ranging biomedical and structural interventions, backed by strong evidence, adequate resources, good policy and strong political will are required for the fight against HIV and TB in high-burden settings. (66) Ultimately, though, underpinning the success of all these interventions are the individuals affected by HIV and TB, and how these individuals utilise and experience PHC services. (67) The importance of a client-centred approach in the delivery of PHC services has long been recognised, and in 2016, building on the PHC principles outlined in Alma-Ata in 1972, (68) the WHO published the 'Framework on integrated people-centred health services'. This framework re-emphasised the critical role of the client-centred approach and the need for healthcare providers to incorporate the views of individuals, families and communities for the holistic provision of essential health services. (67)

## **8.6 Conclusions**

The number of HIV-positive individuals in high-burden settings continues to increase annually across the world. (10) With WHO guidelines now recommending universal access to ART, there will be increasing numbers of individuals being tested for HIV, being diagnosed HIV-positive and starting ART at higher CD4 counts. The PopART trial has provided an excellent opportunity to evaluate key aspects of the provision of community-based HIV POCT and ART regardless of CD4 count, in a programmatic context, ahead of these services being standard care in high-burden settings. Overall, the studies presented for this PhD

dissertation demonstrated both benefits and challenges when conducting household-based HIV POCT and routinely starting HIV-positive individuals on ART at CD4 counts >500 cells/ $\mu$ L. The findings of these studies need to be consolidated, through integration with findings from RCTs and other operational research studies, for the development of a strong evidence base to strengthen the delivery of HIV treatment services in high-burden settings.

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## **Chapter 9: Additional publications contributed to by the PhD candidate since January 2014 and referenced in this PhD dissertation**

1. **Bock P**, Beyers N, Fidler S. Balancing the need to rapidly scale-up and improve clinical outcomes in antiretroviral programmes in developing countries: lessons from an Indian programmatic cohort study. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2014 Oct; 108 (10):599-600.
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