The Impact of Antiretroviral Therapy on Tuberculosis Incidence

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Preamble

Declaration

I, **Nesbert Zinyakatira (ZNYNES001),** hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and has not, in whole or in part, been submitted towards another degree, at this university or elsewhere.

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Abstract

Introduction

Although HIV infection increases the likelihood of developing TB, evidence suggests that starting ART reduces the risk of TB incidence although not to the level of HIV negative people in the population. This study aims to determine the impact of ART on TB incidence in people living with HIV in the Western Cape Province of South Africa.

Methods

This is a retrospective cohort study using routinely collected data of HIV infected individuals aged 15 years and above from public health facilities in the Western Cape Province, South Africa, between 2007 and 2016. A Marginal Structural Model (MSM) with inverse probability of treatment weighting (IPTW) was used to estimate the effect of ART on TB incidence adjusting for measured time-dependent confounding by CD4 count.

Results

ART was associated with a 77.3% (95% CI, 76.7% – 78.0%) reduction in the risk of TB incidence in HIV infected patients. The overall TB incidence was 9 855 per 100 000 patient years (95% CI, 9 798 – 9 912). Patients on ART and those not on ART had a TB incidence of 3 939 and 15 329 per 100 000 patient years respectively. TB incidence was higher in males than females, and higher in patients with lower CD4 count at baseline and during follow-up. TB incidence declined with increasing ART duration and rising CD4 count but remained elevated compared to background incidence.

Conclusion

This study has shown that ART is highly effective at preventing TB in people living with HIV. The recent introduction of universal ART access for everyone living with HIV should contribute to further reducing TB incidence in South Africa and other high HIV and TB burden countries.

Acronyms and Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
CDU	Chronic dispensing unit
EDR	Electronic drug resistance tuberculosis register
EKAPA	Evaluation of the Khayelitsha AIDS program
ETR	Electronic tuberculosis register
HIV	Human Immunodeficiency virus
HAART	Highly active antiretroviral therapy
HR	Hazard ratio
IPT	Isoniazid preventative therapy
IPTW	Inverse probability treatment weighting
JAC	Pharmacy electronic register
K-M	Kaplan-Meier
MSM	Marginal structural model
NHLS	National health laboratory services
PMI	Patient master index
OR	Odds ratio
RR	Risk ratio
SANAC	South African National AIDs Council
TIER.Net	Three integrated electronic registers, HIV electronic register
TB	Tuberculosis
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Health Organisation

Table of contents

List of Tables

List of Manuscript Tables

List of Figures

SECTION A: REASEARCH PROTOCOL

The research protocol was written up in 2015-2016 and reflects what was known at that time.

1. Introduction

1.1 Background

Tuberculosis (TB) remains a major global health problem and ranks alongside human immunodeficiency virus (HIV) as the leading cause of death from communicable diseases globally (World Health Organisation, 2015). The latest estimates by the World Health Organisation (WHO) states that there were 9.6 million new TB cases and 1.5 million TB deaths in 2014 globally. About 1.1 million of the deaths were among HIV negative people and 0.4 million of the deaths were among HIV positive people (World Health Organisation, 2015). These numbers of new cases and deaths are very high, considering that TB is preventable and treatable.

TB remains one of the most frequent opportunistic infections in people living with HIV (Van Rie et al., 2011). Since the early 1980s, the HIV epidemic has led to a major upsurge in TB cases and TB mortality in many countries, especially those in Southern and Eastern Africa (World Health Organisation, 2014). South Africa is noted to have the highest TB incidence in the world, largely resulting from a high population prevalence of HIV infection (Hermans and Manabe, 2015). The WHO notes that globally people living with HIV are 29 times more likely to develop TB disease than those who are HIV-negative (World Health Organisation, 2014).

Even though HIV has been noted to increase the likelihood that a person will develop TB, starting them on antiretroviral treatment (ART) has been seen to reduce their risk of TB (Williams and Dye, 2003, Williams, 2013, Edmonds et al., 2009). ART has been noted to be highly effective in the reduction of mortality and morbidity and also effective in reducing TB in HIV-infected individuals (Van Rie et al., 2011). However, this risk reduction is not to the level of HIV negative people. Various studies have shown risk reductions ranging from about 60% to 80% in TB incidence in patients receiving ART (Santoro-Lopes et al., 2002, Miranda et al., 2007, Golub et al., 2007, Golub et al., 2009, Lawn et al., 2010, Suthar et al., 2012).

High incidence of TB in the first months of ART have been consistently documented across different regions globally (Van Rie et al., 2011, Moore et al., 2007, Girardi et al., 2005, Lawn et al., 2005, Bonnet et al., 2006, Brinkhof et al., 2007, Dembele et al., 2010, Rajasekaran et al., 2009). This is in part a result of the unmasking of subclinical TB during the initial rapid restoration of the immune response (Lawn et al., 2009). The incidence of TB declines the longer patients are on ART in most of the cohorts investigated (Moore et al., 2007, Girardi et al., 2005, Lawn et al., 2005, Brinkhof et al., 2007, Lawn et al., 2009). However, this incidence remains

higher than the background TB incidence in the general population, even after years of being on ART (Lawn et al., 2009, Gupta et al., 2012, Gupta et al., 2015). This elevated long-term TB incidence has been shown to be strongly associated with the time spent at CD4 count <500 cells/mm^3. A CD4 threshold of 350 cells/ μL has been noted as the best predictor which determines whether ART increases or decreases TB incidence in the long term (Williams, 2013).

Starting ART very late and low coverage of ART has been noted to increases population level incidence of TB, however, HIV positive people on ART are expected to live longer and have an elevated risk of TB infection for a much longer time as they remain alive (Williams, 2013). Thus, in the course of HIV infection, starting ART very late increases the lifetime risk of TB, while starting ART very early decreases the lifetime risk of TB.

Many longitudinal clinical studies have treatment or exposure variables and other time-varying covariates that change over time and are measured several times during the study (Daniel et al., 2013). The estimation of the causal effect of ART on TB incidence in patients living with HIV depends on the time-varying confounders that also affect the outcome, and in most cases standard methods give biased estimates of the causal effect in the presence of these time-varying confounders (Hernan et al., 2000). Thus, there is need to control specifically for time-confounding in these types of studies. In looking at the impact of ART on people living with HIV on TB incidence, there is time-varying confounding which occurs when confounders have values that change over time, and an example of this is CD4 count (Hernan et al., 2000, Hernan et al., 2002). Thus, estimating the overall causal effect of a time-varying exposure (ART) would need adjustment of the time-varying confounders (Robins et al., 2000, Hernan et al., 2000).

The double burden of the HIV and TB burden in South Africa has created operational challenges to the health system that has traditionally run vertical programmes for HIV and TB, with treatment delivered by healthcare staff, most often located in separated facilities (Kaplan et al., 2014). The vertical model of delivering HIV and TB care to co-infected patients in South Africa relied upon referral and linkage to care between the two programmes. This creates challenges and inefficiencies in referrals between the two, as referrals depend on patients' resources and health care seeking behaviour which is mostly unmonitored, which in turn results in poor treatment outcomes in patients co-infected with TB and HIV needing access to both services (Kaplan et al., 2014).

TB ascertainment also remains a challenge as there is a lack of robust point-of-care tools for diagnosis in these high HIV prevalence settings (Haraka et al., 2015, World Health Organisation, 2015). In most cases TB diagnosis relies on radiological findings, microscopy, clinical symptoms

and culture which is not routinely done due to lack of capacity and infrastructure (Parsons et al., 2011, Haraka et al., 2015, World Health Organisation, 2015). In addition there is no evidence-based tool to screen for TB in people living with HIV that is universally accepted (Padmapriyadarsini et al., 2011).

1.2 Motivation

There is a paucity of information on TB incidence in HIV patients on ART in high burden HIV settings including South Africa. Understanding the incidence of TB and associated risk factors over time in patients who are on ART is crucial for effective service planning and intervention strategies. Data on the incidence of TB at different levels of CD4 count is also lacking, and these data, if available, would assist in informing models of TB burden as the ART program matures. Thus, the purpose for undertaking this research is to provide insight into the impact of ART on TB incidence.

1.3 Aims and Objectives

1.3.1 Aims

The aim of the study is to investigate the impact of ART on TB in HIV positive patients attending public health facilities in the Western Cape Province.

1.3.2 Objectives

The objectives of the study are:

- To describe TB incidence in patients co-infected with HIV
- To describe temporal trends in TB incidence in patients with HIV
- To describe TB incidence by CD4 count stratum pre-ART
- To describe TB incidence by CD4 count stratum post-ART
- To estimate the impact of ART on TB incidence

2. Methods

2.1 Study Design

A retrospective cohort study of HIV patients between 2007 and 2016 in the Western Cape Province will be conducted. The retrospective cohort study will allow the description of the HIV population over time and measures of association with TB (risk ratio, odds ratio, hazard ratio) (Mann, 2003, Doll, 2001). The study design is justified as it would not be feasible to accrue sufficient patient numbers prospectively, and, exposures and outcomes can be adequately identified retrospectively from the patient level data.

2.2 Population and Sampling

The study population will be a cohort of adult HIV infected patients attending public health facilities in the Western Cape Province, with HIV status first evidence ascertained between 2007 and 2016. Prior to 2007 the data was incomplete as most of the information systems in the province were mostly paper based. The patients must be free of TB disease at HIV first evidence ascertainment. We will extract an anonymous data set of HIV patients and linked TB events, with HIV treatment start dates, TB outcomes and treatment completion dates, all CD4 counts, age and gender. Thus *a priori* sample size of all available HIV patients aged 15 and above and TB events in the province is going to be derived. This should be adequately powered for precise estimates of event rates and the causal effect of ART, given the large number of HIV and TB patients in the Province. First evidence of HIV and TB is based on laboratory diagnosis, HIV and TB electronic registers, pharmacy data and hospital diagnostic codes.

2.3 Inclusion criteria

- HIV positive patients aged 15 years and above, with HIV first evidence ascertained between 2007 and 2016
- Patients must be free of TB at HIV first evidence
- Patients must not be on ART at HIV first evidence

2.4 Key variables

Cohorts will be described by year of HIV first evidence, ART status, age, gender, TB events, TB disease classification, CD4 counts and co-infection with TB pre and post ART.

2.5 Outcomes

The primary outcome in the study will be the incidence of TB in HIV patients. Incident TB will be defined as the first episode of TB between 2007 and 2016. The incidence of TB will be examined pre and post ART exposure.

3. Data sources and analysis

3.1 Data management

Patient registration system in the Western Cape have evolved to an extent that the same unique patient health identifier is used across source electronic patient systems including hospitals, community health centres and clinics (Western Cape Department of Health, 2013). This unique patient identifier issued by the hospital information system (Clinicom), referred to as the patient master index (PMI) (also called folder number or clinicom number) has created new opportunities to assemble and link individual patient level data across multiple source systems, including laboratory data (NHLS), pharmacy data (JAC), chronic disease dispensing data (CDU) and disease management systems for TB and HIV (TIER.Net, EKAPA [electronic HIV registers], ETR and EDR [electronic TB registers for drug sensitive and drug-resistant TB respectively]) (Western Cape Department of Health, 2013).

The province has a near complete disease management information systems for HIV and TB treatment (Western Cape Department of Health, 2013). Data on HIV and TB patients is routinely collected at health facilities where the patients come regularly for their treatment in the province. Selected patient information critical to programme monitoring is recorded and collated into the centralised electronic HIV and TB databases. The province through the Data Centre at the Health Impact Assessment Unit is proactively curating and integrating this individual patient level data from all the different source systems, linking this data on the PMI from the multiple source systems into a master patient list. All the data used is anonymised for analysis using an internal unique identifier which is used when releasing the anonymised patient level data.

Data will be checked and corrected for any inconsistencies, which include age, gender, HIV and TB first evidence dates and ART start dates. Patients with TB prior to HIV will be removed from further analysis. The data will be managed, cleaned and analysed in STATA 15 (StataCorp, 2017).

3.2 Statistical Analysis

- Descriptive statistics will be employed to summarise the characteristics of the HIV and HIV-TB co-infected population in the province.
- TB incidence will be estimated by gender, age groups, year of HIV first evidence, CD4 count stratum at baseline and CD4 count stratum time-varying in patients who have started and have not started ART using the Cox proportional hazards model.
- Kaplan-Meier estimates and curves will be used to describe patients who have started and who have not started ART by gender, age groups, year of HIV first evidence, CD4 count stratum at baseline and time-varying CD4 count stratum.
- To adjust for time-varying confounding, the Cox proportional hazards marginal structural model (MSM) is going to be used to estimate the effect of HIV treatment on the outcomes. This will include the following steps:
    1. Estimate each subject's probability of being treated (treatment weights) each time (monthly), using logistic regression adjusted for baseline and time-varying covariates
    2. Estimate each subject's probability of being censored (censoring weights) each time (monthly), using logistic regression adjusted for baseline and time-varying covariates
    3. Use the treatment and censoring weights to derive the inverse probability of treatment weights
        a. IPTW is defined as the inverse of each subject's probability of his or her treatment history at each time
        b. Weights may need to be truncated if extreme
    4. Fit a weighted Cox model (approximated by a pooled logistic regression model across all times) for the causal effect of treatment, controlling for baseline covariates but not for time-dependent confounders

4 Ethics

4.1 Ethics approval

Ethics approval for this proposed study will be obtained from the University of Cape Town Health Research Ethics Committee (UCT-HREC). In addition, approval will be obtained from the Western Cape Government Department of Health in order to conduct the study using the routine health data. Ethical principles stated in the Declaration of Helsinki 2013 developed by the World Medical Association(World Medical Association, 2013) will be adhered to.

4.2 Subjects confidentiality

All the patient information will be kept strictly confidential (only anonymised data will be received by the researcher) and the analysis will be conducted on anonymised data to ensure that no personal identifying information is used. In addition, the database will be stored on a secure computer, secured with a password to limit access. Should the study be published, there will be no identifying data, as anonymised data will be used, thus confidentiality of the patients will be maintained.

4.3 Risks and benefits Potential risk

The data to be used in the study has not been collected specifically for research study purposes but rather routinely. Hence there are no risks involved in the analysis of this data. The findings hopefully are going to provide information on the impact of ART on the incidence of TB for different HIV patients. This will be useful in devising TB control strategies and interventions in HIV patients on treatment in the country. This study does not carry any direct harm or risk to the general wellbeing of the patients. The study is not going to offer any monetary reimbursement or any direct benefits to the patients.

4.4 Dissemination and presentation of research findings

The analysis will be prepared for the partial fulfilment of the requirements of the Master of Public Health dissertation to the University of Cape Town, Department of Public Health and Family Medicine. Results and findings will be shared with and presented to the Western Cape Government Department of Health, who are the custodians of health data in the province, and other key stakeholders including the University of Cape Town School of Public Health and Family Medicine. It is hoped this will assist them in devising strategies and interventions which will improve health outcomes of HIV patients. An article will be submitted to a peer reviewed medical journal and abstracts will be submitted to conferences for presentation of findings.

4.5 Conflict of interest statement

No conflicts of interest exist in this study.

5 Budget

This dataset is pre-existing and thus no overhead costs are expected and no funding to analyse these data is required.

6 References

BONNET, M. M., PINOGES, L. L., VARAINE, F. F., OBERHAUSER, B. B., O'BRIEN, D. D., KEBEDE, Y. Y., HEWISON, C. C., ZACHARIAH, R. R. & FERRADINI, L. L. 2006. Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden. *AIDS,* 20**,** 1275-9.

BRINKHOF, M. W., EGGER, M., BOULLE, A., MAY, M., HOSSEINIPOUR, M., SPRINZ, E., BRAITSTEIN, P., DABIS, F., REISS, P., BANGSBERG, D. R., RICKENBACH, M., MIRO, J. M., MYER, L., MOCROFT, A., NASH, D., KEISER, O., PASCOE, M., VAN DER BORGHT, S. & SCHECHTER, M. 2007. Tuberculosis after initiation of antiretroviral therapy in low-income and high-income countries. *Clin Infect Dis,* 45**,** 1518-21.

DANIEL, R. M., COUSENS, S., DE STAVOLA, B., KENWARD, M. G. & STERNE, J. 2013. Methods for dealing with time-dependent confounding. *Statistics in medicine,* 32**,** 1584-1618.

DEMBELE, M., SALERI, N., CARVALHO, A. C., SAOUADOGO, T., HIEN, A. D., ZABSONRE, I., KOALA, S. T., SIMPORE, J. & MATTEELLI, A. 2010. Incidence of tuberculosis after HAART initiation in a cohort of HIV-positive patients in Burkina Faso. *Int J Tuberc Lung Dis,* 14**,** 318-23.

DOLL, R. 2001. Cohort studies: history of the method. II. Retrospective cohort studies. *Soz Praventivmed,* 46**,** 152-60.

DUERDEN, M. 2009. What are Hazard ratios. *London: Hayward Medical Communications*.

EDMONDS, A., LUSIAMA, J., NAPRAVNIK, S., KITETELE, F., VAN RIE, A. & BEHETS, F. 2009. Anti-retroviral therapy reduces incident tuberculosis in HIV-infected children. *Int J Epidemiol,* 38**,** 1612-21.

FEWELL, Z., HERNÁN, M. A., WOLFE, F., TILLING, K., CHOI, H. & STERNE, J. A. C. 2004. Controlling for time-dependent confounding using marginal structural models. *Stata Journal,* 4**,** 402-420.

GIRARDI, E., SABIN, C. A., D'ARMINIO MONFORTE, A., HOGG, B., PHILLIPS, A. N., GILL, M. J., DABIS, F., REISS, P., KIRK, O., BERNASCONI, E., GRABAR, S., JUSTICE, A., STASZEWSKI, S., FATKENHEUER, G. & STERNE, J. A. 2005. Incidence of Tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clin Infect Dis,* 41**,** 1772-82.

GOLUB, J. E., PRONYK, P., MOHAPI, L., THSABANGU, N., MOSHABELA, M. & STRUTHERS, H. 2009. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS,* 23.

GOLUB, J. E., SARACENI, V., CAVALCANTE, S. C., PACHECO, A. G., MOULTON, L. H., KING, B. S., EFRON, A., MOORE, R. D., CHAISSON, R. E. & DUROVNI, B. 2007. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS (London, England),* 21**,** 1441-1448.

GUPTA, A., WOOD, R., KAPLAN, R., BEKKER, L.-G. & LAWN, S. D. 2012. Tuberculosis Incidence Rates during 8 Years of Follow-Up of an Antiretroviral Treatment Cohort in South Africa: Comparison with Rates in the Community. *PLoS ONE,* 7**,** e34156.

GUPTA, R. K., RICE, B., BROWN, A. E., THOMAS, H. L., ZENNER, D., ANDERSON, L., PEDRAZZOLI, D., POZNIAK, A., ABUBAKAR, I., DELPECH, V. & LIPMAN, M. 2015. Does antiretroviral therapy reduce HIV-associated tuberculosis incidence to background rates? A national observational cohort study from England, Wales, and Northern Ireland. *The Lancet HIV,* 2**,** e243-e251.

HARAKA, F., GLASS, T. R., SIKALENGO, G., GAMELL, A., NTAMATUNGIRO, A., HATZ, C., TANNER, M., FURRER, H., BATTEGAY, M. & LETANG, E. 2015. A Bundle of Services Increased Ascertainment of Tuberculosis among HIV-Infected Individuals Enrolled in a HIV Cohort in Rural Sub-Saharan Africa. *PLOS ONE,* 10**,** e0123275.

HERMANS, S. & MANABE, Y. 2015. Population-level tuberculosis incidence in the ART era. *Lancet Infect Dis.*

HERNAN, M. A., BRUMBACK, B. & ROBINS, J. M. 2000. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology,* 11**,** 561-70.

HERNAN, M. A., BRUMBACK, B. A. & ROBINS, J. M. 2002. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med,* 21**,** 1689-709.

LAWN, S. D., BADRI, M. & WOOD, R. 2005. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS,* 19**,** 2109-16.

KAPLAN, R., CALDWELL, J., BEKKER, L., JENNINGS, K., LOMBARD, C., ENARSON, D., WOOD, R. & BEYERS, N. 2014. Integration of TB and ART services fails to improve TB treatment outcomes: comparison of ART/TB primary healthcare services in Cape Town, South Africa. *South African Medical Journal,* 104**,** 204-208.

LAWN, S. D., MYER, L., EDWARDS, D., BEKKER, L. G. & WOOD, R. 2009. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS,* 23**,** 1717-25.

LAWN, S. D., WOOD, R., DE COCK, K. M., KRANZER, K., LEWIS, J. J. & CHURCHYARD, G. J. 2010. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis,* 10**,** 489-98.

MANN, C. J. 2003. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg Med J,* 20**,** 54-60.

MOORE, D., LIECHTY, C., EKWARU, P., WERE, W., MWIMA, G., SOLBERG, P., RUTHERFORD, G. & MERMIN, J. 2007. Prevalence, incidence and mortality associated with tuberculosis in HIV-infected patients initiating antiretroviral therapy in rural Uganda. *AIDS,* 21**,** 713-9.

PADMAPRIYADARSINI, C., NARENDRAN, G. & SWAMINATHAN, S. 2011. Diagnosis & treatment of tuberculosis in HIV co-infected patients. *The Indian journal of medical research,* 134**,** 850-865.

PARSONS, L. M., SOMOSKÖVI, A., GUTIERREZ, C., LEE, E., PARAMASIVAN, C. N., ABIMIKU, A. L., SPECTOR, S., ROSCIGNO, G. & NKENGASONG, J. 2011. Laboratory diagnosis of tuberculosis in resource-poor countries: challenges and opportunities. *Clinical microbiology reviews,* 24**,** 314-350.

RAJASEKARAN, S., RAJA, K., JEYASEELAN, L., VIJILAT, S., PRIYA, K., MOHAN, K., PARVEZ, A., MAHILMARAN, A. & CHANDRASEKAR, C. 2009. Post-HAART tuberculosis in adults and adolescents with HIV in India: incidence, clinical and immunological profile. *Indian J Tuberc,* 56**,** 69-76.

ROBINS, J. M., BLEVINS, D., RITTER, G. & WULFSOHN, M. 1992. G-estimation of the effect of prophylaxis therapy for Pneumocystis carinii pneumonia on the survival of AIDS patients. *Epidemiology,* 3**,** 319-36.

ROBINS, J. M., HERNAN, M. A. & BRUMBACK, B. 2000. Marginal structural models and causal inference in epidemiology. *Epidemiology,* 11**,** 550-60.

SANTORO-LOPES, G., FELIX DE PINHO, A. M., HARRISON, L. H. & SCHECHTER, M. 2002. Reduced Risk of Tuberculosis among Brazilian Patients with Advanced Human Immunodeficiency Virus Infection Treated with Highly Active Antiretroviral Therapy. *Clinical Infectious Diseases,* 34**,** 543-546.

STATACORP 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

SUTHAR, A. B., LAWN, S. D., DEL AMO, J., GETAHUN, H., DYE, C., SCULIER, D., STERLING, T. R., CHAISSON, R. E., WILLIAMS, B. G., HARRIES, A. D. & GRANICH, R. M. 2012. Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS Medicine,* 9**,** e1001270.

VAN RIE, A., WESTREICH, D. & SANNE, I. 2011. Tuberculosis in patients receiving antiretroviral treatment: incidence, risk factors and prevention strategies. *Journal of Acquired Immune Deficiency Syndromes (1999),* 56**,** 349-355.

WESTERN CAPE DEPARTMENT OF HEALTH 2013. Strategic approach to patient-level health data harmonisation and integration. Department of Health, Western Cape.

WILLIAMS, B. G. 2013. Could ART increase the population level incidence of TB? *arXiv preprint arXiv:1302.0503*.

WILLIAMS, B. G. & DYE, C. 2003. Antiretroviral Drugs for Tuberculosis Control in the Era of HIV/AIDS. *Science,* 301**,** 1535-1537.

WORLD HEALTH ORGANISATION 2014. Global Tuberculosis Report 2014. Geneva: World Health Organisation.

WORLD HEALTH ORGANISATION 2015. Global Tuberculosis Report 2015. 20th Edition ed. Geneva: World Health Organisation.

WORLD MEDICAL ASSOCIATION 2013. World medical association declaration of helsinki: Ethical principles for medical research involving human subjects. *JAMA,* 310**,** 2191-2194.

SECTION B: STRUCTURED LITERATURE REVIEW

1.1 Introduction

There is a dual epidemic of Tuberculosis (TB) and human immuno-deficiency virus (HIV), posing a major threat to global public health with the interaction between the two escalating the burden of disease and death in many populations (Harries et al., 2010, Suthar et al., 2012b). HIV infection is the strongest risk factor for developing TB disease and it is fuelling its resurgence, as well as the risk of death during TB treatment (Corbett et al., 2003, Harries et al., 2010). TB is the commonest acquired immune-deficiency syndrome (AIDS) defining condition globally (Moreno et al., 2008). TB is also endemic in the HIV negative population (Corbett et al., 2003) in many high HIV-burden countries. Antiretroviral treatment (ART) has been shown to reduce the impact of HIV on TB incidence, with risk of TB being reduced in previous studies by 65% (Suthar et al., 2012).

1.2 Objectives

This literature review seeks to appraise and summarise published articles on:

- Burden of HIV, TB and HIV and TB co-morbidity
- ART treatment and coverage
- TB incidence in HIV patients on and not on ART

1.3 Methodology

1.3.1 Search strategy

A systematic literature review was conducted using the PICO strategy to identify literature regarding TB incidence in HIV patients, either on ART or not on ART. PubMed online database and google scholar were used to search for relevant articles using a combination of search terms that include *'tb incidence', 'HIV', 'ART',' antiretroviral therapy ','adults', 'burden'*. Search was restricted to English language articles only, with no time restriction. A periodic search for new articles for this review was conducted between October 2016 and July 2018, with articles included as appropriate after review. Abstracts and titles of resulting articles were reviewed, with further follow up and review on related articles shown in PubMed. Articles were included in the review if they were relevant to the study objectives.

The search strategy aimed to identify and include studies reporting on the burden of disease of HIV and TB, TB incidence in HIV patients either on treatment or not, impact of ART on TB incidence, ART coverage. An effort was made to be systematic and thorough in finding all the prior studies estimating the impact of ART on TB, without formally seeking to conduct a

systematic review, which would be beyond the scope of this dissertation. Articles on children under the age of 15 were excluded from the review.

1.4 Burden of TB

1.4.1 Global burden of TB

TB remains a global health threat and is the leading cause of morbidity and mortality (Churchyard et al., 2014, Raviglione and Sulis, 2016, World Health Organization, 2017, Floyd et al., 2018). Globally, 10.4 million people are estimated to have been infected with TB in 2016 with 6.3 million of these TB cases reported to the WHO (World Health Organization, 2017). An estimated 90% of these TB cases were adults, 65% were male and 10% of them were living with HIV. South-East Asia Region had 45% of the incident cases, with 25% from the African Region, 17% from Western Pacific Region with smaller proportions of cases occurring in Eastern Mediterranean Region (7%), European Region (3%) and American Region (3%) (World Health Organization, 2017).

Two-thirds of the cases are mainly from seven countries, namely India, Indonesia, China, Philippines, Pakistan, South Africa and Nigeria. The WHO notes that TB is endemic in most of these developing countries due to weak health and surveillance systems, under-diagnosis and underreporting of cases (World Health Organisation, 2015). Results from the global burden of disease study of 2015 focusing on the global burden of TB showed lower estimates of TB incidence and deaths globally but similar trends regionally, although these lower estimates are due to different computational methods used (Kyu et al., 2018).

Despite progress being made in reduction of TB mortality, TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent (World Health Organization, 2017, Floyd et al., 2018, Kyu et al., 2018). There were 1.3 million TB deaths among HIV negative people and an additional 374 000 deaths among HIV positive people in 2016 (World Health Organization, 2017). Africa had 25% of the TB related deaths occurring in the region.

1.4.2 Burden of TB in South Africa

Chaisson and Martinson (2008) state that Africa is facing the worst TB epidemic since the advent of the antibiotic era and it is largely driven by a generalized HIV epidemic. They note that this has been compounded by weak health care systems, inadequate laboratories, and conditions that promote transmission of infection (Chaisson and Martinson, 2008). TB is also noted to be mostly concentrated in Southern Africa where most of the countries in this region apart from South Africa have poor vital registration and incomplete notification systems (Kyu et al., 2018)

South Africa has been noted to have one of the world's worst TB epidemics driven by HIV and accounts for about 4% of the global incident cases (Churchyard et al., 2014, World Health Organization, 2017). South Africa had an estimated incidence of 781 TB cases per 100 000 population in 2016 (World Health Organization, 2017). Churchyard et al (2014) highlight South Africa to have the highest estimates of TB incidence and prevalence, the second highest number of diagnosed multidrug-resistant TB cases, and the largest number of HIV-associated TB cases.

TB incidence trends by province in South Africa have shown consistent declines in recent years, despite incidence in all of them being above 250 per 100 000 population, the level declared to be a health emergency by the WHO (National Iinstitute for Communicable Diseases, 2017). In 2015, the province with the highest incidence was Eastern Cape with 865 cases per 100 000 population, more than three times the lowest incidence of 251 cases per 100 000 in Limpopo (National Iinstitute for Communicable Diseases, 2017). The Western Cape Province had an incidence of 625 per 100 000 people in 2015, a decline from 980 in 2004 (National Iinstitute for Communicable Diseases, 2017).

1.5 Burden of HIV and treatment

1.5.1 Global burden of HIV

Despite the remarkable progress that has been made in curbing the HIV/AIDS epidemic worldwide, the number of people living with HIV/AIDS has been increasing, from 2.4 million in 1985 to 36.9 million in 2017, with disparate levels and trends of the epidemic at country level (Wang et al., 2016, UNAIDS, 2017, UNAIDS, 2018). HIV-related mortality has been declining since the mid-2000s due to the introduction of antiretroviral therapy (ART) (UNAIDS, 2017). However, annual incidence has stayed relatively constant since 2005, after a period of faster decline prior to 2005 (Wang et al., 2016). UNAIDS state that new infections have been reduced by almost half, from a peak in 1996 of about 3.4 million new infections to about 1.8 million new infections in 2017 (UNAIDS, 2018).

More than two thirds of all people living with HIV globally knew their HIV status in 2017, and of those who knew their HIV status 79% are noted to be accessing ART (UNAIDS, 2018). More than half of all people living with HIV (59%) are estimated to be on treatment, and this is due to the global scale-up of ART, with the number of people on ART more than doubling, from an estimate of about 8 million in 2010 to about 21.7 million in 2017 ((UNAIDS, 2018). 51% of the people living with HIV globally are women, and they are noted to have a higher treatment coverage and better adherence to treatment than men (UNAIDS, 2017). The increase in people

on ART was greater for women, 3.3% to 42.4%, than men, 6.4% to 38.6%, between 2005 and 2016 (Wang et al., 2016). There has been an increase in the number of people starting treatment globally each year over time, from about 564 000 in 2005 to around 2.4 million in 2016 (UNAIDS, 2017).

Sub-Saharan Africa is the most profoundly affected region in the world by the HIV epidemic, with 75.4% of infections in 2015, and 6 countries from Southern Africa having a prevalence above 10% (Wang et al., 2016). 19.6 million people in Eastern and Southern Africa are estimated to be living with HIV in 2016, which is more than half of the people living with HIV globally (Williams and Dye, 2003). Despite the high numbers of people living with HIV in these regions, Eastern and Southern Africa have made huge strides in getting people to start ART early (Wang et al., 2016). In people living with HIV in Eastern and Southern Africa at the end of 2017, 81% of the people were aware of their HIV status with about 66% of the people on treatment (UNAIDS, 2018).

The 12.9 million people on ART in Eastern and Southern Africa in 2017 represented an almost threefold increase over 2010 numbers, translated into a coverage increase from 23% to 66% between 2010 and 2016 (UNAIDS, 2017, UNAIDS, 2018). UNAIDS noted that treatment coverage was highest in Botswana at 83% and Rwanda at 80%, but several countries with large populations of people living with HIV (Ethiopia [59%], South Africa [56%] and Mozambique [54%]), reported coverage below the regional average.

1.5.2 HIV burden in South Africa

In South Africa, the number of people living with HIV has increased from an estimated 4.94 million in 2002 to 7.06 million in 2017, an increase of about 43% (Statistics South Africa, 2017). The HIV prevalence in the total population increased from 10.9% in 2002 to 12.6% in 2017 (Statistics South Africa, 2017). The prevalence in the country is slightly higher in adults between the ages of 15 and 49, with an estimated prevalence of 18% (peak in the 25-34 age group) in 2017, in comparison to the other ages (Western Cape Provincial AIDS Council, 2016, Statistics South Africa, 2017). Prevalence in the 15-49 ages was estimated to be higher in women (21.3%) than men (18%) in 2017 (Statistics South Africa, 2017). The increase in the national ART roll-out since its inception in 2005 has resulted in a decline in AIDS related deaths, reversed historical patterns of increasing mortality, and has extended the lifespan of many people in the country (Statistics South Africa, 2017). In 2017, 4.4 million people were estimated to be on ART in South Africa, the largest treatment programme in the world (UNAIDS, 2016, UNAIDS,

2018). UNAIDS estimates 61% of people living with HIV to be on ART in the country in 2017, with more adult women (66%) compared to adult men (53%) living with HIV on ART (UNAIDS, 2018).

1.5.3 HIV burden in the Western Cape Province

In the Western Cape Province, the number of people living with HIV are estimated to have increased from 269 259 to 430 491 between 2007 and 2016, with the number of new infections decreasing from 28 615 to 19 396 in the same period (Johnson et al., 2017). The prevalence of HIV in the province is estimated to have slightly increased from 5.0% to 6.6% between 2007 and 2016, the lowest in the country (Shisana et al., 2014, Johnson et al., 2017). The number of patients on ART are noted to have increased from 32 100 (28 453 for patients aged 15+) in 2007 to 216 025 (208 631 for patients aged 15+) in 2016 (Johnson et al., 2017). The 2015 Western Cape sero-prevalence HIV Antenatal Survey estimated an HIV prevalence of 18.9% in the Western Cape Province among the participants, the lowest in the country (Department of Health, 2017). The participants are expectant mothers; thus, they are expected to have a higher prevalence than the average population as new mothers are, by definition, a sexually active sector of the population not using barrier methods of contraception.

1.5.4 Treatment regimens for HIV

WHO guidelines for initiating ART have evolved over the past 10 to 15 years. In 2002, ART was firstly recommended for HIV infected patients in moderate and advanced stages of infection to limit disease progression to mortality (World Health Organization, 2002, Plazy et al., 2015) whilst others recommended that ART would be more effective if initiated earlier and before advanced HIV disease (Walensky et al., 2009, Grinsztejn et al., 2014). The WHO expanded their recommendations in 2006, which were further reinforced in 2010 with recommendations for ART initiation for HIV patients with CD4 counts lower than 350 cells/μL, when most people are asymptomatic (World Health Organization, 2006, World Health Organization, 2010, Plazy et al., 2015). The WHO guidelines in 2013 suggested an expansion of the ART eligibility criteria at CD4 counts less than 500 cells/μL (World Health Organization, 2013). In addition to the clinical benefits, the expanded eligibility was also premised on the potential to reduce transmission. This was based on findings showing that ART lowered viral load in HIV infected individuals and significantly decreased the risk of HIV transmission within sero-discordant couples (Attia et al., 2009, Cohen et al., 2011).

Prior to 2010 in South Africa, the eligibility for ART in adults included a CD4 count a CD4 cell count ≤ 200 cells/μl , or an AIDS-defining diagnosis (excluding extra-pulmonary TB) (Stinson et al., 2017). These guidelines were then changed in 2010 to a CD4 threshold of < 350 cells/μl for pregnant women and people with TB. These were further changed in 2013 to include patients with a CD4 cell count < 350 cells/μl, all patients with TB and pregnant women irrespective of CD4 count. Further revisions were implemented in 2015 for the provision of ART for all HIV-infected adults with a CD4 cell count ≤ 500 cells/μl.

1.5.5 History of ART in South Africa

South Africa has been rolling out ART for more than 15 years, and the country has the largest number of people living with HIV and has the largest ART programme globally, with over 3.8 million people estimated to be on treatment as of 2016 (Massyn et al., 2016, Johnson et al., 2017). During the first decade of care, South African ART guidelines lagged behind those stipulated by the WHO regarding ART eligibility due to political resistance to ART rollout (Nattrass, 2006, Chigwedere et al., 2008), but in 2011 were brought in line with 2010 WHO recommendations for the first time (Bekker et al., 2014, Plazy et al., 2015). Since coming into line with WHO ART guidelines in 2010, and the announcement of a comprehensive care, management and treatment programme by the Department of Health in late 2003, access to ART in SA has increased dramatically with many more patients being enrolled into treatment.

It is estimated that 86% of HIV positive adults had been diagnosed in the country in 2015, with little variation between the nine provinces (Johnson et al., 2017). The diagnosed adults, 57% were reported to be on ART, with variation between the provinces, from 51% in North West Province to 73% in the Northern Cape Province (Johnson et al., 2017). The authors noted that overall ART coverage varied from 43% in Gauteng to 62% in Northern Cape Province. Meanwhile the South African National HIV prevalence, incidence and behaviour survey estimates ART among people living with HIV to have doubled from 16.6% in 2008 to 31.2% in 2012 (Shisana et al., 2014). They also noted a significant difference between the proportion of men (25.7%) and women (34.7%) on ART, a finding that is due to gender differences in health seeking behaviour as well as the fact that all pregnant women access antenatal care and are tested for HIV, and thus higher rates of ascertainment for women accessing antenatal care facilitating them into treatment (Shisana et al., 2014). The National Department of Health in 2013 noted that the rapid scale-up of ART services in the country resulted in a four-fold increase in the number of people receiving ART between 2009 and 2012 (Department of Health, 2014).

In 2016, South Africa implemented the WHO evidence based guidelines of Universal Test and Treat (UTT), a faster strategy towards attaining the global 90-90-90 targets by 2020 (Department of Health, 2016, Massyn et al., 2016). These guidelines are based on evidence that early initiation on ART results in better clinical outcomes than delayed treatment (Massyn et al., 2016). The global 90-90-90 target, were set by UNAIDS to achieve 90% rate of diagnosis in HIV positive individuals, to provide ART to 90% of diagnosed individuals and to achieve virological suppression in 90% of ART patients (UNAIDS, 2014). Despite 3.8 million people on ART in South Africa, it is estimated that the program is only reaching 53% of those who are eligible for treatment under the new test and treat policy in the country (SANAC, 2017).

1.6 Dynamics of HIV/TB co-infection

1.6.1 Global HIV/TB co-infection

Globally TB and HIV are the biggest threats to public health (Suthar et al., 2012b).
In 2016, 1.4 million (13%) new TB cases were amongst people living with HIV worldwide (World Health Organization, 2017). WHO also estimated 1.3 million TB deaths among HIV negative people and 374 000 deaths among HIV positive people worldwide in 2016. TB is the main cause of mortality and morbidity in people living with HIV and is the most common cause of death in HIV positive adults, and the greatest burden is in sub-Saharan Africa due to the generalized HIV epidemic, especially in Southern Africa where more than 50% of new tuberculosis cases are co-infected with HIV (Corbett et al., 2003, Harries et al., 2010, Rangaka et al., 2014, World Health Organization, 2017).

1.6.2 Risk of HIV/TB co-infection

In a number of different settings, the risk of TB has been demonstrated to be higher in HIV-infected patients. HIV infection is the strongest risk factor for TB and has fuelled its resurgence (Corbett et al., 2003, Harries et al., 2010). WHO (2017) state that HIV-positive people are 20 to 30 times more likely to develop TB disease than HIV-negative people. HIV is noted to be one of the major driving forces for the persisting TB epidemic in Sub-Saharan Africa, and a strong correlation between HIV prevalence and an elevated risk of TB incidence has been observed in the region (Musa et al., 2015). Various studies conducted in different countries of differing HIV prevalence have also shown this strong correlation. In a 28-year retrospective cohort study in Israel, they noted an elevated risk of TB incidence in people living with HIV, more especially those originating from high HIV and TB prevalence countries as compared to the locals (Mor et al., 2013). In another study in England, Wales and Northern Ireland, people living with HIV

originating from sub-Saharan Africa also had higher elevated risk of TB incidence, with 80% of them having HIV and TB co-infection (Zenner et al., 2015).

1.6.3 HIV/TB co-infection in South Africa

In the African region, where the burden of HIV associated TB is highest, 74% of the new TB cases were among people living with HIV and 40% of deaths among HIV-positive people were due to TB (World Health Organization, 2017). South Africa has the largest HIV and one of the largest TB epidemics in the world (Evans, 2013, Massyn et al., 2016, Western Cape Provincial AIDS Council, 2016, Abdool Karim et al., 2009). As of 2017, 60% of people with TB were noted to be living with HIV in the country.

HIV being the key driver of the TB epidemic, the proportion of TB patients who know their HIV status increased considerably from 43.3% in 2008 to 94.8% in 2015 in the country (Massyn et al., 2016). This shows that a high proportion of TB patients know their HIV status in the country. For the Western Cape, the proportion of TB patients knowing their HIV status is estimated to be 96.1%, which is the highest in the country.

In 2015, the average TB and HIV co-infection across South Africa was 56.7% (Massyn et al., 2016). TB patients in Gauteng, Mpumalanga and KwaZulu-Natal had the highest co-infection at 68.4%, 68.1% and 63.6%, respectively. The Eastern Cape, Northern Cape and Western Cape had far lower HIV co-infection at 45.2%, 41.1% and 38.5%, respectively. According to the 2014 World Health Organization Global TB Report, 62% of all TB cases in South Africa are co-infected with HIV and only 66% of these received antiretroviral therapy (ART) during TB treatment (World Health Organisation, 2014).

South Africa currently has the largest antiretroviral programme in the world, which will expand even more as the new policy of universal testing and treating continues to be rolled out (Massyn et al., 2016). It is important that TB patients are aware of their HIV status so that if they are dually infected with TB and HIV, antiretroviral treatment (ART) can be started immediately. In the country, the number of co-infected patients on antiretroviral therapy (ART) increased from 28.0% in 2011 to 84.5% in 2015. ART coverage in the general population is lower than in patients co-infected with HIV and TB, and is estimated to be 59.1% in 2016 and increase from 6.4% in 2007 (Johnson et al., 2017). The Western Cape had the lowest proportion of co-infected patients on ART of 75.7% in 2016 which is higher than the ART coverage in the general population of 53% in the same year (Massyn et al., 2016, Johnson et al., 2017) .

For many years, TB and HIV care were largely separate, however robust efforts have been made to tackle them simultaneously. The integration of TB and HIV services have been mandated in the National Strategic Plan, South African National AIDs council (SANAC) and National TB Programme to ensure that co-infected patients receive appropriate care and treatment (Department of Health, 2014, SANAC, 2017). The policy has stated the need for integration through co-location of the HIV and TB services nationwide. Various initiatives have been implemented since 2012 which include proactive diagnosis of TB among people living with HIV using GeneXpert, integrated HIV/TB services for people in the mining industry, correctional facilities, communities surrounding gold mines and informal settlements, collection and improvements in information's systems on HIV/TB.

1.7 TB incidence in HIV patients on ART

In this section we systematically reviewed the studies estimating TB incidence and associations between ART and TB incidence in HIV-infected patients. We have included studies on TB incidence and the impact of ART, as study objectives cover both. Tables 1 to 3 summarise studies describing the impact of ART on TB incidence in people living with HIV. They include the setting where the study was conducted, methods used, sample size, key findings and summary of the results. We have included studies from developed countries to show the disparities when compared to South Africa.

1.7.1 Characteristics of studies

Forty studies met the inclusion criteria on TB incidence and associations between ART and TB incidence in HIV infected patients, with 15 of the studies from developed countries, and 25 from developing countries (10 from South Africa). Table 1 to 3 describes the characteristics of the included studies conducted in developed countries, developing countries and South Africa respectively.

1.7.2 Study designs, sample sizes and calendar periods

Thirty-eight of the studies were cohort studies (retrospective and prospective), while the remaining two studies were a systematic review and meta-analysis of 11 cohort studies and a meta-analysis of 9 cohort studies respectively. The studies had follow-up periods ranging from 1 to 14 years. Sample sizes of studies conducted in developed countries ranged from 165 to 65 121, and the studies included events between 1980 and 2015. Sample sizes of studies conducted in developing countries ranged from 219 to 67 686, with events from 2003 to 2014.

Sample sizes of studies conducted in South Africa ranged from 264 to 74 074, with events from 1992 to 2016.

Of the 40 studies, 21 studies estimated the association between ART and TB incidence, 10 from developed countries, 5 from developing countries excluding South Africa and 6 from South Africa. Of the 21 studies, 10 studies (5 of these in the developed countries, 4 in developing countries and 1 in South Africa) estimated the impact of ART on TB incidence with adjustment for baseline and time-varying covariates using conventional methods, and 4 studies (3 of these in the developed countries, one in South Africa) used causal analysis to adjust for time-varying confounding. Of the 19 which did not estimate the impact of ART on TB incidence, 5 are from developed countries, 10 from developing countries excluding South Africa and 4 from South Africa. These only estimated TB incidence, and other associations with incidence.

1.7.3 Results from studies

The studies reported results either as measures of association (hazard ratios, risk ratios, odds ratios) or as incidence, with some reporting both. In this section we are going to highlight studies with measures of association that had adjustment for time-varying confounding. For these studies the impact of ART in reduction of TB incidence ranged from 32% to 80%.

In the systematic review and meta-analysis of 11 studies in developing countries by Suther et al (2012), ART was associated with a 65% reduction in TB incidence. They also estimated TB incidence reduction at all CD4 count stratum of 84%, 66% and 57% for CD4 count <200, CD4 count between 200 and 350 and CD4 count >350 respectively. The meta-analysis of 9 cohort studies by Lawn et al (2010), ART was associated with a 67% reduction in TB incidence.

In studies conducted in the developed countries using conventional methods, there were small and substantial reductions in TB incidence associated with ART observed. Jones et al (2000) and Santoro-Lopez et al (2002) estimated an 80% reduction in TB incidence. Moreno et al (2008), Muga et al (2007) and Golub et al (2007), estimated reduction in TB incidence of 74%, 69% and 59% respectively. While in studies that used causal analysis, there were reductions of 73%, 44% and 32% estimated by Huang et al (2015), del Armo et al (2012) and Petit et al (2011) respectively.

Two studies conducted in the developing countries by Lawn et al (2010) and Yirdaw et al (2014) and estimated reduction of TB incidence due to ART of 67% and 68% respectively using conventional methods. While Ayele et al (2015) estimated the reduction in the combined effect of ART and IPT of 60%. In studies from South Africa, Golub et al (2009) estimated a significant

impact of ART on TB incidence reduction of 64%, while Bachman et al (2015) estimated a low reduction of 33% adjusting for time-varying covariates. While in the only study to adjust for time-varying confounding in South Africa, Fairall et al (2008) estimated a 39% reduction in TB incidence.

In the 10 studies that used conventional methods, adjusting for the covariates was more likely to accentuate rather than attenuate the effect of ART on TB incidence, while in the 4 studies with adjustments for time-varying confounding (3 from developed countries and 1 from south Africa), the causal analysis led to further accentuation of the treatment effect.

Table 1: Summary of included studies global /developed countries

Authors, year	setting	Study design and methods	Population and sample seize	Impact of ART estimated	Key findings	HR (95% CI) /incidence (95% CI)
(Huang et al., 2015)	China, Shenzhen	-Cohort study with repeated measure. -Pooled logistic regression and Marginal structural models adjusted for baseline and time-varying covariates.	6 897 Adult HIV patients aged 18+ followed up between December 2003 and February 2014	Yes	ART associated with 73% reduction in TB incidence	-Unweighted model, no covariates: **HR 0.34 (95% CI, 0.26-0.43)** -Unweighted model, baseline and time-varying covariates: **HR 0.29 (95% CI, 0.21-0.38)** -Weighted model, baseline covariates: **HR 0.27 (95% CI, 0.19-0.37)**
(del Amo et al., 2012)	12 cohorts from High income countries (United States and Europe)	-Cohort Study -Time-dependent Cox regression	65 121 HIV positive, ART naïve, AIDS free adults ≥18 years followed up between 1996 and 2007	Yes	-ART associated with a 44% reduction in TB incidence in patients who initiate ART	-Unweighted model, baseline covariates **HR 0.81 (95% CI, 0.67 - 0.97)** -Unweighted model, baseline and time-varying covariates: **HR 1.03 (95% CI, 0.86-1.24)** -Weighted model, baseline covariates: **HR 0.56, (95% CI, 0.44-0.72**)
(Miranda et al., 2007)	HIV treatment facilities, Brazil	-Retrospective cohort study -Cox proportional hazards analysis.	-463 HIV positive adults aged 18+ followed up between 1 January 1995 and 31 December 2001	Yes	-HAART associated with an 80% reduction in TB incidence	**HR 0.2 (95% CI, 0.1- 0.6)**
(Golub et al., 2007)	29 Public clinics, Rio de Janeiro, Brazil	-Retrospective cohort study -Cox proportional hazards regression	11 026 HIV positive patients, between 1 September 2003 and 1 September 2005	Yes	-ART associated with a 59% reduction in TB incidence	-Adjusted HR **0.41 (95%CI, 0.31 – 0.54)** -Unadjusted HR **0.55 (95%CI, 0.45 – 0.68)**
(Girardi et al., 2000)	28 Hospital units, Italy	-Prospective cohort study (multicentre) -Cox proportional hazards regression	2 160 HIV positive adult patients aged 18+, between 1 May 1995 and 30 April 1996	Yes	-ART significantly reduced the risk of TB, with ART associated with a 92% reduction in TB incidence	-Adjusted HR triple ART combination **0.08 (95% CI, 0.01 – 0.88)** -Adjusted HR double ART combination **0.16 (95% CI, 0.03 – 0.74)**

(Santoro-Lopes et al., 2002)	Brazil	-Prospective cohort study -Cox proportional hazards regression	255 HIV positive patients, between January 1991 and December 1994	Yes	-Use of ART reduced incidence of TB in high HIV prevalence areas -ART associated with an 80% reduction in TB incidence	-Adjusted HR **0.2 (95%CI, 0.04 – 1.13)**
(Muga et al., 2007)	6 cities in Spain	-Retrospective and prospective cohort study (multicentre) -Cox proportional hazards regression	2 238 HIV positive patients, between 1980 and 2004	Yes	-ART associated with a 69% reduction in TB incidence	-HR **0.31 (95%CI, 0.17 – 0.54)**
(Jones et al., 2000)	100 clinics and hospital in 11 US cities	-Cohort study -Poisson regression model	Between January 1996 and June 1998	Yes	-The use of HAART reduced the risk of TB, with a risk reduction of 80%	-adjusted RR **0.2 (95% CI, 0.1 – 0.5)**
(Pettit et al., 2011)	Care centre Nashville, TN United States of America	-Observational cohort study -Marginal structural model	-4 534 HIV positive adult patients followed up between January 1998 and December 2008.	Yes	-TB incidence declines with duration on HAART in this low TB incidence setting. -HAART associated with a 32% reduction in TB incidence in the first 180 days since initiation, and a 90% reduction after 180 days initiation	-Weighted model, baseline covariates <180 days since HAART initiation: **HR 0.68 (95% CI, 0.14–3.22**) -Weighted model, baseline covariates>180 days since HAART initiation: **HR 0.10 (95% CI, 0.04–0.31**)
(Moreno et al., 2008)	10 Spanish hospitals	-Multicentre, hospital-based cohort study -Poisson regression	4 268 patients followed up between 1 January 1997 and 31 December 2003.	Yes	-HAART was associated with 74% risk reduction in the incidence of TB -HAART associated with lower TB rates -Women had lower TB rates than men	-adjusted RR **0.26 (95% CI, 0.16–0.40)** -unadjusted RR **0.39 (95% CI, 0.21–0.70)**
(Girardi et al., 2005)	12 cohorts from Europe and North America	-Cohort study. -Multivariate Poisson regression model analysis	12 cohorts with sample size of 17 142 treatment naïve HIV patients between 1996 and 2003.	No	Use of HAART reduces TB incidence	-TB incidence rate 4.69, (95% CI, 3.99-5.39) per 1 000 pyrs - TB incidence rate males 4.3 per 1 000 person-years - TB incidence rate females 5.8 per 1 000 person-years
(Lannoy et al., 2008)	7 Health centres in Brasilia Federal District in Brazil	-Retrospective cohort study -Cox proportional hazard regression	-281 HIV positive adults, ART naive, AIDS program Health Department of Brasilia in 1998, followed up for 60	No	-Non-use of ART was independently associated with increased risk of TB	-TB incidence rate 1.24 (95% CI, 0.66-2.12) per 100-person years

			months between January 1998 and December 2003			
(Zenner et al., 2015)	England, Wales and Northern Ireland	-Retrospective Cohort study -Cox proportional hazard regression	44 050 HIV adult patients aged 15+ between 2000 and 2008 linked to the national TB register and death register	No	Incidence of TB among HIV-diagnosed persons remained very high in the first 6 months after HIV diagnoses.	-Cumulative TB incidence rate 2.13 per 100 person-years -7.2% of the HIV individuals developed TB
(Reboucas et al., 2017)	Salvador, Bahia, Brazil.	-Retrospective cohort study	165 HIV/AIDS patients aged 18 and older on ART for at least six months followed up between January 2013 and December 2015.	No	High incidence of TB observed, and the incidence of TB was significantly associated with biological failure.	8.5% of the patients developed TB within 2 years
(Mor et al., 2013)	National HIV and TB registries, Israel	-Retrospective cohort study -Cox proportional hazards regression	6 579 HIV patients between 1983 and 2010	No	-TB incidence declined with duration on ART -ART associated with reduction in TB incidence	-Overall TB incidence rate 6.9 (95% CI, 1.8-12.0) per 1 000 person-years

Table 2: Summary of included studies Africa/developing countries

Authors, year	setting	Study design and methods	Population and sample seize	Impact of ART estimated	Key findings	HR (95% CI) /incident rates (95% CI)
(Liu et al., 2015)	47 HIV care and treatment clinics in Tanzania	-Prospective observational cohort study. -Cox proportional hazard regressions	67 686 HIV-positive adults (age 15+) enrolled in the HIV care and treatment program between November 2004 and September 2012	Yes	-ART associated with a 72% reduction in TB incidence after 36months on ART -TB incidence lower for patients on ART compared to those not on ART -TB incidence declined with increasing duration on ART. -Male patients and a 53%higher risk of TB than females	-HR (36+ months on ART time-varying) **0.28 (95% CI, 0.25-0.33)** - Males versus females HR 1.53, 95% CI, 1.45-1.60 -TB incidence rate ART naïve patients 7.9 (95% CI, 7.6–8.2) per 100 person-years -TB incidence rate for patients on ART 4.4 (95% CI, 4.2-4.4) per 100 person-years
(Suthar et al., 2012a)	11 studies from developing countries	-Systematic review and meta-analysis of randomised controlled trials, prospective cohort studies, and retrospective cohort studies comparing TB incidence by ART status in HIV-infected adults	11 studies namely -4 from sub-Saharan Africa, - 4 from South America, -1 from Caribbean, -1 from Asia -1 from combination of sub-Saharan Africa, South America, and Asia	Yes	-ART associated with a 65% reduction in TB incidence -ART strongly associated with a reduction in TB incidence across all CD4 count categories.	- CD4 count<200 cells/µl **HR 0.16, (95% CI, 0.07- 0.36)** - 200<CD4 count< 350 cells/µl **HR 0.34, (95% CI, 0.19 - 0.60)** - CD4 count> 350 cells/µl **HR 0.43, (95% CI, 0.30 - 0.63)** - Any level of CD4 count **HR 0.35, (95% CI, 0.28 - 0.44)**
(Yirdaw et al., 2014)	Electronic database of patients under care at 5 HIV/ART care clinics in Ethiopia	-Cohort study -Cox proportional hazard regression	5 407 HIV-positive patients enrolled into HIV care between September 2007 and August 2010	Yes	ART associated with 68% reduction in TB incidence	-adjusted HR: **0.32, (95%CI, 0.24-0.43)** -unadjusted HR: **0.74, (95%CI, 0.58-0.96)**
(Lawn et al., 2010)	Limited resource settings	-9 Cohort studies -Meta-analysis	37 879 HIV-positive adults aged 18+	Yes	-ART associated with a 67% reduction in TB incidence	-Adjusted HR **0.33 (95%CI, 0.27 – 0.39)**
(Ayele et al., 2015)	Dilla University Referral Hospital in Ethiopia	-Retrospective cohort study -Time-dependent Cox regression	- 1 922 adult HIV-positive patients aged 15+ enrolled in chronic care between 2007 and 2013	Yes	60% reduction in TB incidence due to the combined effect of IPT and ART	Combined effect of ART an IPT- -Unadjusted HR **0.35, (95% CI, 0.16 -0.77)** -Adjusted **HR 0.40 (95% CI, 0.18-0.87)**

(Chang et al., 2015)	Electronic clinical care data in the Harvard/APIN PEPFAR Nigeria program, Nigeria	-Retrospective cohort study. -Multivariate Cox proportional hazards regression with time-dependent covariates	-50 320 HIV-positive adults enrolled and followed up between May 2005 and February 2012	No	-TB incidence decreased with longer duration on ART	-Overall TB incidence rate 25.8 (95% CI, 24.7-27.0) cases per 1 000 person-years -6.2% of the patients developed TB after ART initiation
(Assefa et al., 2014)	University of Gondar hospital, northwest Ethiopia	-Retrospective cohort study. -Cox-proportional hazard model	-400 HIV-positive adult patients aged 15+ initiating ART between 1 September 2007 and 30th of August 2008.	No	-High incidence of TB after initiating ART within the first year -Early ART initiation beneficial in reducing TB incidence	-TB incidence rate 2.2 (95% CI, 0.94 - 5.09) per 100 person-years
(Hermans et al., 2010)	HIV clinic, Uganda	-Retrospective cohort study -Cox proportional hazards	5 982 HIV-infected adults initiating ART between January 2003 and January 2009.	No	- Reduction in TB incidence with duration on ART -Incidence TB very high within first 3 months of ART initiation, especially in patients with very low CD4 counts	-TB incidence in the first 2 years 3.14 (95% CI, 2.82-3.49) per 100 person-years -TB incidents rates at 0-3 months 11.25 (95% CI, 9.58-13.21), 3-6 months 6.27 (95% CI ,4.99-7.87), 6-12 months 2.47 (95% CI, 1.87-3.36) 12-24 months and 1.02 (95% CI, 0.80-1.31) -OR after 2 years on ART 2.02 (95%CI, 1.13 – 3.59) -HR CD4 count <50 1.84 (95% CI, 1.25 – 2.70)
(Auld et al., 2013)	Clinics, Mozambique	-Retrospective cohort study -Cox proportional hazards	-2 596 HIV-positive adults aged 15+ initiating ART between 2004 and 2007	No	-Patients with lower CD4 counts had higher TB incidence rates compared to patients with higher CD4 count -High TB incidence among patients observed	TB incidence rate 2.32 (95% CI, 1.80 – 3.05) per 100 person-years
(Akanbi et al., 2013)	HIV clinic, Nigeria	-Retrospective cohort study -Cox proportional hazards	5 093 HIV-positive adults aged 18+ on ART for at least a year between January 2006 and March 2011	No	-TB incidence higher in patients with lower CD4 count -73% reduction in TB incidence associated with ART between the first and fourth year after starting	-TB incidence rate 8.72 (95% CI, 7.15 – 10.63) per 1 000 person-years. -HR in CD4 count>≥350 versus CD4 count <350 after first year of ART 0.47 (95% CI, 0.28 – 0.77)

(Worodria et al., 2011)	Kampala, Uganda	-Prospective cohort study -Cox proportional hazards	-219 HIV-positive patients aged ≥18 initiating ART, followed up for a year	No	-Incidence of ART associated TB noted to be relatively low in this setting of high HIV and TB prevalence	-TB incidence rate (ART associated) 4.3 per 100 person-years
(Alvarez-Uria et al., 2014)	Anantapur, Andhra Pradesh, India	-Retrospective cohort study -Cox proportional hazards regression	-8 374 HIV-positive adult patients pre and post ART aged 16+ followed up between 1 January 2010 to 1 February 2013	No	-Extremely high TB incidence observed -Significant difference incidence of TB before and after ART initiation	-TB incidence rate pre-ART 31.7 (95% CI, 29.8 – 33.7) per 100 person-years -TB incidence rate on-ART 11.4 (95% CI, 10.4 – 12.4) per 100 person-years
(Kassa et al., 2012)	Hospital, Addis Ababa, Ethiopia	-Retrospective cohort study -Cox proportional hazards regression	-4 210 HIV-positive adult patients aged 15+receiving HAART between September 2005 and October 2009	No	-use of HAART reduces TB incidence -Reduction in TB incidence with duration on ART	-TB incidence rate 3.1 (95% CI, 2.58–3.62) per 100 person-years -TB incidence in first year 3.3 (95% CI, 1.17 – 5.43) per 100 person-years -TB incidence in 5 years 0.4 (95% CI, 0.21 – 0.59) per 100 person-years
(Musa et al., 2015)	HIV/AIDS care centre, Kano, Nigeria	-Retrospective cohort study. -Multivariate GEE regression	345 HIV-positive adults aged ≥18 years followed up for 10 years between March 2004 and April 2014	No	-Reduction in TB incidence across all CD4 counts	-TB incidence rate of 17.43 per 1 000 person-years
(Pathmanathan et al., 2017)	Nigeria	-Retrospective cohort study -Cox proportional hazard model	3496 adult HIV patients on ART aged≥ 15 years between January 2004 and December 2012	No	-TB incidence significantly higher in patients with lower CD4 count compared to patients with higher CD4 count -low TB incidence after ART initiation	-TB incidence rate 0.57 per 100 person-years

Table 3: Summary of included studies, South Africa

Authors, year	setting	Study design and methods	Population and sample seize	Impact of ART estimated	Key findings	HR (95% CI) /incident rates (95% CI)
(Bock et al., 2018)	3 Clinics, Western Cape Province, South Africa	-Retrospective cohort study	-2 423 HIV-positive adults aged 18 starting ART, followed up between January 2014 and 30 May 2016	Yes	-73% reduction in TB incidence associated with ART among patients with CD4 count greater than 500 when compared with patients with CD4 count less than 500	-Adjusted HR (CD4>500 versus CD4 ≤500) **0.27 (95% CI, 0.12-0.62)** -TB incidence per 100 person-years 4.41 (95% CI, 3.62-5.39) overall 9.62 (95%CI, 7.27-12.73) CD4 <200 3.15 (95%CI, 2.05-4.83) 201<CD4 <350 3.85 (95%CI, 2.51-5.91) 351<CD4 <500 1.26 (95%CI, 0.57-2.81) CD4 >500
(Kufa et al., 2016)	2 Clinics, Gauteng Province, South Africa	-Prospective cohort -Cox proportional hazards regression	-634 HIV-positive patients aged 18 to 45 years with CD4 counts > 350 cells/µl followed up between June 2011 and June 2012	Yes	-32% reduction in TB incidence associated with ART in patients with CD4 count greater than 350 -TB incidence high in these patients with high CD4 count greater than 350	-adjusted **HR 0.68 (95 % CI, 0.18 – 1.82)** -unadjusted **HR 0.65 (95 % CI, 0.24-1.81)** -Overall TB incidence 2.7 (95 % CI, 1.6 - 4.4) per 100 person-years -on ART TB incidence rate 2.2 (95 % CI, 1.0 – 4.5) per 100 person-years -no ART TB incidence rate 3.4 (95 % CI, 1.6 – 7.0) person-years -TB incidence per 100 person-years 2.4 (95%CI, 1.2-4.8) CD4 >500 3.3 (95%CI, 1.5-7.3) 350<CD4 <500
(Bachmann et al., 2015)	Free State province, South Africa	-Retrospective cohort study -Cox proportional hazards regression	74 074 HIV-positive adult patients aged 16+ followed up between May 2004 and June 2010	Yes	-ART associated with a 33% reduction in TB incidence -Reduction in TB incidence with longer duration on ART -ART effective in preventing TB in patients with low CD4 count (<350 cells/µl)	-adjusted HR **0.67 (95% CI, 0.64 – 0.70)** -unadjusted HR **0.64 (95% CI, 0.57-0.71)** -TB incidence on ART 4.9 per 100 person-years -TB incidence not on ART 9.0 per 100 person-years

(Golub et al., 2009)	2 Clinics, South Africa	-Prospective cohort study -Cox proportional hazards regression	2 778HIV-positive adults aged 18+, between 1 June 2003 and 31 December 2007	Yes	-ART associated with a 64% reduction in TB incidence -High incidence of TB in this population	-Adjusted HR **0.36 (95%CI, 0.25 – 0.51)** -Unadjusted HR **0.62 (95%CI, 0.44 – 0.87)**
(Badri et al., 2002)	Somerset Hospital adult HIV clinic, South Africa	-Clinical trial and prospective cohort study -Poisson regression model	-264 HIV patients in clinical trial on HAART and 770 non-HAART patients in cohort followed up between 1992 and 2001	Yes	-HAART associated with an 80% reduction in TB incidence -HAART has a protective effect on TB incidence in HIV patients	-adjusted RR **0.19 (95% CI, 0.9 – 0.38)** -TB incidence on HAART 2.4 per 100 person-years -TB incidence rate not on HAART 9.7 per 100 person-years
(Fairall et al., 2008)	Free State, South Africa	-Prospective cohort study -Logistic regression models (Marginal structural model)	-14 267 HIV-positive patients aged 16+, followed up between 3 May 2004 and 31 December 2005	Yes	-HAART associated with an 39% reduction in TB incidence	-Unweighted model, no covariates: **HR 2.4 (95% CI, 2.1-2.7)** -Unweighted model, baseline and time-varying covariates: **HR 0.69 (95% CI, 0.54-0.89)** -Weighted model, baseline covariates: **HR 0.61 (95% CI, 0.46 – 0.81)**
(Van Rie et al., 2011)	Johannesburg, South Africa	-Prospective cohort study. -Cox proportional hazards regression	7 536 HIV-positive patients initiating ART between 1 April 2004 and 31 March 2008	No	-Severity of HIV disease associated with TB incidence -Very high TB incidence in the first few months on ART	-TB incidence rate of TB on ART 4.2 (95% CI, 3.8 – 4.5) per 100 person-years - TB incidence rate in first 3 months on ART 21.7 (95% CI, 17.5 - 26.7) per 100 person-years
(Lawn et al., 2009)	Gugulethu, Cape Town, South Africa	-Prospective Cohort study -Poisson regression	1 480 HIV-positive patients initiating ART between September 2002 and March 2006	No	-TB incidence rates are very high, and they decline with an increase in CD4 count	-TB incidence rate per 100 person-years 7.28 (95%CI, 6.32 – 8.36) overall 16.76 (95%CI, 12.76:21.62) CD4 <100 9.27 (95%CI, 7.15:11.82) 101<CD4 <200 5.48 (95%CI, 3.88:7.52) CD4 201<CD4 <300 4.61 (95%CI, 2.92:6.91) CD4 301<CD4 <400 4.23 (95%CI, 2.25:7.24) CD4 401<CD4 <500 1.50 (95%CI, 0.49:3.49) CD4 >500
(Fenner et al., 2017)	3 treatment programmes (2 in	-Retrospective cohort study	-44 260 HIV-positive adult patients aged 16+ starting	No	-Early ART initiation and retention on ART	-TB incidence rate

	Cape Town and 1 in Johannesburg), South Africa	-Parametric survival models -Poisson general additive regression model	ART between 1 January 2000 and 31 December 2014 at three ART programmes		-Reduction in TB incidence with increase in CD4 count on patients on ART	26.2 (95% CI, 25.3–27.0) per 1 000 person-years.
(Gupta et al., 2012)	Cape Town, South Africa	-Prospective cohort study -Poisson regression model	-1 544 HIV-positive adults aged 16+ on ART between September 2002 and May 2006	No	-Reduction of TB incidence with longer duration on ART -ART effective in preventing TB in patient with low CD4 count (<350cells/μl) -TB rates higher than in uninfected population regardless of duration on ART or high CD4 count	-TB incidence rate during ART 7.44 (95% CI, 6.80 – 8.13) per 100 person-years -TB incidence rate first year of ART 12.4 (95% CI, 10.8 – 14.4) per 100 person-years -TB incidence rate between 5-8 years on ART 4.92 (95% CI, 3.64 – 8.62) per 100 person-years

1.7.4 Conclusion (TB incidence and effect of ART)

Most of the studies reviewed were retrospective and prospective cohort studies. These studies vary in terms of sample sizes, settings as a well as the range of results. Despite the variations in study design, size and population most of the studies have shown a reduction in TB incidence due to ART in people living with HIV, with reductions ranging between 32% and 92%. Variation in the results of the included studies could be due to the different study settings and different sample sizes used as well as the different methods applied.

Most of the studies used the Cox regression to model the effect of ART on TB incidence with traditional adjustments to the estimates, while only a few used causal methods of analysis to derive the adjusted estimates. Of the studies which used causal methods between the different settings, adjusting for time-varying confounding resulted in modest further accentuation of the estimate of the effect of ART. In South Africa there is only one study by Fairall et al (2008) that used causal methods, conducted early on in the scale-up of ART in the Free State Province, and they had an estimate of 39% reduction in TB incidence due to ART.

1.8 Conclusion

In this review, we have described the burden TB as well as the burden and treatment of HIV. We have also given a brief description of the dynamics of HIV and TB co-infection and further described the impact of ART in TB incidence in people living with HIV. We have found that TB cases are higher in high HIV prevalence settings in the developing countries particularly in sub-Saharan Africa. We have also identified HIV as the driving force for the high TB incidence in these settings. ART roll-out which is increasing at different paces in the different regions globally is noted to be having an important impact in the reduction of TB incidence. There have been relatively few robust studies in the Southern African context quantifying this impact, using appropriate methods, and including more recent calendar periods.

This study is an opportunity to determine the impact of ART on TB incidence in our high TB and HIV prevalence setting. Very few studies have been conducted at such a population wide level with high levels of outcome ascertainment in patients attending public health sector. The level of patient detail also allows us to adjust for time-varying confounding, which has rarely been done in our setting. The knowledge generated will contribute to the body of literature on the impact of ART on TB incidence in people living with HIV in our settings.

1.9 References

ABDOOL KARIM, S. S., CHURCHYARD, G. J., ABDOOL KARIM, Q. & LAWN, S. D. 2009. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. *Lancet,* 374**,** 921-933.

AKANBI, M. O., ACHENBACH, C. J., FEINGLASS, J., TAIWO, B., ONU, A., PHO, M. T., AGBAJI, O., KANKI, P. & MURPHY, R. L. 2013. Tuberculosis after one year of combination antiretroviral therapy in Nigeria: a retrospective cohort study. *AIDS Res Hum Retroviruses,* 29**,** 931-7.

ALVAREZ-URIA, G., PAKAM, R., MIDDE, M. & NAIK, P. K. 2014. Incidence and mortality of tuberculosis before and after initiation of antiretroviral therapy: an HIV cohort study in India. *J Int AIDS Soc,* 17**,** 19251.

ASSEFA, A., GELAW, B., GETNET, G. & YITAYEW, G. 2014. The effect of incident tuberculosis on immunological response of HIV patients on highly active anti-retroviral therapy at the university of Gondar hospital, northwest Ethiopia: a retrospective follow-up study. *BMC Infect Dis,* 14**,** 468.

ATTIA, S., EGGER, M., MULLER, M., ZWAHLEN, M. & LOW, N. 2009. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *Aids,* 23**,** 1397-404.

AULD, A. F., MBOFANA, F., SHIRAISHI, R. W., ALFREDO, C., SANCHEZ, M., ELLERBROCK, T. V. & NELSON, L. J. 2013. Incidence and determinants of tuberculosis among adults initiating antiretroviral therapy--Mozambique, 2004-2008. *PLoS One,* 8**,** e54665.

AYELE, H. T., VAN MOURIK, M. S. M. & BONTEN, M. J. M. 2015. Effect of isoniazid preventive therapy on tuberculosis or death in persons with HIV: a retrospective cohort study. *BMC Infectious Diseases,* 15**,** 334.

BACHMANN, M. O., TIMMERMAN, V. & FAIRALL, L. R. 2015. Effect of antiretroviral treatment on the risk of tuberculosis during South Africa's programme expansion. *Aids,* 29**,** 2261-8.

BADRI, M., WILSON, D. & WOOD, R. 2002. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet,* 359**,** 2059-64.

BEKKER, L.-G., VENTER, F., COHEN, K., GOEMARE, E., VAN CUTSEM, G., BOULLE, A. & WOOD, R. 2014. Provision of antiretroviral therapy in South Africa: the nuts and bolts. International Medical Press.

BOCK, P., JENNINGS, K., VERMAAK, R., COX, H., MEINTJES, G., FATTI, G., KRUGER, J., DE AZEVEDO, V., MASCHILLA, L., LOUIS, F., GUNST, C., GROBBELAAR, N., DUNBAR, R., LIMBADA, M., FLOYD, S., GRIMWOOD, A., AYLES, H., HAYES, R., FIDLER, S. & BEYERS, N. 2018. 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,* 77**,** 93-101.

CHAISSON, R. E. & MARTINSON, N. A. 2008. Tuberculosis in Africa — Combating an HIV-Driven Crisis. *New England Journal of Medicine,* 358**,** 1089-1092.

CHANG, C. A., MELONI, S. T., EISEN, G., CHAPLIN, B., AKANDE, P., OKONKWO, P., RAWIZZA, H. E., TCHETGEN, E. T. & KANKI, P. J. Tuberculosis Incidence and Risk Factors Among Human Immunodeficiency Virus (HIV)-Infected Adults Receiving Antiretroviral Therapy in a Large HIV Program in Nigeria. Open forum infectious diseases, 2015. Oxford University Press, ofv154.

CHIGWEDERE, P., SEAGE, G. R., 3RD, GRUSKIN, S., LEE, T. H. & ESSEX, M. 2008. Estimating the lost benefits of antiretroviral drug use in South Africa. *J Acquir Immune Defic Syndr,* 49**,** 410-5.

CHURCHYARD, G. J., MAMETJA, L. D., MVUSI, L., NDJEKA, N., HESSELING, A. C., REID, A., BABATUNDE, S. & PILLAY, Y. 2014. Tuberculosis control in South Africa: successes, challenges and recommendations. *S Afr Med J,* 104**,** 244-8.

COHEN, M. S., CHEN, Y. Q., MCCAULEY, M., GAMBLE, T., HOSSEINIPOUR, M. C., KUMARASAMY, N., HAKIM, J. G., KUMWENDA, J., GRINSZTEJN, B., PILOTTO, J. H., GODBOLE, S. V., MEHENDALE, S., CHARIYALERTSAK, S., SANTOS, B. R., MAYER, K. H., HOFFMAN, I. F., ESHLEMAN, S. H., PIWOWAR-MANNING, E., WANG, L., MAKHEMA, J., MILLS, L. A., DE BRUYN, G., SANNE, I., ERON, J., GALLANT, J., HAVLIR, D., SWINDELLS, S., RIBAUDO, H., ELHARRAR, V., BURNS, D., TAHA, T. E., NIELSEN-SAINES, K., CELENTANO, D., ESSEX, M. & FLEMING, T. R. 2011. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med,* 365**,** 493-505.

CORBETT, E. L., WATT, C. J., WALKER, N., MAHER, D., WILLIAMS, B. G., RAVIGLIONE, M. C. & DYE, C. 2003. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med,* 163**,** 1009-21.

DEL AMO, J., MORENO, S., BUCHER, H. C., FURRER, H., LOGAN, R., STERNE, J., PEREZ-HOYOS, S., JARRIN, I., PHILLIPS, A., LODI, S., VAN SIGHEM, A., DE WOLF, W., SABIN, C., BANSI, L., JUSTICE, A., GOULET, J., MIRO, J. M., FERRER, E., MEYER, L., SENG, R., TOULOMI, G., GARGALIANOS, P., COSTAGLIOLA, D., ABGRALL, S. & HERNAN, M. A. 2012. Impact of antiretroviral therapy on tuberculosis incidence among HIV-positive patients in high-income countries. *Clin Infect Dis,* 54**,** 1364-72.

DEPARTMENT OF HEALTH 2014. Department of Health Strategic Plan 2014/15–2018/19 Pretoria: South Africa National Department of Health.

DEPARTMENT OF HEALTH 2016. IMPLEMENTATION OF THE UNIVERSAL TEST AND TREAT STRATEGY FOR HIV POSITIVE PATIENTS AND DIFFERENTIATED CARE FOR STABLE PATIENTS. *In:* HEALTH, S. A. D. O. (ed.). Pretoria, South Africa: South Africa Department of Health.

DEPARTMENT OF HEALTH 2017. The 2015 National Antenatal Sentinel HIV & Syphilis Survey, South Africa. Pretoria: South Africa National Department of Health.

EVANS, D. 2013. *Ten years on ART – where to now?*

FAIRALL, L. R., BACHMANN, M. O., LOUWAGIE, G. C. & ET AL. 2008. Effectiveness of antiretroviral treatment in a south african program: A cohort study. *Archives of Internal Medicine,* 168**,** 86-93.

FENNER, L., ATKINSON, A., BOULLE, A., FOX, M. P., PROZESKY, H., ZURCHER, K., BALLIF, M., FURRER, H., ZWAHLEN, M., DAVIES, M. A. & EGGER, M. 2017. HIV viral load as an independent risk factor for tuberculosis in South Africa: collaborative analysis of cohort studies. *J Int AIDS Soc,* 20**,** 21327.

FLOYD, K., GLAZIOU, P., ZUMLA, A. & RAVIGLIONE, M. 2018. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era. *Lancet Respir Med,* 6**,** 299-314.

GIRARDI, E., ANTONUCCI, G., VANACORE, P., LIBANORE, M., ERRANTE, I., MATTEELLI, A. & IPPOLITO, G. 2000. Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. *Aids,* 14**,** 1985-91.

GIRARDI, E., SABIN, C. A., D'ARMINIO MONFORTE, A., HOGG, B., PHILLIPS, A. N., GILL, M. J., DABIS, F., REISS, P., KIRK, O., BERNASCONI, E., GRABAR, S., JUSTICE, A., STASZEWSKI, S., FATKENHEUER, G. & STERNE, J. A. 2005. Incidence of Tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clin Infect Dis,* 41**,** 1772-82.

GOLUB, J. E., PRONYK, P., MOHAPI, L., THSABANGU, N., MOSHABELA, M. & STRUTHERS, H. 2009. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS,* 23.

GOLUB, J. E., SARACENI, V., CAVALCANTE, S. C., PACHECO, A. G., MOULTON, L. H., KING, B. S., EFRON, A., MOORE, R. D., CHAISSON, R. E. & DUROVNI, B. 2007. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS (London, England),* 21**,** 1441-1448.

GRINSZTEJN, B., HOSSEINIPOUR, M. C., RIBAUDO, H. J., SWINDELLS, S., ERON, J., CHEN, Y. Q., WANG, L., OU, S. S., ANDERSON, M., MCCAULEY, M., GAMBLE, T., KUMARASAMY, N., HAKIM, J. G., KUMWENDA, J., PILOTTO, J. H., GODBOLE, S. V., CHARIYALERTSAK, S., DE MELO, M. G., MAYER, K. H., ESHLEMAN, S. H., PIWOWAR-MANNING, E., MAKHEMA, J., MILLS, L. A., PANCHIA, R., SANNE, I., GALLANT, J., HOFFMAN, I., TAHA, T. E., NIELSEN-SAINES, K., CELENTANO, D., ESSEX, M., HAVLIR, D. & COHEN, M. S. 2014. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis,* 14**,** 281-90.

GUPTA, A., WOOD, R., KAPLAN, R., BEKKER, L.-G. & LAWN, S. D. 2012. Tuberculosis Incidence Rates during 8 Years of Follow-Up of an Antiretroviral Treatment Cohort in South Africa: Comparison with Rates in the Community. *PLoS ONE,* 7**,** e34156.

HARRIES, A. D., ZACHARIAH, R., CORBETT, E. L., LAWN, S. D., SANTOS-FILHO, E. T., CHIMZIZI, R., HARRINGTON, M., MAHER, D., WILLIAMS, B. G. & DE COCK, K. M. 2010. The HIV-associated tuberculosis epidemic—when will we act? *The Lancet,* 375**,** 1906-1919.

HERMANS, S. M., KIRAGGA, A. N., SCHAEFER, P., KAMBUGU, A., HOEPELMAN, A. I. & MANABE, Y. C. 2010. Incident tuberculosis during antiretroviral therapy contributes to suboptimal immune reconstitution in a large urban HIV clinic in sub-Saharan Africa. *PLoS One,* 5**,** e10527.

HUANG, P., TAN, J., MA, W., ZHENG, H., LU, Y., WANG, N., PENG, Z. & YU, R. 2015. Long-Term Effectiveness of Antiretroviral Therapy in China: An Observational Cohort Study from 2003–2014. *International Journal of Environmental Research and Public Health,* 12**,** 8762-8772.

JOHNSON, L. F., DORRINGTON, R. E. & MOOLLA, H. 2017. *Progress towards the 2020 targets for HIV diagnosis and antiretroviral treatment in South Africa.*

JONES, J. L., HANSON, D. L., DWORKIN, M. S. & DECOCK, K. M. 2000. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent Spectrum of HIV Disease Group. *Int J Tuberc Lung Dis,* 4**,** 1026-31.

KASSA, A., TEKA, A., SHEWAAMARE, A. & JERENE, D. 2012. Incidence of tuberculosis and early mortality in a large cohort of HIV infected patients receiving antiretroviral therapy in a tertiary hospital in Addis Ababa, Ethiopia. *Trans R Soc Trop Med Hyg,* 106**,** 363-70.

KUFA, T., CHIHOTA, V., MNGOMEZULU, V., CHARALAMBOUS, S., VERVER, S., CHURCHYARD, G. & BORGDORFF, M. 2016. The incidence of tuberculosis among hiv-positive individuals with high CD4 counts: implications for policy. *BMC Infect Dis,* 16**,** 266.

KYU, H. H., MADDISON, E. R., HENRY, N. J., MUMFORD, J. E., BARBER, R., SHIELDS, C., BROWN, J. C., NGUYEN, G., CARTER, A., WOLOCK, T. M., WANG, H., LIU, P. Y., REITSMA, M., ROSS, J. M., ABAJOBIR, A. A., ABATE, K. H., ABBAS, K., ABERA, M., ABERA, S. F., ABERA HARERI, H., AHMED, M., ALENE, K. A., ALVIS-GUZMAN, N., AMO-ADJEI, J., ANDREWS, J., ANSARI, H., ANTONIO, C.

A., ANWARI, P., ASAYESH, H., ATEY, T. M., ATRE, S., BARAC, A., BEARDSLEY, J., BEDI, N., BENSENOR, I., BEYENE, A. S., BUTT, Z. A., CARDONA, P.-J., CHRISTOPHER, D., DANDONA, L., DANDONA, R., DERIBE, K., DERIBEW, A., EHRENKRANZ, R., EL SAYED ZAKI, M., ENDRIES, A., FEYISSA, T. R., FISCHER, F., GAI, R., GARCIA-BASTEIRO, A. L., GEBREHIWOT, T. T., GESESEW, H., GETAHUN, B., GONA, P., GOODRIDGE, A., GUGNANI, H., HAGHPARAST-BIDGOLI, H., HAILU, G. B., HASSEN, H. Y., HILAWE, E., HORITA, N., JACOBSEN, K. H., JONAS, J. B., KASAEIAN, A., KEDIR, M. S., KEMMER, L., KHADER, Y., KHAN, E., KHANG, Y.-H., KHOJA, A. T., KIM, Y. J., KOUL, P., KOYANAGI, A., KROHN, K. J., KUMAR, G. A., KUTZ, M., LODHA, R., MAGDY, EL RAZEK, H., MAJDZADEH, R., MANYAZEWAL, T., MEMISH, Z., MENDOZA, W., MEZGEBE, H. B., MOHAMMED, S., OGBO, F. A., OH, I.-H., OREN, E., OSGOOD-ZIMMERMAN, A., PEREIRA, D., PLASS, D., POURMALEK, F., QORBANI, M., RAFAY, A., RAHMAN, M., RAI, R. K., RAO, P. C., RAY, S. E., REINER, R., REINIG, N., et al. 2018. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. *The Lancet Infectious Diseases,* 18**,** 261-284.

LANNOY, L. H., CORTEZ-ESCALANTE, J. J., EVANGELISTA MDO, S. & ROMERO, G. A. 2008. Tuberculosis incidence and risk factors among patients living with HIV/AIDS in public health service institutions in Brasilia, Federal District. *Rev Soc Bras Med Trop,* 41**,** 549-55.

LAWN, S. D., MYER, L., EDWARDS, D., BEKKER, L. G. & WOOD, R. 2009. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS,* 23**,** 1717-25.

LAWN, S. D., WOOD, R., DE COCK, K. M., KRANZER, K., LEWIS, J. J. & CHURCHYARD, G. J. 2010. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis,* 10**,** 489-98.

LIU, E., MAKUBI, A., DRAIN, P., SPIEGELMAN, D., SANDO, D., LI, N., CHALAMILLA, G., SUDFELD, C. R., HERTZMARK, E. & FAWZI, W. W. 2015. Tuberculosis incidence rate and risk factors among HIV-infected adults with access to antiretroviral therapy. *AIDS (London, England),* 29**,** 1391-1399.

MASSYN, N., PEER, N., ENGLISH, R., PADARATH, A., BARRON, P. & DAY, C. 2016. District Health Barometer 2015/16. Durban: Health Systems Trust.

MIRANDA, A., MORGAN, M., JAMAL, L., LASERSON, K., BARREIRA, D., SILVA, G., SANTOS, J., WELLS, C., PAINE, P. & GARRETT, D. 2007. Impact of antiretroviral therapy on the incidence of tuberculosis: the Brazilian experience, 1995-2001. *PLoS One,* 2**,** e826.

MOR, Z., LIDJI, M., CEDAR, N., GROTTO, I. & CHEMTOB, D. 2013. Tuberculosis Incidence in HIV/AIDS Patients in Israel, 1983–2010. *PLOS ONE,* 8**,** e79691.

MORENO, S., JARRIN, I., IRIBARREN, J. A., PEREZ-ELIAS, M. J., VICIANA, P., PARRA-RUIZ, J., GOMEZ-SIRVENT, J. L., LOPEZ-ALDEGUER, J., GUTIERREZ, F., BLANCO, J. R., VIDAL, F., LEAL, M., RODRIGUEZ ARENAS, M. A. & DEL AMO, J. 2008. Incidence and risk factors for tuberculosis in HIV-positive subjects by HAART status. *Int J Tuberc Lung Dis,* 12**,** 1393-400.

MUGA, R., FERREROS, I., LANGOHR, K., DE OLALLA, P. G., DEL ROMERO, J., QUINTANA, M., ALASTRUE, I., BELDA, J., TOR, J., PEREZ-HOYOS, S. & DEL AMO, J. 2007. Changes in the incidence of tuberculosis in a cohort of HIV-seroconverters before and after the introduction of HAART. *Aids,* 21**,** 2521-7.

MUSA, B., MUSA, B., MUHAMMED, H., IBRAHIM, N. & MUSA, A. 2015. Incidence of tuberculosis and immunological profile of TB/HIV co-infected patients in Nigeria. *Annals of Thoracic Medicine,* 10**,** 185-192.

NATIONAL IINSTITUTE FOR COMMUNICABLE DISEASES 2017. Microbiologically confirmed tuberculosis 2004 -15 South Africa. National Iinstitute for Communicable Diseases, Division of the National Health Laboratory Service.

NATTRASS, N. 2006. Antiretroviral treatment and the problem of political will in South Africa. *Southern African Journal of HIV Medicine,* 7**,** 29-31.

PATHMANATHAN, I., DOKUBO, E. K., SHIRAISHI, R. W., AGOLORY, S. G., AULD, A. F., ONOTU, D., ODAFE, S., DALHATU, I., ABIRI, O. & DEBEM, H. C. 2017. Incidence and predictors of tuberculosis among HIV-infected adults after initiation of antiretroviral therapy in Nigeria, 2004-2012. *PloS one,* 12**,** e0173309.

PETTIT, A. C., JENKINS, C. A., STINNETTE, S. E., REBEIRO, P. F., BLACKWELL, R. B., RAFFANTI, S. P., SHEPHERD, B. E. & STERLING, T. R. 2011. Tuberculosis Risk Before and After Highly Active Antiretroviral Therapy Initiation: Does HAART Increase the Short-term TB Risk in a Low Incidence TB Setting? *Journal of acquired immune deficiency syndromes (1999),* 57**,** 305-310.

PLAZY, M., DABIS, F., NAIDU, K., ORNE-GLEIMANN, J., BARNIGHAUSEN, T. & DRAY-SPIRA, R. 2015. Change of treatment guidelines and evolution of ART initiation in rural South Africa: data of a large HIV care and treatment programme. *BMC Infectious Diseases,* 15**,** 452.

RANGAKA, M. X., WILKINSON, R. J., BOULLE, A., GLYNN, J. R., FIELDING, K., VAN CUTSEM, G., WILKINSON, K. A., GOLIATH, R., MATHEE, S., GOEMAERE, E. & MAARTENS, G. 2014. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. The Lancet.

RAVIGLIONE, M. & SULIS, G. 2016. Tuberculosis 2015: Burden, Challenges and Strategy for Control and Elimination. *Infectious Disease Reports,* 8**,** 6570.

REBOUCAS, M. C., SILVA, M. O. D., HAGUIHARA, T., BRITES, C. & NETTO, E. M. 2017. Tuberculosis incidence among people living with HIV/AIDS with virological failure of antiretroviral therapy in Salvador, Bahia, Brazil. *Braz J Infect Dis,* 21**,** 562-566.

SANAC 2017. South African national strategic plan on HIV, TB and STIs 2017-2022. Pretoria: South African National AIDS Council, SANAC.

SANTORO-LOPES, G., FELIX DE PINHO, A. M., HARRISON, L. H. & SCHECHTER, M. 2002. Reduced Risk of Tuberculosis among Brazilian Patients with Advanced Human Immunodeficiency Virus Infection Treated with Highly Active Antiretroviral Therapy. *Clinical Infectious Diseases,* 34**,** 543-546.

SHISANA, O., REHLE., T., SIMBAYI, L. C., ZUMA, K., JOOSTE, S., ZUNGU, N., LABADARIOS, D. & ONOYA, D. 2014. South African National HIV Prevalence, Incidence and Behaviour Survey 2012. Cape Town: Human Sciences Research Council.

STATISTICS SOUTH AFRICA 2017. Mid-year population estimates 2017. Pretoria: Statistics South Africa.

STATISTICS SOUTH AFRICA 2018. Mid-year population estimates 2018. Pretoria: Statistics South Africa.

STINSON, K., GOEMAERE, E., COETZEE, D., VAN CUTSEM, G., HILDERBRAND, K., OSLER, M., HENNESSEY, C., WILKINSON, L., PATTEN, G., CRAGG, C., MATHEE, S., COX, V. & BOULLE, A. 2017. Cohort Profile: The Khayelitsha antiretroviral programme, Cape Town, South Africa. *Int J Epidemiol,* 46**,** e21.

SUTHAR, A. B., LAWN, S. D., DEL AMO, J., GETAHUN, H., DYE, C., SCULIER, D., STERLING, T. R., CHAISSON, R. E., WILLIAMS, B. G., HARRIES, A. D. &

GRANICH, R. M. 2012a. Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS Med,* 9**,** e1001270.

SUTHAR, A. B., LAWN, S. D., DEL AMO, J., GETAHUN, H., DYE, C., SCULIER, D., STERLING, T. R., CHAISSON, R. E., WILLIAMS, B. G., HARRIES, A. D. & GRANICH, R. M. 2012b. Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS Medicine,* 9**,** e1001270.

UNAIDS 2014. 90-90-90 An ambitious treatment target to help end the AIDS epidemic. Joint United Nations Programme on HIV/AIDS (UNAIDS).

UNAIDS 2016. Global AIDS update. UNAIDS.

UNAIDS 2017. Ending AIDS, Progress towards the 90-90-90 targets: Global AIDS update 2017. Joint United Nations Programme on HIV/AIDS (UNAIDS).

UNAIDS 2018. UNAIDS data 2018. Joint United Nations Programme on HIV/AIDS (UNAIDS).

VAN RIE, A., WESTREICH, D. & SANNE, I. 2011. Tuberculosis in patients receiving antiretroviral treatment: incidence, risk factors and prevention strategies. *Journal of Acquired Immune Deficiency Syndromes (1999),* 56**,** 349-355.

WALENSKY, R. P., WOLF, L. L., WOOD, R., FOFANA, M. O., FREEDBERG, K. A., MARTINSON, N. A., PALTIEL, A. D., ANGLARET, X., WEINSTEIN, M. C. & LOSINA, E. 2009. When to start antiretroviral therapy in resource-limited settings. *Ann Intern Med,* 151**,** 157-66.

WANG, H., WOLOCK, T. M., CARTER, A., NGUYEN, G., KYU, H. H., GAKIDOU, E., HAY, S. I., MILLS, E. J., TRICKEY, A., MSEMBURI, W., COATES, M. M., MOONEY, M. D., FRASER, M. S., SLIGAR, A., SALOMON, J., LARSON, H. J., FRIEDMAN, J., ABAJOBIR, A. A., ABATE, K. H., ABBAS, K. M., RAZEK, M. M. A. E., ABD-ALLAH, F., ABDULLE, A. M., ABERA, S. F., ABUBAKAR, I., ABU-RADDAD, L. J., ABU-RMEILEH, N. M. E., ABYU, G. Y., ADEBIYI, A. O., ADEDEJI, I. A., ADELEKAN, A. L., ADOFO, K., ADOU, A. K., AJALA, O. N., AKINYEMIJU, T. F., AKSEER, N., LAMI, F. H. A., AL-ALY, Z., ALAM, K., ALAM, N. K. M., ALASFOOR, D., ALDHAHRI, S. F. S., ALDRIDGE, R. W., ALEGRETTI, M. A., ALEMAN, A. V., ALEMU, Z. A., ALFONSO-CRISTANCHO, R., ALI, R., ALKERWI, A. A., ALLA, F., MOHAMMAD, R., AL-RADDADI, S., ALSHARIF, U., ALVAREZ, E., ALVIS-GUZMAN, N., AMARE, A. T., AMBERBIR, A., AMEGAH, A. K., AMMAR, W., AMROCK, S. M., ANTONIO, C. A. T., ANWARI, P., ÄRNLÖV, J., ARTAMAN, A., ASAYESH, H., ASGHAR, R. J., ASSADI, R., ATIQUE, S., ATKINS, L. S., AVOKPAHO, E. F. G. A., AWASTHI, A., QUINTANILLA, B. P. A., BACHA, U., BADAWI, A., BARAC, A., BÄRNIGHAUSEN, T., BASU, A., BAYOU, T. A., BAYOU, Y. T., BAZARGAN-HEJAZI, S., BEARDSLEY, J., BEDI, N., BENNETT, D. A., BENSENOR, I. M., BETSU, B. D., BEYENE, A. S., BHATIA, E., BHUTTA, Z. A., BIADGILIGN, S., BIKBOV, B., BIRLIK, S. M., BISANZIO, D., BRAININ, M., BRAZINOVA, A., BREITBORDE, N. J. K., BROWN, A., BURCH, M., BUTT, Z. A., CAMPUZANO, J. C., CÁRDENAS, R., et al. 2016. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the Global Burden of Disease Study 2015. *The Lancet HIV,* 3**,** e361-e387.

WESTERN CAPE PROVINCIAL AIDS COUNCIL 2016. ANNUAL PROGRESS REPORT 2014/15, PROVINCIAL STRATEGIC PLAN 2012-2016. Western Cape Provincial AIDS Council,South Africa National AIDS Council.

WILLIAMS, B. G. & DYE, C. 2003. Antiretroviral Drugs for Tuberculosis Control in the Era of HIV/AIDS. *Science,* 301**,** 1535-1537.

WORLD HEALTH ORGANISATION 2014. Global Tuberculosis Report 2014. Geneva: World Health Organisation.
WORLD HEALTH ORGANISATION 2015. Global Tuberculosis Report 2015. 20th Edition ed. Geneva: World Health Organisation.
WORLD HEALTH ORGANIZATION 2002. Scaling up antiretroviral therapy in resource-limited settings : guidelines for a public health approach. Geneva, Switzerland: World Health Organization.
WORLD HEALTH ORGANIZATION 2006. Antiretroviral therapy for HIV infection in adults and adolescents : recommendations for a public health approach. 2006 revison. Geneva, Switzerland: World Health Organization
WORLD HEALTH ORGANIZATION 2010. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. Geneva, Switzerland: World Health Organization
WORLD HEALTH ORGANIZATION 2013. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. Geneva, Switzerland World Health Organization.
WORLD HEALTH ORGANIZATION 2017. Global tuberculosis report 2017. World Health Organization.
WORODRIA, W., MASSINGA-LOEMBE, M., MAYANJA-KIZZA, H., NAMAGANDA, J., KAMBUGU, A., MANABE, Y. C., KESTENS, L. & COLEBUNDERS, R. 2011. Antiretroviral treatment-associated tuberculosis in a prospective cohort of HIV-infected patients starting ART. *Clin Dev Immunol,* 2011**,** 758350.
YIRDAW, K. D., JERENE, D., GASHU, Z., EDGINTON, M. E., KUMAR, A. M. V., LETAMO, Y., FELEKE, B., TEKLU, A. M., ZEWDU, S., WEISS, B. & RUFF, A. 2014. Beneficial Effect of Isoniazid Preventive Therapy and Antiretroviral Therapy on the Incidence of Tuberculosis in People Living with HIV in Ethiopia. *PLoS ONE,* 9**,** e104557.
ZENNER, D., ABUBAKAR, I., CONTI, S., GUPTA, R. K., YIN, Z., KALL, M., KRUIJSHAAR, M., RICE, B., THOMAS, H. L., POZNIAK, A., LIPMAN, M. & DELPECH, V. 2015. Impact of TB on the survival of people living with HIV infection in England, Wales and Northern Ireland. *Thorax,* 70**,** 566-73.

SECTION C: MANUSCRIPT[1]

[1] The manuscript follows the author instructions for the Lancet Infectious Diseases. These instructions are included as Appendix B.

Abstract

Introduction

Although HIV infection increases the likelihood of developing TB, evidence suggests that starting ART reduces the risk of TB incidence although not to the level of HIV negative people in the population. This study aims to determine the impact of ART on TB incidence in people living with HIV in the Western Cape Province of South Africa.

Methods

This is a retrospective cohort study using routinely collected data of HIV infected individuals aged 15 years and above from public health facilities in the Western Cape Province, South Africa, between 2007 and 2016. A Marginal Structural Model (MSM) with inverse probability of treatment weighting (IPTW) was used to estimate the effect of ART on TB incidence adjusting for measured time-dependent confounding by CD4 count.

Results

ART was associated with a 77.3% (95% CI, 76.7% – 78.0%) reduction in the risk of TB incidence in HIV infected patients. The overall TB incidence was 9 855 per 100 000 patient years (95% CI, 9 798 – 9 912). Patients on ART and those not on ART had a TB incidence of 3 939 and 15 329 per 100 000 patient years respectively. TB incidence was higher in males than females, and higher in patients with lower CD4 count at baseline and during follow-up. TB incidence declined with increasing ART duration and rising CD4 count but remained elevated compared to background incidence.

Conclusion

This study has shown that ART is highly effective at preventing TB in people living with HIV. The recent introduction of universal ART access for everyone living with HIV should contribute to further reducing TB incidence in South Africa and other high HIV and TB burden countries.

Introduction

Background

The double burden of the human immunodeficiency virus (HIV) and tuberculosis (TB) epidemic and co-infection makes them the biggest threat to public health worldwide (Suthar et al., 2012b, Massyn et al., 2016). TB remains one of the most frequent opportunistic infections in people living with the HIV (Van Rie et al., 2011). The World Health Organisation (WHO) notes that people living with HIV are 16 to 27 times more likely to develop TB disease than those who are HIV negative. Since the early 1980s, the HIV epidemic has led to a major upsurge in TB cases and TB mortality in many countries, especially those in Southern and Eastern Africa (World Health Organisation, 2014).

TB is the main cause of mortality and morbidity in people living with HIV/AIDS, especially in low-income countries (Harries et al., 2010). The greatest burden is in sub-Saharan Africa due to the generalized HIV epidemic (World Health Organization, 2017). South Africa is noted to have the highest TB incidence in the world, largely resulting from a high population prevalence of HIV infection (Hermans and Manabe, 2015).

Although being infected with HIV infection increases the likelihood that a person will develop TB, starting them on antiretroviral treatment (ART) has been seen to reduce their risk of TB (Williams and Dye, 2003, Williams, 2013, Edmonds et al., 2009). This risk reduction, however, is not completely to the same risk for HIV negative people (Williams, 2013). A study looking at TB in patients receiving ART found an 80% reduction in TB incidence (Van Rie et al., 2011). This study also highlighted that the ART program had revolutionized the care of HIV-infected individuals as evidenced by dramatic reductions in morbidity and mortality.

HIV positive people on ART are expected to live longer than those without treatment, and thus have an elevated risk of TB infection over their much longer life span (Williams, 2013). Hence, this could lead to an increase in the population level incidence of TB. Starting ART very late after infection and low coverage of ART also increases the population level incidence of TB (Williams, 2013). Thus, in the course of HIV infection, starting ART very late increases the lifetime risk of TB, while starting ART very early decreases the lifetime risk of TB.

ART outcomes in a non-randomised setting are noted to be biased by confounding by indication (Edmonds et al., 2009). Estimating the impact of ART on TB is complicated by time-varying confounding, and standard epidemiological methods for effect estimation are inadequate in the presence of these time-dependent confounders (Robins et al., 2000). Essentially patients with

more advanced HIV disease are more likely to be started on ART, and the same patients are also likely to develop TB, usually resulting in under-estimation of the true impact of ART on HIV-associated TB incidence if the statistical methods do not explicitly adjust for time-varying confounding.

There is a paucity of information on TB incidence in HIV patients on ART globally as well as in the country. Operational challenges to the health system in South Africa have been created due the HIV and TB programmes being run vertically, with treatment for each delivered in different facilities (Kaplan et al., 2014). This relies on referral and linkage to care between two vertical programmes, which is often suboptimal, and complicates tracking patients between services, and ascertaining TB diagnosis in cohorts of HIV patients.

Understanding the incidence of TB and associated risk factors over time in patients with HIV and who are on ART is crucial for developing effective intervention strategies. Data on the incidence of TB by CD4 count and ART status are lacking and are required to inform models of TB burden as the ART program matures, more especially with the 90-90-90 targets. This study analyses data from a large cohort of patients with HIV, pre and post-ART in those who receive ART, attending public health facilities in the Western Cape Province of South Africa. The primary objective of this study was to describe the impact of ART on TB incidence in patients living with HIV, controlling for time-varying confounding. Secondary objectives were to provide robust estimates of TB case-finding by CD4 count and ART status.

Methods

Study design and setting

This is a retrospective cohort study using routinely collected data of HIV infected adults aged above the age of 15 attending public health facilities in the Western Cape Province, South Africa. The study period was between 2007 and 2016. The retrospective study allowed the description of the HIV cohort over time, event rates and measures of associating with TB (hazard ratios).

Population and sampling

The study population was a cohort of adult HIV infected patients attending public health facilities in the Western Cape Province, with HIV status ascertained between 2007 and 2016. An anonymous data set of all the HIV cohort linked to TB events was extracted.

Inclusion criteria

We included patients aged 15 years and above with HIV first evidence between 2007 and 2016. The patients had to be free of TB at HIV first evidence, and not be on ART at HIV first evidence.

Data source and management

The patient registration system in the Western Cape has evolved to an extent that the same unique patient health identifier is being used across source electronic patient systems across hospitals, community health centre and clinic records is being used(Western Cape Department of Health, 2013). This unique patient identifier issued by the hospital information system (Clinicom), referred to as the patient master index (PMI) (also called folder number or Clinicom number) has created new opportunities to assemble and link individual patient level data across multiple health information source systems, including laboratory data (critical in the diagnosis of TB), pharmacy data, chronic disease data and disease management systems for TB and HIV (Western Cape Department of Health, 2013).

The province has a near complete disease management information system for HIV and TB treatment (Western Cape Department of Health, 2013). Data from HIV and TB patients is routinely collected at health facilities where the patients come regularly for their treatment in the province. All the patient information is recorded and collated into the centralised electronic HIV and TB databases. The Provincial Health Department, through the Provincial Health Data Centre (PHDC), is proactively curating and integrating this individual patient-level data from different source systems, linking the data to the PMI. All data is anonymised prior to the analysis by assignment of unique identifiers valid only for this anonymised dataset. Data was checked and corrected for any inconsistencies, which included age, gender, HIV and TB first evidence dates and ART start dates.

Key variables and outcomes

The primary outcome was defined as the first evidence of TB pre and post initiation of ART, with incident TB defined as the first episode of TB between 2007 and 2016. Potential associations with TB included demographic variables (age and gender), ART start date (ART status), CD4 counts (baseline and time-varying) and year of HIV first evidence. First evidence of HIV and TB is based on laboratory diagnosis, HIV and TB electronic register, pharmacy data and hospital diagnostic codes. Mortality of the patients was ascertained through evidence available from the hospital information systems as well as death registration from the

Department of Home Affairs which was only available between 2011 and 2013. Thus, mortality was not considered a viable and robust outcome, as hospital information systems only record deaths that occur in provincial facilities.

Statistical methods and analysis

Statistical analysis was performed using Stata version 15 (StataCorp, 2017). Standard descriptive statistics were used to characterize the cohort. Time to TB case diagnosis was described with Kaplan-Meier estimates and curves.

Standard epidemiological methods for effect estimation are inadequate in the presence of time-dependent confounders that are themselves affected by previous exposure (Robins et al., 2000). . Thus, the Marginal Structural Model (MSM) with inverse probability of treatment weighting (IPTW) was used to estimate the effect of ART on TB incidence adjusting for measured time-dependent confounding by CD4 count (Robins et al., 2000, Fewell et al., 2004). CD4 count is associated with both the probability of treatment (ART) and the outcome (TB incidence). The study entry was shifted 3 months forward (lagged) for some analyses, due to HIV and TB co-diagnosis and patients presenting with TB testing positive with HIV. Analysis was done on the full and lagged datasets. CD4 counts (time-varying) were only carried forward for a year if no further results were available, in keeping with clinical guidance on repeat CD4 count testing pre-ART (the study predated universal ART provision). No imputation was done for patients with missing baseline or follow-up CD4 counts.

Analysis was done at the person month level, with multiple records per patient in the MSM. Baseline covariates used were age, gender, baseline CD4 count and year of HIV first evidence, while CD4 count was used as the time-varying covariate. Stabilised inverse probability treatment weights were estimated using two logistic regression models. The first model (numerator weights) had ART as the outcome and baseline covariates, restricted cubic splines and months of follow-up as the independent variables, while the second model (denominator weights) had ART as the outcome and baseline covariates, time-varying covariates (CD4), restricted cubic splines for time and months of follow-up as the independent variables. Stabilised inverse probability of censoring weights was also estimated using the two logistic models, but with censoring as the outcome.

The treatment and censoring weights were then combined to estimate the stabilised IPTW. We truncated the stabilised IPTW at the 0.5% and 99.5% percentile based on recommendations of truncating very large weights to ensure a mean weight of 1 (Cole and Hernan, 2008). The mean

weights of the truncated IPTW models were 1.03 and 1.05 for the lagged and full models respectively (supplementary Table 4).

Presented models included the unweighted unadjusted model (representing the crude association between ART and TB incidence), the model adjusted for baseline co-variates (representing traditional adjustment of this association by baseline co-variates), and the model including adjustment for baseline co-variates and additionally including the IPTW's (the causal estimate accounting for time-varying confounding by CD4 count).

Ethical considerations

This study was approved by the University of Cape Town Research Ethics Committee (reference number UCT-HREC 759-2016) and the Western Cape Government, Department of Health, Health Research Committee. Ethical principles stated in the Declaration of Helsinki 2013 developed by the World Medical Association (World Medical Association, 2013) were adhered to. The data extracted was anonymised to keep all patient information confidential.

Results

A total of 494 871 HIV patients linked to 115 374 TB patients met the inclusion criteria in the full data set and 441 310 HIV patients linked to 61 813 TB patients in the lagged dataset excluding patients with potential simultaneous diagnoses of HIV and TB (Figure1). In the final analysis cohort (Table 1), 65% of the HIV patients were female, compared to 55% of TB patients being female (supplementary Table 2). The median age at HIV-first evidence was 31.0 years (IQR, 25.6-38.1, 29.2 for females and 34.3 for males, Table 1 and supplementary Figure 4). The median age at TB first evidence was 32.7 years (IQR, 27.0 – 39.6, 30.4 for females and 35.3 for males, supplementary Table 2 and supplementary Figure 4). The median CD4 count at HIV first evidence was 324 (IQR,182-499), while the median CD4 count at ART start was 242 (IQR, 151-347). A total of 193 727 (39.1%) HIV patients had ever started ART. At baseline, 8.8% of the patients had a missing CD4 count.

TB incidence

The overall TB incidence was 9 855 per 100 000 patient years (95% CI, 9 798 – 9 912) in the full dataset and 5 835 per 100 000 patient years (95% CI, 5 7888 – 5 881) in the lagged dataset. The TB incidence in patients on ART (Table 1 and supplementary Figure 4) was 3 939 per 100 000 patient years (95% CI, 3 888 – 3 992), while the TB incidence in patients not on ART was 15 329 per 100 000 patient years (95% CI, 15 231 – 15 427) in the full dataset. In the lagged dataset, the TB incidence in patients on ART was 3 645 per 100 000 patient years (95% CI, 3 595 – 3 696),

while the TB incidence in patients not on ART was 8 144 per 100 000 patient years (95% CI, 8 066 – 8 222).

The male TB incidence of 16 460 per 100 000 patient years (95% CI, 16 320 – 16 602) was over double the female TB incidence of 7 398 per 100 000 patient years (95% CI, 7 341 – 7 456) in the full dataset, while in the lagged dataset the male TB incidence of 8 297 per 100 000 patient years (95% CI, 8 191 – 8 404) was about 1.7 times greater than the female TB incidence of 4 948 per 100 000 patient years (95% CI, 4 898 – 4 997). TB incidence increased with a decrease in CD4 count in patients on and off ART in both the full and lagged datasets. TB incidence also increased with an increase in age and year of HIV first evidence. During the ten-year follow-up period, 39 234 patients were known to have died (7.9%), with 17 399 and 21 835 dying before and after starting ART respectively.

The Kaplan-Meier (K-M) failure curve in Figure 2 (A and B) showed patients on ART having lower probabilities of TB incidence than patients not on ART, in both the full and lagged dataset. Males had a higher probability than females of TB incidence (supplementary Figure 6 (A and B)). We observed that many of HIV and TB diagnoses were made simultaneously, resulting in a prominent peak in TB incidence within the first few months of HIV diagnosis in the full dataset.

Comparison of baseline and time-varying CD4 count K-M failure curves showed higher probabilities of TB incidence in patients with lower CD4 counts compared to patients with higher CD4 counts (Figure 2 (C and D) and Figure 7 (A and B)), with patients on ART having lower failure probabilities compared to those not on ART. Comparison of CD4 count categories showed higher risk of TB incidence in patients not on ART compared to patients on ART in all strata (Table 1). Older age groups were also more at risk of TB than younger age-groups regardless of ART status (Table 1). The K-M curves also show that the longer the patients are on ART the lower the TB incidence in all the patient strata (gender, age and CD4 count).

Associations with TB incidence

Crude analysis with no covariates showed a 50.5% (95% CI, 49.6% - 51.3%) and 52.5% (95% CI, 51.7% - 53.3%) reduction in TB incidence associated with ART in the full and lagged dataset respectively (Figure 3). While in the crude analysis with baseline covariates, ART was associated with a 72.7% (95% CI, 72.2% - 73.2%) and 67.9% (95% CI, 67.3% - 68.5%) reduction in TB incidence in the full and lagged dataset respectively (Figure 3).

The IPTW marginal structural model (MSM) estimated a 79.6% (95%CI, 79.1% - 80.1%) and 77.3% (95% CI, 76.7% - 78.0%) reduction in TB incidence associated with ART in the full and lagged dataset respectively. These estimates were higher than the unweighted estimates which adjusted for baseline covariates, suggesting the presence of time-varying confounding by CD4 count. Removing the follow-up period during which HIV and TB might have been co-diagnosed (the lagged dataset), only slightly attenuated the adjusted estimates of the effect of ART.

Discussion

The MSM with IPTW was used to estimate the causal effect of ART on TB incidence among people living with HIV adjusting for time-varying confounding. The study has shown that being on ART is associated with an 80% and 77% reduced risk of TB in people living with HIV in the full and lagged dataset respectively. This clearly shows the importance of ART in patients living with HIV in preventing TB disease. The overall TB incidence was 9 855 and 5 835 per 100 000 patient years in the full and lagged dataset respectively. TB incidence was higher in men, older patients, and was strongly associated with immune deficiency represented by CD4 count and increased with an increase in age.

Effect size compared to previous estimates

The effect size in our study is slightly greater than estimates from a previous systematic review and meta-analysis from developing countries and limited resources settings which noted a 65% and 67% reduction in TB incidence associated with ART respectively (Lawn et al., 2010, Suthar et al., 2012). It is much greater than the only previous South African study which used similar methods and found a 39% reduction, although this study was from a very different period early on in the ART programme (Fairall et al., 2008).

This TB risk reduction estimate is comparable to the estimate found in a similar study in China, which showed a 73% reduction of TB incidence associated with ART. However, the effect size estimate is much higher than the estimate by del Amo et al (2012) of 44%, which used similar methods based on 12 cohorts from high income countries. Other related studies which used traditional methods have shown varying estimates, from 73% reduction in Western Cape Province, South Africa (Bock et al., 2018), 60% reduction in Ethiopia (Ayele et al., 2015) and 32% reduction in Gauteng Province, South Africa (Kufa et al., 2016).

The incidence of TB in South Africa has been noted to have been declining, with the decline associated with increased ART coverage (Nanoo et al., 2015), thus this population effect could explain the higher effect size in our study in comparison with other studies.

Ongoing high incidence of TB in spite of ART

Despite ART being shown to reduce TB incidence in adult HIV patients in the Western Cape, there is continued high TB incidence on average in people on ART (3 939 and 3 645 per 100 000 patient years in full and lagged datasets respectively), and patients on ART with CD4 count greater than 500 (1 114 and 1 106 per 100 000 patient years in full and lagged datasets respectively).

The study also showed a decline in TB incidence with longer duration on ART. This has also been evidenced in other studies which have shown a decline in TB incidence the longer patients are on ART (Moore et al., 2007, Girardi et al., 2005, Lawn et al., 2005, Brinkhof et al., 2007, Lawn et al., 2009). Hence the early initiation of ART based on the universal test and treat (UTT) guidelines in the country is going to reduce the lifetime risk of developing TB in people living with HIV. However, other studies have also shown that TB incidence in people living with HIV remains higher than the background TB incidence in the general population, even after years of being on ART (Lawn et al., 2009, Gupta et al., 2012, Gupta et al., 2015).

The higher incidence in patients on long term ART and patients on ART with CD4 count greater than 500 could be due to long term ART not resulting in immune reconstitution to these levels either because of low CD4 count nadir at ART start, or poor retention on ART with representation with advanced disease (Sharma and Soneja, 2011, Osler et al., 2018, Darraj et al., 2018). Use of Isoniazid preventative therapy (IPT) in addition to ART has been noted to be significantly associated with reduced TB incidence (Golub et al., 2007, Rangaka et al., 2014). In our study data on IPT uptake were not available, but it is generally considered to be suboptimal.

Initial high incidence of TB after HIV first evidence

Within the first few months of HIV first evidence there is simultaneous presentation of TB, which is a result of HIV and TB co-diagnosis, making TB incidence very high in this period (initially) in both patients off ART and on ART. These incidences are higher in patients off ART, and this is probably due patients presenting at health facilities when they are very sick, have low CD4 counts and HIV and TB co-diagnosed. This has also been noted in other studies, where during the first weeks of HIV diagnosis TB incidence is very high, with risk factors such as low CD4 counts, TB patients diagnosed with HIV after seeking medical treatment for TB, late presentation by sick patients, poverty and poor socio-economic status (Kwan and Ernst, 2011, Alvarez-Uria et al., 2014). The high incidence of TB in the first months of ART have been consistently documented across different regions globally in other studies as well (Van Rie et al.,

2011, Moore et al., 2007, Girardi et al., 2005, Lawn et al., 2005, Bonnet et al., 2006, Brinkhof et al., 2007, Dembele et al., 2010, Rajasekaran et al., 2009). This is attributed to the unmasking of subclinical TB during the initial rapid restoration of the immune response (Lawn et al., 2009).

Strength and weaknesses of the study

The major strengths of this study in this high HIV and TB burden setting is the better TB ascertainment through linkage of provincial TB and HIV registers and electronic laboratory data through the provincial health data centre. This made this a population-wide study with high levels of outcome ascertainment as they were not only restricted to registered treated TB cases. One of the strengths of this study is the representative nature of the data coming from the public health sector which accounts for about 95% of HIV and TB patients in the Province, and which is thus generalisable to similar populations.

We also had a large sample (494 871 HIV patients linked to 115 374 TB patients and 441 310 HIV patients linked to 61 813 TB patients in the full and lagged dataset respectively) size in comparison to similar studies, which allowed the association between ART and reduction in TB incidence to be estimated more precisely. The marginal structural models used to estimate the ART effectiveness in reducing TB incidence helped to control for any possible time-varying confounding by CD4 count.

The limitations of the study include that some clinically diagnosed TB cases could not be linked due to insufficient recording of unique patient identifiers especially in the earlier years where some were not captured. We did not impute missing CD4 count data (including time-varying CD4 count, which was carried forward for a year if missing), which might have introduced bias and affected the weighting models. Sensitivity analysis of our models with and without the missing CD4 count data did not however show any notable differences in the overall results. A further limitation is that clinical characteristics of TB cases have not been incorporated in this study and data on IPT was not available to use as well.

Conclusion

In summary, our findings demonstrate a substantial reduction in TB incidence in HIV patients due to ART regardless of CD4 count, even though the incidence on ART remains high, including many years after initiation.

Funding

This study was not funded.

Tables and Figures

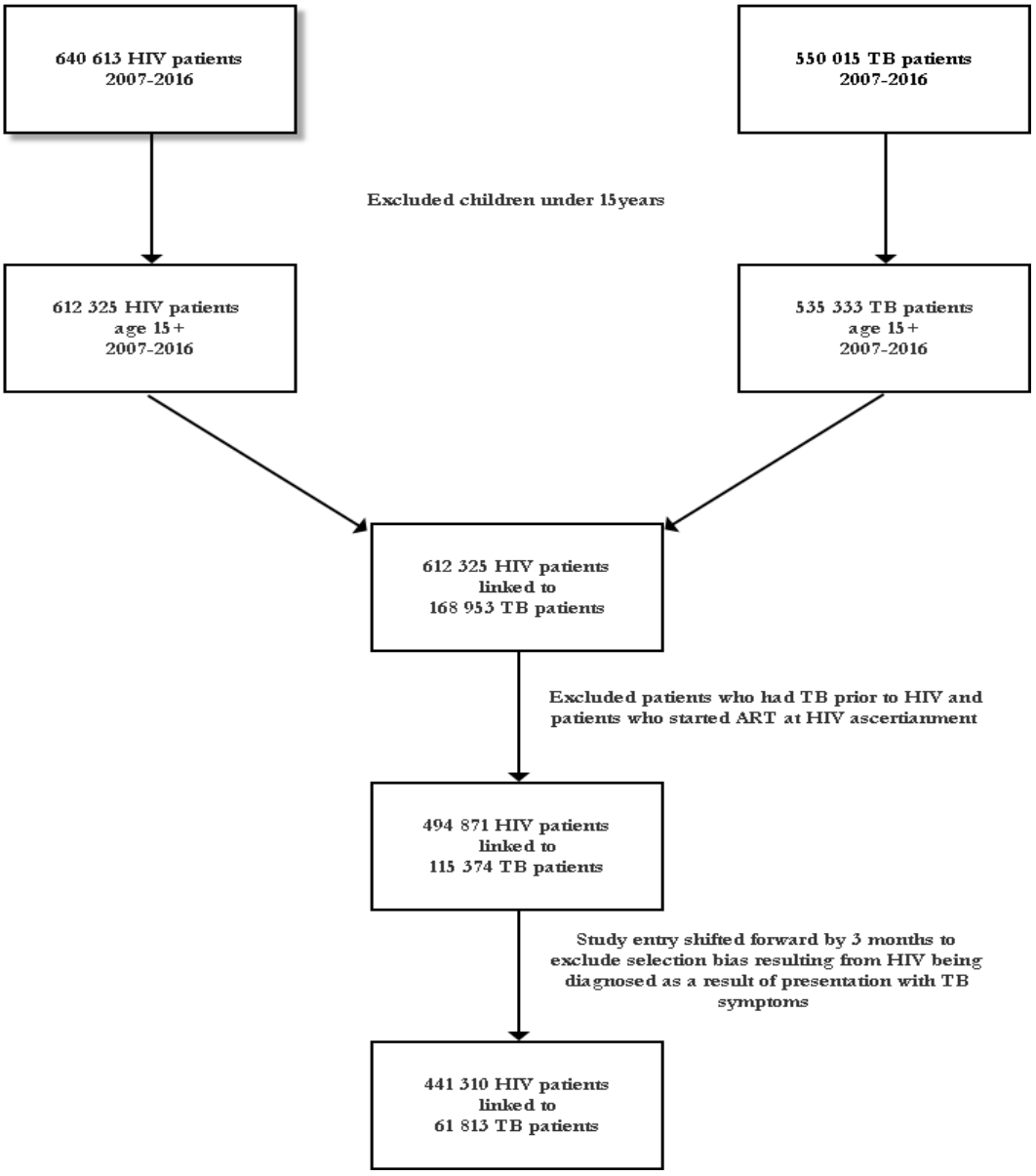

Figure 1: Flow diagram of HIV and TB patients included in the study

Table 1: Baseline characteristics of HIV cohort and associated TB incidence

			Full data set				3 months lag			
			Off ART		On ART		Off ART		On ART	
	N	%	TB incidence / per 100 000 py	95% CI	TB incidence / per 100 000 py	95% CI	TB incidence / per 100 000 py	95% CI	TB incidence / per 100 000 py	95% CI
Total number (N)	494 871		15 329	(15231 : 15427)	3 939	(3888 : 3992)	8 144	(8066 : 8222)	3 645	(3595 : 3696)
Female	321 021	(65%)	11 147	(11049 : 11246)	3 397	(3342 : 3454)	6 801	(6719 : 6885)	3 196	(3141 : 3252)
Male	173 850	(35%)	26 329	(26085 : 26576)	5 432	(5315 : 5551)	11 844	(11664 : 12028)	4 900	(4787 : 5016)
Median age at HIV ascertainment										
Total	31.0	(IQR, 25.6 - 38.1)								
Female	29.2	(IQR, 24.3 - 35.9)								
Male	34.3	(IQR, 28.8 - 41.1)								
Age groups										
15-24	110 531	(22.3%)	8 918	(8777 : 9061)	3 529	(3424 : 3638)	6 275	(6149 : 6405)	3 438	(3333 : 3547)
25-34	214 377	(43.3%)	14 286	(14146 : 14428)	3 701	(3628 : 3776)	7 875	(7762 : 7989)	3 450	(3379 : 3524)
35-44	112 373	(22.7%)	22 373	(22102 : 22647)	4 418	(4305 : 4534)	10 319	(10119 : 10524)	3 977	(3868 : 4089)
45-54	42 377	(8.6%)	26 379	(25862 : 26906)	4 797	(4595 : 5008)	11 490	(11113 : 11881)	4 212	(4019 : 4415)
55-64	12 034	(2.4%)	30 771	(29577 : 32014)	4 836	(4412 : 5301)	12 261	(11401 : 13187)	4 330	(3918 : 4785)
65+	3 177	(0.6%)	31 411	(28734 : 34338)	6 087	(4968 : 7459)	11 761	(9773 : 14154)	5 142	(4088 : 6468)
Year of HIV ascertainment										
2007-2010	233 798	(47.2%)	12 801	(12694 : 12909)	3 828	(3763 : 3894)	8 101	(8010 : 8192)	3 715	(3651 : 3780)
2011-2013	138 774	(28.0%)	16 858	(16644 : 17074)	3 930	(3835 : 4028)	7 804	(7644 : 7967)	3 539	(3447 : 3634)
2014-2016	122 299	(24.7%)	36 285	(35708 : 36870)	4 667	(4490 : 4851)	10 514	(10106 : 10939)	3 487	(3321 : 3660)
Median time to ART in months	6.8	(IQR, 1.3 - 31.8)								
CD4 count category at HIV ascertainment (cells/µl)			**CD4 count baseline**		**CD4 count baseline**		**CD4 count baseline**		**CD4 count baseline**	
0-49	28 953	(5.9%)	176 109	(172908 : 17936	7 753	(7414 : 8108)	23 670	(22151 : 25294)	5 665	(5366 : 5980)
50-199	105 703	(21.4%)	51 515	(50918 : 52119)	5 186	(5076 : 5298)	19 110	(18692 : 19537)	4 652	(4546 : 4761)
200-349	125 898	(25.4%)	15 551	(15345 : 15759)	3 473	(3391 : 3557)	10 849	(10662 : 11040)	3 397	(3314 : 3481)
350-499	98 991	(20.0%)	8 572	(8432 : 8714)	2 995	(2892 : 3101)	6 927	(6792 : 7064)	2 976	(2872 : 3083)
500+	118 560	(24.0%)	5 760	(5664 : 5858)	2 482	(2372 : 2596)	4 830	(4737 : 4926)	2 479	(2369 : 2595)
No CD4 count	16 766	(3.4%)	55 092	(53443 : 56791)	6 818	(5446 : 8537)	25 875	(23817 : 28112)	3 401	(2378 : 4864)
Median CD4 count at HIV ascertainment (cells/µl)	324	(IQR, 182 - 499)								
CD4 count category time-varying (cells/µl)			**CD4 count time-varying**		**CD4 count time-varying**		**CD4 count time-varying**		**CD4 count time-varying**	
0-49			71 675	(70521 : 72848)	25 765	(24844 : 26721)	21 441	(20765 : 22139)	23 610	(22658 : 24603)
50-199			32 717	(32360 : 33079)	11 942	(11680 : 12211)	13 875	(13625 : 14129)	11 376	(11104 : 11655)
200-349			11 960	(11784 : 12139)	4 279	(4159 : 4402)	6 951	(6806 : 7100)	4 201	(4078 : 4327)
350-499			6 754	(6616 : 6895)	1 953	(1872 : 2037)	4 324	(4204 : 4448)	1 909	(1829 : 1993)
500+			4 429	(4330 : 4529)	1 114	(1061 : 1170)	2 849	(2763 : 2937)	1 106	(1053 : 1162)
No CD4 count			32 400	(31840 : 32970)	2 467	(2380 : 2557)	26 878	(26329 : 27438)	2 433	(2347 : 2523)
Median CD4 count at ART start (cells/µl)	242	(IQR, 151 - 347)								

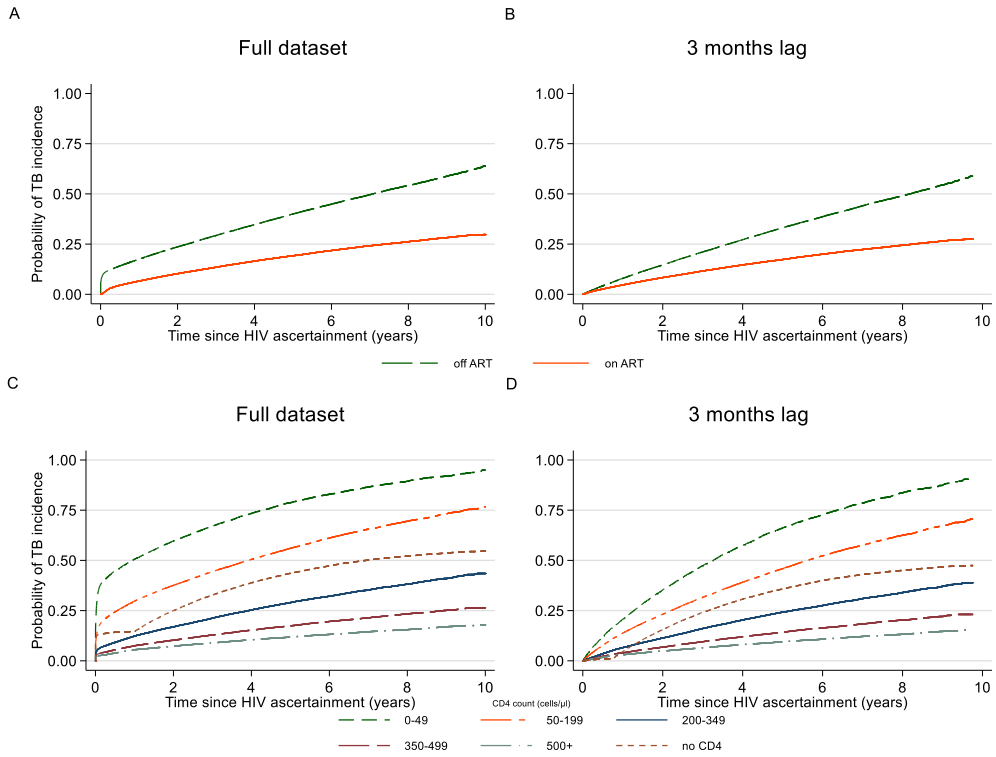

Figure 2: Kaplan-Meier failure estimates time to TB, 2007-2016; by ART status, Full dataset (A) and 3 months lag (B) and by time-varying CD4 count, Full dataset (C) and 3 months lag (D)

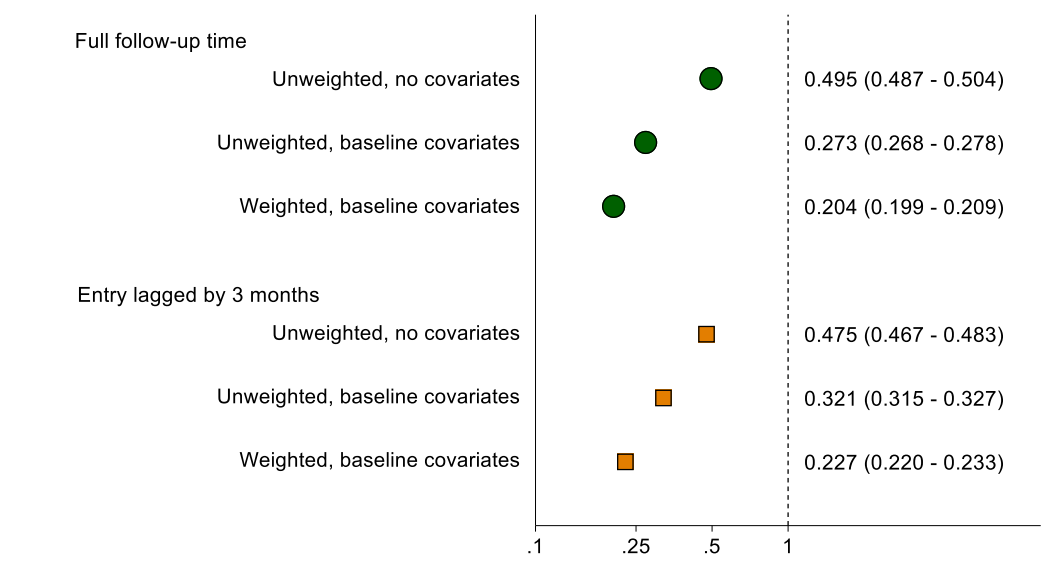

Figure 3: Marginal structural model with inverse probability to weight estimates

Supplementary material

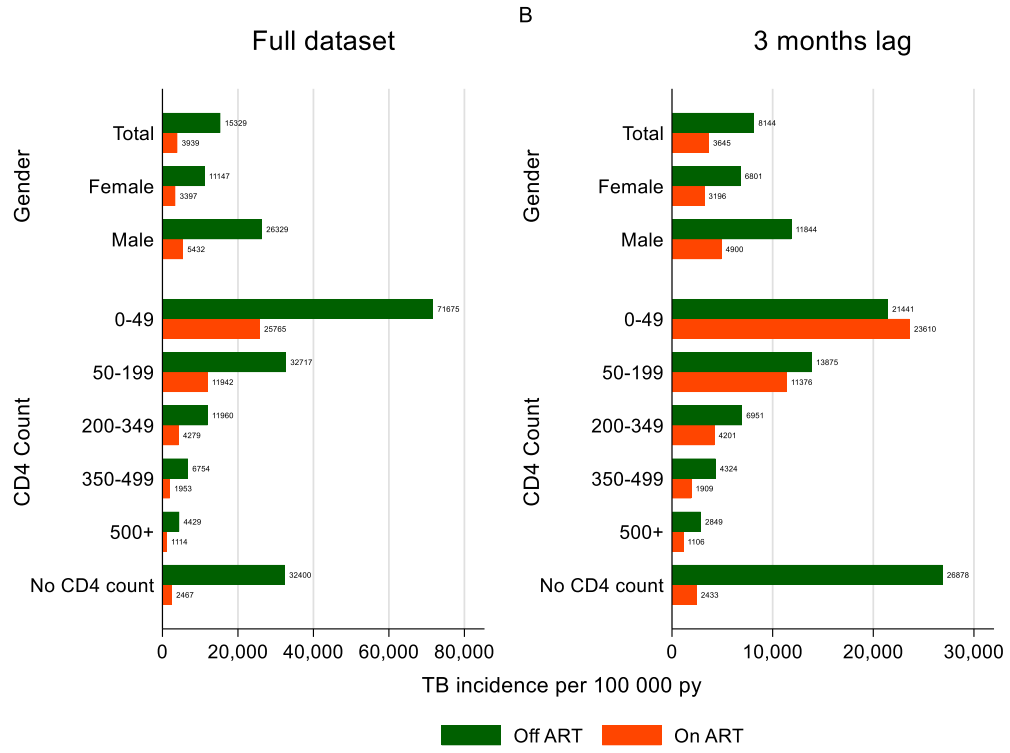

Figure 4: TB incidence by gender and CD4 count, full dataset (A), 3 months lag (B)

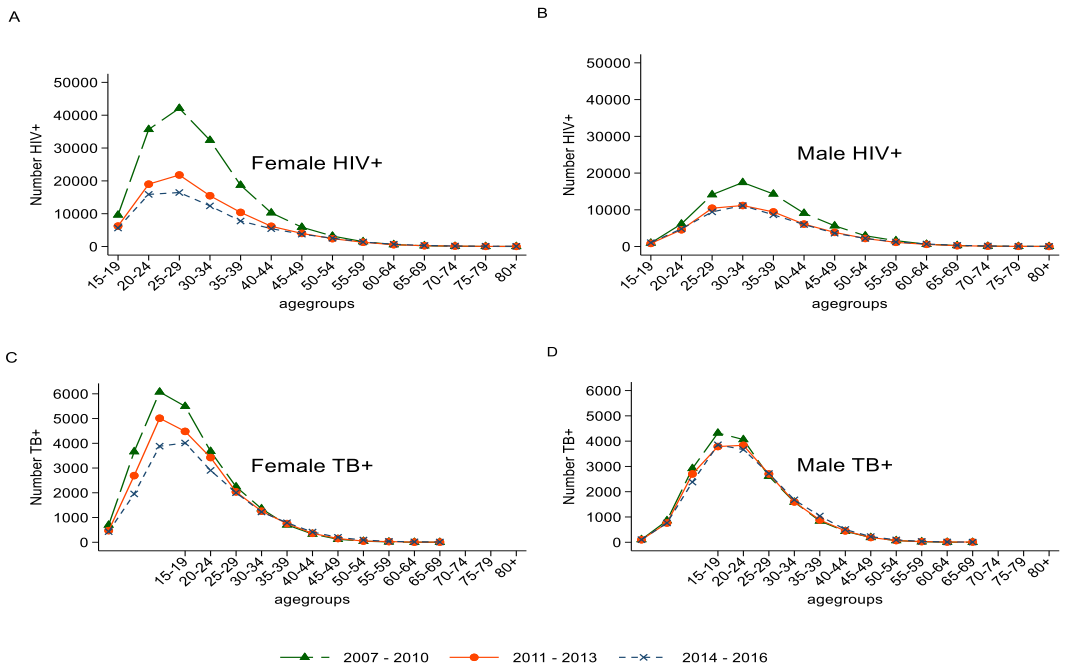

Figure 5: Age distribution of female HIV+ (A), male HIV+ (B), female TB+ (C) and male TB+ (D) patients, 2007-2016

Table 2: Baseline characteristics of HIV-TB co-infected patients, Age 15+, 2007-2016[2]

	On ART		Off ART		Total	
	N	%	N	%	N	%
Total number	93 207		22 167		115 374	
Female	49 110	(52.7%)	14 025	(63.3%)	63 135	(54.7%)
Male	44 097	(47.3%)	8 142	(36.7%)	52 239	(45.3%)
Median age at TB ascertainment						
Total	32.9	(IQR, 27.2 - 39.8)	31.9	(IQR, 26.4 - 38.8)	32.7	(IQR, 27.0 - 39.6)
Female	30.5	(IQR, 25.2 - 37.6)	29.9	(IQR, 24.9 - 36.5)	30.4	(IQR, 25.1 - 37.4)
Male	35.3	(IQR, 30.0 - 41.6)	35.3	(IQR, 29.9 - 41.7)	35.3	(IQR, 30.0 - 41.7)
TB in first 3 months of HIV	51 216	(54.9%)	2 345	(10.6%)	53 561	(46.4%)
Year of TB ascertainment						
2007-2010	42 455	(36.8%)	38 727	(41.5%)	3 728	(16.8%)
2011-2013	37 856	(32.8%)	30 064	(32.3%)	7 792	(35.2%)
2014-2016	35 063	(30.4%)	24 416	(26.2%)	10 647	(48.0%)
Treatment status (TB treated)						
Evidence of TB treatment	49 893	(53.5%)	11 741	(53.0%)	61 634	(53.4%)
TB characteristics on evidence of treatment						
TB classification , N=61 634						
Extra-Pulmonary	10 253	(11.0%)	2 880	(13.0%)	13 133	(11.4%)
Pulmonary	41 097	(44.1%)	10 040	(45.3%)	51 137	(44.3%)
Unknown	41 857	(44.9%)	9 247	(41.7%)	51 104	(44.3%)
Microbiological classification, N=61 634						
Culture/PCR/GeneXpert positive	31 754	(63.6%)	8 742	(74.5%)	40 496	(65.7%)
Smear positive	14 527	(30.2%)	4 072	(34.7%)	18 599	(30.2%)
TB treatment outcomes, N=61 634						
Cured	9 421	(18.9%)	2 126	(18.1%)	11 547	(18.7%)
Died	3 029	(6.1%)	548	(4.7%)	3 577	(5.8%)
Treatment completed	22 857	(45.8%)	5 969	(50.8%)	28 826	(46.8%)
Treatment failure/default/relapse	4 029	(8.1%)	760	(6.5%)	4 789	(7.8%)
Loss-to-follow-up	10 121	(20.3%)	2 259	(19.2%)	12 380	(20.1%)
Drug Resistance						
MDR-TB	1 525	(1.6%)	496	(2.2%)	2 021	(1.8%)
Mono/Poly	165	(0.2%)	66	(0.3%)	231	(0.2%)
XDR-TB	69	(0.1%)	36	(0.2%)	105	(0.1%)

[2] These are based on first TB episodes in HIV-TB co-infected patients

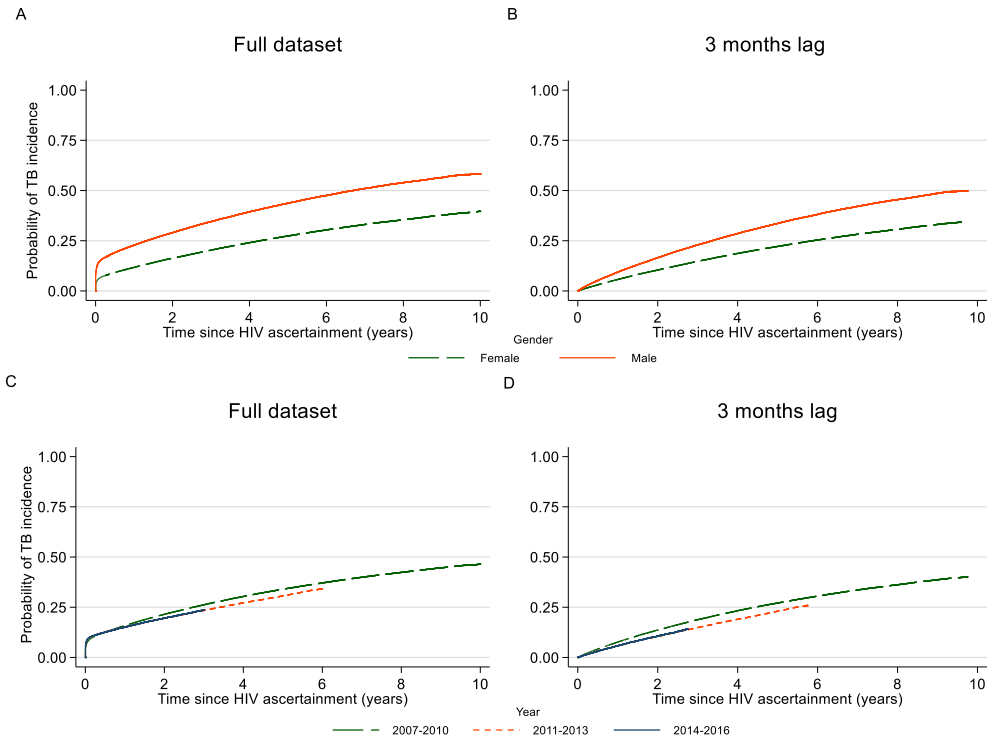

Figure 6: Kaplan-Meier failure estimates time to TB, 2007-2016; by gender, Full dataset (A) and 3 months lag (B) and by year of HIV ascertainment, Full dataset (C) and 3 months lag (D)

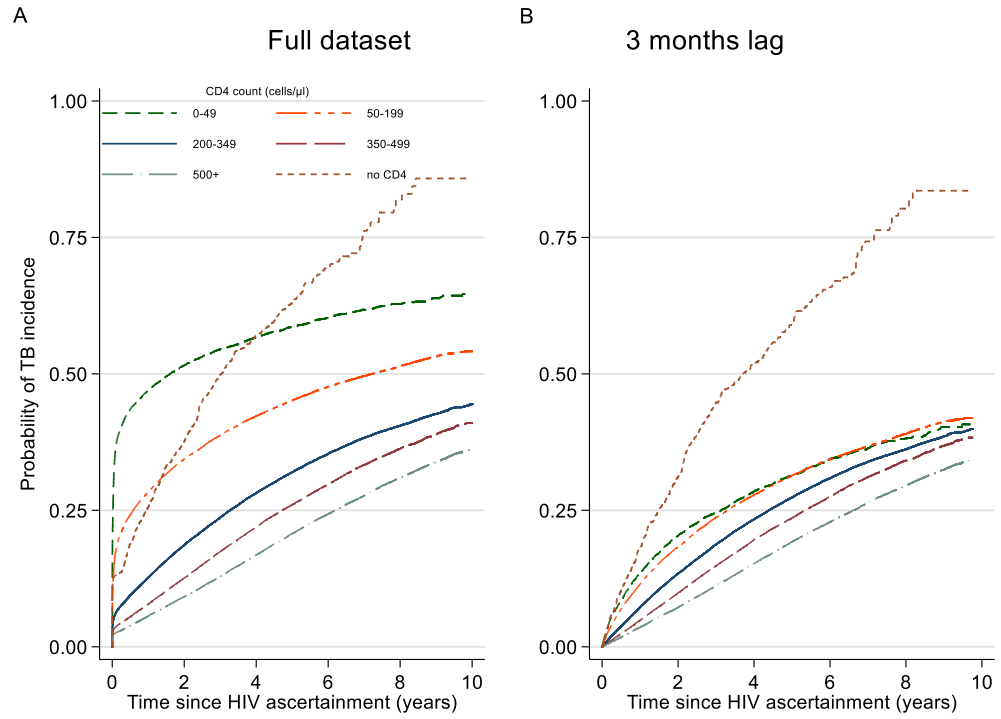

Figure 7: Kaplan-Meier failure estimates time to TB by baseline CD4 count, 2007-2016, Full dataset (A) and 3 months lag (B)

Table 3: MSM with IPTW Models

	Full dataset			3 months lag		
	HR	HR (95% CI)	p-value	HR	HR (95% CI)	p-value
Unweighted model, no covariates						
ART *(reference no ART)*	0.495	(0.487 : 0.504)	0.00	0.475	(0.467 : 0.483)	0.00
constant	0.170	(0.966 : 0.967)	0.00	0.013	(0.012 : 0.014)	0.00
Unweighted model, baseline covariates						
ART *(reference no ART)*	0.273	(0.268 : 0.278)	0.00	0.321	(0.315 : 0.327)	0.00
CD4 count baseline						
0-49	2.922	(2.824 : 3.023)	0.00	0.796	(0.725 : 0.873)	0.00
50-199	1.421	(1.379 : 1.465)	0.00	0.701	(0.645 : 0.762)	0.00
200-349	0.688	(0.667 : 0.710)	0.00	0.474	(0.437 : 0.515)	0.00
350-499	0.455	(0.441 : 0.470)	0.00	0.333	(0.306 : 0.362)	0.00
500+	0.320	(0.309 : 0.331)	0.00	0.235	(0.216 : 0.255)	0.00
no CD4	1	reference		1.000	reference	
Year of HIV ascertainment						
2007-2010	0.822	(0.807 : 0.837)	0.00	0.786	(0.759 : 0.814)	0.00
2011-2013	0.896	(0.878 : 0.914)	0.00	0.800	(0.772 : 0.829)	0.00
2014-2016	1	reference		1.000	reference	
Age group						
15-24	1	reference		0	reference	
25-34	1.112	(1.093 : 1.132)	0.00	1.030	(1.008 : 1.052)	0.01
35-44	1.332	(1.307 : 1.358)	0.00	1.182	(1.154 : 1.211)	0.00
45-54	1.458	(1.423 : 1.494)	0.00	1.292	(1.250 : 1.336)	0.00
55-64	1.454	(1.396 : 1.515)	0.00	1.351	(1.270 : 1.438)	0.00
65+	1.272	(1.167 : 1.387)	0.00	1.319	(1.140 : 1.526)	0.00
Gender_Male *(reference female)*	1.539	(1.520 : 1.558)	0.00	1.427	(1.403 : 1.452)	0.00
Spline						
Spline1	0.971	(0.971 : 0.972)	0.00	0.9970	(0.9966 : 0.9974)	0.00
Spline2	1.003	(1.003 : 1.003)	0.00	1.0006	(1.0005 : 1.0007)	0.00
Spline3	0.9998	(0.9998 : 0.9999)	0.00	0.99996	(0.99994 : 0.99997)	0.00
Spline4	1.00003	(1.00003 : 1.00004)	0.00	1.00002	(1.00001 : 1.00002)	0.00
Spline5	0.99999	(0.99999 : 0.99999)	0.00	0.99999	(0.99999 : 0.999995)	0.00
Spline6	1	reference		0	reference	
cummonth	0.502	(0.497 : 0.506)	0.00	0.874	(0.863 : 0.885)	0.00
constant	0.145	(0.140 : 0.150)	0.00	0.033	(0.030 : 0.036)	0.00
Weighted model, baseline covariates						
ART *(reference no ART)*	0.204	(0.199 : 0.209)	0.00	0.227	(0.220 : 0.233)	0.00
CD4 count baseline						
0-49	3.188	(3.074 : 3.305)	0.00	1.093	(0.984 : 1.215)	0.10
50-199	1.499	(1.453 : 1.547)	0.00	0.886	(0.810 : 0.968)	0.01
200-349	0.700	(0.678 : 0.722)	0.00	0.563	(0.516 : 0.615)	0.00
350-499	0.453	(0.438 : 0.469)	0.00	0.377	(0.345 : 0.412)	0.00
500+	0.312	(0.301 : 0.323)	0.00	0.257	(0.235 : 0.280)	0.00
no CD4	1	reference		1.000	reference	
Year of HIV ascertainment						
2007-2010	0.764	(0.749 : 0.779)	0.00	0.588	(0.562 : 0.615)	0.00
2011-2013	0.880	(0.862 : 0.899)	0.00	0.693	(0.661 : 0.726)	0.00
2014-2016	1	reference		1.000	reference	
Age group						
15-24	1	reference		1	reference	
25-34	1.106	(1.085 : 1.129)	0.00	1.018	(0.990 : 1.048)	0.21
35-44	1.329	(1.300 : 1.358)	0.00	1.176	(1.138 : 1.215)	0.00
45-54	1.452	(1.412 : 1.493)	0.00	1.285	(1.229 : 1.344)	0.00
55-64	1.475	(1.409 : 1.544)	0.00	1.428	(1.314 : 1.552)	0.00
65+	1.224	(1.116 : 1.342)	0.00	1.200	(0.996 : 1.446)	0.06
Gender_Male *(reference female)*	1.499	(1.478 : 1.520)	0.00	1.345	(1.315 : 1.376)	0.00
Spline						
Spline1	0.972	(0.972 : 0.973)	0.00	0.997	(0.996 : 0.997)	0.00
Spline2	1.0031	(1.0030 : 1.0032)	0.00	1.001	(1.001 : 1.001)	0.00
Spline3	0.99986	(0.9998 : 0.9999)	0.00	0.99995	(0.99992 : 0.99997)	0.00
Spline4	1.00003	(1.00003 : 1.00004)	0.00	1.00002	(1.00001 : 1.00003)	0.00
Spline5	0.99999	(0.99998 : 0.99999)	0.00	0.99999	(0.99998 : 0.999995)	0.00
Spline6	1	reference		1	reference	
cummonth	0.516	(0.511 : 0.522)	0.00	0.863	(0.850 : 0.876)	0.00
constant	0.145	(0.140 : 0.150)	0.00	0.040	(0.036 : 0.045)	0.00

Table 4: Summary of stabilised weights

	Full dataset	3 months lag
Minimum	0.069	0.063
Maximum	5.111	7.712
Mean	1.015	1.030
Std. Dev.	0.843	1.157
Variance	0.711	1.339
Skewness	3.688	4.736
Kurtosis	18.241	27.098

References

ABDOOL KARIM, S. S., CHURCHYARD, G. J., ABDOOL KARIM, Q. & LAWN, S. D. 2009. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. *Lancet,* 374**,** 921-933.

AKANBI, M. O., ACHENBACH, C. J., FEINGLASS, J., TAIWO, B., ONU, A., PHO, M. T., AGBAJI, O., KANKI, P. & MURPHY, R. L. 2013. Tuberculosis after one year of combination antiretroviral therapy in Nigeria: a retrospective cohort study. *AIDS Res Hum Retroviruses,* 29**,** 931-7.

ALVAREZ-URIA, G., PAKAM, R., MIDDE, M. & NAIK, P. K. 2014. Incidence and mortality of tuberculosis before and after initiation of antiretroviral therapy: an HIV cohort study in India. *J Int AIDS Soc,* 17**,** 19251.

ASSEFA, A., GELAW, B., GETNET, G. & YITAYEW, G. 2014. The effect of incident tuberculosis on immunological response of HIV patients on highly active anti-retroviral therapy at the university of Gondar hospital, northwest Ethiopia: a retrospective follow-up study. *BMC Infect Dis,* 14**,** 468.

ATTIA, S., EGGER, M., MULLER, M., ZWAHLEN, M. & LOW, N. 2009. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *Aids,* 23**,** 1397-404.

AULD, A. F., MBOFANA, F., SHIRAISHI, R. W., ALFREDO, C., SANCHEZ, M., ELLERBROCK, T. V. & NELSON, L. J. 2013. Incidence and determinants of tuberculosis among adults initiating antiretroviral therapy--Mozambique, 2004-2008. *PLoS One,* 8**,** e54665.

AYELE, H. T., VAN MOURIK, M. S. M. & BONTEN, M. J. M. 2015. Effect of isoniazid preventive therapy on tuberculosis or death in persons with HIV: a retrospective cohort study. *BMC Infectious Diseases,* 15**,** 334.

BACHMANN, M. O., TIMMERMAN, V. & FAIRALL, L. R. 2015. Effect of antiretroviral treatment on the risk of tuberculosis during South Africa's programme expansion. *Aids,* 29**,** 2261-8.

BADRI, M., WILSON, D. & WOOD, R. 2002. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet,* 359**,** 2059-64.

BEKKER, L.-G., VENTER, F., COHEN, K., GOEMARE, E., VAN CUTSEM, G., BOULLE, A. & WOOD, R. 2014. Provision of antiretroviral therapy in South Africa: the nuts and bolts. International Medical Press.

BOCK, P., JENNINGS, K., VERMAAK, R., COX, H., MEINTJES, G., FATTI, G., KRUGER, J., DE AZEVEDO, V., MASCHILLA, L., LOUIS, F., GUNST, C., GROBBELAAR, N., DUNBAR, R., LIMBADA, M., FLOYD, S., GRIMWOOD, A., AYLES, H., HAYES, R., FIDLER, S. & BEYERS, N. 2018. 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,* 77**,** 93-101.

BONNET, M. M., PINOGES, L. L., VARAINE, F. F., OBERHAUSER, B. B., O'BRIEN, D. D., KEBEDE, Y. Y., HEWISON, C. C., ZACHARIAH, R. R. & FERRADINI, L. L. 2006. Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden. *AIDS,* 20**,** 1275-9.

BRINKHOF, M. W., EGGER, M., BOULLE, A., MAY, M., HOSSEINIPOUR, M., SPRINZ, E., BRAITSTEIN, P., DABIS, F., REISS, P., BANGSBERG, D. R., RICKENBACH, M., MIRO, J. M., MYER, L., MOCROFT, A., NASH, D., KEISER, O., PASCOE, M., VAN DER BORGHT, S. & SCHECHTER, M. 2007. Tuberculosis after initiation of antiretroviral therapy in low-income and high-income countries. *Clin Infect Dis,* 45**,** 1518-21.

CHAISSON, R. E. & MARTINSON, N. A. 2008. Tuberculosis in Africa — Combating an HIV-Driven Crisis. *New England Journal of Medicine,* 358**,** 1089-1092.

CHANG, C. A., MELONI, S. T., EISEN, G., CHAPLIN, B., AKANDE, P., OKONKWO, P., RAWIZZA, H. E., TCHETGEN, E. T. & KANKI, P. J. Tuberculosis Incidence and Risk Factors Among Human Immunodeficiency Virus (HIV)-Infected Adults Receiving Antiretroviral Therapy in a Large HIV Program in Nigeria. Open forum infectious diseases, 2015. Oxford University Press, ofv154.

CHIGWEDERE, P., SEAGE, G. R., 3RD, GRUSKIN, S., LEE, T. H. & ESSEX, M. 2008. Estimating the lost benefits of antiretroviral drug use in South Africa. *J Acquir Immune Defic Syndr,* 49**,** 410-5.

CHURCHYARD, G. J., MAMETJA, L. D., MVUSI, L., NDJEKA, N., HESSELING, A. C., REID, A., BABATUNDE, S. & PILLAY, Y. 2014. Tuberculosis control in South Africa: successes, challenges and recommendations. *S Afr Med J,* 104**,** 244-8.

COHEN, M. S., CHEN, Y. Q., MCCAULEY, M., GAMBLE, T., HOSSEINIPOUR, M. C., KUMARASAMY, N., HAKIM, J. G., KUMWENDA, J., GRINSZTEJN, B., PILOTTO, J. H., GODBOLE, S. V., MEHENDALE, S., CHARIYALERTSAK, S., SANTOS, B. R., MAYER, K. H., HOFFMAN, I. F., ESHLEMAN, S. H., PIWOWAR-MANNING, E., WANG, L., MAKHEMA, J., MILLS, L. A., DE BRUYN, G., SANNE, I., ERON, J., GALLANT, J., HAVLIR, D., SWINDELLS, S., RIBAUDO, H., ELHARRAR, V., BURNS, D., TAHA, T. E., NIELSEN-SAINES, K., CELENTANO, D., ESSEX, M. & FLEMING, T. R. 2011. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med,* 365**,** 493-505.

COLE, S. R. & HERNAN, M. A. 2008. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol,* 168**,** 656-64.

CORBETT, E. L., WATT, C. J., WALKER, N., MAHER, D., WILLIAMS, B. G., RAVIGLIONE, M. C. & DYE, C. 2003. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med,* 163**,** 1009-21.

DANIEL, R. M., COUSENS, S., DE STAVOLA, B., KENWARD, M. G. & STERNE, J. 2013. Methods for dealing with time-dependent confounding. *Statistics in medicine,* 32**,** 1584-1618.

DARRAJ, M., SHAFER, L. A., CHAN, S., KASPER, K. & KEYNAN, Y. 2018. Rapid CD4 decline prior to antiretroviral therapy predicts subsequent failure to reconstitute despite HIV viral suppression. *Journal of Infection and Public Health,* 11**,** 265-269.

DEL AMO, J., MORENO, S., BUCHER, H. C., FURRER, H., LOGAN, R., STERNE, J., PEREZ-HOYOS, S., JARRIN, I., PHILLIPS, A., LODI, S., VAN SIGHEM, A., DE WOLF, W., SABIN, C., BANSI, L., JUSTICE, A., GOULET, J., MIRO, J. M., FERRER, E., MEYER, L., SENG, R., TOULOMI, G., GARGALIANOS, P., COSTAGLIOLA, D., ABGRALL, S. & HERNAN, M. A. 2012. Impact of antiretroviral

therapy on tuberculosis incidence among HIV-positive patients in high-income countries. *Clin Infect Dis,* 54**,** 1364-72.

DEMBELE, M., SALERI, N., CARVALHO, A. C., SAOUADOGO, T., HIEN, A. D., ZABSONRE, I., KOALA, S. T., SIMPORE, J. & MATTEELLI, A. 2010. Incidence of tuberculosis after HAART initiation in a cohort of HIV-positive patients in Burkina Faso. *Int J Tuberc Lung Dis,* 14**,** 318-23.

DEPARTMENT OF HEALTH 2014. Department of Health Strategic Plan 2014/15–2018/19 Pretoria: South Africa National Department of Health.

DEPARTMENT OF HEALTH 2016. IMPLEMENTATION OF THE UNIVERSAL TEST AND TREAT STRATEGY FOR HIV POSITIVE PATIENTS AND DIFFERENTIATED CARE FOR STABLE PATIENTS. *In:* HEALTH, S. A. D. O. (ed.). Pretoria, South Africa: South Africa Department of Health.

DEPARTMENT OF HEALTH 2017. The 2015 National Antenatal Sentinel HIV & Syphilis Survey, South Africa. Pretoria: South Africa National Department of Health.

DOLL, R. 2001. Cohort studies: history of the method. II. Retrospective cohort studies. *Soz Praventivmed,* 46**,** 152-60.

EDMONDS, A., LUSIAMA, J., NAPRAVNIK, S., KITETELE, F., VAN RIE, A. & BEHETS, F. 2009. Anti-retroviral therapy reduces incident tuberculosis in HIV-infected children. *Int J Epidemiol,* 38**,** 1612-21.

EVANS, D. 2013. *Ten years on ART – where to now?*

FENNER, L., ATKINSON, A., BOULLE, A., FOX, M. P., PROZESKY, H., ZURCHER, K., BALLIF, M., FURRER, H., ZWAHLEN, M., DAVIES, M. A. & EGGER, M. 2017. HIV viral load as an independent risk factor for tuberculosis in South Africa: collaborative analysis of cohort studies. *J Int AIDS Soc,* 20**,** 21327.

FEWELL, Z., HERNÁN, M. A., WOLFE, F., TILLING, K., CHOI, H. & STERNE, J. A. C. 2004. Controlling for time-dependent confounding using marginal structural models. *Stata Journal,* 4**,** 402-420.

FLOYD, K., GLAZIOU, P., ZUMLA, A. & RAVIGLIONE, M. 2018. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era. *Lancet Respir Med,* 6**,** 299-314.

GIRARDI, E., ANTONUCCI, G., VANACORE, P., LIBANORE, M., ERRANTE, I., MATTEELLI, A. & IPPOLITO, G. 2000. Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. *Aids,* 14**,** 1985-91.

GIRARDI, E., SABIN, C. A., D'ARMINIO MONFORTE, A., HOGG, B., PHILLIPS, A. N., GILL, M. J., DABIS, F., REISS, P., KIRK, O., BERNASCONI, E., GRABAR, S., JUSTICE, A., STASZEWSKI, S., FATKENHEUER, G. & STERNE, J. A. 2005. Incidence of Tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clin Infect Dis,* 41**,** 1772-82.

GOLUB, J. E., PRONYK, P., MOHAPI, L., THSABANGU, N., MOSHABELA, M. & STRUTHERS, H. 2009. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS,* 23.

GOLUB, J. E., SARACENI, V., CAVALCANTE, S. C., PACHECO, A. G., MOULTON, L. H., KING, B. S., EFRON, A., MOORE, R. D., CHAISSON, R. E. & DUROVNI, B. 2007. The impact of antiretroviral therapy and isoniazid preventive therapy on

tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS (London, England),* 21**,** 1441-1448.

GRINSZTEJN, B., HOSSEINIPOUR, M. C., RIBAUDO, H. J., SWINDELLS, S., ERON, J., CHEN, Y. Q., WANG, L., OU, S. S., ANDERSON, M., MCCAULEY, M., GAMBLE, T., KUMARASAMY, N., HAKIM, J. G., KUMWENDA, J., PILOTTO, J. H., GODBOLE, S. V., CHARIYALERTSAK, S., DE MELO, M. G., MAYER, K. H., ESHLEMAN, S. H., PIWOWAR-MANNING, E., MAKHEMA, J., MILLS, L. A., PANCHIA, R., SANNE, I., GALLANT, J., HOFFMAN, I., TAHA, T. E., NIELSEN-SAINES, K., CELENTANO, D., ESSEX, M., HAVLIR, D. & COHEN, M. S. 2014. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis,* 14**,** 281-90.

GUPTA, A., WOOD, R., KAPLAN, R., BEKKER, L.-G. & LAWN, S. D. 2012. Tuberculosis Incidence Rates during 8 Years of Follow-Up of an Antiretroviral Treatment Cohort in South Africa: Comparison with Rates in the Community. *PLoS ONE,* 7**,** e34156.

GUPTA, R. K., RICE, B., BROWN, A. E., THOMAS, H. L., ZENNER, D., ANDERSON, L., PEDRAZZOLI, D., POZNIAK, A., ABUBAKAR, I., DELPECH, V. & LIPMAN, M. 2015. Does antiretroviral therapy reduce HIV-associated tuberculosis incidence to background rates? A national observational cohort study from England, Wales, and Northern Ireland. *The Lancet HIV,* 2**,** e243-e251.

HARAKA, F., GLASS, T. R., SIKALENGO, G., GAMELL, A., NTAMATUNGIRO, A., HATZ, C., TANNER, M., FURRER, H., BATTEGAY, M. & LETANG, E. 2015. A Bundle of Services Increased Ascertainment of Tuberculosis among HIV-Infected Individuals Enrolled in a HIV Cohort in Rural Sub-Saharan Africa. *PLOS ONE,* 10**,** e0123275.

HARRIES, A. D., ZACHARIAH, R., CORBETT, E. L., LAWN, S. D., SANTOS-FILHO, E. T., CHIMZIZI, R., HARRINGTON, M., MAHER, D., WILLIAMS, B. G. & DE COCK, K. M. 2010. The HIV-associated tuberculosis epidemic—when will we act? *The Lancet,* 375**,** 1906-1919.

HERMANS, S. & MANABE, Y. 2015. Population-level tuberculosis incidence in the ART era. *Lancet Infect Dis.*

HERMANS, S. M., KIRAGGA, A. N., SCHAEFER, P., KAMBUGU, A., HOEPELMAN, A. I. & MANABE, Y. C. 2010. Incident tuberculosis during antiretroviral therapy contributes to suboptimal immune reconstitution in a large urban HIV clinic in sub-Saharan Africa. *PLoS One,* 5**,** e10527.

HERNAN, M. A., BRUMBACK, B. & ROBINS, J. M. 2000. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology,* 11**,** 561-70.

HERNAN, M. A., BRUMBACK, B. A. & ROBINS, J. M. 2002. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med,* 21**,** 1689-709.

HUANG, P., TAN, J., MA, W., ZHENG, H., LU, Y., WANG, N., PENG, Z. & YU, R. 2015. Long-Term Effectiveness of Antiretroviral Therapy in China: An Observational Cohort Study from 2003–2014. *International Journal of Environmental Research and Public Health,* 12**,** 8762-8772.

JOHNSON, L. F., DORRINGTON, R. E. & MOOLLA, H. 2017. *Progress towards the 2020 targets for HIV diagnosis and antiretroviral treatment in South Africa*.

JONES, J. L., HANSON, D. L., DWORKIN, M. S. & DECOCK, K. M. 2000. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent Spectrum of HIV Disease Group. *Int J Tuberc Lung Dis,* 4**,** 1026-31.

KAPLAN, R., CALDWELL, J., BEKKER, L., JENNINGS, K., LOMBARD, C., ENARSON, D., WOOD, R. & BEYERS, N. 2014. Integration of TB and ART services fails to improve TB treatment outcomes: comparison of ART/TB primary healthcare services in Cape Town, South Africa. *South African Medical Journal,* 104**,** 204-208.

KASSA, A., TEKA, A., SHEWAAMARE, A. & JERENE, D. 2012. Incidence of tuberculosis and early mortality in a large cohort of HIV infected patients receiving antiretroviral therapy in a tertiary hospital in Addis Ababa, Ethiopia. *Trans R Soc Trop Med Hyg,* 106**,** 363-70.

KUFA, T., CHIHOTA, V., MNGOMEZULU, V., CHARALAMBOUS, S., VERVER, S., CHURCHYARD, G. & BORGDORFF, M. 2016. The incidence of tuberculosis among hiv-positive individuals with high CD4 counts: implications for policy. *BMC Infect Dis,* 16**,** 266.

KWAN, C. K. & ERNST, J. D. 2011. HIV and Tuberculosis: a Deadly Human Syndemic. *Clinical Microbiology Reviews,* 24**,** 351-376.

KYU, H. H., MADDISON, E. R., HENRY, N. J., MUMFORD, J. E., BARBER, R., SHIELDS, C., BROWN, J. C., NGUYEN, G., CARTER, A., WOLOCK, T. M., WANG, H., LIU, P. Y., REITSMA, M., ROSS, J. M., ABAJOBIR, A. A., ABATE, K. H., ABBAS, K., ABERA, M., ABERA, S. F., ABERA HARERI, H., AHMED, M., ALENE, K. A., ALVIS-GUZMAN, N., AMO-ADJEI, J., ANDREWS, J., ANSARI, H., ANTONIO, C. A., ANWARI, P., ASAYESH, H., ATEY, T. M., ATRE, S., BARAC, A., BEARDSLEY, J., BEDI, N., BENSENOR, I., BEYENE, A. S., BUTT, Z. A., CARDONA, P.-J., CHRISTOPHER, D., DANDONA, L., DANDONA, R., DERIBE, K., DERIBEW, A., EHRENKRANZ, R., EL SAYED ZAKI, M., ENDRIES, A., FEYISSA, T. R., FISCHER, F., GAI, R., GARCIA-BASTEIRO, A. L., GEBREHIWOT, T. T., GESESEW, H., GETAHUN, B., GONA, P., GOODRIDGE, A., GUGNANI, H., HAGHPARAST-BIDGOLI, H., HAILU, G. B., HASSEN, H. Y., HILAWE, E., HORITA, N., JACOBSEN, K. H., JONAS, J. B., KASAEIAN, A., KEDIR, M. S., KEMMER, L., KHADER, Y., KHAN, E., KHANG, Y.-H., KHOJA, A. T., KIM, Y. J., KOUL, P., KOYANAGI, A., KROHN, K. J., KUMAR, G. A., KUTZ, M., LODHA, R., MAGDY, EL RAZEK, H., MAJDZADEH, R., MANYAZEWAL, T., MEMISH, Z., MENDOZA, W., MEZGEBE, H. B., MOHAMMED, S., OGBO, F. A., OH, I.-H., OREN, E., OSGOOD-ZIMMERMAN, A., PEREIRA, D., PLASS, D., POURMALEK, F., QORBANI, M., RAFAY, A., RAHMAN, M., RAI, R. K., RAO, P. C., RAY, S. E., REINER, R., REINIG, N., et al. 2018. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. *The Lancet Infectious Diseases,* 18**,** 261-284.

LANNOY, L. H., CORTEZ-ESCALANTE, J. J., EVANGELISTA MDO, S. & ROMERO, G. A. 2008. Tuberculosis incidence and risk factors among patients living with HIV/AIDS in public health service institutions in Brasilia, Federal District. *Rev Soc Bras Med Trop,* 41**,** 549-55.

LAWN, S. D., BADRI, M. & WOOD, R. 2005. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS,* 19**,** 2109-16.

LAWN, S. D., MYER, L., EDWARDS, D., BEKKER, L. G. & WOOD, R. 2009. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS,* 23**,** 1717-25.

LAWN, S. D., WOOD, R., DE COCK, K. M., KRANZER, K., LEWIS, J. J. & CHURCHYARD, G. J. 2010. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis,* 10**,** 489-98.

LIU, E., MAKUBI, A., DRAIN, P., SPIEGELMAN, D., SANDO, D., LI, N., CHALAMILLA, G., SUDFELD, C. R., HERTZMARK, E. & FAWZI, W. W. 2015. Tuberculosis incidence rate and risk factors among HIV-infected adults with access to antiretroviral therapy. *AIDS (London, England),* 29**,** 1391-1399.

MANN, C. J. 2003. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg Med J,* 20**,** 54-60.

MASSYN, N., PEER, N., ENGLISH, R., PADARATH, A., BARRON, P. & DAY, C. 2016. District Health Barometer 2015/16. Durban: Health Systems Trust.

MIRANDA, A., MORGAN, M., JAMAL, L., LASERSON, K., BARREIRA, D., SILVA, G., SANTOS, J., WELLS, C., PAINE, P. & GARRETT, D. 2007. Impact of antiretroviral therapy on the incidence of tuberculosis: the Brazilian experience, 1995-2001. *PLoS One,* 2**,** e826.

MOORE, D., LIECHTY, C., EKWARU, P., WERE, W., MWIMA, G., SOLBERG, P., RUTHERFORD, G. & MERMIN, J. 2007. Prevalence, incidence and mortality associated with tuberculosis in HIV-infected patients initiating antiretroviral therapy in rural Uganda. *AIDS,* 21**,** 713-9.

MOR, Z., LIDJI, M., CEDAR, N., GROTTO, I. & CHEMTOB, D. 2013. Tuberculosis Incidence in HIV/AIDS Patients in Israel, 1983–2010. *PLOS ONE,* 8**,** e79691.

MORENO, S., JARRIN, I., IRIBARREN, J. A., PEREZ-ELIAS, M. J., VICIANA, P., PARRA-RUIZ, J., GOMEZ-SIRVENT, J. L., LOPEZ-ALDEGUER, J., GUTIERREZ, F., BLANCO, J. R., VIDAL, F., LEAL, M., RODRIGUEZ ARENAS, M. A. & DEL AMO, J. 2008. Incidence and risk factors for tuberculosis in HIV-positive subjects by HAART status. *Int J Tuberc Lung Dis,* 12**,** 1393-400.

MUGA, R., FERREROS, I., LANGOHR, K., DE OLALLA, P. G., DEL ROMERO, J., QUINTANA, M., ALASTRUE, I., BELDA, J., TOR, J., PEREZ-HOYOS, S. & DEL AMO, J. 2007. Changes in the incidence of tuberculosis in a cohort of HIV-seroconverters before and after the introduction of HAART. *Aids,* 21**,** 2521-7.

MUSA, B., MUSA, B., MUHAMMED, H., IBRAHIM, N. & MUSA, A. 2015. Incidence of tuberculosis and immunological profile of TB/HIV co-infected patients in Nigeria. *Annals of Thoracic Medicine,* 10**,** 185-192.

NANOO, A., IZU, A., ISMAIL, N. A., IHEKWEAZU, C., ABUBAKAR, I., MAMETJA, D. & MADHI, S. A. 2015. Nationwide and regional incidence of microbiologically confirmed pulmonary tuberculosis in South Africa, 2004–12: a time series analysis. *The Lancet Infectious Diseases,* 15**,** 1066-1076.

NATIONAL IINSTITUTE FOR COMMUNICABLE DISEASES 2017. Microbiologically confirmed tuberculosis 2004 -15 South Africa. National Iinstitute for Communicable Diseases, Division of the National Health Laboratory Service.

NATTRASS, N. 2006. Antiretroviral treatment and the problem of political will in South Africa. *Southern African Journal of HIV Medicine,* 7, 29-31.

OSLER, M., HILDERBRAND, K., GOEMAERE, E., FORD, N., SMITH, M., MEINTJES, G., KRUGER, J., GOVENDER, N. P. & BOULLE, A. 2018. The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa. *Clinical Infectious Diseases,* 66, S118-S125.

PADMAPRIYADARSINI, C., NARENDRAN, G. & SWAMINATHAN, S. 2011. Diagnosis & treatment of tuberculosis in HIV co-infected patients. *The Indian journal of medical research,* 134**,** 850-865.

PARSONS, L. M., SOMOSKÖVI, A., GUTIERREZ, C., LEE, E., PARAMASIVAN, C. N., ABIMIKU, A. L., SPECTOR, S., ROSCIGNO, G. & NKENGASONG, J. 2011. Laboratory diagnosis of tuberculosis in resource-poor countries: challenges and opportunities. *Clinical microbiology reviews,* 24**,** 314-350.

PATHMANATHAN, I., DOKUBO, E. K., SHIRAISHI, R. W., AGOLORY, S. G., AULD, A. F., ONOTU, D., ODAFE, S., DALHATU, I., ABIRI, O. & DEBEM, H. C. 2017. Incidence and predictors of tuberculosis among HIV-infected adults after initiation of antiretroviral therapy in Nigeria, 2004-2012. *PloS one,* 12**,** e0173309.

PETTIT, A. C., JENKINS, C. A., STINNETTE, S. E., REBEIRO, P. F., BLACKWELL, R. B., RAFFANTI, S. P., SHEPHERD, B. E. & STERLING, T. R. 2011. Tuberculosis Risk Before and After Highly Active Antiretroviral Therapy Initiation: Does HAART Increase the Short-term TB Risk in a Low Incidence TB Setting? *Journal of acquired immune deficiency syndromes (1999),* 57**,** 305-310.

PLAZY, M., DABIS, F., NAIDU, K., ORNE-GLEIMANN, J., BARNIGHAUSEN, T. & DRAY-SPIRA, R. 2015. Change of treatment guidelines and evolution of ART initiation in rural South Africa: data of a large HIV care and treatment programme. *BMC Infectious Diseases,* 15**,** 452.

RAJASEKARAN, S., RAJA, K., JEYASEELAN, L., VIJILAT, S., PRIYA, K., MOHAN, K., PARVEZ, A., MAHILMARAN, A. & CHANDRASEKAR, C. 2009. Post-HAART tuberculosis in adults and adolescents with HIV in India: incidence, clinical and immunological profile. *Indian J Tuberc,* 56**,** 69-76.

RANGAKA, M. X., WILKINSON, R. J., BOULLE, A., GLYNN, J. R., FIELDING, K., VAN CUTSEM, G., WILKINSON, K. A., GOLIATH, R., MATHEE, S., GOEMAERE, E. & MAARTENS, G. 2014. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. The Lancet.

RAVIGLIONE, M. & SULIS, G. 2016. Tuberculosis 2015: Burden, Challenges and Strategy for Control and Elimination. *Infectious Disease Reports,* 8**,** 6570.

REBOUCAS, M. C., SILVA, M. O. D., HAGUIHARA, T., BRITES, C. & NETTO, E. M. 2017. Tuberculosis incidence among people living with HIV/AIDS with virological failure of antiretroviral therapy in Salvador, Bahia, Brazil. *Braz J Infect Dis,* 21**,** 562-566.

ROBINS, J. M., HERNAN, M. A. & BRUMBACK, B. 2000. Marginal structural models and causal inference in epidemiology. *Epidemiology,* 11**,** 550-60.

SANAC 2017. South African national strategic plan on HIV, TB and STIs 2017-2022. Pretoria: South African National AIDS Council, SANAC.

SANTORO-LOPES, G., FELIX DE PINHO, A. M., HARRISON, L. H. & SCHECHTER, M. 2002. Reduced Risk of Tuberculosis among Brazilian Patients with Advanced Human Immunodeficiency Virus Infection Treated with Highly Active Antiretroviral Therapy. *Clinical Infectious Diseases,* 34**,** 543-546.

SHARMA, S. K. & SONEJA, M. 2011. HIV & immune reconstitution inflammatory syndrome (IRIS). *The Indian journal of medical research,* 134**,** 866-877.

SHISANA, O., REHLE., T., SIMBAYI, L. C., ZUMA, K., JOOSTE, S., ZUNGU, N., LABADARIOS, D. & ONOYA, D. 2014. South African National HIV Prevalence, Incidence and Behaviour Survey 2012. Cape Town: Human Sciences Research Council.

STATACORP 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

STATISTICS SOUTH AFRICA 2017. Mid-year population estimates 2017. Pretoria: Statistics South Africa.

STATISTICS SOUTH AFRICA 2018. Mid-year population estimates 2018. Pretoria: Statistics South Africa.

SUTHAR, A. B., LAWN, S. D., DEL AMO, J., GETAHUN, H., DYE, C., SCULIER, D., STERLING, T. R., CHAISSON, R. E., WILLIAMS, B. G., HARRIES, A. D. & GRANICH, R. M. 2012a. Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS Med,* 9**,** e1001270.

SUTHAR, A. B., LAWN, S. D., DEL AMO, J., GETAHUN, H., DYE, C., SCULIER, D., STERLING, T. R., CHAISSON, R. E., WILLIAMS, B. G., HARRIES, A. D. & GRANICH, R. M. 2012b. Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS Medicine,* 9**,** e1001270.

UNAIDS 2014. 90-90-90 An ambitious treatment target to help end the AIDS epidemic. Joint United Nations Programme on HIV/AIDS (UNAIDS).

UNAIDS 2016. Global AIDS update. UNAIDS.

UNAIDS 2017. Ending AIDS, Progress towards the 90-90-90 targets: Global AIDS update 2017. Joint United Nations Programme on HIV/AIDS (UNAIDS).

UNAIDS 2018. UNAIDS data 2018. Joint United Nations Programme on HIV/AIDS (UNAIDS).

VAN RIE, A., WESTREICH, D. & SANNE, I. 2011. Tuberculosis in patients receiving antiretroviral treatment: incidence, risk factors and prevention strategies. *Journal of Acquired Immune Deficiency Syndromes (1999),* 56**,** 349-355.

WALENSKY, R. P., WOLF, L. L., WOOD, R., FOFANA, M. O., FREEDBERG, K. A., MARTINSON, N. A., PALTIEL, A. D., ANGLARET, X., WEINSTEIN, M. C. & LOSINA, E. 2009. When to start antiretroviral therapy in resource-limited settings. *Ann Intern Med,* 151**,** 157-66.

WANG, H., WOLOCK, T. M., CARTER, A., NGUYEN, G., KYU, H. H., GAKIDOU, E., HAY, S. I., MILLS, E. J., TRICKEY, A., MSEMBURI, W., COATES, M. M., MOONEY, M. D., FRASER, M. S., SLIGAR, A., SALOMON, J., LARSON, H. J., FRIEDMAN, J., ABAJOBIR, A. A., ABATE, K. H., ABBAS, K. M., RAZEK, M. M. A. E., ABD-ALLAH, F., ABDULLE, A. M., ABERA, S. F., ABUBAKAR, I., ABU-RADDAD, L. J., ABU-RMEILEH, N. M. E., ABYU, G. Y., ADEBIYI, A. O.,

ADEDEJI, I. A., ADELEKAN, A. L., ADOFO, K., ADOU, A. K., AJALA, O. N., AKINYEMIJU, T. F., AKSEER, N., LAMI, F. H. A., AL-ALY, Z., ALAM, K., ALAM, N. K. M., ALASFOOR, D., ALDHAHRI, S. F. S., ALDRIDGE, R. W., ALEGRETTI, M. A., ALEMAN, A. V., ALEMU, Z. A., ALFONSO-CRISTANCHO, R., ALI, R., ALKERWI, A. A., ALLA, F., MOHAMMAD, R., AL-RADDADI, S., ALSHARIF, U., ALVAREZ, E., ALVIS-GUZMAN, N., AMARE, A. T., AMBERBIR, A., AMEGAH, A. K., AMMAR, W., AMROCK, S. M., ANTONIO, C. A. T., ANWARI, P., ÄRNLÖV, J., ARTAMAN, A., ASAYESH, H., ASGHAR, R. J., ASSADI, R., ATIQUE, S., ATKINS, L. S., AVOKPAHO, E. F. G. A., AWASTHI, A., QUINTANILLA, B. P. A., BACHA, U., BADAWI, A., BARAC, A., BÄRNIGHAUSEN, T., BASU, A., BAYOU, T. A., BAYOU, Y. T., BAZARGAN-HEJAZI, S., BEARDSLEY, J., BEDI, N., BENNETT, D. A., BENSENOR, I. M., BETSU, B. D., BEYENE, A. S., BHATIA, E., BHUTTA, Z. A., BIADGILIGN, S., BIKBOV, B., BIRLIK, S. M., BISANZIO, D., BRAININ, M., BRAZINOVA, A., BREITBORDE, N. J. K., BROWN, A., BURCH, M., BUTT, Z. A., CAMPUZANO, J. C., CÁRDENAS, R., et al. 2016. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the Global Burden of Disease Study 2015. *The Lancet HIV,* 3**,** e361-e387.

WESTERN CAPE DEPARTMENT OF HEALTH 2013. Strategic approach to patient-level health data harmonisation and integration. Department of Health, Western Cape.

WESTERN CAPE PROVINCIAL AIDS COUNCIL 2016. ANNUAL PROGRESS REPORT 2014/15, PROVINCIAL STRATEGIC PLAN 2012-2016. Western Cape Provincial AIDS Council,South Africa National AIDS Council.

WILLIAMS, B. G. 2013. Could ART increase the population level incidence of TB? *arXiv preprint arXiv:1302.0503*.

WILLIAMS, B. G. & DYE, C. 2003. Antiretroviral Drugs for Tuberculosis Control in the Era of HIV/AIDS. *Science,* 301**,** 1535-1537.

WORLD HEALTH ORGANISATION 2014. Global Tuberculosis Report 2014. Geneva: World Health Organisation.

WORLD HEALTH ORGANISATION 2015. Global Tuberculosis Report 2015. 20th Edition ed. Geneva: World Health Organisation.

WORLD HEALTH ORGANIZATION 2002. Scaling up antiretroviral therapy in resource-limited settings : guidelines for a public health approach. Geneva, Switzerland: World Health Organization.

WORLD HEALTH ORGANIZATION 2006. Antiretroviral therapy for HIV infection in adults and adolescents : recommendations for a public health approach. 2006 revison. Geneva, Switzerland: World Health Organization

WORLD HEALTH ORGANIZATION 2010. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. Geneva, Switzerland: World Health Organization

WORLD HEALTH ORGANIZATION 2013. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. Geneva, Switzerland World Health Organization.

WORLD HEALTH ORGANIZATION 2017. Global tuberculosis report 2017. World Health Organization.

WORLD MEDICAL ASSOCIATION 2013. World medical association declaration of helsinki: Ethical principles for medical research involving human subjects. *JAMA,* 310**,** 2191-2194.

WORODRIA, W., MASSINGA-LOEMBE, M., MAYANJA-KIZZA, H., NAMAGANDA, J., KAMBUGU, A., MANABE, Y. C., KESTENS, L. & COLEBUNDERS, R. 2011. Antiretroviral treatment-associated tuberculosis in a prospective cohort of HIV-infected patients starting ART. *Clin Dev Immunol,* 2011**,** 758350.

YIRDAW, K. D., JERENE, D., GASHU, Z., EDGINTON, M. E., KUMAR, A. M. V., LETAMO, Y., FELEKE, B., TEKLU, A. M., ZEWDU, S., WEISS, B. & RUFF, A. 2014. Beneficial Effect of Isoniazid Preventive Therapy and Antiretroviral Therapy on the Incidence of Tuberculosis in People Living with HIV in Ethiopia. *PLoS ONE,* 9**,** e104557.

ZENNER, D., ABUBAKAR, I., CONTI, S., GUPTA, R. K., YIN, Z., KALL, M., KRUIJSHAAR, M., RICE, B., THOMAS, H. L., POZNIAK, A., LIPMAN, M. & DELPECH, V. 2015. Impact of TB on the survival of people living with HIV infection in England, Wales and Northern Ireland. *Thorax,* 70**,** 566-73.

Appendix A: Ethics approval forms

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

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

05 December 2016

HREC REF: 759/2016

Prof A Boulle
CIDER
School of Public Health & Family Medicine
5th Floor Falmouth Building-FHS

Dear Prof Boulle

PROJECT TITLE: THE IMPACT OF ANTIRETROVIRAL THERAPY ON TUBERCULOSIS INCIDENCE (MMeD- candidate-N Zinyakatira)

Thank you for your response letter dated 24 November 2016, addressing the issues raised by the Human Research Ethics Committee (HREC).

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

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

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

We acknowledge that the student, N Zinyakatira will also be involved in this study.

Please quote the HREC REF in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

STRATEGY & HEALTH SUPPORT

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REFERENCE: WC 2017RP28 805
ENQUIRIES: Ms Charlene Roderick

University of Cape Town

Anzio Road

Observatory

Cape Town

7925

For attention: Mr Nesbert Zinyakatira

Re: The Impact of Antiretroviral Therapy on Tuberculosis Incidence.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact following people to assist you with any further enquiries in accessing the following information:

Data Centre	Dr Nicki Tiffin	483 0886

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. By being granted access to provincial health facilities, you are expressing consent to provide the department with an electronic copy of the final feedback (annexure 9) within

six months of completion of your project. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the estimated completion date which was submitted, researchers are expected to complete and submit a progress report (Annexure 8) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

MS A VAN DEN BERG

ACTING DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 30 // //23

Appendix B: Journal submission guidelines Lancet Infectious Diseases

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection

Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized

		(*e*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based