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High Incidence of tuberculosis in the first year of antiretroviral therapy in the Botswana National ART programme between 2011 and 2015

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Author Contributions

Study Conception and Design: SG, SM, NZ, LM. Analyzed data: LM, SM, SS, KM. Data management: JN, BK, LB, TC. Data cleaning: QW, LM, TI, TM. Original draft of manuscript: LM. Editing the manuscript: SS, SM, SG, NZ, IK. Sponsor: SG, RM, JM, ME. All authors read the manuscript and approved the text for publication.

Data availability statement

The data sets are the property of the Ministry of Health and Wellness of Botswana; therefore, we cannot share the database publicly in any shape or form. Ministry of Health of Botswana and Wellness requires that any person or institute that wishes to access the data should send their research proposal to the Ministry to be evaluated. Any person who would like to access the data should correspond with the Department of Health Policy, Development, Monitoring and Evaluation (HPDME) at the Ministry of Health of Botswana.

Conflict of Interest

The authors declare no conflict of interest.

Abstract

Objective: Tuberculosis (TB) remains one of the leading causes of mortality and morbidity among people living with HIV. We sought to estimate the incidence of TB in a national database of HIV-infected patients receiving antiretroviral therapy (ART) in Botswana.

Design: A retrospective analysis of HIV-infected adult patients (≥18years) who initiated ART between 2011 and 2015 in the Botswana ART program.

Methods: Multivariable analysis using Cox regression included sex, age, viral load and CD4 counts.

Results: Of 45,729 patients, with a median follow-up of 1·7 years Q1, Q3: 0·5,3·1), 1,791 patients developed TB over a median of 1·5 years (Q1, Q3: 0·3,3·1) of follow-up (IR 1·9 per 100 py; 95% CI 1·8–2·0). At baseline, the median CD4+ T-cell count was 272 cells/μl (Q1:Q3 146, 403). The risk of TB was greatest within the first year of ART (IR 2·9 per 100 py; 95% CI 2·7–3·1) and in patients with CD4 counts below 50 cells/μl (IR 8·3/100 py; 95% CI 7·1–9·7). Patients with viral loads above 10,000 copies/ml at 3 months post ART initiation had two-times higher risk of TB, HR 2.5 (95% CI 1·8–2·3).

Conclusions: We report a high incidence of TB within the first year of ART and in patients with advanced immunodeficiency. Improved screening strategies and virologic monitoring during this early period on ART, coupled with TB preventative treatment, will reduce the burden of TB.

Keywords

Tuberculosis; incidence; IPT; TPT; HIV-1 viral load

Introduction

Tuberculosis (TB) and HIV are leading causes of mortality with tuberculosis currently ranked as the top cause of death worldwide by an infectious disease. [1] In 2017, TB caused 1·3 million deaths among HIV-uninfected individuals, down from 1·4 million in 2016. Whilst a 44% decline in mortality was reported in HIV-infected persons between 2000 and 2017, a third of the deaths in HIV-infected patients are due to TB. [1] Earlier diagnosis and initiation of TB treatment, antiretroviral therapy (ART) and isoniazid preventive therapy (IPT) remain important keys for reducing the burden of HIV-associated TB.

The incidence of tuberculosis in HIV-infected patients is a function of the CD4+ T-cell counts, with most ART programmes in sub-Saharan Africa showing that patients with low CD4+ T-cell counts have the greatest risk of TB disease and mortality. [2, 3] However, several reports in patients with CD4+ T-cell counts above 350 cells/μl have shown that the rate of TB is higher in patients on ART compared to HIV uninfected patients, [4, 5] suggesting that a qualitative defect in the immune response to TB likely drives the risk in this population.

We previously reported a high incidence rate of TB within the first 6 months of ART in a study cohort in Botswana. [6] As is the case in most ART programs in Africa, most cases of TB occur within the first few months of ART initiation reflecting either subclinical [7, 8] or undiagnosed TB. [9, 10] These first few months on ART represent a period of high mortality

risk. [11-13] An analysis of the *Masa* program, the local term for the Botswana national ART program, between 2002 and 2010 showed that mortality was highest within the first 3 months of ART initiation (12·8/100py) and decreased with time on ART. [13, 14] Although the authors did not report on the causes of death, undiagnosed TB is a well-recognized contributor to early mortality. [12, 15]

Botswana, currently listed as a high burden HIV-TB country, has an estimated TB incidence of 353/100 000 population and 60% TB/HIV co-infection rate. [16] Botswana was one of the first countries to provide free ART to its citizens and, in 2016, became the first country in sub-Saharan Africa to provide Dolutegravir (DTG)-based ART as first line therapy. The introduction of Dolutegravir also coincided with a change in guidelines from CD4+ T-cell count based eligibility to “treat all”. By the end of December 2017, just over 300000 patients were registered in the *Masa* program, representing ART coverage of about 84%.[17]

Whilst ART is associated with improved immune function, it may serve as a therapeutic challenge to unmask subclinical disease, thereby triggering presentation of active disease. [9] We therefore sought to determine the incidence and factors associated with TB in the *Masa* program and if there was a change in the incident TB rate with changes to ART eligibility criteria.

Methods

Study population

The *Masa* program has previously been described. [13] The Ministry of Health and Wellness informatics team provided the investigators with a de-identified and delinked dataset from 71,246 patients who initiated ART between 1st of January 2011 to the 31st of December 2016 at 46 ART initiating sites in Botswana. During the period analyzed, first line ART in Botswana consisted of Tenofovir, Emtricitabine and either Efavirenz or Nevirapine. From June 2016, the first line regimen consisted of Dolutegravir, Tenofovir and Emtricitabine.

Inclusion criteria for the analysis

We determined the date of enrolment into the ART programme as the earliest of either the ART initiation date or registration date, when an electronic record was created. We defined the last pre-enrolment CD4 result as baseline. If the ART initiation date was missing, we used the first recorded aspartate transaminase (AST) result, as this is a pre-initiation test. Where an AST result was missing, we used the first recorded viral load and subtracted 90 days from this date to impute the ART initiation date since a viral load is performed 3 months post-ART initiation in accordance with the national ARV guidelines.

In compliance with WHO guidelines, [18] HIV-infected patients are screened for TB prior to ART initiation and at follow-up visits. Any patients with a TB treatment date that was 6 months or less prior to ART initiation were classified as prevalent TB and thus considered to have active TB at the time they registered for ART. We defined all cases occurring after ART initiation incident TB and determined time to TB diagnosis to be time from ART initiation to date of TB treatment. All TB diagnoses in IPMS were confirmed against the TB dataset (OpenMRS) for all TB cases diagnosed at all health facilities in Botswana.

We excluded from analysis records from patients with missing ART dates, aged less than 18 years and those that did not have a documented follow-up visit following ART initiation.

TB case definition

TB was diagnosed following the national TB guidelines. The presence of any one of fever, weight loss, cough or night sweats prompted further investigation using chest x-ray or smear. Culture was only done for patients with a treatment history or those at risk of drug-resistant TB, such as contacts of patients with multi-drug resistant TB (MDR-TB).

Statistical Analysis

The primary outcome for this analysis was the development of incident TB within the 5 years of follow-up. We used chi-square, Wilcoxon rank sum and Kruskall-Wallis tests to determine the differences in baseline characteristics. We used Kaplan-Meier (KM) survival analysis to determine time to incident TB and log rank tests to compare survival distributions. We used Cox regression models to determine risk factors for incident TB and adjusted for age, sex and baseline CD4 count (selected *a priori*), in the multivariate model. We used a person year approach to calculate incidence and defined the follow-up time as time from enrolment to date of TB treatment or last clinic visit. All analysis was conducted in STATA v15.0 (StataCorp LP, College Station, Texas).

Ethical Considerations

This work received ethical approval from The University of Botswana IRB and the Human Research Development Committee (IRB of the Botswana Ministry of Health and Wellness). Informed consent was waived, as this was program data stripped of any personal identifying information.

Results

We received a dataset containing records from 71,246 patients. We excluded records from 4,864 aged below 18 years at the time of initiation (Figure 1). Of the 66,382 patients, 41,447 (62%) did not have a recorded ART initiation date. We therefore used the proxy described earlier, AST or viral load date, to impute the missing dates. There were 8,098 (12%) records that had a missing ART date following this imputation and we dropped these from further analysis. The first and last recorded ART initiation occurred on the 1st of January 2011 and 31st of December 2016 respectively; whilst the last recorded clinic visit occurred on the 31st of October 2017. The overall follow-up time, from ART initiation to recorded last clinic visit, was a median of 1·7 years (Q1:Q3 0·5, 3·1 years) and 1·5 years (Q1:Q3 0·3, 3·1 years) for the incident TB cases.

Sixty-five percent (n=38,017) were female and younger than men, median age 35 years (Q1:Q3 30, 43) compared to 40 years (Q1:Q3 34, 48 p<0.001). Most of the patients were not married (84%), had at least a secondary-level education (65%) and were employed (63%; Table 1). The baseline CD4+ T-cell count was recorded in 37% of the patients (n=21,737) with a median CD4+ T-cell count of 272 cells/μl (Q1:Q3 146, 403). At least 32% (n=6949) of the patients had a CD4 count greater than 350 cells/μl. The CD4 count increased with

year of ART initiation from a median of 212 (Q1:Q3 114, 321) in 2011 to 357 cells/μl (Q1:Q3 188, 531, p<0.001) in 2016 (results not shown). The change in baseline CD4 counts mirrored the change in guidelines in 2013 (CD4 count increase to 350 cells/μl) and 2016 (no CD4 cut-off). Among 50,927 (87%) patients with recorded viral loads, 91% (46,322) of patients were virally suppressed at three months post ART initiation.

There were 1,202 (2%) patients with prevalent TB, with a median baseline CD4 count of 129 cells/μl (Q1:Q3 53, 272) and this was significantly lower than in non-TB patients [median CD4 count: 276 cells/μl (Q1:Q3 151, 407) p<0.001, Table 1]. Furthermore, the median CD4 count did not differ by period of ART initiation, 130 cells/μl (Q1:Q3 53, 287) prior to 2013 and 129 cells/μl (Q1:Q3 56, 237; p=0.63) in the period 2013–2016 (results not shown). Patients with prevalent TB had been on TB treatment for a median of 1·2 months (Q1:Q3 0·6, 2·5) at the time of ART initiation. Compared to those without a TB diagnosis, prevalent TB cases were more likely to be male, initiated ART after 2012 and had lower CD4+ T-cell counts and higher viral loads at baseline (Table 2). The percentage of prevalent cases declined from 2·4% (n=270) in 2011 to 1·5% (n=113, p<0.01) in 2016 (results not shown).

We excluded patients who were on TB treatment at ART initiation (n=1,202) and patients without any recorded visit post enrolment (n=6,452) from further analysis (Figure 1). For the Cox analysis, we censored observations on the 31st December 2016 and therefore excluded patients who initiated ART in 2016 from analysis (n=4,781), thus the remaining 45,729 patients contributed 95222 person years of follow-up. There were 1791 incident cases [incident rate (IR) of 1·9/100 py (95% CI 1·8–2·0)], of which 83% (n=1,486) were identified through merging the ART and the TB database. Just over half of the cases were confirmed through culture or smear (n=925) and 48% (n=866) were diagnosed clinically (745 of these had negative smear or culture results). The median time to incident TB was 202 days (Q1:Q3 32, 621) and was shortest in patients with CD4 counts less than 50 cells/μl and viral loads above 10,000 copies/ml (LR: p<0.001, Figure 2). In addition, the incidence rate was highest in patients with CD4 counts below 50 cells/μl [IR: 8·3/100 py (95% CI 7·1 – 9·7)], compared to an incidence rate of 1·4 (95% CI 1·0–1·9) in patients with CD4 counts above 500 cells/μl (Supplementary Figure 1).

The incidence rate decreased with time on ART from 2·9 per 100 py (95% CI 2·7–3·1) in the first year to 1·2/100 py (95% CI 1·0–1·5) in those who had been on ART for at least 3 years (Figure 3). There was an insignificant increase in the incidence of TB between 4 and 5 years [IR 1·5/100py (95% CI 1·2–2·0), Figure 3)]. In contrast, when we analyzed only the patients with recorded ART initiation dates (n=12,199), the incidence rate decreased from 3·0/100py (95% CI 2·7–3·4) in the first year to 0·7/100py (95% CI 0·4–1·3) [Supplementary Figure 2].

The risk of incident TB was highest for men (aHR 1·99; 95% CI: 1·71–2·33) and patients with viral loads above 10,000 copies/ml (aHR 2·47; 95%CI: 1·82–3·34) (Table 2). Due to the high level of missing CD4 data, we could not include this covariate in the multivariable model. However, in restricted analysis to patients with a recorded ART date, the risk of TB decreased progressively across increasing CD4 categories, compared to the reference category of CD4 < 50 cells/μl (Supplementary Table 1). In a subset of patients with baseline

CD4 count data available (n=13,714), sex (HR=1.93 (95% CI, 1.50–2.47); p<0.01), employment status (HR=0.73 (95% CI, 0.58–0.93); p=0.01), viral load greater than 1000copies/mL (HR=1.69 (95% CI, 1.02–2.81); p=0.04) remained significant predictors similar to the model excluding CD4 count data.

Discussion

Tuberculosis remains a leading cause of mortality and morbidity in HIV infected patients in low resource settings. Using a national, longitudinal dataset from the Botswana ART treatment cohort, we report a TB incidence rate of 1·9/100 py between 2011 and 2015. The incidence of TB was highest within the first year of initiation (IR: 2·9/100py) and dropped to 1·2/100 py in individuals who had been on ART for at least 3years. This shows a time-dependent reduction of TB incidence, suggesting that immune reconstitution may not be optimally restored within short periods on ART as has been previously reported. [19]

Interestingly, we observed a trend toward an increase in the incident rate in patients who had been on ART for 4–5 years and this was not apparent in the restricted analysis. While incident TB decreases with time on ART reflecting restoration of TB-specific immune function [20], it has previously been shown that incidence rates in HIV-infected patients remain higher than background rates in the HIV-uninfected. [21, 22] Furthermore, in a South African cohort, [21] Gupta and colleagues showed an increase in incidence rate at 5 years on ART (IR 4.45 vs. 2.89 at 48–60 months) among patients with new TB episodes. [21] One hypothesis is that patients accrue person-time at low CD4 counts, which drives continued risk of TB. [23] Consistent with this hypothesis, patients with advanced immunodeficiency in our cohort had the highest incidence rate (8.3/100py). However, it is also quite likely that ascertainment bias in our imputed analysis resulted in this apparent increase in TB incidence.

In agreement with previous reports, [4, 24, 25] half of the TB cases occurred within the first 6 months on ART, which could reflect either subclinical or undiagnosed TB. Whilst national guidelines state TB screening should occur at baseline, this likely did not always occur and may explain the cases occurring within 3 months of ART initiation. However, unmasking TB is known to contribute to TB incidence during the first three months of ART and is associated with low CD4 counts. [5, 23] Importantly, in an analysis of the HPTN PopART trial, Bock and colleagues showed that no incident TB cases occurred within the first 3 months of ART in patients with CD4 counts above 500 cells/μl. [5] Therefore with earlier initiation of ART we should observe reduced cases of unmasking TB. However, this will need to be coupled with continued screening for TB in those patients with low baseline CD4 counts..

Although we could not include CD4 count in our multivariable model due to missing data, the risk of TB increased in patients with CD4 counts below 100 cells/μl in the restricted analysis in concordance with previous reports. [21, 25, 26] Furthermore, the time to TB diagnosis was significantly reduced in patients with advanced immunodeficiency and the incidence rate increased 5-fold in patients with CD4 counts below 50 cells/μl compared to those with counts above 500 cells/μl. In like manner, the risk of TB increased in patients

with viral loads >10,000 copies/ml, consistent with a previous analysis of three ART cohorts in South Africa. [27] This is an important finding particularly given that in our cohort, 91% of patients had suppressed viral loads by 3 months post ART. This underscores the need for viral load monitoring not only for monitoring for treatment failure but as a tool to predict individuals likely to develop TB. [27]

Men are at significant risk of TB, and in 2017, 64% of the estimated 10 million new TB cases occurred in men, with a male: female ratio of 2:1. [1] A systematic review of 56 national surveys in both low and middle-income countries reported high burdens of disease in men and gender disparities in access of TB services, although the prevalence ratios were lower in settings with a high HIV prevalence. [28] This disproportionate increase of TB in men begins in adolescence and peaks in the 45–54 years age group [28] suggesting there may be other factors beyond access to care that drive this risk. In addition, men remain infectious for longer, [28] likely driving transmission in the communities and are therefore a key population for TB control strategies.

We believe that this first year on ART could be one where a combination of ART and isoniazid preventive therapy (IPT) would have the greatest impact in reducing both the incidence and TB-related mortality. Results from a modeling study based on Botswana's IPT program showed that for HIV-infected patients, the incidence and mortality benefits outweigh the perceived resistance risks. [29] Furthermore, the REMEMBER trial showed that provision of IPT to people with advanced HIV significantly reduced mortality compared to empiric TB treatment. [30]

Given that 25% of the patients in our cohort had CD4 counts below 150cells/μl and the incident rate of 1.9/100py was higher than that reported in a previous trial of IPT conducted in Botswana (1.26/100py), [31] TB prevention will be an extremely feasible strategy in our programme. A large trial conducted in South Africa in people established on or starting ART showed that provision of 12 months IPT reduced incident TB by 37%. [32] While only 28% of patients in this trial were starting ART when IPT was initiated, a second trial conducted in Ivory Coast (the TEMPRANO trial), showed that a combined early ART and IPT strategy reduced both incident TB and mortality by 44% and 35% respectively [33].

Limitations

The major strength of this study is the national representation arising from analysis of a large dataset using operational data from the Botswana National ARV program. We were also able to match and identify additional TB cases in the population based TB register from the National TB program. However, a major disadvantage of this analysis was the fact that 62% of patients were missing ART initiation data, reflecting the challenges with routine data capture. Although our inference method may have introduced misclassification error of time on ART, we were able to accurately estimate the date of initiation in a subset of patients that had ART dates recorded. Furthermore, restricted analysis in the patients with recorded ART initiation dates showed similar results; therefore we do not think this imputation limits the generalizability of our findings. We were unable to identify patients with latent TB infection in this analysis, neither could we obtain estimates of the patients with extrapulmonary TB as

this was not captured in the database nor is testing for latent TB routinely performed. Since it is estimated that 22% of patients accessing ART care have a positive tuberculin skin test [34], it is likely that these latent cases contribute to incident TB.

We did not have access to either the date or cause of death and could not calculate the mortality rate or determine if these were deaths due to TB. This likely underestimates the incidence estimates we reported given that a previous analysis of the Botswana ART programme showed that the mortality risk is highest within the first three months of ART[14], a period that is also marked by a heightened risk of TB. We also did not have outcome data for the non-TB patients and as a result, we could not perform a competing risk analysis. As this analysis was censored on the 31st of December 2016, only six months after the implementation of the HIV test and treat national programme in Botswana, we did not have sufficient data to look at the impact of early ART initiation on TB incidence.

Conclusion

We have reported in this analysis a high TB incidence within the first year of initiation of ART in Botswana and shown that the risk is associated with both low CD4 counts and high post-ART viral loads. Our results suggest the need for improved TB screening, particularly for those with low CD4 counts, IPT provision at ART initiation to reduce the TB burden in ART programs and routine virologic monitoring to identify those at risk of TB.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. WHO. Global TB report. https://www.who.int/tb/publications/global_report/en/ Acessed 26 September 2018.
2. Westreich D, Fox MP, Van Rie A, Maskew M. Prevalent tuberculosis and mortality among HAART initiators. AIDS 2012; 26(6):770–773. [PubMed: 22313956]

3. Worodria W, Massinga-Loembe M, Mazakpwe D, Luzinda K, Menten J, Van Leth F, et al. Incidence and predictors of mortality and the effect of tuberculosis immune reconstitution inflammatory syndrome in a cohort of TB/HIV patients commencing antiretroviral therapy. J Acquir Immune Defic Syndr 2011; 58(1):32–37. [PubMed: 21654499]
4. Kufa T, Chihota V, Mngomezulu V, Charalambous S, Verver S, Churchyard G, et al. The incidence of tuberculosis among HIV-positive individuals with high CD4 counts: implications for policy. BMC infectious diseases 2016; 16:266. [PubMed: 27286814]
5. Bock P, Jennings K, Vermaak R, Cox H, Meintjes G, Fatti G, et al. Incidence of Tuberculosis Among HIV-Positive Individuals Initiating Antiretroviral Treatment at Higher CD4 Counts in the HPTN 071 (PopART) Trial in South Africa. J Acquir Immune Defic Syndr 2018; 77(1):93–101. [PubMed: 29016524]
6. Mupfumi L, Moyo S, Molebatsi K, Thami PK, Anderson M, Mogashoa T, et al. Correction: Immunological non-response and low hemoglobin levels are predictors of incident tuberculosis among HIV-infected individuals on Truvada-based therapy in Botswana. PloS one 2018; 13(6):e0198711.
7. Worodria W, Massinga-Loembe M, Mayanja-Kizza H, Namaganda J, Kambugu A, Manabe YC, et al. Antiretroviral treatment-associated tuberculosis in a prospective cohort of HIV-infected patients starting ART. Clinical & developmental immunology 2011; 2011:758350.
8. Oni T, Burke R, Tsekela R, Bangani N, Seldon R, Gideon HP, et al. High prevalence of subclinical tuberculosis in HIV-1-infected persons without advanced immunodeficiency: implications for TB screening. Thorax 2011; 66(8):669–673. [PubMed: 21632522]
9. Lawn SD, Wilkinson RJ, Lipman MC, Wood R. Immune reconstitution and “unmasking” of tuberculosis during antiretroviral therapy. American journal of respiratory and critical care medicine 2008; 177(7):680–685. [PubMed: 18202347]
10. Wood R, Middelkoop K, Myer L, Grant AD, Whitelaw A, Lawn SD, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. American journal of respiratory and critical care medicine 2007; 175(1):87–93. [PubMed: 16973982]
11. Lawn SD, Myer L, Bekker LG, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. AIDS 2006; 20(12):1605–1612. [PubMed: 16868441]
12. Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. Prevalent and incident tuberculosis are independent risk factors for mortality among patients accessing antiretroviral therapy in South Africa. PloS one 2013; 8(2):e55824.
13. Farahani M, Vable A, Lebelonyane R, Seipone K, Anderson M, Avalos A, et al. Outcomes of the Botswana national HIV/AIDS treatment programme from 2002 to 2010: a longitudinal analysis. The Lancet Global health 2014; 2(1):e44–50. [PubMed: 25104635]
14. Farahani M, Price N, El-Halabi S, Mlaudzi N, Keapoletswe K, Lebelonyane R, et al. Trends and determinants of survival for over 200 000 patients on antiretroviral treatment in the Botswana National Program: 2002–2013. Aids 2016; 30(3):477–485. [PubMed: 26636931]
15. Lawn SD, Harries AD, Meintjes G, Getahun H, Havlir DV, Wood R. Reducing deaths from tuberculosis in antiretroviral treatment programmes in sub-Saharan Africa. AIDS 2012; 26(17):2121–2133. [PubMed: 22695302]
16. WHO. Botswana TB Country profile. http://stoptb.org/resources/cd/BWA_Dashboard.html. Accessed 01 June 2017.
17. UNAIDS. UNAIDS HIV Factsheet. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdfAccessed 16 November 2018.
18. WHO. WHO Policy on Collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders. In; 2012.
19. Day CL, Moshi ND, Abrahams DA, van Rooyen M, O’Rie T, de Kock M, et al. Patients with tuberculosis disease have Mycobacterium tuberculosis-specific CD8 T cells with a pro-apoptotic phenotype and impaired proliferative capacity, which is not restored following treatment. PloS one 2014; 9(4):e94949.

20. Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. AIDS 2005; 19(18):2109–2116. [PubMed: 16284460]
21. Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. 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 2012; 7(3):e34156.
22. Gupta RK, Rice B, Brown AE, Thomas HL, Zenner D, Anderson L, et al. 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 2015; 2(6):e243–e251. [PubMed: 26423197]
23. Lawn SD, Myer L, Edwards D, Bekker LG, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. AIDS 2009; 23(13):1717–1725. [PubMed: 19461502]
24. Brennan AT, Bonawitz R, Schnippel K, Berhanu R, Maskew M, Long L, et al. Incident tuberculosis in HIV-positive children, adolescents and adults on antiretroviral therapy in South Africa. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2016; 20(8):1040–1045.
25. Chang CA, Meloni ST, Eisen G, Chaplin B, Akande P, Okonkwo P, et al. Tuberculosis Incidence and Risk Factors Among Human Immunodeficiency Virus (HIV)-Infected Adults Receiving Antiretroviral Therapy in a Large HIV Program in Nigeria. Open Forum Infect Dis 2015; 2(4):ofv154.
26. Pathmanathan I, Dokubo EK, Shiraishi RW, Agolory SG, Auld AF, Onotu D, et al. Incidence and predictors of tuberculosis among HIV-infected adults after initiation of antiretroviral therapy in Nigeria, 2004–2012. PloS one 2017; 12(3):e0173309.
27. Fenner L, Atkinson A, Boulle A, Fox MP, Prozesky H, Zürcher K, et al. HIV viral load as an independent risk factor for tuberculosis in South Africa: collaborative analysis of cohort studies. Journal of the International AIDS Society 2017; 20(1):21327–21327. [PubMed: 28691438]
28. Horton KC, MacPherson P, Houben RM, White RG, Corbett EL. Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. PLoS medicine 2016; 13(9):e1002119.
29. Kunkel A, Crawford FW, Shepherd J, Cohen T. Benefits of continuous isoniazid preventive therapy may outweigh resistance risks in a declining tuberculosis/HIV coepidemic. AIDS (London, England) 2016; 30(17):2715–2723.
30. Hosseinipour MC, Bisson GP, Miyahara S, Sun X, Moses A, Riviere C, et al. Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial. Lancet 2016; 387(10024):1198–1209. [PubMed: 27025337]
31. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet 2011; 377(9777):1588–1598. [PubMed: 21492926]
32. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet 2014; 384(9944):682–690. [PubMed: 24835842]
33. Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, Ouassa T, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine 2015; 373(9):808–822. [PubMed: 26193126]
34. Kerkhoff AD, Kranzer K, Samandari T, Nakiyingi-Miiro J, Whalen CC, Harries AD, et al. Systematic review of TST responses in people living with HIV in under-resourced settings: implications for isoniazid preventive therapy. PloS one 2012; 7(11):e49928.

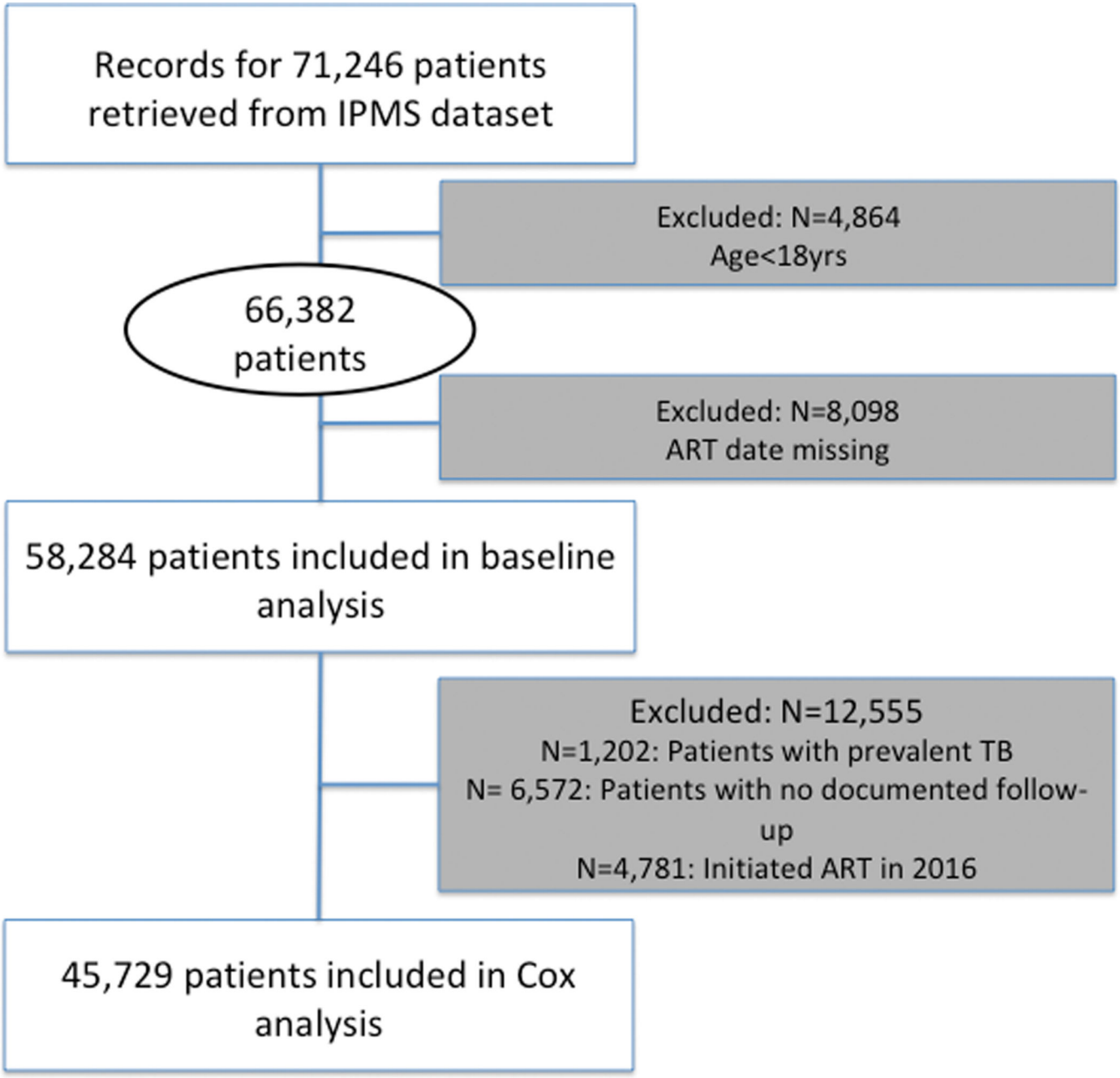

Figure1.
Study Flow diagram.

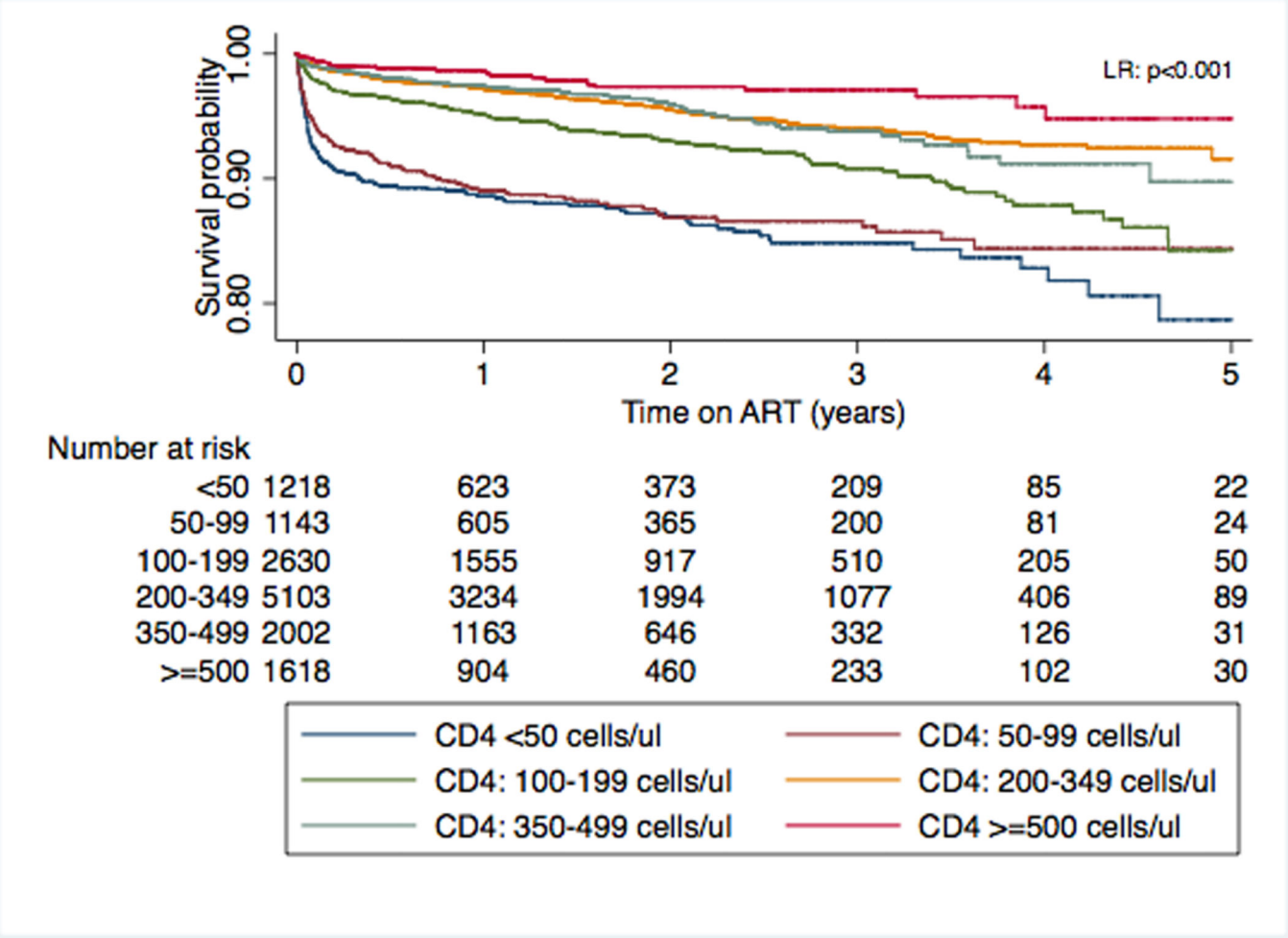

Figure2a.
Time to incidentTB by CD4 category.

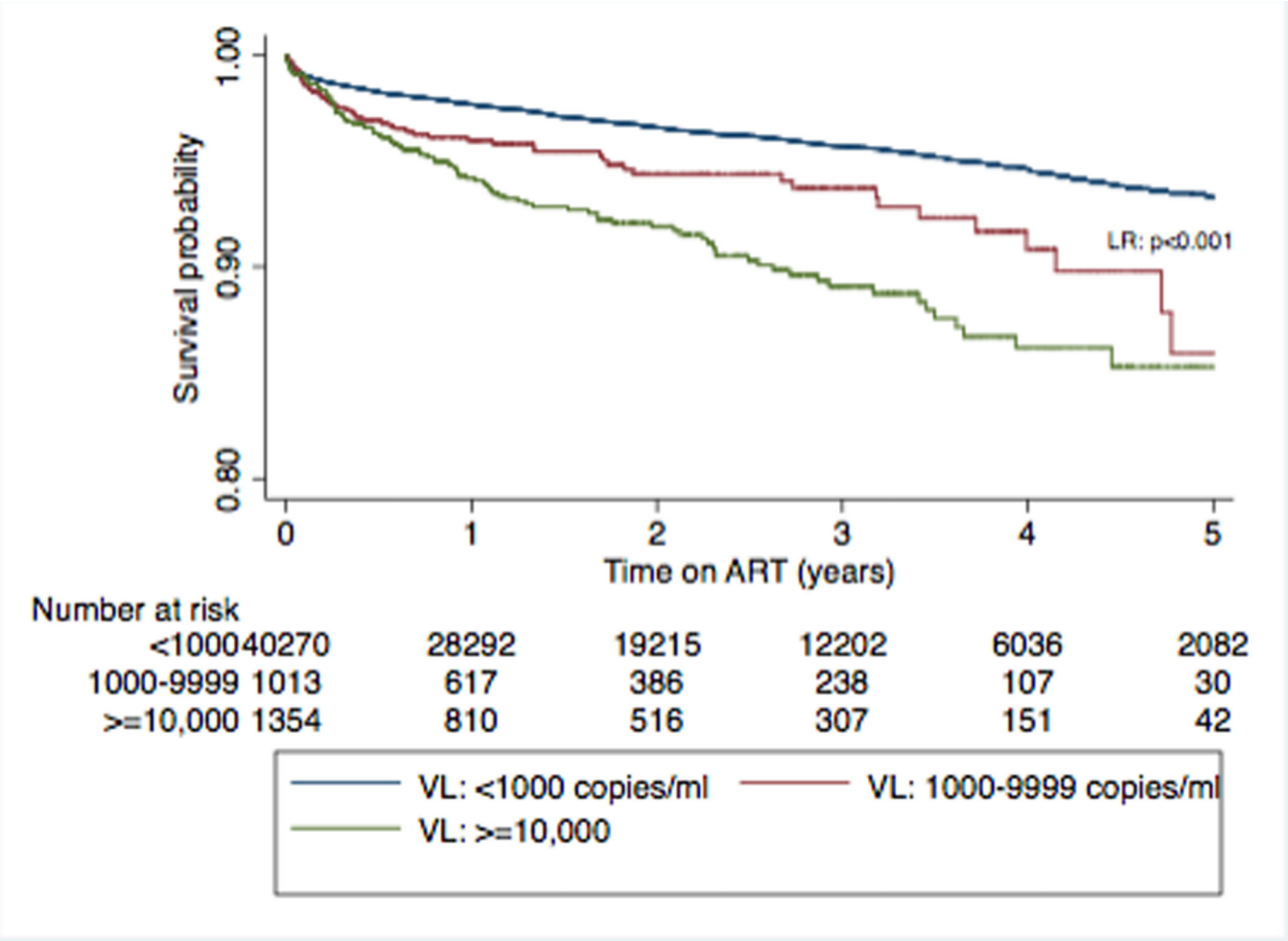

Figure 2b.
Time to incident TB by viral load.

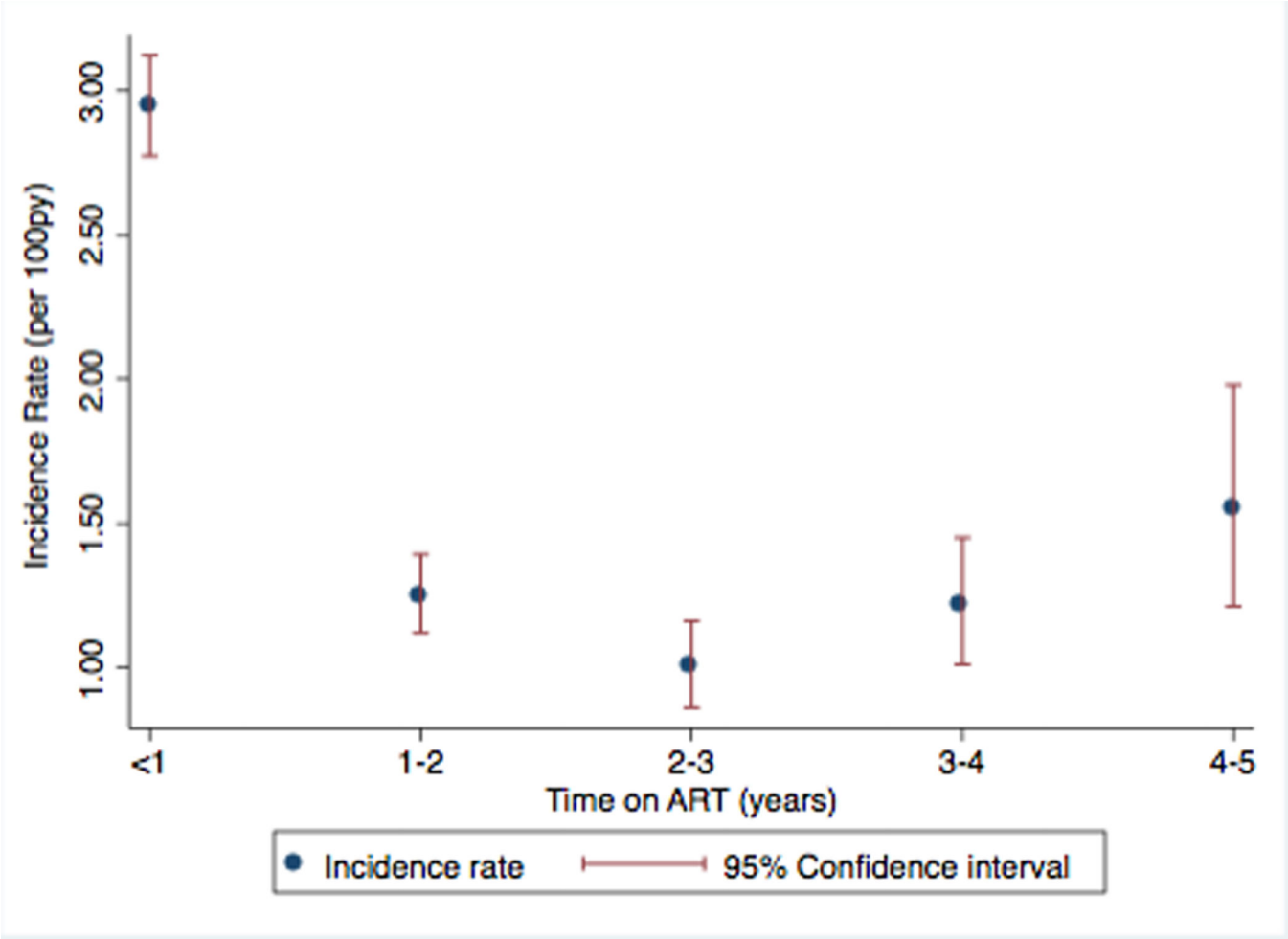

Figure 3.
Trends in TB incidence rate with time on ART.

Table 1:

Baseline features of patients enrolled in the Botswana “Masa” Program, 2011–2016

	All Patients (N=58284)		Prevalent TB (N=1202)		Non-TB (N=57082)		
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**p-value‡**
Male	20 265	35	630	52	19 635	34	<0.001
Female	38 017	65	572	48	37 445	66	
Age (years, median; Q1, Q3)	37	31, 45	37	31, 44	37	31, 45	0.82
Year of ART initiation							
2011–2012	22 785	39	537	45	22 248	39	0.003
2013–2016	35 499	61	665	55	34 834	61	
Marital status							
Single	48 757	84	1 041	87	47 716	84	<0.001
Married	7 993	14	139	12	7 854	14	
Education							
At least secondary-level	22 558	65	489	65	22 069	65	0.77
Employment status							
Employed	27 290	63	536	62	26 754	63	0.77
Unemployed	16 211	37	325	38	15 886	37	
Baseline CD4 count (cells/μl, Median; Q1, Q3) [1]	272	146, 403	129	53, 272	276	151, 407	<0.001
<50	1 967	9	158	24	1 809	9	
50–99	1 811	8	117	17	1 694	8	
100–199	3 821	18	158	24	3 663	17	
200–349	7 189	33	117	17	7 072	34	<0.001
350–499	3 563	16	71	11	3 492	17	
>=500	3 386	16	47	7	3 339	16	
Baseline VL (copies/ml, (N=50 926)							
<1000	47 662	94	918	92	46 744	94	
1 000 – 9 999	1 300	2	25	2	1 275	2	0.02
>=10 000	1 964	4	56	6	1 908	4	

[1] Baseline CD4 counts were available for N= 21737 (n= 668 prevalent TB)

‡ Chi-square and Wilcoxon rank-sum tests were used to test differences between categorical and continuous variables as appropriate, comparing patients with prevalent TB to those who did not have TB at the time of ART initiation.

Table 2:

Risk factors for incident TB in patients enrolled in the Botswana “Masa” Program between 2011 and 2015

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
Age	0.99	0989–0.997	0.002	0.99	0.99–1.00	0.30
Male	1.78	1.63–1.96	<0.001	2.00	1.71–2.33	<0.001
Viral load[1] (cells/ul)						
<1000		Ref				
1000–9999	1.70	1.29–2.23	<0.001	1.98	1.36–2.89	<0.001
>=10,000	2.45	2.01–3.00	<0.001	2.47	1.82–3.35	<0.001
Employed	0.89	0.80–0.99	0.04	0.72	0.62–0.84	<0.001
Literacy[2]	1.23	1.0–1.39	0.001	1.28	1.07–1.54	0.01

[1] Viral load recorded at 3 months post-ART initiation

[2] defined as at least a secondary-level education