High rates of Tuberculosis in patients accessing HAART in rural South Africa

Kogieleum Naidoo, MBChB[1], **Quarraisha Abdool Karim, PhD**[1,3], **Ambika Bhushan, MSc**[1,2], **Kasavan Naidoo, MSc**[1], **Nonhlanhla Yende-Zuma, MSc**[1], **Patricia K Mchunu, BNAP**[1], **Janet Frohlich, DCur**[1], **Farina Karim, MSocSci**[1], **Michele Upfold, BSc Pharm**[1], **Paul Kocheleff, MD**[1], and **Salim S Abdool Karim, MD PhD**[1,3]

[1]Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban

[2]Oxford Department of Public Health, Rosemary Rue Building, Old Road Campus, Headington, Oxford OX3 7LF, United Kingdom

[3]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA

Abstract

Background—The challenge of early Tuberculosis (TB) infection among rural patients accessing HAART in a resource-limited setting with high HIV and TB burden has not been fully quantified.

Methods—This is a retrospective study nested within a prospective study of 969 patients consecutively initiated onto HAART at the CAPRISA AIDS Treatment programme in rural KwaZulu-Natal between January 2007 and December 2010. Patients were screened for clinical symptoms consistent with TB using a standardized checklist, and routine clinical investigations that included sputum microscopy and chest X-Ray diagnosis.

Results—Of 969 HIV-infected patients initiated on HAART, 173 (17.9%; 95% CI: 15.5 to 20.4) had active TB at HAART initiation. TB incidence rates were three fold higher in the first 3 months (early incident TB) following HAART initiation (11.5/100 person years (py); 95%CI: 7.1 to 17.5); compared to 4 – 24 months (late incident TB) post HAART initiation (3.2/100 py; 95%CI: 2.2 to 4.5; incidence rate ratio (IRR): 3.6; 95%CI: 2.0 to 6.4; p value <0.001). Immune status of patients at HAART initiation did not impact TB incidence rates in patients with CD4+ counts <50 (5.3/100) and >200 (4.9/100 py; p=0.81); cells/mm^3. CD4+ count gains achieved 12 months post

HAART initiation were significantly different in patients with early incident TB versus late incident TB; p=0.03.

Conclusion—Rural HIV treatment programmes in TB endemic settings experience high rates of TB irrespective of immunologic status of patients at HAART initiation, or duration on HAART.

Keywords

HIV; TB; tuberculosis; HAART; Africa; KwaZulu-Natal; KZN; South Africa

INTRODUCTION

Tuberculosis (TB) infection contributes substantially to morbidity and mortality among HIV positive patients. Globally, HIV associated TB peaked in 2005 at 1.39 million cases with approximately 15% incident cases and 480 000 deaths[1]. However, 2010 data indicated a continuing burden of HIV-associated TB with 1.1 million cases of TB of which 13% were incident cases and resulting in approximately 350 000 deaths[2]. KwaZulu-Natal, South Africa, is home to approximately 1.2 million HIV-infected individuals with 70% of TB patients co-infected with HIV[3], and a TB notification rate of 1094 cases per 100,000 population[4,5].

The use of highly active antiretroviral therapy (HAART) in HIV-infected patients reduces the risk of developing TB by 70–90%[6–9], and is therefore a key strategy recommended by the World Health Organization (WHO) to prevent TB[10]. Studies from resource-limited settings show that HIV-infected patients have higher rates of TB compared to HIV uninfected patients, and with longer duration on HAART there is a decline in TB incidence rates[11,12]. Notwithstanding the evidence for TB screening and diagnosis, and HAART initiation early during TB therapy[13–16]; the burden of undiagnosed TB at HAART initiation and the number of new TB cases diagnosed during HAART in high HIV and TB settings have not been fully measured. In rural districts of KwaZulu-Natal where the TB and HIV epidemics converge most dramatically, the TB burden and its impact on patients at HAART initiation and during treatment remain poorly documented.

The aim of this study was to measure the prevalence and incidence rates of TB among patients accessing HAART in a rural community-based programme in a high TB and HIV prevalence setting in KwaZulu-Natal, South Africa, and explores its impact on therapeutic outcomes.

METHODS

Study population

We conducted a prospective cohort study among 969 HIV-positive patients initiated onto HAART at the Vulindlela CAPRISA AIDS Treatment programme between January 01, 2007 and December 31, 2010. This rural community outpatient clinic adjoins and receives patients from one of seven primary health care clinics in an area serving a community of about 400,000 people. Eligibility criteria were in accordance with South African Government HIV/AIDS treatment guidelines at the time[17, 18]. Patients were screened for clinical symptoms consistent with TB using a standardized checklist that asked about drenching night sweats, prolonged cough, fever and weight loss by either clinicians or professional nurses at every clinical visit. Patients that screened positive were referred to the adjacent government Primary Health Care Clinic for TB smear testing. Smear positive patients were initiated onto anti-TB therapy while sputum culture testing and antibiotic therapy was offered to all smear negative patients. Smear and culture negative patients with poor response to antibiotics, and those with suspected extra-pulmonary TB were referred to

the local district hospital for chest X-Ray, abdominal ultrasonography or other invasive investigations such as lymph node aspirate, tissue biopsy etc. Access to TB microbiology services was variable and depended on, availability of skilled laboratory staff especially for culture and drug susceptibility testing (DST), and timeous communication of results to site staff and patients. Tuberculin Skin Testing and isoniazid preventive therapy (IPT) was not the currently available standard of care during the study period. Patients were seen monthly for the first 6 months and every three months thereafter unless clinically indicated. Routine demographic, laboratory and clinical data were recorded at baseline and at follow-up visits. Upon TB diagnosis, the following additional information was collected: date and method of diagnosis, TB type (extra-pulmonary tuberculosis (EPTB) or pulmonary tuberculosis (PTB)), TB drug susceptibility pattern, date of TB treatment initiation and completion. Patients who had both PTB and EPTB were then classified as having EPTB. TB was diagnosed and treated as per South African National TB Control Program guidelines[19]. All patients with complications or requiring further investigation and management were referred to the closest district level services about 30 km away.

For the purposes of this study, a patient with a 'history of TB' was defined as having completed TB treatment prior to HAART initiation. Patients with a TB history were classified as having a 'recent history of TB' if they had an episode of TB within the year prior to HAART initiation[20]. A 'prevalent case of TB' was defined as a patient who was already on TB treatment when HAART was initiated. 'Incident TB cases' were defined as new TB cases diagnosed after HAART initiation, and was further classified into "early incident TB" defined as a new TB diagnosis within 3 months of HAART initiation, and "late incident TB" defined as a new TB diagnosis occurring between 4 and 24 months post HAART initiation[20]. A recurrent episode of TB after TB treatment completion or cure for the TB episode present at baseline was regarded as an incident TB case in the prevalent TB group.

Statistical analysis

All reported p-values are two-sided. TB incidence was calculated as number of new TB cases after HAART initiation per 100 person-years (py) of follow up. Data are presented as proportions, means or medians where appropriate. Study duration for patients with no prevalent TB was calculated from HAART initiation date to date of TB diagnosis, or programme exit through LTFU, transfer out, or death. Patients with prevalent TB were included in the incidence calculation and their time on study calculated from the date treatment for prevalent TB was discontinued to either the date of a new TB diagnosis, or to programme exit through loss to follow-up (LTFU), transfer out, or death. All patient data were censored at 24 months of follow-up.

Poisson approximations were used to calculate confidence intervals (CIs) for TB incidence. Kaplan-Meier was used to construct survival curves. Incidence rate ratios (IRR) were used to identify factors associated with early and late incident TB. The following baseline covariates were used to assess factors associated with early and late incident tuberculosis: age, gender, weight, WHO stage HIV disease, number of previous TB episodes, CD4+ counts and viral load. Data was extracted from routinely collected data recorded on standardized case report forms captured on a customized database through datafax. Statistical analysis was performed using SAS (version 9.2; SAS Institute Inc., Cary, NC, USA).

This study was approved by the Biomedical Research Ethics Committee, University of KwaZulu-Natal, ref no: E248/05.

RESULTS

Baseline demographic characteristics

The study comprised 969 HIV infected patients consecutively initiated on HAART between January 2007 and December 2010. The demographic and clinical characteristics at baseline are presented in Table 1. Approximately two-thirds of the cohort was female (67.8%). The mean age of patients was 34.3 years (SD± 9.6 years). The median follow-up time was 11 (IQR: 6.7 to 19.6) months, with 77.3 % (749/969) of patients still in active follow-up at 24 months post HAART initiation. The median baseline CD4+ count amongst patients with early incident TB; late incident TB; with no TB; and in the entire cohort were 101 (IQR 71–139); 112 (IQR 34–204); 131 (IQR 63–187); and 128 (IQR 61–186) cells/mm^3 respectively. The median baseline CD4+ count overall, amongst patients with early incident TB; late incident TB; and with no TB was 128 (IQR 61–186); 101 (IQR 71–139); 112 (IQR 34–204) and 131 (IQR 63–187) cells/mm^3 respectively. Approximately 50% of the cohort presented with clinically evident WHO stage 3 HIV disease.

TB Status at HAART Initiation

At baseline, all 969 patients were offered a TB symptom screening checklist. The diagnosis of active TB (prevalent TB group) was made in 173/969 patients (17.9%; 95% CI: 15.5 to 20.4). Two thirds of patients with baseline prevalent TB (68.6%) had PTB, 24.9% had EPTB; 4.0% had both PTB and EPTB; and 2.3% had TB with the site unspecified. Diagnosis of prevalent PTB (n=119) was made via sputum smear (n=54/119); chest X-Ray (n=54/65); clinical grounds only (n=9/11); and missing data on method of diagnosis (n=2). The diagnosis of prevalent EPTB (n=43) was made via diagnostic radiology (n=25), lymph node aspirate (n=4); joint aspirate (n=1), histology from biopsy specimen (n=2), on clinical grounds (n=5), unknown (n=6). Seven patients had both PTB and EPTB at baseline, diagnosed on sputum smear (n=1/7); chest X-Ray (n=2/7); clinical grounds only (n=2/7), diagnostic radiology (n=1/7); pleural tap (n=1/7). There were 226 patients with a past history of TB (80 in the prevalent TB group and 146 in the group without prevalent TB at baseline), of which 61.5% had an episode of TB within the year prior to HAART initiation (recent past history) (Figure 1). TB prevalence stratified by immune status is presented in Table 2. Prevalent TB was highest among patients with CD4+ counts < 50 cells/mm^3 (25.1%, 47/187; 95% CI: 19.2 to 32.1).

Incident TB Infections

There were 54 new clinical TB cases identified after HAART initiation giving an overall TB incidence rate of 4.5 per 100 person-years (py) (95% CI: 3.3 to 5.8). There were 3 cases of incident TB in the group with prevalent TB at the time of HAART initiation. Early incident TB was three fold higher (11.5/100 py; 95%CI: 7.1 to 17.5) compared to late incident TB (3.2/100 py, 95%CI: 2.2 to 4.5; incidence rate ratio (IRR) 3.6, 95%CI: 2.0 to 6.4; p <0.001) (Figure 2). Diagnosis of incident PTB (N=29) was made via sputum smear (n=7/29); chest X-ray (n=19/29); sputum culture (n=1/3) and clinical grounds only (n=2/29). Diagnosis of incident EPTB (n=23) was made via diagnostic radiology (n=13/19), pleural tap (n=1/1), histology from biopsy specimen (n=1/1), clinical grounds only (n=5/23), unknown (n=3). Two patients with incident TB had both PTB and EPTB which was diagnosed by diagnostic radiology.

Risk factors for early and late incident TB

The rate of early incident TB was almost two-fold higher among female; 13.3 /100 py; (95%CI: 7.6 to 21.3) compared to male patients; 7.3/100 py; (95%CI: 2.0 to 18.8; IRR: 1.8, 95%CI: 0.6 to 7.4; p=0.21), and almost five-fold higher among patients aged between 24

and 34 years (17.8 /100 py, 95%CI: 10.0 to 29.4); compared to 35 years (3.8/100 py, 95%CI: 0.8 to 11.1; IRR: 4.7, 95%CI: 1.3 to 25.2; p=0.01) (Table 3). However, interaction between gender and age was not statistically significant (p=0.10). No other factors were found to be associated with incident TB.

Baseline immune status of patients did not impact overall TB incidence rates; patients with CD4+ counts <50 cells/ mm^3 had TB incidence rates of 5.3/100 py (95% CI: 2.7 to 9.3) compared to 4.9/100 py (95%CI: 2.4 to 9.0) in patients with CD4+ counts >200 cells/mm^3 (p=0.81). Additionally, baseline immune status did not impact rates of incident TB.

TB incidence rates 3 months post HAART initiation among patients with CD4+ counts < 50; between 50 and 200; and > 200 cells/mm^3 were 4.6 (95%CI: 2.1 to 8.8); 2.4 (95%CI: 1.3 to 4.0); and 4.7 (95%CI: 2.0 to 9.2) per 100 py (Table 2).

Impact on therapeutic outcomes

There were 51 incident cases of TB among patients with no prevalent TB at baseline (26 PTB; 25 EPTB), and three incident cases of PTB among patients with prevalent TB at baseline. There was one case of multi-drug resistant TB in this cohort. Patients with incident PTB and EPTB had similar median baseline CD4+ counts, 106 vs. 129 cells/mm^3 (p=0.57), and baseline log viral loads, 5.2 vs. 5.0 (p=0.19); and similar mean CD4+ count increases (p=0.17) and log viral load decreases (p=0.16) from baseline to 12 months post HAART initiation. The median (IQR) months on HAART to a new episode of TB was 3.7 (0.8 to 10.9) and 5.2 (1.6 to 10.8) in the PTB and EPTB groups respectively. Median CD4+ count change from baseline to 12 months post HAART initiation was significantly higher in patients experiencing early incident 167 (IQR 141–235) versus late incident 76 (IQR 32–187) cells/mm^3 TB (p=0.03) (Supplemental Digital Content Table 4).

Mortality Rates

There were 57 deaths in this cohort with an overall mortality rate of 4.3 per 100 py (95% CI: 3.3 to 5.6). There were seven deaths among patients with baseline prevalent TB, mortality rate of 2.7 (95% CI: 1.1 to 5.6) per 100 py; compared to 50 deaths among 796 patients with no baseline prevalent TB, mortality rate of 4.7 (95% CI: 3.5 to 6.3) per 100 py (p=0.20) of follow-up. Patients with at least 1 episode of TB (either past history, prevalent or incident TB) had a lower mortality rate 3.4 (95% CI: 2.0 to 5.4) compared to patients with no TB, 4.5 (95% CI: 3.1 to 6.3) per 100 py (IRR: 0.8, 95%CI: 0.5 to 1.4; p=0.42) of follow-up. There was one death each in the early and late incident TB groups. The causes of death for 29 of 57 patients was known and this included PTB (n=4); EPTB (n=5); complications from severe gastroenteritis (n=6); trauma (n=2); natural causes (n=5); meningitis-unknown cause (n=2); lower respiratory tract infection (n=2); cerebro-vascular accident (n=1), intracranial lesion (n=1), complications from hyperlactatemia (n=1). Causes of death were not available in 28 patients as many of them died at home.

DISCUSSION

In a rural HIV treatment programme in a TB endemic setting, we found unacceptably high TB incidence rates irrespective of baseline immunologic status of patients at HAART initiation, or duration on HAART. We document TB incidence rates of 4.5/100 py of follow-up among HIV-infected patients receiving community-based HAART care in a rural setting. This incidence is higher than reports from other sub-Saharan countries and most other high TB burden settings[2,21,22] and nearly 10-fold higher than reported among HIV negative patients from a setting with similar TB notification rates[23]. Thus, we provide further evidence for continued susceptibility of HAART-accessing patients to TB infection in a

hyper-endemic TB setting sustained over 2 years post HAART initiation. This continued susceptibility to TB despite HAART likely points to on-going community-level and possibly nosocomial TB transmission.

We demonstrate an alarmingly high and consistent TB incidence (Table 2) among all baseline CD4+ count strata during study follow-up. The data show an inverse relationship between time on HAART and TB incidence, corroborating past studies, and likely due to greater TB-specific immune restoration with time spent on HAART[6,24–26]. Further, we highlight the need for close clinical observation in the first few months post HAART initiation by demonstrating highest rates of incident TB, likely due to "unmasked" infection, in the first three months post HAART initiation. Additionally, the continued high rate of new TB infections even at 24 months post HAART initiation is in keeping with published reports showing that, despite its decline with time on HAART, TB incidence among a HAART-accessing HIV population remains higher than in the general HIV-uninfected population[27]. We speculate that the high TB incidence rates observed in this study may be due to either impaired restoration of TB specific immunity when patients are severely immune-compromised (baseline CD4+ counts 200 cells/mm^3) at HAART initiation, or due to high ongoing community level TB transmission. The incidence rates observed is most likely due to a combination of both these factors. Interestingly, although women carry a disproportionate burden of HIV in sub-Saharan Africa, and despite finding a two-fold higher rate of early incident TB in women compared to men; further analysis stratified by age and gender showed no statistically significant difference in risk for either early or late incident TB. Notwithstanding lower pre-HAART CD4+ counts among patients that developed early incident TB; therapeutic outcomes among patients at 12 months post HAART initiation was similar in all groups.

In contrast to our study, published literature demonstrates a far more substantial time dependant reduction in TB incidence among patients on HAART[28–37]. These studies report highest TB incidence during the first 3 months of HAART[10] with a progressive reduction of all forms of TB during the first year of follow-up from 5.77/100 to 2.23/100 py[38]. Published meta-analysis data from developed country cohorts estimate a comparable effect of HAART on TB incidence despite differences in background risk of *M. tuberculosis* infection. These data provide an estimated TB incidence of 3 cases per 1000 py among patients accessing HAART; 10 fold lower compared to the TB incidence rates we found[10]. Findings similar to ours was reported in only one other study, conducted in a densely-populated urban informal settlement with a HIV sero-prevalence of 28% and TB notification rate of >1000/100000 population. In this study, TB incidence was reduced from 22.1 to 4.5/100 py among patients with a median baseline CD4+ count of 96 cells/mm^3 (IQR 46–156), after approximately 3 years of HAART[39].

The vast majority of TB episodes among patients with a previous TB history occurred in the 5-year period immediately prior to HAART initiation, a likely clinical feature of symptomatic HIV disease. We demonstrated a TB prevalence rate of 17.9% among HIV-infected patients initiating HAART, lower than previous reports from a South African community-based HAART program[39]. Other published studies from resource-limited settings report a high TB prevalence at HAART enrolment[25,39] primarily among patients with CD4+ count <50 cells/mm^3. However, data from this study shows high rates of prevalent TB especially in lower baseline CD4+ count strata, and not only among those severely immune compromised[40]. Among patients enrolling on HAART, one in four with CD4+counts <100 cells/mm^3 and one in seven patients with CD4+counts 100 cells/mm^3 had active TB. It is important to note however, that excluding active TB among HIV-infected patients is usually complex owing to high rates of smear-negative TB and difficulty

of diagnosing asymptomatic or subclinical TB, common among patients accessing HAART[41,42].

Unsurprisingly, there was no statistically significant difference in mortality rates among cases with known TB at baseline compared to those without. Mortality studies among HIV-infected patients conducted in this setting have repeatedly demonstrated high rates of undiagnosed TB responsible for as much as 79% of all deaths in HIV-infected patients[43,44]. Mortality rates were similar among patients with new episodes of EPTB as compared to those with new episodes of PTB; 2.3 (95% CI: 0.1 to 13.1) vs. 2.1 (95% CI: 0 to 11.6) per 100 py of follow-up. Interestingly, the mortality rate at 24 months in this study among patients with and without prevalent TB at baseline was very different to 5 year mortality rates of 4.84 and 2.62 per 100 person years of follow up among prevalent TB and TB free patients initiating ART in Cape Town South Africa[45].

While it may be likely that most cases of early incident TB was due to immune reconstitution inflammatory syndrome (IRIS), it remains unclear as to what proportion of incident TB was due to "unmasking" versus "paradoxical" TB IRIS versus new TB infections. It is well understood that IRIS embodies an interpretive crisis since its clinical diagnosis is similar to TB treatment failure, drug toxicities, TB relapse or new AIDS defining illness[46], and cannot be diagnosed by available tests[47]. Although consensus case definitions for TB IRIS have been formulated[20], the translation of these guidelines to the bedside remains poor. It is likely that this study underestimated rates of TB IRIS due to the poor ability to diagnose this phenomenon. In addition, in the absence of chest x-rays, minimally symptomatic or asymptomatic pulmonary disease may be incorrectly attributed to HIV or to other opportunistic infections.

We acknowledge several limitations. This study was conducted in a hyper endemic HIV and TB setting which limits the generalizability of these findings to similar settings. Limited access to chest x-rays in this primary health care setting, especially for asymptomatic patients with low CD4+ counts may have led to significant underreporting of TB; which potentially limits the validity, and to a lesser extent the generalizability of the study. The reliance on TB clinical symptom screening; lack of use of a standardized algorithm for TB screening and diagnosis, together with limited access to TB microscopy services, further contributed to TB cases being missed. The findings from this study highlight the need for enhanced screening and the use of a diagnostic algorithm for TB in a setting with generalized TB and HIV co-epidemics. High rates of smear negative TB and long delays in TB diagnosis may have led to the misclassification of prevalent TB cases as incident TB, especially for episodes that occurred in the first 3 months post-HAART initiation. Data used was routinely collected programmatic data, and missing data elements may have led to an underestimation of the actual burden of TB in this setting. Additionally, TB outcome data was not always readily available for complicated patients referred for hospitalization or for those that were lost-to-follow-up. In contrast to published literature, we report low IRIS estimates, which may be due to the retrospective nature of this study and to the lack of standardised clinical tools for diagnosing IRIS. Molecular strain typing would have been extremely useful in determining if cases of recurrent TB in this cohort were due to relapse or reinfection particularly in patients with early incident TB and in the 3 cases with incident and recurrent TB, but given the lack of cost-effective but unavailable tools such as chest x-rays in this setting, such endeavours were unfortunately unrealistic. It is important to note that our health care facility implemented standard WHO TB infection control measures, and data for this study was collected prior to the programmatic implementation of IPT. The impact of IPT on TB prevalence and incidence in community based HAART programmes remains to be explored, however, in this cohort it is important to note that starting patients

on IPT with HAART may result in many patients with active TB disease having initiated IPT.

CONCLUSION

Our study on the prevalence and incidence of TB in a rural, community-based HIV treatment programme has described a disproportionately high TB burden in patients accessing HAART. Our findings highlight the urgent need to implement TB preventive therapy and TB infection control practices in HAART programmes in endemic settings. TB incidence by baseline CD4+ count is highest among patients with CD4+ <50 cells/mm³,40; however, we also observed high TB incidence rates at higher CD4+ counts. Therefore, despite apparent immunologic recovery among HAART-accessing HIV patients, high TB incidence is still a potent threat, possibly reflecting community and nosocomial TB transmission. The availability of point-of-care diagnostic assays such as GeneXpert that readily diagnose TB while patients queue for services will facilitate TB case finding prior to the start of HAART, thereby reducing TB related morbidity and mortality commonly found among patients newly enrolled into HAART programmes in TB endemic setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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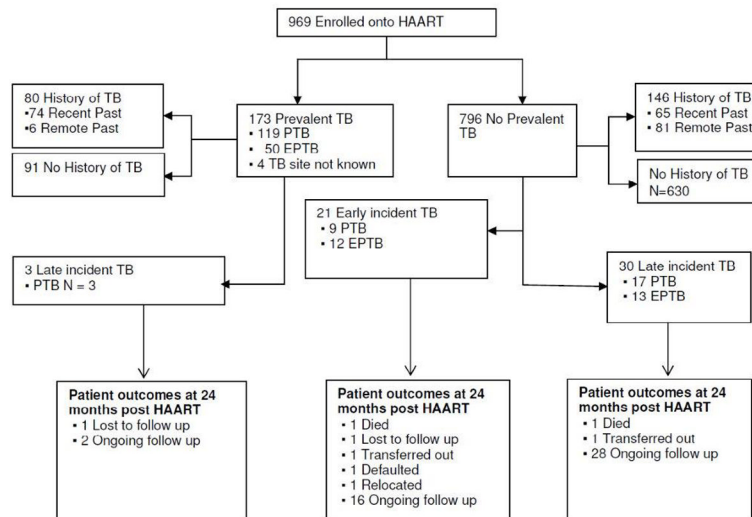
Figure 1. Flow chart depicting TB burden in a community based HAART programme
Definitions: Past history of TB: patient who completed TB treatment prior to HAART initiation; Recent history of TB: episode of TB within the year prior to HAART initiation; Remote history of TB: TB episode more than a year prior to HAART initiation; Prevalent TB: patient for whom treatment was ongoing during HAART initiation. Incident TB: new cases of TB diagnosed after HAART initiation which was further divided into ""early incident" TB" defined as a new TB diagnosis with 3 months of HAART initiation, and late incident TB defined as new TB diagnosis 4–24 months post HAART initiation.; PTB: pulmonary TB; EPTB: extra-pulmonary TB, including cases of both PTB and EPTB; CAT = The Centre for the AIDS Programme of Research in South Africa (CAPRISA) AIDS Treatment Programme
Notes: Past history of TB information was available for 947 individuals. Cohort included all patients enrolled onto HAART between January 2007 and December 2010; with patient follow-up time from enrolment date up until June 2011, when database was closed.
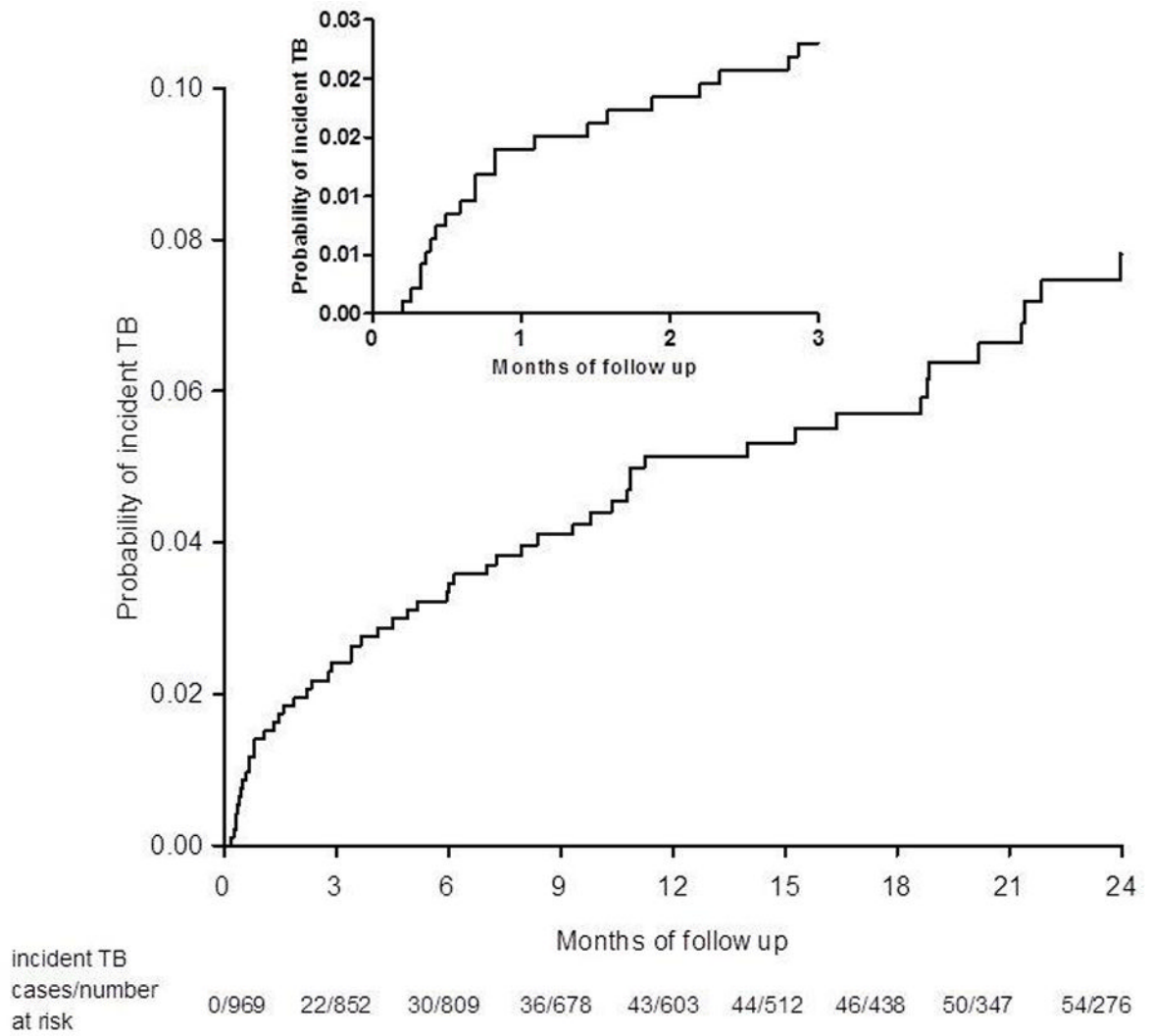
Figure 2.
Kaplan-Meier estimates of cumulative probability of developing early incident TB

Table 1

Baseline characteristics of patients enrolled onto HAART

Characteristics	Overall (N = 969)	No TB (N=745)	Prevalent TB (N=173)	Early incident TB (N=21)	Late incident TB (N=33)
Age (years), mean ± SD[†]	34.3 ± 9.6	34.5±9.8	33.9±8.3	29.3±5.3	35.5±11.3
Number of females, (%) n [‡]	(67.8) 651	(69.2) 509	(59.5) 103	(81.0) 17	(72.7) 24
Weight (kilograms), mean ± SD[*]	61.0 ± 13.5	62.0±14.1	56.9±10.6	62.4±12.6	58.1±11.4
BMI (kg/m^2) <18.5, (%) n [‡‡]	(13.4) 119	(10.9) 75	(23.3) 37	(10.5) 2	(17.2) 5
Viral load (log copies/ml), mean ± SD[**]	4.9 ± 0.9	4.9±0.9	5.3±0.9	5.2±1.1	5.1±0.7
CD4+ cell count (cells/mm^3), median (IQR)[††]	128 (61–186)	139 (71–190)	97 (41–147)	104 (71–139)	112 (34–204)
WHO Stage 3 of HIV Disease, (%) n [***]	(59.3) 567	(49.8) 365	(96.0) 166	(76.2) 16	(71.9) 23
Past history of TB at HAART initiation (%) (N=947)	(23.9) 226	(18.3) 133	(46.8) 80	(23.8) 5	(28.1) 9
Recent past TB history, (%) n	(61.5) 139	(46.6) 62	(92.5) 74	1 (20.0)	3 (33.3)
Remote past TB history, (%) n	(38.5) 87	(53.4) 71	(7.5) 6	4 (80.0)	6 (66.7)

Note: 3 patients who developed late incident TB had prevalent TB

SD = standard deviation, IQR = interquartile range, TB = tuberculosis

BMI =body mass index

[†] 10 patients had missing age

[‡] 9 patients have missing gender

[*] 11 patients had missing weight

[‡‡] 78 patients had missing BMI data

[**] 172 patients had missing viral load

[††] 86 patients had missing CD4+ count data

[***] 13 patients have missing WHO data

Table 2

TB status stratified by CD4+ count

Baseline CD4+ count (cells/mm^3)	Overall (N=969) (%) n	No TB (N=745) (%) n	Prevalent TB (N=173)		* Early incident TB (N=21)		** Late incident TB (N=33)	
			Patients with prevalent TB/n	TB prevalence(95%CI)	Patients with incident TB/person years	Incidence rate per 100 person-years (95% CI)	Patients with incident TB/person years	Incidence rate per100 person-years (95% CI)
Missing	(8.9) 86	(8.5) 63	17/86	19.8 (12.3 to 30.0)	4/14.9	26.9 (7.3 to 68.8)	2/75.6	2.6 (0.3 to 9.6)
CD4+ count <50/ mm^3	(19.3) 187	(17.3) 129	47/187	25.1 (19.2 to 32.1)	3/31.1	9.6 (2.0 to 28.2)	9/195.1	4.6 (2.1 to 8.8)
CD4+ count 50–200/mm^3	(55.2) 535	(56.8) 423	87/535	16.3 (13.3 to 19.7)	12/104.2	11.5 (5.9 to 20.1)	14/586.4	2.4 (1.3 to 4.0)
CD4+ count >200/mm^3	(16.6) 161	(17.4) 130	22/161	13.7 (9.0 to 20.2)	2/33.1	6.0 (0.7 to 21.8)	8/170.8	4.7 (2.0 to 9.2)

n = Number of patients

*
New TB diagnosis in the first 3 months after HAART initiation

**
TB incidence between 4–24 months post HAART initiation

Table 3

Predictors of early and late incident TB

Risk factor	*†Early TB			**Late TB		
	Number with incident TB/person-years	Incidence (95%CI)	Incidence rate ratio	Number with incident TB/person-years	Incidence (95%CI)	Incidence rate ratio
Age (years)						
missing	0/1.3	-		0/2.8		
<24	3/19.2	15.6 (3.2 to 45.6)	4.1 (0.5 to 30.5)	4/97.0	4.1 (1.1 to 10.6)	1.1 (0.2 to 3.8)
24–34	15/84.2	17.8 (10.0 to 29.4)	4.7 (1.3 to 25.2)	14/492.8	2.8 (1.6 to 4.8)	0.8 (0.4 to 1.8)
35+	3/78.7	3.8 (0.8 to 11.1)	reference	15/435.2	3.4 (1.9 to 5.7)	reference
Gender						
missing	0/1.2	-		0/2.8		
Male	4/54.5	7.3 (2.0 to 18.8)	reference	9/326	2.8 (1.3 to 5.2)	reference
Female	17/127.6	13.3 (7.6 to 21.3)	1.8 (0.6 to 7.4)	24/699	3.4 (2.2 to 5.1)	1.2 (0.6 to 3.0)
BMI (kg/m²)						
missing	2/11.9	16.8 (2.0 to 60.7)		4/64.6	6.2 (1.7 to 15.8)	
<18.5	2/18.2	11.0 (1.3 to 39.7)	0.9 (0.1 to 4.3)	5/119.7	4.2 (1.4 to 9.7)	1.6 (0.4 to 5.7)
18.5–25	9/90.7	9.9 (4.5 to 18.8)	0.8 (0.3 to 2.3)	16/527.4	3.0 (1.7 to 4.9)	1.2 (0.5 to 3.2)
>25	8/62.5	12.8 (5.5 to 25.2)	reference	8/316.1	2.5 (1.1 to 5.0)	reference
WHO Clinical Stage of HIV Disease						
missing	0/1.8	-		1/5.6	17.8 (0.5 to 99.2)	
3 or 4	16/89.4	17.9 (10.2 to 29.1)	reference	23/587.6	3.9 (2.5 to 5.8)	reference
1 or 2	5/92.2	5.4 (1.8 to 12.7)	0.3 (0.1 to 0.9)	9/434.6	2.1 (0.9 to 3.9)	0.5 (0.2 to 1.2)
Number of previous episodes of TB						
missing	0/3.3	-		1/14.4	7.0 (0.2 to 38.7)	
0	16/146.2	10.9 (6.3 to 17.8)	reference	21/653.9	3.2 (2.0 to 4.9)	reference
1	5/33.9	14.8 (4.8 to 34.4)	1.3 (0.4 to 3.9)	10/257.1	3.9 (1.9 to 7.2)	1.2 (0.5 to 2.7)
2	-	-		1/102.4	1.0 (0 to 5.4)	0.3 (0 to 1.9)
CD4+ count (cells/µL³) at HAART initiation						
missing	4/14.9	26.9 (7.3 to 68.8)		2/75.6	2.6 (0.3 to 9.6)	-

Risk factor	*†Early TB			**Late TB		
	Number with incident TB/person-years	Incidence (95%CI)	Incidence rate ratio	Number with incident TB/person-years	Incidence (95%CI)	Incidence rate ratio
<50	3/31.1	9.6 (2.0 to 28.2)	1.6 (0.2 to 19.1)	9/195.1	4.6 (2.1 to 8.8)	1.0 (0.3 to 2.9)
50–200	12/104.2	11.5 (5.9 to 20.1)	1.9 (0.4 to 17.6)	14/586.4	2.4 (1.3 to 4.0)	0.5 (0.2 to 1.4)
>200	2/33.1	6.0 (0.7 to 21.8)	reference	8/170.8	4.7 (2.0 to 9.2)	reference
Viral load at HAART initiation(log copies/ml)						
missing	6/31.2	19.2 (7.1 to 41.8)		8/210.4	3.8 (1.6 to 7.4)	-
<5	4/80.7	5.0 (1.4 to 12.7)	0.3 (0.1 to 1.1)	13/387.8	3.4 (1.8 to 5.7)	1.2 (0.5 to 2.9)
5	11/71.5	15.4 (7.7 to 27.5)	reference	12/429.6	2.8 (1.4 to 4.9)	reference