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# Tuberculosis in patients receiving antiretroviral treatment: incidence, risk factors and prevention strategies

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## Abstract

**Objective—**To determine tuberculosis (TB) incidence rates and risk factors among individuals receiving antiretroviral treatment (ART).

**Design—**Observational cohort in Johannesburg, South Africa.

**Methods—**Incident TB was classified as early (<6 months of ART) or late (>6 months of ART) incident TB. CD4 cell counts, viral load (VL), body mass index (BMI) and hemoglobin were measured 6-monthly. Hazard ratios for factors associated with early and late incident TB were assessed using Cox proportional hazards regression.

**Results—**During 13,416 person-years (py) follow-up, 501 TB cases occurred among 7,536 individuals, corresponding to a 10% risk in the first four years of ART, and an overall incidence rate of 4.2 cases/100 py. The highest incidence rate (21.7 /100 py) was observed in the first 3 months of ART among people with CD4 count below 50 cells/mm$^3$. Low baseline CD4 count, anemia, and low BMI were the strongest risk factor for early incident TB. Low updated CD4 count, low updated BMI, anemia, and high VL on ART were strong risk factors for late incident TB.

**Conclusions—**Severity of HIV disease and unfavorable response to ART are associated with early and late incident TB, respectively. Early ART initiation and intensified TB screening at ART initiation are crucial to reduce incident TB.

### Keywords

tuberculosis; TB; antiretroviral treatment; incidence; risk factors; South Africa

## INTRODUCTION

Tuberculosis (TB) remains one of the most frequent opportunistic infections in people living with the Human Immunodeficiency Virus (HIV). In 2007, an estimated 1.37 million HIV-

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associated TB cases occurred globally (1). Antiretroviral treatment (ART) has revolutionized the care of HIV-infected individuals with dramatic reductions in morbidity and mortality, and a 80% reduction in TB incidence rates among people receiving ART (2–8).

Studies across regions have consistently documented high TB incidence in the first months of ART (5,9–14). The high incidence during early phase of ART is, at least in part, due to unmasking of subclinical TB during the initial rapid restoration of the immune response (15,16). In most cohorts, the incidence of TB declined thereafter, but remained higher than the background TB incidence rate in the general population, even after years of receiving ART (5,9,10,12,16). This elevated long term TB incidence has been shown to be strongly associated with the time spent at CD4 count <500 cells/$mm^3$ (16).

Understanding the incidence and risk factors of active TB over time in patients on ART is crucial for the design of effective preventive strategies. We analyzed four years of data from a large cohort of patients initiating ART in Johannesburg, South Africa, to determine TB incidence by time since ART initiation, and assess risk factors separately for early incident TB (first 6 months of ART) and late incident TB (> 6 months of ART).

## METHODS

### Study site and inclusion criteria

The Themba Lethu Clinical Cohort is an open, prospective clinical cohort of adults initiating ART at a single site, hospital based public clinic providing free care in Johannesburg, South Africa. Patients were included in this analysis if they initiated ART between 1 April 2004 and 31 March 2007.

### Patient follow up, HIV and TB care and treatment

Prior to ART initiation, patients attended educational and adherence sessions, were assessed by a physician, and screened for the presence of opportunistic infections. After ART initiation, patients were scheduled for monthly pharmacy visits, clinical visits at month 4 and every 6 months thereafter, and additional visits whenever needed. Laboratory assessments included hemoglobin, CD4 count and plasma HIV viral load (VL) at baseline and each clinical follow-up visit, except for VL which was not performed at baseline. Screening for TB was performed routinely at all clinic visits using a questionnaire for cough or fever for >2 weeks, night sweats, weight loss of > 10%, or lymphadenopathy.

As per South African guidelines, the majority of patients received a first-line ART regimen of stavudine, lamivudine, and either efavirenz or nevirapine. Second-line ART consisted of AZT, didanosine, and ritonavir-boosted lopinavir. TB treatment was provided by the primary health care center closest to the patient's home and followed TB control program guidelines.

Patients more than three months late for a scheduled visit were traced by phone or home visit and categorized as lost to follow-up if alive and not in care. Vital status was also ascertained by consulting the national death registry.

### Definitions of tuberculosis

TB diagnosis was based on South African TB guidelines, in accordance with internationally accepted criteria. Pulmonary TB was diagnosed using smear microscopy or algorithms for smear negative TB that include chest X-ray, culture, and decision of a physician to prescribe a full course of anti-tuberculosis treatment. A case of extrapulmonary TB was defined as a

patient in whom a clinician decided to prescribe a full course of anti-tuberculosis treatment based on clinical, radiological, microbiological or histopathological information. Routine culture for *Mycobacterium tuberculosis* is not recommended by the TB control program.

Incident TB was defined as the first episode of TB after initiation of ART and categorized as early (within 6 months of ART) or late (more than 6 months after ART initiation). Individuals on TB treatment at time of ART initiation were classified as prevalent TB cases and became at risk of incident TB after completion of treatment for prevalent TB. History of TB was defined as treatment for TB prior to ART initiation and prevalent TB at time or ART initiation

### Statistical analysis

Baseline demographics were characterized using standard descriptive statistics. Anemia was defined as a hemoglobin (Hb) value below 13.0 g/dl (men), 12.0 g/dl (women), or 11.0 g/dl (pregnant women); down-adjusted by 0.65 g/dl because of altitude (21). Chi-square tests were used to compare categorical variables and Wilcoxon rank-sum tests for continuous variables by category.

TB incidence rate was defined as the number of TB cases occurring per 100 person years observation at risk after ART initiation. Person-time accrued during treatment for prevalent TB was excluded from the denominator when calculating TB incidence rates. Incidence rates were estimated using Poisson regression models, with each follow-up interval considered separately. The analysis was further stratified by baseline CD4 cell count. Kaplan-Meier method was used to estimate the probability of active TB while on ART. Censoring of patients occurred at death from any cause, loss to follow up or administratively on March 31, 2008.

We estimated hazard ratios and 95% confidence intervals [CI] for risk factors for incident TB (0–3 months, 4–6 months and > 6months) using multivariate Cox proportional hazards regression. Analysis of risk factors for early incident TB included baseline body mass index (BMI), CD4 count, and anemia. Risk factors for late incident TB included time-updated BMI, CD4 count, anemia and viral load.

All data were entered in a clinic data management system, TherapyEdge-HIV (Associated Biological Systems SA). Analysis was performed using SAS versions 9.1.3 (SAS, Cary, North Carolina, USA).

### Ethics approval

The study was approved by the Institutional Review Boards of the University of the Witwatersrand, South Africa and the University of North Carolina at Chapel Hill, USA.

## RESULTS

### Patient population, baseline characteristics and follow up

A total of 7536 people initiated ART between April 1, 2004 and March 31, 2008, contributing 161,000 person-months of observation with a median follow up of 21.4 months. During follow up, 496 patients (6.6%) died and 1036 patients (13.7%) were lost to follow-up. 1556 patients (20.6%) were on TB treatment at time of ART initiation (prevalent TB). 501 patients developed TB on ART (incident TB), of which 284 cases occurred in the first six months of ART (early incident TB) and 217 after the first six months of ART (late incident TB). Of the 501 patients with incident TB, 55 also had a history of prevalent TB,

with a median time of 8 months (interquartile range 3–16) between the end of prevalent TB episode and diagnosis of incident TB.

Patients with prevalent TB had the most advanced disease at time of ART initiation: 42% had CD4<50 cells/mm3, 32% BMI<18.5 kg/m2, and 72% had anemia. Those with early incident TB also had advanced HIV disease, whereas those who developed late incident TB had baseline characteristics similar to those who never experienced TB (Table 1).

## TB incidence rates

The cumulative probability of developing TB on ART was 5.7% (95% CI 5.2–6.3) in the first year of ART, 7.6% (95% CI 6.9–8.3) by the end of the second year, 9% (95% CI 8.2–9.8) by the end of the third year, and 10.1.% (95% CI 8.9–11.5) by the end of the fourth year of ART.

The overall incidence rate of TB on ART was 4.2 (3.8–4.5) per 100 person-years (py). The TB incidence rate was the highest in the first 90 days of ART (13.9 per 100 py, 95% CI 11.9–15.8), dropped by 50% in the 3$^{rd}$ to 6$^{th}$ months of ART (6.3 per 100 py, 95% CI 5.1–7.9), and further decreased with increasing time on ART to 1.6 per 100 py (95% CI 1.2–2.3) in the third year of ART, after which the incidence remained stable (Figure 1, Table 2).

The rate of early incident TB was strongly determined by baseline CD4 count (Figure 1). TB incidence rates in the first 90 days was 21.7 per 100 py (95% CI 17.5–26.7) among those with baseline CD4 count below 50 cells/mm$^3$ compared to 12.8 (95% CI 9.1–18.0), 9.5 (95% CI 6.4–16.2) and 10.2 (95% CI 6.4–16.2) per 100 py for those with baseline CD4 count 50 to 100, 101 to 200, and 200 or more, respectively (test for linear trend p<0.0001).

## Risk factors for early incident TB

Severity of immune suppression at time of ART initiation was associated with the risk of developing active TB in the first six months of ART (Table 3). Compared to those presenting with a CD4 count> 200 cells/mm3, patients with low CD4 count (< 50 cells/mm$^3$) were almost twice as likely to develop TB (adjusted Hazard Ratio (aHR) 1.68, 95% CI 1.03–2.74), those with CD4 count between 50 and 100 tended to have a higher hazard (aHR 1.31, 95% CI 0.78–2.20), whereas those with CD4 count between 100 and 200 were not at increased risk (aHR 1.08, 95% CI 0.66–1.77). Poor nutritional status at time of presentation for ART was also associated with risk of early incident TB, with increasing TB rates as BMI decreased: aHR 1.69 (95% CI 1.18–2.42) and 2.03 (95% CI 1.34–3.07) for those with BMI 18.5 to 24.9 and <18.5, respectively when compared to BMI > 25 kg/m$^2$. The presence of anemia was also independently associated with early incident TB (aHR 2.54, 95%CI 1.92–3.37). A history of TB treatment and being employed at time of ART initiation reduced the risk of early incident TB. Results were similar but less precise when evaluated separately for 0–3 months and 4–6 month categories (data not shown).

## Risk factors for late incident TB

Among individuals who did not experience TB in the first six months of ART, baseline characteristics were not associated with risk of developing late incident TB, except for a history of TB (Table 3). Factors associated with poor response to ART were strongly associated with an increased risk of late incident TB. Current undernutrition (BMI < 18.5) and below-normal BMI (18.5–24.9) increased the hazard of TB (aHR 4.07, 95% CI 2.53–6.57 and aHR 1.71, 95% CI 1.20–2.44, respectively). The hazard of late incident TB was also associated with current CD4 counts less than 350, current anemia and viral load >10,000 copies/ml.

## DISCUSSION

The large sample size of more than 7500 individuals residing in a high TB burden area allowed us to estimate TB incidence rates stratified by CD4 count, and to quantify risk factors for TB separately for the early and later phases of ART. Among people attending a South African inner city ARV clinic, we observed a 10% *four-year* risk of developing TB on ART, compared to the 10% *lifetime* risk in HIV uninfected individuals (17). This burden is in addition to a 20% prevalence of TB at time of presentation for ART. These results highlight that TB will remain a major challenge to the health of people living with HIV in sub-Saharan Africa, even in the era of increasing access to ART.

Similar to a study by Lawn et al in Cape Town, South Africa (16), we observed extremely high incidence rates in the first months of ART, with a point estimate of 21.7 (95% CI 17.5–26.7) cases per 100 py in the first 3 months of ART among those with baseline CD4 counts below 50 cells/$mm^3$. In contrast to the study in Cape Town, we found that high rates of early incident TB were not restricted to those with baseline CD4 cell counts less than 200 cells/$mm^3$. Instead, we observed significantly increased rates of TB in the first 3 months of ART across all CD4 strata. Person characteristics other than CD4 count independently associated with early incident TB were anemia, nutritional status, and lack of employment. A log-linear association between risk of TB and BMI in the range 18.5 and 30 kg/$m^2$ was recently demonstrated in HIV-uninfected individuals (18). Our study confirms this associated in patients receiving ART and extends the association to BMI below 18.5. Similar to our findings, anemia at time of ART initiation was associated with a 3-fold increase in TB risk in Abidjan, but the association did not reach statistical significance in that study (19). The World Health Organization recently recommended replacing stavudine by zidovudine or tenofovir in first line ART regimens (20). Because anemia is a frequent side effect of zidovudine, it could be important to monitor the effect of this increased use of zidovudine on the risk of incident TB.

TB incidence rates dropped dramatically during the first year of HAART and stabilized thereafter. This trend may be related to the rapid positive response to ART in our population, with 90% of people suppressing virus replication by 6 months of ART and dramatic restoration of immune function in the first year of ART (increase of mean CD4 count from 111 to 289 cells/$mm^3$), followed by smaller gains in CD4 cell numbers thereafter (21). The observed TB rate of 1.6 to 2.2 per 100 py in years 2 to 4 of ART is lower than the 3.2 to 4.5 per 100 py incidence rate in years 2 to 4 of ART in Cape Town, South Africa(16), but significantly higher than the 0.18 per 100 py TB incidence rate documented after the first year of ART in Burkina Faso(13). The risk stabalized at a rate about 4 times that of the estimated background TB rate in the South African studies (1.03 and 0.5 per 100 py for Western Cape and Gauteng province, respectively Source: C. Idema, Department of Health). In contrast, the long-term TB incidence rates on ART in Burkina Faso dropped to that of the estimated background rate in the general population. These finding suggest that, while the relative impact of ART is consistent across settings (70 to 90% reduction) (2–8), the level at which the TB incidence rate stabilizes may be more variable and related to the background force of infection in the community.

Among individuals who did not experience early incident TB, the risk of late incident TB was associated with response to treatment. Updated CD4 count was strongly associated with TB risk, with a four-fold increased hazard among people with CD4 count below 50 cells/$mm^3$ compared to those with CD4 count above 350 cells/$mm^3$, similar to the report by Lawn et al. (16). The impact of current poor nutritional status was of the same magnitude as the effect of low CD4 count, with a four-fold higher hazard of TB. Lack of viral suppression (VL> 10,000 copies per ml) was associated with a 2.5-fold increased adjusted hazard.

Previous reports on viral suppression and risk of developing TB have been conflicting. The US and European Antiretroviral Therapy Cohort Collaboration observed an increased risk of TB (aHR 2.21) in patients who did not achieve viral suppression (defined as VL<400 copies/ml) after 6 month of ART (9), whereas updated VL (> 400 copies/ml) was not associated with incident TB in Cape Town (16).

Analyzing routine data from a large, public ART clinic in a high burden country resulted in a large number of patients on ART and TB cases observed, and allowed precise estimates of incidence and hazard rates. The reliance on routine procedures however resulted in limitations. Patients are mainly diagnosed with TB at primary health care clinics, resulting in the lack of bacteriological confirmation of TB and the possibility of misclassification of TB status. Causes of death are unknown in most cases, resulting in possible underestimation of TB rates.

Results of this study generated evidence to support, develop and refine strategies to reduce the burden of TB among people receiving ART (table 4). First, a higher population median CD4 count at ART initiation will significantly reduce the risk of incident TB, reiterating the importance of initiating of ART earlier, as recommended by the WHO (20). Second, prevention of early incident TB will require a shift to a more sensitive intensified case finding strategy. The standard symptom screen (cough or fever for > 2 weeks, night sweats, weight loss of > 10%, chest pain, hempothysis) has been shown to lack sensitivity to detect culture positive TB in HIV infected individuals, and smear microscopy has a sensitivity of just 14% compared with liquid culture in individuals presenting for ART (22). Furthermore, it has been shown that subclinical TB occurs in a substantial proportion of HIV-infected individuals (23–25). While the use of a more sensitive definition of a TB suspect (for example cough or fever of any duration) is highly likely to result in the detection of more cases, research is needed to determine the most optimal, feasible, and cost effective TB screening strategy. Third, there is growing evidence that preventative therapy administered prior to or along with ART has an additive effect on reduction in TB incidence (26–29). In 2010, the South African Department of Health recommended IPT for patients on ART in whom active TB has been excluded, but this recommendation was conditional as current evidence is limited to retrospective cohort studies, not randomized controlled trials. To determine the optimal strategy for preventive therapy among individuals on ART, a number of questions will need to be addressed concurrently, including whether the intervention should be universal or targeted to those in whom infection with *Mycobacterium tuberculosis* is documented by tuberculin skin test or interferon gamma release assay, whether people with a history of TB should be targeted, what the optimal timing of preventive therapy is in relation to initiation of ART, what the optimal drug regimen is, especially in areas with high background isoniazid resistance, and the optimal duration of preventive therapy in people on ART. Fourth, as more patients are on ART for longer period of time, adherence to ART to prevent treatment failure and timely introduction of a second line regimen will become increasingly important in controlling TB among people on ART. Finally, other intervention that could reduce the rate of incident TB include nutritional supplements, treatment of anemia and poverty reduction.

In conclusion, TB remains a major challenge to the health of people living with HIV in sub-Saharan Africa, even among those receiving ART. Severity of HIV disease is the strongest risk factor for prevalent and early incident TB, and response to ART the strongest risk factor for late incident TB. Early initiation of ART will significantly reduce TB incidence among people on ART, but additional interventions such as screening for TB using highly sensitive tools, preventive therapy, nutritional interventions, anemia and poverty reduction may be needed to further reduce the burden of TB among people on ART.

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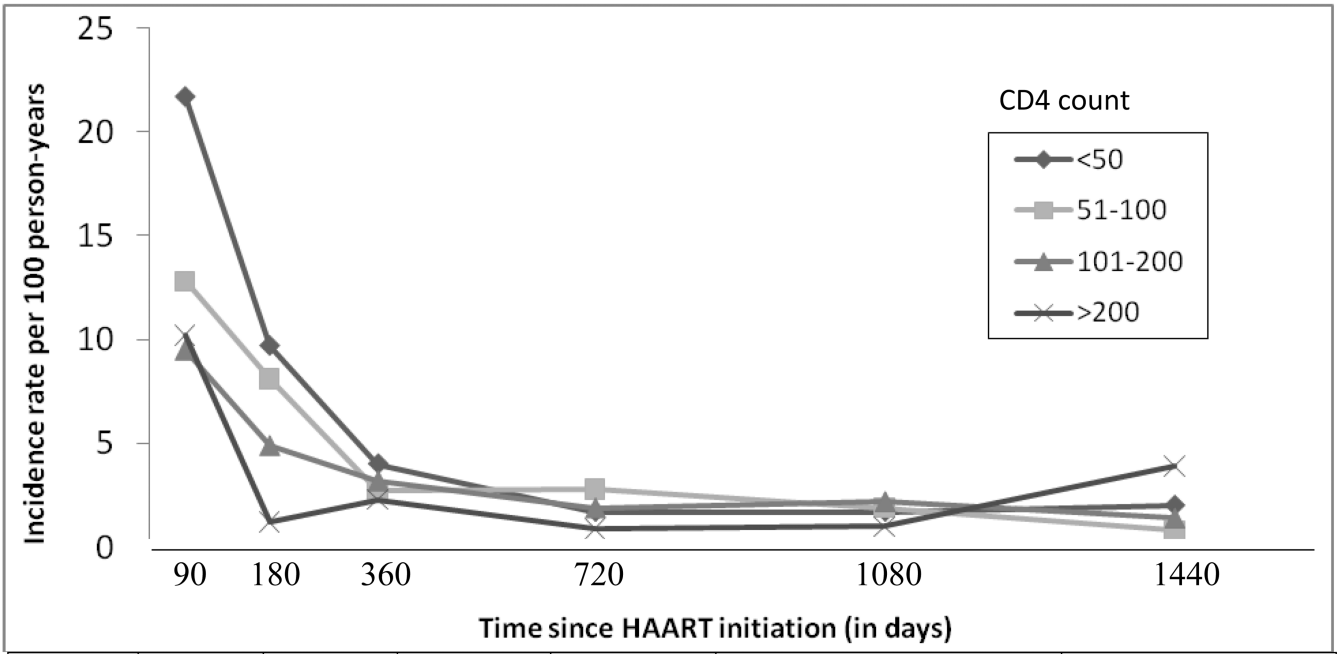


| baseline CD4 | 0-90 d | 91-180 d | 181-360 d | 361-720 d | 721-1080 d | ≥1081 d |
|---|---|---|---|---|---|---|
| **<50** | 86/1843 | 36/1679 | 30/1688 | 19/1518 | 9/796 | 3/345 |
| **51-100** | 33/1148 | 21/1129 | 14/1140 | 22/1031 | 8/577 | 1/273 |
| **101-200** | 43/1977 | 22/1904 | 28/1868 | 24/1676 | 14/903 | 2/375 |
| **>200** | 18/765 | 2/702 | 7/666 | 4/582 | 2/294 | 2/127 |

**Figure 1.**

Incidence rates of tuberculosis (TB) by time on antiretroviral treatment (ART) and baseline CD4 count category (< 50, 51–100, 101–200, > 200 cells/mm$^3$). Numbers in table below figure represent the number of TB cases observed over the total number of people on ART who completed follow up during the respective time periods, by CD4 count category.

## Table 1

Demographic and clinical characteristics of 7536 individuals initiating antiretroviral treatment in Johannesburg, South Africa by timing of developing active tuberculosis

| | Timing of TB | | | |
|---|---|---|---|---|
| | Never TB while on ART | Prevalent TB | Incident TB | |
| | | | Early | Late |
| | ***n=5534*** | ***n=1556*** | ***n=274**** | ***n=172**** |
| **History of TB** | 821 (14.8) | 69 (4.4) | 39 (14.2) | 44 (25.6) |
| **Female gender** | 3830 (69.2) | 904 (58.1) | 171 (62.4) | 106 (61.6) |
| **Mean age** | 36.6 | 36.0 | 36.3 | 36.6 |
| **Employed** | 2098 (37.9) | 492 (31.6) | 90 (32.9) | 56 (32.6) |
| **BMI** | | | | |
| < 18.5 | 844 (15.3) | 496 (31.9) | 69 (25.2) | 29 (16.9) |
| 18.5 – 24.9 | 3032 (54.8) | 866 (55.7) | 156 (56.9) | 97 (56.4) |
| 25.0 – 29.9 | 1118 (20.2) | 153 (9.8) | 35 (12.8) | 37 (21.5) |
| ≥ 30.0 | 540 (9.8) | 41 (2.6) | 14 (5.1) | 9 (5.2) |
| **Low hemoglobin** | 2363 (42.7) | 1120 (72.0) | 183 (66.8) | 89 (51.7) |
| **CD4 count** | | | | |
| Median (IQR) | 99 (37–169) | 58 (22–116) | 56 (13–135) | 93 (42–146) |
| Mean (95% CI) | 119 (116–122) | 79 (75–83) | 84 (73–95) | 102 (89–116) |
| ≤ 50 | 1558 (28.2) | 652 (41.9) | 116 (42.3) | 47 (27.3) |
| 51 – 100 | 988 (17.9) | 357 (22.9) | 50 (18.3) | 34 (19.8) |
| 101 – 200 | 1785 (32.3) | 367 (23.6) | 65 (23.7) | 54 (31.4) |
| 201 – 350 | 537 (9.7) | 62 (4.0) | 15 (5.5) | 12 (7.0) |
| > 350 | 172 (3.1) | 17 (1.1) | 2 (1.8) | 2 (1.2) |
| Missing | 494 (8.9) | 101 (6.5) | 23 (8.4) | 23 (13.4) |
| **Type of TB** | | | | |
| Pulmonary | n/a | 1210 (77.8) | 225 (82.1) | 134 (77.9) |
| Extrapulmonary | n/a | 346 (22.2) | 49 (17.9) | 38 (22.1) |

55 individuals who had prevalent TB and later developed incident TB were included in the prevalent TB category only.

TB=tuberculosis; ART=antiretroviral treatment; BMI=body mass index

## Table 2

Tuberculosis (TB) incidence rate and rate ratios by time since antiretroviral treatment (ART) initiation

| Duration of ART | At risk (n)* | Person-months | TB cases (n) | Incidence rate† (95% CI‡) |
|---|---|---|---|---|
| All of follow-up | 7281 | 144749 | 501 | 4.2 (3.8–4.5) |
| Year 1 | 7234 | 66046 | 375 | 6.8 (6.1–7.5) |
| 0 to 90 days | 6292 | 16994 | 196 | 13.9 (11.9–15.8) |
| 91–180 days | 5943 | 16416 | 88 | 6.3 (5.0–7.7) |
| 181–365 days | 5887 | 32329 | 91 | 3.5 (2.8–4.2) |
| Year 2 | 5277 | 47585 | 83 | 2.2 (1.7–2.6) |
| Year 3 | 2871 | 24188 | 35 | 1.6 (1.1–2.2) |
| Year 4 | 1297 | 6622 | 8 | 1.6 (0.6–2.7) |

CI: confidence interval.

*255 individuals with prevalent TB died or were lost to follow up prior to completion of therapy and were thus never at risk for incident TB.

†Incidence rate given per 100 person-years.

‡95% CIs calculated assuming a Poisson distribution.

## Table 3

Adjusted Hazard ratios (95% CI) for early and late incident tuberculosis (TB) in patients receiving antiretroviral treatment (ART)

| Covariates | Incident TB category | |
|---|---|---|
| | Early incident TB | Late incident |
| **Demographic characteristics** | | |
| **History of TB treatment** | 0.68 (0.50–0.93) | 1.32 (1.00–1.76) |
| **Female gender** | 0.79 (0.61–1.03) | 1.02 (0.75–1.39) |
| **Baseline age > median** | 1.13 (0.88–1.45) | 1.05 (0.78–1.40) |
| **Employed** | 0.76 (0.58–0.99) | 0.88 (0.48–1.29) |
| **Baseline characteristics** | | |
| **Low hemoglobin** | 2.54 (1.92–3.37) | |
| **Body mass index (vs. ≥25 kg/m2)** | | |
| <18.5 | 2.03 (1.34–3.07) | |
| 18.5–24.9 | 1.69 (1.18–2.42) | |
| ≥ 25 | 1. | |
| **CD4 count (vs. > 200 cells/mm$^3$)** | | |
| ≤ 50 | 1.68 (1.03–2.74) | |
| 51 – 100 | 1.31 (0.78–2.20) | |
| 101 – 200 | 1.08 (0.66–1.77) | |
| > 200 | 1. | |
| **Response to ART** | | |
| **Low hemoglobin** | | 1.69 (1.21–2.34) |
| **Body mass index (25 kg/m2)** | | |
| <18.5 | | 4.07 (2.53–6.57) |
| 18.5–24.9 | | 1.71 (1.20–2.44) |
| ≥ 25 | | 1. |
| **CD4 count (cells/mm$^3$)** | | |
| ≤ 50 | | 3.80 (1.99–7.27) |
| 51 – 100 | | 3.28 (1.83–5.88) |
| 101 – 200 | | 1.94 (1.21–3.09) |
| 201 – 350 | | 1.78 (1.17–2.70) |
| ≥350 | | 1. |
| **Proximal viral load (copies/ml)** | | |
| > 10,000 | | 2.52 (1.67–3.82) |
| 401–10,000 | | 1.12 (0.57–2.20) |
| ≤ 400 | | 1. |

## Table 4

Interventions to prevent tuberculosis (TB) by duration of antiretroviral treatment (ART)

| Timing of TB | Rate | Main risk factors | Intervention |
|---|---|---|---|
| Prevalent TB | 20% | • Low CD4 count at ART initiation | • Start isoniazid preventive therapy in patients not yet eligible for ART<br>• Early ART initiation |
| Very early incident TB (first 3 months of ART) | 13.9 per 100 py | • Low CD4 count at ART initiation<br>• Unmasking of subclinical TB with rapid immune reconstitution<br>• Poor nutritional status<br>• Anemia | • Early ART initiation<br>• Screening for subclinical TB<br>- Any symptom for any duration<br>- Culture or novel diagnostics?<br>- Targeted or universal?<br>• Nutritional intervention<br>- For those with baseline BMI below18.5 or 25 kg/$m^2$?<br>• Treat anemia |
| Early incident TB ($3^{rd}$ –$6^{th}$ months of ART) | 6.3 per 100 py | • Low CD4 count at ART initiation<br>• Incomplete immune reconstitution (CD4 remains < 200 cells/$mm^3$)<br>• Poor nutritional status<br>• Anemia | • Early ART initiation<br>• Start isoniazid preventive therapy at 3 months visit<br>- For all or those with pos. PPD?<br>- Primary and/or secondary PT?<br>- For all or those with CD4 < 200 cells/ mm3 at 3 months of ART?<br>- For 6 months, lifelong, or until CD4 reaches certain target?<br>• Treat anemia |
| Late incident TB (> 6 months after ART initiation) | 2.4 per 100 py | • Poor immune response to ART<br>• Virologic failure<br>• Poor nutritional status<br>• History of prior TB treatment<br>• Anemia | • Early initiation of ART<br>• Ensure good adherence to ART<br>• Timely switch to second line regimen if treatment failure<br>• Nutritional intervention<br>- For those with current BMI below18.5 or 25 kg/$m^2$?<br>• Treat anemia |