# Incidence of Tuberculosis in HIV-Infected Patients Before and After Starting Combined Antiretroviral Therapy in 8 Sub-Saharan African HIV Programs

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**Setting:** Eight HIV programs in sub-Saharan Africa.

**Objective:** To describe the incidence of pulmonary and extrapulmonary tuberculosis before and after the start of combined antiretroviral therapy (ART) and investigate associated risk factors.

**Design:** Multicohort study. Adults enrolled between January 2006 and September 2008.

**Results:** A total of 30,134 patients contributed 25,916 person-years of follow-up. The incidence of tuberculosis was 10.5 per 100 person-years during the pre-ART and 5.4 during the ART period. For all types of tuberculosis, incidence was similar in the pre-ART period and initial 3 months of ART but declined over time receiving ART (from 13 per 100 person-years in the first 3 months to 1.5 per 100 person-years after 12 months of therapy). Throughout follow-up, rates of pulmonary tuberculosis remained 2-fold to 3-fold higher than extrapulmonary tuberculosis rates. Smear-negative pulmonary tuberculosis was higher than smear-positive incidence and varied greatly across sites during the pre-ART period. Incidence was lower in rural sites, women, patients without prior history of tuberculosis, body mass index $\geq$18.5 kg/m$^2$, and $\geq$200 nadir CD4 cells per microliter. Recurrence rate was 1.7 per 100 person-years (95% confidence interval: 1.0 to 2.8).

**Conclusions:** Our findings show the high burden that tuberculosis represents for HIV programs and highlight the importance of earlier ART start and the need to implement intensified tuberculosis finding, isoniazide prophylaxis, and infection control.

**Key Words:** combined antiretroviral therapy, cohort studies, HIV, incidence, tuberculosis

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## INTRODUCTION

Tuberculosis is a common cause of morbidity and mortality in patients infected with HIV living in resource-limited countries. In 2009, 22.5 million people were estimated to be living with HIV in sub-Saharan Africa.[1] Furthermore, during the same year, 2.8 million new cases of tuberculosis were reported in Africa, the majority in the sub-Saharan area; and 37% of tuberculosis episodes were diagnosed among HIV-infected patients.[2] The World Health Organization recommends initiating combined antiretroviral therapy (ART) in all patients coinfected with HIV and tuberculosis.[3] Despite the existence of affordable medications, too few coinfected patients receive adequate treatment for both diseases in Africa, and this situation leads to substantial avoidable morbidity and mortality.[1]

HIV infection increases the risk of developing tuberculosis but also modifies the clinical presentation of the disease.[4] HIV-infected patients are twice as likely to experience sputum smear–negative pulmonary tuberculosis (PTB) than HIV-uninfected patients,[5] and extrapulmonary tuberculosis (EPTB) is also more common in HIV-positive patients.[5,6] This contributes to delayed tuberculosis diagnosis, leads to high mortality, and represents an important burden for health systems.

Quantifying the burden that different types of tuberculosis represent for HIV programs during the pre-ART and ART periods is important for program managers. Better understanding of factors associated with incident tuberculosis could help to improve service provision. Previous studies have provided evidence of the decreased risk of tuberculosis in HIV-infected patients who initiate ART.[7–15] However, a few studies have examined rates of smear-positive and smear-negative

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PTB and EPTB or investigated associations with individual factors in HIV programs.

Médecins Sans Frontières (MSF) has provided free ART in resource-limited countries since 2001. In recent years, great efforts have been made to integrate tuberculosis diagnosis and treatment into HIV care. The objective of this analysis was to describe the incidence of smear-positive and smear-negative PTB and EPTB during pre-ART and ART periods in large HIV programs not routinely providing isoniazid prophylaxis in sub-Saharan Africa and to identify individual-level factors associated with incident tuberculosis.

## MATERIALS AND METHODS

### Sites and Cohort Selection

We analyzed data from all MSF-supported HIV programs in sub-Saharan Africa that had started providing care to patients coinfected with HIV and tuberculosis before January 2006, routinely collected information on tuberculosis episodes in the follow-up and care of HIV infections and AIDS (FUCHIA) database (Epicentre; Paris, France), had treated more than 100 patients with tuberculosis, and had less than 10% of data inconsistencies (eg, discrepancies in the number of tuberculosis episodes and dates of diagnosis between the follow-up and tuberculosis questionnaires completed for each patient or record of new tuberculosis cases for patients who received retreatement tuberculosis regimens) and missing data for key tuberculosis-related information (eg, tuberculosis site location, type of tuberculosis, or results of smear microscopy for PTB cases).

All programs were located in areas where the annual tuberculosis incidence rate in the general population exceeded 200 cases per 100,000 population.[16] Asymptomatic HIV-infected patients were seen every 6 months during the pre-ART period and every 3 months after the start of ART. As previously described,[8] all patients who presented for a pre-ART or ART consultation with respiratory symptoms for 2 weeks or more were routinely screened with microscopy of 3 sputum smears for acid-fast bacilli. PTB was diagnosed in patients with symptoms or signs suggestive of tuberculosis such as fever, night sweats, weight loss, chest radiographic findings (where available), and/or lack of response to at least one course of antibiotics. Results of sputum microscopy for acid-fast bacilli determined whether the diagnosis was smear positive or negative. Diagnosis of EPTB was based on the presence of clinical signs or symptoms suggestive of systemic and site-specific tuberculosis (eg, lymphadenopathy, meningism) and radiological, biochemistry, or microscopic findings. Culture of *Mycobacterium tuberculosis* was not routinely available in the programs. Patients with CD4 cell count $<200$ cells per microliter and those with clinical HIV stage 4 were eligible for ART.[17] Isoniazid prophylaxis was not provided to patients.

### Data Collection and Definitions

In agreement with health ministries, at each consultation or hospitalization, individual patient data were prospectively collected using standardized forms and entered into the FUCHIA database. Data collected included sex, age, history and diagnosis of tuberculosis, type of tuberculosis episode, dates of appointment and clinical visits, CD4 cell count measurements, and date of ART start. No patient identifiers were kept in the datasets analyzed.

Patients with incident tuberculosis were those who were diagnosed after 15 days of program inclusion (or 15 days after ART start for analysis during the ART period), given the low proportion of patients diagnosed with smear-positive PTB (32.5%) and the time necessary to diagnose smear-negative PTB and EPTB in the programs.[18] Because in immunocompromised patients, tuberculosis treatment is often initiated rapidly after tuberculosis diagnosis but ART start is delayed for several weeks to maximize treatment adherence and until clinical stabilization of the patient is achieved, patients who initiated ART within 2 months of enrollment and started tuberculosis treatment between enrollment and ART initiation were considered prevalent tuberculosis cases in the pre-ART analysis. Patients who were diagnosed with tuberculosis during the pre-ART period and then started ART were included in the ART analysis. Recurrence was defined as a tuberculosis episode diagnosed during follow-up, at least 3 months after tuberculosis treatment completion.

### Study Population

All HIV-infected adults who entered the programs from January 1, 2006, to September 30, 2008, were eligible for inclusion. Those with prevalent tuberculosis at program entry (n = 3354, 8.3%) or with less than 15 days of follow-up (n = 6865, 18.6%) were excluded.

### Statistical Analysis

Patient follow-up was divided into pre-ART (between 15 days after program entry and up to 15 days after ART start) and ART (from 16 days of ART start) periods. For patients started on therapy, we further split time on ART into $<3$, 3–5, 6–11, and $\geq 12$ months. All analyses were performed separately for the pre-ART and ART periods. For each period considered, we right censored follow-up at dates of first diagnosed tuberculosis episode, death, transfer, last visit, or end of the appropriate period. Patients with less than 3 months of follow-up during the pre-ART period were excluded from pre-ART analyses (83.5% of these had started ART and 8% died or were lost to follow-up within this period).

To investigate associations between incident tuberculosis and programmatic and individual-level factors, we used random effects Poisson models, assuming a gamma distribution for the random parameter, which accounted for potential intraprogram variation. Factors considered were type of treatment site (urban or rural), sex, calendar year at ART initiation or program enrollment (2006 and 2007–2008), age (as a continuous variable), prior history of ART use (naive or experienced), body mass index (BMI: $<18.5$, $\geq 18.5$ kg/m$^2$, and missing[19]), nadir CD4 cell count ($<50$, 50–99, 100–199, $\geq 200$ cells/$\mu$L, and missing), time since ART start, and prior tuberculosis history (recorded history of tuberculosis at program entry, patients with tuberculosis relapse, failure or treated after defaulting). Backward stepwise procedure using $P > 0.10$ for variable exclusion and log-likelihood ratio tests for

association ($P < 0.05$) were used. Sensitivity analyses replacing nadir CD4 cell count by initial CD4 cell counts and restricting the analyses to the subset of patients with available CD4 and BMI information were also performed. All analyses were performed using Stata 10 (StataCorp LP, College Station, TX).

## RESULTS

The 8 HIV programs included were located in 6 African countries, 4 in urban sites, and 4 in rural sites (Table 1). Between January 2006 and September 2008, a total of 40,353 adults entered the programs. After excluding 3354 patients who presented with tuberculosis at program entry and 6865 with <15 days of follow-up in the program (including 401 deaths and 1894 lost to follow-up), we analyzed information from 8998 patients with ≥3 months of pre-ART follow-up and 19,325 patients with >15 days of follow-up on ART (Fig. 1). A total of 7754 person-years [median follow-up = 9.0 months; interquartile range (IQR) 6.0–14.3 months] of pre-ART and 18,162 person-years (median follow-up = 10.6 months, IQR 4.4–17.7 months) of ART follow-up were analyzed. At program inclusion, median age was 34 years, 65.9% of patients were women, and 3.0% were ART experienced (Table 2). Fourteen percent were in World Health Organization stage 4, and median CD4 cell count was 196 cells per microliter. At the end of the study follow-up, 2646 patients had died and 1944 were lost to follow-up.

### Tuberculosis Pre-ART

Nine percent (n = 780) of the 8998 patients who were included in the pre-ART analysis were diagnosed with tuberculosis. Tuberculosis incidence was 10.5 per 100 person-years [95% confidence interval (CI): 9.8 to 11.3] but ranged from 4.4 per 100 person-years to 47.0 per 100 person-years (see **Table, Supplemental Digital Content 1,** http://links.lww.com/QAI/A161). It was slightly higher in patients with lower levels of nadir CD4 cell counts (Fig. 2).

Seventy-four percent of tuberculosis episodes diagnosed were pulmonary, ranging from 52.9% to 91.7% across sites. Incidence of PTB was 7.8 per 100 person-years (95% CI: 7.2 to 8.4; see **Figure A, Supplemental Digital Content 4,** http://links.lww.com/QAI/A164) and ranged from 3.2 to 41.8 per 100 person-years (Fig. 3A). Eighty-one percent of patients with PTB (470 of 581) had available bacteriological results, and 155 (33.0%) of them were smear positive. Incidence of smear-positive PTB was 2.0 per 100 person-years (95% CI: 1.7 to 2.4; see **Figure B, Supplemental Digital Content 4,** http//links.lww.com/QAI/A164) and this was similar across sites (Fig. 3C). Incidence of smear-negative PTB was 4.1 per 100 person-years (95% CI: 3.7 to 4.6) and ranged from 1.9 to 31.0 per 100 person-years (Fig. 3D). Seventy-eight percent of patients diagnosed with smear-negative PTB (247 of 315) had radiological findings suggestive of PTB. Overall rate of EPTB was 2.6 per 100 person-years (95% CI: 2.3 to 3.0; see **Table, Supplemental Digital Content 1,** http://links.lww.com/QAI/A161) and varied from 1.2 to 7.8 per 100 person-years across programs (Fig. 3B).

### Tuberculosis During ART

Five percent (n = 933) of the 19,325 patients included in the ART analysis were diagnosed with tuberculosis. Almost half of these were diagnosed within the first 3 months of ART (50.4%) and 91.7% within the first year of therapy. Tuberculosis incidence was 5.4 per 100 person-years (95% CI: 5.0 to 5.7) and ranged from 3.0 to 10.6 per 100 person-years (see **Table, Supplemental Digital Content 2,** http://links.lww.com/QAI/A162). Incidence decreased with increasing levels of nadir CD4 cell counts (Fig. 2). Among the 19 patients who started second-line ART, no tuberculosis episodes were diagnosed after regimen switch [median time of follow-up on second line was 6.9 months (IQR 4.7–12.3)].

Incidence of PTB was 3.7 (95% CI: 3.5 to 4.0) per 100 person-years (see **Figure A, Supplemental Digital Content 4,** http://links.lww.com/QAI/A164). Eighty-two percent of patients with PTB (544 of 660) had available bacteriological results, and 250 (46.0%) of them were smear positive. Rates of smear-positive and smear-negative PTB were 1.4 per 100 person-years (95% CI: 1.2 to 1.6) and 1.6 per 100 person-years (95% CI: 1.5 to 1.8), respectively (see **Figure B, Supplemental Digital Content 4,** http://links.lww.com/QAI/A164), and similar across programs (Figs. 3C, D). Seventy-six percent of patients diagnosed with smear-negative PTB (223 of 294) had radiological findings suggestive of PTB. Overall incidence of EPTB was 1.5 (95% CI: 1.4 to 1.7) and similar across sites (see **Figure A, Supplemental**

**TABLE 1.** Characteristics of ART Sites, Numbers of Patients, and Duration of Follow-up

| | | | | | No. Adults | | Pre-ART Period | | ART Period | |
|---|---|---|---|---|---|---|---|---|---|---|
| Site | Country | Location | Tuberculosis Cases Per 100,000* | Type of Site | Enrolled | ART Started | No. Adults | No. Person-years | No. Adults | No. Person-years |
| 1 | Guinea—Conakry | Conakry | 287 | Urban | 3451 | 2163 | 1011 | 819 | 1974 | 1494 |
| 2 | Guinea—Conakry | Gueckedou | 287 | Urban | 1072 | 681 | 319 | 259 | 637 | 455 |
| 3 | Kenya | Mathare | 353 | Urban | 1077 | 664 | 404 | 356 | 633 | 636 |
| 4 | Malawi | Chiradzulu | 346 | Rural | 10,028 | 6190 | 3827 | 3265 | 5623 | 4534 |
| 5 | Malawi | Thyolo | 346 | Rural | 5033 | 4655 | 275 | 203 | 4378 | 4714 |
| 6 | Mozambique | Alto Mae | 431 | Rural | 3771 | 3426 | 439 | 425 | 3290 | 3604 |
| 7 | Nigeria | Lagos | 311 | Urban | 808 | 713 | 86 | 64 | 691 | 941 |
| 8 | Uganda | Arua | 330 | Rural | 4894 | 2234 | 2637 | 2363 | 2099 | 1783 |
| Total | | | | | 30,134 | 20,726 | 8998 | 7754 | 19,325 | 18,162 |

*2009 World Health Organization Report on Global Tuberculosis Control.

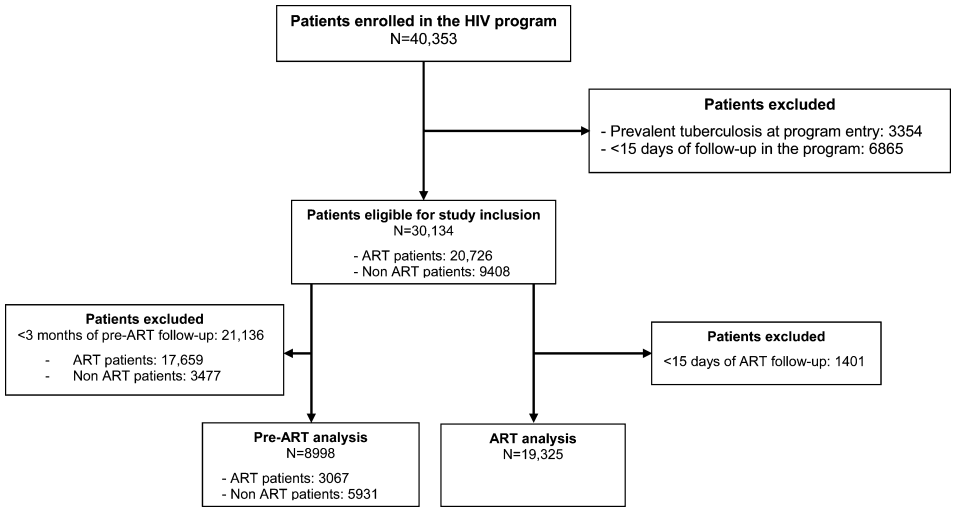


**FIGURE 1.** Study profile. A total of 2646 deaths were recorded: 328 patients (9.8%) with prevalent tuberculosis at program entry, 401 patients (5.8%) with <15 days of follow-up in the program, and 1917 patients (72.4%) eligible for study inclusion (1348 ART patients and 569 non–ART patients). A total of 1944 patients lost to follow-up were recorded: 23 patients (0.7%) with prevalent tuberculosis at program entry, 1894 patients (97.4%) with <15 days of follow-up in the program, and 27 patients (1.4%) eligible for study inclusion (1 ART patient and 26 non–ART patients).

**Digital Content 4,** http://links.lww.com/QAI/A164). Incidence of tuberculosis decreased markedly with time on ART, from 13.0 per 100 person-years (95% CI: 11.9 to 14.2) in the 0 to 3 month period to 1.5 per 100 person-years (95% CI: 1.2 to 1.9) in the ≥12-month period after ART start (see **Table, Supplemental Digital Content 3,** http://links.lww.com/QAI/A163). Both PTB and EPTB incidence decreased after ART initiation, but rates of PTB remained 2-fold to 3-fold higher over time (see **Figure A, Supplemental Digital Content 4**, http://links.lww.com/QAI/A164).

## Factors Associated With Incident Tuberculosis

Incidence of tuberculosis during the ART period was lower in patients treated in rural than in urban sites [adjusted

**TABLE 2.** Patient Characteristics at Enrollment and at ART Initiation, 2006–2008

| | Pre-ART Analysis | | | ART Analysis* | |
|---|---|---|---|---|---|
| | | Excluded (n = 21,136) | | | |
| | Included n = 8998 | Non–ART Patients n = 3477 | ART Patients n = 17,659 | Included n = 19,325 | Excluded n = 1401 |
| Calendar year (%) | | | | | |
| 2006 | 4006 (44.5) | 860 (24.7) | 6735 (38.1) | 6746 (34.9) | 224 (16.0) |
| 2007 | 4552 (50.6) | 1136 (32.7) | 7616 (43.1) | 8943 (46.3) | 295 (21.1) |
| 2008 | 440 (4.9) | 1481 (42.6) | 3308 (18.7) | 3636 (18.8) | 882 (63.0) |
| Sex (%) | | | | | |
| Women | 6557 (72.9) | 2165 (62.3) | 11,133 (63.0) | 12,411 (64.2) | 838 (59.8) |
| Age group (y) | | | | | |
| Median (IQR) | 32.9 (27.0–40.0) | 32.0 (27.0–40.0) | 35.0 (29.0–42.0) | 35.0 (29.1–42.1) | 34.5 (29.1–42.0) |
| Prior history of ART use (%) | | | | | |
| ART experienced | 28 (0.3) | 7 (0.2) | 859 (4.9) | 874 (4.5) | 5 (0.4) |
| Prior history of tuberculosis (%) | | | | | |
| Yes | 221 (2.5) | 132 (3.8) | 931 (5.3) | 1697 (8.8) | 96 (6.9) |
| Clinical stage (%) | n = 8262 | n = 3265 | n = 16,536 | n = 18,427 | n = 1322 |
| 1 or 2 | 5646 (68.3) | 1769 (54.2) | 4970 (30.1) | 5313 (28.8) | 473 (35.8) |
| 3 | 2253 (27.3) | 1135 (34.8) | 8331 (50.4) | 9116 (49.5) | 508 (38.4) |
| 4 | 363 (4.4) | 361 (11.1) | 3235 (19.6) | 3998 (21.7) | 341 (25.8) |
| BMI (%), kg/m$^2$ | n = 8868 | n = 3302 | n = 16,582 | n = 18,293 | n = 1297 |
| <18.5 | 2188 (24.7) | 1206 (36.5) | 6414 (38.7) | 6227 (34.0) | 578 (44.6) |
| ≥18.5 | 6680 (75.3) | 2096 (63.5) | 10,168 (61.3) | 12,066 (66.0) | 719 (55.4) |
| Median (IQR) | 20.3 (18.5–22.3) | 19.5 (17.5–21.6) | 19.4 (17.4–21.5) | 19.7 (17.7–21.8) | 18.9 (16.9–21.0) |
| CD4 cell count (cells/μL) | n = 6937 | n = 2579 | n = 14,503 | n = 15,666 | n = 1118 |
| Median count (IQR) | 398 (286–567) | 331.0 (158.0–505.0) | 132.0 (63.0–203.0) | 142 (70–213) | 132 (58–204) |
| Nadir CD4 cell count (cells/μL) | n = 8553 | n = 2613 | n = 14,463 | n = 17,514 | n = 1170 |
| Median nadir (IQR) | 332 (222–488) | 331.0 (156.0–505.0) | 131.0 (62.0–202.0) | 150 (74–225) | 134 (60–210) |

*Among ART patients only.

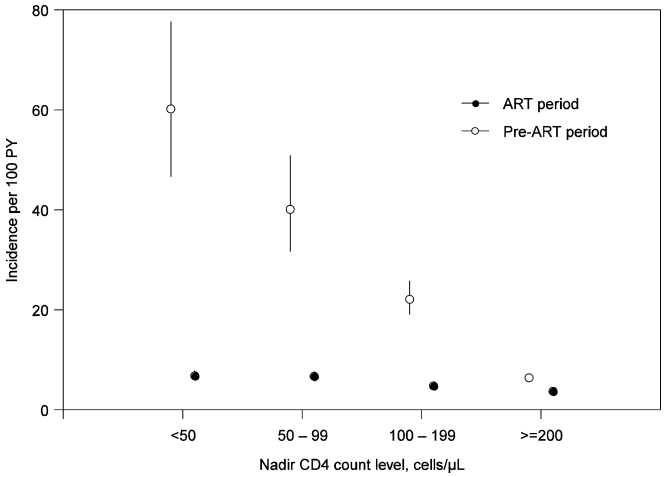


**FIGURE 2.** Incidence of tuberculosis before and after ART initiation by nadir CD4 count level, 2006–2008.

incident rate ratio (aIRR) 0.58, 95% CI: 0.39 to 0.86; Table 3]. Rates were lower in women (aIRR 0.82, 95% CI: 0.71 to 0.94), patients who started therapy in later calendar years (aIRR 0.82, 95% CI: 0.72 to 0.94 for 2007–2008 compared to 2006), and in those with BMI $\geq$18.5 kg/m$^2$ (aIRR 0.51, 95% CI: 0.45 to 0.59).

Individuals with nadir CD4 cell count $>$100 cells per microliter also had lower tuberculosis rates (aIRR 0.84, 95% CI: 0.69 to 1.01 for 100–199; and 0.70, 95% CI: 0.57 to 0.87 for $\geq$200; compared with $<$50 cells/$\mu$L). However, patients with prior history of tuberculosis were more likely to be diagnosed with tuberculosis after ART start (aIRR 1.28, 95% CI: 1.05 to 1.55). Incidence rate ratios of tuberculosis decreased with time on therapy (from 0.48, 95% CI: 0.41 to 0.57, for the 3- to 5-month period, to 0.12, 95% CI: 0.09 to 0.15 for the $\geq$12-month period, compared with the $<$3-month period after ART start). Results of risk factor analysis for incident tuberculosis during the pre-ART period were generally similar to those for the ART period, but the association with calendar year was not statistically significant ($P = 0.63$), and the size of effect was higher for nadir CD4 counts [aIRR 0.44 (95% CI: 0.33 to 0.59) for 100–199 and 0.15 (95% CI: 0.11 to 0.19) for $\geq$200 compared with $<$50 cells/$\mu$L].

Adjusted estimates from sensitivity analyses replacing nadir CD4 by initial CD4 cell counts did not differ except for the smaller magnitude of the estimates observed for initial CD4 count data (data not shown). Results of the risk factor analysis excluding patients with missing CD4 count and BMI data were also similar to those presented here, except for the observed stronger protective effect that having a history of ART use at therapy start had (aIRR 0.46, 95% CI: 0.27 to 0.78) and the lower incidence rate ratio for prior history of tuberculosis (aIRR 1.67, 95% CI: 1.21 to 2.30) during the pre-ART period.

### Tuberculosis Recurrence

Of the 1010 patients diagnosed with tuberculosis during the study period and who remained in care for at least 3 months after completing tuberculosis treatment, 15 (1.5%) had recurrent tuberculosis. Median duration between treatment completion and recurrence was 5.4 months (IQR 4.0–8.1). Overall recurrence rate was 1.7 per 100 person-years (95% CI: 1.0 to 2.8). At 6 months of tuberculosis treatment completion, recurrence rate was 1.7 per 100 person-years (95% CI: 0.8 to 3.4). Median age at time of diagnosis was 37.9 years. Sixty percent were women, and 80.0% were receiving ART at the time of recurrence. For 93.3% of patients, the previous tuberculosis episode was pulmonary and 40.0% of these were smear positive. Sixty-seven percent of recurrences were pulmonary, and 70.0% of these were smear positive.

## DISCUSSION

In these large HIV programs in Africa, we observed high incidences of tuberculosis during the pre-ART and ART periods, 10.5 and 5.4 per 100 person-years, respectively. Incidence of all types of tuberculosis was similar during the pre-ART and initial 3 months of ART use and markedly decreased with time receiving ART. Rates of smear-negative PTB were higher than of smear-positive PTB.

The observed high incidence of tuberculosis during the pre-ART and initial 3 months of ART periods, and higher incidence in patients with lower CD4 count levels, reflects the high prevalence of tuberculosis in Africa[20] and the increased risk of disease in immunocompromised patients. Overall estimates during the ART period correspond closely to those from previous studies in resource-limited countries, with reported rates ranging from 2.4 to 10.5 per 100 person-years.[11,13] However, the rates are approximately 2-fold lower than those reported in a South African community survey where culture, chest radiology, and cytological examinations were performed.[12] As access to these diagnostic tools is often limited in our programs, it is likely that some patients with tuberculosis remain undiagnosed or are diagnosed late. In our cohorts, we observed a decrease in tuberculosis incidence of 88% between the initial 3 months of therapy and the period after the first year of treatment. Some of the patients diagnosed during the first months of ART are likely to represent initially undiagnosed cases of tuberculosis, whereas others may have immune reconstitution inflammatory syndrome.[21–25]

Incidence of both types of tuberculosis declined with duration of ART, but PTB rates remained higher over time (7.8 and 2.6 per 100 person-years for PTB and EPTB in the pre-ART phase and 3.7 and 1.5 per 100 person-years, respectively, in the ART phase). These rates are lower than those reported in other settings,[12,26] which might be related to underdiagnosis in our sites due to passive tuberculosis case detection and diagnostic limitations. The protective effect observed over time on ART is similar to what has been described elsewhere.[12] Approximately 1 of 3 patients diagnosed with PTB in our study had smear-positive tuberculosis, which is the most infectious form of the disease.

We identified several factors associated with incidence of tuberculosis in both the pre-ART and ART periods. Patients attending rural clinics had a 42% lower risk of being diagnosed with tuberculosis. This likely reflects disparities in diagnostic capacity rather than differences in tuberculosis exposure because

**TABLE 3.** Associations Between Site- and Individual-Level Factors and Incident Tuberculosis Before and After ART Initiation, 2006–2008

| | Pre-ART Period | | | | | ART Period | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | IRR | | | | | IRR | |
| | No. Incident Cases | No. Person-years of Follow-up | Incidence Per 100 Person-years (95% CI) | Unadjusted (95% CI) | Adjusted (95% CI) | No. Incident Cases | No. Person-years of Follow-up | Incidence Per 100 Person-years (95% CI) | Unadjusted (95% CI) | Adjusted (95% CI) |
| Type of setting | | | | $P = 0.005$ | $P = 0.004$ | | | | $P = 0.010$ | $P = 0.021$ |
| Urban | 283 | 1358 | 20.8 (18.5 to 23.4) | 1.00 | 1.00 | 275 | 3297 | 8.3 (7.4 to 9.4) | 1.00 | 1.00 |
| Rural | 497 | 6040 | 8.2 (7.5 to 9.0) | 0.39 (0.20 to 0.76) | 0.37 (0.22 to 0.63) | 658 | 14116 | 4.7 (4.3 to 5.0) | 0.60 (0.41 to 0.88) | 0.58 (0.39 to 0.86) |
| Individual factors* | | | | | | | | | | |
| Calendar year | | | | $P = 0.629$ | | | | | $P < 0.001$ | $P = 0.004$ |
| 2006 | 467 | 4159 | 11.2 (10.3 to 12.3) | 1.00 | — | 448 | 9569 | 4.7 (4.3 to 5.1) | 1.00 | 1.00 |
| 2007–2008 | 313 | 3239 | 9.7 (8.6 to 10.8) | 0.96 (0.83 to 1.12) | — | 485 | 7843 | 6.2 (5.7 to 6.8) | 1.27 (1.12 to 1.45) | 0.82 (0.72 to 0.94) |
| Sex | | | | $P < 0.001$ | $P = 0.004$ | | | | $P < 0.001$ | $P = 0.004$ |
| Men | 294 | 1870 | 15.7 (14.0 to 17.6) | 1.00 | 1.00 | 368 | 5932 | 6.2 (5.6 to 6.9) | 1.00 | 1.00 |
| Women | 486 | 5528 | 8.8 (8.0 to 9.6) | 0.62 (0.53 to 0.72) | 0.80 (0.69 to 0.93) | 565 | 11,480 | 4.9 (4.5 to 5.3) | 0.79 (0.69 to 0.90) | 0.82 (0.71 to 0.94) |
| Age (y)† | | | | $P = 0.162$ | | | | | $P = 0.087$ | $P = 0.068$ |
| | — | — | — | 1.01 (1.00 to 1.01) | — | — | — | — | 0.99 (0.99 to 1.00) | 0.99 (0.99 to 1.00) |
| Prior history of ART use | | | | $P = 0.522$ | | | | | $P = 0.001$ | $P = 0.067$ |
| ART naive | 777 | 7379 | 10.5 (9.8 to 11.3) | 1.00 | — | 905 | 16,458 | 5.5 (5.2 to 5.9) | 1.00 | 1.00 |
| ART experienced | 3 | 19 | 15.5 (5.0 to 48.2) | 0.68 (0.21 to 2.20) | — | 28 | 955 | 2.9 (2.0 to 4.2) | 0.53 (0.36 to 0.78) | 0.71 (0.48 to 1.04) |
| Prior tuberculosis history | | | | $P < 0.0001$ | $P < 0.001$ | | | | $P = 0.002$ | $P = 0.018$ |
| No | 722 | 7249 | 10.0 (9.3 to 10.7) | 1.00 | 1.00 | 815 | 15,947 | 5.1 (4.8 to 5.5) | 1.00 | 1.00 |
| Yes | 58 | 149 | 38.9 (30.0 to 50.3) | 3.12 (2.37 to 4.09) | 1.88 (1.42 to 2.47) | 118 | 1465 | 8.1 (6.7 to 9.6) | 1.38 (1.13 to 1.67) | 1.28 (1.05 to 1.55) |
| BMI ($kg/m^2$) | | | | $P < 0.001$ | $P < 0.001$ | | | | $P < 0.001$ | $P < 0.001$ |
| <18.5 | 362 | 1536 | 23.6 (21.3 to 26.1) | 1.00 | 1.00 | 436 | 5260 | 8.3 (7.5 to 9.1) | 1.00 | 1.00 |
| ≥18.5 | 406 | 5777 | 7.0 (6.4 to 7.7) | 0.29 (0.25 to 0.33) | 0.36 (0.31 to 0.42) | 465 | 11,249 | 4.1 (3.8 to 4.5) | 0.47 (0.41 to 0.53) | 0.51 (0.45 to 0.59) |
| Nadir CD4 count (cells/μL) | | | | $P < 0.001$ | $P < 0.001$ | | | | $P < 0.001$ | $P < 0.001$ |
| <50 | 59 | 98 | 60.2 (46.6 to 77.7) | 1.00 | 1.00 | 182 | 2660 | 6.8 (5.9 to 7.9) | 1.00 | 1.00 |
| 50–99 | 68 | 170 | 40.1 (31.6 to 50.9) | 0.68 (0.48 to 0.97) | 0.63 (0.44 to 0.90) | 174 | 2614 | 6.7 (5.7 to 7.7) | 1.00 (0.81 to 1.23) | 1.13 (0.92 to 1.40) |

**TABLE 3.** (*continued*) Associations Between Site- and Individual-Level Factors and Incident Tuberculosis Before and After ART Initiation, 2006–2008

| | Pre-ART Period | | | | | ART Period | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | IRR | | | | | IRR | |
| | No. Incident Cases | No. Person-years of Follow-up | Incidence Per 100 Person-years (95% CI) | Unadjusted (95% CI) | Adjusted (95% CI) | No. Incident Cases | No. Person-years of Follow-up | Incidence Per 100 Person-years (95% CI) | Unadjusted (95% CI) | Adjusted (95% CI) |
| 100–199 | 162 | 732 | 22.1 (19 to 25.8) | 0.41 (0.30 to 0.56) | 0.44 (0.33 to 0.59) | 267 | 5513 | 4.8 (4.3 to 5.5) | 0.70 (0.58 to 0.84) | 0.84 (0.69 to 1.01) |
| ≥200 | 398 | 6180 | 6.4 (5.8 to 7.1) | 0.12 (0.09 to 0.16) | 0.15 (0.11 to 0.19) | 196 | 5361 | 3.7 (3.2 to 4.2) | 0.57 (0.46 to 0.70) | 0.70 (0.57 to 0.87) |
| Time since ART start (mo) | | | | | | | | | $P < 0.001$ | $P < 0.001$ |
| <3 | — | — | — | — | — | 470 | 3619 | 13.0 (11.9 to 14.2) | 1.00 | 1.00 |
| 3–5 | — | — | — | — | — | 215 | 3530 | 6.1 (5.3 to 7.0) | 0.47 (0.40 to 0.55) | 0.48 (0.41 to 0.57) |
| 6–11 | — | — | — | — | — | 171 | 5211 | 3.3 (2.8 to 3.8) | 0.25 (0.21 to 0.30) | 0.26 (0.22 to 0.31) |
| ≥12 | — | — | — | — | — | 77 | 5053 | 1.5 (1.2 to 1.9) | 0.12 (0.09 to 0.15) | 0.12 (0.09 to 0.15) |

*Factors measured at program entry for the pre-ART analysis and at ART start for the ART analysis.
†Age estimates per unit change.
ART, combined antiretroviral therapy; IRR, incidence rate ratio.

rates of smear-positive PTB were similar across sites. Furthermore, women had rates 18% lower than men. This finding is consistent with results from previous studies[8,9,12,16] and could be explained by differences in susceptibility to either infection or reactivation of infection, exposure, reporting of symptoms of disease, or the later presentation of men compared with women in the course of HIV disease. Studies conducted in resource-limited settings have reported that men frequently seek HIV care at a more advanced stage of disease than women.[27,28]

We observed that tuberculosis incidence was 49% lower in patients with normal BMI than in malnourished adults. Poor nutritional status is known to be a risk factor for tuberculosis development,[10,13,29,30] and weight loss is a common consequence of tuberculosis. Tuberculosis incidence was also lower in patients less severely immunosuppressed, and rates of all forms of tuberculosis decreased with time since the start of ART. These findings are consistent with previous research[9,11–13] and highlight the importance of early ART initiation in HIV-infected patients

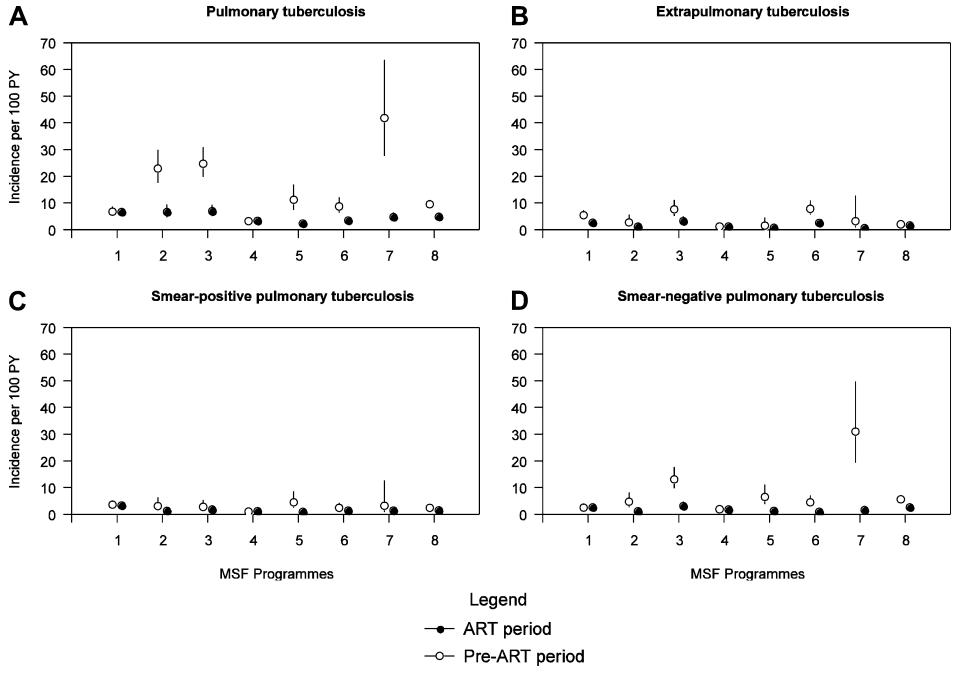


**FIGURE 3.** Incidence of tuberculosis before and after ART initiation by site and type of disease, 2006–2008.

to prevent immune deterioration to levels that increase the risk of tuberculosis and other opportunistic infections.

Patients with prior history of tuberculosis had rates of tuberculosis 28% higher than other patients, and 6-month recurrence rate was 1.7 per 100 person-years. This is consistent with findings from other studies reporting rates 1.46–4.73 higher in patients previously treated for tuberculosis[14,26,31] but differ from those published by Lawn et al[12] who found no evidence of association between recorded history of tuberculosis and incident disease.

The main strengths of our analysis were large sample size, study of various types of tuberculosis during both pre-ART and ART periods, and homogeneity in care provision (including criteria for ART initiation and types of antiretroviral regimens provided) and data collection tools used across programs. Although the quality and success of tuberculosis diagnosis and case finding varied across sites and over time, especially for EPTB and smear-negative PTB, cohort heterogeneity was accounted for in the analysis and calendar year was included as one of the variables in the risk factor analysis. Median duration of follow-up in the programs was relatively short, limiting the time for study of risk factors on late-stage forms of tuberculosis. Despite the number of patients with missing nadir CD4 count and BMI information (5% and 1%, respectively, in the pre-ART analysis and 9% and 5%, respectively, in the ART analysis), sensitivity analyses restricted to the subgroup of patients with available information support the conclusions of the article.

## CONCLUSIONS

Our findings highlight the high burden that tuberculosis represents for HIV programs in Africa and the importance of earlier HIV diagnosis and treatment, and support calls for implementing the 3 I's of tuberculosis control: intensified case finding, isoniazid prophylaxis, and infection control.

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