

Incidence of Tuberculosis During the First Year of Antiretroviral Treatment in West African HIV-Infected Adults

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We estimated tuberculosis incidence during the first year on antiretroviral therapy without isoniazid-preventive treatment in 6938 West African HIV-infected adults at 3.33 cases per 100 person-years (95% CI, 2.85–3.80). In multivariate Poisson models, sites in Côte d'Ivoire, male gender, low body mass index, low hemoglobin, low CD4 count, and young age were significantly associated with higher incidence.

Keywords. antiretroviral treatment; HIV; incidence; tuberculosis; West Africa.

Tuberculosis remains a major cause of morbidity and mortality in people with HIV (PWH), particularly in Sub-Saharan Africa. The World Health Organization (WHO) estimated that of 920 000 PWH who had tuberculosis in 2017, 300 000 died from the disease, including 252 000 (84.0%) in Sub-Saharan Africa [1]. The progressive introduction of antiretroviral therapy (ART) over the last 2 decades has contributed to a decrease in tuberculosis (TB) incidence in PWH, but it remains significantly higher in this population than in the non-HIV-infected population, irrespective of the duration of ART or the level of CD4 lymphocytes [2–4].

Since 2004, the WHO recommends implementing isoniazid preventive treatment (IPT) for prevention of TB in PWH [5, 6]. Despite this recommendation and recent evidence from Côte

d'Ivoire on its effectiveness in reducing overall morbidity and mortality in HIV-infected patients regardless of CD4 count, IPT is rarely implemented for PWH in West Africa [7].

Our hypothesis is that, in the absence of IPT, the incidence of TB remains high among patients on ART, particularly in West Africa. In this study, we analyzed data from the follow-up of patients on ART participating in the International epidemiologic Databases to Evaluate AIDS (IeDEA) collaboration in West Africa to estimate the incidence of TB and look at the risk factors associated with the occurrence of the disease in the first year on ART.

METHODS

We carried out a retrospective cohort analysis enrolling patients initiated on ART in sites from the IeDEA West Africa Cohort, an international epidemiological research collaboration among 16 adult HIV treatment centers in 9 West African countries [8]. Four outpatient HIV clinics with recognized quality for TB data collection contributed to this study: the day care center of the Sourou Sanou University teaching hospital (HDJ/CHUSS) in Bobo Dioulasso, Burkina Faso; the CRFC, Infectious and tropical Disease department, Fann University Teaching Hospital (CRFC/SMITD) in Dakar, Senegal; and the CePreF and CIRBA HIV clinics, both in Abidjan, Côte d'Ivoire.

We included in our analyses all HIV-infected patients aged ≥ 16 years who started ART from 2010 to 2016 and who had ≥ 1 follow-up visit post-ART initiation, excluding those with prevalent TB. Patients were followed up according to usual site procedures. ART was initiated in patients with $CD4 \leq 350$ $CD4/mm^3$ in all sites except in CIRBA, where it was initiated at $CD4 \leq 200$ before 2012 and ≤ 350 $CD4/mm^3$ thereafter. TB diagnosis was done according to the national TB program (NTP) recommendations of each country. Active screening for symptoms suggestive of tuberculosis (fever, cough, night sweats, weight loss) was conducted, per routine, at ART initiation and at each visit only in the CePreF-CI since 2009. No patient received IPT.

Data were abstracted from patient charts by a data clerk. Information collected included sociodemographic characteristics, TB history, ART initiation date, CD4 counts and HIV RNA, new or ongoing TB at the visit, and patient status (death, loss to follow-up, and last visit date). All participating clinical centers obtained authorization from national or local ethics committees for data transfer, exploitation, and statistical analysis.

We defined (i) history of TB as TB reported more than 6 months before ART initiation, (ii) prevalent TB as TB reported between 6 months before and 1 week after ART initiation, and (iii) incident TB as the first TB episode reported after

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Table 1. Patient Characteristics at Initiation of Antiretroviral Therapy

	No. ^a	All Patients (n = 6938)	No Incident TB (n = 6749)	Patients With Incident TB (n = 189)	P Value
		No. (%) or Median (IQR)	No. (%) or Median (IQR)	No. (%) or Median (IQR)	
Center (country)					<.001
CEPREF (Cdl)		2615 (37.7)	2563 (38.0)	52 (27.5)	
CIRBA (Cdl)		1506 (21.7)	1409 (20.9)	97 (51.3)	
HDJ/CHUSS (BF)		2354 (33.9)	2322 (34.4)	32 (16.9)	
CRCF/SMITD (SN)		463 (6.7)	455 (6.7)	8 (4.2)	
ART starting year					.03
≤2012		3930 (56.6)	3808 (56.4)	122 (64.6)	
>2012		3008 (43.4)	2941 (43.6)	67 (35.4)	
Age, y					.38
16–30		1132 (16.3)	1100 (16.4)	32 (16.9)	
30–50		4722 (68.1)	4587 (68.3)	135 (71.4)	
≥50		1053 (15.2)	1031 (15.3)	22 (11.6)	
Age, y	6907	38.5 (32.4–45.7)	38.5 (32.3–45.7)	38.8 (32.8–45.4)	.69
Gender					
Female		4889 (70.5)	4788 (70.9)	101 (53.4)	<.001
Male		2049 (29.5)	1961 (29.1)	88 (46.6)	
BMI, kg/m ²	5773				
≥21		2691 (46.6)	2661 (47.0)	30 (25.6)	<.001
16–21		2638 (45.7)	2573 (45.5)	65 (55.6)	
≤16		444 (7.7)	422 (7.5)	22 (18.8)	
BMI, kg/m ²	5773	20.7 (18.4–23.5)	20.7 (18.4–23.5)	19.1 (16.8–21.1)	<.001
TB history	4148				
Yes		582 (14.0)	561 (13.9)	21 (18.4)	.21
No		3566 (86.0)	3473 (86.1)	93 (81.6)	
CD4, cells/mL	6261				
≥500		559 (8.9)	554 (9.1)	5 (2.9)	<.001
200–500		2776 (44.3)	2728 (44.8)	48 (27.6)	
<200		2926 (46.7)	2805 (46.1)	121 (69.5)	
CD4, cells/mL	6261	214.0 (99.0–323.0)	216.0 (100.0–324.0)	136.0 (48.8–236.8)	<.001
Hemoglobin level, g/dL	5245				
≥11		2473 (47.1)	2420 (47.6)	53 (33.3)	<.001
9–11		1838 (35.0)	1782 (35.0)	56 (35.2)	
<9		934 (17.8)	884 (17.4)	50 (31.4)	
Hemoglobin level, g/dL	5245	10.8 (9.3–12.0)	10.8 (9.4–12.0)	10.0 (8.2–11.4)	<.001
Serum creatinine, μmol/L	2949	65.0 (10.1–81.0)	65.0 (10.6–81.3)	9.15 (6.5–58.0)	<.001

Abbreviations: ART, antiretroviral treatment; BF, Burkina Faso; BMI, body mass index; CePreF, Centre de Prise en charge de Recherche et de Formation, Abidjan, Côte d'Ivoire; Cdl, Côte d'Ivoire; CIRBA, Centre Intégré de Recherches Biocliniques d'Abidjan, Abidjan, Côte d'Ivoire; CHUSS, Hôpital du Jour du Centre Hospitalier Universitaire Sourou Sanou, Bobo Dioulasso, Burkina Faso; CRCF/SMITD, Centre Régional de Recherche et de Formation à la Prise en Charge Clinique, Service des Maladies Infectieuses et Tropicales du Centre Hospitalier National Universitaire de Fann, Dakar, Senegal; SN, Senegal; TB, tuberculosis.

1 week following ART initiation and during the first year of follow-up. We considered the risk period to be the time between ART initiation and the date of incident TB, death, last follow-up visit, or 1 year after ART initiation, whichever occurred first.

We calculated crude TB incidence rates and their confidence intervals for the overall cohort and each site. We used univariate Poisson models with an offset term to estimate TB incidence rates according to different factors (center, sex, age, body mass index [BMI], previous TB history, year of ART initiation, CD4 count, and hemoglobin level) and corresponding relative risks (RRs). Using a multivariate Poisson model including factors significantly associated with TB incidence at a threshold of .05 in univariate analyses and age that was forced in the model, we

estimated the standardized TB incidence rate in the lowest-risk group. We used the missing indicator variable (MIV) method for other observations with missing values on BMI, CD4 cell count, TB history, and Hb level. We performed analyses using R Studio, version 1.1.456 (R Development Core Team, Vienna, Austria). All *P* values were 2-sided and were considered statistically significant if <.05.

RESULTS

Of 7216 patients who initiated ART and had ≥1 follow-up visit, 275 (3.8%) had prevalent TB at ART initiation, and 6938 were included in the analysis (Supplementary Figure 1). Of those,

Table 2. Univariate and Multivariate Analyses of TB Incidence and Risk Factors During the First Year on ART; leDEA Cohort, West Africa (2010–2016)

	Cases	PY	Univariate Analysis			Multivariate Analysis ^a		
			Incidence Cases/ 100 PY (95% CI)	Crude RR (95% CI)	PValue	Standardized Incidence Cases/ 100 PY (95% CI)	Adjusted RR (95% CI)	PValue
Center								
HDJ/CHUSS (BF)	32	2064.7	1.55 (1.07–2.15)	1	<.001	0.14 (0.03–0.47)	1	<.001
CRCF/SMITD (SN)	8	379.9	2.11 (0.63–6.03)	1.35 (0.58–2.80)		0.15 (0.01–1.75)	1.12 (0.18–3.75)	
CePReF (Cdl)	52	2000.3	2.60 (1.17–5.66)	1.68 (1.09–2.63)		0.39 (0.05–2.21)	2.84 (1.71–4.73)	
CIRBA (Cdl)	97	1233.0	7.87 (3.70–16.52)	5.08 (3.45–7.68)		0.57 (0.08–3.24)	4.16 (2.50–6.93)	
Gender								
Female	101	4066.9	2.48 (2.03–3.00)	1	<.001	0.14 (0.03–0.47)	1	<.001
Male	88	1611.0	5.46 (3.35–8.78)	2.20 (1.65–2.93)		0.28 (0.04–1.49)	2.06 (1.32–3.18)	
Age, y								
≥50	22	842.0	2.61 (1.67–3.86)	1	.43	0.14 (0.03–0.47)	1	.01
30–50	135	3880.9	3.48 (1.45–8.29)	1.33 (0.87–2.15)		0.33 (0.04–2.66)	2.36 (1.16–5.69)	
16–30	32	927.0	3.45 (1.29–8.89)	1.32 (0.77–2.30)		0.56 (0.06–4.90)	4.06 (1.78–10.49)	
BMI, kg/m²								
≥21	30	2317.4	1.29 (0.88–1.81)	1	<.001	0.14 (0.03–0.47)	1	<.001
16–21	65	2167.3	3.00 (1.34–6.56)	2.32 (1.52–3.62)		0.27 (0.04–1.57)	1.99 (1.21–3.36)	
≤16	22	307.7	7.16 (2.79–17.33)	5.53 (3.16–9.55)		0.66 (0.08–4.28)	4.77 (2.47–9.17)	
TB history								
No	93	2778.7	3.35 (2.71–4.07)	1	.21			
Yes	21	458.4	4.58 (2.25–8.76)	1.37 (0.83–2.15)				
ART starting year								
>2012	67	2268.1	2.95 (2.30–3.72)	1	.20			
≤2012	122	3409.9	3.58 (2.08–6.10)	1.21 (0.90–1.64)				
CD4, cells/mL								
≥500	5	437.6	1.14 (0.41–2.46)	1	<.001	0.14 (0.03–0.47)	1	.02
200–500	48	2368.6	2.03 (0.32–12.55)	1.77 (0.78–5.11)		0.15 (0.01–1.74)	1.09 (0.42–3.72)	
<200	121	2320.5	5.21 (0.85–31.67)	4.56 (2.07–12.90)		0.25 (0.02–2.80)	1.79 (0.71–6.00)	
Hemoglobin level, g/dL								
≥11	53	2041.8	2.60 (1.96–3.36)	1	<.001	0.14 (0.03–0.47)	1	.002
9–11	56	1465.3	3.82 (1.98–7.21)	1.47 (1.01–2.15)		0.17 (0.02–0.95)	1.21 (0.72–2.03)	
<9	50	681.0	7.34 (3.76–13.99)	2.83 (1.92–4.16)		0.34 (0.05–1.98)	2.47 (1.44–4.23)	

Abbreviations: ART, antiretroviral treatment; BF, Burkina Faso; BMI, body mass index; CePReF, Centre de Prise en charge de Recherche et de Formation, Abidjan, Côte d'Ivoire; Cdl, Côte d'Ivoire; CIRBA, Centre Intégré de Recherches Biocliniques d'Abidjan, Abidjan, Côte d'Ivoire; CHUSS, Hôpital du Jour du Centre Hospitalier Universitaire Sourou Sanou, Bobo Dioulasso, Burkina Faso; CRCF/SMITD, Centre Régional de Recherche et de Formation à la Prise en Charge Clinique, Service des Maladies Infectieuses et Tropicales du Centre Hospitalier National Universitaire de Fann, Dakar, Senegal; PY, person-years; RR, relative risk; SN, Senegal; TB, tuberculosis.

^an = 4249 (2689 observations deleted due to missing data).

4889 (70.5%) were women, their median age (interquartile range [IQR]) was 38.5 (32.4–45.7) years, the median BMI was 20.7 (18.4–23.5) kg/m², the median CD4 count was 214 (99.0–323.0) cells/mL, and 582 (14.0%) patients had a TB history reported (Table 1).

Patients were followed up for a median risk period (IQR) of 1.00 (0.73–1.00) years, with 5679.31 person-years of risk period accrued during the study. A total of 189 TB cases were reported, for an overall incidence rate of 3.33 cases per 100 person-years (95% CI, 2.85–3.80) (Supplementary Table 1). The median time from ART initiation to incident TB (IQR) was 2.84 (0.92–5.55) months.

The crude TB incidence rate differed significantly between sites, with 7.87 (95% CI, 3.70–16.52), 2.60 (95% CI, 1.17–5.66),

2.11 (95% CI, 0.63–6.03), and 1.55 (95% CI, 1.07–2.15) cases per 100 person-years in CIRBA (Abidjan), CePReF (Abidjan), CRCF/SMT (Dakar), and HDJ/CHUSS (Bobo Dioulasso), respectively ($P < .001$).

The standardized TB incidence rate in the first year on ART in the lowest-risk group, that is, females aged ≥50 years followed at the HDJ/CHUSS (Bobo Dioulasso) with BMI ≥21 kg/m², CD4 count ≥500 cells/mL, and hemoglobin ≥11g/dL, was 0.14 (95% CI, 0.03–0.47) cases per 100 person-years. In multivariate analysis, TB incidence remained significantly higher in sites in Côte d'Ivoire, in male patients, in patients with low CD4 count, in those with low BMI, in those with a low hemoglobin count, and in the youngest patients (Table 2).

DISCUSSION

TB incidence during the first year on ART was high in 4 West African outpatient HIV clinics not yet implementing IPT at the time of the study. The incidence rate, roughly 3300 cases per 100 000 population, was 10 to 20 times higher than the estimated TB incidence in the general population of the 3 countries.

This is not surprising in the absence of IPT. A high TB incidence has been reported in the first weeks following ART introduction, due either to TB unmasking Immune Reconstitution Inflammatory Syndrome (IRIS) in patients with low CD4 or ART-associated TB during the first months of ART [9]. An early observational study conducted in Brazil showed the superiority of combined ART and IPT compared with ART or IPT alone to reduce TB incidence in PWH [10]. In addition, several observational studies conducted in Africa and a cluster randomized trial conducted in Brazil have shown that using IPT in ART-treated adults in high-incidence settings significantly reduces TB incidence [11–15]. IPT was not implemented in any of the health facilities included in our analysis during the study period. In Côte d'Ivoire and Burkina Faso, IPT was not yet recommended by the national TB and HIV programs. In Senegal, although recommended since 2015, IPT was not available at the CRCF/SMITD.

In our study, TB incidence was significantly higher in Côte d'Ivoire than in Senegal and Burkina Faso. This could be partly explained by the epidemiology of TB in those countries. Indeed, TB incidence in the general population was estimated to 159, 139, and 52 cases per 100 000 in 2015 in Côte d'Ivoire, Senegal, and Burkina Faso, respectively [1]. Site characteristics may also explain this difference; in Côte d'Ivoire, the crude TB incidence rate was significantly higher in CIRBA than in CePREF, possibly because first ART was initiated earlier in CePREF during the whole study duration, compared with CIRBA, where ART was initiated ≤ 350 cells/mm³ in 2012, and second, CePREF implemented systematic active TB screening starting in 2009. As reported previously, a previous TB history, low CD4 count, young age, and male gender were associated with higher TB incidence [16–19], as were anemia and low BMI. These risk factors should be taken into account for a particularly exhaustive screening and TB diagnostic process when initiating ART.

Our study has limitations. First, we may have underestimated TB incidence due to the lack of standardized procedures for TB diagnosis and missed TB in those patients who died or those who were lost to follow-up, further contributing to underestimation of TB incidence. Second, we chose to define incident TB as occurring after the first week on ART, and this time cutoff may not always be appropriate to distinguish between undiagnosed prevalent TB and incident TB including unmasking IRIS. Third, we were unable to consider other key co-factors explaining TB incidence such as tuberculin skin test, BCG immunization, or socio-economic status, which were not collected [20–22].

Even if it is well established that ART is associated with a considerable reduction in the risk of TB in PWH, the results from our study emphasize again the need for TB-preventive therapy in PWH initiating ART even in countries with TB incidence below 100 cases per 100 000 population, such as Burkina Faso. The countries participating in this study have now started implementing pilot or large-scale programs to provide IPT to PWH starting ART, but access to tuberculosis-preventive therapy remains limited in West Africa. Expanding access to tuberculosis-preventive therapy should be a priority to reduce tuberculosis incidence and mortality in PWH in West African countries.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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