Tuberculosis after Initiation of Antiretroviral Therapy in Low-Income and High-Income Countries

The Antiretroviral Therapy in Low-Income Countries Collaboration of the International epidemiological Databases to Evaluate AIDS (IeDEA) and The ART Cohort Collaboration[a]

We examined the incidence of and risk factors for tuberculosis during the first year of highly active antiretroviral therapy in low-income (4540 patients) and high-income (22,217 patients) countries. Although incidence was much higher in low-income countries, the reduction in the incidence of tuberculosis associated with highly active antiretroviral therapy was similar: the rate ratio for months 7–12 versus months 1–3 was 0.48 (95% confidence interval, 0.36–0.64) in low-income countries and 0.36 (95% confidence interval, 0.26–0.50) in high-income countries. A low CD4 cell count at the start of therapy was the most important risk factor in both settings.

In industrialized countries, HAART has substantially improved the prognosis of HIV-infected patients. In resource-constrained settings, where 90% of people with HIV infection or AIDS live, access to HAART has improved in recent years: ~1.65 million people living with HIV infection or AIDS were receiving treatment in low- and middle-income countries in June 2006, representing ~24% of the estimated 6.8 million people in urgent need of antiretroviral treatment [1].

The responses to HAART appear to be similar in low-income and high-income settings [2], although the mortality rate is higher in resource-limited settings, particularly in the first months after the commencement of HAART [3]. Tuberculosis (TB) is the most common HIV-associated illness in resource-poor settings; it is often diagnosed in patients who commence HAART, and it is associated with immune reconstitution disease [4]. We examined the incidence of new TB events during the first year of HAART in resource-limited and industrialized settings, and we identified risk factors associated with new TB events.

Methods. The Antiretroviral Therapy in Low-Income Countries (ART-LINC) Collaboration is a network of antiretroviral treatment programs in Africa, Latin America, and Asia [3, 5]. Data from the ART-LINC Collaboration were compared with those from the ART Cohort Collaboration (ART-CC), a collaboration of cohort studies of HIV-infected patients in Europe and North America [6]. We included 15 ART-LINC programs (Botswana [Gaborone], Brazil [Porto Alegre and Rio de Janeiro], Ivory Coast [Abidjan], India [Chennai], Kenya [Eldoret], Nigeria [Lagos], Malawi [Lilongwe], Morocco [Casablanca], Senegal [Dakar], South Africa [Cape Town, Khayelitsha, and Soweto], Thailand [Bangkok], and Uganda [Kampala]) and 11 ART-CC cohorts (Canada [British Columbia HAART Observational Medical Evaluation and Research and South Alberta Clinic Cohort], France [Aquitaine Cohort and French Hospital Database on HIV], Germany [Cologne/Bonn Cohort and Frankfurt HIV Cohort], Italy [Italian Cohort of Antiretroviral-Naive Patients], The Netherlands [AIDS Therapy Evaluation Project Netherlands], United Kingdom [Royal Free Hospital Cohort], United States [Collaborations in HIV Outcomes Research US], and Switzerland [Swiss HIV Cohort Study]). Patients who had not previously received antiretroviral therapy, who were aged ⩾16 years, who had a known date of commencement of HAART, and who had a documented baseline CD4 cell count were eligible. HAART was defined as any antiretroviral combination therapy that included ⩾3 drugs.

Programs in lower-income countries routinely screened patients for TB before they commenced HAART, and 14 programs (93%) performed microscopic evaluation of sputum specimens in addition to clinical examination. All sites had access to chest radiography, and 13 sites (87%) had access to culture. The end point was new pulmonary or extrapulmonary TB after HAART initiation, defined as a diagnosis of a TB episode at least 6 months after the last TB episode [7]. Time was measured from the start of HAART and ended at whichever of the following events occurred first: new TB event or death, last follow-up visit, or month 12 after the commencement of HAART. Incidence rates were calculated for the first year of HAART and for months 1–3, 4–6, and 7–12. We used random-effects Weibull regression models to estimate hazard ratios, accounting for heterogeneity between treatment programs. The following variables were considered: age, sex, baseline CD4 cell count, and treatment regimen. Clinical stage was unavailable for 47%

Received 13 April 2007; accepted 21 July 2007; electronically published 22 October 2007.
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Clinical Infectious Diseases 2007; 45:1518–21

1058-4838/2007/4511-0020$15.00
DOI: 10.1086/522986

of patients from low-income settings and was not considered. Similarly, the (predominantly heterosexual) route of transmission was not recorded low-income settings. We used Poisson regression (with robust SEs) to compare the incidence of new TB events in low-income and high-income countries. Analyses were performed using Stata software, version 9.2 (Stata). Results are presented as incidences (per 100 person-years), hazard ratios, and incidence rate ratios with 95% CIs.

Results. There were 4540 eligible patients from resource-limited settings. The median year of commencement of HAART was 2002, the median age of patients was 36 years, and 3301 patients (51%) were women. Treatment was started at a median CD4 cell count of 107 cells/μL. Most patients (3125 [69%]) started with a 3-drug regimen that included a nonnucleoside reverse-transcriptase inhibitor. There were 22,217 patients from 12 cohorts from Europe and North America. For these patients, the median year of commencement of HAART was 1999, and the median age was 36 years; 5486 patients (25%) were women. The median CD4 cell count at baseline was 234 cells/μL.

In the first year of HAART, 258 new TB events were diagnosed during 3468 person-years of follow-up in low-income settings, and 205 events were diagnosed during 20,416 person-years of follow-up in industrialized settings. Incidence rates in the first year on HAART were 7.4 cases per 100 person-years (95% CI, 6.6–8.4 cases per 100 person-years) and 1.0 case per 100 person-years (95% CI, 0.88–1.2 cases per 100 person-years), respectively. Rates in months 1–3, 4–6, and 7–12 were 10.7 cases per 100 person-years (95% CI, 8.9–12.9 cases per 100 person-years), 7.5 (95% CI, 5.9–9.5 cases per 100 person-years), and 5.2 cases per 100 person-years (95% CI, 4.1–6.4 cases per 100 person-years), respectively, in low-income settings. There were 1.7 cases per 100 person-years (95% CI, 1.4–2.1 cases per 100 person-years), 1.0 case per 100 person-years (95% CI, 0.76–1.3 cases per 100 person-years), and 0.62 cases per 100 person-years (95% CI, 0.48–0.80 cases per 100 person-years), respectively, in high-income settings. As shown in figure 1, relative decreases in the incidence during the first year of HAART were similar: the rate ratio for months 7–12 versus months 1–3 was 0.48 (95% CI, 0.36–0.64) in low-income countries and 0.36 (95% CI, 0.26–0.50) in high-income countries ($P = .21$ for difference).

Median baseline CD4 cell counts in patients who developed TB and in those who did not develop TB were 75 cells/μL (interquartile range, 27–148 cells/μL) and 110 cells/μL (interquartile range, 37–212 cells/μL), respectively, in low-income settings. Corresponding figures in high-income countries were 80 cells/μL (interquartile range, 33–211 cells/μL) and 235 cells/μL (interquartile range, 100–380 cells/μL), respectively. The risk of a new TB event increased substantially in patients with low CD4 cell counts at baseline, both in low-income settings and high-income settings (table 1). The hazard ratios for patients

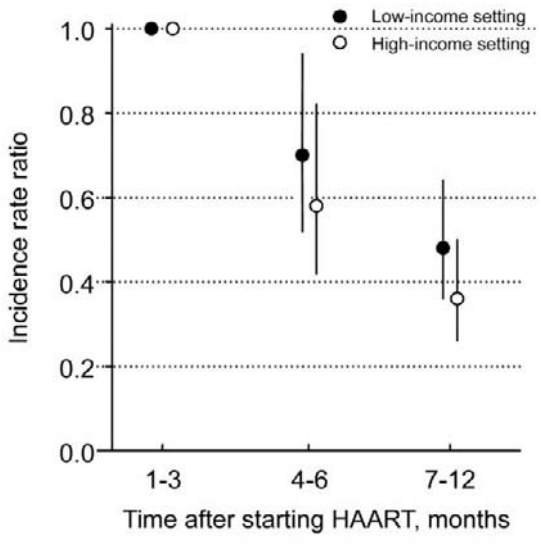

Figure 1. Incidence rate ratios of new tuberculosis events during the first year of HAART in low-income and high-income settings.

with a CD4 cell count of <100 cells/μL, compared with those who had a count $\geq$100 cells/μL, were 1.82 (95% CI, 1.40–2.36) and 3.47 (95% CI, 2.62–4.60), respectively. Younger age and male sex were associated with TB in low-income settings, whereas heterosexual transmission or a history of injection drug use were risk factors in high-income countries.

Discussion. We analyzed the incidence of and risk factors associated with new TB events during the first year of HAART in resource-limited and industrialized settings. The incidence was much higher in low-income countries, reflecting the high ongoing risk for TB infection and reinfection. The relative reduction observed during the first year of HAART was, however, comparable, and advanced immunodeficiency was the most important risk factor in both settings.

Our study has several limitations. As detailed elsewhere [3, 5], a substantial number of patients from low-income settings had to be excluded because of missing data, and the findings from low-income settings may therefore be less generalizable than those from Europe and North America. Incomplete ascertainment of TB events may also have been a problem in low-income settings, particularly during the first months of HAART. The mortality rate was considerably higher in low-income countries during these months, but information on causes of death is not available [5]. Also, incidence rates are a weighted average of site-specific rates and will have been affected by variation in background rates, as well as by differences in diagnostic procedures. Therefore, we focused on relative changes in TB rates. This comparative study was restricted to the first year of HAART. A previous analysis performed by the ART-CC [8] found that the incidence continued to decrease, although at 3 years, it was still considerably higher than in the

Table 1. Risk factors for tuberculosis diagnosed in the first year after commencement of HAART.

	Patients from low-income settings (n = 4540)		Patients from high-income settings (n = 22,217)	
Variable	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Baseline CD4 cells count		<.001		<.001
<25 cells/μL	1.0		1.0	
25–49 cells/μL	0.89 (0.58–1.35)		1.63 (1.04–2.56)	
50–99 cells/μL	1.09 (0.76–1.55)		0.95 (0.60–1.50)	
100–199 cells/μL	0.60 (0.42–0.87)		0.49 (0.31–0.78)	
200–350 cells/μL	0.68 (0.44–1.06)		0.39 (0.25–0.62)	
>350 cells/μL	0.21 (0.09–0.46)		0.15 (0.08–0.27)	
Age		.003		.53
<30 years	1.0		1.0	
30–39 years	0.97 (0.70–1.35)		1.37 (0.88–2.12)	
40–49 years	0.93 (0.63–1.36)		1.36 (0.84–2.20)	
⩾50 years	0.34 (0.17–0.68)		1.32 (0.76–2.30)	
Sex		<.001		.68
Male	1.0		1.0	
Female	0.63 (0.49–0.82)		0.93 (0.66–1.31)	
First-line antiretroviral regimen		.35		.16
1 NNRTI plus 2 NRTIs	1.0		1.0	
1 PI plus 2 NRTIs	0.88 (0.48–1.59)		1.03 (0.73–1.47)	
Other or unknown	1.42 (0.84–2.40)		0.67 (0.39–1.14)	
Transmission group				.004
Heterosexual	NA		1.0	
Injection drug user	…		0.85 (0.56–1.28)	
Man who has sex with men	…		0.54 (0.37–0.77)	
Other	…		0.55 (0.32–0.95)	

NOTE. Hazard ratios are mutually adjusted (multivariable analysis). NA, not assessed (predominantly heterosexual transmission); NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor (including boosted PI regimens).

general population, probably reflecting the persistence of deficits in immune function [9].

In contrast to the previous ART-CC analysis [8], we included all patients, independent of whether they had received a diagnosis of AIDS at the time that they started HAART. Unfortunately, the ART-CC database does not, at present, include information on the specific AIDS-defining events that individuals had experienced before starting HAART, and this was also not consistently recorded in low-income settings. Similar to other studies from lower-income countries, male sex and younger age were associated with higher risk of TB [10, 11]. The higher rates of TB among patients who acquired HIV infection via heterosexual sex in high-income settings are probably a consequence of the relatively large number of immigrants from areas where TB is endemic [12].

TB is a common cause of death among HIV-infected adults in low-income settings who are not receiving antiretroviral therapy, but it is diagnosed before death in only approximately one-half of those with autopsy-proven disease [13]. Additional studies are needed to examine the contribution of TB to the high initial mortality rate among patients who are starting HAART in low-income countries. Studies with longer follow-up periods will help clarify the long-term effect of HAART on the incidence of TB and of the potential for HAART to contribute to TB control in low-income countries. Our results support the use of relative TB incidence rates in models of TB control. Finally, the decrease in the risk of TB with increasing CD4 cell count at baseline underscores the need for earlier diagnosis and treatment of HIV infection in both settings, but particularly in low-income countries.

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Steering committees and collaborating centers. The ART-LINC Steering Committee and list of collaborators is available at the ART-LINC Web site (http://www.art-linc.org), and the Steering Committee and a list of ART-CC collaborators is available at the ART-CC Web site (http://www.art-cohort-collaboration.org).

Acknowledgments

Financial support. The ART-LINC Collaboration is funded by the US National Institutes of Health (Office of AIDS Research) and the French Agence Nationale de Recherches sur le Sida (ANRS). The ART Cohort Collaboration is funded by the UK Medical Research Council.

Potential conflicts of interest. M.M. has received travel grants from GlaxoSmithKline. P.R. has received research funding from Boehringer-Ingelheim and Merck and has received honoraria for speaking engagements or advisory board participation from Gilead Sciences, Boehringer-Ingelheim, Roche, Tibotec, GlaxoSmithKline, and Theratechnologies. J.M.M. has received recent research funding or honoraria as speaker/consultant from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Chiron, Cubist, Merck, Novartis, GlaxoSmithKline, Gilead Sciences, Oxford Immunotec, Pfizer, Roche, and Theravance. A.M. has received a consultancy honorarium from Bristol-Myers Squibb. All other authors: no conflicts.

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