Tuberculosis after initiation of antiretroviral therapy in low-income and high-income countries.

Martin Brinkhof, Matthias Egger, Andrew Boulle, Margaret May, Mina Hosseinipour, Eduardo Sprinz, Paula Braitstein, Francois Dabis, Peter Reiss, David Bangsberg, et al.

Brief report

Tuberculosis following initiation of antiretroviral therapy in low-income and high-income countries

Running title: Tuberculosis on antiretroviral therapy

The ART-LINC Collaboration of the International epidemiological Databases to Evaluate AIDS (IeDEA) and the ART Cohort Collaboration*

*Writing committee listed at end of report

Correspondence to:
Martin Brinkhof PhD
Department of Social & Preventive Medicine
University of Berne
Finkenhubelweg 11
CH-3012 Bern
Switzerland
brinkhof@ispm.unibe.ch
Phone +41 31 631 35 55
Fax +41 31 631 35 20

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Abstract

We examined tuberculosis incidence and risk factors during the first year of highly active antiretroviral therapy (HAART) in low-income (4,540 patients) and high-income countries (22,217 patients). Although incidence was much higher in low-income countries, the reduction with HAART was similar: the rate ratio (95% confidence interval) comparing months 7-12 with 1-3 was 0.48 (0.36 to 0.64) in low-income and 0.36 (0.26 to 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.

Introduction

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

The responses to HAART appear similar in low-income and high-income settings,[2] but mortality is higher in resource-limited settings, particularly in the first months after starting HAART.[3] Tuberculosis (TB) is the most frequent HIV-associated illness in resource-poor settings, often diagnosed in patients starting HAART, and 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 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 ART-LINC 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 from Botswana (Gaborone), Brazil (Porto Alegre, Rio de Janeiro), Côte d'Ivoire (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 12 ART-CC cohorts from Canada (British Columbia HAART Observational Medical Evaluation and Research, South Alberta Clinic Cohort), France (Aquitaine Cohort, French Hospital Database on HIV), Germany (Cologne/Bonn Cohort, 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 of America (Collaborations in HIV Outcomes Research US), and Switzerland (Swiss HIV Cohort Study). Patients who had not previously received antiretroviral therapy, were aged 16 years or older, with known date of starting HAART and a documented baseline CD4 count were eligible. HAART was defined as any antiretroviral combination therapy including 3 or more drugs.

Programs in lower income countries routinely screened patients for TB before starting HAART, and 14 (93%) used sputum microscopy in addition to clinical examination. All sites had access to chest X-ray and 13 (87%) had access to culture. The endpoint was new pulmonary or extra-pulmonary TB after HAART initiation, defined as a diagnosis at least 6 months after the last TB episode.[7] Time was measured from the start of HAART and ended at the earliest of: the date of a new TB event or death; the date of the last follow-up visit; or month 12 after starting HAART. Incidence rates were calculated for the first year on 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

in 47% of patients from low-income settings and not considered. Similarly, the (predominantly heterosexual) route of transmission was not recorded low-income settings. We used Poisson regression (with robust standard errors) to compare the incidence of new TB events in low-income and high-income countries. Analyses were done in Stata (version 9.2, College Station, TX, USA). Results are presented as incidence rates (per 100 person-years), hazard ratios and incidence rate ratios with 95% confidence intervals (95% CI).

Results

There were 4,540 eligible patients from resource-limited settings. The median year of starting HAART was 2002, the median age was 36 years and 3,301 (51%) patients were women. Treatment was started at a median CD4 cell count of 107 cells/μL. Most patients (3,125; 69%) started with a three-drug regimen including a non-nucleoside reverse transcriptase inhibitor (NNRTI). There were 22,217 patients from 12 cohorts from Europe and North America. The median year of starting HAART was 1999, median age was 36 years and 5,486 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 3,468 person-years of follow-up in low-income settings and 205 events during 20,416 person-years in industrialized settings. Incidence rates in the first year on HAART were 7.4 (95% CI 6.6 to 8.4) and 1.0 (0.88 to 1.2) per 100 person-years, respectively. Rates in months 1-3, 4-6 and 7-12 were 10.7 (8.9 to 12.9), 7.5 (5.9 to 9.5), and 5.2 (4.1 to 6.4) per 100 person-years in low-income settings and 1.7 (1.4 to 2.1), 1.0 (0.76 to 1.3), and 0.62 (0.48 to 0.80) in high-income settings. As shown in Figure 1, declines during the first year of HAART were similar: the rate ratio (95% CI) comparing months 7-12 with 1-3 was 0.48 (0.36 to 0.64) in low-income and 0.36 (0.26 to 0.50) in high-income countries (p=0.21 for difference).

Median (interquartile range) baseline CD4 counts in patients developing and not developing TB were 75 (27-148) and 110 (37-212) cells/μL in low-income settings. Corresponding figures in high-income countries were 80 (33-211) and 235 (100-380) cells/μL. The risk of a new TB event was increased substantially in patients with low

CD4 counts at baseline, both in low-income and high-income settings (Table 1). The hazard ratio for patients with a CD4 count of less than 100 cells/μL as compared to those with a count of 100 cells/μL or more was 1.82 (95% CI 1.40 to 2.36) and 3.47 (2.62 to 4.60), respectively. Younger age and male sex were associated with TB in low-income settings, whereas heterosexual transmission or a history of intravenous drug use were risk factors in high-income countries.

Discussion

We analyzed the incidence 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 re-infection. 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 in the first months of HAART. Mortality is 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 differences in diagnostic procedures. We therefore focused on relative changes in TB rates. This comparative study was restricted to the first year of HAART. A previous analysis of the ART Cohort Collaboration (ART-CC)[8] showed that the incidence continued to decline, although at 3 years it was still considerably higher than in the 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, independently of whether they had an AIDS diagnosis at the time of starting 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 in lower-income countries male sex and younger age were associated with higher risk of TB.[10;11] The higher rates among heterosexually infected patients in high-income settings are probably a consequence of the relatively large number of immigrants from areas endemic for TB.[12]

Tuberculosis is a common cause of death in HIV-positive adults not receiving antiretroviral therapy in low-income settings, but it is diagnosed prior to death in only about half of those with autopsy-proven disease.[13] Further studies are needed to examine the contribution of TB to the high initial mortality among patients starting HAART in low-income countries. Studies with longer follow up will help clarify the long-term effect of HAART on TB incidence, and the potential of 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 decline in the risk of TB with increasing CD4 cell count at baseline underscores the need for earlier diagnosis and treatment of HIV in both settings, but particularly in low-income countries.

Writing committee

Martin W.G. Brinkhof, Matthias Egger, Andrew Boulle, Margaret May, Mina Hosseinipour, Eduardo Sprinz, Paula Braitstein, Francois Dabis, Peter Reiss, David R. Bangsberg, Martin Rickenbach, Jose M. Meda, Landon Myer, Amanda Mocroft, Denis Nash, Olivia Keiser, Margaret Pascoe, Stefaan van der Borght, Mauro Schechter.

Steering committes and collaborating centers

See www.art-linc.org for the ART-LINC Steering Committee and list of collaborators and www.art-cohort-collaboration.org for the Steering Committee and a list of ART-CC collaborators.

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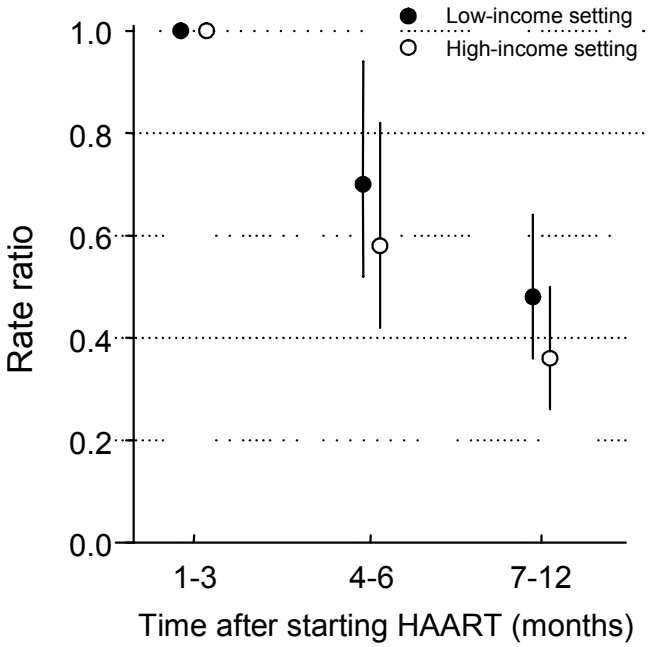
Table 1. Risk factors for tuberculosis diagnosed in the first year after starting highly active antiretroviral therapy. Hazard ratios are mutually adjusted (multivariable analysis).

	Low-income settings (N=4540)		High-income settings (N=22217)	
Variable	**Hazard ratio (95% CI)**	**P**	**Hazard ratio (95% CI)**	**P**
Baseline CD4 count (cells/µL)		<0.0001		<0.0001
<25	1.0		1.0	
25-49	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 (years)		0.003		0.53
<30	1.0		1.0	
30-39	0.97 (0.70-1.35)		1.37 (0.88-2.12)	
40-49	0.93 (0.63-1.36)		1.36 (0.84-2.20)	
50+	0.34 (0.17-0.68)		1.32 (0.76-2.30)	
Sex		0.0007		0.68
Male	1.0		1.0	
Female	0.63 (0.49-0.82)		0.93 (0.66-1.31)	
First line regimen		0.35		
1 NNRTI + 2 NRTIs	1.0		1.0	
1 PI + 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				0.0036
Heterosexual	N.a.		1.0	
Injection drug use			0.85 (0.56-1.28)	
MSM			0.54 (0.37-0.77)	
Other			0.55 (0.32-0.95)	

NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor (including boosted PI-regimens); N.a.: not assessed (predominantly heterosexual transmission)

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



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