Tuberculosis and the risk of opportunistic infections and cancers in HIV-infected patients starting ART in Southern Africa

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Abstract

OBJECTIVES To investigate the incidence of selected opportunistic infections (OIs) and cancers and the role of a history of tuberculosis (TB) as a risk factor for developing these conditions in HIV-infected patients starting antiretroviral treatment (ART) in Southern Africa.

METHODS Five ART programmes from Zimbabwe, Zambia and South Africa participated. Outcomes were extrapulmonary cryptococcal disease (CM), pneumonia due to *Pneumocystis jirovecii* (PCP), Kaposi's sarcoma and Non-Hodgkin lymphoma. A history of TB was defined as a TB diagnosis before or at the start of ART. We used Cox models adjusted for age, sex, CD4 cell count at ART start and treatment site, presenting results as adjusted hazard ratios (aHR) with 95% confidence intervals (CI).

RESULTS We analysed data from 175 212 patients enrolled between 2000 and 2010 and identified 702 patients with incident CM (including 205 with a TB history) and 487 with incident PCP (including 179 with a TB history). The incidence per 100 person-years over the first year of ART was 0.48 (95% CI 0.44–0.52) for CM, 0.35 (95% CI 0.32–0.38) for PCP, 0.31 (95% CI 0.29–0.35) for Kaposi's sarcoma and 0.02 (95% CI 0.01–0.03) for Non-Hodgkin lymphoma. A history of TB was associated with cryptococcal disease (aHR 1.28, 95% CI 1.05–1.55) and *Pneumocystis jirovecii* pneumonia (aHR 1.61, 95% CI 1.27–2.04), but not with Non-Hodgkin lymphoma (aHR 1.09, 95% CI 0.45–2.65) or Kaposi's sarcoma (aHR 1.02, 95% CI 0.81–1.27).

CONCLUSIONS Our study suggests that there may be interactions between different OIs in HIV-infected patients.

keywords tuberculosis, opportunistic infections, cancer, HIV, risk factors, antiretroviral treatment programmes, history of tuberculosis

Introduction

HIV-infected patients are at high risk for opportunistic infections (OIs) such as tuberculosis (TB), cryptococcal meningitis (CM) and *Pneumocystis jirovecii* pneumonia (PCP) (Corbett *et al.* 2002; Holmes *et al.* 2003). In many resource-constrained settings, TB is the most common AIDS-defining illness, and TB and CM are leading causes

of mortality in patients initiating antiretroviral treatment (ART) in Africa (Lawn *et al.* 2008; Park *et al.* 2009).

There may be important interactions between different HIV-associated opportunistic infections (Corbett *et al.* 1999, 2002; Havlir & Barnes 1999; Holmes *et al.* 2003; Jarvis *et al.* 2010). HIV replication is influenced by co-infections with *M. tuberculosis* and other opportunistic pathogens due to infection-induced activation of immune cells, which favours viral replication (Lawn 2004). Furthermore, TB patients often suffer from impaired pulmonary function after successful treatment of TB (Pasipanodya *et al.* 2007; van Zyl Smit *et al.* 2010; Ehrlich *et al.* 2011). It is possible that such damage facilitates entry of environmental pathogens and their dissemination in the human body leading to opportunistic infections (Corbett *et al.* 2002; Park *et al.* 2009; Jarvis *et al.* 2010).

We analysed a large collaborative dataset of more than 175 000 HIV-infected patients on ART from five treatment programmes in Southern Africa to study the incidence of respiratory and non-respiratory OIs and the importance of a history of TB.

Methods

We analysed data from patients enrolled from 1 January 2000 until 1 May 2011 in five ART programmes participating in the International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA, see www.iedea-sa.org) collaboration in Zimbabwe (Newlands Clinic, Harare), Zambia (Center for Infectious Disease Research, CIDRZ, Lusaka) and South Africa (Khayelitsha, Tygerberg and Thembalethu ART programmes) (Egger *et al.* 2011). IeDEA-SA is part of the IeDEA network, which includes similar networks in other regions of Africa, Latin America and the Caribbean, Asia and North America (see www.iedea.org). Data are collected at each site as part of routine monitoring at programme enrolment and each follow-up visit. All study sites have local institutional review board or ethics committee approval to collect data and participate in IeDEA-SA. We did not perform any sample size calculations but included all adult patients ($\geq$16 years) recorded in the IeDEA-SA database with a known ART start date from sites that systematically recorded OI episodes. The selection of eligible patients is shown in Supplementary Figure S1 (online only).

We examined the importance of TB as a risk factor for the clinically well-defined diseases CM, PCP, Non-Hodgkin lymphoma and Kaposi's sarcoma, based on the diagnostic criteria used in the treatment programmes. TB episodes included pulmonary and extrapulmonary episodes; CM episodes were defined as extrapulmonary cryptococcal disease and PCP as pneumonia due to *P. jirovecii* as coded by the sites. History of TB was defined as a diagnosis before or at start of ART.

We measured follow-up time from the start of ART to the earliest of either onset of an eligible OI, death or last follow-up visit. Data were analysed using Cox models adjusted for age, sex, CD4 cell count at ART initiation and treatment site to control for between-programme variations. Because the exposure variable of interest (a history of TB) is also a stage defining illness (e.g. pulmonary TB is a WHO stage III disease), we did not adjust for WHO clinical stage: inclusion of WHO stage would have biased the estimate for history of TB. In addition, clinical stages are not consistently reported across programmes. Incidence was calculated per 100 person-years over the first year of ART. Results are presented as medians with interquartile ranges (IQR) and crude hazard ratios (HR) and adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI). All analyses were performed in STATA version 11.2 (Stata Corporation, College Station, TX, USA).

Results

We included 175 212 patients with 320 459 person-years of follow-up. The largest programme contributing data was CIDRZ (n = 146 859), followed by Thembalethu (n = 15 356), Khayelitsha (n = 8173), Tygerberg (n = 2602) and Newlands (n = 2222). A total of 108 521 patients (61.9%) were women. Median age at ART start was 35 years (interquartile range [IQR] 29.8–41.6) and median CD4 cell count 131 cells/μL (IQR 64–205 cells/μL) (Supplementary Table S1). Overall, 52 062 patients (31.1%) were lost to follow-up, 1639 (0.9%) transferred out and 14 409 (8.2%) died. A total of 34 460 patients (19.7%) had a history of TB; 16 951 (49.2%) of TB episodes were diagnosed at ART start, 6315 (18.3%) occurred within 2 years prior to ART start and 11 194 (32.5%) episodes were diagnosed more than 2 years before the start of ART.

There were 702 patients with incident CM occurring at or after ART initiation (including 205 with a history of TB), 487 with incident PCP (including 179 with a history of TB), 633 with incident Kaposi's sarcoma (including 139 with a history of TB) and 40 patients with an incident Non-Hodgkin lymphoma (including eight with a history of TB) (Table 1). The incidence of CM over the first year of ART was 0.48 per 100 person-years (95% CI 0.44–0.52), PCP incidence during the same period was 0.35 (95% CI 0.32–0.38), Kaposi's sarcoma incidence 0.31 (95% CI 0.29–0.35) and Non-Hodgkin

lymphoma incidence 0.02 per 100 person-years (95% CI 0.01–0.03).

A history of any TB was associated with CM (aHR 1.28, 95% CI 1.05–1.55) and PCP (aHR 1.61, 95% CI 1.27–2.04). In contrast, a history of TB was not associated with Non-Hodgkin lymphoma (aHR 1.09, 95% CI 0.45–2.65) or Kaposi's sarcoma (aHR 1.02, 95% CI 0.81–1.27). Additional analyses showed that a history of extrapulmonary TB was more strongly associated with CM than either a history of any TB or a history of pulmonary TB (Supplementary Table S2, online only). When excluding patients from the largest ART programme, a history of any TB remained associated with incident CM (aHR 1.40, 95% CI 1.03–1.91) and incident PCP (aHR 1.49, 95% CI 1.03–2.17). Low CD4 cell counts were also a risk factor for CM and PCP (Supplementary Table 2). TB was the most frequent OI with an incidence of 2.19 (95% CI 2.11–2.28) cases per 100 person-years over the first year after ART start.

Discussion

We analysed a large collaborative dataset of HIV-infected patients starting ART in five large treatment programmes in Southern Africa. We found that a history of TB was associated with both a respiratory and a non-respiratory OI but not with AIDS-defining cancers.

After successful treatment of TB, many patients have functional lung impairment and complications such as bronchiectasis, emphysematous changes and fibrotic bands (Pasipanodya *et al.* 2007; Ehrlich *et al.* 2011). A study on cryptococcal disease from a cohort in Cape Town, South Africa, suggested that a history of TB may be an independent risk factor for subsequent development of CM, based on 707 patients, of whom 13 developed a CM episode (Jarvis *et al.* 2010). Post-TB lung damage may facilitate entry of the ubiquitously found fungus *C. neoformans* into the blood system and its dissemination. The same may also be true for PCP caused by the fungus *P. jirovecii*, which is also found in the environment (Morris *et al.* 2002). PCP has previously been shown to be associated with tobacco use in HIV-infected patients (Miguez-Burbano *et al.* 2005), indicating an association with smoking-induced impaired lung function. Interestingly, we also found that for CM, the association was stronger in patients with extrapulmonary TB. These patients are frequently severely ill with disseminated disease complicated by acute respiratory distress syndromes in the lungs (Penner *et al.* 1995).

Alternatively, the observed association could reflect that patients with more advanced disease (e.g. with a history of extrapulmonary TB) are at a higher risk for subsequently developing another OI episode (Corbett *et al.* 2002; Holmes *et al.* 2003). A history of TB could thus be a marker for more advanced disease. Adaptive immunity to *M. tuberculosis* in humans mainly depends on CD4 T cells and the mediators interferon-γ and tumour necrosis factor (Ernst 2012). TB infection causes immune activation, which is associated with disease progression in HIV-infected patients (Wallis *et al.* 1993; Shafer & Edlin 1996; Lancioni *et al.* 2011) and may lead to reduced immune cell function and immune regulation. Studies from South Africa, however, failed to show a worse immunological outcome among patients with TB (Lawn *et al.* 2006; Boulle *et al.* 2010).

A history of TB was not associated with AIDS-defining cancers in our study. This is reassuring, indicating that the associations found with CM and PCP may be real, and not only due to confounding by clinical stage, due to residual confounding by immunodeficiency or due to closer follow-up and more complete ascertainment of OIs in patients with a history of TB. However, we stress that

Table 1 Hazard ratios for developing AIDS-defining opportunistic infections and cancers after starting antiretroviral treatment (ART) in 175 212 HIV-infected patients

		Association with a history of any TB					
Characteristic	Total number of events	HR	(95% CI)	*P*-value	aHR	(95% CI)	*P*-value
AIDS-defining respiratory and non-respiratory opportunistic infections							
Cryptococcal meningitis	702	1.64	(1.39–1.93)	<0.0001	1.28	(1.05–1.55)	0.015
Pneumocystis jirovecii pneumonia	487	2.34	(1.94–2.81)	<0.0001	1.61	(1.27–2.04)	<0.0001
AIDS-defining cancers							
Non-Hodgkin lymphoma	40	0.92	(0.43–2.01)	0.84	1.09	(0.45–2.65)	0.85
Kaposi's sarcoma	633	1.05	(0.87–1.27)	0.57	1.02	(0.81–1.27)	0.89

Models were adjusted for age, sex, CD4 cell count at ART start and treatment site. *P* values are from Wald tests.
ART, antiretroviral therapy; HR, hazard ratios; aHR, adjusted hazard ratios; ND, not defined; TB, tuberculosis; 95% CI, 95% confidence interval.

other factors not measured in our study could nevertheless explain the observed association between a history of TB and other OIs. For example, conditions such as silicosis or immunological deficits independent of CD4 cell counts could increase the risk of both TB and other OIs (Corbett *et al.* 1999, 2002; Jarvis *et al.* 2010).

Our study is limited by the potential under-ascertainment of OIs, particularly prior to ART start, due to lack of laboratory capacities or high costs for tests in some of the HIV treatment programmes. Indeed, the incidence for OIs reported in this study was lower compared to other studies (Corbett *et al.* 2002; Brinkhof *et al.* 2007; Fenner *et al.* 2011), but as previously reported, the incidence for TB was higher compared to CM or PCP. In addition, our results might have been influenced by the heterogeneous nature of the ART programmes from three different countries and the lack of uniform case definitions and ascertainment of diagnosis (Fenner *et al.* 2011). Finally, our analysis of observational data may be influenced by residual confounding and survival bias as the most severely ill patients may die before ART can be initiated. However, we adjusted our analyses for the most important confounding factors, and we were interested in ratio measures, rather than absolute differences.

In conclusion, our results suggest a role for interactions between different OIs in HIV-infected patients. A history of TB may be a marker for more severe disease and a worse immune recovery after ART start. It also highlights the significance of post-TB lung disease, which has received increasing attention over the past few years (van Zyl Smit *et al.* 2010; Ehrlich *et al.* 2011), and its potential role as a co-factor for OIs. Further research is needed to study the interactions between TB and other respiratory and non-respiratory OIs in HIV-infected patients, with a focus on the mechanisms that underlie the interactions between OIs and its impact on the immune recovery after starting ART.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Selection of study population.

Table S1. Characteristics of patients in antiretroviral treatment programs.

Table S2. Hazard ratios for cryptococcal meningitis (CM), *Pneumocystis jirovecii* pneumonia (PCP), and AIDS-defining cancers after starting antiretroviral treatment (ART) in 175 212 HIV-infected patients.

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