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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 programs 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 analyzed data from 175,212 patients enrolled between 2000–2010 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.

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Keywords

tuberculosis; opportunistic infections; cancer; HIV; risk factors; antiretroviral treatment programs; 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 favors viral replication (Lawn 2004). Furthermore, TB patients often suffer from impaired pulmonary function after successful treatment of TB (Ehrlich et al. 2011; Pasipanodya et al. 2007; van Zyl Smit et al. 2010). 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; Jarvis et al. 2010; Park et al. 2009).

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

METHODS

We analyzed data from patients enrolled from January 1, 2000 until May 1, 2011 in five ART programs 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 Themba Lethu ART programs) (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 program enrollment 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 calculations but included all adult patients (≥ 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 1 (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 programs. 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 analyzed using Cox models adjusted for

age, sex, CD4 cell count at ART initiation, and treatment site to control for between-program 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 programs. 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 program contributing data was CIDRZ (n=146,859), followed by Themba Lethu (n=15,356), Khayelitsha (n=8,173), Tygerberg (n=2,602), and Newlands (n=2,222). 108,521 patients (61.9%) were females. 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 1). Overall, 52,062 patients (31.1%) were lost to follow-up, 1,639 (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, 6,315 (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 8 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 2, online-only). When excluding patients from the largest ART program, 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 analyzed a large collaborative dataset of HIV-infected patients starting ART in five large treatment programs 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 (Ehrlich et al. 2011; Pasipanodya et al. 2007). 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 (Lancioni et al. 2011; Shafer and Edlin 1996; Wallis et al. 1993) 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 (Boulle et al. 2010; Lawn et al. 2006).

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 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 programs. Indeed, the incidence for OIs reported in this study was lower compared to other studies (Brinkhof et al. 2007; Corbett et al. 2002; 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 programs 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 (Ehrlich et al. 2011; van Zyl Smit et al. 2010), and its potential role as a cofactor 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

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

Characteristic	Total number of events	Association with a history of any TB			
		HR (95% CI)	*P* value	aHR (95% CI)	*P* value
AIDS-defining respiratory and non-respiratory opportunistic in- fections					
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