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Tuberculosis Risk Before and After Highly Active Antiretroviral Therapy Initiation: Does HAART Increase the Short-term TB Risk in a Low Incidence TB Setting?

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Abstract

Objective—To evaluate the short- and long-term effects of highly active antiretroviral therapy (HAART) on tuberculosis (TB) risk, compared to risk without HAART in a low TB incidence setting.

Design—An observational cohort study among HIV-infected persons in care at the Comprehensive Care Center (Nashville, TN) between January 1998 and December 2008.

Methods—A marginal structural model was used to estimate the effect of HAART on short- (≤ 180 days) and long-term (> 180 days) TB risk, with CD4+ lymphocyte count incorporated as a time-updated covariate.

Results—Of 4,534 HIV-infected patients, 34 developed TB (165/100,000 p-y; 20,581 person-years [p-y] of follow-up). Seventeen cases occurred among persons not on HAART or > 30 days after HAART discontinuation (212/100,000 p-y; 8,019 p-y of follow-up). Seventeen occurred among persons on HAART (135/100,000 p-y; 12,562 p-y of follow-up); ten in the first 180 days (402/100,000 p-y; 2,489 p-y of follow-up) and 7 after more than 180 days (69/100,000 p-y; 10,073 p-y of follow-up). After adjusting for the most recent CD4+ lymphocyte count, the risk of TB in the first 180 days of HAART exposure relative to no HAART was 0.68 (0.14–3.22, $p=0.63$).

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Conclusions—In this low TB incidence setting, the TB rate in the first 180 days of HAART was almost twice as high as persons not on HAART. However, after adjusting for most recent CD4+ count there was no significant difference in TB risk between these two groups. This suggests that low recent CD4+ lymphocyte count influences TB risk during the first 180 days of HAART.

Keywords

tuberculosis; *M. tuberculosis* infection; tuberculosis risk; human immunodeficiency virus; highly active antiretroviral therapy

Introduction

In the United States (US) during 2009, there were an estimated 13,000 new cases of tuberculosis (TB) and 1,300 (10%) were estimated to be among human immunodeficiency virus (HIV) infected persons¹. TB risk is higher among HIV-infected persons with lower CD4+ lymphocyte counts^{2–5}. To prevent TB, as well as other HIV-related illnesses and death, current US guidelines recommend initiation of highly active antiretroviral therapy (HAART) when the CD4+ lymphocyte count falls below 500 cells/mm³.⁶ HAART decreases TB risk up to 70–90% in HIV-infected populations^{7–10} by restoring CD4+ lymphocytes and deficits in cell-mediated immunity. However, TB risk is high in the 3–6 months following HAART initiation^{11–16}.

This high risk may be partially due to incomplete immune restoration and “unmasking” of previously undiagnosed TB in the setting of immune reconstitution^{17;18}. TB-associated immune reconstitution inflammatory syndrome (IRIS) is an important early complication of antiretroviral therapy resulting from a rapid restoration of TB-specific immune responses. New TB infection and previously undiagnosed TB may also contribute to the high TB risk during this period. Alternatively, the high TB risk during this period may reflect the low CD4+ lymphocyte counts at which highly active antiretroviral therapy (HAART) is initiated.

Routine screening and treatment for latent TB infection (LTBI) has been shown to reduce the risk of active TB in HIV-infected patients¹⁹. In the US, it is recommended that all HIV-infected persons are tested for latent LTBI at entry into care with a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) regardless of their TB risk²⁰. However, it is known that adherence to these screening guidelines is poor^{21;22}. HIV-infected persons should receive isoniazid preventive therapy if they have a positive diagnostic test for LTBI, have a negative diagnostic test for LTBI but were a close contact to an infectious pulmonary TB case, or have a history of untreated or inadequately treated healed TB regardless of LTBI diagnostic testing²⁰.

It is important to improve our understanding of the epidemiology of TB, specifically soon after starting HAART. The decision to initiate or re-initiate HAART is guided by CD4+ lymphocyte counts. HAART affects CD4+ lymphocyte counts, which in turn affects TB risk. Therefore, CD4+ lymphocyte count is a confounder that lies on the causal pathway between HAART exposure and TB risk (Figure 1). We are aware of only two studies that have assessed TB risk in the same population before and after HAART initiation, and have appropriately adjusted for the most recent CD4+ lymphocyte count as a time-updated covariate using a marginal structural model^{23;24}. However, neither of these studies was performed in a cohort of adults from a low-incidence TB setting. Additionally, neither of these studies incorporated the duration of HAART exposure into the marginal structural model, therefore they did not assess both the short-term and long-term effect of HAART on TB disease.

Methods

Patient Population

We conducted an observational cohort study among patients receiving HIV care at the Comprehensive Care Center (CCC), a multidisciplinary clinic in Nashville, TN. Patients were included in this study if they were HIV-1 seropositive and had ≥ 2 provider visits at the clinic between January 1, 1998 and December 31, 2008. Screening for LTBI in this cohort was done using tuberculin skin testing; IGRA testing was not in use at the CCC during the study period. This study was approved by the Vanderbilt Institutional Review Board.

Study Definitions

Patients were considered TB cases if they had been diagnosed with active TB after their first visit to the CCC. Tuberculosis diagnoses were classified as either culture-confirmed or culture-negative. A diagnosis of culture-negative (i.e., clinical) TB was based on the provider's clinical judgment or the combination of clinical judgment plus a pathological specimen with caseating or necrotizing granulomas, and/or acid fast bacilli that was not culture-positive for *M. tuberculosis*, in addition to a clinical response to anti-TB therapy. Extrapulmonary TB cases were defined as any extrapulmonary disease, even if pulmonary disease was also present. Disseminated TB cases were defined as a positive blood culture for *M. tuberculosis* or miliary disease on chest radiography. An initial review of all such cases was conducted using the electronic medical record (EMR) database and the diagnoses "tuberculosis" or "PPD." Hard copy charts were reviewed to confirm all TB diagnoses. Date of TB diagnosis was defined as the date of anti-TB treatment initiation. Tuberculosis diagnosed prior to first CCC visit and recurrent TB was excluded.

Unmasking TB-associated immune reconstitution inflammatory syndrome (IRIS) was defined as an active TB case presenting within 3 months of starting HAART and one of the following: 1) increased intensity of the clinical presentation, specifically any inflammatory signs or symptoms or 2) a paradoxical reaction after initiation of anti-TB therapy²⁵. For all cases of TB diagnosed within 3 months of HAART initiation, re-initiation, or regimen change, hard copy charts were reviewed to determine if the criteria for unmasking TB-associated IRIS were met.

Demographic and laboratory data were obtained via the EMR. Hard copy charts were reviewed to validate laboratory data obtained from the EMR and to identify any data missing from the EMR. Baseline CD4+ lymphocyte and HIV-1 RNA values were defined as the first available values within 120 days prior to or up to 365 days after the first study visit. CD4+ lymphocyte values and HIV-1 RNA values at HAART initiation and TB diagnosis were defined as the first available values within 120 days prior to the respective event.

Utilization of HAART was determined and validated by chart review for all patients in the study period. HAART was defined as a regimen that contained two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a protease inhibitor (PI), a non-nucleoside reverse-transcriptase inhibitor (NNRTI), or a third NRTI; one NRTI, one PI, plus one NNRTI; two PIs plus one NRTI or one NNRTI; or any regimen containing enfuvirtide plus at least one other agent. Antiretroviral therapy data (including regimen start and stop dates) were entered into an electronic medical record by medical providers at the time of the patient encounter and validated by systematic chart review. If the chart noted that the patient had not taken the prescribed antiretroviral therapy, the patient was coded as not taking antiretroviral therapy during that time period.

Length of HAART exposure was defined as the time on HAART since most recent regimen initiation. A patient was determined to be on HAART if they received ≥ 7 consecutive days of HAART and off HAART if they had not received HAART for >30 days.

Laboratory methods

HIV-1 RNA in plasma was quantified by reverse transcriptase polymerase chain reaction (RT-PCR). CD4+ lymphocytes were quantified by flow cytometry. The median frequency of CD4+ lymphocyte count measurement was every 3.0 months (IQR: 1.9–4.0) over the entire study period, every 3.2 months (IQR: 2.2–5.5) when not on HAART, every 2.0 months (IQR: 1.1–3.7) in the first 180 days following HAART initiation, and every 3.0 months (IQR: 2.3–4.1) thereafter.

Statistical analysis

Fisher's exact tests were used to compare categorical variables between categories. Wilcoxon Rank Sum and Kruskal-Wallis tests compared continuous variables between two or more than two categories, respectively. A marginal structural model was constructed for improved adjustment of CD4+ lymphocyte count, a time-dependent confounder affected by HAART exposure^{26–28}. The marginal structural model had two components: 1) a model for predicting the probability of being on HAART, used to create inverse probability weights incorporated in the primary model; and 2) the primary model from which odds ratios for the risk of TB were computed. The model for predicting the probability of being on HAART for a given month included time since study entry (in months), whether the patient was on HAART during the preceding month, most recent CD4+ lymphocyte count, a variable indicating whether the patient had had a prior CD4+ lymphocyte count measurement, sex, race (black, non-black, unknown), age at study entry, foreign-born status (foreign-born, not foreign-born, unknown), and use of injection drugs. The primary model included time since study entry (in months) and current HAART status (not on HAART, ≤ 180 days of HAART, or >180 days of HAART). Results are reported with weights truncated at the 1st and 99th percentiles. All statistical tests were two-sided. P-values <0.05 were considered statistically significant. Statistical analyses were performed using R version 2.11.1 (www.r-project.org). Analysis scripts are posted at <http://biostat.mc.vanderbilt.edu/ArchivedAnalyses>.

Results

There were 4,534 HIV-infected patients in care; median age at first visit was 38 years, 77% were male, 36% were black, 5% were foreign born, and 12% had injection drug use (IDU) as an HIV risk factor. The median baseline CD4+ lymphocyte count was 320 cells/mm³ (IQR: 154–513 cells/mm³), median baseline CD4 percentage 21% (IQR: 12–30%), and median baseline HIV-1 RNA 15,982 copies/mL (IQR: 929–80,348 copies/mL). There were 3,492 (77%) persons who initiated HAART during the study period and the median CD4+ lymphocyte count prior to HAART initiation was 242 (IQR: 102–405). There were 1,056 (23%) patients who received at least one screening TST; 63 (1.4%) patients received at least 6 months of isoniazid preventive therapy during the study period.

Thirty-four patients developed TB during the study period (165/100,000 p-y; 20,581 p-y of follow-up): 18 pulmonary cases, 12 extrapulmonary cases, and 4 cases of disseminated disease. Patients with TB were more likely to be male, black, foreign-born, and to report heterosexual contact as an HIV risk factor. They were also more likely to have a lower baseline CD4+ lymphocyte count/percentage and a higher baseline HIV-1 viral load. The frequency of CD4+ lymphocyte count measurements was similar between persons who developed and did not develop TB (Table 1).

Seventeen TB cases occurred among persons not on HAART or >30 days after HAART discontinuation (212/100,000 p-y; 8,019 p-y of follow-up). Seventeen TB cases occurred among persons on HAART (135/100,000 p-y; 12,562 p-y of follow-up). Of these 17 TB cases, 10 occurred in the first 6 months of HAART (402/100,000 p-y; 2,489 p-y of follow-up) and 7 occurred after more than 6 months of HAART (69/100,000 p-y; 10,073 p-y of follow-up) (Table 2).

Patients who developed TB while not on HAART, while on HAART ≤ 6 months, and while on HAART >6 months were similar with respect to age, race, HIV risk factor, baseline CD4+ lymphocyte count/percent, baseline HIV-1 viral load, and proportion with culture positivity (Table 2). Using a marginal structural model and adjusting for time-updated CD4+ lymphocyte count, age, sex, race, foreign born status, and injection drug use, the risk of TB after at least 180 days of HAART was 0.10 compared to persons not on HAART (95% CI 0.03–0.31, $p < 0.0001$). The risk of TB in the first 180 days following HAART initiation was 0.68 compared to persons not on HAART (95% CI 0.14–3.22, $p = 0.63$). The risk of TB was higher in the first 180 days of HAART than after 180 days: OR=7.01 (95% CI 1.35–36.31, $p = 0.02$) (Table 3). Results were similar when only adjusting for time-updated CD4+ lymphocyte counts (not shown).

The median time to TB diagnosis from time of HAART initiation, re-initiation, or regimen change was 144 days (IQR: 41–399 days). There were 7 cases of TB diagnosed within 3 months of HAART initiation, re-initiation, or regimen change. Five of these cases met criteria for unmasking TB-associated IRIS. The first case presented with cervical and supraclavicular lymphadenopathy as well as multiple hypodense ring-enhancing lesions in the chest and abdomen on computed tomography. The second case presented with bilateral supraclavicular lymphadenopathy and the third with multiple splenic lesions. The fourth case presented with splenomegaly and replacement of the spleen with soft tissue masses as well as right supraclavicular lymphadenopathy. The final case presented with head and neck lymphadenopathy.

Among these 5 provisional unmasking TB-associated IRIS cases, the median change in CD4+ lymphocyte count from the time of HAART initiation or re-initiation to TB diagnosis was +38 cells/mm³ (IQR: 0, +44), the median change in CD4+ lymphocyte percentage was +2% (IQR: 0, +8%), the median change in HIV-1 viral load was –75,920 copies/mL (IQR: –268,123, 0) (Table 4).

Of 34 TB cases, 9 (26%) had TST performed as routine screening prior to TB diagnosis. Of the 9 patients screened, 4 had a positive test, 3 of whom completed treatment for latent TB infection. Six (18%) of these patients had TST performed as routine screening prior to initiation of any HAART. None of the patients with unmasking TB-associated IRIS underwent screening for TB with TST prior to HAART initiation.

Discussion

The TB rate during the first 180 days following HAART initiation (402/100,000 p-y) was higher than the TB rate in those persons not on HAART (212/100,000 p-y) and those on HAART more than 180 days (69/100,000 p-y). However, after incorporating HAART use as a time-updated exposure and adjusting for CD4+ lymphocyte count as a time-updated covariate, the TB risk was not significantly increased. In fact, the adjusted point estimate of TB risk suggests that HAART may even be protective in the first 180 days after initiation. Two previous studies utilizing the marginal structural model methodology assessed TB risk before and after HAART initiation, but did not evaluate TB risk by duration of HAART

exposure. Additionally, these cohorts were both in high TB-incidence settings, and one was a cohort comprised only of children^{23;24}.

Our results suggest that low CD4+ lymphocyte counts influence the high TB risk during the first 180 days following HAART initiation. This finding supports the earlier initiation of HAART at higher CD4+ lymphocyte counts to prevent TB disease.

Other causes of elevated TB risk during the period shortly following HAART initiation, such as new TB infection or previously undiagnosed TB are unlikely in this low-incidence, resource-rich setting of HIV patients in care. With this analysis, however, we cannot rule out unmasking TB-associated IRIS as a cause of elevated TB risk shortly following HAART initiation.

Data regarding the incidence of unmasking TB-associated IRIS in low TB incidence settings is unknown and exists mainly as case reports^{17;29-31}. We found that 5 (71%) of 7 TB cases diagnosed in the first 3 months following HAART initiation (or 15% of all TB cases in this cohort) met the definition for unmasking TB-associated IRIS. In this cohort only 6 (18%) of 34 underwent screening for TB with a tuberculin skin test (TST) prior to initiation of any HAART. None of the five patients with unmasking TB-associated IRIS underwent screening for TB with TST prior to HAART initiation. It is possible that these cases could have been detected prior to HAART initiation had screening for TB been performed.

Tuberculosis risk does decline with greater time on HAART and in our study the rate dropped to 69/100,000 p-y after 180 days on HAART. This corresponded to a 90% reduction in the risk of TB compared to not being on HAART after adjusting for CD4+ lymphocyte count. This is consistent with the risk reduction reported in previous studies⁷⁻¹⁰, including one other low-incidence cohort from the United States, which reported an 80% reduction in TB risk⁹.

The main limitation of our study is the low number of TB cases. This was a retrospective study and therefore some TB cases may have been missed. However, this is unlikely since TB is a reportable disease and persons were in care. This analysis should be repeated in a larger low-TB incidence cohort.

Additional limitations of our study are due to its retrospective, observational nature. First, although we adjusted for CD4+ lymphocyte count, sex, race, age, foreign-born status, and intravenous drug use, the association between HAART use and TB could be confounded by other factors not included in our analysis.

Second, the frequency of CD4+ lymphocyte measurements could impact results. Specifically, when CD4+ lymphocyte counts are increasing/decreasing, the most recent value will tend to underestimate/overestimate its true value. This could lead to underestimation of the adjusted TB risk in the first 180 days following HAART initiation, presumably the time of most rapid change in CD4+ lymphocyte counts. However, CD4+ lymphocyte count measurements were frequent (median once every 3.0 months), and especially frequent during the first 180 days of HAART exposure (median once every 2.0 months), so we do not expect this potential bias to be great. It is also worth noting that the frequency of CD4+ lymphocyte count measurements was similar between those who developed and did not develop TB.

A final limitation lies in the completeness of documentation of HAART interruptions. If a patient was misclassified as taking HAART when they were not, this could lead to an overestimation of TB risk among those persons taking HAART. This type of bias should be limited by the extensive chart review for identification and documentation of interruptions.

In conclusion, crude TB risk in the first 6 months of HAART was higher than the risk in those persons not on HAART. However, this risk did not remain elevated after adjusting for the most recent CD4+ lymphocyte count and HAART exposure. This suggests that the elevated risk during this period is related at least in part to low recent CD4+ lymphocyte counts. These results emphasize the importance of screening for TB prior to the receipt of any HAART and they underscore the need to maintain a clinical vigilance for TB, specifically shortly following HAART initiation. This is particularly true for HIV-infected persons at the highest risk for TB in a low incidence setting including the foreign-born and those with low CD4+ lymphocyte counts. These results also support the earlier initiation of HAART at higher CD4+ lymphocyte counts to prevent TB disease.

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Figure 1.
Association between CD4+ lymphocyte count, HAART, and TB

Table 1

Clinical and demographic characteristics of the study population (N=4,534)

Characteristic	Non-TB Cases N=4,500	TB Cases N=34	P-value
Male Sex Number (%)	3,438 (76%)	31 (91%)	0.04
Age at first visit in years Median (IQR)	38 (31–44)	37 (31–41)	0.40
Black Race Number (%)	1,596 (35%)	19 (56%)	0.02
Foreign Born Number (%)	204 (5%)	7 (21%)	≤0.01
IDU as HIV risk factor Number (%)	518 (12%)	7 (21%)	0.11
Male-Male Sexual Contact as HIV Risk Factor-Number (%)	1,841 (41%)	11 (32%)	0.38
Heterosexual Contact as HIV Risk Factor-Number (%)	1,026 (23%)	15 (44%)	≤0.01
Baseline Absolute CD4+ lymphocytes (cells/mm ³)-Median (IQR)	322 (156–516)	179 (120–354)	≤0.01
Baseline Percentage CD4+ lymphocytes-Median (IQR)	21 (12–30)	15 (10–23)	0.03
Baseline HIV-1 RNA copies/mL Median (IQR)	15,836 (911–80,196)	43,061 (6,765–228,777)	0.02
Visits during study period Median (IQR)	14 (6–29)	35 (17–47)	≤0.01
Frequency of CD4+ lymphocyte count measurement (months)-Median (IQR)	3.2 (2.2–5.1)	3.0 (1.9–4.1)	<u>0.49</u>
Person-years of follow-up	20,486	95	

IQR: interquartile range; IDU: Injection Drug Use

CD4+ lymphocyte count and percent were available for 4,462 and 4,459 of 4,534 patients, respectively.

HIV-1 RNA was available for 4,450 of 4,534 patients.

Table 2

Characteristics of the 34 TB Cases According to Timing of TB Diagnosis in Relation to HAART initiation.

Characteristic	No HAART* N=17	TB while on HAART ≤ 6 months N = 10	TB on HAART >6 months N = 7	P-value
Male sex Number (%)	16 (94%)	9 (90%)	6 (86%)	0.77
Age at first visit in years Median (IQR)	37 (32–40)	34 (30–41)	39 (32–44)	0.73
Black race Number (%)	12 (71%)	6 (67%)	5 (71%)	1.00
Injection drug use (IDU) as HIV risk factor Number (%)	5 (29%)	1 (10%)	1 (14%)	0.54
Male-Male Sexual Contact as HIV Risk Factor-Number (%)	5 (29%)	3 (30%)	3 (43%)	0.80
Heterosexual Contact as HIV Risk Factor-Number (%)	6 (35%)	6 (60%)	3 (43%)	0.44
Baseline Absolute CD4+ lymphocytes (cells/mm ³)-Median (IQR)	220 (156–300)	128 (44–147)	270 (149–372)	0.16
Baseline Percentage CD4+ lymphocytes (cells/mm ³)-Median (IQR)	15 (12–22)	11 (7–25)	17 (12–29)	0.44
Baseline HIV-1 RNA copies/mL Median (IQR)	54,747 (9,727–274,972)	36,000 (7,227–130,050)	9,771 (1,827–54,212)	0.40
Culture positive TB cases Number (%)	13 (76%)	4 (40%)	4 (57%)	0.15
TB Incidence Rates (95% CI) per 100,000 p-y of follow-up	212 (132–341)	402 (216–747)	69 (33–146)	

* The group not on HAART includes patients naïve to HAART and those who had discontinued HAART >30 days prior to TB diagnosis.

Table 3

Marginal Structural Model*

	Odds Ratio 95% Confidence Interval	P-value
Reference: Not on HAART		
<180 days since most recent HAART initiation	0.68 (0.14–3.22)	0.63
>180 days since most recent HAART initiation	0.10 (0.03–0.31)	<0.0001
Reference: >180 days of HAART		
<180 days since most recent HAART initiation	7.01 (1.35–36.31)	0.02

* Adjusted for most recent CD4, age, sex, race, age at study entry, foreign-born status, and use of injection drugs.

Table 4

Changes in laboratory parameters among IRIS cases

N=5	At HAART initiation	At TB Diagnosis	Absolute Change
Absolute CD4+ lymphocytes (cells/mm ³)-Median (IQR)	171 (61–195)	195 (99–225)	+38 (0, +44)
Percentage CD4+ lymphocytes- Median (IQR)	13 (8–30)	16 (15–25)	+2 (0, +8)
HIV-1 RNA copies/mL Median (IQR)	160,361 (100,000–324,881)	24,080 (9,055–56,758)	−75,920 (−268,123–0)