Published in final edited form as:

J Acquir Immune Defic Syndr. 2016 August 15; 72(5): 572–578. doi:10.1097/QAI.0000000000001018.

Timing of Antiretroviral Treatment, Immunovirologic Status and TB Risk: Implications for Test and Treat

April C. PETTIT, MD, MPH[1,2], **Adell MENDES, MPH**[3], **Cathy JENKINS, MS**[2,4], **Sonia NAPRAVNIK, PhD**[5], **Aimee FREEMAN, MA**[3], **Bryan E. SHEPHERD, PhD**[2,4], **David DOWDY, MD**[3], **John GILL, MB, ChB, MsC**[6], **Anita RACHLIS, MD**[7], **Richard MOORE, MD**[8], and **Timothy R. STERLING, MD**[1,2] **for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) investigators of International epidemiologic Databases to Evaluate AIDS (IeDEA)**

[1]Vanderbilt University, Department of Medicine, Division of Infectious Diseases, Nashville TN, US

[2]Vanderbilt University Tuberculosis Center, Nashville, TN, US

[3]Johns Hopkins University, Bloomberg School of Public Health, Baltimore MD, US

[4]Vanderbilt University, Department of Biostatistics, Nashville TN, US

[5]University of North Carolina, Department of Medicine, Division of Infectious Diseases, Chapel Hill NC, US

[6]Southern Alberta, HIV Clinic, Calgary, Alberta, Canada

[7]Sunnybook Research Institute, Sunnybrook Health Sciences Center, Toronto Ontario, Canada

[8]Johns Hopkins University, Department of Medicine, Division of Infectious Diseases, Baltimore MD, US

Abstract

Background—TB risk and mortality increase in the six months following HAART initiation. This short-term risk may be a consequence of HAART initiation and immune reconstitution. Alternatively, it may be due to confounding by low CD4+ counts and high HIV viral loads (VL). We assessed TB risk before and after HAART initiation while appropriately controlling for time-updated laboratory values and HAART exposure.

Methods—We conducted an observational cohort study among persons enrolled in the North American AIDS Cohort Collaboration on Research and Design from 1998 through 2011. A marginal structural model was constructed to estimate the association of HAART initiation and TB risk. Inverse probability weights for the probability of HAART initiation were incorporated.

Corresponding Author: April C. Pettit, MD, MPH, Vanderbilt University, 1161 21st Avenue South, A2200MCN, Nashville, TN 37232; Phone: (615) 343-0574; Fax: (615) 343-6160; april.pettit@vanderbilt.edu.

These results were presented in part at the Conference on Retroviruses and Opportunistic Infections, March 3–6, 2014, Boston, MA, Abstract #833 and the 19th International Workshop on HIV Observational Databases, March 26–28, 2015, Catania, Italy, Oral Abstract #3.

Conflicts of Interest: All authors declare no conflicts of interest.

Results—Among 26,342 patients, 94 TB cases were diagnosed during 147,557 person-years (p-y) of follow-up. Unadjusted TB rates were 93/100,000 p-y (95% Confidence Interval [CI]: 63, 132) prior to HAART initiation, 203/100,000 p-y (95% CI: 126, 311) ≤6 months following HAART initiation, and 40/100,000 p-y (95% CI: 29, 55) >6 months on HAART. After controlling for time-updated laboratory values, the adjusted odds of TB ≤6 months following HAART initiation and >6 months was 0.65 (95% CI: 0.28, 1.51) and 0.29 (95% CI: 0.16, 0.53), respectively.

Conclusions—TB risk in the first 6 months following HAART initiation is not higher than prior to HAART initiation after adjusting for CD4+ count and VL. These findings suggest that short-term TB risk may be related to low CD4+ counts and high VL near HAART initiation and support early HAART initiation to decrease TB risk.

Keywords

antiretroviral therapy; immune reconstitution inflammatory syndrome; marginal structural model; tuberculosis

INTRODUCTION

TB remains an important public health problem, particularly among HIV-infected persons[1]. Highly active antiretroviral therapy (HAART) is associated with decreases in TB risk by restoring CD4+ T lymphocytes and cell-mediated immunity[2–5]. However, TB risk and mortality has been observed to increase transiently in the 3–6 months following HAART initiation[6–14]. One hypothesis for this short-term increased risk is the unmasking of subclinical TB through immune restoration on HAART, which manifests in its most severe form as TB-associated immune reconstitution inflammatory syndrome (IRIS)[15,16]. In contrast, confounding by low CD4+ counts and high HIV viral loads prior to HAART initiation and in the 6 months following HAART initiation could explain the increased risk of TB after starting HAART.

Two randomized controlled trials have evaluated the effect of HAART initiation at higher CD4+ counts on incident TB risk as a secondary outcome[17–19]. While the number of TB cases were higher among the delayed treatment arms, the exact timing of the TB cases in relation to HAART initiation and the exact CD4+ count and viral load at the time of TB diagnosis are unclear (as CD4+ count and viral load may have varied from enrollment to time of TB diagnosis). These studies were not designed to evaluate the impact of HAART initiation and laboratory biomarkers (CD4+counts and viral load) on TB incidence during the first months following HAART initiation.

Alternatively, observational data can be utilized to assess the effect of HAART initiation on TB risk, while controlling for the time-dependent confounding of CD4+ count and viral load. Four previous observational studies have assessed TB risk in the same population of adults before and after HAART initiation, appropriately adjusting for time-updated covariates using marginal structural models[20]. The first study found a decreased risk of incident TB following HAART initiation, but HAART duration was not incorporated into the adjusted model[21]. The next three studies all found no effect of HAART initiation on

short-term incident TB. However, these studies either assessed HAART use in an intention-to-treat (ITT) format in which gaps in HAART use were not incorporated[22,23], assessed only a 3-month duration of HAART exposure in the adjusted model[22,23], or were limited by a low number of TB cases[24]. Assessment of HAART exposure in an ITT format may lead to an underestimation of the protective effective of HAART on TB risk compared to an as-treated format.

Given the varying methods and discrepant results from previous studies, we aimed to evaluate both the short-term and long-term effect of HAART on TB risk while appropriately controlling for time-varying HAART use and time-updated laboratory biomarkers (CD4+ counts and HIV viral loads). We sought to overcome the limitations of previous studies by evaluating the effect of HAART initiation on incident TB risk in a large, well-characterized cohort of HIV-infected persons, by incorporating both a 3-month and a 6-month duration of HAART exposure into the adjusted model, and by assessing HAART use in both an ITT and as-treated format.

METHODS

Patient population

We conducted an observational cohort study among HIV-infected adults enrolled in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) between 1998 and 2011[25]. Data for this study were from 13 cohorts: AIDS Linked to the IntraVenous Experience (ALIVE), Fenway Community Health Center (Fenway), Case Western Reserve University Immunology Unit Patient Care and Research Database (CWRU), AACTG Longitudinal Linked Randomized Trials (ALLRT), University of Alabama at Birmingham 1917 Clinic Cohort (UAB), Kaiser Permanente Northern California (KPNC), University of North Carolina Chapel Hill HIV Clinic (UCHCC), Montreal Chest Institute Immunodeficiency Service Cohort (MONT), Johns Hopkins HIV Clinical Cohort (JHHCC), HAART Observational Medical Evaluation and Research (HOMER), Vanderbilt Comprehensive Care Clinic HIV Cohort (VAND), Southern Alberta Clinic Cohort (SAC), and University of Washington HIV Cohort (UW). All sites were located in the United States or Canada, both resource-rich countries with low TB incidence. Patients were included if they were HIV-1 seropositive, had ≥2 visits within 12 months of the initial visit date, and were HAART-naïve. Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Persons with TB cases prior to enrollment were included and followed for additional TB episodes if there was a gap of at least 240 days between TB episodes. Additionally, persons with TB cases diagnosed within 30 days of the initial visit were excluded to remove prevalent TB cases from the analysis.

Study definitions

TB diagnoses were classified in accordance with US Centers for Disease Control and Prevention (CDC) guidelines as either culture-confirmed or culture-negative and were validated by local investigators via standardized abstraction forms[26]. Culture-negative disease was established by either: 1) signs, symptoms, and chest radiography consistent with

TB; 2) pathologic findings including necrotizing granulomas and acid fast bacilli or; 3) a positive nucleic acid amplification test and a clinical response to anti-TB therapy. NA-ACCORD sites participating in this study included all sites able to validate TB diagnoses based on this definition. The date of TB diagnosis was defined as the date of initiation of anti-TB therapy. Demographic and laboratory data were obtained. Study baseline was defined as the initial visit date. Baseline CD4+ lymphocyte count and HIV-1 RNA values were defined as the first available values within 120 days before or up to 7 days after the initial visit date.

Person-time was contributed from the time of the initial visit date until first TB diagnosis, loss to follow-up, death, or administrative censoring. The date of administrative censoring varied by cohort and ranged from December 2009 to December 2011. Loss to follow-up was defined as a gap of more than 12 months between available laboratory results; these patients were censored at the time of 12 months after their last available laboratory results.

HAART was defined as a regimen that contained at least three antiretroviral drugs including a protease inhibitor (with or without ritonavir boosting), a non-nucleoside reverse transcriptase inhibitor, a nucleoside reverse transcriptase inhibitor, an integrase inhibitor, or an entry inhibitor. Antiretroviral therapy not meeting the definition of HAART, was defined as not being on HAART. A person was considered on HAART after at least 7 days of exposure. HAART status was assessed in two ways: 1) intention-to-treat (ITT), in which once a person initiated HAART any subsequent gaps in HAART exposure were ignored and 2) as-treated (AT), in which gaps in HAART exposure were accounted for and the clock for duration of HAART exposure was re-started at each HAART initiation or re-initiation. The ITT analysis was performed in order to mimic a clinical trial investigating the impact of HAART initiation on incident TB. The AT analysis was performed in order to utilize the available real-world data accounting for patients stopping and re-starting HAART.

Statistical analysis

Chi-square and Wilcoxon Rank Sum tests were used to compare categorical and continuous variables, respectively. A marginal structural model was constructed to appropriately adjust for CD4+ lymphocyte count, a time-dependent confounder affected by HAART exposure. The marginal structural model had 3 components used to create inverse probability weights (IPW) incorporated into the primary model. The first was a logistic regression model for predicting the probability of HAART exposure in each month. The second component of the marginal structural model was a logistic regression model predicting the probability of loss to follow-up in each month. These models included time since initial visit date in months (including a quadratic), age at initial visit date (years), sex, race (black, non-black), foreign-born status (US or Canadian born, not-US or Canadian born), NA-ACCORD site, year of enrollment, injection drug use as HIV risk factor, baseline CD4+ lymphocyte count, baseline HIV-1 RNA, and current CD4+ count (including the square root); current HIV viral load (including log transformed) was also included in the model predicting the probability of loss to follow-up in each month. If a patient had more than one CD4+ or HIV viral load measurement during a given month, the average of these measurements was utilized; if a patient did not have a measurement during a given month, the value from the previous

month was carried forward. The third component of the marginal structural model was a logistic regression model predicting the probability of missing baseline laboratory values. This model included the same variables as the first two with the exception of time since study entry and CD4+ or HIV-1 RNA laboratory values.

A weighted pooled logistic regression model including robust standard errors was used to estimate the odds ratio (OR) for the risk of TB. The weights from the three components described above were multiplied to obtain the single weight incorporated into this model. This model included current HAART status (not on HAART, ≤180 days of HAART, or >180 days of HAART), time since initial visit date in months (including a quadratic), age at initial visit date (years), sex, race (black, non-black), foreign-born status (US or Canadian born, not-US or Canadian born), year of enrollment, injection drug use as HIV risk factor, baseline CD4+ lymphocyte count, and baseline HIV-1 RNA. The probability of starting (ITT and AT analyses) or stopping (AT analysis) HAART was estimated and incorporated into the weighted pool logistic regression model with inverse probability weights throughout the entire follow-up, including post-HAART initiation. The 180 day cut-off was chosen for the main analysis based on our findings of an elevated crude TB risk during this time period (Table 2). Additionally, a second set of analyses included HAART status with 90 days duration (not on HAART, ≤90 days of HAART, or >90 days of HAART) to be consistent with previous studies[22,23]. Sensitivity analyses including TB cases and follow-up during the first 30 days after enrollment was performed as done in a previous study[22].

Results are reported with stabilized weights truncated at the first and 99th percentiles. Findings using stabilized weights truncated at the fifth and 95th as well as the tenth and 90th percentiles were also assessed. The median of the untruncated stabilized weights was 0.98 (interquartile range [IQR] 0.58–1.34). All statistical tests were 2-sided. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using STATA version 13 (College Station, Texas, US).

RESULTS

There were 26,342 patients included in this study; these patients were followed for a total of 147,557 person-years (median 5.4 years). The median age at initial visit date was 39 years, 80% were male, 29% were black, 5% were non-US or Canadian born, and 17% reported injection drug use as an HIV risk factor. The median baseline CD4+ lymphocyte count was 301 cells per cubic milliliter (Interquartile Range [IQR]: 142–490 cells/mL^3), and median HIV-1 viral load was 23,751 copies per milliliter (IQR: 1,710–100,000 copies/mL). Baseline CD4+ lymphocyte count was missing for 777 (2.9%) and baseline HIV-1 viral load was missing for 1,104 (4.2%). There were 21,342 (81.0%) patients who initiated HAART during the study period and the median CD4+ count at HAART initiation was 262 cells/mL^3 (IQR: 154–370).

There were 124 patients who were diagnosed with TB after enrollment in NA-ACCORD. There were 10 patients with TB diagnoses both before and after enrollment in NA-ACCORD; 3 were excluded because there were <240 days between the date of TB diagnosed before enrollment and after enrollment. Of the 121 remaining TB cases, 27 were

excluded due to occurring within the first 30 days after enrollment. There were no patients with more than one TB case both occurring after enrollment. Therefore, 94 patients who developed TB during the study period were included in the primary analysis (64 per 100,000 p-y). The median time from enrollment to TB diagnosis was 390 days (IQR: 95–1,038 days).

Of the 94 patients with TB, 66 (70.2%) had pulmonary disease and 23 (24.5%) had extrapulmonary disease; site of disease was unknown for 5 (5.3%). TB cases were laboratory confirmed by smear or culture for 60 (63.8%); 41 (43.6%) were culture-positive and 38 (40.4%) were smear-positive. Patients with TB were more likely to be black, foreign born, and report injection drug use as an HIV risk factor. They were also more likely to have a lower baseline CD4+ lymphocyte count and higher baseline viral load. There were no differences in the median frequency of CD4+ measurements during the study period (Table 1).

Intention-to-treat analysis

In the ITT analysis, 31 TB cases occurred among persons prior to HAART initiation (93 per 100,000 p-y [95% CI: 63, 132]; 33,371 p-y of follow-up). Sixty-three TB cases occurred among persons after HAART initiation (55 per 100,000 p-y [95% CI: 42, 71]; 114,186 p-y of follow-up). Of these 63 cases, 21 occurred in the first 6 months following HAART initiation (203 per 100,000 p-y [95% CI: 126, 311]; 10,329 p-y of follow-up) and 42 occurred after more than 6 months of HAART (40 per 100,000 p-y [95% CI: 29, 55]; 103,857 p-y of follow-up) (Table 2).

In the adjusted marginal structural model, the aOR for the risk of TB among persons on HAART of any duration was 0.39 (95% CI: 0.22, 0.70) compared to those not on HAART. The aOR for TB in the first 6 months following HAART initiation was 0.65 (95% CI: 0.28, 1.51) and 0.29 (95% CI: 0.16, 0.53) after more than 6 months on HAART, compared to persons not on HAART (Table 3). The results were similar when HAART use was categorized as not on HAART, ≤ 3 months since HAART initiation, and over 3 months on HAART (Table 4). Results were also similar when stabilized IPW were truncated at the 5^{th} and 95^{th} percentiles or were truncated at the 10^{th} and 90^{th} percentiles (Supplementary Digital Content, Table 1).

There were 27 TB cases which occurred within the first 30 days after enrollment in NA-ACCORD. In a sensitivity analysis in which cases diagnosed within 30 days of the initial visit were included, the aOR for the risk of TB among persons in the first 6 months following HAART initiation was 0.36 (95% CI: 0.21, 0.64) compared to persons not on HAART. The aOR for the risk of TB among person after more than 6 months on HAART was 0.16 (95% CI: 0.10, 0.26) (Table 5).

As-treated analysis

In the as-treated analysis, 48 TB cases occurred among persons not on HAART (70 per 100,000 p-y [95% CI: 51, 92; 69,046 p-y of follow-up). Forty-six TB cases occurred among persons on HAART (59 per 100,000 p-y [95% CI: 43, 78; 76,511 p-y of follow-up). Of these 46 cases, 22 occurred in the first 6 months of HAART (152 per 100,000 p-y [95% CI: 95,

229]; 14,510 p-y of follow-up) and 24 occurred after more than 6 months of HAART (37 per 100,000 p-y [95% CI: 24, 56]; 64,001 p-y of follow-up) (Table 2).

Using the adjusted marginal structural model, the aOR for the risk of TB among persons on HAART of any duration was 0.35 (95% CI: 0.20, 0.61) compared to those not on HAART. The aOR for TB in the first 6 months following HAART initiation was 0.82 (95% CI: 0.38, 1.78) and 0.12 (95% CI: 0.06, 0.24) after more than 6 months on HAART, compared to persons not on HAART (Table 3). Results were similar when 3-months of HAART use was assessed (Table 4) and when varying the truncation of the stabilized weights (Supplementary Digital Content, Table 2).

In the sensitivity analysis including TB diagnosed within 30 days of the initial study visit, the aOR for the risk of TB among persons in the first 6 months following HAART initiation was 0.42 (95% CI: 0.24, 0.72) compared to persons not on HAART. The aOR for the risk of TB among persons after more than 6 months on HAART was 0.07 (95% CI: 0.04, 0.14) (Table 5).

DISCUSSION

In our study, the crude TB rate appeared to be highest in the first 6 months following HAART initiation (203 per 100,000 p-y [95% CI: 126, 311]) compared to the rate among those not on HAART (93 per 100,000 p-y [95% CI: 63, 132]) and those on HAART for more than 6 months (40 per 100,000 p-y [95% CI: 29, 55] (Table 2). However, after incorporating time-updated HAART exposure and controlling for time-updated CD4+ lymphocyte counts and HIV viral loads, HAART reduced the long-term odds of incident TB by 61% which is consistent with the findings of previous studies[2–5]. Moreover, HAART did not appear to increase the risk of TB during the first six months following HAART initiation (Table 3). The apparent increased crude TB risk during the first 6 months was confounded by low CD4+ lymphocyte counts and high HIV viral loads at the time of and for the first 6 months following HAART initiation.

It can be difficult in an observational study to determine if TB cases diagnosed shortly after entry into care are incident or prevalent cases. A previous study in the HIV-CAUSAL Collaboration excluded TB cases diagnosed in the first 30 days after enrollment in an attempt to exclude potentially prevalent cases[22]. Similar to HIV-CAUSAL, we found that inclusion of these cases in a sensitivity analysis led to an overestimation of the beneficial effect of HAART initiation on TB risk. Regardless, we found no evidence that HAART increased the risk of incident TB shortly following HAART initiation.

This study sought to overcome the limitations of previous studies in two important ways. First, we assessed HAART exposure in both an ITT and as-treated format. We hypothesized that the ITT analysis might underestimate the protective effect of HAART on TB risk. When comparing the results of our ITT and as-treated analysis using both the 6-month and the 3-month cutoff for categorization of HAART, the confidence intervals consistently overlapped (Tables 3–4). Therefore, we found no differences in the results based on the treatment of HAART exposure in an ITT or as-treated format.

Second, we categorized early HAART exposure using both a 3-month and a 6-month cutoff. We hypothesized that the 3-month cutoff might underestimate the effect of early HAART initiation on TB risk. When comparing the results using the 3-month and 6-month cutoff, the confidence intervals were again consistently overlapping in both the ITT and as-treated analyses (Tables 3–4). Therefore, we also found no differences in the results based on the categorization of early HAART exposure using a 3-month or 6-month cutoff.

These findings suggest that the "HIV test and treat" strategy should not lead to an increased TB risk early following HAART initiation[27]. This theoretical strategy would require universal HIV-testing and initiation of HAART immediately following diagnosis, regardless of CD4+ lymphocyte counts. Using this strategy, TB risk could potentially be decreased both by reducing the amount of time at which a patient's CD4+ lymphocyte count remains low and by decreasing HIV transmission. The impact of this strategy has been modeled using data from sub-Saharan Africa and shown that TB incidence rates in 2050 would be reduced by 66–97.7% depending on how quickly a patient initiated HAART following HIV diagnosis[28].

One limitation of this study is that the low number of TB events that limit the power to identify statistically significant differences. It is possible that some cases of TB were missed if they were not documented in the medical record. However, this is unlikely given that TB is a reportable disease in the US and Canada and these patients were receiving care for HIV-infection. A second limitation is that the clinical data required to determine if a TB case was due to immune reconstitution inflammatory syndrome (IRIS), particularly the short-term change in CD4+ counts and viral loads following HAART initiation, was not available. Further study is needed to determine if HAART would decrease the risk of TB-associated IRIS after adjustment for time-updated laboratory biomarkers. Thirdly, it is possible that the association between HAART exposure and TB risk could be confounded by other factors not included in our adjusted analyses. An additional limitation pertains the generalizability of these findings to resource-limited and high TB incidence settings.

In conclusion, we found that although the crude TB risk was highest in the first 6 months following HAART initiation, after controlling for CD4+ count and HIV viral load during this period, HAART was not associated with an increased the risk of TB. These findings highlight the need for continued vigilance for TB and close clinical follow-up shortly following HAART initiation given the elevated crude TB rates in the first 6 months following the initiation of HAART. They also support the theory that the "test and treat" strategy for HIV-infection should not lead to an increased TB risk in the early period following HAART initiation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

NA-ACCORD Collaborating Cohorts and Representatives:

AIDS Link to the IntraVenous Experience: Gregory D. Kirk

Adult AIDS Clinical Trials Group Longitudinal Linked Randomized Trials: Constance A. Benson and Ronald J. Bosch

Fenway Health HIV Cohort: Stephen Boswell, Kenneth H. Mayer and Chris Grasso

HAART Observational Medical Evaluation and Research: Robert S. Hogg, P. Richard Harrigan, Julio SG Montaner, Angela Cescon and Hasina Samji

HIV Outpatient Study: John T. Brooks and Kate Buchacz

HIV Research Network: Kelly A. Gebo and Richard D. Moore

Johns Hopkins HIV Clinical Cohort: Richard D. Moore

John T. Carey Special Immunology Unit Patient Care and Research Database, Case Western Reserve University: Benigno Rodriguez

Kaiser Permanente Mid-Atlantic States: Michael A. Horberg

Kaiser Permanente Northern California: Michael J. Silverberg

Longitudinal Study of Ocular Complications of AIDS: Jennifer E. Thorne

Multicenter Hemophilia Cohort Study–II: James J. Goedert

Multicenter AIDS Cohort Study: Lisa P. Jacobsoncand Gypsyamber D'Souza

Montreal Chest Institute Immunodeficiency Service Cohort: Marina B. Klein

Ontario HIV Treatment Network Cohort Study: Sean B. Rourke, Ann N. Burchell and Anita R. Rachlis

Retrovirus Research Center, Bayamon Puerto Rico: Robert F. Hunter-Mellado and Angel M. Mayor

Southern Alberta Clinic Cohort: M. John Gill

Studies of the Consequences of the Protease Inhibitor Era: Steven G. Deeks and Jeffrey N. Martin

Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy: Pragna Patel, John T. Brooks

University of Alabama at Birmingham 1917 Clinic Cohort: Michael S. Saag, Michael J. Mugavero, and James Willig

University of North Carolina at Chapel Hill HIV Clinic Cohort: Joseph J. Eron and Sonia Napravnik

University of Washington HIV Cohort: Mari M. Kitahata, Heidi M. Crane and Daniel R. Drozd

Vanderbilt Comprehensive Care Clinic HIV Cohort: Timothy R. Sterling, David Haas, Sally Bebawy, and Megan Turner

Veterans Aging Cohort Study: Amy C. Justice, Robert Dubrow, and David Fiellin

Women's Interagency HIV Study: Stephen J. Gange and Kathryn Anastos

NA-ACCORD Study Administration:

Executive Committee: Richard D. Moore, Michael S. Saag, Stephen J. Gange, Mari M. Kitahata, Keri N. Althoff, Rosemary G. McKaig, Amy C. Justice and Aimee M. Freeman

Administrative Core: Richard D. Moore, Aimee M. Freeman and Carol Lent

Data Management Core: Mari M. Kitahata, Stephen E. Van Rompaey, Heidi M. Crane, Daniel R. Drozd, Liz Morton, Justin McReynolds, and William B. Lober

Epidemiology and Biostatistics Core: Stephen J. Gange, Keri N. Althoff, Alison G. Abraham, Bryan Lau, Jinbing Zhang, Jerry Jing, Elizabeth Golub, Shari Modur, Cherise Wong, Brenna Hogan, Weiqun Tong and Bin Liu

Source of Funding: This work was supported by grants U01-AI069918, U01-AA013566, U01-AA020790, U01-AI31834, U01-AI34989, U01-AI34993, U01-AI34994, U01-AI35004, U01-AI35039, U01-AI35040, U01-AI35041, U01-AI35042, UM1-AI35043, U01-AI37613, U01-AI37984, U01-AI38855, U01-AI38858, U01-AI42590, U01-AI68634, U01-AI68636, U01-AI69432, U01-AI69434, U01-DA036935, U01-HD32632, U10-EY08052, U10-EY08057, U10-EY08067, U24-AA020794, U54-MD007587, UL1-RR024131, UL1-TR000083, F31-DA037788, G12-MD007583, K01-AI071754, K01-AI093197, K08-AI104352, K23-EY013707, K24-DA00432, K24-AI065298, KL2-TR000421, MO1-RR-00052, N02-CP55504, P30-AI027763, P30-AI094189, P30-AI110527, P30-AI27757, P30-AI27767, P30-AI036219, P30-AI50410, P30-AI54999, P30 AI110527, P30-MH62246, R01-AA16893, R01-CA165937, R01-DA04334, R01-DA11602, R01-DA12568, R24-AI067039, R56-AI102622, Z01-CP010214, and Z01-CP010176 from the National Institutes of Health, USA; contract CDC200-2006-18797 from the Center's for Disease Control and Prevention, USA; contract 90047713 from the Agency for Healthcare Research and Quality, USA; contract 90051652 from the Health Resources and Services Administration, USA; grants TGF-96118, HCP-97105, CBR-86906, CBR-94036 from the Canadian Institutes of Health Research, Canada; Canadian Institutes of Health Research (CIHR) New Investigator award (A. Burchell); Ontario Ministry of Health and Long Term Care; and the Government of Alberta, Canada. Additional support was provided by the Intramural Research Program of the National Cancer Institute, and National Institutes of Health.

References

1. World Health Organization. Global Tuberculosis Report 2015. Available at: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1 Accessed 3/7/2016
2. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. Lancet. 2002; 359(9323):2059–2064. [PubMed: 12086758]
3. Jones JL, Hanson DL, Dworkin MS, DeCock KM, Group AASoHD. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent Spectrum of HIV Disease Group. Int J Tuberc Lung Dis. 2000; 4(11):1026–1031. [PubMed: 11092714]
4. Santoro-Lopes G, de Pinho AM, Harrison LH, Schechter M. Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy. Clin Infect Dis. 2002; 34(4):543–546. [PubMed: 11797184]
5. Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS. 2007; 21(11):1441–1448. [PubMed: 17589190]
6. Lawn SD, Myer L, Bekker LG, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. AIDS. 2006; 20(12):1605–1612. [PubMed: 16868441]
7. Bonnet MM, Pinoges LL, Varaine FF, et al. Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden. AIDS. 2006; 20(9):1275–1279. [PubMed: 16816556]
8. Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. AIDS. 2005; 19(18):2109–2116. [PubMed: 16284460]
9. Seyler C, Toure S, Messou E, Bonard D, Gabillard D, Anglaret X. Risk factors for active tuberculosis after antiretroviral treatment initiation in Abidjan. Am J Respir Crit Care Med. 2005; 172(1):123–127. [PubMed: 15805184]
10. Moore D, Liechty C, Ekwaru P, et al. Prevalence, incidence and mortality associated with tuberculosis in HIV-infected patients initiating antiretroviral therapy in rural Uganda. AIDS. 2007; 21(6):713–719. [PubMed: 17413692]
11. Girardi E, Sabin CA, d'Arminio MA, et al. Incidence of Tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. Clin Infect Dis. 2005; 41(12):1772–1782. [PubMed: 16288403]
12. Sterling TR, Lau B, Zhang J, et al. Risk factors for tuberculosis after highly active antiretroviral therapy initiation in the United States and Canada: implications for tuberculosis screening. J Infect Dis. 2011; 204(6):893–901. [PubMed: 21849286]

13. Koenig SP, Rodriguez LA, Bartholomew C, et al. Long-term antiretroviral treatment outcomes in seven countries in the Caribbean. J Acquir Immune Defic Syndr. 2012; 59(4):e60–e71. [PubMed: 22240464]
14. Moore DM, Yiannoutsos CT, Musick BS, et al. Determinants of early and late mortality among HIV-infected individuals receiving home-based antiretroviral therapy in rural Uganda. J Acquir Immune Defic Syndr. 2011; 58(3):289–296. [PubMed: 21857358]
15. Lawn SD, Wilkinson RJ, Lipman MC, Wood R. Immune reconstitution and "unmasking" of tuberculosis during antiretroviral therapy. Am J Respir Crit Care Med. 2008; 177(7):680–685. [PubMed: 18202347]
16. Breen RA, Smith CJ, Cropley I, Johnson MA, Lipman MC. Does immune reconstitution syndrome promote active tuberculosis in patients receiving highly active antiretroviral therapy? AIDS. 2005; 19(11):1201–1206. [PubMed: 15990574]
17. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365(6):493–505. [PubMed: 21767103]
18. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis. 2014; 14(4):281–290. [PubMed: 24602844]
19. INSIGHT START Study Group. Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015; 373(9):795–807. [PubMed: 26192873]
20. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000; 11(5):550–560. [PubMed: 10955408]
21. Fairall LR, Bachmann MO, Louwagie GM, et al. Effectiveness of antiretroviral treatment in a South African program: a cohort study. Arch Intern Med. 2008; 168(1):86–93. [PubMed: 18195200]
22. HIV-CAUSAL Collaboration. Impact of antiretroviral therapy on tuberculosis incidence among HIV-positive patients in high-income countries. Clin Infect Dis. 2012; 54(9):1364–1372. [PubMed: 22460971]
23. Opportunistic infections and AIDS malignancies early after initiating combination antiretroviral therapy in high-income countries. AIDS. 2014; 28(16):2461–2473. [PubMed: 25265230]
24. Pettit AC, Jenkins CA, Stinnette SE, et al. Tuberculosis risk before and after highly active antiretroviral therapy initiation: does HAART increase the short-term TB risk in a low incidence TB setting? J Acquir Immune Defic Syndr. 2011; 57(4):305–310. [PubMed: 21423024]
25. Gange SJ, Kitahata MM, Saag MS, et al. Cohort profile: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Int J Epidemiol. 2007; 36(2):294–301. [PubMed: 17213214]
26. Case definitions for infectious conditions under public health surveillance. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1997; 46(RR-10):1–55.
27. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009; 373(9657):48–57. [PubMed: 19038438]
28. Lawn SD, Harries AD, Williams BG, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? Int J Tuberc Lung Dis. 2011; 15(5):571–581. [PubMed: 21756508]

Table 1

Clinical and Demographic Characteristics of the Study Population

Characteristic N=26,342	**Non-TB Cases N=26,248**	**TB Cases N=94**	***P*-value**
Male sex, number (%)	20,984 (80%)	75 (80%)	0.53
Age at enrollment in years, median (IQR)	39 (32–46)	38 (32–44)	0.33
Black race, number (%)	7,659 (29%)	37 (39%)	**0.02**
Foreign Born, number (%)	1,190 (5%)	18 (19%)	**<0.001**
IDU as HIV risk factor, number (%)	4,399 (17%)	30 (32%)	**<0.001**
Baseline absolute CD4+ lymphocytes (cells/mm3), median (IQR)	302 (142–490)	151 (60–279)	**<0.001**
Baseline HIV-1 RNA copies/mL, median (IQR)	23,729 (1,701–100,000)	60,700 (4,400–188,764)	**0.006**
Frequency of CD4+ lymphocyte count measurement (months), median (IQR)	3.2 (2.7–3.9)	3.2 (2.1–4.0)	0.61
Person-years of follow-up	147,361	196	

HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; TB, tuberculosis;

Table 2

TB Incidence According to Time From HAART Initiation

	Intention to Treat			As Treated		
Time Interval	**TB cases**	**Follow-up (p-y)**	**TB incidence (per 100,000 p-y) 95% CI**	**TB cases**	**Follow-up (p-y)**	**TB incidence (per 100,000 p-y) 95% CI**
Off HAART	31	33,371	93 63, 132	48	69,046	70 51, 92
HAART initiation- ≤3 months	8	5,217	153 66, 302	10	7,864	127 61, 234
>3 months −≤6 months	13	5,112	254 135, 434	12	6,646	181 93, 315
>6 months	42	103,857	40 29, 55	24	64,001	37 24, 56
Overall	94	147,557	64 51, 78	94	147,557	64 51, 78

CI, confidence interval; HAART, highly active antiretroviral therapy; p-y, person-years; TB, tuberculosis

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2017 August 15.

Table 3

Tuberculosis Risk Using 6 Month HAART Cut-off-Marginal Structural Model

Characteristic	Intention to Treat Analysis		As Treated Analysis	
	aOR[a]	95% CI	aOR[a]	95% CI
HAART status				
Not on HAART	Reference	Reference	Reference	
≤6 months of HAART	0.65	0.28, 1.51	0.82	0.38, 1.78
>6 months of HAART	**0.29**	**0.16, 0.53**	**0.12**	**0.06, 0.24**

aOR, adjusted odds ratio; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; mL, milliliters; US, United States

[a]Adjusted for baseline age, sex, race, Non-US or Canadian born, injection drug use as HIV transmission factor, baseline CD4+ count, baseline HIV-1 viral load, time since study entry (months), and year of enrollment.

Table 4

Tuberculosis Risk Using 3 Month HAART Cut-off-Marginal Structural Model

Characteristic	Intention to Treat Analysis		As Treated Analysis	
	aOR[a]	95% CI	aOR[a]	95% CI
HAART status				
Not on HAART	Reference	Reference	Reference	Reference
≤3 months of HAART	0.40	0.15, 1.07	0.60	0.25, 1.46
>3 months of HAART	**0.39**	**0.22, 0.69**	**0.27**	**0.15, 0.50**

aOR, adjusted odds ratio; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; mL, milliliters; US, United States

[a]Adjusted for baseline age, sex, race, Non-US or Canadian born, injection drug use as HIV transmission factor, baseline CD4+ count, baseline HIV-1 viral load, time since study entry (months), and year of enrollment.

Table 5

Tuberculosis Risk Using 6 Month HAART Cut-off (Including TB Cases Diagnosed in the First 30 Days Following Enrollment)-Marginal Structural Model

Characteristic	Intention to Treat Analysis		As Treated Analysis	
	aOR[a]	95% CI	aOR[a]	95% CI
HAART status				
Not on HAART	Reference	Reference	Reference	Reference
≤6 months of HAART	0.36	0.21, 0.64	0.42	0.24, 0.72
>6 months of HAART	**0.16**	**0.10, 0.26**	**0.07**	**0.04, 0.14**

aOR, adjusted odds ratio; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; mL, milliliters; US, United States

[a]Adjusted for baseline age, sex, race, Non-US or Canadian born, injection drug use as HIV transmission factor, baseline CD4+ count, baseline HIV-1 viral load, time since study entry (months), and year of enrollment.