Antiretroviral Therapy Initiation and Tuberculosis (TB) Risk in the United States (US) and Canada

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ABSTRACT (updated)

Background: Among HIV-uninfected persons in the US, TB incidence is ~ 3/100,000 person-years (p-y). Previous studies of HIV-infected persons in the US have found rates of ~200/100,000 p-y while on highly active antiretroviral therapy (HAART) and >700/100,000 p-y while not on HAART. HAART decreases TB risk over the long-term, but TB incidence is high shortly following HAART initiation. Previous studies have not assessed TB risk before and after HAART initiation in the same large population of HIV-infected persons from the US and Canada, and therefore both the short- and long term effects of HAART on TB risk in this population.

Methods: We conducted an observational cohort study among HIV-infected persons in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) from 1998 through 2011. Data were contributed by 11 cohorts and patients were included if they had ≥ 2 visits within the first12 months. Person-time was contributed from enrollment in NA-ACCORD until first TB diagnosis, loss to follow-up, death, or administrative censoring. TB cases diagnosed after enrollment were included and were defined as culture-confirmed or culture-negative according to Centers for Disease Control and Prevention guidelines. TB diagnosis and diagnosis date were validated via standardized abstraction forms.

Results: Among 29,660 HIV-infected patients (158,293 p-y of follow-up), 164 TB cases (102 culture-confirmed, 62 culture-negative) were diagnosed (104/100,000 p-y; 95% CI 88-121/100,000 p-y). Median follow-up was 4.1 years (IQR: 1.8-7.6 years). TB incidence varied according to time from HAART initiation (Table 2).

Conclusions: In this large North American cohort, TB incidence before HAART initiation was lower than previously described. Consistent with previous studies, TB incidence was highest during the first 6 months following HAART initiation. TB incidence declined after 6 months of HAART exposure, but still exceeded that of HIV-uninfected persons even after 4 years on HAART. This highlights the continued need for vigilance for TB among HIV-infected persons, particularly shortly following HAART initiation.

BACKGROUND

- In the US in 2012, the reported TB case rate was 3.2 cases per 100,000 p-y among HIV-infected and HIV-uninfected persons combined.[1]
- Previous studies of HIV-infected persons in the US have found TB case rates of ~200/100,000 p-y while on HAART and >700/100,000 p-y while not on HAART.[2] HAART decreases TB risk over the long-term, but TB incidence is high shortly following HAART initiation.[3]
- Previous studies have not assessed TB risk before and after HAART initiation in the same large population of HIV-infected persons from the US and Canada, and therefore both the short- and long term effects of HAART on TB risk in this population.

METHODS

Patient population

- Observational cohort study among HIV-infected persons in the North American AIDS Cohort Collaboration on Research and Design from 1998-2011.
- Data were contributed by 11 cohorts including: AIDS Link to the IntraVenous Experience (ALLIVE), AACTG Longitudinal Linked Randomized Trials (ALLRT), Johns Hopkins HIV Clinical Cohort (JHHCC), Montreal Chest Institute Immunodeficiency Service Cohort, (MONT) Case Western Reserve University Immunology Unit Patient Care and Research Database (CWRU), Southern Alberta Clinic Cohort (SAB), University of Alabama at Birmingham 1917 Clinic Cohort (UAB), University of North Carolina Chapel Hill HIV Clinic (UCHCC), University of Washington HIV Cohort (UW), Vanderbilt Comprehensive Care Clinic HIV Cohort (VAND), and Fenway Community Health Center (Fenway).
- Patients were included if they had at least 2 visits within the first 12 months.
- TB cases diagnosed after enrollment were included. TB cases diagnosed prior to enrollment in NA-ACCORD and recurrent TB cases were excluded.

Study definitions

- TB diagnoses were classified as either :
  1) Culture-confirmed : isolation of *M. tuberculosis* from a clinical specimen
  2) Culture-negative: signs and symptoms compatible with TB or clinical evidence of current disease, treatment with two or more anti-TB medications, and a completed diagnostic evaluation.
- Person-time was contributed from the time of enrollment into NA-ACCORD until first TB diagnosis, loss to follow-up, death, or administrative censoring.
- TB diagnosis and diagnosis date were validated via standardized abstraction forms.
- CD4 at HAART initiation was defined at the CD4 closest to the date of HAART initiation within a window for -120 days and +7 days.
- CD4 at TB diagnosis was defined as the CD4 closest to the date of TB diagnosis within a window of -45 days and +45 days.

Statistical analysis

- For continuous variables, median and interquartile range (IQR) are shown and 95% CIs computed. Comparisons were made using the Wilcoxon rank-sum test.
- For categorical variables, number (%) are shown. Comparisons were made using the Fisher's exact test.
- Exact Binomial Confidence intervals were calculated for TB incidence rates.
- Each TB case which occurred while on HAART was matched to 10 controls who initiated HAART but did not develop TB. Patients were eligible as controls if:
  1. There was a CD4+ count available within a window of -120/+7 days of HAART initiation and this CD4+ value was within a window of +/- square root (CD4+ count) of the CD4+ count value of the TB case at HAART initiation.
  2. There was a CD4+ count available within a window of +/- 30 days from a date corresponding to the duration of time between HAART initiation and TB diagnosis for the TB case.
- Mixed effects linear regression was used to compare the change in CD4 count from HAART initiation to TB diagnosis among persons who developed TB to those who did not develop TB; matching group was included as a random effect.
- All P-values were two-sided. P-values <0.05 were considered statistically significant.

RESULTS

Table 1. Demographic characteristics of the study population.

Characteristic N=29,660	Persons who did not develop TB after enrollment N=29, 496	Persons who developed TB after enrollment N=164	P-value
Male sex N (%)	22, 813 (77%)	121 (74%)	0.30
Age at enrollment Median (IQR)	38 (32-44)	37 (31-43)	0.43
Black race N (%)	11, 946 (40%)	82 (50%)	0.02
Born outside the US/ Canada N (%)	2, 415 (8%)	52 (32%)	<0.001
Injection Drug Use N (%)	6, 136 (21%)	51 (31%)	0.002

Table 2. TB incidence according to time from HAART initiation.

Time Interval	TB cases	Person-Years of follow-up	TB incidence rate per 100,000 p-y	95% Confidence Interval
Off HAART	108	72,028	150	123-181
HAART initiation-≤3 months	14	5,063	277	151-464
>3 months-≤6 months	15	4,746	316	177-521
>6 months-≤9 months	5	4,373	114	37-267
>9 months-≤1 year	2	4,341	46	6-166
>1 year-≤2 years	5	14,529	34	11-80
>2 years-≤3 years	5	11,784	42	14-99
3 years-≤4 years	5	9,622	52	17-121
>4 years	5	31,806	16	5-37

Table 3. Clinical characteristics of TB cases

Characteristic N=164	Number	Percent
Smear Positive	81	49%
Culture Positive	102	62%
TST or IGRA completed prior to TB diagnosis	32	19%
Treatment for latent TB infection prior to TB diagnosis	21	13%
Drug resistance		
Rifamycin	3	2%
Isoniazid	7	4%
MDR (Isoniazid and Rifamycin)	1	0.6%
Rifabutin-based therapy	63	38%

TST: Tuberculin Skin Test; IGRA: Interferon Gamma Release Assay; MDR: Multi-drug resistant

Table 4. Change in CD4 from HAART initiation for TB Cases Within 6 Months of HAART Initiation and Matched Controls (matched by CD4 at HAART initiation)

Characteristic	TB Cases N=23	Controls N=230
CD4 at HAART initiation (cells/mL^3)	78 (15-152)	78 (21-148)
Change CD4 from HAART initiation to TB or a similar time interval for controls	0 (-11, 80)	70 (0-175)
Linear Regression Model		P-value
Change in CD4 from HAART initiation to TB or a similar time interval for controls (95% CI)	-98 (-152, -43)	<0.001

LIMITATIONS

- Follow up for TB was passive and cases not documented in the medical record were not included ,which could lead to under-ascertainment of TB cases.
- Clinical information to determine whether a TB case was due to TB-associated immune reconstitution inflammatory syndrome (IRIS) were not collected.

CONCLUSIONS

- In this large North American cohort, TB incidence before HAART initiation was lower than previously described.
- Consistent with previous studies, TB incidence was highest during the first 6 months following HAART initiation. TB incidence declined after 6 months of HAART exposure, but still exceeded that of HIV-uninfected persons even after 4 years on HAART. These results highlight the continued need for vigilance for TB among HIV-infected persons, particularly shortly following HAART initiation.
- The change in CD4 from HAART was substantially lower (97 cells/mL^3 lower) among TB cases occurring within the first 6 months following HAART initiation compared to controls. This suggests that the TB risk may remain high in the 6 months following HAART initiation due to a prolonged low CD4+ count following study entry, despite HAART initiation.

REFERENCES

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