
Original article

Risk of tuberculosis after antiretroviral treatment initiation: a comparison between efavirenz and nevirapine using inverse probability weighting

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Background: There is a high incidence of tuberculosis (TB) early after antiretroviral therapy (ART) initiation. This historical cohort study evaluated the association of efavirenz (EFV) compared to nevirapine (NVP) with post-ART TB among patients initiated on first-line ART from 2005 to 2009 in a large, urban HIV clinic in Uganda.

Methods: Hazard ratios (HR) for developing TB were computed using multivariable Cox proportional hazards models with inverse weighting of the probability of being prescribed NVP or EFV (calculated by a multivariable logistic regression model), stratifying by baseline CD4+ T-cell count. Adjustment for time-updated CD4+ T-cell count, restriction of the analysis to patients remaining in follow-up and a TB-free survival analysis were performed as sensitivity analyses.

Results: ART was initiated in 5,797 patients; 66% were women with a mean age of 37 years (sd 9) and a median baseline CD4+ T-cell count of 117 cells/mm³ (IQR 43–182). Overall, 60% (n=3,484) were initiated on NVP and 40% (n=2,313) on EFV. In the first 2 years of ART, 377 patients developed TB. The use of EFV compared to NVP was independently associated with higher TB incidence in patients with a baseline CD4+ T-cell count <100 cells/mm³ (HR 2.05 [95% CI 1.29, 3.27]; P=0.003), but not at higher CD4+ T-cell counts (HR 0.71 [95% CI 0.39, 1.31]; P=0.428). These estimates were robust to all sensitivity analyses.

Conclusions: There was a higher incidence of TB in patients with baseline CD4+ T-cell counts <100 cells/mm³ initiated on EFV compared to those initiated on NVP. Further research in a trial setting or a larger multisite observational cohort is needed to confirm these findings.

Introduction

HIV-infected patients have a higher risk of developing tuberculosis (TB) than HIV-uninfected patients [1]. Antiretroviral therapy (ART) can reduce this risk by an estimated 67% according to a recent meta-analysis [2,3]. It will remain at a higher level than that of the general population, however, possibly due to persisting immune response defects, incomplete CD4+ T-cell recovery or high re-infection rates [2]. Early after starting ART, the risk of TB is very high, which is due to unmasking of previously existent but subclinical TB [3,4]. Many studies have reported on risk factors associated with the development of active TB after ART initiation, with the most important being low baseline CD4+ T-cell count, low time-updated CD4+ T-cell count, male sex and low body weight at ART initiation [3,5–7].

First-line ART regimens prescribed in most low- and middle-income countries are standardized and typically consist of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI), thereby preserving protease inhibitors (PIs) for second-line regimens [8]. The choice of ART at the patient level is made by the
prescribing clinician and is not governed by strict guidelines. Often the choice is based on non-clinical factors, such as availability resulting from stock-outs or delivery of specific drug combinations by different donors.

Several studies have investigated the association between the incidence of TB after ART initiation and the use of PIs or NNRTIs in both TB-low and -high prevalent settings [6, 9–11], but none have addressed the risk of TB associated with specific NNRTIs. An association could have implications on prescribing guidelines throughout TB-high prevalent HIV care settings. We aimed to evaluate the association of post-ART TB incidence with efavirenz (EFV)- compared to nevirapine (NVP)-containing regimens, and whether this association differed in separate, clinically relevant CD4+ T-cell count strata.

Methods

Setting

The Infectious Diseases Institute (IDI) is part of Makerere University College of Health Sciences in Kampala, Uganda. Its focus is on prevention, care and treatment of HIV-infected patients, on research into HIV/AIDS and related diseases in the African setting, and on training of African healthcare workers in HIV/AIDS management. At the time of this analysis, the Adult Infectious Diseases Clinic (AIDC) had registered >26,000 HIV-infected patients since its inception in 2002, of whom >8,000 had initiated ART and >10,000 were in active follow-up. Treatment of HIV followed Ugandan national guidelines [12], and diagnosis and treatment of TB was offered on-site and also followed national guidelines [13]. The AIDC and its treatment protocols for HIV and TB have been described in detail before [14–16]. CD4+ T-cell counts were measured every 6 months, and more often on indication. Diagnosis of TB was based on acid fast bacilli microscopy (of sputum or a lymph node aspirate), chest radiology, abdominal ultrasonography or on clinical suspicion. Mycobacterial culture was not routinely available. All care at the IDI was free of charge.

Choice of first-line ART

At the time of our study, ART was recommended in patients with a CD4+ T-cell count of <250 cells/mm³ [17]. Available first-line antiretroviral drugs were stavudine (d4T), zidovudine (AZT) and lamivudine (3TC) as NRTIs, and NVP and EFV as NNRTIs. Choice of first-line ART was at the discretion of the prescribing medical officer but was dependent on various factors. First, it depended on which funding institution was to provide the ART for that particular patient: ART from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) in collaboration with the Ugandan Ministry of Health (MoH) was mainly d4T/3TC/NVP in a fixed-drug combination tablet, whereas ART from the United States President's Emergency Plan for AIDS Relief consisted mainly of AZT/3TC with EFV [18]. In June 2008, the MoH issued guidelines to switch all patients on a d4T-based regimen to an AZT-based regimen, which led to GFATM/MoH also providing AZT/3TC, offered as a fixed-drug combination tablet with NVP [12]. Second, if a patient was on rifampicin-based treatment for active TB, the preferred ART was EFV-based to avoid the interaction between rifampicin and NVP, in accordance with the World Health Organisation (WHO) and national ART and TB treatment guidelines [13, 19]. Therefore, among patients in whom active TB could not be identified at the time of ART initiation but who the prescribing medical officer suspected of harbouring subclinical TB (for example, patients with very low CD4+ T-cell counts or a low body mass index), he/she would have been more likely to prescribe an EFV-based regimen to avoid switching of ART after a diagnosis of unmasking TB. Last, EFV is contraindicated in pregnancy. Therefore, EFV-based regimens are less likely to be prescribed in women of child-bearing age who have no other pressing indication to start EFV [19].

Data collection

Data on clinical parameters, WHO stage, ART and adherence, toxicities and opportunistic infections were routinely collected at each clinic visit (every 4 weeks) and were entered into a database to which laboratory data were added electronically. The TB diagnosis was validated by pharmacy data on TB drug prescriptions, as previously described [14]. Regular clinic monitoring and evaluation of this database by verification with the patient’s medical notes were performed by a team of trained nurses and medical officers.

Ethical approval

The Institutional Review Boards of the IDI, the Makerere University College of Health Sciences and the Uganda National Council for Science and Technology gave permission to collect and use these clinical data for clinical research. We extracted anonymised data for our study from this database.

Study design, selection criteria and study outcome

We used a historical cohort study design. All patients who were initiated on first-line EFV- or NVP-based ART at the IDI between January 2005 and December 2008 were eligible for inclusion. Patients with a history of active TB or patients who were on treatment for TB at ART initiation were excluded, as were patients whose chart was unavailable for review to ascertain their TB diagnosis. Observations after switching to second-line ART were also excluded from the analysis.
The study outcome was incident TB in the first 2 years of first-line ART.

Definitions

Incident TB was defined by the start of TB treatment irrespective of a TB diagnosis made in our clinic or elsewhere and whether the diagnosis was based on bacteriological testing or on clinical suspicion. This definition was chosen as mycobacterial cultures were not routinely available and as a substantial proportion of TB cases were sputum-smear-negative. We defined loss to follow-up (LFU) in patients on ART as no documented clinic attendance for >90 days [20]. Baseline CD4+ T-cell counts were the closest recorded values to the ART start date, with maximum 6 months pre- and 15 days post-ART initiation.

Statistical methods

As outlined above, prescription of an EFV- or NVP-based regimen was not due to chance alone but was related to multiple factors. When estimating an association of the ART regimen and the risk of TB, not controlling for these systematic differences between the two groups would lead to ‘bias by indication’ [21,22]. Therefore, the probability (or propensity score) of being prescribed an EFV- or NVP-based regimen was calculated for each individual in our study [23]. This was done by fitting a multivariable logistic regression model for the prescription of EFV or NVP, including all the factors potentially associated with NNRTI assignment in our setting: sex, age, baseline CD4+ T-cell count, weight, year of ART initiation and ART funding source. We thereby assumed to also cover the most important unmeasurable factors. We did not include different NRTI-backbone regimens due to collinearity: NVP or EFV were almost always (94%) combined with the same NRTIs (NVP with 3TC and d4T and EFV with 3TC and ZDV). Hypothetical interactions between these variables were also included to arrive at a saturated model, which was then used to predict the probability of treatment exposure for each individual in the study.

A survival model was fitted using inverse probability weighting; each patient received a weight inversely proportional to their propensity score [21]. Incidence rates of TB in the first 2 years of first-line ART were calculated per 100 person-years at risk. Hazard ratios (HRs) were computed using a multivariable Cox proportional hazards model with time-varying covariates stratified by baseline CD4+ T-cell count. HRs were initially calculated for four strata of baseline CD4+ T-cell count (<50, 50–99, 100–199 and ≥200 cells/mm3), which were then collapsed to a smaller number of strata based on statistical inference and clinical relevance. The covariates used in the calculation of the propensity scores were excluded. Cumulative incidence curves were generated using survival analysis and were compared using the log-rank test for equality of survivor functions. Patients were censored at the time of death or transfer to another clinic, at the date of the last visit to the clinic for patients lost to follow-up, or at the last visit date before December 2009 for patients initiated on ART after December 2007.

To further explore the potential association between NNRTI use and TB incidence, we performed a number of sensitivity analyses. To assess whether an effect was mediated via factors other than CD4+ T-cell count increase, we included time-updated CD4+ T-cell count (per 100 cells/mm3 higher count) as a covariate in the stratified Cox proportional hazards model (sensitivity analysis 1). To assess whether an effect could be influenced by differential mortality rates in the two groups, we performed a TB-free survival analysis using a combined end point of incident TB or death during the first 24 months on ART (sensitivity analysis 2). In this model we maintained the same stratification and covariates as in the first sensitivity analysis. Last, we explored differential follow-up in the model including time-updated CD4+ T-cell counts by restricting our patient population to those who had not died, were not transferred out or were lost to follow-up (sensitivity analysis 3).

Interactions between variables were investigated and tested using the Wald test, and were included in the model if significant. All statistical tests were two-sided at an α-value of 0.05 and were conducted using STATA version SE 11.1 (College Station, TX, USA).

Results

Patient characteristics and follow-up

A total of 5,797 patients were included in the analysis. The majority were women (66%) with a mean age of 37 years (sd 8.7) and a median baseline CD4+ T-cell count of 117 cells/mm3 (IQR 43–182). A total of 3,484 (60%) patients were started on an NVP-based regimen, and 2,313 patients (40%) were started on an EFV-based regimen. Baseline characteristics of the two groups are shown in Table 1.

At 2 years after ART initiation, 2,895 (50%) patients were still in active follow-up, 282 (5%) had died, 590 (10%) had been transferred to a different clinic and 728 (13%) were LFU. A total of 1,302 (22%) had not yet reached 2 years on ART at the time of censorship of the data, but were not lost. Follow-up differed slightly among the two groups: deaths and LFU were similar (5% versus 5% deaths and 14% versus 11% LFU); more patients on EFV were transferred-out compared to those on NVP (18% versus 5%); and as EFV became more widely available in later years, more patients on EFV had not completed 2 years on ART in December.
2009 (36% versus 13%). In the two groups, similar median last CD4+ T-cell counts were found before death (108 cells/mm³ [IQR 26–189] in the NVP group versus 105 cells/mm³ [IQR 25–142] in the EFV group), at loss to follow-up (174 cells/mm³ [IQR 95–288] versus 153 cells/mm³ [IQR 84–254]) and at transfer (159 cells/mm³ [IQR 95–288] versus 153 cells/mm³ [IQR 84–254]). Censoring in the EFV group was distributed evenly between patients with a baseline CD4+ T-cell count <100 cells/mm³ and those with higher baseline CD4+ T-cell counts (36% and 32%, respectively).

Incidence of TB after ART and associated risk factors

In the first 2 years of ART, 377 patients developed TB in 6,616 person-years of follow-up, which amounted to an incidence rate of 6.2 (95% CI 5.3, 7.2) per 100 person-years at risk. The median inverse of the propensity score (the weight) was 6.2 (IQR 1.1–16.2). In the initial baseline CD4+ T-cell count strata, EFV use compared to NVP use seemed to be associated with higher TB incidence in patients with lower CD4+ T-cell counts, and with a lower TB incidence in patients with higher CD4+ T-cell counts, although the adjusted HRs were only statistically significant in the group of patients with a CD4+ T-cell count between 50 and 100 cells/mm³ (Table 2). On further collapsing of the baseline CD4+ T-cell count strata to ≥100 or <100 cells/mm³, patients initiated on EFV in the lower stratum (<100 cells/mm³) were found to have a higher TB incidence than patients initiated on NVP (HR 2.05 [95% CI 1.29, 3.27]; P=0.003), whereas there was no association in patients initiated at a higher CD4+ T-cell count (HR 0.71 [95% CI 0.39, 1.31]; P=0.278). The estimates of the baseline multivariable Cox proportional hazards model and of the three sensitivity analyses are shown in Table 3.

We investigated whether differential CD4+ T-cell count restoration in both groups could explain the association between EFV use and TB in the lower baseline CD4+ T-cell count stratum. Including time-updated CD4+ T-cell count in the model led to almost no change in the estimates regarding EFV use compared to NVP use (Table 3; sensitivity analysis 1). The results showed the previously described protective effect of a higher time-updated CD4+ T-cell count on TB incidence [5].

Despite overall mortality not being different between the groups, we explored whether differential timing of death could have led to a differential risk of being diagnosed with TB. The TB-free survival analysis showed similar results: the risk of being diagnosed with TB or of dying was higher in patients with a low baseline CD4+ T-cell count initiated on EFV, and lower in those with a high baseline CD4+ T-cell count (Table 3; sensitivity analysis 2).

We then went on to assess whether differential LFU could underlie the association between EFV use and higher risk of TB in patients with low baseline CD4+ T-cell counts. Restricting our patient population to those remaining in care (n=4,197) had little effect on the estimates (Table 3; sensitivity analysis 3).

Figure 1 shows the cumulative incidence of TB in EFV and NVP users stratified by the baseline CD4+ T-cell count strata.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>All patients</th>
<th>Nevirapine</th>
<th>Efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>5,797 (100)</td>
<td>3,484 (60.1)</td>
<td>2,313 (39.9)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>3,847 (66.4)</td>
<td>2,375 (68.3)</td>
<td>1,470 (63.6)</td>
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<tr>
<td>Mean age, years (sd)</td>
<td>37.2 (8.7)</td>
<td>37.1 (8.8)</td>
<td>37.5 (8.6)</td>
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<tr>
<td>Weight</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55 kg, n (%)</td>
<td>2,784 (48.0)</td>
<td>1,695 (48.7)</td>
<td>1,089 (47.1)</td>
</tr>
<tr>
<td>≥55 kg, n (%)</td>
<td>3,013 (52.0)</td>
<td>1,789 (51.3)</td>
<td>1,224 (52.9)</td>
</tr>
<tr>
<td>WHO stage*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I and II, n (%)</td>
<td>2,184 (37.7)</td>
<td>1,237 (35.5)</td>
<td>947 (40.9)</td>
</tr>
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<td>III, n (%)</td>
<td>2,282 (39.4)</td>
<td>1,399 (40.2)</td>
<td>883 (38.2)</td>
</tr>
<tr>
<td>IV, n (%)</td>
<td>1,321 (22.8)</td>
<td>841 (24.1)</td>
<td>480 (20.8)</td>
</tr>
<tr>
<td>Median baseline CD4+ T-cell count, cells/mm³ [IQR]*</td>
<td>117 (43–182)</td>
<td>105 (37–176)</td>
<td>138 (53–190)</td>
</tr>
<tr>
<td>Baseline CD4+ T-cell count ≥200 cells/mm³, n (%)</td>
<td>974 (16.8)</td>
<td>544 (15.6)</td>
<td>430 (18.6)</td>
</tr>
<tr>
<td>100–199 cells/mm³, n (%)</td>
<td>2,159 (37.2)</td>
<td>1,198 (34.4)</td>
<td>961 (41.6)</td>
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<tr>
<td>50–99 cells/mm³, n (%)</td>
<td>921 (15.9)</td>
<td>597 (17.1)</td>
<td>324 (14.0)</td>
</tr>
<tr>
<td>&lt;50 cells/mm³, n (%)</td>
<td>1,540 (26.6)</td>
<td>1,003 (28.8)</td>
<td>537 (23.2)</td>
</tr>
</tbody>
</table>

*Data on WHO stage and baseline CD4+ T-cell count were not available for 10 patients (7 on nevirapine and 3 on efavirenz) and 203 patients (142 on nevirapine and 61 on efavirenz), respectively.
The use of EFV- compared to NVP-based first-line ART in patients with a baseline CD4+ T-cell count <100 cells/mm³ was associated with a higher TB incidence in the first 2 years after ART initiation. This effect was not seen in patients initiated on EFV with a higher baseline CD4+ T-cell count; if anything, there seemed to be a trend in the opposite direction. To our knowledge, no previous studies on differences in post-ART TB rates between the different NNRTIs have been done.

The reported higher TB incidence with the use of EFV in patients with very low CD4+ T-cell counts could be a result of the prescribing medical officer’s excellent recognition of a high likelihood of subclinical TB. Such patients would be initiated on EFV to avoid switching at a later stage due to interactions with TB medication. The methodology used in our analysis makes this explanation unlikely, however. The inverse probability weighting approach minimized bias by indication by adjusting for factors which could make the medical officer suspect subclinical TB, such as low CD4+ T-cell count, low body weight and male sex. Residual confounding by these same covariates was explored and was not found. CD4+ T-cell count, as the main predictor

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of TB incidence post-ART initiation [5], was controlled for twice in our analysis: baseline CD4+ T-cell count was included in our propensity score calculation and our multivariable model included time-updated CD4+ T-cell count. The effect was also robust to analyses to investigate whether it could be explained by differential mortality or loss to follow-up. Despite all these measures, we still found an independent effect of EFV in patients starting ART with low CD4+ T-cell counts. We therefore conclude that the effect reported is a real EFV-related effect.

Our finding is surprising, as the comparable efficacies of NVP and EFV have been demonstrated by several randomized controlled trials and have been corroborated by a meta-analysis [24,25], after initial cohort studies suggested EFV to be more effective [26–29]. Both drugs have similar virological success rates, and no differences in immunological response, HIV viral load decline, mortality or progression to AIDS have been found. It thus seems unlikely that the higher risk of TB with EFV in patients with low CD4+ T-cell counts is due to differences in effectiveness of HIV treatment. Explanations are speculative, but could include a direct relationship between the use of EFV and active TB, other than via HIV-1 viral load or CD4+ T-cell count. Recent evidence showed that EFV is associated with lower vitamin D levels, whereas NVP was not [30]. In turn, patients with active TB disease are known to have lower vitamin D levels [31]. A recent paper found a temporal association between low seasonal vitamin D levels and increased new TB case notifications in South Africa [32], sparking interest in low vitamin D levels as a risk factor of TB disease. It has been suggested that the increased risk of TB in patients with low vitamin D levels could be increased in patients with HIV, particularly in patients with very low CD4+ T-cell counts [33]. Alternatively, NVP metabolites have been shown to modify tryptophan [34]. Indoleamine 2,3 dioxygenase, is an enzyme which controls tryptophan degradation and has been implicated in the host’s ability to form granulomas to contain TB disease [35].

Further research is needed to solidify these findings, preferably in a randomized controlled trial setting or, if not feasible, in larger multi-site observational cohort studies or by a meta-analysis. If this effect is consistently found, it should spark a debate on NNRTI initiation guidelines in patients with low CD4+ T-cell counts in high TB prevalent settings.

We cannot exclude the possibility of other factors influencing the prescription of EFV versus NVP. If present, these were unmeasurable and therefore unable to be corrected for. The weighted analysis would have accounted for the earlier wide-scale availability of NVP leading to more complete follow-up in that group. It is unclear why more patients on EFV were transferred out. It could possibly simply be due to the time period; IDI’s active transfer-out policy was initiated when the clinic became overburdened and when IDI started supporting the Kampala City Council Clinics to enable the transfers (in 2007). This coincided with the time period in which more patients were being initiated on EFV instead of NVP, due to the phasing out of d4T (mid-2008). Other limitations of our analysis were the lack of microbiological confirmation of TB diagnoses, the historical cohort study design and the use of routinely collected data with incomplete data and outcome ascertainment.

In conclusion, there was a higher incidence of TB in patients with baseline CD4+ T-cell counts <100 cells/mm3 initiated on EFV compared to those initiated on NVP using a method minimizing bias by indication. Further research in a trial setting or a larger multi-site observational cohort is needed to confirm these findings.

Acknowledgements

SMH, YCM, ANK and FvL conceived and designed the experiments. SMH, ANK and FvL analysed the data. All authors wrote the manuscript, and read and met the ICMJE criteria for authorship. All authors agree with the manuscript’s results and conclusions. SMH wrote the first draft.

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Disclosures statement

All authors declare no competing interests.

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