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Incidence and risk factors for tuberculosis at a rural HIV clinic in Uganda, 2012–2019; A retrospective cohort study

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Abstract

Background Tuberculosis (TB) is the leading cause of death among people living with HIV (PLHIV). Antiretroviral therapy (ART) initiation lowers the risk of HIV-associated TB. Earlier studies have shown TB incidence to be high in the first year of ART. We undertook a study to (1) assess the incidence of TB and (2) associated factors among persons initiating ART in a rural cohort.

Methods We conducted a retrospective cohort analysis study among PLHIV aged ≥ 18 years, initiated on ART from January 1, 2012, to December 31, 2019, and TB disease-free at the time of ART initiation, at Kalisizo ART clinic. TB disease incidence was calculated by dividing the number of new TB cases by the total follow-up time expressed per 100 person-years among persons followed up until the date of incident TB disease, loss to follow-up, transfer out, death or censored at the end of the study; whichever occurred first. Factors associated with TB disease incidence were assessed in the multivariable analysis by Poisson regression analysis at 5% significance level.

Results For the period 2012 to 2019, 2,589 PLHIV were initiated on ART; 57% (1,470/2,589) were female. Females were more likely to be aged below 35 years while males were more likely to be aged 25–44 years ($p < 0.001$). Eighty-seven per cent (1,269/1,470) of females compared to 78% (866/1,119) of males were in WHO clinical stage 1 ($p < 0.001$). Sixty-one TB disease events were observed in 7,363 person-years. The overall TB disease incidence was 0.83 (95% CI: 0.63–1.06) per 100 person-years. Males were more likely than females to develop TB disease, adjusted incidence rate ratio (adj IRR) 2.13 (95% CI: 1.27–3.57) per 100 person-years, $p = 0.004$. Compared to using ART for 0–5 months, time on ART was associated with a lower TB incidence rate at 6–12 months, 13–24 months, > 24 months (adj IRR 0.20 (95% CI: 0.09–0.46), 0.14 (95% CI: 0.06–0.33), 0.16 (95% CI: 0.08–0.31) $p < 0.001$ respectively).

Conclusions and recommendations Incidence of TB among PLHIV on ART was low in this rural population. Clinicians offering care to people with HIV in the rural setting should have a heightened index of suspicion for TB disease.

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Keywords TB incidence during ART, Tuberculosis in HIV patients, TB/HIV prevalence, Tuberculosis in rural areas, Africa, Tuberculosis, TB

Background

TB remains a leading cause of morbidity and mortality among people living with HIV (PLHIV). In 2022, of the estimated 10.6 million people who developed TB globally, 6.3% were PLHIV [1]. Relatedly, of the estimated 1.3 million deaths caused by TB, 13% were PLHIV. Uganda is on the global lists of 30 high-burden TB and HIV-associated TB countries with an estimated annual TB incidence of 234 cases per 100,000 population [2]. There is a huge variation in TB incidence in the 136 districts in the country with Bukedea district in the East having the lowest TB incidence at 94 cases per 100,000 population and Kalangala district in Central Uganda having the highest incidence at 1,313 cases per 100,000 population [3]. Of the 94,000 estimated incident TB cases in Uganda in 2022, 32% occurred among PLHIV [4]. PLHIV are 15–21 times more likely to develop active TB disease than HIV-negative people [5]. Studies conducted in South Africa showed TB incidence to be high in the first year of antiretroviral therapy (ART) [6, 7]. An earlier study conducted in an urban HIV clinic in Uganda reported incident TB rates after ART initiation of 11.25, 6.27 and 2.47 per 100 person-years at 0–3, 3–6, and 6–12 months respectively [8]. In this study, incident TB was associated with baseline CD4 count < 50 cells/mm^3 and male sex. ART is one of the key prevention strategies that reduces TB disease incidence among PLHIV by up to 70% (range 54 to 92%), [9, 10] others being tuberculosis preventive therapy (TPT) [11] and intensified TB case finding [12]. However, despite the widespread increase in ART coverage in Uganda, the decrease in TB disease among PLHIV over the last 20 years has been modest [13–15]. Certain risk factors for TB such as diabetes, undernutrition, alcohol use disorder, smoking, household pollution, and intestinal helminth co-infection have been described in the literature [16–23]. These risk factors may be different for people living in urban and rural areas [24–27].

Studies of TB incidence among PLHIV have mainly utilized data from urban cohorts. Data on TB incidence in the rural communities are scanty and may differ from urban areas. Understanding TB incidence and associated factors in rural communities may be useful in designing strategies to improve TB prevention and care programs in these specific areas [28]. We, therefore, set out to assess the incidence and risk factors for TB disease in a rural cohort of PLHIV in Uganda.

Methods

Study design and setting

We conducted a retrospective cohort analysis among PLHIV enrolled in care between January 2012 to December 2019 who were TB disease-free at the time of starting ART at the Kalisizo ART clinic of the Rakai Health Sciences Program (RHSP). The RHSP is a collaborative biomedical research and service delivery organization with its headquarters in Kalisizo, Kyotera District, a rural district in south-central Uganda. Districts with above-average TB incidence are concentrated in the central region. The RHSP organization offers integrated HIV and TB prevention and care services to mainly agrarian, semi-urban and fishing communities that form part of the catchment area for the ART clinic. TB screening and diagnostic testing are parts of the standard of care for all PLHIV. At the HIV clinic, TB screening was performed at every clinic visit using the World Health Organization (WHO) recommended four-symptom screen (W4SS) that comprises of current cough, fever, night sweats, and weight loss. For PLHIV who reported anyone of the symptoms in the W4SS, an evaluation for TB disease was performed which involved sputum microscopy and/or GeneXpert test when it later became available. Where bacteriological tests were negative, chest X-rays were performed. For people with advanced HIV disease or who were very sick and/or unable to produce a sputum, a urine lipoarabinomannan (LAM) test was performed as part of the diagnostic work up to exclude TB disease. In 2016, universal ART was provided to all PLHIV irrespective of the CD4 counts in line with the Uganda Ministry of Health's "test and treat" policy [29]. CD4 cell count tests were inconsistently done under routine service. A dolutegravir-based ART regimen was rolled-out as the preferred first-line treatment for all PLHIV in 2018 [30]. TPT was not routinely offered to PLHIV until later in 2019.

Study population and eligibility criteria

The study population were adults seeking HIV care at the Kalisizo RHSP ART clinic between January 2012 to December 2019.

Inclusion criteria

All clients aged 18 years and over enrolled into care at the ART clinic were included in the study.

Exclusion criteria

We excluded clients who did not have any follow-up visit in the first 6 months of starting ART.

Data collection and quality management

We collected data on the start date of ART initiation, ART regimen, baseline WHO clinical stage, baseline CD4 counts and social demographics (age and sex) from the electronic ART register. These data were abstracted from the database into MS Excel files. We also collected data on TB diagnosis, date of diagnosis and treatment regimen from the paper-based TB laboratory and TB clinic registers present at the health facility. All data were anonymized before analysis. The data were reviewed for completeness and consistency. The Excel files were then exported to STATA version 15.1 (StataCorp, College Station, Texas, USA). The data were again checked for consistency using backward and forward linkage checks before analysis.

Study outcomes

Our primary outcome was TB incidence rate. For our study purpose we considered all study participants to be TB disease-free until a diagnosis of TB disease was confirmed in the TB treatment register. We defined an incident TB case as the occurrence of the first tuberculosis episode confirmed bacteriologically with at least one positive Xpert Mycobacterium tuberculosis/rifampicin (MTB/RIF) assay or positive Acid-fast Bacilli (AFB) microscopy- or determined to be TB disease by a clinician in a PLHIV who was taking ART. PLHIV who developed TB disease were censored at the date TB diagnosis was made. PLHIV who did not develop TB were censored on the pre-set date of 31st December 2019. PLHIV who were reported to have died, lost to follow-up, or transferred out were censored on the date of their last clinic visit.

Statistical analysis

Study variables were summarized as absolute numbers and proportions. We estimated the total person-time in the cohort. TB incidence rate was calculated by dividing the number of new TB cases by the total follow-up time expressed per 100 person-years among persons followed up until December 31, 2019, or until the date of incident TB, loss to follow-up, transfer out, or death; whichever occurred first.

A Poisson regression analysis was used to determine the association between TB incidence and age, sex, baseline WHO clinical stage, timing of change of ART policy and timing in change of ART regimen. Variables significant at $p \leq 0.2$ in the univariate analysis were used for the multivariable analysis. Universal variable of age, and variables of interest (timing of change of ART policy and roll-out of dolutegravir-based ART regimen) were forced into the model. Significance was determined at 5%.

Ethics statement

This activity of analyzing retrospective PEPFAR program data was reviewed, the need for consent to participate waived, and approved by the Uganda Virus Research Institute, Research and Ethics Committee (reference no. GC/127/19/05/654). This activity was also reviewed by CDC, deemed research not involving human subjects, and was conducted consistent with applicable federal law and CDC policy. The Research was cleared by the Uganda National Council for Science and Technology (reference no. SS334ES). Permission to access the data was obtained from the RHSP administration.

Results

For the period January 2012 to December 2019, a total of 2969 PLHIV were initiated on ART. Of these 2929, 142 clients were below 18 years. An additional 144 clients did not have a follow-up visit in the first 6 months while an effective date for ART initiation could not be established for 94 clients. The remaining 2,589 PLHIV were initiated on ART. During the study period 298 clients were lost to follow-up while 19 clients died before TB disease was observed. Table 1 describes the baseline demographic and clinical characteristics of the individuals included in the analysis. Fifty-seven percent (1,470/2,589) were female. Females were more likely to be aged 18–35 years while males more likely to be aged 25–44 years ($p < 0.001$). Of the 2,589 PLHIV included in the analysis, 87% (1,269/1,470) females compared to 78% (866/1,119) males were in WHO clinical stage 1 ($p < 0.001$).

Fifty-one percent (745/1,470) of the females in the cohort were initiated on ART in the 2012–2015 four-year period before the change in ART initiation guidelines while 49% (725/1,470) were initiated during the later four-year period of 2016–2019; 46% (514/1,119) of the males in the cohort were initiated on ART during the period 2012–2015 while 54% (605/1,119) were initiated on ART in the later period of 2016–2019. More PLHIV overall and more men but not women in the cohort were initiated on ART in the later period 2016–2019 ($p = 0.017$).

Seventy-four percent (1,089/1,470) of the females in the cohort were initiated on ART in the period 2012–2017 before the roll-out of the dolutegravir-based ART regimen, while 26% (381/1,470) were initiated on ART in the later period of 2018–2019. Seventy-one percent (795/1,119) of the males in the cohort were initiated on ART during the period 2012–2017 before the roll-out of dolutegravir-based ART regimen while 29% (324/1119) were initiated on ART in the later period of 2018–2019. There was no statistically significant difference in the proportions of men and women in the cohort who were initiated on ART before and after the roll-out of dolutegravir-based ART regimen ($p = 0.086$). During the study

Table 1 Demographic and baseline characteristics of a cohort of adults aged ≥ 18 years living with HIV initiated on antiretroviral therapy at a rural HIV clinic in Kyotera district, South-central Uganda, 2012–2019

		Female *N* (%)	Male *N* (%)	*p*-value
Overall		1470 (57%)	1119 (43%)	-
Age (years)				
	18–24	348 (24%)	90 (8%)	**< 0.001**
	25–34	648 (44%)	480 (43%)	
	35–44	345 (23%)	392 (35%)	
	45+	129 (9%)	157 (14%)	
Baseline WHO clinical stage				
	Stage I	1269 (87%)	866 (78%)	**< 0.001**
	Stage II	129 (9%)	130 (12%)	
	Stage III/IV	59 (4%)	110 (10%)	
ART policy				
	Pre-T&T (2012–2015)	745 (51%)	514 (46%)	**0.017**
	T&T (2016–2019)	725 (49%)	605 (54%)	
Use of dolutegravir-based ART regimen				
	No (2012–2017)	1089 (74%)	795 (71%)	0.086
	Yes (2018–2019)	381 (26%)	324 (29%)	

ART = antiretroviral therapy, T&T = Test and Treat strategy, WHO = World Health Organization

period CD4 counts test results were found to be inconsistently entered into the database.

There were 61 TB diagnoses among people who initiated ART during 7,363 person-years of observation; 27 of these were diagnosed during the first six months of starting ART. The median time from start of ART to TB disease diagnosis was 26 (interquartile range, [IQR] 10–55) days. Table 2 shows the incidence of TB for clients initiated on ART. Overall, TB incidence was 0.83 (95% confidence interval [CI]: 0.63 to 1.06) per 100 person-years. TB incidence was 1.29 (95% CI: 0.91 to 1.78) per 100 person-years for males versus 0.53 (0.34 to 0.80) per 100 person-years for females, with an adjusted incidence rate ratio (IRR) of 2.13 (95% CI: 1.27 to 3.57). TB incidence was highest in the first 6 months of ART at 3.39 (95% CI: 2.23 to 4.93) per 100 person-years and decreased to 0.65 (95% CI: 0.26 to 1.35) during 7–12 months of ART, 0.46 (95% CI: 0.19 to 0.95) in months 13–24, and 0.50 (95% CI: 0.31 to 0.78) after 24 months of ART. We observed no age-related differences in TB incidence nor differences related to treatment policy changes.

Table 3 shows the association between incident TB and some demographic and clinical variables for those who had been on ART for less than six months. TB incidence during ART was independently associated with male sex (adjusted IRR 2.85 (95% CI: 1.33 to 6.14) per 100 person-years), WHO clinical stage II (adjusted IRR 3.50 (95% CI: 1.43 to 8.55), and stage III/V (adjusted IRR 5.21 (95% CI: 1.98 to 13.71)). Although there was a difference in TB incidence when we compared the period before and after the roll-out of the dolutegravir-based ART regimen, this difference was not statistically significant (adjusted IRR 2.51 (95% CI: 0.84–7.49)).

Table 4 shows TB incidence among PLHIV aged 18 years and older who initiated and had been on ART for at least six months between 2012 and 2019. TB incidence was 0.58 (95% CI: 0.40 to 0.81) per 100 person-years. We did not observe significant differences by sex, age, baseline WHO clinical stage, nor ART initiation policy timeline or time on ART.

Discussion

The incidence rate of TB disease in this rural cohort of PLHIV initiating ART was low in comparison to prior urban based studies [8, 31]. The median time from the start of ART to the diagnosis of TB disease was 26 (IQR 10–55) days implying that TB incidence was highest within the first two months of starting ART. This is similar to a finding of a study that was conducted in an urban clinic in Malawi where TB incidence was highest in the first month of initiating ART [32]. However, the median time from the start of ART to TB disease diagnosis found in our study is significantly shorter than that reported from Ethiopia of 6 years [33]. A possible explanation for this difference could be the fact that our study included all cases of new TB disease diagnoses while the Ethiopian study excluded those cases that could have been prevalent TB cases in the determination of TB incidence. Consistent with our findings, the Ethiopian study demonstrated a declining incidence of TB disease over time among clients initiated on ART.

In our study, incident TB was highest within the first 6 months of starting ART compared to later (3.39 versus 0.58 cases per 100 person-years). In terms of trend, these findings were similar to those reported by an earlier study conducted by Hermans et al. on a large HIV urban cohort in which the incidence rates of TB were 11.25, 6.27, and

Table 2 Factors independently associated with TB incidence in adults ≥ 18 years living with HIV from the first day of starting antiretroviral therapy (ART) at a rural ART clinic in Kyotera district, South-central Uganda, 2012–2019

Variable		Incident cases	person-years	Incidence per 100 py (95%CI)	IRR (95%CI)	*p*-value	adj IRR (95%CI)	*p*-value
Overall		**61**	**7,363**	**0.83 (0.63–1.06)**				
Sex								
	Female	24	4,490	0.53 (0.34–0.80)	Ref.		Ref	
	Male	37	2,873	1.29 (0.91–1.78)	2.41 (1.44–4.04)	< 0.001	**2.13 (1.27–3.57)**	**0.004**
Age (years)								
	18–24	5	564	0.89 (0.29–2.07)	Ref.		Ref	
	25–34	22	2,805	0.78 (0.49–1.19)	0.88 (0.33–2.34)	0.804	0.94 (0.36–2.47)	0.894
	35–44	21	2,591	0.81 (0.50–1.24)	0.91 (0.34–2.43)	0.856	1.00 (0.37–2.71)	0.997
	45+	13	1,402	0.93 (0.49–1.59)	1.04 (0.37–2.93)	0.933	1.27 (0.43–3.69)	0.666
Baseline WHO clinical stage								
	Stage I	43	6,238	0.69 (0.50–0.93)	Ref.		Ref	
	Stage II	13	789	1.65 (0.88–2.82)	2.39 (1.28–4.47)	0.007	**2.26 (1.21–4.21)**	**0.01**
	Stage III/IV	5	329	1.52 (0.49–3.54)	2.20 (0.85–5.71)	0.105	1.84 (0.73–4.61)	0.195
ART policy								
	Pre-T&T (2012–2015)	38	5,468	0.69 (0.49–0.95)	Ref.		Ref	
	T&T (2016–2019)	23	1,895	1.21 (0.77–1.82)	1.75 (1.04–2.94)	0.035	1.00 (0.50–2.01)	0.994
Roll out of dolutegravir-based regimen								
	Before (2012–2017)	51	6,876	0.74 (0.55–0.98)	Ref.		Ref	
	After (2018–2019)	10	487	2.05 (0.99–3.78)	2.77 (1.40–5.48)	0.003	1.44 (0.64–3.23)	0.382
Time on ART (months)								
	0–5	27	797	3.39 (2.23–4.93)	Ref.		Ref	
	6–12	7	1,069	0.65 (0.26–1.35)	0.19 (0.08–0.44)	< 0.001	**0.20 (0.09–0.46)**	**< 0.001**
	13–24	7	1,512	0.46 (0.19–0.95)	0.14 (0.06–0.31)	< 0.001	**0.14 (0.06–0.33)**	**< 0.001**
	24+	20	3,984	0.50 (0.31–0.78)	0.15 (0.08–0.26)	< 0.001	**0.16 (0.08–0.31)**	**< 0.001**

ART = antiretroviral therapy, IRR = Incidence rate ratio, adj IRR = adjusted incidence rate ratio, T&T = Test and Treat strategy, WHO = World Health Organization

2.47 cases per 100 person-years at 0–3, 3–6, and 6–12 months, respectively [8]. However, the overall incidence rate of 0.83 TB cases per 100 person-years observed in our study was lower than the ≥ 3 TB cases per person-years observed in the earlier urban cohort studies conducted in Uganda's capital, Kampala, [8, 31] 8.6/100 person-years in Ethiopia,[34] 4.4/100 person-years in South Africa, [35] and 1.66/100 person-years in Nigeria [36].

We could have underestimated the TB incidence if we presume that in the worst-case scenario all PLHIV who were either lost to follow-up or died had TB disease. However, only 12% of the PLHIV included in the analysis were lost to follow-up. This loss to follow-up rate is lower compared to that reported in other cohort studies [8, 35]. We believe that the observed lower TB incidence rate in our study in comparison to that reported in the urban cohort studies conducted in Kampala was because of the rural setting in which our study was conducted.

Our study findings may have been different because of the different study designs employed and the method of assessing the primary outcome. We used a retrospective cohort analysis while the urban study conducted by Worodria et al. [31] used a prospective cohort design. In the retrospective cohort design some relevant data may not have been recorded resulting in some cases being missed. This would have the effect of reporting an incidence rate in our rural cohort that is lower than would be expected. The lower incidence rate of TB reported in our study may have been a reflection of a decline in TB incidence across all settings rather than a rural-urban difference in TB incidence considering data published from the same research setting and the region showed declining trends in TB incidence at the time [14, 37, 38].

Whereas it can be argued that the observed lower TB incidence rate in the rural cohort might reflect the observed phenomenon of declining TB incidence trends among PLHIV in the region, there is no evidence to support this thinking since to our knowledge there are no earlier studies conducted in rural cohorts in Uganda to provide a comparison. Given that an analysis from a

Table 3 Factors independently associated with TB incidence in adults ≥ 18 years living with HIV on antiretroviral therapy from 0 to < 6 months at an HIV clinic in Kyotera district, South-central Uganda, 2012–2019

Variable		Incident cases	person-years	Incidence per 100 py (95%CI)	IRR (95%CI)	*p*-value	adj IRR (95%CI)	*p*-value
Overall		**27**	**797**	**3.39 (2.23–4.93)**				
Sex								
	Female	8	467	1.71 (0.74–3.37)	Ref.		Ref	
	Male	19	330	5.77 (3.47-9.00)	3.37 (1.47–7.71)	0.004	**2.85 (1.33–6.14)**	**0.007**
Age (years)								
	18–24	3	117	2.57 (0.53–7.52)	Ref.		Ref	
	25–34	11	350	3.14 (1.57–5.62)	1.22 (0.34–4.39)	0.761	0.80 (0.24–2.64)	0.717
	35–44	8	237	3.37 (1.45–6.64)	1.31 (0.35–4.96)	0.691	0.77 (0.22–2.67)	0.685
	45+	5	92	5.42 (1.76–12.64)	2.10 (0.50–8.83)	0.309	1.31 (0.32–5.44)	0.708
Baseline WHO clinical stage								
	Stage I	15	671	2.24 (1.25–3.69)	Ref.		Ref	
	Stage II	7	87	8.05 (3.24–16.59)	3.60 (1.46–8.90)	0.006	**3.50 (1.43–8.55)**	**0.006**
	Stage III/IV	5	39	13.86 (4.18–30.01)	5.75 (2.08–15.91)	< 0.001	**5.21 (1.98–13.71)**	**< 0.001**
ART policy								
	Pre-T&T (2012–2015)	13	401	3.24 (1.73–5.54)	Ref.		Ref	
	T&T (2016–2019)	14	396	3.54 (1.94–5.94)	1.09 (0.51–2.33)	0.819	0.72 (0.26–2.01)	0.534
Roll out of dolutegravir-based regimen								
	Before (2012–2017)	18	610	2.95 (1.75–4.66)	Ref.		Ref	
	After (2018–2019)	9	186	4.83 (2.21–9.17)	1.64 (0.73–3.66)	0.228	2.51 (0.84–7.49)	0.099

ART = antiretroviral therapy, IRR = Incidence rate ratio, adj IRR = adjusted incidence rate ratio, T&T = Test and Treat strategy, WHO = World Health Organization

recently published review showed the odds of a person developing TB in an urban slum setting were 3–5 times higher than the respective national levels, we believe that the TB incidence in our rural cohort was lower than the level reported in the urban cohort because there exists a true difference between the epidemiology of TB in rural settings compared to urban settings [39].

The timing of our study could possibly explain the lower TB incidence we report here. Earlier urban cohort studies looked at PLHIV being initiated on ART at lower CD4 cell count according to the HIV treatment guidelines that were in place at the time. Although we did not have access to routine CD4 cell counts, our study looked at a period when HIV treatment was increasingly expanded to cover PLHIV with higher CD4 cell counts including the period where initiation of ART became universal irrespective of the CD4 cell counts. We used WHO clinical staging as an indicator for immune suppression because the CD4 cell counts were not routinely available. Although, the WHO clinical staging may not accurately reflect the true level of HIV-related immune suppression, as its sensitivity in predicting immune suppression is about 51–60% for CD4 threshold from ≤ 250 to ≤ 200 cells/mm^3, [40, 41] its use was a practical way of initiating persons on ART in resource limited settings where CD4 cell counts were not widely available or consistently used at the time. The absence of CD4 cell counts would not substantially alter our study findings since the majority (over 80%) of PLHIV were in WHO clinical stage 1. This means PLHIV in our study, were initiated on ART when their immunity was not yet significantly damaged and hence the reported lower TB incidence rate. Furthermore, the recent ART regimens are more potent in suppressing HIV compared to the earlier regimens [42, 43]. These potent ART regimens could have contributed to the lower TB incidence rate observed among PLHIV in the rural cohort compared to the urban cohorts.

We also compared our study findings with a recent multi-center study conducted by Kazibwe et al. [44] in Uganda, that assessed the incidence of TB among PLHIV on ART in 11 different centers of excellence located country wide and mainly in the urban areas. Although the PLHIV assessed in the Kazibwe et al. study had been initiated on both TPT and ART, the TB incidence rate of 1.85 per 100 person-years reported in their study was still higher when compared to the 0.83 cases per 100 person-years observed in our study where TPT had not been routinely initiated; less than 5% of PLHIV were documented to have initiated TPT. This further supports our belief that the low TB incidence rate in our study

Table 4 Factors independently associated with TB incidence in adults ≥ 18 years living with HIV on antiretroviral therapy for at least 6 months at an HIV clinic in Kyotera district, South-central Uganda, 2012–2019

Variable		Incident cases	person-years	Incidence per 100 py (95%CI)	IRR (95%CI)	*p*-value	adj IRR (95%CI)	*p*-value
Overall		**34**	**5,845**	**0.58 (0.40–0.81)**				
Sex								
	Female	16	3,569	0.45 (0.26–0.73)	Ref.		Ref	
	Male	18	2,276	0.79 (0.47–1.25)	1.76 (0.90–3.46)	0.099	1.67 (0.83–3.37)	0.152
Age (years)								
	18–24	2	382	0.52 (0.06–1.89)	Ref.		Ref	
	25–34	11	2,135	0.52 (0.26–0.92)	0.98 (0.22–4.41)	0.982	1.00 (0.21–4.75)	0.996
	35–44	13	2,138	0.61 (0.32–1.04)	1.16 (0.26–5.11)	0.844	1.14 (0.23–5.62)	0.873
	45+	8	1,190	0.67 (0.29–1.32)	1.28 (0.28–5.99)	0.750	1.29 (0.25–6.60)	0.763
Baseline WHO clinical stage								
	Stage I	31	5,599	0.55 (0.38–0.79)	Ref.		Ref	
	Stage II	2	137	1.46 (0.18–5.27)	2.63 (0.64–10.85)	0.180	2.57 (0.62–10.72)	0.194
	Stage III/IV	1	100	1.00 (0.03–5.59)	1.81 (0.24–13.69)	0.567	1.60 (0.21–12.32)	0.652
ART policy								
	Pre-T&T (2012–2015)	25	4,587	0.55 (0.35–0.80)	Ref.		Ref	
	T&T (2016–2019)	9	1,258	0.72 (0.33–1.36)	1.31 (0.61–2.81)	0.483	1.30 (0.52–3.24)	0.578
Roll-out of dolutegravir-based regimen								
	Before (2012–2017)	33	5,655	0.58 (0.40–0.82)	Ref.		Ref	
	After (2018–2019)	1	190	0.53 (0.01–2.93)	0.90 (0.12–6.61)	0.918	0.58 (0.08–4.46)	0.6
Time on ART (months)								
	6–12	7	694	1.01 (0.41–2.08)	Ref.		Ref	
	13–24	7	1,451	0.48 (0.19–0.99)	0.48 (0.17–1.36)	0.167	0.46 (0.16–1.30)	0.145
	24+	20	3,700	0.54 (0.33–0.83)	0.53 (0.23–1.26)	0.153	0.53 (0.20–1.43)	0.21

ART = antiretroviral therapy, IRR = Incidence rate ratio, adj IRR = adjusted incidence rate ratio, T&T = Test and Treat strategy, WHO = World Health Organization

was indeed due to the urban-rural difference in the risk of factors for TB. Recently published literature has highlighted the role of TB/intestinal helminth co-infection in explaining some of the urban-rural difference in TB epidemiology [28].

Our study also found male sex to be associated with incident TB just like the Hermans et al. study [8]. While the Hermans et al. study found incident TB to independently associated with baseline CD4 count < 50 cells/mm^3, our study found incident TB to be independently associated with WHO clinical stage II and III/IV. These observations are similar when we take WHO clinical staging as a proxy indicator for level of immune suppression. Our study was not able to assess CD4 counts because of the significantly high level of missingness following the change of treatment guidelines from CD4 count-based guidance to universal treatment irrespective of CD4 count [30]. Studies from other regions have reported a drastic decline in CD4 count testing during similar study periods [45, 46]. In addition to the above factors, a recent review and metanalysis reported underweight, low CD4 count, anemia, lack of isoniazid TB preventive therapy, and lack of co-trimoxazole as risk factors for TB incidence in sub-Saharan Africa.47] Tobacco smoking, [19, 20, 48] household air pollution, [49, 50, 51] occupation, [52] incarceration, [53] and crowded living conditions, [39] are other risk factors for incident TB. Our study was not able to assess these factors because of the limitations inherent in our study design.

Our study compared the periods before and after the roll-out of dolutegravir-based ART regimen in 2018 for both cut-off durations on ART of less than 6 months, and at least 6 months or more. Although TB incidence was high in the period after the roll-out of the dolutegravir-based ART regimen, the association of this variable with TB incidence was not statistically significant when we considered both duration categories of being on ART for less than 6 months and being on ART for at least 6 months. An earlier study conducted in a high-income country showed an increase in Immune Reconstitution Inflammatory Syndrome (IRIS) incidence with initiation of dolutegravir-based ART regimen attributed to possibly

the rapid immune reconstitution caused by dolutegravir [54]. However, recent studies have not shown an association between an increase in IRIS and dolutegravir-based ART regimens.42, 55].

Our study did not find a significant association between TB incidence and the period before or after introduction of dolutegravir. It was a surprise finding that the period after the introduction of dolutegravir did not have an impact on TB incidence. The lack of significant association was possibly due to a short follow-up period of 3 years (2017–2019) versus a longer follow-up period of 5 years (2012–2016) before the introduction of dolutegravir. However, we have no reason to believe that an equal or even longer follow-up period after the introduction of dolutegravir would have produced different results. Our study findings seem to agree with a study conducted in Tanzania that showed TB incidence to have dropped among PLHIV by 12.4% from 1.7 cases per 100 person-years in 2011 to 1.49 cases per 100 person-years in 2014 [37]. This study was conducted before the transition to dolutegravir-based ART regimen. Both these findings seem to suggest that other factors including starting ART early before the immunity is damaged play a bigger role in lowering the incidence of TB than a particular ART regimen.

TB incidence was not associated with age in our study. This finding is similar to those reported by earlier studies in sub-Saharan Africa [8, 35]. This finding might be due to the younger population and its pyramid structure that leaves small proportions of persons in the elderly age category who have an increased risk of TB disease.

Study limitations

The information on TB diagnosis was abstracted from TB treatment registers. These registers do not have a provision for categorizing TB-IRIS. Furthermore, the W4SS results, CD4 cell count results, and clinical features that would have been used to ascertain TB-IRIS expected to occur within 3–6 months of ART initiation were not routinely entered into the routine HIV database. Additionally, we could not rule out the possibility that some clients labeled as ART initiators could have been silent transfers from other programs and thus ART experienced. Some of the cases we considered to be incident TB in the 3–6-month window period could have been prevalent TB disease. None the less, our results were presented with a categorization of 6 months cut-off having a possibility of prevalent TB cases in mind. Even after this categorization, the incidence of TB after 6 months was still much lower than would be expected among PLHIV who have been on ART for 6 months and above.

This study may have underestimated the incidence rate of TB since already published survey data indicate that 56% of patients with at least one symptom suggestive of TB disease are not offered sputum and/or CXR investigations in the country [56]. However, the possibility of this being the case is very low in our study because we used a well characterized ART cohort at a research setting. It may also be possible that some clients developed TB disease and received treatment from another health facility and were never registered for TB treatment at the ART clinic. However, this was unlikely to have occurred in this cohort since after obtaining a diagnosis of TB disease, the client is registered for treatment in the same facility and the clinic operates a strong psychosocial support and community outreach program that uncovers such situations in a timely manner.

Our results may not be representative of the incidence of TB disease in the public health setting because our study was conducted in a research facility where patient care, retention, and follow-up may be above average compared to other settings in the region. However, our results support other findings of TB disease incidence studies. The long follow-up period of nearly eight years (2012–2019) and the inclusion of all eligible individuals in the study as opposed to sampling are additional strengths of the study.

Conclusions and recommendations

The incidence of TB among PLHIV on ART was low in this population who started ART at an early clinical stage and continues to decrease with increasing duration on ART. Clinicians offering care to people with HIV in the rural setting should pay higher attention to the possibility of concomitant TB disease in the newly diagnosed PLHIV and also have a heightened index of suspicion for TB disease in the first 6 months after starting ART.

Abbreviations

ART	Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IRIS	Immune Reconstitution Inflammatory Syndrome
PLHIV	People living with Human Immunodeficiency Virus
RHSP	Rakai Health Sciences Program
TB	Tuberculosis

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Author contributions

I.S., V.S., and S.J.R. participated in the conceptualization, design, data acquisition, analysis, interpretation of the results, preparation of the manuscript, review of the manuscript, and decision to publish.A.N, A.S., A.N.M., and G.N. participated in data acquisition, and decision to publish.D.L., A.G.F., R.M., and S.Z. participated in the interpretation of the results, preparation of the manuscript, review of the manuscript, and decision to publish.

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Data availability

The datasets accessed, generated, and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This activity of analyzing retrospective PEPFAR program data was reviewed, the need for consent to participate waived, and approved by the Uganda Virus Research Institute, Research and Ethics Committee (reference no. GC/127/19/05/654). This activity was also reviewed by CDC, deemed research not involving human subjects, and was conducted consistent with applicable federal law and CDC policy. The Research was cleared by the Uganda National Council for Science and Technology (reference no. SS334ES). Permission to access the data was obtained from the RHSP administration.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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