

Tuberculosis Incidence among HIV Infected Children on HAART and their Clinical Profile, Retrospective Cohort Study, South West Ethiopia

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Abstract

Background: Children aged below 15 years, carries almost 80% of the global burden of Human Immunodeficiency Virus. Sadly, Human Immunodeficiency Virus contribute for 50% of tuberculosis. In 2017, an estimated 1 million children became ill with TB and 230 000 children died of TB. Even though the use of HAART reduces TB incidence, wide Studies are showing opposing finding. Tuberculosis and Pneumonia are predominantly common among HIV infected children. Ethiopia is one of 22 the high TB burden country. The purpose of this study was to investigate the effect of highly active anti-retro viral therapy on the incidence of tuberculosis among children and their clinical profiles.

Methods: A retrospective cohort study design was used on 800 HIV-positive Children younger than 15years old; from 2009 to 2014. Incidence rate was calculated by open Epi. Kaplan-Meier technique and the generalized log-rank test was used to construct and compare the tuberculosis-free survival probabilities for both Pre-HAART and HAART following children. Cox proportional hazards model was used to assess predictors of TB.

Results: In HAART cohort the incidence of TB is (70) 3.59 per 100PYO at (2.8, 4.538 with 95% CI). In HAART naive (87) 4.63 per 100 PYO (3.705, 5.706 with 95% CI). The Kaplan Meir analysis for the overall comparison showed (log rank test statistic=1.029, DF=1, P=0.310). The predictors for TB incidence in this study are CD4 below threshold, gender being female and WHO clinical stage III or IV.

Conclusion: Though the incidence in HAART cohort looks lower mathematically, there is no statistically significant difference. TB, Pneumonia, Diarrhea, and Dermatitis are the most clinically profiled opportunistic infections.

Keywords: Tuberculosis • Opportunistic infection • Children

Abbreviations: TB: Tuberculosis • HAART: Highly Active Antiretroviral Therapy • HIV: Human Immunodeficiency Virus • IQR: Inter Quintile Range

Introduction

On the sphere of the world TB is the most common opportunistic illness and the leading cause of death among HIV infected children [1,2]. In 2017, 10 million people get ill with TB, and 1.6 million death were reported because of (including 0.3 million among people with HIV). In the same year, an estimated 1 million children became sick with TB and 2,30,000 children died of TB (including children with HIV associated TB) [3]. Children younger than 15 years, carries almost 80% of the global burden of HIV/AIDS. Sadly, HIV/AIDS contribute for 50% of tuberculosis [4]. According to WHO, there were an estimated 0.9 million new cases of TB amongst people who were HIV-positive, 72% of whom were living in Africa [4]. TB and HIV have a complex interaction. HIV alters the course of TB, making a rapid progression of latent TB infection to active TB disease [5,6]. People with Latent TB have lifetime risk of 10-15% to develop active TB disease. The risk of developing TB in HIV-infected children in a TB endemic setting is 20 times higher than in HIV-uninfected children [7]. Without treatment, 15-50% of HIV-positive infants and children will develop active TB within two years after becoming infected with

TB [8]. Around 80% of the cases are from 22 countries [9]. Ethiopia is one of the 22 high TB burden countries. In Ethiopia TB/HIV co-infection incidence is 10 per one thousand and 18 per one thousand among children <14 years. The case notification for TB is 6% with rapid diagnostic tool. TB preventive treatment is reached for 47% [10]. HAART has shown marked reduction in the incidence of Tuberculosis [11-13]. Despite the use of Antiretroviral Therapy (ART), the incidence of TB remains substantially higher in HIV positive children than in the general pediatrics population [12].

Bacterial pneumonia and tuberculosis were the most common incident and prevalent infections in both ART-naive and ART-exposed children. IRIS Fever, respiratory infections, lymphadenopathy, hepatosplenomegaly, diarrhea failure to thrive, recurrent or persistent pneumonia herpes zoster *Pneumocystis jirovecii* pneumonia are most profiled clinical condition. Although Ethiopia is one of the 22 high TB burden countries and TB/HIV co-infection are public problem. The clinical profile of HIV infected children is rarely investigated, and the effect of HAART on TB incidence is poorly described. So far, it is still possible to reach only 6% TB notification and 47% of TB preventive treatment. With this situation given, along with a paucity of

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literature, effective health care would not be realized. Even the existing evidence showed wide variation across context in clinical profile of HIV infected children. Besides, there are opposing finding about the effect of HAART on TB incidence. Hence, this study was conducted seeking an answer for the research question in the study area. The concrete evidences that the study has come up with, would add a drip in the existing ocean of knowledge.

Research Methodology

Study design and setting

A retrospective cohort study was conducted. We reviewed patient chart, clinical record and ART data base for five years from 2009 to 2014. The study was conducted in selected ART clinics found in southwest Ethiopia. South West Ethiopia encompasses three zones namely, Kafa, Sheka and Bench Maji.

Source and study population

All children younger than 15 years having a follow up care in ART clinic in south west Ethiopia are source population. While all randomly selected HIV positive under 15 years old children registered from September 2009 to August 2014 in south west Ethiopia are study population.

Exposure: Highly Active Antiretroviral Treatment (HAART) for at least 2 months.

Outcome: TB illness.

Inclusion and exclusion criteria

Inclusion: All under 15 years old children on HAART or Pre-HAART follow up who were registered from September 2009 to August 2014.

Exclusion: All under 15 years old children who started anti-TB treatment at the beginning of follow up and/or diagnosed as TB patient.

Sample size and sampling procedure

A total of 844 sample sizes were calculated with double population proportion formula by considering the following assumption:

α = Type one error (0.05)

$Z_{\alpha/2}$ = Critical value at 95% level of significance

$Z_{1-\beta}$ = Standard normal distribution value corresponding to power (90%)

Ration = 1:1

Hospitals in each zone namely Bench Maji, Kefa, Sheka, Jimma and Ilubabor were included. After having these lists of ART clinics that provide ART service for less than 15 years of age, and with proportional allocation

methods, samples were selected from each ART clinic with systematic random sampling technique for both ART and Pre ART cohort.

Data collection tool and procedure

A standardized tool which has been adapted from existing literature was used. Adapted tools was translated to local language by language expertise. Then relevant data was collected from patient's pre-ART and ART follow up logbooks, Data base and other clinical records. Data was collected by data clerk with experience in ART clinic.

Data entry and analysis

Data was checked for completeness on daily basis. Completed questioner was coded and double entry was made in EpiData version 3.1 statistical package. After exporting to SPSS version 23 data was processed and cleaned by running frequency, sorting and cross tabing. Besides, assumption was examined. The risk of developing TB among patients in each cohort group was assessed using the person-time method. All patients were at risk of developing tuberculosis during follow-up period. The Incidence rate was calculated with an Open Epi software. The Kaplan-Meier technique and the generalized log-rank test was used to construct and compare the tuberculosis-free survival probabilities curves of the two groups. Cox proportional hazards model was used to assess predictors of incidence of TB. Variables with P-value <0.05 at 95% confidence level was considered as statistically significant.

Ethical considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) of Mizan-Tepi University. Written permission was obtained from Bench Maji, kefa, Sheka, Jimma and Ilubabor Zonal Health Department. Moreover, a verbal permission was obtained from selected facility administration before starting data collection. Informed consent was not needed from patients, since the study was conducted through review of medical records, the individual patients was not subjected to any harm.

Results

Socio-demographic and baseline characteristics

From the total sample 844, 94.8% (800) children were retrospectively followed. Half of them, 400 children were HAART naive and 400 were on HAART. The median follows up period for HAART naive was 56.5 months with IQR of 22 and for HAART cohort 60 months with IQR of 24. Totally the HAART naive children were followed for 1624.17 child year time while the HAART cohort were followed for 1567.25 child year time. The median and Inter Quintile Range (IQR) of age of HAART cohort were 9 and 6 years respectively. The corresponding values for the Pre-ART cohort were 7 and 5 years respectively. The characteristics of the children are shown in Table 1.

Table 1. Characteristics of study subjects with respect to TB status.

Variables	Active TB	
	No [n] (%)	Yes [n] (%)
Sex	Male	343 88
	Female	299 70
Treatment	HAART naive	313 87

	HAART	329	71
CD4	Below threshold	163	111
	Above threshold	479	47
Age	Less than 1	20	9
	1 to 3	103	34
WHO clinical stage	3 to 5	92	24
	5 to 14	427	91
WHO clinical stage	Stage I and II	595	85
	Stage III and IV	47	73

Clinical profile and incidence of HAART

During the five year follow up 506 OIs occurred in 248 children (31%). The most common reported OIs were Pneumonia (22%) and TB (20%) (Figure 1). In HAART cohort the incidence of TB was (70) 3.59 per 100PYO at (2.8, 4.538 with 95% CI). On the other hand, Tuberculosis incidence rate among children on pre-ART was (87) 4.63 per 100 PYO (3.705%, 5.706% with 95% CI).

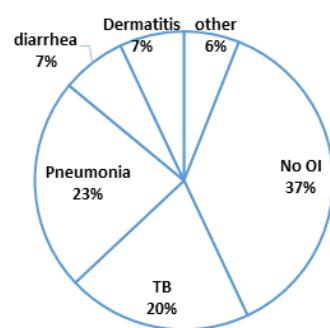


Figure 1. Magnitude of opportunistic infection.

Comparison of tuberculosis incidence between children HAART and HAART Naive

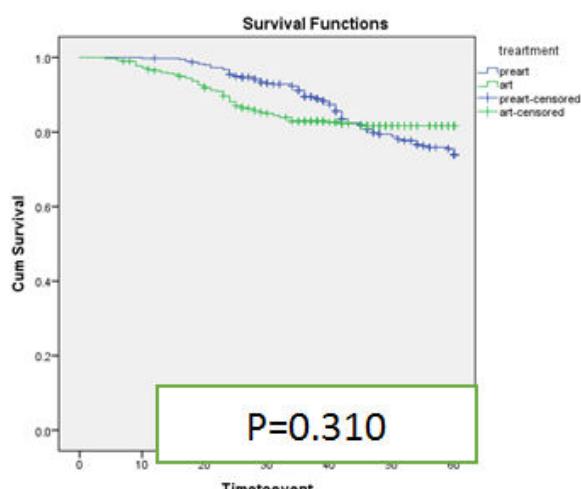


Figure 2. Kaplan Meier estimate of cumulative probability of developing TB.

The Incidence of TB in HAART looks mathematically lower than the incidence in Pre-HAART. However, the overall probability of not developing tuberculosis in the HAART cohort was not significantly different from non-HAART cohort, i.e., the risk of developing TB is statistically similar with Pre-HAART group Kaplan Meir analysis (log rank test statistic=1.029, df=1, P=0.310) (Figure 2). Baseline immunological and clinical status were further used as strata. The result showed that HAART cohort had significantly greater chance of not developing TB than that of the non-HAART cohort across strata CD4 below threshold for age (log rank test statistic=5.052, df=1, p=0.025) (Figure 3).

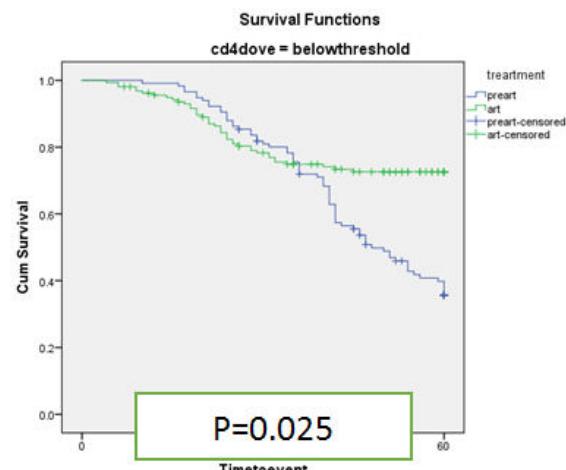


Figure 3. Kaplan Meier estimates of probability of developing TB for CD4 below threshold strata.

But no significant difference was observed in the stratum of above threshold (log rank test statistic=7.31, df=1, p=0.70). There was no significant difference in both groups in the WHO stages 1 or 2 stratum (log rank test=0.96, df=1, P=0.756) but HAART cohort significantly greater probability of not developing TB than non-HAART in WHO clinical stage 3 or 4 stratum (log rank test=31.46, df=1, P<0.0001).

Predictors of tuberculosis incidence among children on HAART

In the multivariable Cox-regression analysis, WHO clinical stage, initiation time of ART, level of adherence to ART, and duration on ART were significant predictors of TB incidence. Children on WHO clinical stages III and IV get TB infection 3 times (AHR=3.0, 95% CI 1.2-7.7) higher than those on WHO clinical stages I and II.

Those study subjects with "Fair" & "Poor" adherence level to ART had 4 times (AHR=4.0, 95% CI 1.5-10.8) more risk to develop TB than those study subjects with "Good" ART adherence. Subjects who initiated late their ART had 4 times (AHR=4.0, 95% CI 1.5-10.6) more risk to get TB infection than

those who early started. Children who took ART for less than or equal to 6 months were 5.5 times (AHR=5.5, 95% CI 1.5-20.6) at higher risk of TB infection than their counterparts (Table 2).

Table 2. Predictors of Tb with cox regression analysis.

Variables	Active TB		Cox regression		
	No [n] (%)	Yes [n] (%)	HR	95% CI	P-value
Sex	Male	343 (53.4%)	88 (55.7%)	1	
	Female	299 (46.6%)	70 (44.3%)	1.397	1.012-1.927 0.042
Treatment	HAART naive	313 (48.8%)	87 (55.1%)	1	
	HAART	329 (51.2%)	71 (44.9%)	1.372	0.997-1.889 0.052
CD4	Above threshold	479	47	1	
	Below threshold	163 (25.4%)	111 (70.3)	4.039	2.817-5.791 0
WHO clinical stage	Stage I and II	595	85	1	
	Stage III and IV	47	73	0.182	0.130-0.255 0

Discussion

The incidence of tuberculosis among children on HAART in this study was 3.59 per 100 child-years and the incidence of tuberculosis observed in HAART naive group was 4.63 per 100 Child-years, mathematically it seems low, however there is no statistically significant difference between the two groups. This finding is different from studies that supported the use of HAART significantly reduce incidence of tuberculosis [12-15].

In the present study high TB incidence was observed among CD4 count strata below threshold for age during follow-up period. The result depicted an opposite relationship between duration on HAART and TB incidence, which is in line with other study, and this may be due to better TB-specific immune repair with time spent on HAART [16]. Furthermore, in the first few months after HAART initiation we indicated highest rates of TB incidence, possibly due to "unmasked" infection, in the first three months after HAART initiation. Besides, the persistent high rate of new TB infections even after 24 months of HAART initiation were clearly indicated in published studies [17]. We demonstrated that the high TB incidence rates observed in this study may be due to high ongoing community level TB transmission. Poor knowledge of the community and poor health care access.

The finding that was depicted by this study, there is no statistical difference on the incidence of tuberculosis among the two groups, might be explained by the fact that immune dysfunction persists even during successful antiretroviral treatment. Furthermore, it might be due to inability of ART to restore TB-specific, interferon-g secreting CD4 cells as sighted by Badri et al. and Bonnet et al. [18,19]. Poor adherence level could be another justifying reason because it has been found to be a risk factor for TB incidence [20]. The self-reported adherence level in this study is 79%. The type of regimen might also matter on the potency level for ART.

Compared to studies that revealed high incidence of TB we found lower TB incidence among HIV infected children on HAART. The justification for lower Incidence rate in this study could be related to difference in study setting and period. Comparing with studies conducted in Ethiopia, the low incidence rate observed in this study might be as a result of limited access to health care service, poor quality health care, poor access to reliable diagnostic modalities, and poor screening practice. The lower incidence can

also be attributed to incompleteness of data on some patients which could brought under estimation of incidence. CD4 cell count below threshold was the determinant factor found significant for tuberculosis incidence. This is in line with findings of studies conducted in different parts of Ethiopia [21-23]. Besides age is another factor yet it was found insignificant. Children whose age is below 3 years have higher risk of tuberculosis than older children.

Conclusion

The effect of HAART on TB incidence among HIV infected children in this study is not significant. This does not necessarily mean HAART has no effect on TB, rather, this might indicate other extraneous factors. However, stratified analysis for children with CD4 count below threshold, HAART has shown a significant reduction of TB incidence. Tuberculosis incidence in the study area was relatively high enough to be a public health problem. The predictors for TB incidence in this study are CD4 below threshold, gender being female and WHO clinical stage III or IV.

Recommendations

ART program managers and coordinators shall improve and strengthen the program. By designing strategies and tactical approach that address lost to follow up and drop, TB screening and diagnostic capacity and adherence level.

Ethics Approval and Consent

Ethical clearance was obtained from the Institutional Review Board (IRB) of Mizan-Tepi University. Permissions was obtained from Bench Maji, Kefa, Sheka, Jimma and Ilubabor Zonal Health Department. Moreover, a verbal permission was obtained from selected facility administration before starting data collection. Informed Written consent was obtained from patients who had access in the period of data collection. Otherwise the informed consent was not needed from the patients absent during data collection period, since the study is conducted through review of medical records, the individual patients will not be subjected to any harm as far as the confidentiality is kept.

Availability of Data and Materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing Interest

We have declared that we do have neither financial nor non-financial interest.

Funding

Mizan Tepi university has sponsored this study. The university has involved on supervising the data collection process. Additionally, in evaluating the proposal and the research report.

Competing Interest

We have declared that we do have neither financial nor non-financial interest.

Authors' Contributions

Mr. Firew Tiruneh, Principal investigator, has prepared the protocol, designed the study, supervised the data collection, conduct the analysis and critically reviewed the manuscript. Mr. Yared Deyas, Co-investigator, assisted in data collection and prepared the manuscript.

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