Incidence and Predictors of Tuberculosis among HIV Positive Children at University of Gondar Referral Hospital, Northwest Ethiopia: A Retrospective Follow-Up Study

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Background. The aim of this study was to determine the incidence of tuberculosis and its predictors among HIV positive children. Worldwide, there are approximately nine million new TB cases each year and 13% coinfectected with HIV [1, 2]. In 2011, there were estimated 9.2 million new cases of TB, with ten percent of those occurring in children, almost one million new pediatric cases each year [3–5]. TB is among the top ten causes of death among children [6]. One of three HIV coinfectected patients dies because of TB and the disease will become worse if it was left untreated [7]. TB accounts for 26% of AIDS-related deaths, of which 99% occur in developing countries [8]. In resource limited countries, TB is the most common opportunistic infection in children with HIV [9–12].

Several studies in Africa have shown that the incidence of TB among HIV positive children ranges from 1 to 9.9 per 100 PY [13–17].

In previous studies, severe wasting, severe immune suppression, anemia, and WHO stage IV were all independently associated with a higher risk of TB. In addition, the use of antiretroviral drugs for more than 180 days reduced the risk of TB [13]. Early initiation of ART (particularly before 12 weeks of age) in HIV infected infants regardless of clinical or CD4 count criteria significantly reduces mortality and TB incidence. Isoniazid preventive therapy (IPT) for TB-exposed infants is an important additional TB prevention strategy [18].

In Ethiopia, childhood TB is still a major cause of hospital admission and death [13]. In 2011, the number of new HIV infections among children was 13 000, 19% of eligible children younger than 15 years old receiving antiretroviral therapy [2]. But studies on various aspects of childhood tuberculosis are rare. Hence, studying the incidence of tuberculosis and its predictors among HIV positive children will have a great importance for the health care system in making appropriate adjustments and allocating resources as a solution.
2. Methods

2.1. Study Design and Setting. A retrospective follow-up study was conducted in August 2013 at the University of Gondar Referral Hospital pediatrics HIV care clinic, which is located in Northwest Ethiopia. The hospital is the only tertiary hospital located in the historical city of Gondar, serving for more than five million people. During the study period, there were a total of 907 children ever enrolled into pediatrics chronic HIV care and follow-up clinic, 597 ever started ART, and the rest were pre-ART.

2.2. Definition of Tuberculosis. In the study setting, TB is diagnosed using chest radiology, fine needle aspiration, and cytology with very high clinical suspicion. When a child is diagnosed with active TB, the treatment is given according to the national TB treatment guideline. The event of this study was new occurrence of TB, which is defined as occurrence of TB in HIV infected children during the follow-up period at any time after enrollment to pediatrics HIV care clinic. Children, who were lost, died, or transferred out or did not develop the events until the last visit were considered as censored. In this study, severe immunodeficiency was defined as CD4 count below the threshold according to the child’s age; for infants CD4 <1500/mm$^3$ (<25%), 12–35 months <750 mm$^3$ (<20%), 36–59 months <350 mm$^3$ (<15%), and five years and above <200/mm$^3$ (<15%). Those HIV positive children above the threshold were classified as not severe immunodeficiency.

2.3. Inclusion and Exclusion Criteria. All HIV positive children below 15 years of age and newly enrolled into pediatric chronic HIV care clinic at the University of Gondar Referral Hospital from September 2006 to August 2010 were included in this study (Figure 1). Those HIV positive children who started anti-TB treatment at the beginning of the follow-up and those with incomplete baseline information such as CD4 count and hemoglobin (Hgb) level were excluded from the study. Finally, two hundred seventy-one children who fulfilled the inclusion criteria were included in this study.

2.4. Data Collection. All available information on patient registration book was checked and an appropriate data extraction tool was prepared. Then, data were extracted from patients’ registration book by two health professionals who had ART training and have been working in HIV care clinic.

2.5. Data Analysis. Data were entered and cleaned using EPI INFO version 3.5.3 and exported to SPSS version 20 for analysis. Nutritional status was assessed using Anthro plus software. Summary statistics and incidence density rate were calculated. Life table was used to estimate the cumulative probability of TB free survival and Kaplan-meier to estimate the median TB free survival time. Bivariate and multivariate Cox proportional hazards model was used to identify predictors of time to TB occurrence. Adjusted Hazard Ratio (AHR) with 95% confidence intervals (CI) was computed and statistical significance was considered at $P$ value $\leq$ 0.05.

3. Ethical Considerations

Ethical clearance was obtained from the institutional review board of the University of Gondar. Formal letter of permission was obtained from the chief executive officer of the hospital. The Pediatrics ART head gave the consent for extracting data from records. Patients’ names and identification numbers were not extracted to ensure confidentiality of patient information.

4. Results

4.1. Sociodemographic Characteristics of the Study Participants. Two hundred seventy-one HIV infected children were included in the analysis. The mean age was 6.42 ($\pm$ 3.53 SD) years and 41% of them were under 5 years. Slightly more than half (51.7%) of them were females and about 85% of them were from urban areas. One in every eight (12.5%) children was double orphan, who lost both of their partners, and one-third of them were living with more than 5 family sizes (Table 1).

4.2. Baseline Clinical Characteristics of Study Participants. Slightly more than half (53.9%) of HIV positive children had a baseline CD4 count of 350 and above. About 16% of them were anemic during enrolment. The baseline median CD4...
4.4. Predictors of Time to TB Occurrence. In bivariate Cox-regression analysis, paternal orphans, baseline WHO clinical stage IV, and having baseline anemia and being ambulatory and inappropriately vaccinated were significantly associated with incidence of TB among HIV positive children. However, in multivariate Cox-regression analysis, being inappropriately vaccinated and having baseline anemia and ambulatory functional status remained significant predictors of TB occurrence.

Those HIV infected children who had inappropriate vaccination were about 8 times (AHR 8.03 (95% CI; 4.61–13.97)) higher risk of developing TB at any time as compared to the counterpart. Those HIV infected children who had baseline anemia are 2.2 (AHR 2.23 (95% CI; 1.19–4.15)) times higher risk of developing TB at any time as compared to those HIV infected children who had no baseline anemia. HIV infected children who had ambulatory function status at enrollment were at 1.9 (AHR 1.99 (95% CI; 1.04–3.81)) times higher risk of developing TB compared to those who were working (Table 2).

5. Discussion

This study revealed that the overall incidence density rate of TB among HIV positive children at University of Gondar Referral Hospital was 4.9 PY. It was similar with the finding from a cohort study in Tanzania (5.2 cases per 100 PY) [13]. But, this finding is higher than that of studies done in Kenya and South Africa which were 1.4 and 1.0 per 100 PY, respectively [14, 15]. The discrepancies in incidence rate may be due to the difference in follow-up period of the studies and the difference in the overall burden of TB in the general population. But the rate was lower than the finding from a cohort study in Felege Hiwot Referral Hospital (Northern Ethiopia) which was 9.9 per 100 PY (7 cases out of 56 children followed up for 70.50 PY) [19]. This may be due to the difference in the study population (mixed adult and pediatric).

This study found that HIV positive children with baseline anemia had 2.23 times higher risk of developing TB as compared to nonanemic children which is similar to the studies done in Tanzania and Northern Ethiopia [13, 19]. This could be due to the fact that children were affected by infections when their Hgb level is lower than 12 g/dL. As a result, they become at higher risk for TB.

This study also found that patients with baseline ambulatory functional status had 2 times higher risk of developing TB as compared to working functional status. This finding is similar to the study done in Northern Ethiopia [20]. This could be due to the fact that patients lose their functional status as a result of many infectious diseases when they are anemic.

This study also revealed that patients who were not appropriately vaccinated had 8.03 times higher risk of developing TB as compared to vaccinated children. Similar finding in Tanzania showed that BCG scar was associated with a reduced risk of TB, as research showed BCG vaccination considerably reduced the risk of TB, both among individuals with and without HIV infection [21].

Unlike the previous studies, the current study found that baseline clinical factors like immune suppression, WHO stage, ART status, and nutritional status were not associated
Table 2: Cox-regression analysis of predictors of incidence of TB among HIV infected children at University of Gondar Referral Hospital (n = 271).

| Variables                      | TB incidence |     |     |     |     |     |     |     |     |     |     |     |
|--------------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                                | Event        | Censored | CRH (95% CI) | AHR (95% CI) |
| Sex                            |              |     |     |     |     |     |     |     |     |     |     |     |
| Male                           | 28           | 103 |     | 1   |     |     |     |     |     |     |     |     |
| Female                         | 26           | 114 | 0.84 (0.49–1.43) |     |     |     |     |     |     |     |     |     |
| Age                            |              |     |     |     |     |     |     |     |     |     |     |     |
| <5                             | 18           | 93  | 0.87 (0.41–1.84) |     |     |     |     |     |     |     |     |     |
| 5–9                            | 25           | 77  | 1.33 (0.65–2.69) |     |     |     |     |     |     |     |     |     |
| 10–14                          | 11           | 47  | 1   |     |     |     |     |     |     |     |     |     |
| Residence                      |              |     |     |     |     |     |     |     |     |     |     |     |
| Urban                          | 44           | 187 |     | 1   |     |     |     |     |     |     |     |     |
| Rural                          | 10           | 30  | 1.58 (0.79–3.15) |     |     |     |     |     |     |     |     |     |
| Family size                    |              |     |     |     |     |     |     |     |     |     |     |     |
| ≤2                             | 6            | 23  | 1   |     |     |     |     |     |     |     |     |     |
| 3–4                            | 31           | 119 | 0.94 (0.39–2.26) |     |     |     |     |     |     |     |     |     |
| ≥5                             | 17           | 75  | 0.82 (0.32–2.07) |     |     |     |     |     |     |     |     |     |
| Parental status                |              |     |     |     |     |     |     |     |     |     |     |     |
| Both parents alive             | 22           | 116 |     | 1   |     |     |     |     |     |     |     |     |
| Paternal orphan                | 17           | 39  | 2.05 (1.09–3.87) |     |     |     |     |     |     |     |     |     |
| Maternal orphan                | 7            | 27  | 1.26 (0.54–2.95) |     |     |     |     |     |     |     |     |     |
| Double orphan                  | 5            | 29  | 0.90 (0.34–2.38) |     |     |     |     |     |     |     |     |     |
| Not recorded                   | 3            | 6   | 2.27 (0.68–7.58) |     |     |     |     |     |     |     |     |     |
| WHO clinical stage             |              |     |     |     |     |     |     |     |     |     |     |     |
| I                              | 10           | 73  |     | 1   |     |     |     |     |     |     |     |     |
| II                             | 13           | 59  | 1.49 (0.65–3.41) |     |     |     |     |     |     |     |     |     |
| III                            | 23           | 71  | 2.06 (0.98–4.33) |     |     |     |     |     |     |     |     |     |
| IV                             | 8            | 14  | 3.66 (1.44–9.29) |     |     |     |     |     |     |     |     |     |
| Anemia                         |              |     |     |     |     |     |     |     |     |     |     |     |
| Anemia                         | 15           | 27  | 2.47 (1.36–4.49) | 2.23 (1.19–4.15) |     |     |     |     |     |     |     |     |
| No Anemia                      | 39           | 190 |     | 1   |     |     |     |     |     |     |     |     |
| Immunodeficiency               |              |     |     |     |     |     |     |     |     |     |     |     |
| Severe                         | 20           | 77  | 1.08 (0.62–1.87) |     |     |     |     |     |     |     |     |     |
| Not severe                     | 34           | 140 |     | 1   |     |     |     |     |     |     |     |     |
| ART at initial                 |              |     |     |     |     |     |     |     |     |     |     |     |
| Yes                            | 22           | 90  | 1.10 (0.64–1.91) |     |     |     |     |     |     |     |     |     |
| No                             | 32           | 127 |     | 1   |     |     |     |     |     |     |     |     |
| IPT                            |              |     |     |     |     |     |     |     |     |     |     |     |
| Yes                            | 28           | 114 | 1.09 (0.64–1.85) |     |     |     |     |     |     |     |     |     |
| No                             | 26           | 118 |     | 1   |     |     |     |     |     |     |     |     |
| CPT                            |              |     |     |     |     |     |     |     |     |     |     |     |
| Yes                            | 53           | 212 | 0.82 (0.11–5.96) |     |     |     |     |     |     |     |     |     |
| No                             | 1            | 5   | 1   |     |     |     |     |     |     |     |     |     |
| Past TB treatment history      |              |     |     |     |     |     |     |     |     |     |     |     |
| Yes                            | 11           | 34  | 0.82 (0.11–5.96) |     |     |     |     |     |     |     |     |     |
| No                             | 43           | 183 |     | 1   |     |     |     |     |     |     |     |     |
| Functional status              |              |     |     |     |     |     |     |     |     |     |     |     |
| Working                        | 13           | 88  |     | 1   |     |     |     |     |     |     |     |     |
| Ambulatory                     | 37           | 111 | 2.21 (1.17–4.19) | 1.99 (1.04–3.81) |     |     |     |     |     |     |     |     |
| Bedridden                      | 4            | 18  | 1.50 (0.49–4.61) |     |     |     |     |     |     |     |     |     |
| Vaccination status             |              |     |     |     |     |     |     |     |     |     |     |     |
| Vaccinated                     | 22           | 174 |     | 1   |     |     |     |     |     |     |     |     |
| Not appropriately vaccinated   | 31           | 22  | 7.86 (4.54–13.62) | 8.03 (4.61–13.97) |     |     |     |     |     |     |     |     |
| Not recorded                   | 1            | 21  | 0.36 (0.05–2.64) | 0.42 (0.06–3.15) |     |     |     |     |     |     |     |     |
| Nutritional status             |              |     |     |     |     |     |     |     |     |     |     |     |
| Normal                         | 19           | 84  |     | 1   |     |     |     |     |     |     |     |     |
| Stunted                        | 35           | 133 | 1.07 (0.61–1.87) |     |     |     |     |     |     |     |     |     |

COR = Crude hazard ratio, AOR = Adjusted Hazard Ratio, and CI = confidence interval.
with occurrence of TB. For instance, a study in Tanzania reported severe wasting (RR 1.8, 95% CI 1.3–2.5), severe immune suppression (RR 2.6, 95% CI 1.8–3.8), and WHO stage IV (RR 4.5, 95% CI 2.4–8.5) were all independently associated with a higher risk of TB [21]. In addition, the use of antiretroviral drugs for more than 180 days reduced the risk of TB by 70% (RR 0.3, 95% CI 0.2–0.4) [21]. The discrepancy might be due to methodology, study setting, and time variations.

The retrospective nature of the study was one of the limitations of this study. As a result, some of the important predictors which had a significant association with the TB occurrence in other studies like income were not included in this study.

6. Conclusion

Incidence of TB was high among HIV infected children, especially after the first six months of enrolment in HIV care. The baseline anemia, ambulatory functional status, and those who were not appropriately vaccinated were significantly associated with the incidence of tuberculosis. Therefore, early diagnosis and treatment of anemia and strengthening immunization program are recommended to reduce the risk of TB occurrence among HIV infected children.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors’ Contribution

Sualiha Gebeyaw wrote the proposal, participated in data collection, analyzed the data, and drafted the paper. Kefyaelw Addis Alene and Akilew Awoke Adane approved the proposal with some revisions and participated in data collection, analysis, and paper writing. All authors read and approved the final paper.

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