Time to Switching to Second-line Antiretroviral Therapy and Its Predictors Among HIV/AIDS Infected Children at General Hospitals, Northern Ethiopia: A Survival Analysis

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Abstract

Background

With expanding access to pediatric antiretroviral therapy, a growing amount of patients in the developing world has switched to second-line therapy, and some requiring third-line medications. A delay in switch increases mortality and risk of developing opportunistic infections. There remain limited and often conflicting estimates on the use of second-line ART in children. Thus, this study intended to determine the incidence and predictors of switching to second-line antiretroviral therapy among children.

Methods

Retrospective follow up study was conducted by reviewing all charts. Data were collected by extraction tool; entered using Epi-data; cleaned and analyzed by STATA V-14. Kaplan-Meier curve, log-rank test, and life table were used for data description and adjusted hazard ratios and p-value for analysis by Cox proportional hazard regression. Any variable at $P \leq 0.25$ in the bi-variable analysis was taken to multivariate analysis and significance was declared at $P \leq 0.05$. Data were presented using texts, tables, and figures.

Results and conclusion

Analysis was conducted on 424 charts with total person-time observation of 11686.1 child-months and incidence switch rate of 5.6 (95% CI 4.36-7.09) per 1000 child-month-observations. Being orphaned [AHR=2.36; 95%CI: 1.10-5.07], suboptimal ART adherence [AHR= 2.10; 95% CI: 1.12-3.92], drug toxicity [AHR= 7.05; 95% CI: 3.61-13.75], advanced recent WHO stage [AHR=2.75; 95%CI: 1.05-7.15], and initiating ART with TB co-infection [AHR=3.08; 95%CI: 1.26-7.51] were significantly associated with switch to second-line ART regimen. Moreover, long duration of ART follow up [AHR=0.75; 95% CI: 0.71-0.81] was found to be protective against switching. Hence, it is better to give priority for strengthening the focused evaluation of tuberculosis co-infection and treatment failure with continuous adherence monitoring. Further research is also needed to evaluate the effect of drug resistance.

Background

The short-term effectiveness of Anti-Retroviral Therapy (ART) among children is undisputed (1-5). A growing amount of patients in the developing world has switched to second-line therapy and some requiring third line medications (6-8). Highly Active Anti-Retroviral Therapy (HAART) refers drugs that serve to increase the life expectancy of children infected with Human Immunodeficiency Virus (HIV) (9). Switching to second-line ART was defined as changing $\geq 2$ new drugs including a class-switch from Protease Inhibitors (PI) to Non-Nucleoside Reuptake Inhibitors (NNRTI) or vice versa irrespective of reasons, or changing two drugs with documented treatment failure, or change of both Nucleoside Reuptake Inhibitors (NRTIs) and change from Ritonavir (RTV) to Lopinavir (LPV/r) with reason documented as treatment failure (10-12).
There remain limited and often conflicting estimates on the use of second-line ART in children ranging from 2–35% switching at 2-5 years after ART initiation worldwide (3, 4, 13-15). Nonetheless, concerns have been raised that patients may be experiencing long periods with virologic failure (11, 16). Many individuals who failed for first-line ART in sub-Saharan Africa never initiate second-line ART or do so after significant delay (15, 17).

Delays in shifting to second-line combination ART are frequently noted among HIV-infected children in Low and Middle Income Countries (LMIC) (18, 19). A delay in switch increases mortality and risk of developing opportunistic infections (17, 20). Prolonged treatment with a failed regimen could result in 46% raised chance of failure to second-line therapy,(20, 21) increased drug toxicity,(22) and increased drug resistance (23) which may end up with exhaustion to available treatment and drive up program costs (15, 22, 24, 25).

Ethiopia is one of the high HIV-burden countries and does not have appropriate ART drug formulations for children beyond 2nd line (11). A solitary study in Ethiopia at Black Lion hospital regarding this area of study, which determined only the incidence of the switch to second-line ART, reported that among those children who failed to respond for the first-line regimen 14.4% were switched to second-line ART with a mean delay of 24 months (20).

Albeit, this significant delay in switching and scarcity of data related to this topic, there are no studies conducted to evaluate factors that predict switching to second-line ART regimens among children throughout the country. Hence, this study designed to assess the time from ART initiation to second-line switch and to identify factors that predict a switch.

Methods

An institution-based retrospective follow-up study was employed at general hospitals in Northern Ethiopia by reviewing charts of HIV/AIDS infected children who started to receive ART from January 2014 to December 2018. There are five general governmental hospitals that provide ART care services in the study area (Mekelle General Hospital, Quiha General Hospital, Alamata General Hospital, Maichew General Hospital, and Korem General Hospital).

Study population

All HIV/AIDS infected children before 18th birthday who were taking first-line ART at selected public general hospitals, Northern Ethiopia. Those charts of children with incomplete documentation and no visit after ART initiation were excluded.

Sample size determination and sampling procedure

Single population proportion formula was used to calculate the required sample size by considering the following assumptions: 95% confidence level, 5% margin of error, 47.9% proportion of switch (p) and
52.1% proportion of survivors (1-p) from a study conducted at Black Lion hospital(26) which brought the largest sample size (N=383.4). Thus, the total sample size required for the study was 384. Afterward, the hospitals were selected using a cluster sampling technique considering each hospital as a cluster. Among those clusters, lottery method was used to select the three hospitals (Mekelle general hospital, Alamata general hospital, and Lemlem Karl hospital), and five years ART data were reviewed from charts of all children receiving first-line ART at each cluster.

**Operational definitions and Measurements**

**Event/Switch** was considered when (i) commencement of ≥2 new drugs including a class-switch from PI to NNRTI or vice versa irrespective of the cause, (ii) addition of new drug class, or (iii) change of ≥1 NRTIs or change from RTV to LPV/r with reason documented as treatment failure (10-12). Censored were those who did not switch to the second-line regimen during follow-up including lost, transfer outs, died, exceed 18th birthday during follow up, and on first-line at the end of follow-up. Children were at risk of switching from ART start until the earliest of switch or censor. The time scale was measured in months. A patient was considered a defaulter if no follow-up visit for ≥3 months and adherence was measured based on the 2017 national ART score cut-offs (11, 12).

**Data collection instruments and procedure**

A data extraction checklist was used to collect the data after developed from the national HIV treatment guideline(11), ART monitoring chart, and related articles. The tool comprised of socio-demographic, clinical and laboratory-related, treatment-related and other factors. The lists of participants were taken from the ART data clerk and unique ART numbers were used to find charts from the hospital card room. Four data collectors (BSc nurses) and one supervisor (MSc fellow) were recruited and the data collection was accomplished from April 1-26 /2019.

**Data processing, analysis, interpretation, and presentation**

Data were coded, cleaned, and entered into Epi-data and analyzed using STATA V-14. Then the data were described using frequency tables, percent, and median. Life-table was used to estimate the cumulative probabilities of switching at different time intervals. Kaplan Meier’s curve was considered to estimate median switching time during the follow-up period and log-rank tests to compare survival curves among the categories of each covariate.

Those variables having P≤0.25 in the bi-variable analysis were included to multivariate analysis. Variance inflation factor was used to check multi co-linearity (mean vif=1.33), and proportional hazard assumptions were checked using the global test (p>χ² =0.26). Furthermore, Harrell’s C was also computed (C=0.9935) and Cox-Snell residuals to check model fitness. In the multivariate analysis, the presence and strength of association was declared using an adjusted hazard ratio with 95% CI at P≤0.05. Finally, results were presented using texts, tables, and graphs.
Data quality assurance

Data collectors and supervisors received one-day training. A pretest was conducted on 20 (5%) charts that were randomly selected. The collected data were audited on daily basis by the principal investigator and supervisor. Whenever there appear incompleteness and uncertainty of recording, the filled information was crosschecked with source data soon. Individual records with incomplete data during data collection were excluded.

Results

An overall 502 (198 cases from Alamata, 165 from Mekelle and 139 from Lemlem Karl hospitals) children below 18 years of age were started ART. Of those, 78 charts (69 records because of missing data and nine with no follow-up after ART initiation) were excluded from the analysis. Finally, four hundred twenty-four (N=424) children aged less than 18 years who fulfilled the eligibility criteria were incorporated for analysis.

Socio-demographic characteristics

Children were followed for a minimum of 6 months and a maximum of 60 months with a median follow-up of 24.4 months. The study finding showed that two hundred eleven (49.8%) children were males, of which 16.6% fulfilled the switch criteria while this was true among 14.4% of female participants. The median age of children at ART initiation was 9 years with a minimum of 6 and a maximum of 214 months at the start. A significant proportion (23.3%) of children aged 5-10 years met at least one of the switch criteria followed by >10 years of age (14.6%). The study result also revealed that 154 (36.3%) children were orphaned who lost either one or both parents; of which 34 (22.1%) eligible for second-line ART regimens (Table 1).

Table 1: Distribution of socio-demographic characteristics among HIV/AIDS infected children in public general hospitals, Northern Ethiopia, 2020 (N=424)
## ART Outcome

| Independent variables | Categories         | Switched | Expected | Not switch | Expected | Total   |
|-----------------------|--------------------|----------|----------|------------|----------|---------|
|                       |                    | Observed (%) |          | Observed (%) |          | Count (%) |
| Age at ART initiation | <5 yrs             | 6 (5.5)   | 16.9     | 104 (94.5) | 93.1     | 110 (25.9) |
|                       | 5-10               | 35 (23.3) | 23       | 115 (76.7) | 127      | 150 (35.4) |
|                       | >10                | 24 (14.6) | 25.1     | 140 (85.4) | 138.9    | 164 (38.7) |
| Sex                   | Female             | 30 (14.1) | 32.7     | 183 (85.9) | 180.3    | 213 (50.2) |
|                       | Male               | 35 (16.6) | 32.3     | 176 (83.4) | 178.7    | 211 (49.8) |
| Parent Status         | Both alive         | 31 (11.5) | 41.4     | 239 (88.5) | 228.6    | 270 (63.7) |
|                       | Either Died        | 19 (19.4) | 15       | 79 (80.6)  | 83       | 98 (23.1)  |
|                       | Both Died          | 15 (26.8) | 8.6      | 41 (73.2)  | 47.4     | 56 (13.2)  |

**Abbreviation:** ART, antiretroviral therapy

### Clinical and laboratory-related characteristics

The study finding notified that 50% of the participants had less than 475 cells/mm³ at the initiation. Again, 111 (26.2%) children who started ART with advanced WHO clinical stage 25 (22.5%) were identified to be switched to second-line ART regimens whereas 20.4% of those started with CD4 count less than 200 cells/mm³ fulfilled the switch criteria. Meanwhile, 201 (47.4%) children had no access to a viral load investigation (Table 2).

**Table 2:** Clinical and laboratory-related characteristics of HIV/AIDS infected children in public general hospitals, Northern Ethiopia, 2020 (N=424)
| Independent variables | Category       | Switched |                  | Not switched |                  | Total (%) |
|-----------------------|----------------|----------|------------------|--------------|------------------|------------|
|                       |                | Observed | Expected         | Observed     | Expected         |            |
| WFA at baseline       | < 3rd          | 39 (15.7)| 38               | 209 (84.3)   | 210              | 248 (58.5) |
|                       | 3rd - 97th     | 26 (15.2)| 26.2             | 145 (84.8)   | 144.8            | 171 (40.3) |
|                       | > 97th         | 0        | 0.8              | 5 (100)      | 4.2              | 5 (1.2)    |
| HFA at baseline       | < 3rd          | 54 (15.7)| 52.6             | 289 (84.3)   | 290.4            | 343 (80.9) |
|                       | 3rd - 97th     | 6 (11.1) | 8.3              | 48 (88.9)    | 45.7             | 54 (12.7)  |
|                       | > 97th         | 5 (18.5) | 4.1              | 22 (81.5)    | 22.9             | 27 (6.4)   |
| WHO stage at ART start| Early          | 40 (12.8)| 48               | 273 (87.2)   | 265              | 313 (73.8) |
|                       | Advanced       | 25 (22.5)| 17               | 86 (77.5)    | 94               | 111 (26.2) |
| WHO stage at last visit| Early         | 56 (14.2)| 60.4             | 338 (85.8)   | 333.6            | 394 (92.9) |
|                       | Advanced       | 9 (30)   | 5                | 21 (70)      | 25.4             | 30 (7.1)   |
| CD4 count at baseline | ≤200           | 10 (20.4)| 7.5              | 39 (79.6)    | 41.5             | 49 (11.6)  |
|                       | >200           | 42 (16.3)| 39.6             | 216 (83.7)   | 218.4            | 258 (60.8) |
|                       | Unknown        | 13 (11.1)| 17.9             | 104 (88.9)   | 99.1             | 117 (27.6) |
| The most recent CD4 count | ≤200        | 15 (53.6)| 4.3              | 13 (46.4)    | 23.7             | 28 (6.6)   |
|                       | >200           | 26 (12.9)| 30.8             | 175 (87.1)   | 170.2            | 201 (47.4) |
|                       | Unknown        | 24 (12.3)| 29.9             | 171 (87.7)   | 165.1            | 195 (46)   |
| Access to viral load  | No             | 14 (7)   | 30.8             | 187 (93)     | 170.2            | 201 (47.4) |
|                       | Yes            | 51 (22.9)| 34.2             | 172 (77.1)   | 188.8            | 223 (52.6) |
| VL at initiation      | <1000          | 6 (13.6) | 6.7              | 38 (86.4)    | 37.3             | 44 (10.4)  |
|                       | ≥1000          | 7 (35)   | 3.1              | 13 (65)      | 16.9             | 20 (4.7)   |
Considerably, study participants acquired opportunistic infections at baseline and after initiation of ART were 38.9% and 25.2% respectively. Moreover, 20.6% and 27.1% of those children having OI at baseline and after initiation respectively met the switch criteria (Table 3).

**Table 3:** Distribution of Opportunistic Infections among HIV/AIDS infected children in public general hospitals, Northern Ethiopia, 2020 (N=424)

|                  | Unknown | <1000 | ≥1000 | Unknown |
|------------------|---------|-------|-------|---------|
|                  | 52 (14.4) | 23 (14.2) | 28 (47.5) | 14 (6.9) |
|                  | 55.2 | 24.8 | 9 | 31.1 |
|                  | 308 (85.6) | 139 (85.8) | 31 (52.5) | 189 (93.1) |
|                  | 304.8 | 137 (85.8) | 50 | 171.9 |
|                  | 360 (84.9) | 162 (38.2) | 59 (13.9) | 203 (47.9) |

**Abbreviations:** ART, antiretroviral therapy; WFA, weight for age; HFA, height for age; WHO, world health organization; VL, viral load
| Covariates                                      | Category | ART Outcome | Switched | Not switched | Total (%) |
|------------------------------------------------|----------|-------------|----------|--------------|-----------|
|                                                 |          | Observed (%) | Expected | Observed (%) | Expected |
| Opportunistic infections at baseline            |          |              |          |              |           |
| No                                              |          | 31 (12)      | 39.7     | 228 (88)     | 219.3     |
| Yes                                             |          | 36 (11.4)    | 48.6     | 281 (88.6)   | 268.4     |
| Anemia                                          |          | 1 (6.7)      | 2.3      | 14 (93.3)    | 12.7      |
| Diarrhea                                        |          | 13 (20.3)    | 9.8      | 51 (79.7)    | 54.2      |
| SAM                                             |          | 6 (17.1)     | 5.4      | 29 (82.9)    | 29.6      |
| TB                                              |          | 14 (27.5)    | 7.8      | 37 (72.5)    | 43.2      |
| Pneumonia                                       |          | 19 (25)      | 11.7     | 57 (75)      | 64.3      |
| URTI                                            |          | 6 (24)       | 3.8      | 19 (76)      | 21.2      |
| UTI                                             |          | 3 (75)       | 0.6      | 1 (25)       | 3.4       |
| Candidiasis                                     |          | 1 (33.3)     | 0.5      | 2 (66.7)     | 2.5       |
| Oral thrush                                     |          | 2 (20)       | 1.5      | 8 (80)       | 8.5       |
| Meningitis                                      |          | 1 (20)       | 0.8      | 4 (80)       | 4.2       |
| Total                                           |          | 34 (20.6)    | 25.3     | 131 (79.4)   | 139.7     |
| Opportunistic infections after ART initiation    |          | 36 (11.4)    | 48.6     | 281 (88.6)   | 268.4     |
| No                                              |          | 36 (11.4)    | 48.6     | 281 (88.6)   | 268.4     |
| Yes                                             |          | 9 (34.6)     | 4        | 17 (65.4)    | 22        |
| Anemia                                          |          | 10 (31.2)    | 5        | 22 (68.8)    | 27.1      |
| Diarrhea                                        |          | 6 (21.4)     | 5        | 22 (78.6)    | 23.7      |
| SAM                                             |          | 6 (22.2)     | 5        | 21 (77.8)    | 22.9      |
| TB                                              |          | 10 (31.2)    | 5        | 22 (68.8)    | 27.1      |
| Condition       | Count (%) | Incidence | Severe Incidence | Total (%) |
|-----------------|-----------|-----------|------------------|-----------|
| Pneumonia       | 13 (31.7) | 6.3       | 28 (68.3)        | 41 (9.7)  |
| URTI            | 6 (31.6)  | 2.9       | 13 (68.4)        | 19 (4.5)  |
| UTI             | 0         | 0.6       | 4 (100)          | 4 (0.9)   |
| Candidiasis     | 2 (22.2)  | 1.4       | 7 (77.8)         | 9 (2.1)   |
| Oral thrush     | 1 (50)    | 0.3       | 1 (50)           | 2 (0.5)   |
| Meningitis      | 3 (42.9)  | 1.1       | 4 (57.1)         | 7 (1.7)   |
| Total           | 29 (27.1) | 16.4      | 78 (72.9)        | 107 (25.2)|

**Abbreviations:** ART, antiretroviral therapy; SAM, severe acute malnutrition; TB, tuberculosis; URTI, upper respiratory tract infection; UTI, urinary tract infection

**Treatment-related and other factors**

Three hundred twenty-nine (80.9%) participants started with NNRTIs based ART regimen with NVP-based dominating with 200 (47.2%) whereas 46 (10.8%) and 35 (8.3%) children started ABC-based and boosted PI-based regimens respectively. Sixty-four (15.1%) children had previous ART exposure and 31 (7.3%) did not take any OI prophylaxis. One hundred twenty (28.3%) children had not disclosed their serostatus on ART start; 117 (27.6%) had suboptimal adherence as well as 133 (31.5%) and 101 (23.8%) developed adverse effects and substituted their initial first-line regimen during follow-up respectively (Table 4).

**Table 4:** Distribution of treatment-related and other factors among HIV/AIDS infected children in public general hospitals, Northern Ethiopia, 2020 (N=424)
| Independent variables          | Category | Switched  |          | Expected | Not switched |          | Total (%) |
|-------------------------------|----------|-----------|----------|----------|--------------|----------|------------|
|                               |          | Observed  | Expected |          | Observed     | Expected |            |
|                               |          | (%)       | (%)      | (%)      | (%)          | (%)      |            |
| Previous ART exposure         | No       | 61 (16.9) | 55.2     | 299      | 304.8        | 360      | 360 (84.9) |
|                               | Yes      | 4 (6.2)   | 9.8      | 60       | 54.2         | 64       | 64 (15.1)  |
| OI prophylaxis                | No       | 1(3.2)    | 4.8      | 30       | 26.2         | 31       | 31 (7.3)   |
|                               | Yes      | 64 (16.3) | 60.2     | 329      | 332.8        | 393      | 393 (92.7) |
| Disclosure status             | No       | 18 (15)   | 18.4     | 102      | 101.6        | 120      | 120 (28.3) |
|                               | Yes      | 47 (15.5) | 46.6     | 257      | 257.4        | 304      | 304 (71.7) |
| Adherence to ART              | Sub-optimal | Poor | 16 (25.8) | 9.5     | 46 (74.2)    | 52.5     | 62 (14.6)  |
|                               | Fair     | 12 (21.8) | 8.4      | 43       | 46.6         | 55(13)   | 55(13)     |
|                               | Optimal  | 37 (12.1) | 46.9     | 270      | 259.1        | 307      | 307 (72.4) |
|                               | Good     | 37 (12.1) | 46.9     | 270      | 259.1        | 307      | 307 (72.4) |
| Baseline ART regimen          | NVP-based | 37 (18.5) | 30.7     | 163      | 169.3        | 200      | 200 (47.2) |
|                               | ABC-based | 5 (10.9)  | 7.1      | 41       | 38.9         | 46       | 46 (10.8)  |
|                               | EFV-based | 19 (13.3) | 21.9     | 124      | 121.1        | 143      | 143 (33.7) |
|                               | LPV/r-based | 4 (11.4) | 5.4      | 31       | 29.6         | 35       | 35 (8.3)   |
| ART drug Toxicity             | No       | 13 (4.5)  | 44.6     | 278      | 246.4        | 291      | 291 (68.6) |
|                               | Yes      | 52 (39.1) | 20.4     | 81       | 112.6        | 133      | 133 (31.4) |
| ART drug substitution         | No       | 0         | 49.5     | 323      | 273.5        | 323      | 323 (76.2) |
|                               | PI to NNRTI | 44 (100) | 6.7      | 0        | 37.3         | 44       | 44 (10.4)  |
Moreover, 65 (15.33%) satisfied at least one switch criterion of which only 31 (47.7%) children switched to second-line regimens while the rest 52.3% of those fulfilled the criteria remained on first-line. The rest 359 (84.67%) were censored with seven (1.7%) children died during follow up, 61 (14.4%) transferred out to other facilities, and 35 (8.2%) lost during the follow-up period. Additionally, two-third (64.6) of those considered, as switch were attributable to first-line treatment failure.

**Comparison of Survival status using Kaplan Meier**

The Kaplan Meier switch curve increased stepwise as the follow-up time increased and it crosses the survival function at a survival probability of 0.5 (Figure 1).

**Survival function and an incidence rate of second-line ART switch**

The total child-month observation was 11686.1 child-months with the incidence switch rate of 5.6 (95% CI 4.36-7.09) per 1000 child-months of observation. The median survival time was found to be 58.7 months. The cumulative probabilities of switch at 12, 24, 36, 48 and 60 months were 0.053, 0.08, 0.13, 0.24 and 0.52 respectively.

**Predictors of switching to second-line ART**

Some variables such as WFA, HFA, recent CD4 count, baseline viral load, drug substitution, and OI prophylaxis were left out of the final model since they have less than 20% predicted events per cell. Additionally, age at ART start and recent viral load were further excluded for violation of proportionality assumptions, and pneumonia due to multi-collinearity effect.

Afterward, in the final Cox proportional hazard model, Being orphaned, suboptimal ART adherence, drug toxicity, advanced recent WHO stage, initiating with TB co-infection at baseline and duration of follow-up.
were found to be independent predictors of switching to second-line ART regimen (Table 5).

**Table 5**: Bi-variable and Multivariate analysis output for HIV/AIDS infected children in public general hospitals, Northern Ethiopia, 2020 (N=424)
| Covariates          | Category   | Switched | Not switched | P>|z| | Crude HR (95% CI) | P>|z| | Adjusted HR (95% CI) |
|---------------------|------------|----------|--------------|-----|-----------------|-----|-------------------|
| **Parent status**   | Both alive | 31       | 239          | -   | -               | -   | -                 |
|                     | Either died | 19       | 79           | 0.026 | 1.92 (1.08 - 3.41) | 0.039* | 2.13 (1.04 - 4.38)* |
|                     | Both died   | 15       | 41           | 0.001 | 2.81 (1.52 - 5.22) | 0.027* | 2.36 (1.10 - 5.07)* |
| **OI at baseline**  | Yes        | 34       | 131          | 0.012 | 1.87 (1.15 - 3.05) | 0.710 | 1.15 (0.56 - 2.37) |
|                     | No         | 31       | 228          | -   | -               | -   | -                 |
| **OI after ART**    | Yes        | 29       | 78           | <0.001 | 2.47 (1.51 - 4.04) | 0.182 | 1.77 (0.77 - 4.09) |
| **Adherence to ART**| Optimal    | 37       | 270          | -   | -               | -   | -                 |
|                     | Sub-optimal | 28      | 89           | <0.001 | 2.51 (1.53 - 4.11) | 0.021* | 2.10 (1.12 - 3.92)* |
| **ART exposure**    | Yes        | 4        | 60           | -   | -               | -   | -                 |
|                     | No         | 61       | 299          | 0.215 | 1.90 (0.69 - 5.23) | 0.139 | 0.43 (0.14 - 1.31) |
| **ART drug toxicity**| Yes        | 52       | 81           | <0.001 | 5.68 (3.08 - 10.49) | <0.001* | 7.05 (3.61 - 13.75)* |
|                     | No         | 13       | 278          | -   | -               | -   | -                 |
| **Baseline WHO**    | Early-stage | 40       | 273          | -   | -               | -   | -                 |
|                     | Advanced stage | 25   | 86           | 0.011 | 1.91 (1.16 - 3.16) | 0.997 | 1.00 (0.50 - 2.00) |
| **Recent WHO stage**| Early-stage | 56       | 338          | -   | -               | -   | -                 |
|                     | Advanced    | 9        | 21           | <0.001 | 4.20 | 0.039* | 2.75 |
|                          | stage |  |  |  |  |
|--------------------------|-------|---|---|---|---|
| **Baseline CD4**         |       |   |   |   |   |
| Failed                   | 10    | 39| 0.127| 1.72| 0.658| 0.83| (0.36 - 1.92)  |
|                         | Normal| 42| 216| -  | -  | -  | -  |
|                         | Unknown| 10| 39| -  | -  | -  | -  |
| **Anemia after ART start**| No | 56| 342| -  | -  | -  | -  |
|                         | Yes | 9 | 17| <0.001| 4.51| 0.054| 0.22| (0.05 - 1.02)  |
| **Diarrhea after ART initiation**| No | 59| 337| -  | -  | -  | -  |
|                         | Yes | 6 | 22| 0.121| 1.95| 0.744| 0.82| (0.26 - 2.62)  |
| **Malnutrition at baseline**| No | 59| 330| -  | -  | -  | -  |
|                         | Yes | 6 | 29| 0.168| 1.81| 0.132| 2.31| (0.78 - 6.89)  |
| **Malnutrition after ART start**| No | 59| 338| -  | -  | -  | -  |
|                         | Yes | 6 | 21| 0.039| 2.45| 0.183| 0.40| (0.11 - 1.53)  |
| **TB at baseline**       | No | 51| 322| -  | -  | -  | -  |
|                         | Yes | 14| 37| <0.001| 4.03| 0.013*| 3.08| (1.26 - 7.51)* |
| **TB after ART initiation**| No | 55| 337| -  | -  | -  | -  |
|                         | Yes | 10| 22| 0.093| 1.79| 0.112| 2.23| (0.83 - 5.98)  |
| **Follow up duration**   | 65    | 359| <0.001| 0.89| <0.001*| 0.75| (0.71 - 0.81)* |

**Note:** *significant at 5% level of significance

**Abbreviations:** OI, opportunistic infection; ART, anti-retroviral therapy; WHO, world health organization; CD4, HIV helper cell count; TB, tuberculosis
Discussion

This study was aimed to determine the incidence and predictors of switching to second-line ART regimen among HIV/AIDS infected children. The median survival time was 58.7 months with an overall incidence switching rate of 5.6 (95% CI 4.36-7.09) per 1000 child-month-observations. Being orphaned, suboptimal ART adherence, drug toxicity, advanced recent WHO stage, baseline TB infection, and duration of follow-up were found to be independent predictors of the second-line switch.

The overall cumulative incidence of the switch at five years in this study was 52% (95% CI 39.61-66.34). This was higher than reports of previous studies; 31.6% in Asia-Pacific and African countries (27) and 21% in Europe and Thailand (13). In this study, the median survival time was 58.7 months which is longer than the findings of previous studies; 35 months from a global pooled estimate by CIPHER (28), and 30 months in Europe and Thailand (13). The possible explanation could be the advancements in the diagnostic and therapeutic measures recently including more frequent visits and increased access to viral load that enables early detection and monitoring of ART responses including adherence as well as the increase in access and variety of more potent drugs nowadays than in the past (11).

Having tuberculosis at ART start was significantly associated with switching to second-line ART drugs [AHR=3.08; 95%CI: 1.26-7.51]. This could be rationalized as tuberculosis infection facilitates viral replication by activating the immune system, which then leads to viral load increment. Again, this will in turn accelerate rapid HIV/AIDS disease progression which cross-react with the ART drug action (11) leading to increased replication of drug-resistant mutations and thus a higher chance of switching.

The other factor that showed significant association was ART drug toxicity. Children who developed drug adverse effects were seven times at higher hazard of a switch than those with no drug toxicity during follow-up [AHR= 7.05; 95% CI: 3.61-13.75]. This finding was supported by a previous study conducted in West African countries (29). This might be because intolerance to ART drugs is an important barrier to adherence leading to treatment discontinuation, risking viral rebound, and drug resistance (9, 11). The major cause of drug discontinuation in the first 3-6 months after ART initiation is drug toxicity.

The study finding also notified that being orphan children was significantly associated with the switch to second-line regimens. From the beginning, children are dependent on their parents and require continual support due to their age and developmental stages. Parents play an undeniable role in the provision of effective pediatric ART service by encouraging children to take ART drugs timely, as prescribed, assist in case of sub-optimal adherence, attend follow-up based on appointments, and avoid the sense of loneliness. On the contrary, orphaned children will miss doses and follow-up visits, difficulty with adherence, and even may not fully understand healthcare instructions. Besides, poor palatability of drugs, frequent adverse effects, limited formulations, and frequent dosing requirements (9, 11) may lead to poor adherence and exacerbate the level of negligence.
This study revealed that children who diagnosed as advanced WHO stage at last visit were at higher hazard of a switch than those who defined as in the early WHO stages [AHR=2.75; 95%CI: 1.05-7.15]. Earlier pediatric studies did not examined the WHO stage at the last follow up visit. However, previous studies investigated the WHO stage at baseline and reported as an independent predictor of switching, which was not found statistically significant in the current study. The possible justification for the discrepancy could due to advancement in the management strategies and short follow-up visit recommendations in the recent ART guideline (11). Consequently, it will enable early detection, control, and management of adverse events, and opportunistic infections through strict and focused service provision for children who start ART with advanced WHO stage in terms of treatment regimen selection, diagnostic and monitoring workups, and repeated follow-up visits.

The current study also showed that those children having sub-optimal adherence for ART regimens were 2.1 times at higher hazard of switch compared to their counterparts [AHR= 2.10; 95% CI: 1.12-3.92]. This report was in agreement with the previous study result (29). The possible reason for this could be due to the role of a high level of sustained adherence to ART treatment outcomes. Optimal adherence is necessary to reduce the risk of ART drug resistance and decrease the chance of HIV transmission by suppressing viral replication and improving immunological and clinical outcomes. On the other hand, HIV/AIDS infected children and adolescents frequently come upon with poor adherence to ART drugs. Several reasons could be stated for this including limited choice of pediatric ART formulations, poor palatability of some drug preparations, the requirement of multiple pills with frequent dosing, as well as occurrence of potential adverse effects and drug interaction in pediatric regimens. Adherence could also be affected by the age and developmental stage of children since the pediatric age group needs support from others to take medication timely and also may face difficulties in swallowing tablets (9, 11).

A long duration of follow up was also reported as having a protective effect on a switch to second-line ART [AHR=0.75; 95% CI: 0.71-0.81]. This finding contradicts the results of a West African study (29). The difference could be, unlike the current study which incorporates all children started on first-line ART, the West African study considered children that experienced first-line ART failure and estimated switch to second-line among only those who failed for first-line ART drugs. We can also put justifications for our results. Children who had been on ART for a prolonged period will have improved adherence and adaptation. This is because the level of adherence in children increases with time, and the need for adaptation to daily ART drug intake in the early ART follow-up periods may hamper the patient's response to ART drugs resulting in inadequate viral suppression and thus the emergence of resistant mutations (9). This may also be related to the increased chance of occurrence of different rapid effects such as IRIS within the early months of ART initiation.

**Conclusion**

The overall cumulative incidence of the second-line switch was higher than in previous studies. A remarkable delay in switching to second-line ART drugs was observed. Furthermore, children who had ART drug toxicity, TB at ART initiation, advanced WHO clinical stage after ART initiation, non-adherence to
ART regimen, those who were orphaned, and on ART for a short period were at higher hazard of switching.

**Abbreviations**

ABC, abacavir; AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; BSc, bachelor of science; MSc, master of science; EFZ, Efavirenz; HFA, height for age; HIV, human immunodeficiency virus; LMIC, low and middle income countries; LPV/r, lopinavir/ritonavir; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; OI, opportunistic infections; PI, protease inhibitors; SAM, severe acute malnutrition; TB, tuberculosis; URTI, upper respiratory tract infection; UTI, urinary tract infection; VL, viral load; WFA, weight for age; WHO, world health organization

**Declarations**

**Ethical approval and consent to participate:** Ethical approval was obtained (ERC 1272/2019) from the institutional review board (IRB) of Mekelle University, college of health sciences. The IRB waived such that the research could be done by record review without contacting patients since the study was conducted through a review of medical records. Permission letters were obtained from each hospital administration and respective hospital ART coordinators. All information was kept confidential and no individual identifiers were collected.

**Accordance statement:** I affirm that all methods were carried out in accordance with relevant research guidelines and regulations.

**Consent for publication:** Not applicable

**Data availability statement:** Additional data that can support the study findings and conclusions can be shared upon reasonable and legal request via ‘bayayibignabez@gmail.com’

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**Authors’ contributions**

MS, TM & DA participated in the study conception and proposal development as well as collection and interpretation of data. MS, DA & TM participated in data entry, cleaning, and performed the statistical analysis. MS drafted, compiled, edited and formatted the manuscript for publication. All authors read, critically revised, and approved the final manuscript and agreed to be accountable for all aspects of the work.
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Figures
Figure 1

Overall Kaplan Meier failure estimate of HIV/AIDS infected children in public general hospitals, Northern Ethiopia, 2020 (N=424). The Y-axis represents the probability of second-line ART switch whereas the X-axis indicates the follow-up time in months. The red vertical and horizontal lines were reference lines added to ease graph interpretation (median time to switch estimation).