Retention in care among HIV-positive patients initiating second-line antiretroviral therapy: a retrospective study from an Ethiopian public hospital clinic

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Background: Access to second-line antiretroviral therapy (ART) for HIV-positive patients remains limited in sub-Saharan Africa. Furthermore, outcomes of second-line ART may be compromised by mortality and loss to follow-up (LTFU).

Objective: To determine retention in care among patients receiving second-line ART in a public hospital in Ethiopia, and to investigate factors associated with LTFU among adults and adolescents.

Design: HIV-positive persons with documented change of first-line ART to a second-line regimen were retrospectively identified from hospital registers, and data were collected at the time of treatment change and subsequent clinic visits. Baseline variables for adults and adolescents were analyzed using multivariate Cox proportional hazards models comparing subjects remaining in care and those LTFU (defined as a missed appointment of ≥ 90 days).

Results: A total of 383 persons had started second-line ART (330 adults/adolescents; 53 children) and were followed for a median of 22.2 months (the total follow-up time was 906 person years). At the end of study follow-up, 80.5% of patients remained in care (adults and adolescents 79.8%; children 85.7%). In multivariate analysis, LTFU among adults and adolescents was associated with a baseline CD4 cell count ≤ 100 cells/mm³ and a first-line regimen failure that was not confirmed by HIV RNA testing.

Conclusions: Although retention in care during second-line ART in this cohort was satisfactory, and similar to that reported from first-line ART programs in Ethiopia, our findings suggest the benefit of earlier recognition of patients with first-line ART failure and confirmation of suspected treatment failure by viral load testing.

Keywords: HIV; second-line; antiretroviral therapy; loss to follow-up; Ethiopia; sub-Saharan Africa; retention in care

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to have undetectable HIV viremia. These findings are valid for both adults and children (11–13).

Irregular drug intake is an important cause of treatment failure. Hence it is possible that patients with first-line failure due to inadequate drug adherence are at high risk of a subsequent treatment failure on second-line ART (14). Irregular drug intake exists for many reasons. Ensuring adequate retention in care is one major challenge for ART programs in resource-limited settings. In a review based on 39 cohorts in sub-Saharan Africa, nearly one-third of patients did not remain in care 3 years after starting ART, with loss to follow-up (LTFU) accounting for 59% of the cases and death for 41% of the cases (15).

Irregular treatment has been associated with increased mortality and morbidity, as well as with virological failure and the selection of HIV drug resistance (16, 17). In Ethiopia, a free public ART program was introduced in 2005 and since then the number of persons starting ART has steadily increased. In 2014, the number of persons initiated on ART treatment was 362,000 – equal to a treatment coverage of 61% (1, 18). As a consequence, both HIV-related mortality and HIV incidence have decreased in the country (1, 18, 19). The number of patients on second-line ART remains low in Ethiopia; 1.7% of all ART recipients. The low number reflects difficulties in the recognition of subjects eligible for second-line therapy as well as restricted access to such treatment, a predicament Ethiopia shares with many other sub-Saharan African countries (20). In order to optimize second-line ART programs, it is important to understand the outcome of such therapy and identify predictors of adverse treatment outcomes. In this retrospective study, we have determined the retention in care among patients initiating second-line ART in a large public ART clinic in Ethiopia and investigated the factors in the switch to second-line ART that are associated with subsequent LTFU in adults and adolescents.

Methods

Setting

The study was conducted at the outpatient ART clinic at Adama Regional Hospital. Adama, the economic capital of the Oromia region, is located in Central Ethiopia, and has an estimated population of 300,000 inhabitants. This ART service was introduced in 2005 and is considered to be the second largest HIV clinic in Ethiopia. HIV care, including ART initiation and monitoring, is provided by specially trained nurses who follow national guidelines. Physicians are available for consultation and are responsible for the switch of therapy to second-line regimens. Clinical and/or immunological criteria (the occurrence of new HIV-related conditions and the absence of CD4 cell response, respectively, as defined by WHO) (2), are used for the identification of suspected first-line ART failure. Since 2010, suspected treatment failure has been routinely confirmed by HIV RNA determination. Second-line regimens are prescribed following recommendations in national HIV guidelines, which involves the replacement of the NNRTI component with a protease inhibitor (PI), and with the switch of one or both nucleos(t)ides (NRTI) from the first-line regimen. Drug resistance testing for selection of antiretroviral drugs for second-line ART is not available.

Study design

All persons who, according to hospital registers, had initiated second-line ART before July 27, 2014 (3 months before the collection of data) were eligible for inclusion. Second-line ART was defined as a modification of a first-line ART regimen to a PI-containing regimen and could occur either due to first-line treatment failure or because of side effects to first-line antiretroviral drugs. Patients who were alive at the time of data collection and who did not meet criteria for LTFU were considered to remain in care. Persons with the documented transfer of care to another health facility were not included in this analysis. LTFU was defined as having missed a scheduled appointment by 90 days or more. Subjects of all ages were eligible for inclusion, but for the analysis of factors associated with LTFU, only adults and adolescents (defined as persons aged 15 years or greater) were included.

Participant data was collected retrospectively from ART registers at the clinic until any of the following events: death, transfer of care, LTFU, or up to 3 months before the start of data collection. Characteristics recorded at the last visit preceding the initiation of second-line ART were used as baseline variables.

Data collection and analysis

According to the standard procedure at the clinic, medical information is obtained by health workers at each clinic visit following standardized questionnaires (including detailed socio-economic data at the first clinic visit), and entered into patient cards. Information from patient cards is transferred to an electronic register at regular intervals. Data for this study was primarily collected from patient cards, whereas an electronic register was used when information from patient cards could not be retrieved. Data on antiretroviral drug combinations and HIV RNA were also collected from prevailing pharmacy and laboratory registers, respectively. Study data was entered into a research database by one of the authors (SW; October to December 2014), using subject-specific study codes.

The primary outcome was retention in care after the initiation of second-line ART. For the analysis of risk factors for LTFU only adults and adolescents were included. Adults and adolescents remaining in care were compared to those meeting the criteria for LTFU. Patients with documented mortality or transfer of care were excluded from this analysis. The following variables were selected...
and included for analysis of risk factors for LTFU: age, gender, CD4 cell count strata, WHO clinical stage, the performance of viral load testing prior to regimen change, functional status, education, marital status, access to household electricity, and access to a household water supply. Time-at-risk was defined as the number of days on a second-line regimen at the clinic before a study endpoint. The Mann-Whitney U test was used to compare CD4 cell counts between patients LTFU and patients still in care. Associations between baseline factors and LTFU were first analyzed in a univariate analysis. Factors with \( p < 0.3 \) in univariate analysis were further analyzed in a multivariate Cox model, using backward step-by-step exclusion, removing the least significant variable, until all remaining variables had a \( p < 0.05 \). Kaplan-Meier curves were used to ensure that all variables included in the model fulfilled the proportional hazards assumption.

SPSS for Windows version 22 was used for all statistical analyses.

**Ethical approval**

Ethical approval was granted from the Institutional Review Board at the Oromia Regional Health Bureau. Due to the retrospective study design and its objective to analyze LTFU, individual informed consent was not sought. To ensure confidentiality, all study data was managed under code.

**Results**

**Study participants**

Among 427 eligible patients, 383 subjects were included (330 adults/adolescents, 53 children). Among the excluded 44 persons, 25 were excluded due to missing data (mainly persons who had initiated second-line ART in other clinics), and 19 were excluded because they had initiated PI-based first-line ART (these were mainly children who had been exposed to NNRTI in utero). At the initiation of second-line ART, the median age was 36.6 years (interquartile range [IQR] 30.0–42.0) for adults/adolescents and 11.2 years (IQR 7.3–13.8) for children. The median CD4 cell count was 126 cells/mm\(^3\) (IQR 65.5–226.0) for adults/adolescents and 154 cells/mm\(^3\) (IQR 88–319) for children. The baseline characteristics of these subjects are shown in Tables 1 and 2.

**Indications for second-line ART**

**Adults/adolescents**

The indication for second-line ART was treatment failure in 216 (65.5%) cases, side effects on first-line ART in 74 (22.4%) cases, and other stated reasons in 6 (1.8%) cases. In 34 (10.3%) cases, the reason was not stated. Among the 216 subjects with treatment failure, 182 (84.3%) fulfilled immunological criteria, and 71 (32.9%) fulfilled clinical criteria. Treatment failure was confirmed by viral load testing in 182 (84.3%) subjects. At the time of treatment switch, the median viral load was 72,900 copies/mL (IQR 29,350–220,500; > 10,000 copies/mL in 164 [92%] cases).

**Children**

Thirty-seven subjects (69.8%) changed to a second-line regimen due to treatment failure, 14 (26.4%) changed due to side effects on a first-line regimen, 1 (1.9%) due to initiation of tuberculosis treatment, and 1 (1.9%) for unknown reasons. Among the 37 children with first-line treatment failure 32 (86.5%) fulfilled immunological criteria, and 14 (37.8%) fulfilled clinical criteria. Treatment failure was confirmed by viral load testing in all 37 subjects. The median viral load was 92,300 copies/mL (IQR 38,200–323,500; > 10,000 copies/ml in 35 [95%] cases).

**Retention in care**

Overall retention in care was 80.5%, whereas 18.9% met criteria for LTFU.

**Adults/adolescents**

At the end of follow-up, 256/321 (79.8%) patients remained in care of the total 330. The nine patients unaccounted for were censored due to recorded transfer of care to another health facility. Two (0.6%) were confirmed dead, and 63 (19.6%) met the definition of LTFU. Among the 63 patients LTFU, nine returned to care at the study clinic during the follow-up period. The 330 adults/adolescents were followed for a median of 22.1 months (783 person years). For patients who were LTFU, the median follow-up time was 8.7 months. The CD4 cell count at the last follow-up visit was higher for patients who remained in care (median 429 cells/mm\(^3\) [IQR 261–607]), compared to subjects LTFU (median 209 cells/mm\(^3\) [IQR 68–369]), \( p < 0.01 \).

**Children**

At the end of follow-up, 42/49 (85.7%) patients remained in care of the total 53. The four patients unaccounted for were censored due to recorded transfer of care to another health facility. None were confirmed dead, and 7 (14.3%) met the definition of LTFU. Among those LTFU, three returned to care at the study clinic during the follow-up period. The 53 children were followed for a median of 23.5 months (123 person years). For the subjects who were LTFU, the median time on second-line ART was 6.4 months. The CD4 cell count at the last follow-up visit was higher for subjects who remained in care (median 673 cells/mm\(^3\) [IQR 433–785]) than for the patients who were LTFU (median 374 cells/mm\(^3\) [IQR 210–826]), but this difference did not reach statistical significance (\( p = 0.22 \)).

**Risk factors for LTFU during second-line ART in adults and adolescents**

In univariate Cox analysis, the following variables showed an association with LTFU (\( p < 0.3 \)): CD4 cell count...
Table 1. Characteristics of adults and adolescents at initiation of second-line ART with regard to subsequent retention in care

| Age category (Years) | Total, n (%) (N = 330) | Retention in care, n (%) (n = 267) | No retention in care, n (%) (n = 63) |
|----------------------|-------------------------|----------------------------------|----------------------------------|
| 15–29                | 102 (31.0)              | 85 (31.8)                        | 17 (27.0)                        |
| 30–39                | 141 (42.7)              | 113 (42.3)                       | 28 (44.4)                        |
| ≥ 40                 | 87 (26.4)               | 69 (25.8)                        | 18 (28.6)                        |

| Gender               |                         |                                  |                                  |
|----------------------|-------------------------|----------------------------------|----------------------------------|
| Female               | 180 (54.5)              | 142 (53.2)                       | 38 (60.3)                        |
| Male                 | 150 (45.5)              | 125 (46.8)                       | 25 (39.7)                        |

| CD4 category (cells/mm³) | Total, n (%) (N = 330) | Retention in care, n (%) (n = 267) | No retention in care, n (%) (n = 63) |
|--------------------------|-------------------------|----------------------------------|----------------------------------|
| ≥ 100                    | 192 (58.2)              | 161 (60.3)                       | 31 (49.2)                        |
| < 100                    | 131 (39.7)              | 101 (37.8)                       | 30 (47.6)                        |
| N/A                      | 7 (2.1)                 | 5 (1.9)                          | 2 (3.2)                          |

| WHO stage category      | Total, n (%) (N = 330) | Retention in care, n (%) (n = 267) | No retention in care, n (%) (n = 63) |
|-------------------------|-------------------------|----------------------------------|----------------------------------|
| Stage 1–2               | 109 (33.0)              | 97 (36.3)                        | 12 (19.0)                        |
| Stage 3–4               | 216 (65.5)              | 166 (62.2)                       | 50 (79.4)                        |
| N/A                     | 5 (1.5)                 | 4 (1.5)                          | 1 (1.6)                          |

| Functional status       |                         |                                  |                                  |
|-------------------------|-------------------------|----------------------------------|----------------------------------|
| Able to work            | 261 (79.1)              | 220 (82.4)                       | 41 (65.1)                        |
| Unable to work          | 65 (19.7)               | 43 (16.1)                        | 22 (34.9)                        |
| N/A                     | 4 (1.2)                 | 4 (1.5)                          | 0 (0.0)                          |

| First-line ART failure confirmed by HIV RNA testing | Total, n (%) (N = 330) | Retention in care, n (%) (n = 267) | No retention in care, n (%) (n = 63) |
|---------------------------------------------------|-------------------------|----------------------------------|----------------------------------|
| Yes                                                | 178 (53.9)              | 162 (60.7)                       | 16 (25.4)                        |
| No                                                 | 141 (42.7)              | 98 (36.7)                        | 43 (68.3)                        |
| N/A                                                | 11 (3.3)                | 7 (2.6)                          | 4 (6.3)                          |

| Reasons for switch to second-line ART              | Total, n (%) (N = 330) | Retention in care, n (%) (n = 267) | No retention in care, n (%) (n = 63) |
|---------------------------------------------------|-------------------------|----------------------------------|----------------------------------|
| Treatment failure                                 | 216 (65.5)              | 187 (70.0)                       | 29 (46.0)                        |
| Side effect                                        | 74 (22.4)               | 58 (21.7)                        | 16 (25.4)                        |
| Other                                              | 6 (1.8)                 | 5 (1.9)                          | 1 (1.6)                          |
| N/A                                                | 34 (10.3)               | 17 (6.4)                         | 17 (27.0)                        |

| Education                                          | Total, n (%) (N = 330) | Retention in care, n (%) (n = 267) | No retention in care, n (%) (n = 63) |
|---------------------------------------------------|-------------------------|----------------------------------|----------------------------------|
| No education                                       | 58 (17.6)               | 43 (16.1)                        | 15 (23.8)                        |
| Primary education or higher                        | 268 (81.2)              | 221 (82.8)                       | 47 (74.6)                        |
| N/A                                                | 4 (1.2)                 | 3 (1.1)                          | 1 (1.6)                          |

| Marital status                                     | Total, n (%) (N = 330) | Retention in care, n (%) (n = 267) | No retention in care, n (%) (n = 63) |
|---------------------------------------------------|-------------------------|----------------------------------|----------------------------------|
| Married                                            | 145 (43.9)              | 117 (43.8)                       | 28 (44.4)                        |
| Not married                                        | 181 (54.8)              | 147 (55.1)                       | 34 (54.0)                        |
| N/A                                                | 4 (1.2)                 | 3 (1.1)                          | 1 (1.6)                          |

| Running water                                      | Total, n (%) (N = 330) | Retention in care, n (%) (n = 267) | No retention in care, n (%) (n = 63) |
|---------------------------------------------------|-------------------------|----------------------------------|----------------------------------|
| Yes                                                | 171 (51.8)              | 138 (51.7)                       | 33 (52.4)                        |
| No                                                 | 133 (40.3)              | 109 (40.8)                       | 24 (38.1)                        |

Discussion

Among patients starting second-line ART at a hospital-based clinic in Ethiopia, 80.5% remained in care after a median of 22.2 months of follow-up, a finding that supports the continued and expanded provision of second-line ART in the Ethiopian public health system. The main cause of attrition among both adults and adolescents and children was LTFU after starting second-line ART, which occurred in 18.9% of study subjects. In adults and adolescents, LTFU was associated with CD4 cell counts <100 cells/mm³ at the time of the switch to second-line ART (HR 2.24; 95% CI: 1.31, 3.84), and first-line ART failure not confirmed by viral load testing (HR 2.50; 95% CI: 1.34, 4.66) (Table 3).

The rate of LTFU on second-line ART in our population is slightly higher compared to data from other second-line ART programs in sub-Saharan Africa and Asia, reporting proportions of LTFU ranging from 3.6 to 12% at 6 months (10, 22), 3.0–17% at 12 months (23–25), and 3.0–8.0% at 24 months (26, 27), respectively. The slightly higher rate of LTFU may be a general Ethiopian phenomenon, regardless whether patients are in first-line or second-line ART. Several studies have previously shown high rates of LTFU among both adults and adolescents, and children starting first-line ART in Ethiopia (28–31). Unpublished data, collected at the clinic where this study was conducted, indicates a LTFU rate of 28% among adults and adolescents on first-line ART. Another study from the same patient up-take area reports that 34% of the children on first-line ART were LTFU (31).
Table 2. Characteristics of children (age <15 years)* at initiation of second-line ART with regard to subsequent retention in care

|                          | Total, n (%) | Retention in care, n (%) | No retention in care, n (%) |
|--------------------------|--------------|--------------------------|----------------------------|
| (N = 53)                 | (N = 46)     | (N = 7)                  |                            |
| Age (years)              |              |                          |                            |
| ≤ 7                      | 27 (50.9)    | 24 (52.2)                | 3 (42.9)                   |
| > 7                      | 26 (49.1)    | 22 (47.8)                | 4 (57.1)                   |
| N/A                      | 0 (0.0)      | 0 (0.0)                  | 0 (0.0)                    |
| Gender                   |              |                          |                            |
| Male                     | 25 (47.2)    | 24 (52.2)                | 1 (14.3)                   |
| Female                   | 27 (50.9)    | 21 (45.7)                | 6 (85.7)                   |
| N/A                      | 1 (1.9)      | 1 (2.2)                  | 0 (0.0)                    |
| CD4 category (cells/mm³) |              |                          |                            |
| < 200                    | 30 (56.6)    | 26 (56.5)                | 4 (57.1)                   |
| > 200                    | 19 (35.8)    | 17 (37.0)                | 2 (28.6)                   |
| N/A                      | 4 (7.5)      | 3 (6.5)                  | 1 (14.3)                   |
| BMI (kg/m²)              |              |                          |                            |
| < 15                     | 22 (41.5)    | 20 (43.5)                | 2 (28.6)                   |
| > 15                     | 26 (49.1)    | 22 (47.8)                | 4 (57.1)                   |
| N/A                      | 5 (9.4)      | 4 (8.7)                  | 1 (14.3)                   |
| First-line ART failure confirmed by HIV RNA testing | | | |
| Yes                      | 37 (69.8)    | 35 (76.1)                | 2 (28.6)                   |
| No                       | 15 (28.3)    | 10 (21.7)                | 5 (71.4)                   |
| N/A                      | 1 (1.9)      | 1 (2.2)                  | 0 (0.0)                    |
| Reasons for switch to second-line ART | | | |
| Treatment failure        | 37 (69.8)    | 35 (76.1)                | 2 (28.6)                   |
| Side effect              | 14 (26.4)    | 10 (21.7)                | 4 (57.1)                   |
| Other                    | 1 (1.9)      | 0 (0.0)                  | 1 (14.3)                   |
| N/A                      | 1 (1.9)      | 1 (2.2)                  | 0 (0.0)                    |
| At least one parent alive | | | |
| Yes                      | 36 (67.9)    | 31 (67.4)                | 5 (71.4)                   |
| No                       | 6 (11.3)     | 5 (10.9)                 | 1 (14.3)                   |
| N/A                      | 11 (20.8)    | 10 (21.7)                | 1 (14.3)                   |

ART, antiretroviral treatment; BMI, body mass index.

*Four patients with documented transfer of care were excluded.

Hence it appears that retention in care during the second-line ART, in this study, was not worse than that in Ethiopian patients on first-line regimens.

The uncertainty of classifying true outcomes is an inherent problem of studies on LTFU. Different explanations for LTFU in ART programs in sub-Saharan Africa have been described (32–34). In a district of Southern Ethiopia, the tracing of patients with LTFU revealed that 48% had died. In other cases, patients had registered for ART care at other facilities or resorted to alternative therapies (33). The low mortality rate (0.5%) in our study is likely an underestimate, and may reflect inadequately recorded mortality. The association between LTFU and indicators of advanced disease (such as low CD4 cell counts at the time of treatment switch and poor CD4 cell count increase at the last follow-up visit) suggest that unrecognized mortality explains a proportion of LTFU among our participants. However, the fact that a number of LTFU subjects did return to the clinic and resumed care during the study period shows that there are different explanations for LTFU. The second-line ART recipients lost to follow-up must be traced to gain a better understanding of the underlying mechanisms.

As is true for most ART programs in low-income countries, HIV RNA testing is not available for the routine monitoring of patients on first-line ART, and the identification of treatment failure still mainly depends on clinical and immunological criteria. In addition to the poor sensitivity of these criteria for detecting patients with viremia during ART, some patients with immunological and/or clinical signs of treatment failure have suppressed HIV RNA replication. In these cases, other medical conditions, in particular opportunistic infections such as tuberculosis, may be present; the modification of ART will not benefit such individuals. Since the introduction of HIV RNA testing in patients considered for second-line ART at the study clinic no patient with suspected treatment failure switched regimen in case of undetectable viremia. Routine HIV RNA testing for patients on first-line ART (irrespective of clinical or immunological characteristics) has been shown to identify treatment failure in its earlier stages, leading to less delay in the switch to second-line regimens (35). In addition, viral load testing has been shown to be a useful tool for improving and maintaining adherence (36).

Studies from first-line ART programs in Ethiopia have found various factors to be associated with subsequent LTFU, namely, characteristics related to medical and socio-economic condition, as well as the type of health care facility (37, 38). The same pattern has been observed among children starting first-line ART in Ethiopia (31). Factors associated with LTFU during second-line ART have hitherto not been studied. However, in findings similar to ours, advanced disease at treatment initiation has been found to be linked to the increased risk of death and treatment failure in adults starting second-line ART in other settings (20, 23). In addition, higher age and viral load at the time of the regimen switch have been associated with treatment failure in adults starting second-line ART (39).

The results of our study, performed in patients treated at a hospital-based public ART clinic in sub-Saharan Africa, suggest that earlier recognition of first-line treatment failure and subsequent regimen switch could lead to improved outcomes of second-line ART. Emphasis should
be placed on expanding access to viral load testing in HIV programs, training ART prescribers how to recognize suspected treatment failure, and improving systems for tracing patients with LTFU. Other interventions may also be needed, such as the improved diagnosis of incident opportunistic infections and socio-economic support (35).

### Limitations
This study was based on retrospectively collected register data. However, patient information at this clinic has been collected and registered following structured questionnaires, and the proportion of missing data was low. The size of the study population was limited; with a larger number of participants, additional factors associated with LTFU could possibly have been identified. Since the number of children on second-line ART was low, and mechanisms of LTFU are likely to be different from those in adults and adolescents, we did not analyze the factors associated with LTFU in children.

#### Table 3. Cox proportional hazards model for LTFU for adults and adolescents

| Variable                                      | Univariate | Multivariate Before step-by-step exclusion | Multivariate After step-by-step exclusion |
|-----------------------------------------------|------------|-------------------------------------------|-----------------------------------------|
|                                               | HR (95% CI) | p                                              | HR (95% CI)    | p                                              | HR (95% CI)    | p                                              |
| Age category (years)                          |            |                                               |                                |                                               |                                |                                               |
| 15–29                                         | 1.0        |                                               |                                |                                               |                                |                                               |
| 30–39                                         | 0.9 (0.46–1.76) | 0.764                                       | 1.03 (0.57–1.86) | 0.933                                       |                                |                                               |
| > 40                                          |            |                                               |                                |                                               |                                |                                               |
| Gender                                        |            |                                               |                                |                                               |                                |                                               |
| Female                                        | 1.0        |                                               |                                |                                               |                                |                                               |
| Male                                          | 1.15 (0.69–1.91) | 0.596                                       |                                |                                               |                                |                                               |
| CD4 category (cells/mm$^3$)                   |            |                                               |                                |                                               |                                |                                               |
| ≥ 100                                         | 1.0        |                                               |                                |                                               |                                |                                               |
| < 100                                         | 1.93 (1.16–3.20) | 0.012*                                      | 2.36 (1.36–4.09) | 0.002**                                     | 2.24 (1.31–3.84) | 0.003**                                     |
| WHO stage category                            |            |                                               |                                |                                               |                                |                                               |
| Stage 1–2a                                    | 1.0        |                                               |                                |                                               |                                |                                               |
| Stage 3–4                                     | 1.51 (0.80–2.86) | 0.205*                                      | 1.02 (0.51–2.04) | 0.952                                       |                                |                                               |
| Functional Status                             |            |                                               |                                |                                               |                                |                                               |
| Able to Work                                  | 1.0        |                                               |                                |                                               |                                |                                               |
| Unable to Work                                | 1.97 (1.17–3.33) | 0.011*                                      | 1.59 (0.89–2.85) | 0.119                                       |                                |                                               |
| First-line failure confirmed by HIV RNA testing|            |                                               |                                |                                               |                                |                                               |
| Yes                                           | 1.0        |                                               |                                |                                               |                                |                                               |
| No                                            | 2.11 (1.16–3.83) | 0.014*                                      | 2.08 (1.09–3.98) | 0.026**                                     | 2.50 (1.34–4.66) | 0.004**                                     |
| Education                                     |            |                                               |                                |                                               |                                |                                               |
| Primary education or higher                   | 1.0        |                                               |                                |                                               |                                |                                               |
| No education                                  | 1.74 (0.97–3.13) | 0.064*                                      | 1.58 (0.83–2.97) | 0.161                                       |                                |                                               |
| Marital status                                |            |                                               |                                |                                               |                                |                                               |
| Not married                                   | 1.0        |                                               |                                |                                               |                                |                                               |
| Married                                       | 1.05 (0.64–1.74) | 0.848                                       |                                |                                               |                                |                                               |
| Running water                                 |            |                                               |                                |                                               |                                |                                               |
| No                                            | 1.0        |                                               |                                |                                               |                                |                                               |
| Yes                                           | 1.22 (0.72–2.07) | 0.453                                       |                                |                                               |                                |                                               |
| Electricity                                   |            |                                               |                                |                                               |                                |                                               |
| No                                            | 1.0        |                                               |                                |                                               |                                |                                               |
| Yes                                           | 1.06 (0.58–1.91) | 0.859                                       |                                |                                               |                                |                                               |

HR, hazard ratio; CI, confidence interval.

*Variables with $p < 0.3$ in univariate analysis were included in the multivariate model.

In the multivariate model a backward step-by-step exclusion Cox proportional hazards model was used. **$p < 0.05$ were considered significant.

*aAccording to clinical staging for severity of HIV disease (21).*
Although the majority of participants had started second-line ART as a result of confirmed or suspected first-line treatment failure, we also included persons who had had treatment modification for other reasons. It is possible that retention in care, as well as factors associated with LTFU, differ with regard to the reason for changing to second-line ART. However, we did not find that indications for starting second-line ART were associated with LTFU.

Conclusions

Retention in care during second-line ART at this Ethiopian clinic was satisfactory for both adults and adolescents and children. LTFU among adults and adolescents was associated with advanced immunosuppression at the time of ART regimen switch, and first-line treatment failure not confirmed by HIV RNA testing. These findings support the continued provision of second-line ART in the Ethiopian health system, with the confirmation of suspected treatment failure by viral load testing. This will require increased access to both virological monitoring and second-line antiretroviral drugs, as well as interventions to improve retention in care. Earlier recognition of first-line failure and the switch to second-line regimen before advanced immunosuppression has developed are likely to improve the outcomes of second-line ART.

Author's contributions

SW developed the data collection tools, undertook data analysis and drafted the manuscript. SW, PB, and TTB designed and initiated the study, provided academic supervision as well as the structure and content of the paper. AR contributed to academic supervision, statistical analysis and data presentation. GJ assisted in data collection and design. All authors have read and approved the final manuscript.

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Conflict of interest and funding

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