HIV-infected adolescents in southern Africa can achieve good treatment outcomes: results from a retrospective cohort study

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**Objectives:** In this study we examine whether adolescents treated for HIV/AIDS in southern Africa can achieve similar treatment outcomes to adults.

**Design:** We have used a retrospective cohort study design to compare outcomes for adolescents and adults commencing antiretroviral therapy (ART) between 2004 and 2010 in a public sector hospital clinic in Bulawayo, Zimbabwe.

**Methods:** Cox proportional hazards modelling was used to investigate risk factors for death and loss to follow-up (LTFU) (defined as missing a scheduled appointment by ≥3 months).

**Results:** One thousand, seven hundred and seventy-six adolescents commenced ART, 94% having had no previous history of ART. The median age at ART initiation was 13.3 years. HIV diagnosis in 97% of adolescents occurred after presentation with clinical disease and a higher proportion had advanced HIV disease at presentation compared with adults [WHO Stage 3/4 disease (79.3 versus 65.2%, \( P < 0.001 \)]. Despite this, adolescents had no worse mortality than adults, assuming 50% mortality among those LTFU (6.4 versus 7.3 per 100 person-years, \( P = 0.75 \)) with rates of loss to follow-up significantly lower than in adults (4.8 versus 9.2 per 100 person-years, \( P < 0.001 \)). Among those who were followed for 5 years or more, 5.8% of adolescents switched to a second-line regimen as a result of treatment failure, compared with 2.1% of adults (\( P < 0.001 \)).

**Conclusion:** With adolescent-focused services, it is feasible to achieve good outcomes for adolescents in large-scale ART programs in sub-Saharan Africa. However, adolescents are at high risk of treatment failure, which compromises future drug options. Interventions to address poor adherence in adolescence should be prioritized.

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**Keywords:** adolescent, adolescent friendly services, AIDS, antiretroviral, antiretroviral therapy, cohort study, HIV, Zimbabwe

**Introduction**

Over the past decade, southern Africa has seen a marked decline in antenatal HIV prevalence, and also in mother-to-child HIV transmission (MTCT) rates as a result of effective preventive interventions [1,2]. Increasing numbers of HIV-infected children are now surviving to adolescence and beyond because of antiretroviral therapy...
(ART). In addition, about a third of HIV-infected infants have slow-progressing disease, and substantial numbers of infants infected at the peak of the HIV epidemic in the 1990s are presenting to clinical services for the first time in adolescence [3]. The age-profile of the paediatric epidemic is, thus, changing, and over coming years adolescents are likely to contribute a bigger proportion accessing HIV care than younger children [2].

The continuing scale-up of interventions to prevent MTCT promises further declines in MTCT rates but will not impact upon the existing maturing cohort of HIV-infected children [4]. Paediatric HIV programs in Africa have, however, focused mainly on infants and younger children to date, and relatively little attention has been paid to adolescents. Adolescence is a period of profound physical, cognitive and psychological development; adolescents confront many sociocultural changes and risk-taking behaviours generally become more prevalent [5]. These factors place considerable challenges on adolescents and chronic disease management can worsen during this period [5]. Whether such factors may prevent adolescents achieving good clinical outcomes on ART in Africa is uncertain due to the sparse evidence base [4,6–8]. ART adherence among adolescents has been shown to be poor particularly among those with high-risk behaviours, and virological outcomes among HIV-infected adolescents have been shown to be worse than those in adults [9–12].

We conducted a retrospective cohort study to investigate loss to follow-up (LTFU) and mortality among adolescents in a large public sector HIV treatment programme in Zimbabwe, and compared treatment outcomes to those among adults treated in the same facility.

Methods

Study setting

Patients were drawn from the Mpilo Hospital HIV Clinic in Bulawayo, Zimbabwe’s second largest city. Mpilo clinic has provided ART since April 2004, with decentralization of care of adult patients stable on ART to primary care level from 2006, and has accumulated a large cohort of adolescent patients. HIV care at Mpilo is provided by the public sector in partnership with Médecins Sans Frontières (MSF) and other organizations. Although ART initiation was carried out by doctors, routine clinical care was provided mainly by nurses trained in HIV management, with supervision from on-site doctors.

From 2007, additional services for adolescents were introduced, following group discussions with adolescents to identify their needs, and workshops to address stigmatizing behaviours among staff. Adolescents were engaged in service planning decisions through nominated peer representatives. Adolescent-specific activities included peer and non-peer counselling, and a youth club. Activities were designed to promote resilience among adolescents and focused not only on medical issues such as promoting adherence, but on the particular social challenges faced by HIV-positive adolescents, such as bullying and stigma. Participation was promoted by including social activities. Although both adult and adolescent defaulters were actively traced, the adolescent tracing programme was better resourced and integrated into community structures. For additional information on adolescent services see Appendix I, http://links.lww.com/QAD/A344.

Inclusion criteria

Study participants were adolescents and adults who initiated ART at Mpilo ART clinic between April 2004 and November 2010. Adolescents were defined as those aged 10 and less than 19 years at time of initiation of ART. Longitudinal patient data were analysed from time of first clinic visit to most recent follow-up before December 2010. Data was not available for patients following decentralization. Treatment was provided in accordance with Zimbabwean National Guidelines, with individuals eligible for ART if they had a CD4+ cell count less than 200 cells/µl and/or WHO stage III or IV HIV disease. CD4+ cell count tests were performed free of charge, although availability was limited during 2007 and 2008. Viral load testing was not available.

Data collection

At each clinic visit, comprehensive data including drug regimen, disease stage, incident AIDS-related illness, adverse drug reactions, weight, height for adolescents, laboratory results as well as the individual’s next scheduled visit, were routinely recorded using FUCHIA software (Epicentre, Paris, France). Drug regimen information was cross checked against pharmacy data for accuracy. Mortality data were obtained through on-going systematic patient follow-up activities, notification by family and through death register review.

Data analysis

Relevant demographic and clinical information were extracted from FUCHIA and analysed using STATA (version 10; Stata-Corp, College Station, Texas, USA). Comparison of means and proportions was done using the two-tailed t-test and χ² tests, respectively. For nonparametric data the Mann–Whitney U test was used. Cox proportional hazards modelling was used to investigate risk factors for mortality and LTFU, with variables significant at the P<0.2 level in univariate analyses being included in the multivariate model. The proportional hazards assumption was tested using log plots. Z-scores for adolescent anthropometric data were derived using WHO standards [13]. CD4+ cell counts were considered current if they were measured within 3 months of the time point of interest.
The potential impact of unrecorded deaths among those lost to follow-up on mortality was investigated by performing a sensitivity analysis, using 30, 50 and 70% probability of death among those who were LTFU. These probabilities were obtained from the estimates of mortality among those defaulting from ART programs reported in a previous meta-analysis [14].

Definitions
Patients were considered LTFU if they were at least 3 months overdue a scheduled visit, with date of LTFU calculated as the mid-point between last attended appointment and the subsequent appointment missed. Records of patients LTFU were continually updated and in the event that an individual returned to the clinic their status was amended and they would continue to contribute person time in the analysis. Patients whose routine HIV care was decentralized to primary care services or transferred to an HIV centre outside Bulawayo were considered to have transferred out of the programme.

Treatment failure was defined as a new or recurrent WHO stage IV condition or a fall to pretherapy CD4\(^+\) cell count or 50% drop in CD4\(^+\) cell count from the peak value or a CD4\(^+\) cell count persistently below 100 cells/\(\mu\)l after 6 months of treatment, as per WHO 2006 recommendations [15].

Ethical considerations
Ethical approval for the study was obtained from Mpilo Hospital Ethical Review Board. Individual consent from patients to use clinical data was not obtained. No personal identification information was collected and records were anonymized to maintain patient confidentiality.

Table 1. Baseline characteristics of study participants.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total n = 11136</th>
<th>Adults n = 9360</th>
<th>Adolescents n = 1776</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3726 (33.4%)</td>
<td>2876 (30.7%)</td>
<td>850 (47.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median age (IQR) (years)</td>
<td>34.7 (26.7–42.1)</td>
<td>36.8 (31.1–44.0)</td>
<td>13.3 (11.4–15.3)</td>
<td>–</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Referral from VCT/self-referral(^a)</td>
<td>1679 (15.1%); (1679/11 108)</td>
<td>1630 (17.5%); (1630/9334)</td>
<td>49 (2.8%); (49/1774)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of previous ART use</td>
<td>15.7% (1747/11 1136)</td>
<td>17.6% (1644/9360)</td>
<td>5.8% (103/1776)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHO Stage III/IV</td>
<td>67.3% (6963/10 343)</td>
<td>65.2% (5727/8784)</td>
<td>79.3% (1236/1559)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median height for age z score (IQR)</td>
<td>–</td>
<td>–</td>
<td>–2.5 (–3.4 to –1.6); (n = 485)</td>
<td>–</td>
</tr>
<tr>
<td>Median BMI for age z score (IQR)</td>
<td>–</td>
<td>–</td>
<td>–1.6 (–2.6 to –0.68); (n = 485)</td>
<td>–</td>
</tr>
<tr>
<td>Median (IQR) CD4(^+) cell count at ART initiation (cells/(\mu)l)</td>
<td>149 (75–222); (n = 4221)</td>
<td>144 (75–211); (n = 3441)</td>
<td>183 (78–289); (n = 780)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4(^+) cell count &lt;200 cells/(\mu)l at ART initiation</td>
<td>2856 (67.7%); (n = 4221)</td>
<td>2429 (70.6%); (n = 3441)</td>
<td>427 (54.7%); (n = 780)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>585 (5.2%)</td>
<td>494 (5.3%)</td>
<td>89 (5.0%)</td>
<td>0.633</td>
</tr>
</tbody>
</table>

\(^a\)Remainder diagnosed following HIV-indicator illness.

Results

Baseline characteristics
Between April 2004 and November 2010, 13 746 individuals commenced ART (children, adolescents and adults); after exclusion of 28 records due to missing data, we extracted information on 9 360 adults and 1 776 (13% of cohort) adolescents. The increase in numbers starting ART was highest for adolescents, increasing seven-fold over the study period. As observed in other HIV care programmes, the majority of adults commencing ART were women, with men tending to present with more advanced disease compared with women (WHO stage III/IV disease: 72.7 versus 61.8%, P < 0.001; CD4\(^+\) cell count less than 200 cells/\(\mu\)l: 74 versus 61% P < 0.001 in males versus females, respectively). This difference was not observed among adolescents (WHO Stage III/IV disease 81 versus 78%, P = 0.065 and CD4\(^+\) cell count less than 200 cells/\(\mu\)l 51 versus 53%, P = 0.38, in males versus females, respectively).

The median age at ART initiation among adolescents, more than 95% of whom were vertically infected, was 13.3 years and 94% had no history of previous ART use. Only 2.6% of ART-naive adolescents entered the programme via freestanding voluntary counselling and testing (VCT) services compared to 18.3% of adults (P < 0.001), the remainder being diagnosed after presentation with an HIV-related illness. At ART initiation, adolescents had significantly more advanced disease and lower haemoglobin levels, but paradoxically had higher CD4\(^+\) cell counts (Table 1).

Treatment outcomes are derived from a total of 22 127 person-years of follow-up, of which 3 478 person-years were contributed by adolescents. The median duration on treatment was 567 (interquartile range 223–1082) days for adolescents and 490 (191–947) days for adults.
Outcomes following antiretroviral therapy initiation

The rate of LTFU was approximately twice as high in adults when compared with adolescents at each follow-up interval (9.2/100 versus 4.8/100 person-years; hazard ratio = 1.9, P < 0.001). The rate of recorded deaths was higher in adolescents than in adults (log rank test P < 0.001). However, when adjusted for likely mortality rates (30–70%) among those lost to follow-up, there was no difference in mortality between the two groups (Fig. 1). As in other HIV programs, rates of death and LTFU were highest in the first 6 months following initiation of ART in both groups, and CD4+ cell count gains were largest in the first 12 months of treatment. Importantly, the proportion of adolescents under follow-up who switched to a second line regimen during the study period was nearly three times that observed in adults (Table 2).

Risk factors for death and loss to follow-up

Haemoglobin less than 11 g/dl, CD4+ cell count less than 200 cells/μl and BMI z score less than −2 at initiation were associated with an increased risk of death among adolescents, although only haemoglobin remained significantly associated with risk of death on multivariate analysis (Table 3). Among adults, sex, age, CD4+ cell count less than 200 cells/μl, haemoglobin less than 11 g/dl, WHO stage III/IV, BMI less than 18 kg/m² and later year of initiation were all associated with risk of death on univariate analysis. Haemoglobin and year of initiation remained associated with death on multivariate analysis, as did CD4+ cell count less than 200 cells/μl, which was the strongest independent-risk factor, hazard ratio = 8.4, P = 0.037 (Table 3). Among adults, male sex and later years of ART initiation were independently associated with risk of LTFU. These associations were not observed for adolescents (Table 3).

Discussion

The main finding of this study was the high retention rates and low mortality rates among adolescents enrolled...
in a public sector HIV care service. Although there are few direct data for adolescents in HIV programs, what evidence there is has generally shown worse treatment outcomes among adolescents than among adults [7,9,11,16,17]. The rates of retention in care for adolescents in this large cohort exceed those previously documented for this age-group in other African HIV care programs [7,8,18], and are considerably higher than the range of 70–77% for programme retention at 24 months reported in a systematic review of HIV treatment outcomes by Fox and Rosen [19].

The high rate of retention in care among adolescents that was observed in this cohort is remarkable because this group faces considerable barriers to accessing and remaining in HIV care [20]. Current HIV diagnosis and care services are mainly aimed at adults, infants and young children and local perceptions often tend to exclude HIV-infected adolescents, many of whom are orphans. Transition from paediatric to adult services may also increase the risk of interruption in care. The number of adolescents who initiated ART increased seven-fold over the study period, compared with a two-fold increase in the numbers of adults. By the end of the study period 23% of all actively followed patients were adolescents, a far higher proportion than seen in facilities elsewhere in the country (Data from Ministry of Health and Child Welfare, Zimbabwe). This finding, previously noted [3], is likely to reflect the success of adolescent friendly services in improving access and retention in care.

Only a minority of adolescents were tested through VCT services. VCT services largely neglect adolescents and provider-initiated testing and counselling in health facilities is not routinely offered to this age group. The legal requirement for guardian consent for HIV testing of a person aged under 16 years in Zimbabwe may also be a barrier to testing, especially as many children may have no guardian or experience changing guardianship [21,22]. The majority of adolescents were diagnosed with HIV following presentation with a clinical illness. Interestingly, while the proportion of adolescents presenting with advanced disease stage was significantly higher than in adults, adolescents had higher baseline CD4+ cell counts than did adults as well as better immune reconstitution at 12 months following ART initiation. Although adolescent mortality rates were no higher than those in adults, with earlier identification and treatment, adolescents would be expected to achieve even better treatment outcomes. The discrepancy between disease stage and CD4+ cell count in this age-group has been noted in other studies, and may be due to a poor ‘quality’ of immune response despite preserved counts. A potential important implication is that CD4+ cell count may not be an appropriate criterion for starting ART in older children [12,17].

As expected, markers of advanced disease such as anaemia, low CD4+ cell count and low BMI were associated with an increased risk of death. The lack of observed association between tuberculosis (TB) at initiation and mortality contrasts other findings [23], and may be a result of underreporting of (TB), furthermore, TB was managed at a separate site, where national guidelines at the time advised late initiation, a practice now discouraged by WHO [23]. Some

Table 2. Treatment outcomes at 6, 12, 24, 36, 48 and 60 months for adults and adolescents commencing ART between April 2004 and November 2010.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N (%)</th>
<th>At 6 months</th>
<th>At 12 months</th>
<th>At 24 months</th>
<th>At 36 months</th>
<th>At 48 months</th>
<th>At 60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (N = 9360)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Known deaths (%)</td>
<td>279 (3.0%)</td>
<td>363 (3.9%)</td>
<td>458 (4.9%)</td>
<td>487 (5.2%)</td>
<td>505 (5.4%)</td>
<td>512 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up (%)</td>
<td>663 (7.1%)</td>
<td>994 (10.1%)</td>
<td>1284 (13.7%)</td>
<td>1448 (15.9%)</td>
<td>1604 (17.1%)</td>
<td>1664 (17.7%)</td>
<td></td>
</tr>
<tr>
<td>Decentralized/moved out of area (%)a</td>
<td>8 (0.1%)</td>
<td>22 (0.2%)</td>
<td>213 (2.3%)</td>
<td>874 (9.3%)</td>
<td>1388 (14.8%)</td>
<td>1660 (17.7%)</td>
<td></td>
</tr>
<tr>
<td>Still actively followed (%)</td>
<td>8667 (92.4%)</td>
<td>8363 (89.2%)</td>
<td>7360 (78.5%)</td>
<td>6468 (68.9%)</td>
<td>5811 (62.0%)</td>
<td>5475 (58.4%)</td>
<td></td>
</tr>
<tr>
<td>Switched to second-line regimen (%)b</td>
<td>28 (0.3%)</td>
<td>42 (0.5%)</td>
<td>62 (0.7%)</td>
<td>78 (0.8%)</td>
<td>97 (1.0%)</td>
<td>116 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count ≥200 cells/μl (%)</td>
<td>757 (55.8%)</td>
<td>314 (47.0%)</td>
<td>86 (72.3%)</td>
<td>25 (78.1%)</td>
<td>6 (60%)</td>
<td>8 (60%)</td>
<td></td>
</tr>
<tr>
<td>Adolescents (N = 1776)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known deaths (%)</td>
<td>68 (3.8%)</td>
<td>84 (4.7%)</td>
<td>109 (6.1%)</td>
<td>121 (6.8%)</td>
<td>130 (7.3%)</td>
<td>133 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up (%)</td>
<td>63 (3.5%)</td>
<td>88 (4.9%)</td>
<td>124 (6.0%)</td>
<td>147 (8.2%)</td>
<td>160 (9.0%)</td>
<td>164 (9.2%)</td>
<td></td>
</tr>
<tr>
<td>Decentralized/moved out of area (%)a</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (0.2%)</td>
<td>6 (0.3%)</td>
<td>8 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Still actively followed (%)</td>
<td>1641 (92.0%)</td>
<td>1597 (89.6%)</td>
<td>1533 (86.0%)</td>
<td>1495 (81.8%)</td>
<td>1468 (82.3%)</td>
<td>1458 (81.8%)</td>
<td></td>
</tr>
<tr>
<td>Switched to second-line regimen (%)b</td>
<td>4 (0.2%)</td>
<td>7 (0.4%)</td>
<td>16 (1.0%)</td>
<td>34 (2.3%)</td>
<td>59 (4.0%)</td>
<td>84 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count ≥200 cells/μl (%)</td>
<td>294 (83%)</td>
<td>236 (91%)</td>
<td>124 (91%)</td>
<td>91 (89%)</td>
<td>53 (78%)</td>
<td>22 (75.9%)</td>
<td></td>
</tr>
<tr>
<td>Median CD4+ cell count (IQR)c</td>
<td>411 (261–620)</td>
<td>504 (355–733)</td>
<td>578 (384–831)</td>
<td>603 (400–789)</td>
<td>395 (207–604)</td>
<td>361 (237–657)</td>
<td></td>
</tr>
</tbody>
</table>

IQR, interquartile range.

aAfter transfer out of programme or decentralization, no further update of outcomes occurred.
bAmong individuals under active follow-up at time point of interest.
cFor those with a CD4+ test result within 3 months of the time point of interest.

Adolescents thus need to be prioritized in clinical care and provider-centered programs aimed at improving access to VCT services and adherence support. It is crucial to focus on mainstreaming adolescent-friendly programs for antiretroviral therapy (ART) in the health sector. Health care providers as well as the health system itself need to be trained to better understand the biological, psychological, and social needs of this population. This must include training on the importance of early intervention and the need for a higher CD4+ cell count threshold for treatment initiation in adolescents [24]. The use of clinic-based strategies, such as outreach to schools and homes, could also be beneficial. However, there remain other barriers to appropriate care and treatment adherence for these adolescents, including the need to target challenges such as stigma, cultural attitudes towards adherence, and limited family support. In conclusion, the high rates of treatment outcomes among adolescents in this cohort suggest potential strategies to improve care and reduce barriers to treatment in this vulnerable age-group.
coinfected individuals are, therefore, likely to have died prior to initiation, outside of Mpilo hospital and the association between TB and LTFU may reflect additional unrecorded deaths. The association between male sex and risk of LTFU among adults has been documented in other studies, and likely reflects the poor health-seeking behaviour among men [24,25]. Increasing LTFU with increasing programme years may highlight the increasing challenge of following up patients in large and/or expanding programmes.

A concerning finding was that use of second-line ART regimen due to treatment failure was significantly higher in adolescents than in adults despite adults being more treatment-experienced than adolescents, and also exceeded the national average use of second-line ART.

### Table 3. Factors at initiation of antiretroviral therapy associated with risk of death and lost to follow-up in adolescents and adults.

<table>
<thead>
<tr>
<th>Risk factors for death</th>
<th>Adolescents Univariate</th>
<th>Multivariate</th>
<th>Adults Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>0.8 (0.6–1.2)</td>
<td>0.25</td>
<td>2.6 (0.9–7.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>One year increase in age at initiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count (cells/µl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ ≥200</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>CD4+ &lt;200</td>
<td>2.9 (1.5–5.5)</td>
<td>0.001</td>
<td>2.8 (0.8–10.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hb ≥11</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Hb &lt;11</td>
<td>2.7 (1.2–6.4)</td>
<td>0.02</td>
<td>3.2 (1.0–9.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td>–</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>1.1 (0.5–2.3)</td>
<td>0.84</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>WHO disease staging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>1.6 (1.0–2.9)</td>
<td>0.06</td>
<td>0.96 (0.2–3.7)</td>
<td>0.95</td>
</tr>
<tr>
<td>III/IV</td>
<td>2.4 (1.9–3.0)</td>
<td>&lt;0.001</td>
<td>1.8 (0.8–3.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Anthropometric scores*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI z score ≥2/2≥18 kg/m²</td>
<td>1.0</td>
<td>–</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>BMI z score &lt;2/2&lt;18 kg/m²</td>
<td>1.8 (0.3–6.8)</td>
<td>0.013</td>
<td>0.65 (0.22–1.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb ≥11</td>
<td>1.0</td>
<td>–</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Hb &lt;11</td>
<td>1.25 (0.7–2.4)</td>
<td>0.48</td>
<td>1.4 (1.1–1.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Height age z score ≥2</td>
<td>1.4 (0.8–2.3)</td>
<td>0.22</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Height age z score &lt;2</td>
<td>0.83 (0.7–0.9)</td>
<td>0.001</td>
<td>0.97 (0.7–1.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>Per 1 year increase in year of initiation</td>
<td>0.7 (0.6–0.8)</td>
<td>&lt;0.001</td>
<td>0.7 (0.52–0.98)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

| Risk factors for LTFU                  | Adolescents Univariate | Multivariate | Adults Univariate | Multivariate |
|----------------------------------------|                        |              |                  |              |
| Sex                                    |                        |              |                  |              |
| Male                                   | 1.0                    | 1.0          | 1.0              | 1.0          |
| Female                                 | 1.16 (0.9–1.6)         | 0.34         | 1.0 (0.66–1.61)  | 0.90         |
| One year increase in age at initiation |                        |              |                  |              |
| CD4+ cell count (cells/µl)             |                        |              |                  |              |
| CD4+ ≥200                              | 1.0                    | –            | 1.0              | –            |
| CD4+ under 200                         | 1.34 (0.8–2.2)         | 0.24         | 1.0 (0.8–1.2)    | 0.78         |
| Haemoglobin (g/dl)                     |                        |              |                  |              |
| Hb ≥11                                 | 1.0                    | –            | 1.0              | 1.0          |
| Hb <11                                 | 1.25 (0.7–2.4)         | 0.48         | 1.4 (1.1–1.7)    | 0.01         |
| Pulmonary TB                           |                        |              |                  |              |
| No                                     | 1.0                    | –            | 1.0              | 1.0          |
| Yes                                    | 1.48 (0.8–2.7)         | 0.21         | 1.4 (1.2–1.7)    | <0.001       |
| WHO disease staging                    |                        |              |                  |              |
| I/II                                   | 1.0                    | –            | 1.0              | 1.0          |
| III/IV                                 | 0.8 (0.54–1.19)        | 0.28         | –                | –            |
| Anthropometric scores*                 |                        |              |                  |              |
| BMI z score ≥2/2≥18 kg/m²              | 1.0                    | –            | 1.0              | 1.0          |
| BMI z score <2/2<18 kg/m²              | 1.33 (0.9–2.0)         | 0.20         | 1.12 (0.72–1.77) | 0.60         |
| Height age z score ≥2                  | 0.93 (0.6–1.5)         | 0.76         | 0.98 (0.60–1.60) | 0.94         |
| Height age z score <2                  | 1.17 (1.1–1.3)         | 0.005        | 1.01 (0.83–1.20) | 0.89         |

HR, hazard ratio. Risk factors significant at the P≤0.2 level were included in the multivariate model. Sex and age were included in multivariate model a-priori.

BMI categorized as z score at least −2 or less than −2 in adolescents; BMI categorized as at least 18 kg/m² or less than 18 kg/m² in adults. Height not recorded in adults.
cell count measurements were not regularly
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e et al.
A surprising prevention success: why did the HIV
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[76x98]was diagnosed using clinical and immunological criteria,
confirm treatment failure. Given that treatment failure
available and HIV viral load testing was not available to
in our cohort [14,33]. Data on adherence was not
of death among those LTFU would impact mortality rates
carry out a sensitivity analysis to assess how likely rates
or not be receiving treatment. A proportion of adults and
in another potential factor as treatment outcomes for
chronic childhood illnesses are greatly influenced by
guardians’ awareness and willingness to invest time and
effort into accessing care [31]. HIV-infected children may
be at especially high risk of subtle forms of neglect
because of maternal illness, as guardians tend to invest less
in unhealthy children who are adopted or maternal
orphans [32]. Poor adherence not only leads to treatment
failure in a setting where treatment options are limited but
also leads to risk of onward horizontal transmission of
drug-resistant strains.

This study reports on a large cohort of HIV-infected
adolescents treated in a single centre in sub-Saharan Africa.
The large numbers, long duration of follow-up and
availability of detailed individual-level data which was
systematically entered into an electronic database are major
strengths. Furthermore, this study reports from a cohort
managed in a public sector clinic, and therefore the findings
are likely to be more generalizable than data from cohorts
enrolled in research studies including clinical trials.

The study is subject to all the limitations of a retrospective
cohort study design, such as incomplete data. Anthropo-
metric measures were less comprehensively recorded
than other variables. Omissions in assessment and
underrecording in patient notes are likely causes. CD4+ cell count measurements were not regularly
carried out because of logistical reasons. CD4+ results at
initiation were only available for 44% of adolescents and
37% of adults. However, outcomes did not differ between
those who had and who did not have CD4+ cell counts at
initiation (Appendix 2, http://links.lww.com/QAD/
A344). Common to studies of this type, ascertainment
of reasons for LTFU was incomplete. Patients rarely
notified the clinic when relocating to another region or
country for personal reasons and some of those recorded,
as LTFU will have moved to other areas where they may
or not be receiving treatment. A proportion of adults and
adolescents who were lost to follow-up are likely to have
died. We have however attempted to account for this by
carrying out a sensitivity analysis to assess how likely rates
of death among those LTFU would impact mortality rates
in our cohort [14,33]. Data on adherence was not
available and HIV viral load testing was not available to
confirm treatment failure. Given that treatment failure
was diagnosed using clinical and immunological criteria,
which have poor accuracy, particularly among children,
the actual numbers who failed treatment are likely to have
been higher in both groups.

Follow-up data were not available for patients whose care
was decentralised. The impact of this on overall outcomes
is likely to be insignificant as decentralization generally
occurred after 2 years on ART while most of the LTFU
and mortality was highest in the first 6 months of
commencing ART, with relatively modest increases in
mortality and LTFU seen after 24 months on ART.

Children have been a priority target for primary HIV
prevention efforts in Africa for many years now, but
relatively little attention has been paid to the complex
health needs of HIV-infected adolescents [34]. Our results
show that by developing dedicated adolescent friendly
services and by involving adolescents in their own
management, many of the inherent challenges of keeping
young people in care may be overcome. However,
effective strategies to address the poor adherence in this
age group are needed to further improve treatment
outcomes. In addition, there is an urgent need to address
barriers to access to HIV testing and to develop HIV-
testing facilities targeted towards adolescents.

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A.S. conducted the analysis which was reviewed by
R.A.F. contributed to interpretation of study findings. All
authors contributed to writing the study manuscript.

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Conflicts of interest
The authors have no conflicts of interest to declare.

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1. Halperin DT, Mugurungi O, Hallett TB, Muchini B, Campbell B,
Magure T, et al. A surprising prevention success: why did the HIV


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