The Rate of Switching from First-line to Second-line Antiretroviral Therapy Among People Living with HIV in Aden City, Yemen: A retrospective cohort study

Naif Mohammed Al-Haidary
alhidary2000@gmail.com

Department of Medical Microbiology and Immunology, Faculty of Medicine and Health Sciences, Sana'a University

Enas Abobakr Radman
International Rescue Committee (IRC), Yemen

Research Article

Keywords: HIV, Antiretroviral Therapy, Second-line Treatment, ART Switching, Yemen

Posted Date: June 5th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4442218/v1

License: ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.
Abstract

Background

Effective management of antiretroviral therapy (ART) is crucial in combating the global HIV pandemic. This study, the first of its kind in Yemen, investigates the rate and determinants of switching from first-line to second-line ART among people living with HIV (PLWH) in Aden City, Yemen.

Methods

A retrospective cohort study was conducted using data from PLWH who started first-line ART at Al-Wahda Hospital from 2007 to May 2022. Patients in prevention of mother-to-child transmission (PMTCT) programs, those already on second-line ART at enrollment, and those with less than 3 months of follow-up were excluded. Cumulative incidence curves and multivariable proportional hazards models were used to identify factors associated with switching, considering death and loss to follow-up as competing risks. Analyses were carried out using IBM SPSS version 26.

Results

Out of 149 patients, 18 (12.1%) switched to second-line ART with a cumulative incidence rate of 1.8 per 100 person-years. Significant factors for switching included being older than 33 years (HR: 1.45, 95% CI: 1.12–1.89), having WHO stage 3 disease (HR: 1.58, 95% CI: 1.21–2.06), and being on a TDF-FTC-EFV-based first-line regimen (HR: 1.35, 95% CI: 1.03–1.77).

Conclusions

The study highlights key factors associated with switching to second-line ART in Yemen, emphasizing the need for targeted interventions and continuous patient monitoring to enhance treatment outcomes. These findings are consistent with regional data from other resource-limited settings.

Introduction

HIV has been a significant global health challenge since its identification in the 1980s, leading to high morbidity and mortality [1–3]. Antiretroviral therapy (ART) has revolutionized HIV treatment, significantly improving the lifespan and quality of life for those infected [1, 4, 5]. However, the durability of first-line ART regimens and the need for second-line treatments remain critical, especially in resource-limited settings like Yemen [2, 6].

In Yemen, managing HIV is particularly challenging due to limited healthcare resources, ongoing conflicts, and fragile infrastructure. In 2007, HIV treatment services were established in only five out of
twenty-two main governorates, resulting in low access to services and poor treatment outcomes [7]. The city's only facility providing ART free of charge for PLWH is located in Al-Wahda Hospital, operating under the National AIDS & STIs Control Program in cooperation with the WHO [8]. Despite these efforts, little is known about the situation of HIV infection in Yemen. Previous studies have shown that ART services are limited and often disrupted due to internal conflicts, affecting treatment outcomes and leading to higher rates of switching to second-line regimens [7, 9].

This study, the first of its kind in Yemen, aims to assess the rate and determinants of switching from first-line to second-line ART among PLWH in Aden City. Understanding these factors is essential for optimizing treatment strategies, improving patient outcomes, and supporting the national HIV program in Yemen. By integrating findings from similar studies in resource-limited settings, this research provides a comprehensive view of the challenges and potential solutions for HIV treatment in Yemen [7, 9]

**Methods**

**Study Design and Population:**

This retrospective cohort study included PLWH who began first-line ART at Al-Wahda Hospital from 2007 to May 2022. Patients in PMTCT programs, those already on second-line ART at enrollment, and those with less than 3 months of follow-up were excluded. De-identified data were extracted from the National AIDS & STIs Control Program database, which includes comprehensive clinical and demographic information.

**Data Collection and Statistical Analysis:**

Data were collected on patient demographics, clinical characteristics, and ART regimens. Cumulative incidence curves were used to estimate the time to switching, while multivariable proportional hazards models identified factors associated with switching, considering death and loss to follow-up as competing risks. The models adjusted for age, gender, WHO stage, and first-line regimen. Statistical analyses were performed using IBM SPSS version 26, ensuring robust analysis through sensitivity checks and validation against existing literature.

**Ethical Considerations:**

Ethical approval was obtained from the Al-Wahda Hospital Ethics Committee and the National AIDS & STIs Control Program. Patient confidentiality was maintained by anonymizing the data.

**Results**

**Patient Characteristics:**

The study included 149 patients, with 63.8% being male and a mean age of 33 years. Third of the patients were women (36.2%), and what is worth noticing is that almost half of them were pregnant (44.4%).
Table 1 Socio-demographic characteristics of the study population

<table>
<thead>
<tr>
<th>Baseline socio-demographic characteristics</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>149 patients</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>95</td>
<td>63.8</td>
</tr>
<tr>
<td>Female</td>
<td>54</td>
<td>36.2</td>
</tr>
<tr>
<td>Age groups (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>11</td>
<td>7.4</td>
</tr>
<tr>
<td>10-19</td>
<td>8</td>
<td>5.4</td>
</tr>
<tr>
<td>&gt;19</td>
<td>130</td>
<td>87.2</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>48</td>
<td>32.2</td>
</tr>
<tr>
<td>Married</td>
<td>97</td>
<td>65.1</td>
</tr>
<tr>
<td>Widowed</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Divorced/Separate</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Missing data</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>22</td>
<td>14.8</td>
</tr>
<tr>
<td>Less than primary</td>
<td>11</td>
<td>7.2</td>
</tr>
<tr>
<td>Primary</td>
<td>62</td>
<td>41.6</td>
</tr>
<tr>
<td>Secondary</td>
<td>50</td>
<td>33.6</td>
</tr>
<tr>
<td>More than secondary</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not employed</td>
<td>95</td>
<td>63.8</td>
</tr>
<tr>
<td>Government</td>
<td>8</td>
<td>5.4</td>
</tr>
<tr>
<td>Private</td>
<td>46</td>
<td>30.6</td>
</tr>
</tbody>
</table>

The Clinical characteristics of the study population are shown in the following table.

Table 2 Clinical characteristics of the study population
Baseline clinical characteristics | Number (n=149) | %
--- | --- | ---
WHO staging | WHO stage 1 | 47 | 31.6
 | WHO stage 2 | 9 | 6.0
 | WHO stage 3 | 60 | 40.3
 | WHO stage 4 | 31 | 20.8
 | Missing data | 2 | 1.3
Pregnancy | Pregnant | 24 | 16.1 (44.4 female)
 | Not pregnant | 125 (30 female) | 83.9 (55.6 female)
ART regimen | AZT-3TC-EFV | 30 | 20.1
 | AZT-3TC-NVP | 22 | 14.8
 | D4T-3TC-EFV | 5 | 3.4
 | TDF-FTC-DTG | 22 | 14.8
 | TDF-FTC-EFV | 59 | 39.6
 | Other regimens | 11 | 7.4
ART regimen change | No | 38 | 25.5
 | Once | 69 | 46.3
 | More than once | 42 | 28.2
Co-infections | HBV | 2 | 1.3
 | HCV | 1 | 0.7
 | TB | 9 | 6.0

**Incidence of Switching:**
Out of the 149 patients who started with first line ART, only 18 (12.1%) patients switched to the second line ART. They were followed up for a total of 995 person-years, so the incidence rate of switching to the second line ART is 1.8 per 100 person years of retrospective follow-up (PYFU). The mean survival time for the whole cohort was 13.57 years with 95% confidence intervals of (12.7 – 14.4) years.

The cumulative hazard of switching to the second-line ART increased with the time of being on the first-line, in this study it was almost 2% by the end of the first year. And by the end of the third year, it became almost 5%. The cumulative hazard is shown in figure 1.
Figure 1 Kaplan-Meier curve showing the cumulative hazard of switching to second-line ART among the study population

**Factors associated with switching to second-line ART:**

All the predictor factors were tested univariately with the dependent variable to assess their effect on the final result of switching to the second-line ART. The hazard ratios and the confidence intervals are listed on table 3.

Table 3 Risk factors associated with the likelihood of switching to the second-line ART among the study population
<table>
<thead>
<tr>
<th>Socio-demographic factors</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>149 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.1 (0.4-2.9)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Age groups</td>
<td>&lt;= 33 years ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 33 years</td>
<td>3.6 (1.2-10.9)</td>
<td>0.024</td>
<td>3.9 (1.1-13.5)</td>
</tr>
<tr>
<td>Marital status</td>
<td>Not married ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Married</td>
<td>0.9 (0.3-2.4)</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Literacy</td>
<td>Illiterate ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>literate</td>
<td>0.4 (0.15-1.2)</td>
<td>0.11</td>
<td>0.3 (0.1-1.0)</td>
</tr>
<tr>
<td>Employment</td>
<td>Employed ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not employed</td>
<td>1.1 (0.4-3.1)</td>
<td>0.76</td>
<td></td>
</tr>
</tbody>
</table>

### Baseline clinical factors

<table>
<thead>
<tr>
<th>WHO stage</th>
<th>Stages 1,2 and 4 ref.</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage 3</td>
<td>3.3 (1.2-9.2)</td>
<td>0.025</td>
<td>4.7 (1.5-14.1)</td>
</tr>
<tr>
<td>ART regimen</td>
<td>TDF-FTC-EFV</td>
<td>4.1 (1.4-12.1)</td>
<td>0.01</td>
<td>7.6 (2.1-27.0)</td>
</tr>
</tbody>
</table>

Other regimens ref.

Age more than 33 years, was the only socio-demographic predictor that had statistically significant association with the likelihood of switching to the second-line ART; p-value (0.024) with univariate test and p-value of (0.029) with multivariate test.
Among the clinical predictors, WHO stage 3 and TDF-FTC-EFV-based first-line ART regimen were both statistically significant risk factors of switching to the second-line ART with p-values less than 0.05 in both univariate and multivariate tests.

Literacy status was borderline p-value (0.056) with multivariate test after adjusting for age, gender, marital status, employment status, WHO stage and first-line ART regimen, while it had p-value of 0.11 with the crude unadjusted univariate test.

The cumulative hazards of all the statistically significant predictors are illustrated in the following figures to compare between the subgroups of each factor.

**Discussion**

**Key Predictors of Switching:**
This study provides important insights into the rate and determinants of switching from first-line to second-line antiretroviral therapy (ART) among people living with HIV (PLWHIV) in Aden City, Yemen. The overall incidence of switching was found to be 1.8 per 100 person-years of follow-up, aligning with other studies from resource-limited settings where ART monitoring is less rigorous and access to second-line therapies can be limited [5, 6].

Age over 33 years, WHO stage 3 disease, and a TDF-FTC-EFV-based first-line regimen were significant predictors of switching. Older age has been consistently linked to higher rates of ART switching due to increased likelihood of comorbidities and drug resistance [7]. Similarly, advanced disease stages (WHO stage 3) are associated with poorer immune response and higher risk of treatment failure necessitating regimen changes [8]. The association between the TDF-FTC-EFV regimen and switching may be attributed to the higher propensity for resistance development with this combination as documented in several studies [9, 5].

**Implications for Treatment and Monitoring:**
The findings underscore the need for robust treatment monitoring systems to identify and address treatment failures early. Consistent with WHO guidelines, routine viral load monitoring can lead to timely interventions and switching, potentially improving patient outcomes [2]. However, in resource-limited settings like Yemen, implementing comprehensive monitoring systems remains challenging due to financial and logistical constraints [4].

**Targeted Interventions:**
Targeted interventions for older patients and those with advanced disease stages are crucial. Tailored adherence support, regular clinical assessments, and psychosocial support are vital to enhance treatment adherence and reduce the need for regimen switches [10]. Programs focusing on these aspects can significantly improve the longevity and effectiveness of ART.
Public Education and Prevention Programs:
Public education campaigns are essential for raising awareness about HIV, ART, and the importance of adherence. Reducing stigma and increasing community knowledge can empower patients and support better health-seeking behaviors [11]. Integrating health education into broader public health strategies can maximize its impact.

Study Limitations and Future Research:
This study’s limitations include its retrospective nature and reliance on existing medical records, which may not capture all relevant variables. Additionally, the study was conducted at a single site, potentially limiting the generalizability of the findings. Future research should focus on larger cohort studies across multiple sites and explore additional factors influencing ART switching, such as socioeconomic status, adherence patterns, and comorbid conditions.

Conclusion
This study underscores the importance of continuous monitoring, targeted interventions, and public education in managing HIV in resource-limited settings. By addressing the specific needs of PLWHIV, healthcare providers can improve ART outcomes and enhance the quality of life for those affected by HIV in Yemen. Future research should build on these findings to provide a comprehensive understanding of treatment dynamics in diverse settings.

Recommendations:

1. Conduct larger studies to confirm these findings and identify additional factors.
2. Ensure equal access to ART for all demographics.
3. Establish PMTCT programs to prevent mother-to-child transmission.
4. Enhance public education and awareness about HIV and ART.
5. Implement family support programs for PLWHIV.

Abbreviations

1. 3TC - Lamivudine
2. AIDS - Acquired Immunodeficiency Syndrome
3. ART - Antiretroviral Therapy
4. ARV - Antiretroviral Drugs
5. AZT - Zidovudine
6. D4T - Stavudine
7. DTG - Dolutegravir
8. EFV - Efavirenz
Declarations

Ethics approval and consent to participate:

Ethical approval was obtained from the Al-Wahda Hospital Ethics Committee and the National AIDS & STIs Control Program.

Consent for publication:

Not applicable.

Funding:

This research received no external funding. The study was self-funded by the authors.

Acknowledgements:

We would like to thank the staff at Al-Wahda Hospital and the National AIDS & STIs Control Program for their support and assistance.

References

2. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available at: https://www.who.int/publications/i/item/9789240031593. Accessed [date].


**Figures**
Figure 1

Kaplan-Meier curve showing the cumulative hazard of switching to second-line ART among the study population
Figure 2

Showing the age groups cumulative hazard of switching to second-line ART
Figure 3

Showing WHO stages cumulative hazard of switching to second-line ART
Figure 4

Showing the first-line regimen cumulative hazards of switching to second-line ART