Predictors of Failure on Second-line Antiretroviral Therapy with Protease Inhibitor Mutations in Uganda

Hellen Musana (musana_hellen@yahoo.com)  
Makerere University

Ssensamba Jude Thaddeus  
Makerere University  https://orcid.org/0000-0003-3939-4951

Mary Nakafeero  
Center for Innovations in Health Africa (CIHA Uganda)

Henry Mugerwa  
Joint Clinical Research Centre

Flavia Matovu Kiweewa  
Makerere University

David Serwadda  
Makerere University

Francis Ssali  
Joint Clinical Research Centre

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Abstract

Introduction Failure on second-line antiretroviral therapy (ART) with protease inhibitor (PI) mutations is on the rise. However, there is a paucity of information on the factors associated with this observation in the context of low-income countries. Knowledge of underlying factors is key if we are to minimize the number of PLHIV switched to costly third-line ART. Our study investigated the factors associated with failure on second-line ART with PI mutations.

Methods We conducted a matched case-control analysis of patients’ records kept at the Joint Clinical Research Center, starting from January 2008 to May 2018. We matched records of patients who failed the second-line ART with major PI mutations (cases) with records of patients who were virologically suppressed (controls) by a ratio of 1:3. Data analysis was conducted using STATA Version 14, and descriptive statistics comparing cases and controls were generated. Categorical variables were compared with the outcome, failure on second line ART with PI mutations using the Chi-square and Fisher’s exact tests where appropriate. Conditional logistic regression for paired data was used to assess the association between the outcome and exposure variables, employing the backward model building procedure was done.

Results Of the 340 reviewed patients’ records, 53% were women, and 6.2% had previous Tuberculosis treatment. Males (aOR 2.64 CI: 1.0-4.64), type of second-line ART (aOR 3.92 CI: 1.15-13.38), and Tuberculosis treatment while on second-line ART (aOR7.08 CI: 2.35-21.29) highly predicted failure on second-line ART with PI mutations.

Conclusion Males and patients concomitantly on Tuberculosis treatment while on second-line ART are at a higher risk of failing on second-line ART with PI mutations. HIV/AIDS response programs should give special attention to this group of people if we are to minimize the need for expensive third-line ART. More extensive explorative studies to ascertain underlying factors are recommended.

Background

Antiretroviral therapy (ART) remains the only scalable biomedical alternative for reducing the impact and effect of HIV/AIDS in Sub Saharan Africa, which disproportionately carries 70% of the global HIV burden [1]. Uganda, whose current HIV prevalence is 6.2% [2], is among the ten high burden countries that account for almost 80% of all people living with HIV in this region [3]. By 2017, an estimated 1.3 million Ugandans were living with HIV, of whom 67% were on ART [4].

Second-line Antiretroviral Therapy

In sub-Saharan Africa, the proportion of HIV positive patients on second-line ART is between 1-5% [5-7], and is expected to rise to 0.5-3.0 and 0.8-4.6 million people between 2020 and 2030 [8]. In Uganda, 3.77% of PLHIV are on second-line ART [4] which is composed of a PI-based regimen of boosted lopinavir or atazanavir, and a recycled NRTI [9]. Moreover, the rising number of patients on second-line ART presents limited options to providers of HIV/AIDS care, more so in developing Africa whose health systems are still dependent on foreign aid to provide ART [10, 11]. Beyond the high cost of second-line regimens, failure on first-line ART has been mostly associated with poor adherence [12, 13], which, if not addressed, means that patients initiated on second-line ART are also likely to fail on this regimen. Failure on second-line ART (having two subsequent viral counts of or greater than 1000 copies/ml, done at least 3-6 months apart) means that care providers have to switch such patients to third-line ART [9] which is associated with a higher pill burden and toxicities [14].

Failure on second-line Antiretroviral Therapy

Studies in limited-resource settings have reported second-line ART failure rates of 21.8%, 23.1%, 26.7%, and 38.0% at 6, 12, 24, and 36 months of initiation on second-line ART respectively among adults [15]. That said, second-line ART failure is further complicated by major PI mutations; M46I/L, N88S, V82A/F/T/S/M, I84IV, and I54V/A/S, G48V/M/Q and L76V, which decrease susceptibility to the PIs [16]. The prevalence of second-line ART failure with PI mutations is estimated in the range of 18.5 to 40% and is predicted to rise further as more patients are switched to second-line regimens [17-19]. However, there is a paucity of information in developing countries on the factors for failure on second-line ART with PI mutations. The few studies conducted have pointed at age, and Tuberculosis treatment as factors. For example, in a small cohort of 44 patients, Chimbetete et al. 2018 found age as the only factor associated with failure on second-line ART with PI mutations whereby patients above 24 years of age were at a higher risk of failing with major PI mutations [20]. Another study among children less than three years of age highlighted; timing of Tuberculosis treatment while on second-line ART and protease inhibitor dosing strategy [21].

More research and information on the factors associated with failure on second-line ART with PI mutations is critical to inform public health experts, HIV/AIDS policy makers and implementers on how best to minimize the likelihood of having more patients switched to third-line ART which costs eighteen and seven higher than the lowest price of first and second-line ART respectively [14], is more intolerable, and cost more in terms of resources required for its provision [22]. To our knowledge, this study provides the first body of evidence to understand the factors associated with second-line failure with PI mutations in the context of Uganda.

Methods

The study was conducted at the Joint Clinical Research Center (JCRC), a high-volume HIV/AIDS health and research care facility located in Wakiso district, Uganda. Currently, the institution takes care of over 15,402 people living with HIV/AIDS (PLHIV), of whom 17% are on second-line ART. We reviewed records of routinely collected clinic data on PLHIV for the period between January 2008 and May 2018. This period coincided with the period when JCRC started conducting viral load monitoring and the period with the most updated information the researchers could get during data collection. A customized data collection tool was developed to capture data on variables of interest for both cases and their corresponding matched controls. Cases were records of patients...
who failed on second-line ART with major PI mutations. At the same time, controls were records of patients on second-line ART who were virologically suppressed at the time (month and year) the cases occurred (time of genotype). A matching ratio of 1:3 was chosen to increase the power of the study.

Sample size:
Of the 154 records of patients with major PI mutations (cases), we reviewed 85 (49.4%) files since 66 case files were rejected because of incomplete information, and three could not be matched. The cases were matched against 255 controls (See Figure 1).

Inclusion and Exclusion Criteria
For cases, we included all patients who failed on second-line ART between Jan 2008 and May 2018, had complete data, and possessed major PI mutations. On the other hand, records of matchable virologically suppressed patients on second-line ART with complete records were chosen as controls. Incomplete and unmatchable records were excluded from the analysis.

Study variables
The dependent variable was failure on second-line ART (≥1000 viral copies/milliliter of blood) with major HIV drug-resistant PI mutations, while independent variables were: age, gender, viral load at the initiation of the second-line of ART, type of first-line and second-line ART regimen, presence of comorbidities, and history of Tuberculosis management while on second-line ART.

Data collection
Data were abstracted from hard copy and online patient case management files kept by the JCRC clinic. It was after that entered onto a hard copy abstraction tool designed by the researchers. During the data abstraction process, we did not include any patient identifier information. We collected information on patients': age, gender, viral load, and CD4 before initiation of second-line ART, comorbidities while on second-line ART, and concomitant treatment for Tuberculosis while on second-line ART. We minimized the loss of data integrity by engaging two research assistants to abstract the same data. In cases where the two records disagreed, original patient case files traceable by a short-term numeric identifier were revisited to solve the queries. The patient identifier sheet was kept under key and lock by the researchers.

Data analysis:
The abstracted raw data were double entered into MS Excel and compared to rule out discrepancies. The final dataset was exported to Stata Version 14 (Stata Corp LP, College Station, Texas) software for analysis. Descriptive statistics comparing the cases and controls were generated. Categorical variables were compared with the outcome, second-line ART failure with major PI mutations using the Chi-square test and Fisher's exact test where appropriate. Testing for multicollinearity was done using the variance inflation factors (VIF) approach. Conditional logistic regression for paired data was used to obtain the odds ratios measuring the magnitude of the association between the outcome and the exposure variables. The backward model building procedure was used in which all variables that were significant at the 20% level of significance at the simple regression stage were considered for the multiple regression model. Only factors that were significant at the 5% level were maintained in the final model. Results were reported as the multivariable-adjusted odds ratios with their corresponding 95% confidence intervals (CI) for associations between exposure variables and the outcome.

Ethical Considerations
Regulatory approval to proceed with the study was sought from the Makerere University Higher Degrees Institutional Review Board (FWA 00011353), and written permission to use the data was granted by the JCRC administration. Patient confidentiality was ensured throughout the project's lifetime. We eliminated any patient identifier information, all hard copy data was kept under lock and key, and electronic data was password protected.

Results
Of the 340 patients' records we reviewed, 53% (n=179) belonged to women, of whom 33% (n=28) were cases. The majority (83.2%) of the patients' understudy had an NNRTI based regimen for their 1st line ART, while 91.8% (n=312) were on Alluvia for their second-line ART. Only 11% (n=36) of the study population had comorbidities, the majority of whom (75%) were in the control arm. Relatedly, 6% (n=21) of the clients were concurrently on second-line ART and TB treatment, of whom the majority (67%) were cases. The median age, CD4 count, and viral load at the start of second-line ART was 38 years, 115 cells, and 67,965 viral copies per ml of blood plasma, respectively. Cases were associated with lower median CD4 counts (68.5) and higher median viral counts (233,700 [p-value= <0.001]) at the start of second-line ART. There was a statistically significant difference in gender (p-value= <0.001), second-line regimens (p-value= 0.001), and being on Tuberculosis treatment while on second-line ART (p-value= <0.001) among cases and controls (Table 1).

Table 1: Study Descriptive Characteristics
Table 2: A gender-based comparison of descriptive study characteristics

| Characteristic                        | Controls | Cases | Total | p-value |
|---------------------------------------|----------|-------|-------|---------|
|                                       | n (col %) | n (col %) | n (col %) |         |
| **Gender**                            |          |       |       |         |
| Female                                | 151 (59.2) | 28 (32.9) | 179 (52.6) | <0.001  |
| Male                                  | 104 (40.8) | 57 (67.1) | 161 (47.4) |         |
| Total                                 | 255 (100) | 85 (100) | 340 (100) |         |
| **Type of second-line drug**          |          |       |       |         |
| Alluvia                               | 241 (94.5) | 71 (83.5) | 312 (91.8) | 0.001   |
| Atazanavir                            | 8 (3.1)    | 4 (4.7)   | 12 (3.5)   |         |
| Other drugs                           | 6 (2.4)    | 10 (11.8)  | 16 (4.7)   |         |
| Total                                 | 255 (100) | 85 (100) | 340 (100) |         |
| **TB treatment**                      |          |       |       |         |
| No                                    | 246 (97.2) | 71 (83.5) | 317 (93.8) | <0.001  |
| YES                                   | 7 (2.8)    | 14 (16.5)  | 21 (6.2)   |         |
| Total                                 | 253 (100) | 85 (100) | 338 (100) |         |
| **Type of first-line drug**           |          |       |       |         |
| NNRTI based                           | 217 (85.1) | 66 (77.6) | 283 (83.2) | 0.111   |
| NON-NNRTI based                       | 38 (14.9)  | 19 (22.4)  | 57 (16.8)  |         |
| Total                                 | 255 (100) | 85 (100) | 340 (100) |         |
| **Other comorbidities**               |          |       |       |         |
| No                                    | 226 (89.3) | 76 (89.4) | 302 (89.3) | 0.983   |
| Yes                                   | 27 (10.7)  | 9 (10.6)   | 36 (10.7)  |         |
| Total                                 | 253 (100) | 85 (100) | 338 (100) |         |
| **Age at start of 2nd line: median (IQR)** |       |       |       |         |
| 38(32-46)                             | 38(31-46)  | 38(32-46)  | 0.300     |         |
| **CD4 at start of 2nd line: median (IQR)** |       |       |       |         |
| 130(62-250)                           | 68.5(18-181) | 115(41-234) | 0.079  |         |
| **VL at start of 2nd line: median (IQR)** |       |       |       | <0.001  |
| 43005.5(13645.5-135553.5)             | 233700(65985.5-601989) | 67965(18846.5-189160) |         |         |

* Missing data on two observations, ¥ Missing data on 128 observations, TB: Tuberculosis, VL: Viral Load, IQR: Interquartile Range
### Table 1: Antiretroviral Therapy (ART) Regimens

| Gender | Controls | Cases | Total | Controls | Cases | Total | Overall |
|--------|----------|-------|-------|----------|-------|-------|---------|
|        | n (col %) | n (col %) | n (col %) | n (col %) | n (col %) | n (col %) | n (col %) |
| lluvia  | 143(94.7) | 25(89.3) | 168(93.9) | 98(94.2) | 46(80.7) | 144(89.4) | 312(91.8) |
| tazanavir | 5(3.3) | 3(10.7) | 8(4.5) | 3(2.9) | 1(1.8) | 4(2.5) | 12(3.5) |
| other drugs | 3(2.0) | 0(0) | 3(1.7) | 3(2.9) | 10(17.5) | 13(8.1) | 16(4.7) |
| total | 151(100) | 28(100) | 179(100) | 104(100) | 57(100) | 161(100) | 340(100) |

### Table 2: Comorbidities

| Comorbidity | Controls | Cases | Total | Controls | Cases | Total | Overall |
|-------------|----------|-------|-------|----------|-------|-------|---------|
| None        | 146(97.3) | 23(82.1) | 169(94.9) | 100(97.1) | 48(84.2) | 148(92.5) | 317(93.8) |
| Treatment   | 4(2.7) | 5(17.9) | 9(5.1) | 3(2.9) | 9(15.8) | 12(7.5) | 21(6.2) |
| total | 150(100) | 28(100) | 178(100) | 103(100) | 57(100) | 160(100) | 338(100) |

### Table 3: Factors for Failure on Second-line ART with PI Mutations

| Factor | p-value | Odds Ratio (CI) |
|--------|---------|----------------|
| Gender | <0.001  | 2.64 (1.0-4.64) |
| Type of second-line ART | 0.029  | 3.92 (1.15-13.38) |
| Being on Tuberculosis treatment while on second-line ART | >0.001 | 7.54 (2.69-21.08) |

Viral Load, IQR: Interquartile Range, ART: Antiretroviral Therapy

Table 2 shows that by gender disaggregation, 57 cases (67%) were males, of whom 81% (n=46) were on Alluvia for their second-line ART. Furthermore, of all patients with comorbidities at the start of second-line ART, 47% (n=17) of them were males in the control arm. The proportion of female cases who were on TB treatment at the start of second-line therapy was slightly higher (17.9%) compared to male cases (15.8%). However, this could be attributable to lesser numbers of female cases. Relatedly, female cases had a higher median viral count at the start of second-line ART (233,700) compared to their male counterparts (139,901).

Factors for failure on second-line ART with PI mutations

Multicollinearity among the exposure variables was investigated prior to the model building. All of the VIFs were below 10 indicating the absence of multicollinearity. Table 3 shows that gender, type of second-line regimen, and tuberculosis treatment while on second-line ART were associated with failure with PI mutations at the simple regression stage. Males had higher odds of failure with PI mutations compared to females (uOR=3.09, [CI: 1.8-5.31]). Relatedly, patients who had “other” PIs for their second-line ART were more likely to fail with PI mutations (uOR=5.66, [CI: 1.92-16.66]) compared to those who had alluvia as their second-line regimen. Patients concurrently on Tuberculosis treatment and second-line ART were also more likely to fail on treatment with PI mutations compared to colleagues with no Tuberculosis treatment at initiation on second-line therapy (uOR=7.54, [CI: 2.69-21.08]). At multiple regression analysis, gender (p= 0.001), type of second-line ART (p= 0.029), and being on Tuberculosis treatment while on second-line ART (p< 0.001) were significantly associated with failure on second-line therapy with PI mutations. Specifically, males (aOR=2.64, [CI: 1.0-4.64]), patients on “other” PI-based regimens (aOR=3.92, [CI: 1.15-13.38]), and patients concurrently on Tuberculosis treatment while on
second-line ART (aOR=7.08, [CI: 2.35-21.29]) had higher adjusted odds of failure on second-line ART with PI mutations when adjusted for other variables in the final model. Generally, all three factors were more prevalent among males (Table 2).

### Table 3: Complete case analysis

| Characteristic                     | Unadjusted OR (95% CI) | p-value | Adjusted OR (95% CI) | p-value |
|-----------------------------------|------------------------|---------|----------------------|---------|
| **Gender**                        |                        |         |                      |         |
| Female                            | 1.00                   |         | 1.00                 |         |
| Male                              | 3.09(1.80-5.31)        | <0.001  | 2.64(1.50-4.64)      | 0.001*  |
| **Type of second-line drugs**     |                        |         |                      |         |
| Alluvia                           | 1.00                   |         | 1.00                 |         |
| Atazanavir                        | 1.59(0.44-5.82)        | 0.483   | 2.23(0.54-9.20)      | 0.269   |
| Other drugs                       | 5.66(1.92-16.66)       | 0.002   | 3.92(1.15-13.38)     | <0.001* |
| **TB treatment**                  |                        |         |                      |         |
| No                                | 1.00                   |         | 1.00                 |         |
| Yes                               | 7.54(2.69-21.08)       | <0.001  | 7.08(2.35-21.29)     | <0.001* |
| **Type of 1st line drug**         |                        |         |                      |         |
| NNRTI based                       | 1.00                   |         |                      |         |
| NON-NNRTI based                   | 1.81(0.92-3.55)        | 0.085   | -                    | -       |
| **Other comorbidities**           |                        |         |                      |         |
| No                                | 1.00                   |         | 1.00                 |         |
| Yes                               | 1.00(0.44-2.26)        | 1.000   | -                    | -       |
| **Age at start of 2nd line**      |                        |         |                      |         |
| No                                | 0.99(0.97-1.01)        | 0.300   | -                    | -       |
| Yes                               | 0.99(0.99-1.00)        | 0.079   | -                    | -       |

¶ Wide confidence interval due to small sample size  
* Statistically significant at the 5% level

### Discussion

#### Failure on second-line ART with PI mutations and gender

Our study showed that the majority of the cases were males (67.1%) (Table 1), and were more likely to fail on second-line ART with PI mutations (p=0.001). This is in agreement with other studies conducted in developing countries that have shown that male HIV patients are more likely to present to HIV care facilities with advanced disease as compared to their female counterparts [23, 24]. Moreover, studies conducted in Ethiopia and South Africa have cited advanced HIV/AIDS as a critical predictor for failure on second-line ART [25, 26]. Furthermore, research has shown that males are more prone to virological failure while on second-line ART than females [27, 28], attributable to poor adherence and higher odds of alcohol consumption while on ART [29, 30]. However, our findings are contrasted by a South African study, which showed that 60% of patients who failed second-line ART with PI mutations were women [31]. That said, our findings continue to highlight male HIV positive patients as a key vulnerable population that needs special attention if we are to maintain them on second-line ART over an extended period.

#### Age and failure on second-line ART with PI mutations

A study by Chimbetete et al. (2018) found that younger patients (< 24 years of age) were associated with lower odds of PI mutations at failure on second-line ART [20]. However, our study did not find any statistical difference concerning age and failure on second-line ART with PI mutations. We recommend more studies to understand the factors behind younger HIV/AIDS patients on second-line ART having lower odds of PI mutations at failure.

#### HIV/TB Coinfection and Second-line ART failure with PI mutations

Concomitant Tuberculosis treatment while on second-line ART was higher among cases (67%) and significantly associated with second-line failure with PI mutations (p=0.001). Our findings are in line with a study conducted by Rossouw et al. 2015, which found that children on Tuberculosis treatment while on second-line ART were more likely to fail on second-line therapy with PI mutations [21]. This is attributable to factors such as higher pill burden [32, 33], HIV/TB coinfection being associated with advanced HIV/AIDS [34], and the fact that Rifabutin is not readily available in the resource-limited settings as a replacement for Rifampicin which is known to reduce the pharmacokinetic levels of PIs and consequently their efficacy [35, 36]. Our study calls on HIV care providers to provide more personalized attention, counseling, and support to patients concurrently on TB and second-line ART as they are at a high risk of failure with PI mutations. Furthermore, HIV clinical care specialists have to weigh options of initiating patients with TB on PIs carefully.

#### Type of second-line ART with failure on second-line ART with PI mutations

Patients who had “other” PIs like saquinavir and nelfinavir had higher odds of failure on second-line ART with PI mutations (p=0.029) compared to counterparts on Alluvia or Atazanavir. This
could be associated with the higher pill burden of "other" PIs like saquinavir [37] and their low genetic barrier to resistance and reduced bioavailability [38]. We recommend to HIV clinical care specialists to give priority to prescribing PIs of higher genetic barrier resistance, and periodically review and assess patients on PIs such as saquinavir for resistance.

**Significance of the study**

To our knowledge, this study is the first endeavor to investigate the factors associated with failure on second-line ART with PI mutations in Uganda. The study was conducted within an HIV care provision setting, which reflects ground reality, and our measures were based on WHO standards for assessing failure on second-line ART. Due to existing data management mechanisms for data validity at JCRC, data used for this study was relatively good and reliable. More importantly, we employed a robust data collection system and trained all staff involved in the data collection and management process to minimize errors and ensure the quality and validity of results.

**Study Limitations**

Our study had a couple of limitations. First, we excluded 69 (45%) files under the "case" arm, and 68 (21%) files under the "control" arm due to incompleteness, which could have affected the findings. However, we worked with data of over 50% of the whole population of interest which is generalisable. Second, there might have been original data entry errors since our analysis was solely based on routinely collected project data. Third, our study was conducted within the limitations of case-control studies, with the odds ratios unstable as reflected by the wide confidence intervals. This was minimised by increasing the power of the study. Finally, based on available data, we could not assess poor adherence. That said, our findings provide a platform for more extensive longitudinal studies to understand further the underlying factors and co-factors for second-line ART failure with PI mutations within low-income settings.

**Conclusion**

Our findings provide new insights that male patients, HIV patients co-infected with TB, and patients on PIs such as saquinavir are more likely to fail on second-line ART with PI mutations. It is recommendable that HIV care providers in developing countries design factor specific interventions such as counselling and evaluations if we are to minimize the number of patients switching to costly third-line ART.

**Abbreviations**

AIDS: Acquired immunodeficiency syndrome, aOR: Adjusted Odds Ratio, ART: Antiretroviral Therapy, CD4: Cluster of Differentiation 4, CI: Confidence Interval, HIV: Human Immunodeficiency Virus, IQR: Interquartile Range, JCRC: the Joint Clinical Research Center, NRTIs: Nucleoside/Nucleotide Reverse Transcriptase Inhibitors, NNRTIs: Non-nucleoside Reverse Transcriptase Inhibitors, PIs: Protease Inhibitors, PLHIV: People Living with HIV/AIDS, TB: Tuberculosis, uOR: Unadjusted Odds Ratio, VIF: Variance Inflation factor and VL: Viral Load

**Declarations**

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**Authors' contributions**

HM conceived, conceptualized, and designed the study. DS, JST, FS, and HM reviewed and critiqued the study protocol. HM participated in data collection. HM, FMK, JST, and MN participated in designing the analytical framework for the study. HM, MN, HM and FMK analyzed the data. HM and JST drafted the manuscript. HM, JST, HM, FS, FMK, DS, and MN participated in reviewing the manuscript. All authors read and approved the final manuscript.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Author Details**

1. Makerere University, College of Health Sciences, School of Public Health, Kampala, Uganda
2. Joint Clinical Research Centre, Kampala, Uganda
3. Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda
4. Center for Innovations in Health Africa (CIHA Uganda), Kampala, Uganda
Ethics approval and consent to participate

Our study was approved by the Makerere University School of Public Health Higher Degrees Research Ethics Committee (FWA00011353). The administration of JCRC granted permission to access patient case files for data collection.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to ethical requirements by the ethics committee but are available from the corresponding author on reasonable request.

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**Figures**

![Baseline cohort of 2nd Line patients](image-url)

**Figure 1**

Study Sampling Strategy