Rate and predictors of HIV virological failure among adults on first-line antiretroviral treatment in Dar Es Salaam, Tanzania

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Abstract

Introduction: Monitoring resistance to first line Antiretroviral therapy (ART) is crucial in preventing accumulation of viral mutations following the implementation of the World Health Organization “treat all” initiative. We estimated the rate and predictors of virological treatment failure among adults living with HIV/AIDS in Dar es Salaam, Tanzania.

Methodology: A retrospective cohort study involving adults aged 18 and above receiving first line ART in Dar es Salaam between 2016 and 2018 were recruited using multistage random sampling. Clinical and laboratory data were extracted from Care and Treatment Clinic database-2 (CTC2) followed by participant’s interviews. Adjusted Cox-regression modelling was used to determine independent predictors of treatment failure.

Results: A total of 340 participants with mean age of 37 were recruited. Overall, 10.59% had virological failure and the rate of failure was 5.24 (95% CI:3.72-7.27) per 100 person-months at risk with a median failure time of 18 months. Independent predictors of treatment failure were being a male (Adjusted hazard ratio (aHR) 2.78, 95%CI:1.16;6.63), having used treatment for less than two years (aHR, 12.48, 95%CI:3.64-22.71) and co-infection with Tuberculosis (aHR 2.1, 95%CI: 1.0;5.9).

Conclusions: HIV virological failure occurs early during treatment in this population. Male clients, co-infected with Tuberculosis were at higher risk of ART failure within two years of treatment. Substantial stride has been made towards the achievement of the last UNAIDS 90 goal but tailored counseling and close monitoring of HIV/TB co-infected male clients following ART initiation could accelerate efforts to close the gap. Further studies on pre-treatment drug resistance mutations are called for.

Key words: First line antiretroviral drugs; HIV; virological failure; predictors; Tanzania.
874 HIV infected individual on first-line ART reported treatment failure rates of 23.3% and 33.9% at 6 and 12 months [15]. In 2015 Tanzania adopted the WHO “treat all” recommendation with establishment of routine viral load monitoring [1]. A study conducted in 2017 to evaluate pre-treatment and acquired HIV drug resistance mutations in Dar es Salaam city indicated a 30% pre-treatment drug resistance mutation in ART naïve clients [16]. Effective routine HIV viral load monitoring to timely detect treatment failure and potential drug resistance were strongly recommended in the country [12,17]. Moreover, understanding the rate and predictors of ART treatment failure is of paramount in informing failure cascade and timing for switching to second line treatment [18,19]. This study therefore seeks to estimate the rate and predictors of first line ART failure following the introduction of routine viral load monitoring in Tanzania.

Methodology
Study design
This was a retrospective cohort study of all adults living with HIV/AIDS (PLHIV) on first line ART attending care and treatment clinics (CTC) in Dar es Salaam, Tanzania. The study recruited all participants who were on ART during the period January 2016 to December 2018 in the selected HIV CTC in the city.

Study setting and population
The study was conducted in Dar es Salaam metropolitan city of Tanzania with a population of 5,495,569 and HIV prevalence of 4.3% among adults aged 15-49 [3]. The region has a total of five administrative municipalities with 116 CTCs. Recent survey indicated that 55% of people living with HIV/AIDS in the city were not aware of their status and only 43% of those who were aware of their status were on ART [3]. The region had a total of 11064 clients on ART and of these 10,743 (97%) clients were on first line ART treatment. All PLHIV aged 18 and above who were on first line ART for at least 6 months as of January 2016 with at least two viral load results were eligible for inclusion in the study. Participants were excluded if they were too sick to be interviewed or were mentally ill.

Sample size calculation
Sample size was calculated based on the Kelsey formula for qualitative (binary) outcome (treatment failure/no treatment failure) [20]. Estimates of treatment failure of 30% among exposed group and 15% among unexposed group were used [14]. With an estimated 10% non-response rate, 80% statistical power and two tailed alpha level of 95%, a total of 340 patients on treatment for at least 6 months were required.

Sampling procedures
All five municipalities of Dar es Salaam city were involved in this study. Multistage sampling procedure was used where 10 facilities (2 from each municipal) were systematically selected from a list of high-volume CTC obtained from each municipal. High volume facility was defined as a facility with 500 or more clients on ART. The number of participants selected from each facility was based on the number of clients in each of the selected facility. In each facility, computer generated random numbers were used to select participants to participate in the study. CTC2 cards of all the selected random numbers were identified, and data was extracted from the CTC database accordingly.

Data sources and data collection
Baseline and follow up socio-demographic, clinical and laboratory data were extracted from each study participant’s medical records. Treatment failure was defined as having last two consecutive high viral load results less than 1000 copies/ml [1]. All participants recruited were contacted and invited for a face-to-face interview using structured questionnaire during their next clinic visits. The interview collected additional information of relevance in the assessment of predictors of treatment failure that are not usually recorded in the CTC2 card such as distance from the facility, marital status, education level; behavioral data such as food and alcohol consumption and reported data on adherence to ART. Adherence was assessed using 8-items Morisky scale [21].

Data analysis
Categorical variables were summarized using frequency distributions while continuous variables were summarised using mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Kaplan Meier method was used to estimate time to treatment failure. Participant person time started from the date of treatment initiation until 31 December 2018. Differences in the rate of treatment failure between different groups were examine using Log-Rank test. Cox-regression modelling was used to determine predictors of treatment failure. All predictors with p-value ≤ 0.2 in bivariate analyses were entered into a multivariable Cox- regression models to identify independent predictors for treatment failure. Two models were run one with age, CD4 count and distance
from the facility set as continuous predictors and the second with the same variables set as categorical predictors. Time varying variables in the analysis were all measured at baseline. The best parsimonious model was based on the lowest Akaike Information Criterion. All analyses were two-tailed, and significance level was set at 5%.

**Ethical consideration**

The protocol for this study was reviewed and approved by the Ethical Review committee of the Muhimbili University of Health and Allied Science, Tanzania with reference number DA.287/298.0/D34 dated 24 January 2018. Permission to conduct the study was sought from the city, municipal and health facility administrative authorities. All participant granted written informed consent before any interview.

**Results**

A total of 340 eligible participants receiving ART were randomly selected proportional to the number of those eligible in each of the included facility. The mean age of the study participants was 37 (Standard deviation 10). Two third of the participants (67.9%, N = 231) were female, (42.9%, N = 146) were aged above 40 with half (56.5%, N = 192) reporting to have either not attended school or competed primary school. Moreover, half (N = 179) of the participants were married or cohabiting and nearly three quarter (70.8%) were unemployed. Use of public transportation, alcohol consumption and having more than two meals per day were common (Tables 1). Half (55.9%, N = 190) of the participants were on ART for more than two years with median treatment time of 2.3 years (IQR 0.8-3.8). The median CD4 count was 351 cells/ ml (IQR 285 -1402). A total of 175 (51.5%) participants were in the WHO clinical stage 3 and majority (96.5%) on TDF/3TC/EFV ART combination. TB co-infection rate in this population was 7.1% with drug adherence (good-medium) proportion of 41.59% (Table 2).

**Table 1.** Distribution of socio-demographics characteristics of the study participants.

| Variables               | n (%)       |
|-------------------------|-------------|
| **Age group (years)**   |             |
| 18-24                   | 34 (10.00)  |
| 25-30                   | 59 (17.35)  |
| 31-39                   | 101 (29.71) |
| 40 and above            | 146 (42.94) |
| **Gender**              |             |
| Male                    | 109 (32.06) |
| Female                  | 231 (67.94) |
| **Education**           |             |
| None/Primary            | 192 (56.50) |
| Secondary/College/University | 148 (43.50) |
| **Marital status**      |             |
| Married/cohabiting      | 170 (50.00) |
| Single                  | 129 (37.90) |
| Widowed/ separated      | 41 (12.10)  |
| **Municipality of origin** |    |
| Kinondoni               | 99 (29.11)  |
| Ubungo                  | 73 (21.47)  |
| Ilala                   | 57 (16.76)  |
| Temeke                  | 86 (25.30)  |
| Kigamboni               | 25 (7.36)   |
| **Occupation**          |             |
| Employed                | 99 (29.11)  |
| Unemployed              | 241 (70.88) |
| **Means of transport**  |             |
| Public                  | 305 (89.81) |
| Private                 | 11 (3.13)   |
| Walking                 | 24 (7.06)   |
| **Distance to health facility (in km)** | |
| < 5                     | 196 (57.58) |
| ≥ 5                     | 144 (42.42) |
| **Frequency of food per day (meals)** | |
| 1-2                     | 15 (4.32)   |
| More than 2             | 325 (95.68) |
| **Do you take alcohol** |             |
| Yes                     | 227 (66.82) |
| No                      | 113 (33.18) |

**Table 2.** Distribution of clinical characteristics of the study participants.

| Variables                           | n (%)     |
|-------------------------------------|-----------|
| **Time on ART**                     |           |
| 6 months to 2 years                 | 150 (44.1) |
| More than two years                 | 190 (55.9) |
| **Initial CD4**                     |           |
| Less 350                            | 136 (49.8) |
| 350-                                | 137 (50.2) |
| **WHO HIV clinical stage**          |           |
| Stage 1                             | 60 (17.6)  |
| Stage 2                             | 92 (27.1)  |
| Stage 3                             | 175 (51.5) |
| Stage 4                             | 13 (3.8)   |
| **ART regime used**                 |           |
| TDF/3TC/EFV                         | 328 (96.5) |
| AZT/3TC/NVP/EFV/DTG/ETC             | 12 (3.5)   |
| **TB co-infection**                 |           |
| Yes                                 | 24 (7.1)   |
| No                                  | 316 (92.9) |
| **Adherence**                       |           |
| Good                                | 20 (6.02)  |
| Medium                              | 121 (35.57)|
| Poor                                | 199 (58.41)|

*Adherence based on Morisky scale.*
| Variable                        | ART Virological failure | Follow up time (months) | Cases | Rate per100 | 95%CI        |
|--------------------------------|-------------------------|-------------------------|-------|-------------|-------------|
| **Age group (years)**          |                         |                         |       |             |             |
| 18-24                          | 250.97                  | 13                      | 5.18  | 3.01-8.92   |             |
| 25-30                          | 187.17                  | 10                      | 5.34  | 2.88-9.92   |             |
| 31-40                          | 113.50                  | 6                       | 5.29  | 2.37-11.77  |             |
| Above 40                       | 134.00                  | 7                       | 5.19  | 2.48-10.89  |             |
| **Gender**                     |                         |                         |       |             |             |
| Male                           | 230.73                  | 14                      | 6.06  | 3.59-10.24  |             |
| Female                         | 455.67                  | 22                      | 4.83  | 3.18-7.33   |             |
| **Education**                  |                         |                         |       |             |             |
| None/Primary                   | 436.53                  | 21                      | 4.81  | 3.14-7.38   |             |
| Secondary /College/ university | 249.87                  | 15                      | 6.00  | 3.62-9.96   |             |
| **Marital status**             |                         |                         |       |             |             |
| Married/cohabiting             | 226.20                  | 11                      | 4.86  | 2.69-8.78   |             |
| Single                         | 418.77                  | 23                      | 5.49  | 3.65-8.27   |             |
| Widowed/ separated             | 41.43                   | 2                       | 4.82  | 1.21-19.30  |             |
| **Residence**                  |                         |                         |       |             |             |
| Kinondoni MC                   | 60.10                   | 3                       | 4.94  | 1.59-15.32  |             |
| Ubungo MC                      | 163.13                  | 9                       | 5.52  | 2.87-10.60  |             |
| Ilala MC                       | 159.30                  | 9                       | 5.69  | 2.94-10.86  |             |
| Temeke MC                      | 233.10                  | 11                      | 4.72  | 2.61-8.86   |             |
| Kigamboni MC                   | 70.17                   | 4                       | 5.70  | 2.14-15.19  |             |
| **Occupation**                 |                         |                         |       |             |             |
| Employed                       | 110.53                  | 7                       | 6.33  | 1.87-18.13  |             |
| Unemployed                      | 575.87                  | 29                      | 5.04  | 2.77-9.57   |             |
| **Means of transport**         |                         |                         |       |             |             |
| Public                         | 616.43                  | 32                      | 5.19  | 3.67-7.34   |             |
| Private                        | 21.50                   | 1                       | 4.65  | 0.65-33.02  |             |
| Walking                        | 48.47                   | 3                       | 6.19  | 1.90-19.19  |             |
| **Time on ART**                |                         |                         |       |             |             |
| 6 months to 2 years            | 141.47                  | 11                      | 7.78  | 4.31-14.04  |             |
| More than two years            | 544.93                  | 25                      | 4.59  | 3.09-6.79   |             |
| **Distance to health facility (km)** |                     |                         |       |             |             |
| < 5                            | 395.20                  | 22                      | 5.57  | 3.67-8.45   |             |
| ≥ 5                            | 291.20                  | 14                      | 4.81  | 2.85-8.11   |             |
| **Adherence**                  |                         |                         |       |             |             |
| Good                           | 41.33                   | 2                       | 4.84  | 1.21-19.35  |             |
| Medium                         | 244.17                  | 12                      | 4.92  | 2.79-8.65   |             |
| Poor                           | 400.90                  | 22                      | 5.49  | 3.61-8.33   |             |
| **Initial CD4**                |                         |                         |       |             |             |
| Less 350                       | 350.70                  | 19                      | 5.42  | 3.46-8.49   |             |
| 350+                           | 228.83                  | 11                      | 4.81  | 2.66-8.56   |             |
| **Do you take alcohol**        |                         |                         |       |             |             |
| Yes                            | 227.77                  | 12                      | 5.27  | 2.99-9.28   |             |
| No                             | 458.63                  | 24                      | 5.23  | 3.50-7.80   |             |
| **Frequency of food per day (meals)** |                 |                         |       |             |             |
| 1-2                            | 29.63                   | 2                       | 6.75  | 1.96-12.23  |             |
| More than 2                    | 656.77                  | 34                      | 5.18  | 2.36-8.11   |             |
| **WHO HIV clinical stage**     |                         |                         |       |             |             |
| Stage 1                        | 93.33                   | 5                       | 5.36  | 2.23-12.87  |             |
| Stage 2                        | 28.33                   | 2                       | 7.06  | 1.78-28.22  |             |
| Stage 3                        | 513.87                  | 27                      | 5.25  | 3.60-7.66   |             |
| Stage 4                        | 50.87                   | 2                       | 3.93  | 0.98-15.72  |             |
| **TB co-infection**            |                         |                         |       |             |             |
| Yes                            | 168.53                  | 11                      | 6.53  | 3.61-11.79  |             |
| No                             | 517.87                  | 25                      | 4.83  | 3.26-7.14   |             |
| **ART regime used**            |                         |                         |       |             |             |
| TDF/3TC/EFV                     | 636.73                  | 33                      | 5.18  | 3.38-7.29   |             |
| AZT/3TC/NVP/EFV/DTG/ETC         | 49.67                   | 3                       | 6.04  | 1.94-18.73  |             |
Rate of first line ART failure among adults living with HIV/AIDS

Of the 340 participants recruited, 36 (10.59%) had first line ART virological treatment failure. The overall rate of treatment failure was 5.24 (95% CI = 3.72-7.27) per 100 person-months. The median viral load among those who experienced virological failure was 1800 copies per ml as compared to 500 copies/ml among those who experienced successful viral suppression. The median failure time was 18 months and this was higher among male, single, those with less than 350 CD4 count and those who were on ART for less than two years. Treatment failure was higher among those with poor adherence or TB co infection (Table 3).

Independent predictors of first line ART failure

Results of crude and adjusted cox regression modeling of predictors of ART failure are presented in Table 4. Being a male client was associated with almost three times (aHR 2.78, 95%CI 1.16;6.63) higher rate of failure as compared to female clients. Being on treatment for less than two years was associated with 12 times higher rates of first line ART failure (aHR 12.48, 95%CI: 3.64; 22.71) as compared to those who were on treatment for more than two years. Moreover, co-infection with tuberculosis was associated with twice the rate of ART treatment failure (aHR 2.1, 95%CI: 1.0;5.9) as compared to those without TB co-infection.

Discussion

This study provides crucial data on the rate and predictors of first line ART virological failure in an urban population in Tanzania to inform strategy to achieve the UNAIDS third 90 goal. The overall treatment failure was 10.59% with a median failure time of 18 months. The rate of treatment failure was comparable to an estimate of 14.9% published earlier in the city from a cohort involving 2,403 adults [14]. Similar estimates have also been published in Ethiopia (11.5% and 14.7%), Lesotho (8.8%) and South Africa (9.9%) [9,19,22,23]. However, our estimate was lower compared to an estimate of 16% from a systematic review in sub Saharan Africa, 17% in Cameroon, 26% in Northern Ethiopia and 41.3% in rural Gabon [10,24,25]. Similar to what was reported in Addis Ababa Ethiopia, the urban nature of our study site and well established health system and follow up mechanism may have contributed to the relatively lower estimates in our study compared to average estimate for the whole of sub Saharan Africa [26]. The medium time to first line ART failure was 18 months which is consistency to those published from Ethiopia (17.5 months) and South Africa (16 months) but lower than estimates from Northern Ethiopia [23, 27]. Moreover, our study indicated that clients who have been on treatment for less than 2 years were more likely to experience treatment failure than those who have been on treatment for more than 2 years. These findings have also been reported in studies conducted in Ethiopia and South Africa [28,29]. The earlier treatment failure might be due to higher level of pre-treatment drug resistance mutations which has recently been reported to be high in the city (30%) [16]. Moreover, these results may be attributed to early treatment related factors which includes side effects, use of unfavorable taste brand, complication and/or interaction with existing treatment of opportunistic infection and/or missing opportunity for adherence counselling due to shortage of staffs [30]. The rate of treatment failure was higher among men than female in this study population corroborating findings from elsewhere in Africa and beyond [10,31-33]. Men have been reported to have low HIV testing rate resulting into late diagnosis consequently having low CD4 count and severe disease stage. Moreover, occupational nature of men, societal demands in African context, high level of alcohol consumption and low clinic attendance for ART refill could results into poor adherence, high rate of TB co-infection and early drop out [10,11,23,33]. Men have also been reported to have poor HIV status disclosure, which is of paramount in treatment support and adherence [34, 35]. Opportunistic infection particularly Tuberculosis have been associated with treatment complications and/or virological failure [11,29,36]. Tanzania uses an intensive six months Rifampicin-based TB treatment regimen (2 months of Rifampicin, Isoniazid and Ethambutol) and 4 months of Rifampicin and Isoniazid). Studies have shown that Rifampicin-based regimen may interact with ART particularly Nevirapine based ART resulting into subtherapeutic blood levels and possible virologic failure [37,38]. HIV infected individual co-infected with tuberculosis in this study were twice more likely to experience treatment failure that those without tuberculosis. Studies have shown that HIV/TB co-infected individual are more likely to have lower CD4 count, higher HIV disease clinical stage and poor treatment outcomes [39, 40]. Moreover, increased pill burden has also been attributed to drug-drug interaction that also affect safety, adherence and response [41]. The results presented in this paper should be interpreted in light of the following limitations. Firstly, we selected individuals who were still attending CTC clinics who may have good access to treatment and hence less virological failure.
Table 4. Adjusted cox regression analysis of independent predictors of first line ART virological failure among adults in Dar es Salaam, Tanzania.

| Variable                           | cHR (95%CI)       | aHR (95%CI)       | p-value |
|------------------------------------|-------------------|-------------------|---------|
| **Age group (years)**              |                   |                   |         |
| 18-24                              | 1.15 (0.45-2.94)  |                   |         |
| 25-30                              | 1.03 (0.38-2.79)  |                   |         |
| 31-39                              | 1.27 (0.41-3.93)  |                   |         |
| 40 and above                       | 1                 |                   |         |
| **Gender**                         |                   |                   |         |
| Male                               | 1.77 (0.88-3.59)  | 2.78 (1.16-6.63)  | 0.02    |
| Female                             | 1                 | 1                 |         |
| **Education**                      |                   |                   |         |
| None/Primary                       | 0.58 (0.29-1.18)  | 0.68 (0.43-2.00)  | 0.57    |
| Secondary/college                  | 1                 | 1                 |         |
| **Marital status**                 |                   |                   |         |
| Married/cohabiting                 |                   |                   |         |
| Single                             | 1.33 (0.63-2.82)  |                   |         |
| Widowed/ separated                 | 1.07 (0.23-4.99)  |                   |         |
| **Municipal of residence**         |                   |                   |         |
| Kinondoni                          | 1                 |                   |         |
| Ubungo                             | 1.76 (0.45-6.81)  |                   |         |
| Ilala                              | 1.95 (0.51-7.51)  |                   |         |
| Temeke                             | 0.94 (0.25-3.51)  |                   |         |
| Kigamboni                          | 1.72 (0.37-8.03)  |                   |         |
| **Occupation**                     |                   |                   |         |
| Unemployed                         | 0.67 (0.45-6.97)  | 0.59 (0.38-8.13)  | 0.89    |
| Employed                           | 1                 | 1                 |         |
| **Means of transport**             |                   |                   |         |
| Private                            |                   |                   |         |
| Public                             | 1.03 (0.13-7.68)  |                   |         |
| Walking                            | 1.69 (0.17-16.39) |                   |         |
| **Distance to health facility (km)**|                   |                   |         |
| < 5                                | 1                 | 1                 |         |
| ≥ 5                                | 0.76 (0.38-2.49)  | 0.76 (0.38-2.51)  | 0.45    |
| **Do you take alcohol**            |                   |                   |         |
| Yes                                |                   |                   |         |
| No                                 | 0.92 (0.42-6.17)  |                   |         |
| **WHO HIV clinical HIV**           |                   |                   |         |
| Stage 1                            | 1                 |                   |         |
| Stage 2                            | 1.50 (0.29-0.78)  | 0.69 (0.46-47.37) | 0.19    |
| Stage 3                            | 0.82 (0.31-2.17)  | 0.62 (0.10-25.30) | 0.73    |
| Stage 4                            | 0.21 (0.02-1.92)  | 0.54 (0.43-29.08) | 0.24    |
| **ART regime used**                |                   |                   |         |
| TDF/3TC/EFV                        | 1                 |                   |         |
| AZT/3TC/NVP/EFV/DTG/ETC            | 1.89 (0.55-6.43)  |                   |         |
| **TB co-infection**                |                   |                   |         |
| Yes                                | 1                 |                   |         |
| No                                 |                   |                   |         |
| **Initial CD4**                    |                   |                   |         |
| Less than 350                      | 1.24 (0.57-2.69)  |                   |         |
| 350+                               | 1                 |                   |         |
| **Adherence**                      |                   |                   |         |
| Good                               | 1                 |                   |         |
| Medium                             | 1.35 (0.29-6.21)  |                   |         |
| Poor                               | 1.57 (0.35-6.98)  |                   |         |
| **Time on ART**                    |                   |                   |         |
| 6 months to 2 years                | 4.89 (2.09-21.44) | 12.48 (3.64-22.71)| 0.00    |
| More than two years                | 1                 | 1                 |         |
However, the potential role of pre-treatment drug resistance strain which may not be affected by adherence or access to ART may offset this limitation. Secondly, collection of behavioral data such as those related to food habits, alcohol consumption and self-reported adherence may suffer from desirability bias. Thirdly, given that this was a secondary data analysis of existing surveillance we did not collect detailed information about the use of other drugs that either may have interaction with ART or those causing immunosuppression.

Conclusions

HIV virological treatment failure occurs early during ART treatment, and associated with multiple factors, including potential for pre-treatment drug resistance viral mutation. Tanzania has made a significant stride in achieving the last UNAIDS 90. Enhancing care and strategic counseling and follow up for HIV infected men and those with HIV/TB co-infection could reduce first line ART failure. More studies on drug resistance viral mutations are called for.

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Authors’ contributions

FGS, collected, analyzed the data, interpreted the results, and wrote the first draft of the manuscript, ODP, SSM, and CG interpreted the results and critically revised the manuscript, EJM, designed the study, analyzed the data, interpreted the results, and critically revised the manuscript. All authors read and approved the final version of the manuscript.

References

1. World Health Organization (2015) Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. Available: http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/. Accessed 17 June 2020.

2. Mendez-Lopez A, McKee M, Stuckler D, Granich R, Gupta S, Noori T, Semenza JC (2019) Population uptake and effectiveness of test-and-treat antiretroviral therapy guidelines for preventing the global spread of HIV: an ecological cross-national analysis. HIV Med 20: 501–512.

3. NBS (2018) HIV Impact Survey report 2018. National Bureau of Statistics, Dar es Salaam, Tanzania, 2018. Available: https://phia.icap.columbia.edu/wp-content/uploads/2016/09/THIS_Final.pdf. Accessed 18 June, 2020.

4. UNAIDS (2014) 90-90-90 An Ambitious Treatment Target to Help End the AIDS Epidemic, UNAIDS, Geneva, Switzerland, 2014. Available: https://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf. Accessed 6 May 2020.

5. Boender TS, Kityo CM, Boerma RS, Hamers RL, Ondoo P, Wellington M, Siwale M, Nankya I, Kaudha E, Akanmu AS, Botes ME, Steegen K, Calis JC, Rinke de Wit TF, Sigaloff KC (2016) Accumulation of HIV-1 drug resistance after continued virological failure on first-line ART in adults and children in sub-Saharan Africa. J Antimicrob Chemother 71: 2918-2927.

6. Etta EM, Mavhandu L, Manhaeve C, McGonigle K, Jackson P, Rekosh D, Hamarskjold ML, Besson SG, Tebit DM (2017) High level of HIV-1 drug resistance mutations in patients with unsuppressed viral loads in rural northern South Africa. AIDS Res Ther 14: 36.

7. Kityo C, Thompson J, Nankya I, Hoppe A, Ndashimye E, Warambwa C, Mambule I, van Oosterhout JJ, Woolf-Kalouskian K, Bertagnolio S, Easterbrook PJ, Muyengenyi P, Walker AS, Paton Nl; Europe Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial Team (2017) HIV Drug Resistance Mutations in Non-B Subtypes After Prolonged Virological Failure on NNRTI-Based First-Line Regimens in Sub-Saharan Africa. J Acquir Immune Defic Syndr 75: e45–e54.

8. Poos AFY, Ndashimye E, Avino M, Gibson R, Kityo C, Kyyeune F, Nankya I,電ones-Mateu ME, Arts EJ; The Ugandan Drug Resistance Study Team (2019) The Ugandan Drug Resistance Study Team. First-line HIV treatment failures in non-B subtypes and recombinants: a cross-sectional analysis of multiple populations in Uganda. AIDS Res Ther 16: 3.

9. Ayele G, Tessema B, Amsalu A, Ferede G, Yismaw G (2018) Prevalence and associated factors of treatment failure among HIV/AIDS patients on HAART attending University of Gondar Referral Hospital Northwest Ethiopia. BMC Immunol 19: 37.

10. Desta AA, Wolead ragey TW, Futuwi N, Gebrehiwot GT, Gebru GG, Berhe AA, Godefay H (2020) HIV virological non-suppression and factors associated with non-suppression among adolescents and adults on antiretroviral therapy in northern Ethiopia: a retrospective study. BMC Infect Dis 20: 4.

11. Haile D, Tekele A., Gashaw K, Demelash H, Nigatu D (2016) Predictors of Treatment Failure among Adult Antiretroviral Treatment (ART) Clients in Bale Zone Hospitals, South Eastern Ethiopia. PloS One 11: e0164299.

12. Svärj M.S., Mloka D, Neogi U, Meini G, Mugusi F, Incardona F, Zazzi M, Sönnerborg A (2017) Drug resistance testing through remote genotyping and predicted treatment options in human immunodeficiency virus type 1 infected Tanzanian subjects failing first or second line antiretroviral therapy. PloS One 12: e0178942.

13. Bulage L, Ssewanyana I, Nankabirwa V, Nsabuga F, Kihembo C, Pande G, Ario AR, Matovu JK, Wanyenze RK, Kiyaga C (2017) Factors Associated with Virological Non-suppression among HIV-Positive Patients on Antiretroviral Therapy in Uganda, August 2014-July 2015. BMC Infect Dis 17: 326.

14. Hawkins C, Ulega N, Liu E, Aboud S, Mugusi F, Chalamilla G, Sando D, Aris E, Carpenter D, Fawzi W (2016) HIV virological failure and drug resistance in a cohort of Tanzanian HIV-infected adults. J Antimicrob Chemother 71: 1966-1974.

15. Telele NF, Kalu AW, Marrone G, Gebre-Selassie S, Fekade D, Tegbaru B, Sönnerborg A (2018) Baseline predictors of antiretroviral treatment failure and lost to follow up in a multicenter countrywide HIV-1 cohort study in Ethiopia. PloS One 13: e0200505.

16. Barabona G, Mahiti M, Masoud S, Mbelele P, Mgunya AS, Minja L, Sunguya B, Shigemi U, Matsuda M, Hachiya A, Iwatani Y, Lyamuya E, Uneo T (2019) Pre-treatment and
acquired HIV drug resistance in Dar es Salaam, Tanzania in the era of tenofovir and routine viral load monitoring. J Antimicrob Chemother 74: 3016-3020.

17. Mosha F, Ledwaba J, Ndugulile F, Ng'ang'a Z, Nsubuga P, Morris L, Kasubi M, Swai A, Vercauteren J, Vandamme AM (2014) Clinical and virological response to antiretroviral drugs among HIV patients on first-line treatment in Dar-es-Salaam, Tanzania. J Infect Dev Ctries 8: 845-852.

18. Etoori D, Ciglenecki I, Ndlangamandla M, Edwards CG, Jobanputra K, Pasipamire M, Maphalala G, Yang C, Cabasso I, Kaboré SM, Goiri J, Teck R, Kerschberger B (2018) Successes and challenges in optimizing the viral load cascade to improve antiretroviral therapy adherence and rationalize second-line switch in Swaziland. J Int AIDS Soc 21: e25194.

19. Labhardt ND, Ringera I, Lejeune TI, Cheleboi M, Wagner S, Muhairwe J, Klimkait T (2017) When patients fail UNAIDS' last 90 - the "failure cascade" beyond 90-90-90 in rural Tanzania. J Infect Dev Ctries 8: 845-852.

20. Morris L, Kasubi M, Swai A, Vercauteren J, Vandamme AM (2014) Clinical and virological response to antiretroviral drugs among HIV patients on first-line treatment in Dar-es-Salaam, Tanzania. J Infect Dev Ctries 8: 845-852.

21. Labhardt ND, Ringera I, Lejeune TI, Cheleboi M, Wagner S, Muhairwe J, Klimkait T (2017) When patients fail UNAIDS' last 90 - the "failure cascade" beyond 90-90-90 in rural Tanzania. J Infect Dev Ctries 8: 845-852.

22. Muhairwe J, Klimkait T (2017) When patients fail UNAIDS' last 90 - the "failure cascade" beyond 90-90-90 in rural Tanzania. J Infect Dev Ctries 8: 845-852.

23. Labhardt ND, Ringera I, Lejeune TI, Cheleboi M, Wagner S, Muhairwe J, Klimkait T (2017) When patients fail UNAIDS' last 90 - the "failure cascade" beyond 90-90-90 in rural Tanzania. J Infect Dev Ctries 8: 845-852.

24. Kelsey J, Whittemore A, Evans, A, Thompson W (1996) Methods in Observational Epidemiology. Oxford: Oxford University Press.

25. Morisky DE, Green LW, Levine DM (1989) Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 24: 67-74.

26. Fox MP, Cutsem GV, Giddy J, Maskew M, Keiser O, Prozesky H, Wood R, Hernán MA, Sterne JA, Egger M, Boule A; IeDEA-SA collaboration (2012) Rates and predictors of failure of first-line antiretroviral therapy and switch to second-line ART in South Africa. J Acquir Immune Defic Syndr 60: 428-437.

27. Hailu GG, Hagos DG, Hagos AK, Washun AH, Ajemaa TA (2018) Virological and immunological failure of HAART and associated risk factors among adults and adolescents in the Tigray region of Northern Ethiopia. PloS One 13: e0196259.

28. Ayele TA, Worku A, Kebede Y, Alamu K, Kasim A, Shkedy Z (2017) Choice of initial antiretroviral drugs and treatment outcomes among HIV-infected patients in sub-Saharan Africa: systematic review and meta-analysis of observational studies. Syst Rev 6: 173.

29. Tchouwa GF, Eymard-Duvernay S, Counil A, Lamare N, Serrano L, Butel C, Bertagnolio S, Mpoudi-Ngole E, Raizes E, Aghokeng AF; EHRICA Study Group (2018) Nationwide Estimates of Viral Load Suppression and Acquired HIV Drug Resistance in Cameroon. eClinicalMedicine 4: 21-27.

30. Mekuria LA, Nieuwkerk PT, Yalew AW, Sprangers MA, Prins JM (2016) High level of virological suppression among HIV-infected adults receiving combination antiretroviral therapy in Addis Ababa, Ethiopia. Antivir Ther 21: 385-96.

31. Waldenstrøm SA, Kufa T, Barron P, Chirombo BC, Cheyip M, Ayalew K, Lombard C, Manda S, Diale K, Pillay Y, Puran AJ, Teshome Yimer Y, Yalew AW (2015) Magnitude and Predictors of Anti-Retroviral Treatment (ART) Failure in Private Health Facilities in Addis Ababa, Ethiopia. PloS One 10: e0126026.

32. Enderis BO, Hebo SH, Debir MK, Sidamo NB, Shimer MS (2019) Predictors of Time to First Line Antiretroviral Treatment Failure among Adult Patients Living with HIV in Public Health Facilities of Arba Minch Town, Southern Ethiopia. Ethiop J Health Sci 29: 175-186.

33. Cohen K, Meintjes G (2010) Management of individuals requiring antiretroviral therapy and TB treatment. Curr Opin HIV AIDS. 5: 61-69.

34. Cerrone M, Bracchi M, Wasserman S, Pozniak A, Meintjes G, Cohen K, Wilkinson RJ (2020) Safety implications of combined antiretroviral and anti-tuberculosis drugs. Expert Opin Drug Saf 19: 23-41.

35. Bell LCK, Noursadeghi M (2018) Pathogenesis of HIV-1 and Mycobacterium tuberculosis co-infection. Nat Rev Microbiol 16: 80–90.

36. Shankar EM, Vignesh R, Ellegård R, Barathan M, Chong YK, Bador MK, Rukumani DV, Sabet NS, Kamarulzaman A, Velu V, Larsson M (2014) HIV–Mycobacterium tuberculosis co-infection: a 'danger-couple model' of disease pathogenesis. Patholog Diag 70: 110–118.

37. Tormheim JA, Dooley KE (2018) Challenges of TB and HIV co-treatment: updates and insights. Curr Opin HIV AIDS. 13: 486-491.

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