# The relative contributions of HIV drug resistance, nonadherence and low-level viremia to viremic episodes on antiretroviral therapy in sub-Saharan Africa

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**Introduction:** To achieve viral suppression among more than 90% of people on antiretroviral therapy (ART), improved understanding is warranted of the modifiable causes of HIV viremic episodes. We assessed the relative contributions of drug-resistance, nonadherence and low-level viremia (LLV) (viral load 50–999 cps/ml) on viremic episodes in sub-Saharan Africa.

**Methods:** In a multicountry adult cohort initiating nonnucleoside reverse transcriptase inhibitor-based first-line ART, viremic episodes (viral load ≥1000 cps/ml) were classified as first, viral nonsuppression at 12 months; second, virological rebound at 24 months (after initial viral suppression at 12 months); third, failure to achieve viral resuppression at 24 months (after viremic episode at 12 months). We used adjusted odds ratios from multivariable logistic regression to estimate attributable fractions for each risk factor.

**Results:** Of 2737 cohort participants, 1935 had data on pretreatment drug resistance (PDR) and at least 1 viral load outcome. Viral nonsuppression episodes [173/1935 (8.9%)] were attributable to nonadherence in 30% (35% in men vs. 24% in women) and to PDR to nonnucleoside reverse transcriptase inhibitors in 10% (15% in women vs. 6% in men). Notably, at contemporary PDR prevalences of 10–25%, PDR would explain 13–30% of viral nonsuppression. Virological rebound episodes [96/1515 (6.3%)] were mostly attributable to LLV (29%) and nonadherence (14%), and only rarely to PDR (1.1%). Failures to achieve viral resuppression [66/81 (81.5%)] were mostly attributable to the presence of acquired drug resistance (34%) and only rarely to nonadherence (2.4%).

**Conclusion:** Effective adherence interventions could substantially reduce viral nonsuppression (especially in men) and virological rebound (especially during LLV), but

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would have limited effect on improving viral resuppression. Alternative ART regimens could circumvent PDR and acquired resistance.



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## Introduction

The 2020 global targets of having 90% of all HIV infected people being diagnosed, 90% of those diagnosed being on antiretroviral therapy (ART) and 90% of patients on ART achieving viral suppression, mark the roadmap to elimination of the AIDS epidemic as a public health threat by 2030 [1]. By December 2018, an estimated 62% of people living with HIV in low and middle-income countries (LIMC) were receiving ART, of whom 86% had viral suppression – falling short of the 90 goals [2].

There are few data on the relative contributions of some of the factors associated with and predictive of viremic episodes during ART in LIMC [3–5] (Fig. 1). Non-adherence to ART has been documented as a major determinant of viremic episodes [6–8]. Drug resistance to the widely used nonnucleoside reverse transcriptase inhibitors (NNRTI) efavirenz (EFV) and nevirapine (NVP), when present before ART initiation, has also been identified as a major determinant of failure to achieve initial viral suppression and a driver of treatment switches [9–11]. The impact of pretreatment drug resistance (PDR) is particularly concerning as rising PDR prevalences between 10 and 25% have been reported across sub-Saharan Africa [12]. Drug resistance is also acquired during virological failure, especially due to suboptimal adherence and is considered a key determinant for failure to achieve viral resuppression despite interventions to improve adherence [3,13,14]. Low-level viremia (LLV), defined as a plasma viral load between 50 and 1000 cps/ml, has been associated with virological rebound after initial viral suppression [5,15,16] (Fig. 1).

To inform intervention strategies to enhance sustained viral suppression, we aimed to untangle the relative contributions of the key modifiable risk factors, that is PDR and acquired drug resistance (ADR), nonadherence and LLV, that are associated with viremic episodes in ART-treated populations in sub-Saharan Africa.

## Methods

### Study design and population

Pan-African Studies to Evaluate Resistance-Monitoring was a prospective cohort of HIV-1-infected adults (≥18 years) conducted between 2007 and 2014, at 13 sites in six African countries (Kenya, Nigeria, South Africa, Uganda, Zambia, Zimbabwe), as profiled previously [9]. Care and treatment was based on local standard of care. For the present analysis, we included all participants who received

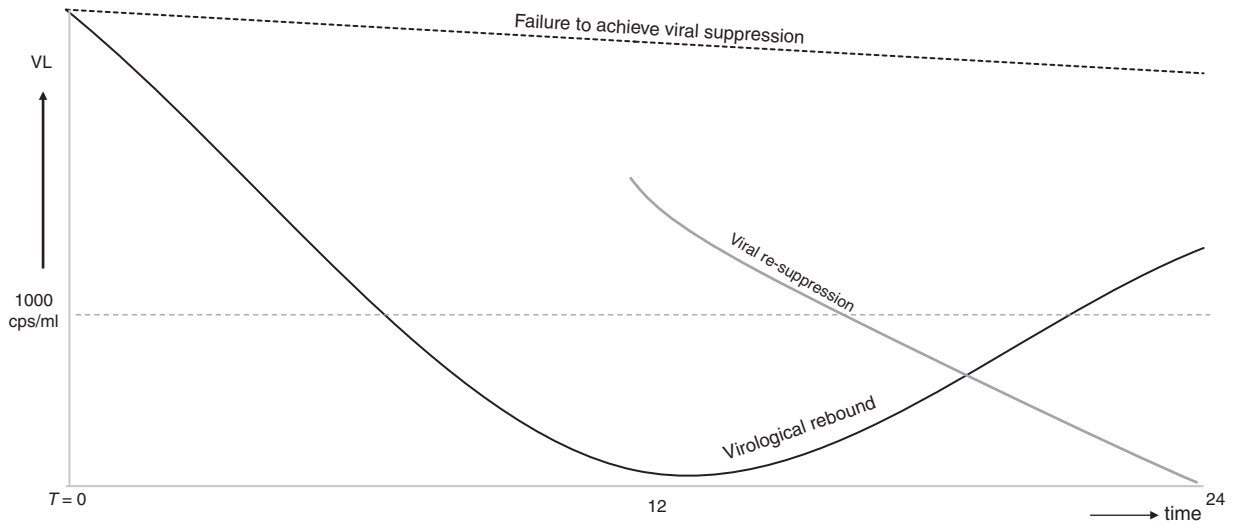


**Fig. 1. A schematic illustration of viremic episodes during antiretroviral treatment in HIV infected patients.**

first-line ART containing an NNRTI and two nucleoside reverse transcriptase inhibitor (NRTIs), who had a genotypic resistance test result available at ART initiation and a viral load test result at year 1 and/or 2. Self-reported 30-day adherence was recorded every 3 months using visual analog score (VAS), with a participant classified as nonadherent if the 12 or 24 months average VAS was 95% or less. Demographic, clinical and laboratory data were collected using standard case report forms which were aggregated in a Web-based data system. All participants provided written informed consent. The study was approved by the national and local research ethics committees at the collaborating sites and by the Amsterdam UMC, University of Amsterdam (Amsterdam, Netherlands).

### Virological analysis

HIV viral load was determined on cryopreserved plasma samples at ART initiation and annually thereafter, using NucliSens EasyQ real-time (version 2.0; bioMérieux, Lyon, France) or COBAS Ampliprep/COBAS Taqman assay (Roche, Branchburg, New Jersey). Sanger sequencing was done on samples with viral load greater than or equal to 1000 cps/ml; drug resistance was defined as the presence of at least one major drug resistance mutation included in the International Antiviral Society–USA mutation list of December 2019 associated with the NNRTIs NVP or EFV [17]. Viral load measurements at month 12 and 24 of ART were classified as viremic episode ($\geq$1000 cps/ml) or viral suppression ($<$1000 cps/ml) (WHO-defined threshold) [18] and additionally as LLV (50–999 cps/ml).

### Statistical analysis

Descriptive statistics were summarized by frequencies and percentages. Multivariable logistic regression with robust standard errors (to account for clustering of observations within sites) was used to assess associations between:

(1) PDR and nonadherence (independent variables) and viral nonsuppression at month 12 or at 24 (dependent variable), in all participants.
(2) PDR, nonadherence and LLV at month 12 (independent variables) and virological rebound at month 24 (after initial viral suppression at month 12) (dependent variable).
(3) Drug resistance at month 12 (ADR) and nonadherence (independent variables) and failure to achieve viral resuppression at month 24 (after viremic episode at month 12) (dependent variable).

Models were adjusted from a set of potential confounders: age, sex, calendar year of treatment initiation, prior antiretroviral use, type of NNRTI and NRTI, pre-ART viral load and $CD4^+$ cell count, WHO clinical stage and BMI. A two-sided $P$ value of 0.05 or less was considered significant. Due to significant interactions (at $\alpha = 0.05$ level), we reported stratified analyses by sex for the association between PDR and viral nonsuppression at 12 and 24 months; and by ART regimen [tenofovir (TDF) + lamivudine or emtricitabine (XTC) + EFV vs. non-TDF + XTC + EFV/NVP) for the association between LLV and virological rebound [19,20].

Using the adjusted associations from these models, we estimated attributable fractions among the exposed and population attributable fractions (PAF). We estimated the proportions of viremic episodes that were due to PDR, nonadherence and LLV, respectively. The PAF was defined as the proportion of viremic episodes that could have been prevented in case the risk factor was averted [i.e. optimal adherence ($\geq$95%), absence of resistance and absence of LLV]. We estimated the PAFs based on maximum likelihood method [21] using the *punaf* syntax in Stata version 12 (StataCorp LP, College Station, Texas, USA) [22].

## Results

### Patient characteristics

Of 2737 participants who initiated first-line ART, 1935 (71%) had data on PDR and a viral load result after year 1 and/or 2 of ART. 60% were women, median age was 37 (IQR 32–43) years. Initial ART regimens were TDF + XTC + EFV (33%), non-TDF + XTC + EFV (30%), non-TDF + XTC + NVP (37%). The proportion of participants with PDR was 4.1% (80/1941), and with nonadherence was 13.0% (252/1935) in month 0–12, 7.4% (112/1515) in month 12–24 and 12.7% (221/1744) in month 0–24. PDR and nonadherence levels did not differ between sexes.

### Risk factors of viremic episodes

#### *Viral nonsuppression at month 12 and 24*

The proportion of participants with viral nonsuppression was 8.9% (173/1935) at month 12 with 10.9% (85/779) in men and 7.6% (88/1156) in women ($P = 0.013$), and 11% (192/1744) at month 24 -with 11%, (117/1060) in women and 11% (75/684) in men ($P = 0.962$).

PDR was independently associated with the risk of viral nonsuppression at month 12 [adjusted odds ratio (aOR) 5.6, 95% confidence interval (CI) 2.3–14.1] and month 24 (aOR 5.4, 95% CI 2.1–13.7), and this effect was about two times greater in women than men ($P$ for interaction = 0.013) (Table 1). Nonadherence was associated with viral nonsuppression at month 12 (aOR 6.0, 95% CI 4.4–8.1) and month 24 (aOR 5.3, 95% CI 4.0–7.0), and this effect was greater in men than women at month 12, but not at month 24 (Table 1).

#### *Virological rebound*

1515 (78.3%) of the participants had viral suppression at month 12 and a viral load result available at month 24.

**Table 1. Viral nonsuppression attributable to pretreatment drug resistance or nonadherence after 12 and 24 months of antiretroviral therapy.**

| | Month 12 | | | | Month 24 | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristic | *N* | No. of events | aOR (95% CI) | Attributable fraction (95% CI) | *N* | No. of events | aOR (95% CI) | Attributable fraction (95% CI) |
| Overall | 1935 | 173 | | | 1744 | 192 | | |
| PDR[a] | 80 | 24 | 5.6 (2.3–14.1) | 10.3 (2.7–17.3) | 57 | 20 | 5.4 (2.1–13.7) | 7.1 (1.9–12.1) |
| Nonadherence | 252 | 66 | 6.0 (4.4–8.1) | 29.5 (22.0–36.2) | 221 | 68 | 5.3 (4.0–7.0) | 25.8 (19.7–31.5) |
| Women | 1156 | 88 | | | 1060 | 117 | | |
| PDR | 49 | 16 | 8.6 (3.4–21.6) | 14.5 (5.3–22.9) | 37 | 15 | 7.5 (3.4–16.6) | 9.4 (4.6–14.0) |
| Nonadherence | 140 | 29 | 5.1 (3.1–8.3) | 24.3 (14.4–33.2) | 136 | 41 | 5.3 (3.6–7.8) | 25.3 (16.7–33.1) |
| Men | 779 | 85 | | | 684 | 75 | | |
| PDR | 31 | 8 | 3.9 (1.3–12.1) | 6.3 (−0.7–12.9) | 20 | 5 | 3.7 (0.73–18.8) | 4.3 (−3.1–11.1) |
| Nonadherence | 112 | 37 | 7.1 (5.0–10.1) | 34.8 (27.0–41.9) | 85 | 27 | 5.3 (2.8–10.2) | 26.3 (12.8–37.7) |

PDR was defined as any NNRTI mutation according to the 2019 International AIDS Society-USA mutation list. Nonadherence was defined as mean VAS score <95%. Multivariable logistic regression analysis with odds ratios adjusted for age, sex, type of initial NNRTI and NRTI, WHO clinical stage, calendar year of ART initiation, prior exposure to antiretroviral drugs and pre-ART viral load and $CD4^+$ cell count. ART, antiretroviral therapy; aOR, adjusted odds ratio; CI, confidence interval; EFV, efavirenz; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PDR, pretreatment drug resistance; VAS, visual analog score; XTC, lamivudine or emtricitabine.
[a]*P* for interaction between PDR and sex was 0.017 at month 12 and 0.288 at month 24.

The proportion of participants with virological rebound at month 24 was 6.3% (96/1515).

PDR was not independently associated with the risk of virological rebound (aOR 1.4, 95% CI 0.46–4.1).

The proportion of participants with LLV at month 12 was 9.1% (138/1515), and LLV was independently associated with the risk of virological rebound (aOR 6.4, 95% CI 3.8–10.7), and this effect was greater among participants on non-TDF + XTC + NVP/EFV compared with those on TDF + XTC + EFV ($P$ for interaction = 0.025) (Table 2).

Nonadherence was independently associated with the risk of virological rebound (aOR 3.5, 95% CI 2.1–5.7) (Table 2).

*Failure to achieve viral resuppression*

For 81 of 173 (47%) participants who had viremic episode at month 12, a genotypic resistance test result at month 12 and viral load test result at month 24 was available. Overall 81.5% (66/81) failed to achieve viral resuppression at month 24.

Among participants with viremic episode at month 12, 69% (56/81) had one or more acquired resistance mutations and only 5.4% (3/56) achieved viral resuppression. ADR was strongly associated with failure to achieve viral resuppression (aOR 18.1, 95% CI 3.5–93.7).

The proportion of participants who had nonadherence in month 12–24 was 21% (17/81), but this was not independently associated with failure to achieve viral resuppression (aOR 2.3, 95% CI 0.89–6.0).

**Table 2. Virological rebound attributable to pretreatment drug resistance, nonadherence or low-level viremia.**

| Characteristic | *N* | No. of events | aOR (95% CI) | Attributable fraction (95% CI) |
|---|---|---|---|---|
| Overall[a] | 1515 | 96 | | |
| PDR | 41 | 5 | 1.4 (0.46–4.1) | 1.1 (−3.1–5.1) |
| Adherence | 112 | 22 | 3.5 (2.1–5.7) | 13.7 (6.4–20.3) |
| LLV at year 1 | 138 | 36 | 6.4 (3.8–10.7) | 28.6 (18.0–37.9) |
| TDF + XTC + EFV | 408 | 16 | | |
| PDR | 13 | 0 | 1.0 | |
| Adherence | 24 | 3 | 3.5 (0.77–16.3) | 12.4 (−7.5–28.7) |
| LLV at year 1 | 34 | 3 | 1.5 (0.22–10.6) | 5.5 (−25.3–28.8) |
| Non TDF + XTC + EFV/NVP | 1107 | 82 | | |
| PDR | 28 | 5 | 1.7 (0.58–5.2) | 2.0 (−2.5–6.3) |
| Adherence | 88 | 19 | 3.9 (2.3–6.6) | 14.3 (6.6–21.4) |
| LLV at year 1 | 104 | 33 | 7.7 (5.1–11.6) | 32.2 (23.7–39.7) |

PDR and ADR defined as any NNRTI mutation according to the 2019 International AIDS Society-USA mutation list. Adherence was defined as mean 30-day adherence with VAS score <95% as nonadherence. LLV, defined as 50–1000 cps/ml. Multivariable logistic regression analysis with odds ratios adjusted for; age, sex, type of initial NNRTI and NRTI, WHO clinical stage, BMI, calendar year of ART initiation, prior exposure to antiretroviral drugs, pre-ART viral load and $CD4^+$ cell count. ADR, acquired drug resistance; aOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; EFV, efavirenz; LLV, low-level viremia; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PDR, pretreatment drug resistance; VAS, visual analog score; TDF, tenofovir; XTC, lamivudine or emtricitabine.
[a]*P* for interaction between LLV and type of ART regimen was 0.025.

**Table 3. Relative contributions of various risk factors to viremic episodes among participants on first-line antiretroviral therapy in sub-Saharan Africa.**

| Potential modifiable risk factor | Viral nonsuppression (month 12)[a] | | | Viral rebound (month 24)[a] | | | Failure to achieve viral resuppression |
|---|---|---|---|---|---|---|---|
| | All (%) | Men (%) | Women (%) | All (%) | TDF/XTC/EFV (%) | Non TDF/XTC/EFV (%) | Attributable fraction (%) |
| PDR | | | | | | | |
| Cohort prevalence (4.1%)[b] | 10 | 6 | 15 | 1 | 0 | 2.0 | – |
| Plausible prevalences (10–25%) | 10–30 | 10–24 | 17–36 | 3–6 | 0 | 4–11 | – |
| Nonadherence | | | | | | | |
| Cohort prevalence[b] | – | – | – | – | – | – | – |
| 0–12 months (13%) | 30 | 35 | 24 | – | – | – | – |
| 12–24 months (7.4%)[c] | – | – | – | 14 | 12 | 14 | – |
| 12–24 months (21%)[d] | – | – | – | – | – | – | 2.4 |
| Plausible prevalences (10–30%) | 15–37 | 16–40 | 13–34 | 10–28 | 11–29 | 11–29 | 1–3 |
| LLV | | | | | | | |
| Cohort prevalence (9.1%) | – | – | – | 29 | 6 | 32 | – |
| Plausible prevalences (5–15%) | – | – | – | 8–23 | 1.9–5.6 | 9–24 | – |
| Acquired drug resistance | | | | | | | |
| Cohort prevalence (69%)[b] | – | – | – | – | – | – | 34 |
| Plausible prevalences (60–90%) | – | – | – | – | – | – | 37–42 |

Drug resistance was defined as any NNRTI mutation according to the 2019 International AIDS Society-USA mutation list. Nonadherence was defined as mean VAS score <95%; LLV defined as 50–1000 cps/ml; – Not applicable. LLV, low-level viremia; PDR, pretreatment drug resistance; NNRTI, nonnucleoside reverse transcriptase inhibitor; VAS, visual analog score.

[a]Stratified analysis due to significant interaction.

[b]Cohort estimates are slightly larger than projected prevalences as they also take into account the effect of other predictor values included in the model.

[c]Nonadherence among participants with viral suppression at 12 months.

[d]Nonadherence among participants with viral nonsuppression at 12 months.

## Attributable fractions for viremic episodes

### *Viral nonsuppression at month 12 and 24*

Summaries of attributable fractions are shown in Table 3. In the cohort, the prevalence of PDR was 4.1% and the fraction of viral nonsuppression attributed to PDR was 10.3% (95% CI 2.7–17.3%) at month 12 and 7.1% (95% CI 1.9–12.1%) at month 24. This can be interpreted as, that 10.3 and 7.1% of the viral nonsuppression episodes could have been averted by controlling for PDR. The fraction of viral nonsuppression attributed to PDR were consistently higher in women compared with men (Table 1). When estimating the fractions of viral nonsuppression for populations with contemporary prevalence estimates of PDR (10–25% as reported by WHO [12]), the attributable fractions are estimated at 13–30% (Supplementary Fig. 1, http://links.lww.com/QAD/B765).

In the overall cohort, the prevalence of nonadherence was 13% in month 0–12 and 12.7% in month 0–24, and the fraction of viral nonsuppression episodes attributed to nonadherence was 29.5% (95% CI, 22.0–36.2%) in month 0–12, and 25.8% (95% CI, 19.7–31.5%) in month 0–24; and was higher for men in month 0–12 only (Table 1). This can be interpreted as that ensuring optimal ART adherence could avert 30% of viral nonsuppression episodes in the first year and 26% during the first 2 years of ART. Similarly, across a range of plausible prevalences of nonadherence at 10–30%, the fractions of viral nonsuppression attributable to nonadherence would be 15–37% (Supplementary Fig. 1, http://links.lww.com/QAD/B765).

### *Virological rebound*

In the cohort, the fraction of virological rebound episodes attributable to PDR was 1.1% (95% CI −3.1–5.1%) (Table 2). The fraction of virological rebound episodes attributable to nonadherence was 13.7% (95% CI 6.4–20.3%) and did not significantly vary between ART regimens (Table 2). The fraction of virological rebound episodes attributable to LLV was 28.6% (95% CI, 18.0–37.9%), and was higher in participants on non-TDF + XTC + EFV/NVP than those on TDF + XTC + EFV (Table 2). These findings can be interpreted as that in this cohort controlling for PDR, nonadherence or LLV could avert 1.4, 13.7 and 28.6% of virological rebound episodes, respectively.

Across a range of plausible prevalences of PDR (10–25%), nonadherence (10–30%) and LLV (5–15%), the attributable fractions of virological rebound episodes was estimated to range between 3–6%, 10–28% and 8–23%, respectively (Supplementary Fig. 2, http://links.lww.com/QAD/B766).

### *Failure to achieve viral resuppression*

In the cohort, the fraction of failure to achieve viral resuppression attributable to acquired drug resistance was 33.9% (95% CI 21.5–55.4%). whereas the fraction of

failure to achieve viral resuppression attributable to nonadherence was 2.4% (95% CI −0.39–5.2%).

Across a range of plausible prevalences of acquired resistance (60–90%) and nonadherence (10–30%), attributable fractions of failures to achieve viral resuppression were higher for acquired resistance (37–42%) than nonadherence (1–3%) (Supplementary Fig. 3, http://links.lww.com/QAD/B767).

## Discussion

The study provides novel insights into the relative contributions of the key potentially modifiable risk factors for viremic episodes in patients receiving first-line NNRTI-based ART in sub-Saharan Africa. Viral nonsuppression episodes were attributable mainly to nonadherence but also to PDR. On the other hand, virological rebound episodes were mostly attributable to LLV and nonadherence and rarely to PDR. Failures to achieve viral resuppression were mostly attributable to the presence of acquired drug and only rarely to nonadherence.

Overall nonadherence accounted for the largest fraction of cohort participants with viral nonsuppression (30% in the first year, 26% in the first 2 years of ART). Addressing the challenges of adherence, especially early during ART, therefore, remains a key intervention for improving the global target for viral suppression [23].

In this cohort, PDR accounted for a smaller, but nonetheless important fraction of viral nonsuppression (10% in the first year, 7% in the second year of ART). This finding is particularly relevant given that recent data suggest high prevalence of NNRTI-associated PDR in many settings in sub-Saharan Africa [12]. The recent WHO HIVDR report indicates that, of the 18 countries that monitored PDR between 2014 and 2018, 12 reported national estimates between 10 and 25% [12]. In those settings, PDR could potentially explain a substantial (13–30%) fraction of viral nonsuppression episodes. Moreover, our study adds that PDR explains a much higher fraction of viral nonsuppression for women (15%) than for men (6%). These findings therefore, provide further support to ongoing or planned efforts in many LIMC to accelerate the transition from NNRTI-based to dolutegravir-based first-line ART to circumvent the increasing impact of NNRTI-associated PDR [24].

By contrast, our findings suggested that PDR plays a negligible role in virological rebound, explaining only ~1% of the episodes. These findings are in line with a recent study in South African women initiating ART during pregnancy which found that PDR plays a minor role in explaining virological rebound after initial viral suppression (<10%), whereas nonadherence accounted for the vast majority (>90%) [4].

We estimated that the largest fraction of virological rebound could be explained by the occurrence of LLV (29%), in addition to nonadherence (14%). It should be noted, however, that the attributable fraction of LLV was much larger for the less potent ART regimens, based on thymidine analogs and NVP, rather than TDF + XTC + EFV (Atripla) (32 vs. 6%). This hypothesis is supported by earlier observations of higher potency of TDF + XTC + EFV and its availability as a fixed-dose combination [20,25]. Our study finding expands on previous studies, including a large study in South Africa, which found that patients with LLV are at higher risk of virological failure and decreased durability of viral resuppression [5]. In addition, LLV has been correlated with increased risk of drug resistance, immunological failure, non-AIDS comorbidities, clinical progression to AIDS, death as well as potential increased risk of HIV transmission [26]. This suggest potential programmatic benefits of using lower viral load thresholds to trigger clinical actions such as adherence interventions.

Available data from the literature indicate that 60–90% of patients failing NNRTI-based regimen have ADR mutations [14]. Among cohort participants with viremic episode at month 12, 69% had acquired at least one drug resistance mutation. Presence of acquired resistance accounted for a high-attributable fraction (34%) of patients who failed to achieve viral resuppression on their first-line ART regimen at 24 months. A study from a routine clinical setting in Uganda also found that only 26% of patients with viremic episode and detected resistance resuppressed on a continued first-line ART even with high-level adherence [3]. In our cohort, only 18.5% achieved viral resuppression overall, and in those who had acquired resistance only 5.4% achieved resuppression. This highlights the potential limited benefits of adherence interventions during late diagnosis of virological failure in patients failing on NNRTI-based treatment, warranting rapid switching to second-line therapy instead [3,27].

The main strengths of this study are its prospective multicountry design, and the setting of high-burden countries with increasing levels of PDR, which enhances its relevance for policy makers. Our study has some limitations. First, the study focused on NNRTI-based first-line ART only. Further studies are needed to provide insights on the cause of viremic episode with integrase inhibitors, following the transition to dolutegravir-based ART. Second, our study relied on a self-reported adherence measure, which, although valid and widely used, has potential for underestimating the effect of nonadherence on viremic episode [28–30]. Viral load and therapeutic drug monitoring tests are more objective and are thus preferred alternatives. Moreover, we did not

collect data on underlying determinants of nonadherence and thus were not able to elucidate the observed sex-differences.

Third, there were few participants with the characteristic and outcome of interest in some of the models leading to wide CIs. This highlights the need for additional meta-analysis to precisely determine the attributable fractions of key determinants of viremic episodes. Lastly, frequency of viral load testing was limited in our cohort and we did not collect information on enhanced adherence counseling among those with viremic episode. Despite this, our data have relevance for current practice given that many LMIC still have substantial gaps in their viral load coverage and cascade [12].

## Conclusion

In conclusion, our study provides insight into the relative contribution of potential modifiable factors for viremic episodes in people living with HIV who receive ART, that could be addressed to improve attainment of the UNAIDS-defined global target for more than 90% viral suppression. Our findings suggest an important role of PDR to NNRTIs on failure to achieve initial viral suppression, but not in viral rebound. Viral rebound is predominantly attributable to nonadherence and LLV. High rates of acquired resistance limit the ability to achieve viral resuppression among those failing treatment, prompting need for rapid regimen switching. Our study findings recommend exploring more sensitive viral load thresholds to detect viremic episodes, enhanced adherence interventions particularly early during ART and accelerated rollout of dolutegravir first-line ART in populations with high-PDR prevalence, to circumvent the negative impact of emerging NNRTI-associated PDR.

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Authors' contributions: T.F.R.W. is the PASER principal investigator. C.M.K., M.S., S.A., M.W., M.D.J., P.I., K.M., W.S., T.S.B., P.O., K.C.E.S., T.F.R.W. and R.L.H. established the cohort and supervised data collection. RLH and SCI conceived the study. S.C.I. performed the statistical analysis, with input from R.L.H. and S.B. S.C.I., T.F.R.W., S.B. and R.L.H. drafted the article. All authors provided valuable input to interpretation of the data and critically reviewed the article for important intellectual content. All authors reviewed and approved the final version of the article.

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## Conflicts of interest

There are no conflicts of interest.

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