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High levels of acquired HIV drug resistance following virological non-suppression in HIV-infected women from a high-risk cohort in Uganda

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Abstract

HIV drug resistance (HIVDR) is of increasing health concern, especially among key populations. We investigated the prevalence of virological suppression (VS), prevalence and correlates of HIVDR in HIV-infected women, enrolled in a high-risk cohort. We enrolled 267 women initiated on first-line antiretroviral therapy (ART) between 2015 and 2018. Participants' plasma samples were analysed for HIV RNA viral load (VL) and genotypic resistance testing was performed on those with VL non-suppression (defined as VL≥1,000 copies/mL). We used the Stanford HIVDR database-algorithm to assess HIVDR mutations and logistic regression to assess risk factors for VL non-suppression and HIVDR. We observed an overall VS prevalence of 76.0% (203/267) and detected respective ADR prevalence to NNRTIs and NRTIs of 81.3% (CI; 67.4-91.1) and 45.8% (CI; 31.4-60.8) among the 48 successfully genotyped VL non-suppressors. NNRTI mutations were observed in 81.3% (39/48) of the genotyped participants and 45.8% (22/48) had both NRTI and NNRTI mutations. The mutation K103N was detected in 62.5% (30/48) of participants, 41.7% (20/48) had M184V/I, 14.6% had K65R and 12.5% (6/48) had thymidine analog mutations (TAMs). None of the analysed potential risk factors including age and duration on ART were significantly correlated with VL non-suppression or HIVDR. Whereas high levels of NNRTI mutations support the transition to dolutegravir, the presence of NRTI mutations especially TAMs may compromise dolutegravir-based regimens or other second-line ART options. The moderate VS prevalence and high HIVDR prevalence therefore calls for timely ART switching and intensive adherence counseling.

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Introduction

The future success of antiretroviral therapy (ART) is being undermined by HIV drug resistance (HIVDR) which reduces the efficacy of the available regimens and limits treatment options, especially in resource limited settings.[1] HIVDR and sub-optimal adherence drive treatment failure among individuals on ART.[2] Monitoring of HIVDR is a prudent public health undertaking, more so in key populations that include the fisherfolk and female sex workers (FSWs) who are more vulnerable to, and have a higher prevalence of HIV in low and middle-income countries (LMICs).[3–5] Commercial sex is a key epidemic driver that largely sustains HIV transmission among high-risk sub-populations and its subsequent spread to the general population.[6] In Uganda, the prevalence of HIV among FSWs is estimated at 35.4%, nearly five times higher than the 7.6% among women in the general population.[7,8] Despite the ongoing interventions to reduce new infections, the HIV incidence rate among FSWs remains high at approximately 1.8-3.8 per 100 person-years.[7,9] As such, FSWs and their clients account for approximately 18% of new HIV infections in Uganda today.[5]

To achieve the UNAIDS 90-90-90 targets as a means of ending the AIDS epidemic by 2030,[10] the Ugandan government is committed to improving access to HIV care and treatment for all, including several key populations.[11] ART roll-out among FSWs has been a challenge due to the criminalization of sex work in Uganda.[12,13] This coupled with several other hindrances such as stigma, have complicated the implementation of the recently adopted universal “test and treat” policy in this highly mobile population, thereby raising concerns of retention, adherence, prompt ART initiation,[14] virological non-suppression and potential development of HIVDR.[15] Studies in Rwanda [16] and South Africa [1] detected HIVDR among 77.1% and 73.7% of FSWs with virological non-suppression, respectively.

Despite the considerable progress by the National HIV programmes to promptly initiate newly infected individuals on ART,[8] virological failure (VF) has been detrimental,[17] especially to individuals initiated on efavirenz/nevirapine-based (EFV/NVP) first-line regimens.[18,19] Besides non-adherence, the emergence of acquired drug resistance (ADR) during ART has been identified as a major driver of VL non-suppression that subsequently jeopardizes ART efficacy.[17,18] The ever-growing HIVDR has been observed with increasing

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ART coverage across the East African region.[18,20] Ultimately, there is a need for ADR surveillance,[17] especially where universal ART is being implemented as recommended by the World Health Organization (WHO).[21] Assessment of HIVDR patterns is required to prevent the spread of resistant strains and to assist in selecting potent subsequent regimens. However, routine HIVDR testing remains a huge economic challenge in LMICs such as Uganda. The Ugandan Ministry of Health (MoH) consolidated guidelines for the prevention and treatment of HIV do not universally promote routine HIVDR testing. Although viral load (VL) monitoring is recommended by the MoH,[22] its implementation is hampered by the high testing costs. In this study, we investigated the prevalence of VS, patterns and correlates of HIVDR in a cohort of FSWs enrolled under the universal "test and treat" ART program in Kampala, Uganda.

Methods

Study design, population and setting

This was a cross-sectional study conducted in an open cohort of women attending the Good Health for Women Project (GHWP)-clinic implementing HIV test and treat policy, between 2015 and 2018. The GHWP enrolled women engaged in commercial sex irrespective of their HIV status and provided voluntary HIV counseling and testing (VHCT) services in the GHWP-clinic, situated in Kampala, within areas where commercial sex work is booming as previously described.[23] The clinic enrolled, retained and supported HIV-positive and HIV-negative FSWs (at a high risk of HIV transmission and HIV infection, respectively), and those that sero-converted during the course of the study. The GHWP-clinic offered repeated VHCT for women that previously tested negative, provided HIV treatment, screened for and treated TB, treated and managed STIs, provided both male and female condoms and other contraceptives, treated children <5 years of the participants and encouraged the participants to bring their regular male sexual partners to the clinic for HIV testing, prevention and care services.

In the GHWP-clinic, HIV-positive FSWs initiating ART received the recommended first-line ART regimen of two NRTIs and one NNRTI. The second-line ART regimen consisted of two NRTIs unused in the first-line regimen with a ritonavir-boosted protease inhibitor (PI).[24]

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Since 2014, the GHWP-clinic has collaborated with the MoH to implement viral load monitoring of participants on ART, in accordance with the national treatment guidelines. VL testing is recommended 6 months after ART initiation and 12 months afterwards for all suppressed individuals. For VF cases, three sessions of intensive adherence counseling, are given monthly and a repeat VL test one month after the third counseling session. For individuals with persistent VF, a regimen switch is done.[24] Field workers tracked the women using phone calls and short message texts to ensure they attend their clinical and counseling appointments.

Our analyses included all HIV-positive FSWs aged 18 years and above, who were receiving first-line ART including those with previous ART exposure but excluded participants with incomplete clinical and socio-demographic data. We retrieved from the biorepository, samples of consented participants and obtained from the archives their matching clinical and socio-demographic data.

Viral load and genotypic testing

Viral load (VL) testing was performed using the COBAS TaqMan 48 (Roche HIV-1 v2.0) with a detection cut-off of 20 HIV-RNA copies/mL. Based on the Ugandan national HIV treatment guidelines,[22] participants with VL≥1000 copies/mL were regarded as virologically non-suppressed. We performed HIV genotypic resistance testing on plasma samples of participants with non-suppressed VLs using a validated in-house Sanger sequencing assay as previously described.[17] The HIV polymerase sequences spanning the entire protease (codons 1-99) and reverse transcriptase amino terminus (codons 1-320) were generated from chromatogram data using RECall.[25] We assessed HIVDR using the Stanford HIVdb algorithm Version 8.9.[26] Following the WHO criteria,[27] all sequences classified as low-, intermediate- or high level resistance were reported as resistant. Based on the Stanford DRM penalty scores, a drug penalty score ≤14 defined susceptibility to-, while a score ≥15 defined resistance to a particular drug.[28] We also characterized sequences by the presence of surveillance drug resistance mutations (SDRMs).[29] To identify any contamination, we examined sequence relatedness by creating a maximum-likelihood phylogenetic tree with 1000 bootstraps using RaxML.[30]

Statistical analysis

Participants' socio-demographic, clinical and virological parameters were summarized with descriptive statistics (means, standard deviations, medians, and interquartile ranges [IQR]) for continuous variables. Similarly, categorical variables were summarized using frequencies, proportions, and percentages. Where required, confidence intervals were calculated at a 95% level. Associations between categorical variables were assessed using chi-square and Fisher's exact test. Logistic regression was performed to assess the risk factors of VL non-suppression and ADR in both univariate and multivariate models. Explanatory variables that had a p-value ≤ 0.25 in the univariate model were included in a multivariate model in a stepwise approach to establish the independent predictors of VL non-suppression at a significance p-value of ≤ 0.05. The explored explanatory variables included: age, marital status, education level, duration on ART and HIV-1 RNA VL. The outcome measure from logistic regression analyses was the odds ratio. Data analysis was performed using STATA version 14 (Stata Corp. College Station, Texas, USA).

Results

Demographic and clinical characteristics of participants

Figure 1 and Table 1 present the summarized characteristics of the study participants. We enrolled 267 participants, with a median age of 30 years (IQR; 26-34) and the majority (70.0%) were of primary level education. Most of the participants were either divorced, separated or widowed (75.0%). At least 84% of participants had been on ART for at most one year: 25.1% had been on ART for <6 months, while 59.2% had been on ART for 6-12 months. The majority of participants (97.4%) were on tenofovir (TDF)+lamivudine (3TC) +efavirenz (EFV) ART regimen.

Prevalence and potential correlates of viral load non-suppression

Of the 267 participants, 203 had VL<1000 RNA copies/mL hence the overall prevalence of VS of 76.0% (95% CI; 70.4-81.0) as shown in Table 2. An overall median VL of 4.4 Log10 copies/mL (IQR; 3.7-5.1) was observed among participants with VL non-suppression (Table 2); 62.5% of the VL non-suppressors were aged 30 years and below (Table 3). The median duration on ART for participants with VL non-suppression was 11 months (IQR; 6.0-18.0)

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post-ART initiation. At univariate level, participants aged 30 years and below had a significantly higher VL non-suppression estimate, however, after adjusting for marital status, though still higher in the younger age group, the difference was not statistically significant. Similarly, ART regimen and duration on ART were not associated with VL non-suppression in the logistic regression analysis (Table 3).

Prevalence of acquired HIV drug resistance and predicted resistance and susceptibility to second-line drugs

Of the 48 virological non-suppressors successfully genotyped, 39 (81.3%) had HIV variants with predicted resistance to at least one of the recommended drugs. This represents an overall HIV ADR prevalence of at least 14.6% (39/267) in the sampled population of participants on ART (Figure 1). Since 16 of the VF cases had no sequences due to unsuccessful genotyping, the overall prevalence of ADR presumably ranges between 14.6% and 20.6% (55/267), assuming all the 16 had HIVDR. The prevalence of ADR to both of the used NNRTIs, nevirapine and efavirenz was 81.3% (39/48). For the NRTIs, the prevalence of HIV ADR to both 3TC and FTC was 45.8% while 22.9% of virological non-suppressors had HIV variants resistant to TDF. We noted that 45.8% of the VF cases had HIV variants resistant to both NRTIs and NNRTIs-dual resistance (Figure 2).

From the Stanford HIVdb algorithm analysis, only 10.4% of sequences of virological non-suppressors encoded HIV variants resistant to AZT and 22.9% encoded HIV variants predicted as resistant to TDF, the two NRTIs recommended in Uganda's second-line regimen. However, the proportion of variants with predicted resistance generally increased when NRTIs were analysed in recommended combinations (Figure 3). For instance, 45.8% of the virological non-suppressors harboured HIV variants predicted as resistant to a second-line regimen comprising AZT/TDF+3TC as NRTIs. None of the sequences had predicted resistance to the ritonavir-boosted PIs, atazanavir and lopinavir, which are recommended components of Uganda's second-line regimen (Figure 3).

Prevalence and patterns of surveillance drug resistance mutations associated with drug resistance

In the 48 sequences, the most prevalent NRTI SDRMs were M184V/I and K65R, and these were detected in 41.7% (20/48) and 14.6% (7/48) participants respectively (Figure 4). Thymidine analog mutations (TAMs) were detected in 12.5% (6/48) participants; both

type-1 TAMs (M41L, L210W, and T215Y) and type-2 TAMs (D67N, K219E, and K70R) were detected. The most prevalent NNRTI SDRMs were K103N (62.5%; 30/48), G190A (22.9%; 11/48) and P225H (18.8%; 9/48). (Figure 4 and Table 4). No participant had acquired resistance mutations to PIs, though in our secondary analysis, one participant (2.1%; 1/48) had a transmitted PI SDRM, M46L present with both NRTI and NNRTI SDRMs (Table 4).

Potential correlates of acquired HIV drug resistance

The median VL among women with HIVDR was 4.4 log10 (IQR; 3.9-5.2). Of the 48 VF cases successfully genotyped, 11 (20.5%) had been on first-line ART for <6 months while the rest had been on treatment for a median duration of 12 months (IQR; 8-34). Results from the univariate models indicated that ADR was slightly higher among participants aged above 30 years, however, this difference was not statistically significant. Other risk factors including HIV RNA VL, marital status, and duration on ART were not predictors of ADR (Table 5).

Discussion

This study determined the virological suppression prevalence and assessed the prevalence, patterns of and the potential correlates for acquired HIVDR among FSWs attending a "test and treat" ART programme in Kampala, Uganda. We report an overall VS prevalence of 76.0%, which is consistent with VS prevalence from other sub-Saharan regions and elsewhere.[21,31] This prevalence though higher than the national estimate of 62.9% among females aged 15 to 64,[8] is below the UNAIDS 90% target. The moderate VS prevalence reported in this study could be attributable to a consistent close monitoring system in the form of continued ART access, VL testing, and adherence counseling in this urban cohort. We noted that VF cases had high viral loads (median of 4.4 log 1og 10), probably due to the use of less potent NNRTI-based regimens of reduced susceptibility that could not effectively suppress viral replication. As observed from our analysis, resistance to EFV stood at 81.3% due to NNRTI mutations detected in this population. These high VL levels are likely to increase the risk of HIV transmission to sexual networks in this population.

The estimated ADR prevalence of 81.3% among the VL non-suppressors in this study concurs with previous ADR prevalence in sub-Saharan Africa.[21,32] Comparable ADR

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prevalence of 76.1% was reported by Kaleebu *et al* in a general population,[17] von Braun *et al* estimated it at 82.8% among ART-experienced Ugandan adults at an urban outpatient clinic[33] and Omooja *et al* observed an ADR prevalence of 73.2% in a key population of fisher-folk. [34] The high ADR prevalence among FSWs, close to estimates from the general population, suggests that the Ugandan ART programmes across all populations, face similar challenges that sustain high ADR prevalence. We observed a high prevalence of ADR driven by NNRTI mutations among VL non-suppressors, an indicator of the low genetic barrier of NNRTIs, thus demonstrating the need for routine HIVDR testing to guide timely ART switch in key populations. NNRTI mutations were detected in all the 39 participants with ADR of whom 22 had acquired both NRTI and NNRTI mutations. This finding is consistent with a recent study in Cameroon [32] and several others that report the increasing NNRTI-selected mutations in sub-Saharan Africa.[21,35,36]

The overall ADR prevalence of at least 14.6%, in this sample population of individuals on ART, is higher than a pooled estimate of 9.7% among adults from LMICs [21] corroborating the need for potent regimens to cope with the emerging HIV drug resistant strains. Currently, the Ugandan MoH is switching patients from NNRTI-based regimens to a more potent DTG-based first and second-line ART regimens.[37] DTG is associated with better treatment outcomes due to its higher efficacy, a high genetic barrier to resistance and improved tolerability.[21] Recent investigations in Uganda and elsewhere support the replacement of NNRTIs with DTG.[16,38,39] These findings highlight the essence of HIVDR testing in ART programmes in Uganda where currently resistance testing is recommended for only individuals failing the second-line regimens, to guide on the most potent third-line ART regimens.[22] Without resistance testing, 9 (18.7%) of the VF cases could have been unnecessarily switched to second-line ART regimens while 81.3% could have been maintained on a failing first-line regimen, leading to poor treatment outcomes. The high ADR levels among VL non-suppressors highlight the need to strengthen adherence counseling, condom use, and retention of women at high risk of HIV infection in the continuum of HIV care.

We identified mutations expected and observed by previous studies [21,32,34,36,40–42] in settings where the first-line regimens consist of NRTIs and NNRTIs. The most frequently

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detected NRTI mutations were M184IV and K65R associated with reduced susceptibility to 3TC and FTC [43,44] while TAMs also raise concern as they cause cross-resistance to other NRTIs.[45] However, M184IV and K65R confer reduced HIV virological fitness and increase viral susceptibility to AZT,[46] so 3TC and TDF, the two NRTIs that form the current first and second-line ART regimen backbones used in Uganda [22] may still be useful. This may be substantiated by the observation that 89.6% and 77.1% of the sequences of VF cases encoded HIV variants predicted as susceptible to AZT and TDF. Currently, a combination of two NRTIs (either AZT+3TC or TDF+3TC or ABC+3TC) with either boosted PIs (one of ATV/r and LPV/r) or DTG comprise Uganda's second-line regimen.[22] However, Only 54.2% of the analysed sequences encoded viruses predicted as susceptible to both drugs in a combination of either AZT+3TC or TDC+3TC, raising concerns on the efficacy of NRTIs (especially 3TC) in second-line regimen in settings with increased prevalence of NRTI resistance. The detected NNRTI mutations K103N, P225H, and G190A that reflect the extensive use of NNRTI-based regimens have been known to compromise ART activity of any EFV/NVP-based regimens over the years.[26,44] The presence of cross-resistance mutations that include L100I and Y181C among others, suggests that the efficacy of second-generation NNRTIs not used in our setting (Rilpivirine and Etravirine) is already compromised, hence further supporting the transition to DTG. The PI mutation M46L detected in one participant's sequence is usually a transmitted rather than an acquired HIV DRM,[28,47] suggesting a possibility of undisclosed prior exposure to PIs or of transmitted drug resistance to this individual. However, M46L is incapable of reducing the susceptibility to the existing PIs on its own unless when combined with other major PI mutations, reducing viral susceptibility to all PIs except darunavir.[28] All the 48 HIV sequences of VF cases encoded viruses susceptible to the ritonavir-boosted PIs, predicting an appreciable efficacy of PIs if used in this setting.

Although we did not find any statistically significant predictors of both virological non-suppression and acquired HIVDR, sub-optimal adherence, though not assessed here could have played a role. For instance, 18.7% of VL non-suppressors lacked SDRMs implying sub-optimal adherence could have jeopardized ART success. More to that, 97.8% were initiated on efavirenz, whose associated neuropsychiatric events such as dizziness, hallucinations,

and psychosis are known to elicit treatment discontinuation, thus compromising adherence.[48,49] Generally, our findings are broadly consistent with global trends showing growing HIV-1 drug resistance with increasing ART coverage.[18,20] Uganda's ART coverage has increased by three-fold in the last five years and this probably explains the increasing HIVDR levels we currently observe.[5,18]

The potential limitations of this study were that being a cross-sectional study, the analyses did not include participants lost to follow-up which could have resulted in an overestimated VS. Also, Sanger sequencing omits low-frequency DRMs whose relevance we did not explore. We genotyped only individuals with VLs ≥1000 copies/mL and yet HIVDRMs have been detected in individuals with VLs<1000 copies/mL.[50] We could not sequence 16/64 VF cases, both events possibly leading to underestimation or overestimation of HIVDR prevalence. Furthermore, we never assessed for pretreatment drug resistance which potentially drives VF or subsequent accumulation of additional resistance mutations over time post-ART initiation. Though the high prevalence of NNRTI-associated mutations in this study supports the current transition to DTG, we did not analyze for resistance to DTG, yet this could guide treatment to yield beneficial results to individuals on a DTG-containing regimen. Future advances in HIVDR surveillance in Uganda should promote HIVDR testing at low viremia (≤400 copies/mL) following the switch to a DTG-based first-line regimen.

Conclusion

The present study demonstrates a moderate level of VS in a cohort of FSWs in Uganda. The high prevalence of ADR highlights the need to timely switch VL non-suppressors to potent ART regimens guided by genotypic resistance testing and the need to strengthen adherence counseling. The observed high levels of NNRTI mutations support the current transition to dolutegravir, although, the elevated prevalence of NRTI mutations may compromise the recommended NRTI-containing second-line ART options.

Abbreviations

HIV-1: human immunodeficiency virus type l; ART: antiretroviral therapy; WHO: world health organization; NNRTI: non-nucleoside reverse transcriptase inhibitors; NRTI:

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nucleoside reverse transcriptase inhibitor; Pol: polymerase; VL: viral load; VF: virological failure; ADR: acquired drug resistance; RNA: ribonucleic acid; HIVDR: HIV drug resistance; FSW: female sex workers; LMICs: low and middle income countries; MoH: Ministry of Health; VS: virological suppression; PMTCT: prevention of mother-to-child transmission; TAMs: thymidine analog mutations. VHCT: voluntary HIV counseling and testing; LSHTM: London school of Hygiene and Tropical Medicine.

Ethics approval and consent to participate

Ethical approval for this study was granted by the Uganda Virus Research Institute-Research and Ethics Committee (UVRI-REC Federalwide Assurance [FWA] FWA No. 00001354) and the Uganda National Council for Science and Technology (UNCST FWA No. 00001293). All study participants provided written informed consent for their participation.

Consent for publication

Not applicable.

Availability of data and materials

Sequence data generated during the current study are available in GenBank repository, accession numbers: MH166811-MH166834, MH166836-MH166837, and MK499283-MK499323. The datasets generated and/or analysed during the study are not publicly available due to ethical impediment but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

FS and DS conceived the study; DS, PK, and FS designed the study; FS, SL, MN, SEN, FN DBL, NB, JO, DPK, DS, and PK performed the experiments; WS, YM, JS, RNN generated the data; FS, DS, JO, RNN analysed the data; FS, JO and DS wrote the first draft; DS and DPK supervised the study at all stages, DS, DBL, NB, and MN validated the sequencing reactions. All co-authors participated in writing, reviewing and approving the final manuscript.

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Figure 1: Study profile

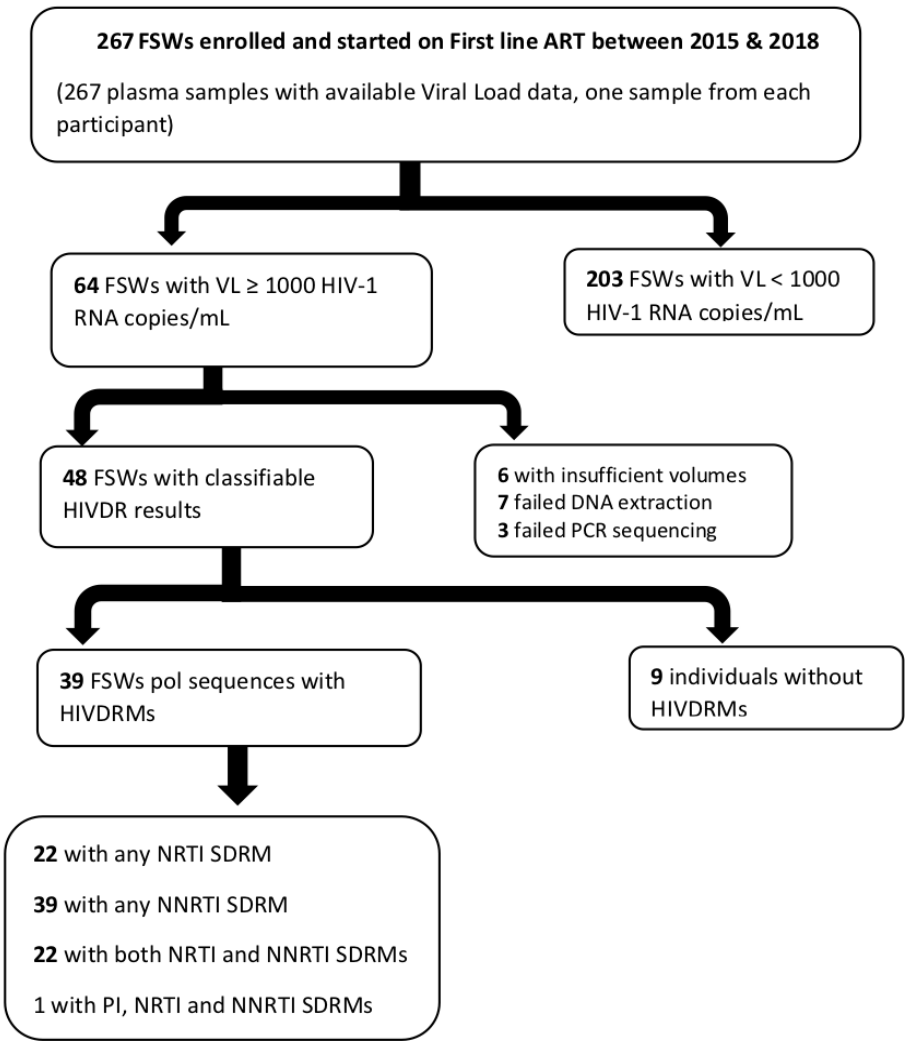

Figure 1: Study profile

HIVDRMs; HIV drug resistance mutations, ART; antiretroviral therapy, VL; viral load, Pol; polymerase, NRTI; Nucleotide/Nucleoside Reverse Transcriptase Inhibitor, NNRTI; Non-Nucleoside Reverse Transcriptase Inhibitor. SDRM; Surveillance drug resistance mutation; FSWs; Female sex workers

Figure 2: Prevalence of HIV acquired drug resistance by drug/drug class used among 48 virological non-suppressors

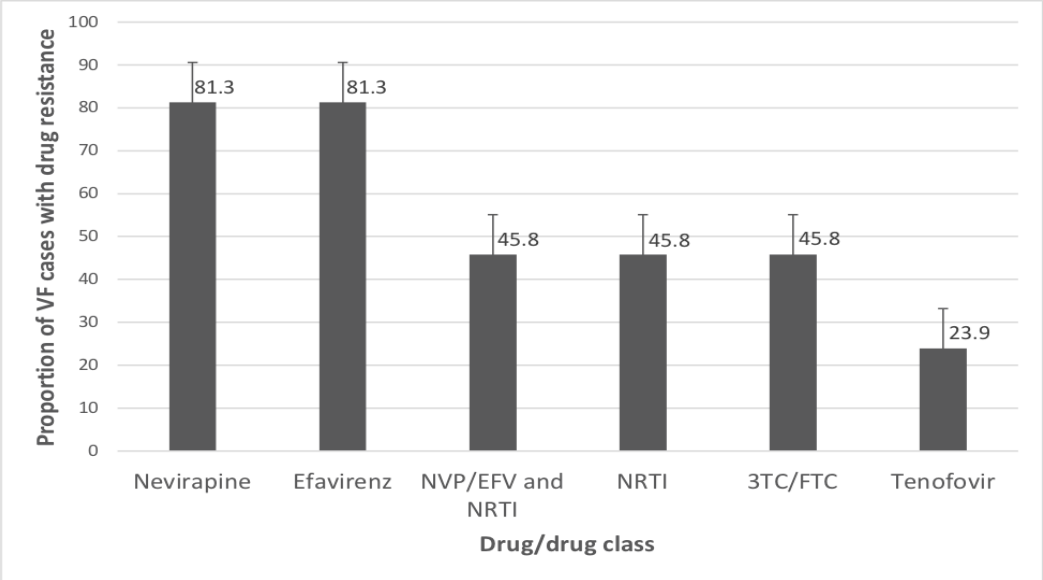

Figure 2: Prevalence of HIV acquired drug resistance by drug/drug class used among 48 virological non-suppressors

HIVDR was determined using Stanford HIVdb: Viral sequences with low-, intermediate-or high-level resistance were designated as resistant.

Acquired HIV drug resistance was defined as the presence of HIV variants designated as resistant to at least one of the recommended drugs in the NNRTI, NRTI and PI classes.

Prevalence of ADR was defined as the proportion of HIV sequences with resistant variants with the total number of analysed sequences (48) being the denominator.

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Figure 3: Predicted viral resistance to second-line ART drugs used in Uganda among 48 virological non-suppressors

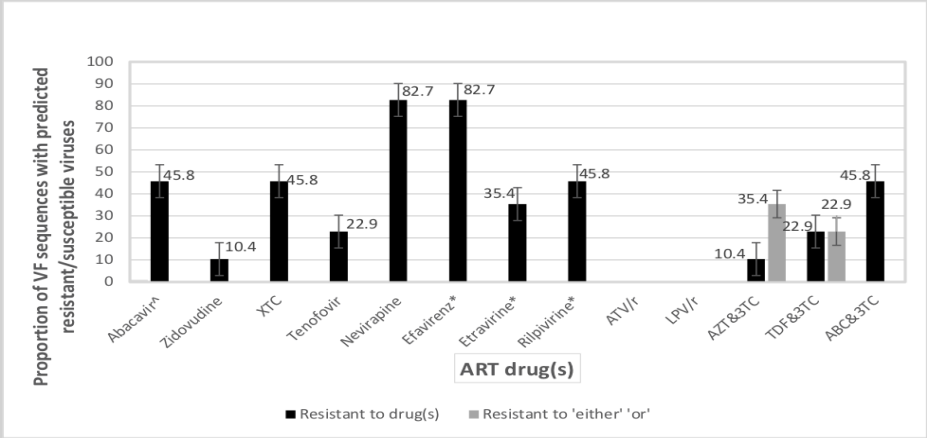

Figure 3: Predicted viral susceptibility and resistance to second-line ART drugs used in Uganda among the 48 virological non-suppressors

"Susceptible to" represents the proportion of HIV sequences with a DRM penalty score of ≤ 14 on the Stanford HIVdb algorithm. "Resistance to" represents the proportion of HIV sequences with a DRM penalty score ≥15. In both cases the denominator is the total number of HIV sequences analysed (48). For two-drug combinations, we subdivided (where applicable) predicted resistance into resistance to both drugs and resistance to either of the drugs but not to both.

^Abacavir is recommended as an alternative component (to Zidovudine) in the second-line regimens for only children below 10 years of age.

** The NNRTIs Etravirine, Rilpivirine and Efavirenz are **NOT** among the second-line ART regimens and the new national guidelines recommend phasing out all NNRTIs and replacing them with Dolutegravir. Their inclusion here is to emphasize on their reduced susceptibility.*

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Figure 4: Proportions and patterns of acquired HIV-1 drug resistance among participants experiencing viral load non-suppression

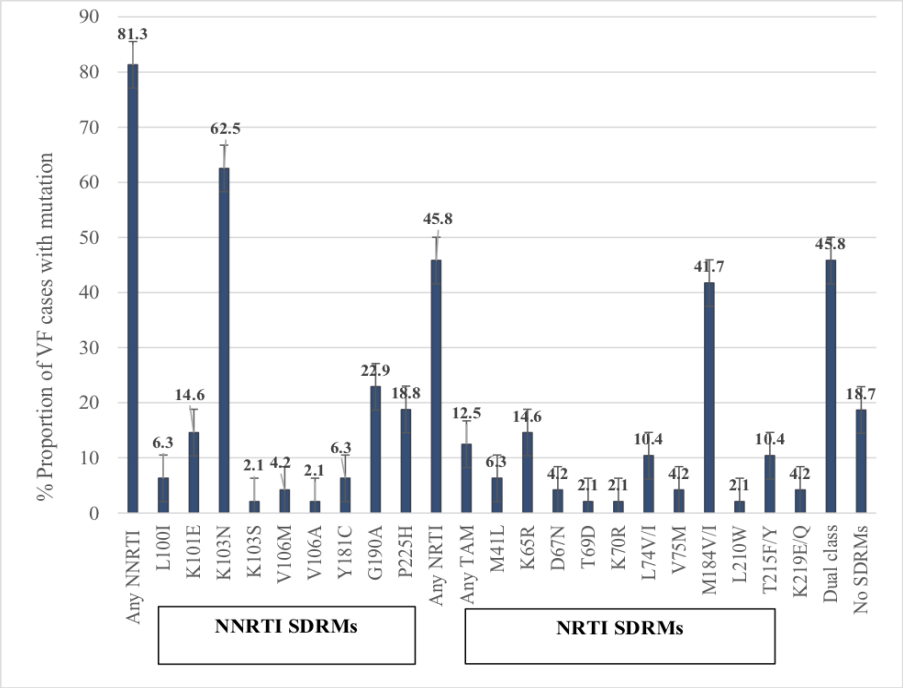

Figure 4. Proportions and patterns of acquired HIV-1 drug resistance among participants experiencing viral load non-suppression

SDRM; Surveillance drug resistance mutation, VF; Virological failure, NRTI; Nucleotide/Nucleoside Reverse Transcriptase Inhibitor, NNRTI; Non-Nucleoside Reverse Transcriptase Inhibitor

The Mutations represented here are those listed as SDRM according to Stanford HIV drug resistance database. The denominator used is 48 (the number of successfully sequenced VF cases).

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Table 1: Demographics and clinical characteristics of participants

N=267

Variable	Frequency	Percentage (%)
Age (years) Median 30 (IQR; 26-34)		
≤ 30	137	51.3
> 30	130	48.7
Education level		
Primary[1]	187	70.0
Secondary[2]	80	30.0
Marital status[α]		
Married	13	4.9
Separated*	198	75.0
Never married	53	20.1
First-line ART regimen		
AZT + 3TC + EFV	1	0.4
AZT + 3TC + NVP	4	1.5
TDF + 3TC + EFV	260	97.4
TDF + 3TC + NVP	2	0.7
Duration on ART (Months)		
< 6	67	25.1
6-12	158	59.2
13-24	32	12.0
≥ 25	10	3.7

**Separated, widowed or divorced*

[1]Either primary or no education, [2]Either Secondary, tertiary or higher education

Indicated symbol % in parentheses represents a percentage, TDF; tenofovir, 3TC; lamivudine, NVP; nevirapine, AZT; zidovudine, EFV; efavirenz, IQR; interquartile range.

[α]Marital status missing for 3 participants.

Table 2: Virological suppression prevalence among participants on first-line ART in Uganda

	Virological outcomes				
	Duration on ART				**Total**
	< 6 months	**≥ 6 months**			
		6 - 12	**12 - 24**	**≥ 25**	
VL <1000 RNA copies/mL	47	135	20	1	203
VL ≥1000 RNA copies/mL	20	23	12	9	64
Total	**67**	**158**	**32**	**10**	**267**
Median Log10 VL (IQR)	4.3 (3.8-5.1)	4.7 (3.9-5.3)	4.1 (3.4-4.8)	3.7 (3.3-4.7)	4.4 (3.7-5.1)
Virological suppression prevalence	47/67 (70.1%)	135/158 (85.4%)	20/32 (62.5%)	1/10 (10.0%)	203/267 (76.0%)
95% Confidence Interval	57.7-80.7	79.0-90.5	43.7-78.9	0.3-44.5	70.4-81.0

(N=267)

VL; viral load, ART; antiretroviral therapy, IQR; interquartile range

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Table 3: Factors associated with viral load non-suppression in a cohort of women at high risk of HIV infection

(N=267)

	Univariate analysis				**Multivariate analysis**		
Variables	VL non-suppression (n/N)	Crude OR	95% CI.	*P*-value	Adjusted OR**	95% CI	*P*-value
Age (years)[β]				0.041			0.084
> 30	24/130	Ref			Ref		
≤ 30	40/137	1.8	1.02-3.24		1.7	0.93-3.08	
Marital status[α]				0.147			0.292
Married	4/13	Ref			Ref		
Separated*	42/198	0.6	0.18-2.06		0.6	0.17-2.00	
Never married	18/53	1.2	0.31-4.28		0.9	0.25-3.63	
Education level				0.568			
Secondary[2]	21/80	Ref					
Primary[1]	43/187	0.8	0.46-1.53				

CI; confidence interval, OR; odds ratios, Ref; reference group, VL; viral load

VL non-suppression; defined as VL ≥1000 HIV-1 RNA copies/mL

*** Only variables with a p-value of ≤ 0.25 included in this analysis, β –a priori confounder.*

**Separated, widowed or divorced*

[1]Either primary or no education, [2]Either Secondary, tertiary or higher education.

[α]Marital status missing for 3 participants.

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This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Table 4: The distribution of surveillance DRMs in 39 virological non-suppressors

S/No.	Sequence Id.	NRTI SDRMs	NNRTI SDRMs	PI SDRMs
1	V17_11_001	D67N, T69D, K70R, M184V, T215FV, K219Q	K103S, G190A, P225H	None
2	V17_11_003	K65R, M184V	K101E, Y181C, G190A	None
3	V17_11_004	M184V	V106A, P225H	None
4	V17_11_005	M184V, T215FI	K101E, G190A	None
5	V17_11_006	None	K103N, P225H	None
6	V17_11_008	K65R, M184V	K103N	None
7	V17_11_009	L74I, M184V	K103N, P225H	M46L
8	V17_11_010	M41L, D67N, L74V, M184V, L210W, T215Y	K103N, Y181C, G190A	None
9	V17_11_011	None	K103N	None
10	V17_11_012	L74I, M184I	K103N, Y181C, P225H	None
11	V17_11_013	M184V	K101E, G190A	None
12	V17_11_017	M184V	K103N	None
13	V17_11_018	M184V	K103N	None
14	V17_11_020	None	K103N	None
15	V17_11_022	M41L, M184V, T215F	G190A	None
16	V17_11_024	K65R, V75M, M184V	L100I, K103N	None
17	V17_11_025	None	K101E	None
18	V17-11-026	M184I	K103N, P225H	None
19	V17-11-031	M41L, M184V, T215F	K103N	None
20	V18_08_072	None	K103N	None
21	V18_08_074	None	K103N	None
22	V18_08_080	L74V, M184IV	L100I, K101E, K103N, G190A	None
23	V18_08_084	K65R, V75M, M184V	L100I, K103N	None

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24	V18_08_093	None	K103N	None
25	V18_08_096	None	K103N	None
26	V18_08_097	K65R	K103N, V106M	None
27	V18_08_099	K65R, M184V	K103N, P225H	None
28	V18_08_176	None	K103N	None
29	V18_08_178	None	K103N	None
30	V18_08_181	None	K103N	None
31	V18_08_183	None	K103N	None
32	V18_08_184	None	K103N	None
33	V18_08_185	None	K103N	None
34	V18_08_189	None	K101E, G190A, P225H	None
35	V18_08_190	L74I, M184V	K103N, P225H	None
36	V18_08_193	K65R	K103N, V106M	None
37	V18_08_196	M184V, K219E	K103N, G190A	None
38	V18_08_197	None	K103N, G190A	None
39	V18_08_199	None	K101E, G190A	None

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Table 5: Factors associated with acquired drug resistance among participants with viral load non-suppression (VL ≥1000 RNA copies/mL)

	Univariate analysis			
Variables	ADR (n/N)	Crude OR	95% CI.	*P*-value
Age (years)				0.067
> 30	19/20	Ref		
≤ 30	20/28	0.1	0.01-1.15	
Education level				0.532
Secondary[2]	13/17	Ref		
Primary[1]	26/31	1.6	0.37-6.98	
Marital status				0.625
Married	2/3	Ref		
Separated*	28/33	2.8	0.21-37.03	
Never married	9/12	1.5	0.10-23.07	
Duration on ART				0.409
<6 months	8/11	Ref		
6+ months	31/37	1.9	0.40-9.49	
RNA Viral load				0.340
≤ 4.0 Log10 copies/mL	6/9	Ref		
> 4.0 Log10 copies/mL	33/39	2.8	0.54-14.12	

**Separated, widowed or divorced; Ref: reference group*

[1]Either primary or no education, [2]Either Secondary, tertiary or higher education.

ADR; acquired drug resistance, OR; odds ratio, CI; confidence interval, ART; antiretroviral therapy

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