HHS Public Access

Author manuscript

HIV Med. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

HIV Med. 2021 March ; 22(3): 201–211. doi:10.1111/hiv.13006.

Virologic failure and HIV drug resistance among adults living with HIV on second-line antiretroviral therapy in the Asia-Pacific

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Abstract

Objectives—To assess second-line antiretroviral therapy (ART) virologic failure and HIV drug resistance-associated mutations (RAMs), in support of third-line regimen planning in Asia.

Methods—Adults >18 years on second-line ART for ≥6 months were eligible. Cross-sectional data on HIV viral load (VL) and genotypic resistance testing were collected or testing was conducted between July 2015 and May 2017 at 12 Asia-Pacific sites. Virologic failure (VF) was defined as VL>1000 copies/mL with a second VL >1000 within 3–6 months. FASTA files were submitted to Stanford HIVdb and RAMs compared to the IAS-USA 2019 mutations list. VF risk factors were analyzed using logistic regression.

Results—Of 1378 patients, 74% were male and 70% acquired HIV through heterosexual exposure. At second-line switch, median age was 37 years (IQR 32–42) and median CD4 count was 103 cells/μL (IQR 43.5–229.5); 93% received regimens with boosted protease inhibitors (PI). Median duration on second-line was 3 years. Amongst 101 patients (7%) with VF, CD4 >200 cells/μL at switch (OR=0.36, 95%CI 0.17–0.77 vs. CD4 ≤50), and HIV exposure through male-male sex (OR=0.32, 95%CI 0.17–0.64 vs. heterosexual) or injecting drug use (OR=0.24, 95%CI 0.12–0.49) were associated with reduced VF. Of 41 (41%) patients with resistance data, 80% had

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at least one RAM to non-nucleoside reverse transcriptase inhibitors (NNRTI), 63% to NRTIs, and 35% to PIs. Of those with PI RAMs, 71% had ≥2.

Conclusions—There were low proportions with VF and significant RAMs in our cohort, reflecting the durability of current second-line regimens.

Keywords

Second-line antiretroviral therapy; virologic failure; drug resistance; HIV; Asia

Introduction

Efforts to expand antiretroviral therapy (ART) coverage for all people living with HIV (PLHIV) have resulted in an estimated 23.3 million PLHIV on ART globally by the end of 2018, of whom 3.2 million are in the Asia-Pacific region (1). With increasing numbers of PLHIV on ART and longer durations of therapy, first-line treatment failures have become more common, and increasing numbers of PLHIV have initiated second-line ART. Whilst earlier estimations of the proportion of patients on second-line ART in resource-limited settings were between 1–5% (2), in a more recent study of nearly 17,000 HIV-positive adults on ART in seven countries in Asia, 19% were on a second-line regimen (3).

Until recently WHO HIV treatment guidelines recommended a second-line treatment regimen of two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted protease inhibitor (PI) as part of public health approach (4). Current WHO guidelines recommend two NRTIs and dolutegravir as the preferred second-line regimen (5). Reported virologic failure (VF) rates among adults on second-line therapies vary depending on the definitions of VF used, subpopulations studied, and measurement time points. Rates of VF among adults on second-line ART between 8–41% have been reported in resource-limited settings (6). In addition, previous studies suggest poor adherence rather than resistance as the cause of VF during second-line ART (6, 7).

WHO guidelines recommend routine viral load (VL) monitoring (4) and expanding HIV drug resistance (DR) testing (8). However, VL monitoring is not consistently available across the region, and access to genotype testing to inform optimal ART choice is severely constrained (9, 10). The WHO has also recommended that national programs develop policies for third-line ART that includes antiretroviral drugs (ARVs) such as darunavir, raltegravir, and dolutegravir; however, access remains restricted by high cost and implementation barriers (11–13). Maximizing the durability of second-line regimens, quantifying needs for third-line therapy and reducing the costs of newer antiretroviral regimens are emerging global priorities (14–16).

As increased prevalence of antiretroviral resistance threatens the maintenance of virally suppressive ART, a broader understanding of the durability of second-line ART and HIV drug resistance-associated mutations (RAMs) would facilitate evidence-based regional projections of third-line regimen needs and advocacy efforts around optimizing life-long ART. We therefore conducted a cross-sectional study to assess VF and RAMs among adults

living with HIV on second-line ART within the TREAT Asia HIV Observational Database (TAHOD), a regional cohort study of IeDEA Asia-Pacific.

Methods

Study design and study population

A combination of prospective cross-sectional data and retrospective data collection were used to conduct this study. Participating HIV treatment sites were classified as *"testing sites"* if they did not perform routine viral load (VL) and/or genotypic resistance testing and these tests were obtained for the purposes of the study. *"Data sites"* were those where routine VL and/or genotypic resistance testing were already conducted, and data could be extracted from medical records. Six testing sites participated in Cambodia (N=1), Indonesia (N=2), Malaysia (N=1), and Vietnam (N=2). Six data sites participated in Hong Kong SAR (N=1), India (N=1), Japan (N=1) Philippines (N=1), Singapore (N=1), and South Korea (N=1). Patients were eligible for inclusion into the study if they were ≥18 years old, had been on second-line ART for at least six months, and had not received mono- or dual-antiretroviral regimens as first-line ART.

Data collection and definitions

At testing sites, VL and genotypic resistance testing was performed prospectively on eligible patients between June 2016 and May 2017. Patients with a first VL >1000 copies/mL were required to have a repeat VL measured within three months. All those with a second VL >1000 copies/mL underwent genotypic resistance testing. Genotyping was performed using Sanger Sequencing. At data sites, available VL and genotypic resistance testing data between July 2015 and December 2016 were retrospectively collected from the medical records of eligible participants. Viral load and genotypic resistance testing at data sites was conducted in line with national or local guidelines. This ranged from viral load testing every 3, 6 or 12 months on virologically suppressed, stable patients. Indications for genotypic resistance testing ranged from a single VL >500 copies/mL, a single VL >1000 copies/mL, or two consecutive VL >1000 copies/mL within 3 months, after ruling out other causes such as poor adherence. Demographic, clinical and laboratory data were captured directly into a study Case Report Form (CRF) at testing sites, and into the study electronic database at data sites.

For this analysis, virologic failure was defined as (i) testing sites: VL >1000 copies/mL with a second confirmed VL measurement of >1000 copies/mL within three months; (ii) data sites: VL >1000 copies/mL with a second confirmed VL measurement of >1000 copies/mL within six months or a single VL >1000 copies/mL with evidence of at least one RAM on subsequent genotype resistance testing. Genotypic sequence (FASTA) files were submitted to the Stanford University HIV Drug Resistance Database (Stanford HIVdb) version 8.8 for genotyping (17) and the Rega HIV-1 Subtyping Tool version 3 for subtyping (18, 19). RAMs were defined according to the IAS-USA 2019 mutations list (20), excluding minor protease inhibitor (PI) mutations. Evidence of HIV drug resistance on genotypic resistance testing was interpreted as being the presence of any RAM from this list.

Statistical analysis

Factors associated with VF were analyzed using logistic regression. World Bank country income group was adjusted *a priori*. Variables with p <0.1 in the univariate analysis were included in the multivariate model using backward stepwise selection process. Variables with p <0.05 in the final multivariate model were considered statistically significant. The proportions and patterns of RAMs were reported descriptively with confidence intervals calculated using the exact binomial method. To account for variations in VL testing patterns and potential bias in the definitions of VF used, we conducted a sensitivity analysis defining virologic failure as a single VL >1000 copies/mL, irrespective of subsequent viral load or genotype resistance testing, for both testing and data sites. Data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata software version 14.2 (Stata Corp., College Station, TX, USA).

Ethical considerations

Ethics approvals were obtained from respective local institutional review boards of all participating sites, the data management and biostatistical center (The Kirby Institute, UNSW Sydney), and the coordinating center (TREAT Asia/amfAR). Written informed consent was obtained from testing site participants prior to enrolment. For data sites where anonymized data were collected, written informed consent was obtained only if required by the local ethics committee.

Results

A total of 642 patients from six testing sites and 736 patients from six data sites were eligible for inclusion in the study. Three patients from testing sites were lost to follow up during the study. Of the total 1378 patients included, there were 1023 males (74%), and 964 (70%) acquired HIV through heterosexual contact (Table 1). The median age at switch to second-line ART was 37 years (IQR 32–42), median CD4 cell count at switch was 103 cells/μL (IQR 43.5–229.5), and 1281 (93%) were on second-line regimens with nucleoside reverse transcriptase inhibitors (NRTI) and boosted protease inhibitors (PI). The main NRTIs used during second-line were lamivudine (1016/1336, 76%), tenofovir (972/1336, 73%), and emtricitabine (243/1336, 18%). The main boosted PIs used in second-line were lopinavir (735/1345, 55%) and atazanavir (529/1345, 39%). The main integrase inhibitors used in second-line were raltegravir (65/78, 83%) and dolutegravir (8/78, 10%). Of the 1378 study participants, 873 (63%) had switched to second-line ART due to virologic failure, 221 (16%) due to virologic and immunologic failure, and 233 (17%) due to clinical failure alone or in combination with virologic and/or immunologic failure. The median duration on second-line ART up to the time of the first VL test during the study period was 3 years (IQR 1–5).

Virologic failure

Confirmed VF occurred in 101 (7%) patients, 26 (26%) were from testing sites, and 75 (74%) were from data sites. Factors associated with VF are shown in Table 2. In the multivariate analysis, adjusting for Word Bank country income group, those with HIV exposure through male-to-male sex (OR=0.29, 95%CI 0.10–0.83, p=0.020) and injecting drug use (IDU) (OR=0.22, 95%CI 0.08–0.60, p=0.003) were less likely to have VF

compared those exposed to HIV through heterosexual sex. Patients with CD4 cell count >200 cells/μL at the time of switching to second-line ART were less likely to fail compared to those with CD4 ≤50 cells/μL (OR=0.36, 95%CI 0.17–0.77, p=0.008).

In our sensitivity analysis on the 248 (18%) of patients with only a single VL >1000 copies/mL we found that HIV exposure through male-male sex (OR=0.32, 95%CI 0.17–0.64, p=0.001), IDU (OR=0.24, 95%CI 0.12–0.49, p <0.001), and other or unknown HIV exposure (OR=0.50, 95%CI 0.27–0.91, p=0.024) were all less likely to have a single VL >1000 copies/mL compared to heterosexual mode of exposure (Table 3). Patients who lived in high-income countries were less likely to experience a single VL >1000 copies/mL compared to those who lived in low and upper-middle income countries (OR=0.38, 95%CI 0.17–0.84, p=0.017). CD4 cell count at time of switch to second-line was not associated with a single VL >1000 copies/mL in this analysis.

HIV subtypes and drug resistance-associated mutations of patients with virologic failure

Of the 101 patients with confirmed VF, 41 (41%) patients had a FASTA file available: 17/41 (41%) were from testing sites, and 24/41 (59%) were from data sites. Of these, 39 (95%) had genotypic resistance test results for both reverse transcriptase (RT) and protease (PR) gene regions, with four (4.0%) with integrase gene results. Overall, there were 40 RT-gene regions, 40 PR-gene regions, and 4 integrase-gene regions available for genotyping. Predominant HIV-1 subtypes consisted of subtype C (20/41, 49%), A1 (9/41, 22%), and CRF01_AE (7/41, 17%).

Of the 41 patients with FASTA files available, 40 were on an NRTI+PI-based second-line regimen. A total of 34/41 (83%) patients had at least one RAM. Including only patients with the specific gene region available in the denominator, 32 of 40 (80%) had a non-nucleoside reverse transcriptase inhibitor (NNRTI) RAM, 25 of 40 (63%) had an NRTI RAM, 14 of 40 (35%) had a PI RAM, and 0 of 4 (0%) had an integrase strand transfer inhibitor (INSTI) RAM. There were 13/39 (33%) patients with both NRTI and major PI RAMs. Among patients with major PI RAMs, 4/14 (29%) had one RAM, 5/14 (36%) had two RAMs, and 5/14 (36%) had three or more RAMs.

The most common NNRTI RAMs were K103N (10/40, 25%) and Y181C (10/40, 25%). The most common NRTI RAMs were M184V (22/40, 55%), M41L (14/40, 35%), and D67N (11/40, 28%) (Figure 1). The most common PI RAMs were I50L (4/40, 10%), Q58E (4/40, 10%), N88S (4/40, 10%), and L90M (4/40, 10%).

Of the 60 patients with confirmed VF for whom FASTA files were not available, 51 were from data sites. These FASTA files were not available as sites had difficulty retrieving historical FASTA files due to the retrospective nature of the data collection from the data sites

When we allowed for inclusion of FASTA files from those with a single VL >1000 copies/mL, an additional 13 patients had FASTA files available. As with those with confirmed VF, the most common HIV-1 subtypes were subtype C, CRF01_AE and A1. Compared to those with confirmed VF, similar proportions of those with a single VL >1000

copies/mL had at least one RAM (70% vs. 83%), an NNRTI RAM (70% vs. 80%), an NRTI RAM (54% vs. 60%), a PI RAM (30% vs. 35%), and an INSTI RAM (0% vs. 0%). Patterns of RAMs were also similar to those with confirmed VF and are presented in Figure 2.

Discussion

In our study of adults on second-line ART in the Asia-Pacific region, the rate of virologic failure was 7%. A CD4 cell count >200 cells/μL at switch to second-line ART, and MSM and IDU HIV exposure were associated with a reduced odds of VF. Of the 41% of VF patients with FASTA files available, almost all (40/41) were on an NRTI + PI second line regimen and 62% had NRTI RAMs, 36% had PI RAMs, and 33% had both NRTI and PI RAMs. Of those with PI RAMs, 72% had ≥2. The most common NNRTI RAMs were K103N and Y181C. The most common NRTI RAMs were M184V, M41L, and D67N. The most common PI RAMs were I50L, Q58E, N88S, and L90M.

The 7% virologic failure rate amongst adults on second line ART for a median of 3 years in our cohort is lower than that documented by other studies in Asia using similar definitions of VF, for example recent studies of adults living with HIV on second line ART in India and Vietnam found rates of VF of 15.8% and 9.5% respectively (21, 22). The relatively low rate of VF we observed is encouraging and likely a reflection of the level of care available at our participating sites, which are primarily tertiary care or referral centers with the resources to support VL monitoring and drug resistance testing, as well as support for treatment adherence. The substantially higher proportion of patients with VF from data sites might be a reflection of a more complicated case mix of patients seen at data sites, ascertainment bias, or sociodemographic or clinical differences between data site and testing site study populations, such as age, duration on second line ART, proportion on second line INSTI regimens, and the proportion on second line ART due to VF.

Other studies in the Asia region have identified increasing age, higher baseline VL, poorer ART adherence, and specific second-line ART regimens such as non-lopinavir, non-atazanavir PI regimens, as risk factors for second-line failure (21–25). However, our observation of associations between HIV exposure through male-male sex and IDU with reduced odds of second-line VF has not been frequently reported (14, 26). This association may reflect the increasing focus of regional HIV services and ART programs on key populations in more recent years.

The proportion of second-line VF patients with NNRTI RAMs in our study was comparable to levels documented in other studies in Asia; however, we found substantially lower proportions of patients with NRTI and PI RAMs (21, 22, 27–29). With approximately one-third of genotyped patients who had confirmed viral failure on second-line ART having no NRTI RAMs, and nearly two-thirds having no major PI RAMs, our study also emphasizes that VL elevation alone is not enough to switch to a new regimen. It also highlights the importance of adherence strengthening prior to considering costly alternative treatment options and a potential need for broader access to HIV DR testing in the region in order to identify those patients that truly require switching to third-line ART regimens (30–32). A recent study of an adult South African cohort found that many patients with VF on a boosted

PI resuppressed after a period of intense adherence counseling (33). Although cost and logistical challenges mean that individualized genotype resistance testing in support of treatment regimen optimization remains unfeasible in the region, an analysis of strategies for patients failing second-line ART found that genotype assays and an appropriate third-line regimen were cost-effective in resource-limited settings, compared to a population-based approach that included no genotyping (34). A South African study of adults on lopinavir-based second-line ART regimen that found the majority failed due to poor drug exposure, highlights the potential value of using hair and plasma lopinavir concentrations in diagnosing the cause of VF, and of targeted genotypic resistance testing in patients where VF is not explained by poor drug exposure (35).

As documented in other resource-limited settings, the high prevalence of NNRTI mutations amongst those genotyped in our cohort may be an indication of extensive drug resistance prior to the start of second-line ART (36). K103N is associated with ongoing resistance to nevirapine and efavirenz (37), and its high frequency amongst those genotyped in our cohort suggests recycling these widely used NNRTIs in third-line regimens in Asia might be limited. In addition, the high prevalence of etravirine-associated mutations such as Y181C, G190A, and A98G raise concerns around continued susceptibility to this newer generation NNRTI (30) and potential limitations to its use in third-line therapy.

The most common NRTI and PI RAMs amongst those genotyped in our cohort are consistent with the RAMs identified in other studies from the region (22, 27, 38). M184V, the predominant NRTI mutation found in our study, has been shown to confer high-level resistance to lamivudine and emtricitabine (39). The high prevalence of thymidine analogue mutations we observed supports the need for better access to routine viral load testing in the region as these mutations suggest delayed detection of treatment failure and a patient remaining on a failing first-line ART regimen for some time (36, 40). Whilst found in a lower proportion than documented in other cohorts, the small proportion of those genotyped with a K65R mutation is of note as it is associated with multi-NRTI resistance and a high level of resistance to tenofovir (41, 42).

Maintaining patients with virologic failure on a failing second-line PI/r-based regimen raises concerns over the development of resistance to third-line PI options such as darunavir. Whilst data from Asia is limited, a recent study in South Africa found that 57% of participants in a third-line antiretroviral therapy program had some degree of resistance to darunavir at third-line initiation (43), and a study of patients failing second-line ART in Nigeria estimated that patients developed a median of 0.6 PR mutations for every 6 months on a failing second-line regimen (44). Common PI mutations among our cohort, such as L90M, M46I and V82A have been found to be associated with resistance to nelfinavir and sanquinavir, indinavir, and lopinavir, respectively (45), a concern given 53% of our cohort were on second-line lopinavir. In addition, the L76V mutation found in a small proportion of our cohort is of concern as it can confer cross resistance to PIs such as darunavir that can be used for third-line therapy in resource limited settings (45–47).

Discussion and interpretation of our results should take account of a number of limitations. The study sites are mostly tertiary care and referral centers, and therefore not necessarily

representative of all HIV-related clinical care centers within a country. A substantial number of FASTA files were not available for analysis, raising concerns around the generalizability of our findings. Data on adherence and the results of previous HIV DR tests were not available, limiting the interpretation of study results because the contribution of suboptimal adherence to virologic failure could not be explored and we were not able to determine which of the prevalent RAMs might have been present prior to the start of second-line ART. It should also be noted that prediction of clinical outcomes from genotypic resistance testing is challenging, and the utility of resistance testing in the public health approach to ART management remains uncertain (48). Nevertheless, because of the number of sites involved, countries represented, and the strict definition of second-line ART virologic failure applied, we believe our results are a reasonable reflection of second-line VF rates, associated factors, and RAMs in the Asia-Pacific region.

In conclusion, only 7% of adults on second-line ART in our Asia-Pacific regional cohort had confirmed virologic failure, but our study suggests that between one-third to over half of them had some level of resistance to the medicines they were being treated with. Broader implementation of routine viral load monitoring would identify those in need of enhanced adherence support before the emergence of substantial HIV drug resistance and treatment failure necessitated the use of costly resistance testing and third-line ART regimens.

Acknowledgements

The authors are grateful to the study participants and all site staff for their commitment to the study. The TASER-2 Study Group: PS Ly, V Khol, National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia; MP Lee, PCK Li, W Lam, YT Chan, Queen Elizabeth Hospital, Hong Kong SAR; N Kumarasamy, C Ezhilarasi, Chennai Antiviral Research and Treatment Clinical Research Site (CART CRS), VHS-Infectious Diseases Medical Centre, VHS, Chennai, India; TP Merati, DN Wirawan, F Yuliana, KT Amijaya, Faculty of Medicine Udayana University & Sanglah Hospital, Bali, Indonesia; E Yunihastuti, D Imran, A Widhani, A Citra, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; J Tanuma, S Oka, T Nishijima, National Center for Global Health and Medicine, Tokyo, Japan; A Kamarulzaman, I Azwa, Tan Chin Heng, N Raman, University Malaya Medical Centre, Kuala Lumpur, Malaysia; R Ditangco, MK Pasayan, ML Mationg, Research Institute for Tropical Medicine, Muntinlupa City, Philippines; OT Ng, PL Lim, LS Lee, PS Ohnmar, Tan Tock Seng Hospital, Singapore (note: OT Ng was also supported by the NMRC Clinician Scientist Award (MOH-000276), which had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.); JY Choi, Na S, JM Kim, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; KV Nguyen, HV Bui, DTH Nguyen, DT Nguyen, National Hospital for Tropical Diseases, Hanoi, Vietnam; CD Do, AV Ngo, LT Nguyen, Bach Mai Hospital, Hanoi, Vietnam; AH Sohn, JL Ross, B Petersen, TREAT Asia, amfAR - The Foundation for AIDS Research, Bangkok, Thailand; MG Law, A Jiamsakul, R Bijker, D Rupasinghe, The Kirby Institute, UNSW Sydney, NSW, Australia.

Funding support was provided through a grant to amfAR, The Foundation for AIDS Research from ViiV Healthcare, and a grant from the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, and the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Fogarty International Center, as part of the International Epidemiology Databases to Evaluate AIDS (IeDEA; U01AI069907). The Kirby Institute is funded by the Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, UNSW Sydney. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the governments or institutions mentioned above.

Conflicts of Interest

AHS has received grants to her institution from ViiV Healthcare. ML has received grants to his institution from Gilead Sciences, Janssen Cilag and ViiV Healthcare. The other authors declare no conflicts of interest related to this study.

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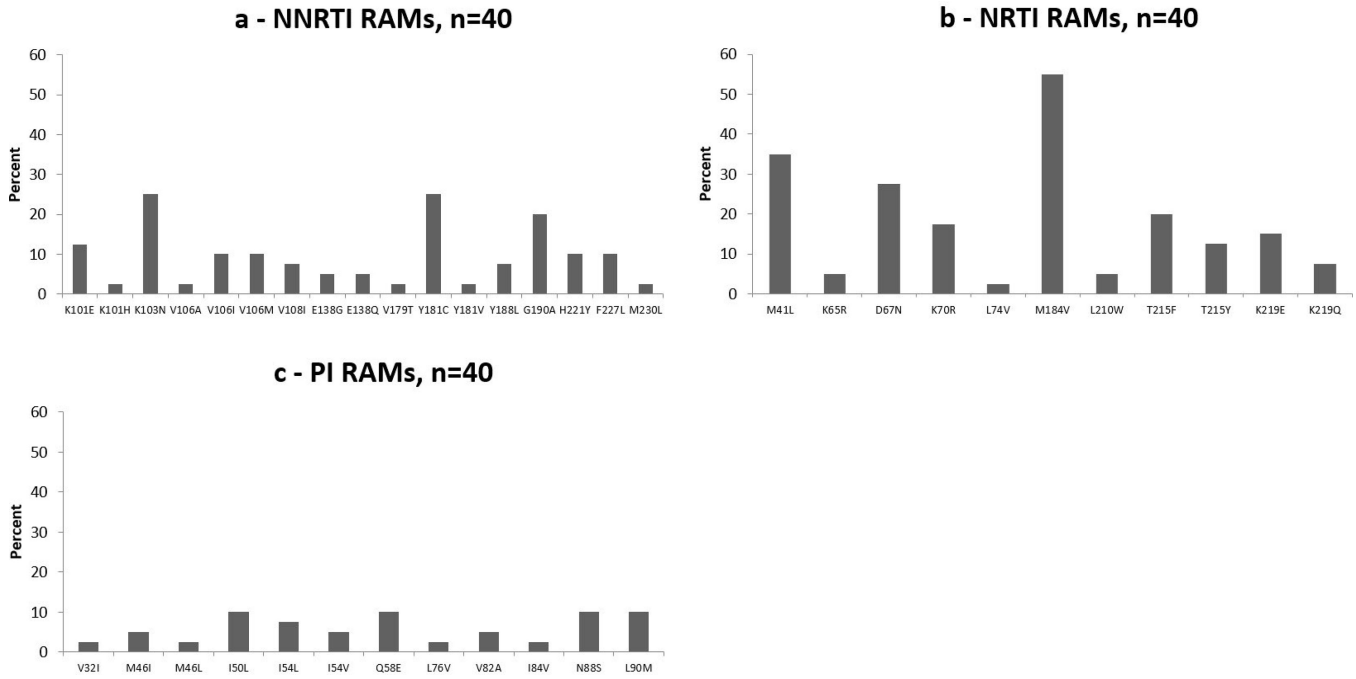

Figure 1:

Resistance-associated mutations among those with confirmed virologic failure on second-line antiretroviral therapy

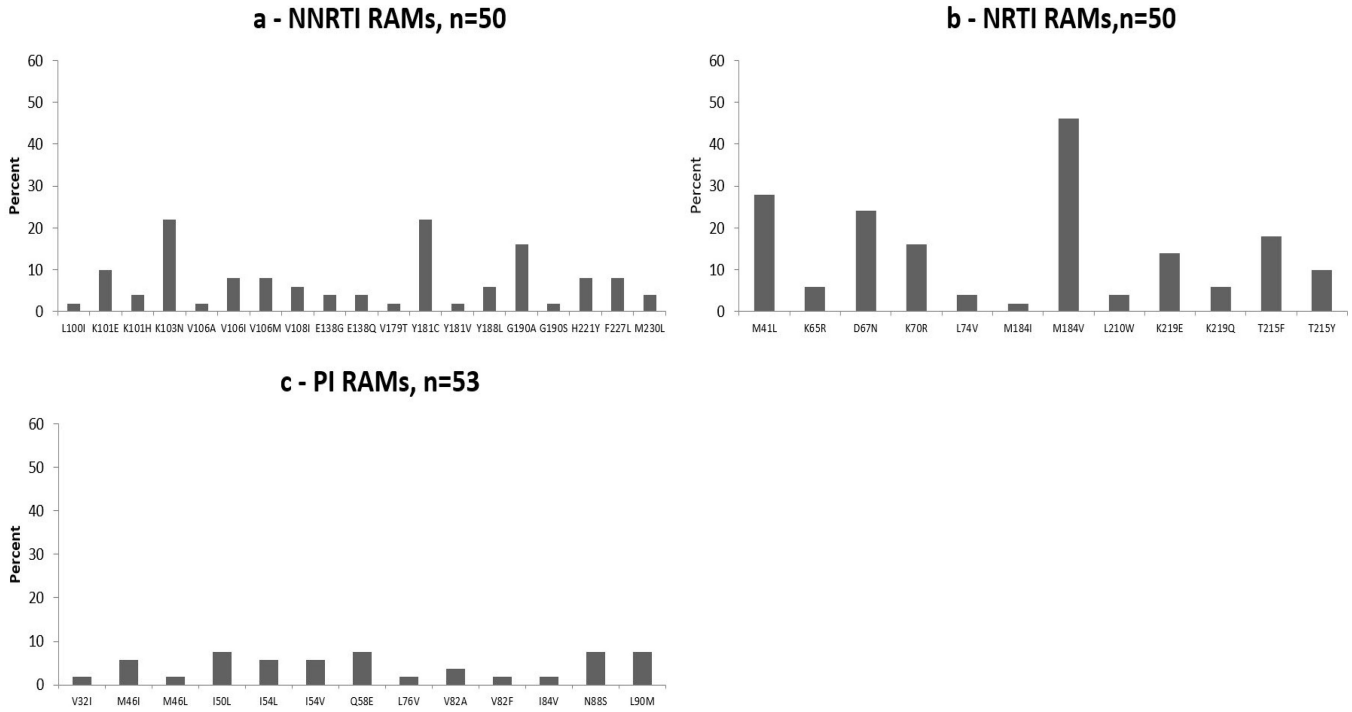

Figure 2:

Resistance-associated mutations among those with a single VL >1000 copies/mL on second-line antiretroviral therapy

Table 1:

Patient characteristics

	Total patients (%) N =1378	Data site patients (%) N=736	Testing site patients (%) N=642
Age at switch to second-line ART (years)	Median =37, IQR (32–42)	Median =39, IQR (34–44.5)	Median =44, IQR (30–39)
≤30	290 (21)	113 (15)	177 (28)
31–40	645 (47)	316 (43)	329 (51)
41–50	337 (24)	231 (31)	106 (17)
>50	106 (8)	76 (10)	30 (5)
Duration on second line ART (years)	Median = 3, IQR (1–5)	Median = 2, IQR (1–5)	Median = 3, IQR (2–6)
Sex			
Male	1023 (74)	570 (77)	453 (71)
Female	355 (26)	166 (23)	189 (29)
HIV mode of exposure			
Heterosexual contact	964 (70)	570 (77)	394 (61)
Male-male sex	134 (10)	91 (12)	43 (7)
Injecting drug use	172 (12)	5 (1)	167 (26)
Other/Unknown	108 (8)	70 (10)	38 (6)
CD4 at switch to second-line (cells/μL)	Median =103, IQR (43.5–229.5)	Median =178.5, IQR (70–306)	Median =67.5, IQR (27–149)
≤50	298 (22)	81 (11)	217 (34)
51–100	209 (15)	73 (10)	136 (21)
101–200	217 (16)	108 (15)	109 (17)
>200	304 (22)	210 (29)	94 (15)
Not reported	350 (25)	264 (36)	86 (13)
Second-line ART Regimen			
NRTI+PI	1281 (93)	653 (89)	628 (98)
Integrase inhibitor combination	78 (6)	74 (10)	4 (1)
Other combination	19 (1)	9 (1)	10 (2)
Reason for switching to second-line ART			
Virologic failure only	873 (63)	687 (93)	186 (29)
Immunologic failure only	51 (4)	11 (1)	40 (6)
Virologic and immunologic failure	221 (16)	17 (2)	204 (32)
*Other reasons	233 (17)	21 (3)	212 (33)
World Bank country income group			
Lower + upper middle	1267 (92)	625 (85)	642 (100)
High	111 (8)	111 (16)	0 (0)

NRTI: Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor

*Other reasons include clinical failure only; virologic and clinical failure; immunologic and clinical failure; and virologic, immunologic and clinical failure

Table 2:

Factors associated with confirmed virologic failure in patients on second-line antiretroviral therapy

			Univariate			Multivariate		
	Total patients	**Total virologic failures(%)**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**p**
Total	**1378**	**101**						
Age at switch to second-line ART (years)					0.547			
≤30	290	21(21)	1					
31–40	645	50(50)	1.08	(0.63, 1.83)	0.785			
41–50	337	26(26)	1.07	(0.59, 1.95)	0.822			
>50	106	4(4)	0.50	(0.17, 1.50)	0.217			
Sex								
Male	1023	69(69)	1					
Female	355	32(32)	1.37	(0.88, 2.12)	0.159			
HIV mode of exposure					0.002			**0.001**
Heterosexual contact	964	89(89)	1			**1**		
Male-male sex	134	4(4)	0.30	(0.11, 0.84)	0.021	**0.29**	**(0.10, 0.83)**	**0.020**
Injecting drug use	172	4(4)	0.23	(0.08, 0.65)	0.005	**0.22**	**(0.08, 0.60)**	**0.003**
Other/Unknown	108	4(4)	0.38	(0.14, 1.05)	0.062	0.39	(0.14, 1.09)	0.073
CD4 at switch to second-line (cells/μL)					0.061			**0.020**
≤50	298	24(24)	1			**1**		
51–100	209	17(17)	1.01	(0.53, 1.93)	0.974	0.97	(0.50, 1.86)	0.923
101–200	217	10(10)	0.55	(0.26, 1.18)	0.125	0.48	(0.22, 1.03)	0.058
>200	304	11(11)	0.43	(0.21, 0.89)	0.023	**0.36**	**(0.17, 0.77)**	**0.008**
Not reported	350	39(39)						
Second-line ART Regimen					0.200			
NRTI+PI	1281	95(95)	1					
Integrase inhibitor combination	78	3(3)	0.50	(0.15, 1.61)	0.246			
Other combination	19	3(3)	2.34	(0.67, 8.18)	0.183			

	Total patients	Total virologic failures(%)	Univariate OR	95% CI	P	Multivariate OR	95% CI	p
Reason for switching to second-line ART					0.075			
Virologic failure only	873	75(75)	1					
Immunologic failure only	51	1(1)	0.21	(0.03, 1.56)	0.128			
Virologic and immunologic failure	221	15(15)	0.77	(0.44, 1.38)	0.384			
*Other reasons	233	10(10)	0.48	(0.24, 0.94)	0.032			
World Bank country income group								
Lower + upper middle	1267	95(95)	1			1		
High	111	6(6)	0.70	(0.30, 1.65)	0.420	1.34	(0.54, 3.29)	0.526

P-values in bold represent significant covariates in the final model. Global p-values are test for heterogeneity excluding missing values.

World Bank country income group was included in the multivariate model a priori.

NRTI: Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor.

*Other reasons include clinical failure only; virologic and clinical failure; immunologic and clinical failure; and virologic, immunologic and clinical failure

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Table 3:

Factors associated with a single VL >1000 copies/mL in patients on second-line antiretroviral therapy

			Univariate			Multivariate		
	Total patients	**Total with VL >1000(%)**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Total	**1378**	**248**						
Age at switch to second-line ART (years)					0.009			
≤30	290	39(16)	1					
31–40	645	117(47)	1.43	(0.96, 2.11)	0.076			
41–50	337	78(31)	1.94	(1.27, 2.96)	0.002			
>50	106	14(6)	0.98	(0.51, 1.89)	0.950			
Sex								
Male	1023	183(74)	1					
Female	355	65(26)	1.03	(0.75, 1.41)	0.859			
HIV mode of exposure					<0.001			**<0.001**
Heterosexual contact	964	216(87)	1			**1**		
Male-male sex	134	10(4)	0.28	(0.14, 0.54)	<0.001	**0.32**	**(0.17, 0.64)**	**0.001**
Injecting drug use	172	9(4)	0.19	(0.10, 0.38)	<0.001	**0.24**	**(0.12, 0.49)**	**<0.001**
Other/Unknown	108	13(5)	0.47	(0.26, 0.86)	0.015	**0.50**	**(0.27, 0.91)**	**0.024**
CD4 at switch to second-line (cells/μL)					0.446			
≤50	298	39(16)	1					
51–100	209	32(13)	1.20	(0.72, 1.99)	0.478			
101–200	217	37(15)	1.37	(0.84, 2.22)	0.212			
>200	304	38(15)	0.95	(0.59, 1.53)	0.829			
Not reported	350	102(41)						
Second-line ART Regimen					0.623			
NRTI+PI	1281	233(94)	1					
Integrase inhibitor combination	78	11(4)	0.74	(0.38, 1.42)	0.363			
Other combination	19	4(2)	1.20	(0.39, 3.65)	0.749			

	Total patients	Total with VL >1000(%)	Univariate OR	95% CI	p	Multivariate OR	95% CI	p
Reason for switching to second-line ART					<0.001			**<0.001**
Virologic failure only	873	203(82)	1			**1**		
Immunologic failure only	51	1(0)	0.07	(0.01, 0.48)	0.007	**0.09**	**(0.01, 0.66)**	**0.018**
Virologic and immunologic failure only	221	27(11)	0.46	(0.30, 0.71)	<0.001	**0.55**	**(0.35, 0.86)**	**0.009**
*Other reasons	233	17(7)	0.26	(0.15, 0.44)	<0.001	**0.28**	**(0.17, 0.47)**	**<0.001**
World Bank country income group								
Lower + upper middle	1267	241(97)	1			1		
High	111	7(3)	0.29	(0.13, 0.62)	0.002	**0.38**	**(0.17, 0.84)**	**0.017**

P-values in bold represent significant covariates in the final model. Global p-values are test for heterogeneity excluding missing values.

World Bank country income group was included in the multivariate model a priori.

NRTI: Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor

*Other reasons include clinical failure only; virologic and clinical failure; immunologic and clinical failure; and virologic, immunologic and clinical failure

HIV Med. Author manuscript; available in PMC 2022 March 01.