Pretreatment HIV drug resistance in Sri Lanka, 2021

Final report

Acronyms

3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral (drug)
AZT	zidovudine
DBS	dried blood spots
DTG	dolutegravir
EFV	efavirenz
EID	early infant diagnosis
FTC	emtricitabine
HIV	human immunodeficiency virus
HIVDR	HIV drug resistance
INSTI	Integrase Strand Transfer Inhibitors
LVP/r	ritonavir-boosted lopinavir
NAT	nucleic acid amplification test
NARI	National AIDS Research Institute
NRL	National Reference Laboratory
NSACP	National STI & AIDS Control Program
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside or nucleotide reverse transcriptase inhibitor
PDR	pretreatment HIV drug resistance
PI	protease inhibitor
PLHIV	People living with HIV
TDF	tenofovir
TLD	Tenofovir+Lamivudine+Dolutegravir
WHO	World Health Organization

1. INTRODUCTION

HIV Drug Resistance (HIVDR) emerges when HIV replicates in the presence of antiretroviral drugs. HIVDR affects the ability of a particular drug or combination of drugs to block the replication of the virus. HIVDR negatively impacts the effectiveness of antiretroviral (ARV) drugs, increases the number of AIDS-associated deaths, new HIV infections and antiretroviral therapy (ART) programme costs[1,2]. The surveillance of HIVDR is therefore a key component of the comprehensive and effective HIV response. The World Health Organization recommends that HIV treatment scale-up should always be accompanied by measures to monitor and improve the quality of ART delivery and surveillance of HIVDR, including the surveillance of pretreatment HIV drug resistance (PDR) in populations initiating ART and the surveillance of acquired HIV drug resistance (ADR) in populations receiving ART[3].

The prevalence of PDR is increasing at a substantial rate in low- and middle-income countries. The recent WHO 2019 report shows an increase in PDR with increased rollout and long-term use of ART[4]. In 12 of 18 countries reporting survey data to WHO between 2014 and 2018, levels of PDR to the non-nucleoside reverse transcriptase inhibitors (NNRTIs); efavirenz (EFV) and/or nevirapine (NVP) exceeded 10% among adults initiating first-line ART[4]. PDR to NNRTIs has been associated with poor virological outcomes, impaired immune recovery, and reduced durability of NNRTI-based regimens[1,5,6]. A modelling study further predict an increase in HIV incidence, mortality and overall programmatic costs attributed to high levels of PDR[1,6]. To prevent the impact of PDR, WHO recommended the use of dolutegravir (DTG) based ART as the preferred first-line ART[7]. Although DTG-based ART is expensive, a generic fixed dose combination of tenofovir disoproxil fumarate, lamivudine and DTG 300/300/50 mg ("TLD") has been made available at an affordable price through the Medicines Patent Pool for countries especially in sub-Saharan Africa. However, access to more affordable DTG-based ART in countries outside the Medicines Patent Pool is a challenge and rapid transition to the new drugs may be further hindered by logistics constraints.

Under the public health approach, HIV treatment in Sri Lanka constitutes three sequential standardized regimens[8]. This includes a non-NRTI (NNRTI) core drug with 2 NRTIs (mainly EFV+XTC+TDF) as the first-line regimen. Upon treatment failure, patients are switched to a

ritonavir boosted first generation protease inhibitors (PI) (lopinavir/ritonavir, LPV/r or atazanavir/ritonavir, ATV/r) + 2 new or recycled NRTIs as the second-line regimen followed by a switch to integrase strand inhibitors (INSTIs) with 2 new or recycled NRTIs as third-line ART. The 2020 treatment guidelines recommend the use of DTG-based ART in first and second-line as per the WHO guidelines and the country has initiated the transition process.

Sri Lanka has made significant progress towards epidemic control with NSACP committing to achieving the UNAIDS 95-95-95 targets by 2025. There are however still significant gaps in the 1st and 3rd treatment goals with the overall 90-90-90 progress being at 51-95-84 based on 2019 data[9]. Overall treatment coverage among all HIV infected patients is estimated at 51%. Approximately 98% (1803) of the patients on ART are adults aged 15 years or older and 2% are children[10]. Among these patients, 95.7% (1766) are on first- line ART while 4.3% of the patients are on second- line regimens[10]. Overall majority of the patients were on NNRTI-based ART (85.5% overall, 86.3% adults and 61.9% children) consisting of efavirenz-based ART (97.3%) and nevirapine based ART (2.7%), PI's (10.1% overall, 9.4% adults and 38.1% children) consisting of LPV/r, 65.1%, ATV/r (31.7%) and darunavir/ritonavir (DRV/r) (3.2%) and 4.3% on INSTIs all in adults and consisting only raltegravir-based regimen.

Overall data on HIVDR is scarce in Sri Lanka. Although Sri Lanka hasn't conducted a national representative survey, routine HIVDR from patients failing treatment is normally done to guide patient management. A recent assessment of these data included 85 patients failing ART, of which 50 (59%) were on NNRTI based first-line, 21 (25%) were on PI-based regimen, 5 (5.9%) on integrase inhibitors and regimen was unknown in 9 (10.6%) of the patients[11]. HIVDR was only assessed for protease and reverse transcriptase region. Overall HIVDR mutation was detected in 66% (56/85), NNRTI DRMs in 59% (50 of 85), NRTI DRMs in 44% (37 of 85), dual NRTI and NNRTI DRMs in 37% (31 of 85) and 1.2% (1 of 85) for PI DRMs[11].

The observed sub-optimal viral suppression and high levels of ADR among patients failing treatment, and the rise in NNRTI treatment globally may also suggest a high risk of PDR in Sri Lanka. In order to inform the optimal selection of first-line regimen and ensure the attainment of epidemic control by 2025 as proposed in the current Sri Lanka strategic plan, the country

conducted a PDR survey in 2021. This report presents the findings of the first nationally representative HIVDR survey conducted among ART initiators in Sri Lanka.

2. OBJECTIVES

Primary objectives:

To determine:

1. Nationally representative prevalence estimates of HIV pretreatment drug resistance among adults initiating antiretroviral therapy (ART), regardless of prior ARV exposure history.
2. Nationally representative prevalence estimates of HIV pretreatment drug resistance among adults initiating antiretroviral therapy (ART), with no known history of prior ARV exposure
3. Nationally representative prevalence estimates of HIV pretreatment drug resistance to NNRTI-based ART among adults initiating antiretroviral therapy (ART), with no known history of prior ARV exposure

Secondary objectives:

1. To determine the proportion of adults initiating ART with history of prior ART exposure.
2. To determine the proportion of adults initiating ART without history of prior ART exposure.
3. To determine the proportion of adults initiating ART whose ART history is classified as unknown (i.e. no documentation of exposure history).
4. To describe the pattern of drug resistance mutations (DRMs) among adults initiating ART.

3. METHODS

3.1 Survey design

A cross-sectional survey was carried out following the WHO-recommended methods for PDR survey using a census of all clinics[12] providing ART in Sri Lanka. ART facilities with small cohort of PLHIV newly initiating ART were excluded from the sampling frame. Overall, the excluded clinics accounted for 7.3% (25/341) of the population initiating treatment in 2019 which is within

the 10% recommended by WHO[12]. The sample size was calculated based on WHO-recommended assumptions using the probability proportional to proxy size method and adjusted with finite population correction using the WHO sample size calculator tool. The expected sample was 163. The sample was assigned proportionally to the cohort of PLHIV newly initiating ART in each of the 18 ART facilities included in the sampling frame.

3.2 Participants enrolment

Eligible individuals were consecutively enrolled from January 2021 to July 2021. The enrolment period was extended to six months due to failure to attain the projected sample size possibly due to the ongoing COVID-pandemic. Demographic and clinical data were collected.

Inclusion criteria	Exclusion criteria
• Adults with HIV-1 infection who can legally provide and do provide informed consent. (Those below the consenting age of 18 years, i.e. 15 - 17, consent from the parental/legal guardian and assent from the minor will be obtained) • ART initiators, with or without prior ARVs exposure	• Patients reinitiating ART who have experienced ART interruption for <3 months, after stopping ART (this does not include patients who have been exposed to antiretrovirals for prophylaxis) • Patients already receiving ART transferring in from another facility

3.3 Laboratory procedures

After obtaining consent from participants for blood collection, 7 ml of venous EDTA whole blood was collected from all study participants and shipped to NRL at Colombo within 24 hours under cold storage. AT NRL, dried blood spots was prepared in accordance with WHO guidelines with 75ul of blood per each spot and packaged appropriately with desiccants and humidity indicators and stored at -80^{0}C until shipment to NARI in India, Pune for genotyping. At NARI, HIV protease and reverse transcriptase Pol gen regions were amplified and sequenced.

3.4 Data analysis

ART initiators were defined as PLHIV initiating or reinitiating first-line regimen. The WHO/BCCfE HIVDR quality control tool was used for post-testing quality assurance[13]. The Stanford HIVdb tool was used to define as "HIV drug resistance" the sequences classified as low-level, intermediate or high-level resistance[14]. Any HIV drug resistance was defined as resistance to at least one of the following drugs: nevirapine, efavirenz, any NRTI, ritonavir-boosted darunavir, lopinavir, and atazanavir. HIV drug resistance to NNRTI was defined as resistance to nevirapine and/or efavirenz; HIV drug resistance to protease inhibitors (PI) was defined as resistance to ritonavir-boosted darunavir, lopinavir, and/or atazanavir. HIV subtype was assigned using the Stanford HIVdb subtyping tool [14].

Weighted statistical analysis was performed using STATA 15.1 (StataCorp, College Station, TX, USA) following the WHO recommendations for the all–sites survey design[12]. Odds ratios were estimated by logistic regression. Study design-weighted proportions and 95% confidence intervals were calculated. The weights were calculated per site considering the estimated eligible population and the number of individuals enrolled.

4. RESULTS

4.1 Clinical and demographic characteristics

A total of 194 ART initiators were enrolled in the survey during the six-months survey period. Of these 12 samples were rejected at NARI as they had been exposed to room temperature for >14 days due to shipment logistic challenges. Majority of the participants enrolled in the survey were of male gender 78.6% (95%CI, 69.4–87.9) and ≥25 years old, 80.0% (95%CI 74.2-85.3) (Table 1). 25.6% (95%CI, 17.1-34.1) initiated ART with a CD4 count <200 cells/mm^3. The proportions of participants with low CD4 counts<200 cells/mm^3 differed by clinic sites being particularly high in Kalutara (56%, 5/9), Anarudhapura (50%, 3/3), Matale (50%, 2/2), Jaffna (50%, 1/1) Ragama (43.8%, 7/16) and Kandy (42%, 5/7) (Fig 1)

The proportion of ART initiators with prior ARV exposure was 18.2% (95%CI 9.9–26.6). All prior ARV exposures were due to ART (previous disengagement from treatment). The proportion of participants with prior ARV exposure differed by clinic site, being highest in Kalutara (5/9, 56%),

Gampaha (1/3, 33%), Kurunegala (30%, 3/10), Colombo (21/76, 28%) and Chilaw (1/5, 20%) (Fig 2). Persons with prior ARV exposure were also likely to be heterosexuals (23.7% (95%CI 6.9-40.6) than MSM (13.5%, 95%CI 3.0-24), the difference was however not statistical significant.

Of the 194 patients in the survey, 69.9% (95%CI 50.9-89.0) were planned to be started on an NNRTI containing ART, 21.3%, (95%CI 7.9-34.6) on DTG and 4.1%, (95%CI 1.0-7.7) on PI- and on 2.9% (0-6.8) raltegravir- based regimen.

Table 1. Demographic and clinical characteristics of ART initiators, Sri Lanka 2021

	ART initiators (N=194)	
	n	%, 95% CI
Gender		
Female	36	21.0 (11.7-30.2)
Male	157	78.6 (69.4–87.9)
Others	1	<0.5
Age (years, mean)		41.9 (35.5-48.3)
≤25	36	20.2 (14.7-25.8)
>25	157	80.0 (74.2-85.3)
CD4 count (cells/mm^3)		385.8(324.9-446.7)
<200	53	29.1 (20.0-38.3)
≥200	117	70.9 (61.7-80.0)
Perceived HIV risk factor		
Heterosexual	63	34.1 (23.6-44.5)
Bisexual	19	8.1 (2.6-13.7)
Female sex worker	1	0.1 (0-0.2)
Client of FSW	2	0.04 (0-1.7)
Men who have sex with men	67	34.2 (24.1-44.2)
IDU	1	0.04 (0-0.1)
MTCT	1	1.2 (0-3.7)
HIV +ve partner	2	1.2 (0-3.2)
Various combinations	6	2.3 (0.8-3.8)
Unknown	28	13.9 (3.1-24.7)
Others	4	2.4 (0-5.9)
Prior ARV exposure		
Yes	40	18.2 (9.9–26.6)
No	154	81.2 (73.4–90.1)
Type of prior ARV exposure		

Previous ART use	37	92.5 (84.8-100)
Unknown	4	7.5 (0-15.2)
NNRTI only	23	65.4 (46.7-84.2)
PI	10	24.0 (7.3-40.6)
INI	3	8.2 (0-16.8)
Unknown	1	2.4 (0-8.7)
Planned regimen		
EFV-based ART	122	69.9 (50.9-89.0)
LPV-r/ATV-r	8	4.1 (1.0-7.7)
DTG-based ART	51	21.3 (7.9-34.6)
RAL-based ART	8	2.9 (0-6.8)
Unknown	5	1.8 (0-4.6)

[a] Study design-weighted proportions and 95% confidence intervals. Antiretroviral therapy initiators were defined as people living with HIV initiating or reinitiating first-line regimen.
ART: antiretroviral therapy; ATV-r; atazanavir boosted ritonavir; CI: confidence interval; EFV: efavirenz; DTG: dolutegravir; FSW: Female sex workers; IDU: Injection drug use; LPV-r: lopinavir boosted ritonavir; MTCT: Mother-to-child-transmission; not applicable; NVP: nevirapine; PI: protease inhibitors; RAL: raltegravir.

Figure 1. CD4+ cell count among ART initiators, Sri Lanka 2021

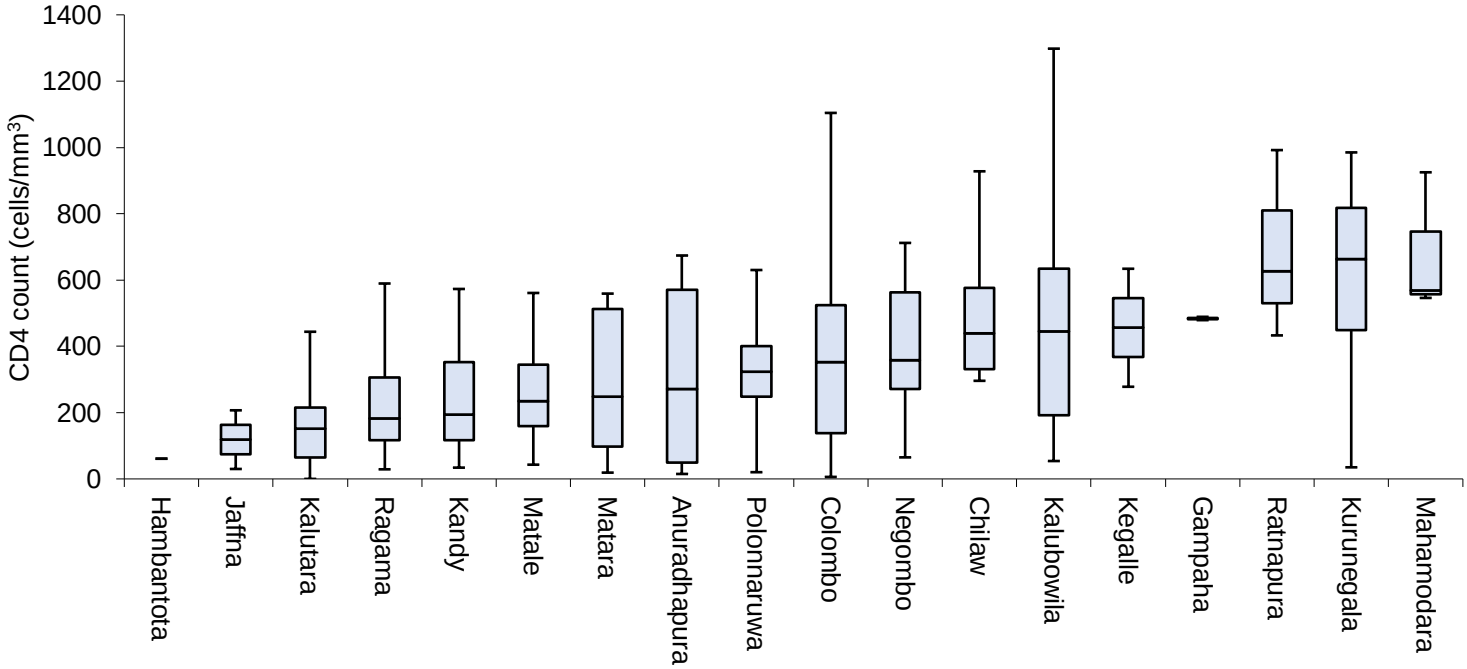
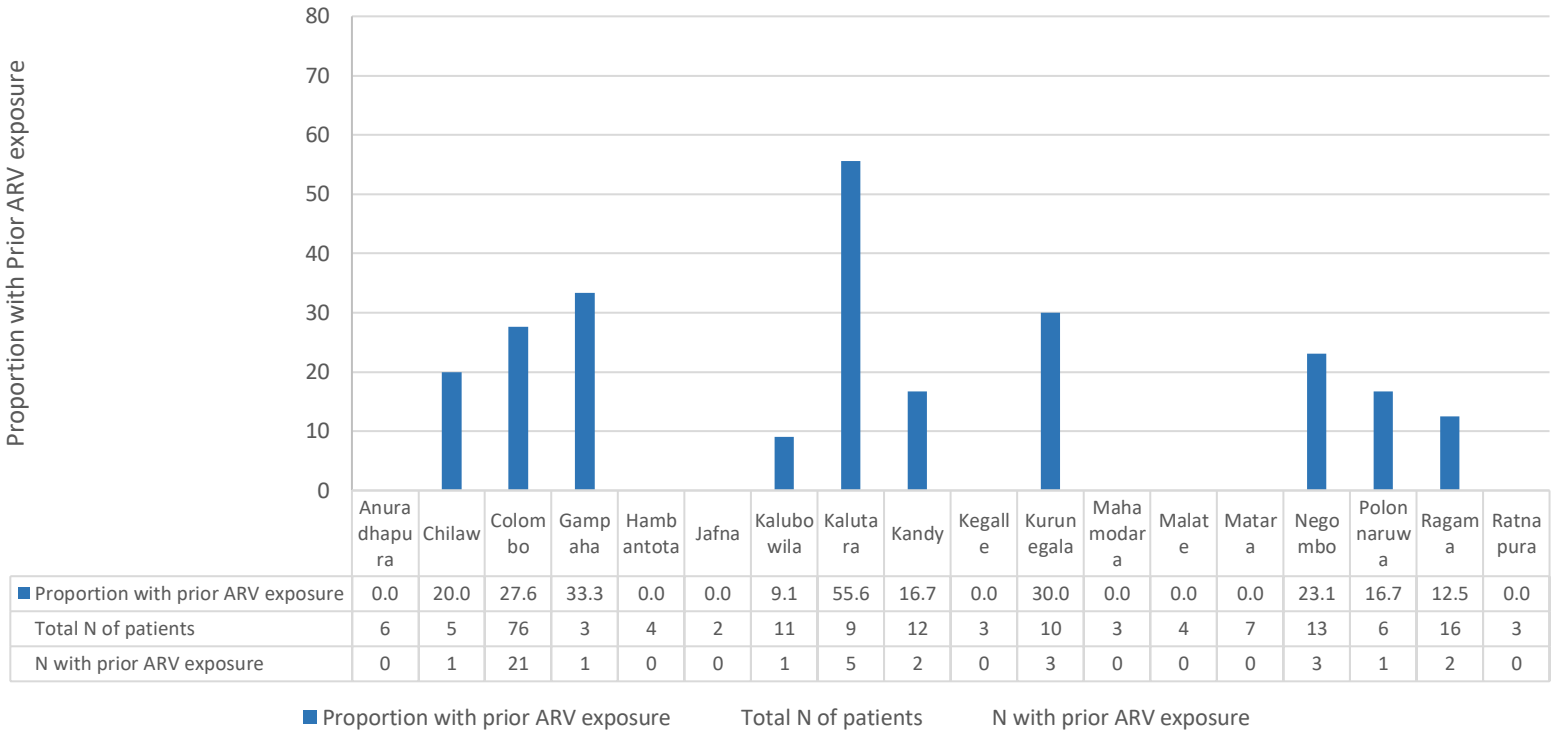


Figure 2. Proportion of patients starting ARV by prior ARV exposure at the study sites



	Anuradhapura	Chilaw	Colombo	Gampaha	Hambantota	Jafna	Kalubowila	Kaluta ra	Kandy	Kegalle	Kurunegala	Mahamodara	Malate	Matara	Negombo	Polonnaruwa	Ragama	Ratnapura
Proportion with prior ARV exposure	0.0	20.0	27.6	33.3	0.0	0.0	9.1	55.6	16.7	0.0	30.0	0.0	0.0	0.0	23.1	16.7	12.5	0.0
Total N of patients	6	5	76	3	4	2	11	9	12	3	10	3	4	7	13	6	16	3
N with prior ARV exposure	0	1	21	1	0	0	1	5	2	0	3	0	0	0	3	1	2	0

4.2 Pretreatment HIV drug resistance

Of the 194 samples, shipped to NARI 181 were accepted for genotyping. Of these 162 had a successful genotype representing a 90% genotyping success rate. A further 12 were excluded due to quality assurance including 11 that had genetic distance of <0.5%. Subsequently 150 were used to estimate PDR prevalence.

The overall prevalence of resistance to EFV/NVP was 8.4% (95%CI 4.6-15.0) but differed among those reporting having prior ARV exposure 24.4% (95%CI 13.8-39.5) compared to those reporting as ARV naïve 4.6% (95%CI 1.6-12.8) (odds ratio 4.6, 95% CI: 1.3–16.6, *p=0.021*). PDR to EFV/NVP was also nearly twice as high among women (14.1%, 95%CI 6.1-29.4) compared to men 10.5% (95%CI 5.4-19.6) (*p=0.340*). K103N/H/T was the most commonly observed NNRTI resistance mutation. Of the 12 patients with PDR to EFV/NVP, 8 had were planned to be initiated on EFV/NVP, 3 on DTG and 1 on LPV-r containing regimen.

Overall PDR prevalence to any drug was 11.2% (95%CI 6.6-18.5) while that to NRTIs was low at 3.8% (95%CI 1.1-12.1) and no PI PDR was observed in the study (Table 2). PDR to NRTI was driven mainly by ZDV resistance due to presence of thymidine analogue mutations (TAMs). Prevalence of PDR to second-generation NNRTI was also low ranging from 2.5% (95%CI 0.8-8.0) for doravirine, 2.0% (95%CI 0.7-6.1) for rilpivirine and 1.0% (95%CI 0.2-4.7) for etravirine.

Overall prevalence of PDR to any drug varied also between sub-groups being high in participants >25 years old (11.5%, 95%CI 6.3-19.9) compared to those ≤25 years old (10.3, 95%CI 1.9-39.9), in participants reporting being heterosexual (18.4%, 95%CI 8.4-35.7), compared to those reporting being bisexual (8.0%, 95%CI 3.7-16.4) and men who have sex with men (3.4%, 95%CI 1.0-10.8) (Table 3). Participants with CD4 counts of >200 cps/mL (15.8%, 95%CI 9.1-26.2) also had comparatively high PDR prevalence as compared to those with CD4 counts ≤200 cells/µl (6.4%, 95%CI 2.1-17.6) (Table 3).

The prevalence of drug resistance by drug class and drug are presented in ***Table 2 and Figure 3 & 4***.

The prevalence of drug resistance mutations presents at ≥1% of all sequences analysed are shown in Fig 5 % 6 found in Annex 1 &2.

HIV-1 subtype C (71%) was the commonly observed subtype followed by subtype B (11.4%). Other HIV-1 subtypes observed were CRF01_AE (4.3%), A (2.9%) and CRF_02_AG (2.1%) (Figure A1, Annex 2).

Table 2. Prevalence of pretreatment HIV drug resistance among ART initiators, Sri Lanka 2021

		All		Women		Men		ARV naive		With Prior ARV exposure	
		n/N	% (95% CI) [a]								
Any	Any HIVDR	15/150	11.2 (6.6-18.5)	5/28	14.1 (6.1-29.4)	10/121	10.5 (5.4-19.6)	7/116	8.0 (3.4-17.8)	8/34	24.4 (13.8-39.5)
NRTI	Any	4/150	3.8 (1.1-12.1)	0/28	-	4/121	4.8 (1.4-15.2)	4/116	4.5 (1.5-13.2)	0/34	-
	ABC	0/150	-	0/28	-	0/121	-	0/116	-	0/34	-
	3TC or FTC	0/150	-	0/28	-	0/121	-	0/116	-	0/34	-
	TDF	0/150	-	0/28	-	0/121	-	0/116	-	0/34	-
	ZDV	2/150	1.6 (0.3-8.0)	0/28	-	2/121	2.0 (0.4-10.3)	2/116	2.0 (0.4-9.6)	0/34	-
NNRTI	EFV or NVP	12/150	8.4 (4.6-15.0)	5/28	14.1 (6.1-29.4)	7/121	7.0 (3.1-14.7)	4/116	4.6 (1.6-12.8)	8/34	24.4 (13.8-39.5)
	DOR	5/150	2.5 (0.8-8.0)	1/28	2.3 (0.4-12.7)	4/121	2.6 (0.9-7.6)	1/116	0.6 (0.1-3.2)	4/34	10.4 (4.2-23.4)
	ETR	2/150	1.0 (0.2-4.7)	1/28	2.3 (0.4-12.7)	1/121	0.6 (0.1-2.9)	1/106	0.6 (0.1-3.2)	1/34	2.5 (0.7-8.4)
	RPV	4/150	2.0 (0.7-6.1)	2/28	4.6 (0.7-23.7)	2/121	1.4 (0.4-4.5)	1/106	0.6 (0.1-3.2)	3/34	7.9 (3.1-18.6)
PI/r	ATV/r, DRV/r or LPV/r	0/150	-	0/28	-	0/121	-	0/106	-	0/34	-
	ATV/r	0/150	-	0/28	-	0/121	-	0/106	-	0/34	-
	DRV/r	0/150	-	0/28	-	0/121	-	0/106	-	0/34	-
	LPV/r	0/150	-	0/28	-	0/121	-	0/106	-	0/34	-
INSTI	Any	-	-	-	-	-	-	-	-	-	-
	BIC	-	-	-	-	-	-	-	-	-	-
	CAB	-	-	-	-	-	-	-	-	-	-
	DTG	-	-	-	-	-	-	-	-	-	-
	EVG	-	-	-	-	-	-	-	-	-	-
	RAL	-	-	-	-	-	-	-	-	-	-

[a] Study design–weighted proportion and 95% confidence interval.

HIVDR was defined as the presence of a penalty score ≥15 using the Stanford HIVdb algorithm.

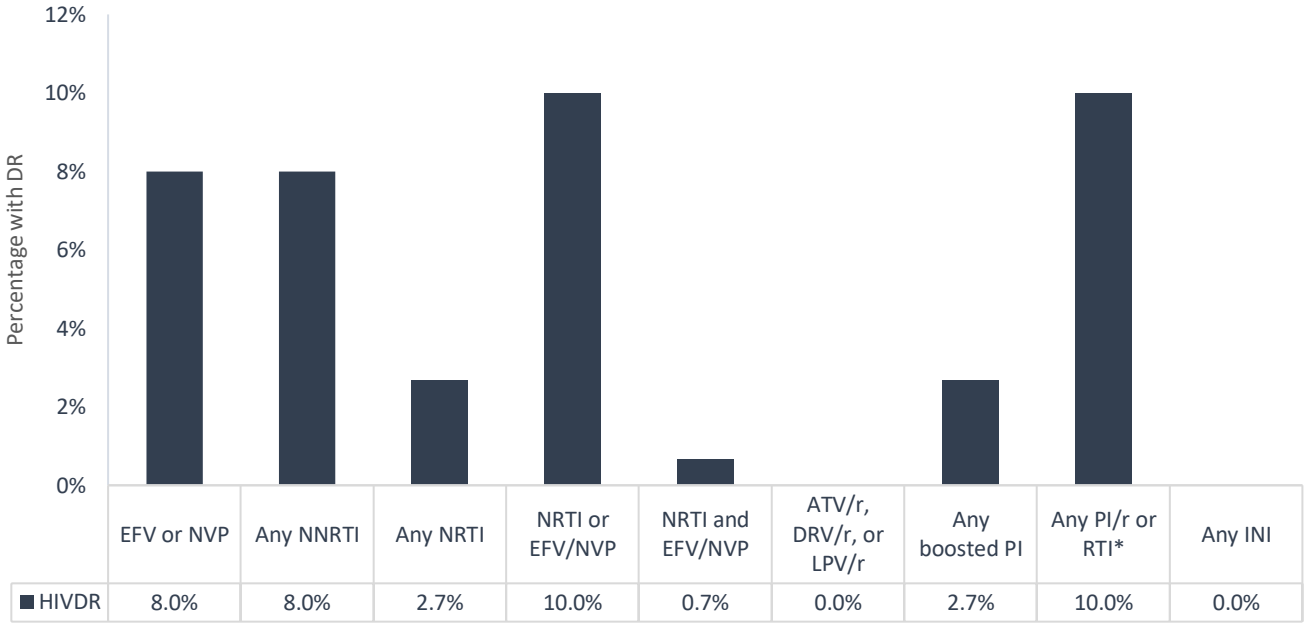
ABC: abacavir; ATV/r: atazanavir/ritonavir; BIC: bictegravir; CAB: cabotegravir; DOR: doravirine; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; ETV: etravirine; EVG: elvitegravir; INSTI: integrase strand transfer inhibitor; LPV/r: lopinavir/ritonavir; ND: no data; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NVP: nevirapine; PI/r: boosted protease inhibitor; RAL: raltegravir; RPV: rilpivirine; TDF: tenofovir; ZDV: zidovudine; 3TC/FTC: lamivudine/emtricitabine.

Table 3. Prevalence of pretreatment HIV drug resistance among ART initiators, by sub-populations in Sri Lanka 2021

	All *		ART naïve individuals		Prior ARV drug exposed individuals	
Resistance by drug class	n/N	Prevalence (mean, 95%CI)	n/N	Prevalence (mean, 95%CI)	n/N	Prevalence (mean, 95%CI)
Any HIVDR	15/150	11.2 (6.6-18.5)	7/116	8.0 (3.4-17.9)	8/34	24.4 (13.8-39.5)
NNRTI resistance	12/150	8.4 (4.6-15.0)	4/116	4.5 (1.5-13.3)	8/34	24.4 (13.8-39.5)
NRTI resistance	4/150	3.8 (1.1-12.1)	4/116	4.7 (1.4-14.5)	0/34	-
PI resistance	0/150	-	0/116	-	0/34	-
NNRTI+NRTI resistance	1/150	1.0 (0.1-8.7)	1/106	1.2 (0.1-10.4)	0/34	-
NNRTI+NRTI+PI resistance	0/150	-	0/116	-	0/34	-
Resistance by gender						
Women	5/28	14.1 (6.1-29.4)	1/20	3.4 (0.4-25.3)	4/8	55.4 (17.1-88.2)
Men	10/121	10.5 (5.4-19.6)	6/87	8.9 (3.7-20.1)	4/25	16.2 (6.8-34.0)
Resistance by age group						
≤25 years old	2/28	10.3 (1.9-39.9)	1/25	8.5 (0.9-49.1)	1/3	31.4 (6.6-74.9)
>25 years old	13/122	11.5 (6.3-19.9)	6/96	9.2 (3.6-21.5)	7/31	23.8 (10.8-44.6)
Resistance by HIV infection risk factor						
Bisexual						
Yes	2/18	13.6 (2.8-46.7)	1/16	10.1 (1.0-54.7)	1/2	45.8 (2.6-96.4)
No	13/132	10.9 (6.0-19.2)	6/100	7.7 (3.0-18.5)	7/32	23.2 (10.3-44.3)
Heterosexual						
Yes	9/50	18.4 (8.4-35.7)	3/35	10.4 (2.4-35.4)	6/15	42.5 (20.6-67.7)
No	6/100	7.2 (3.0-16.1)	4/81	6.8 (2.2-19.2)	2/19	9.1 (2.3-30.2)
Men who have sex with men						
Yes	2/51	3.4 (1.0-10.8)	2/45	3.8 (1.1-12.7)	0/6	-
No	13/99	14.9 (8.4-25.1)	5/71	10.3 (3.8-25.3)	8/28	29.7 (14.5-51.4)
Resistance by CD4 levels						
≤200 cps/mL	3/45	6.4 (2.1-17.6)	2/36	4.4 (1.1-15.9)	1/9	15.8 (1.6-68.2)
>200 cps/mL	12/87	15.8 (9.1-26.2)	5/63	11.9 (4.4-28.6)	7/24	28.8 (15.5-47.2)

HIVDR was defined as the presence of a penalty score ≥15 using the Stanford HIVdb algorithm.

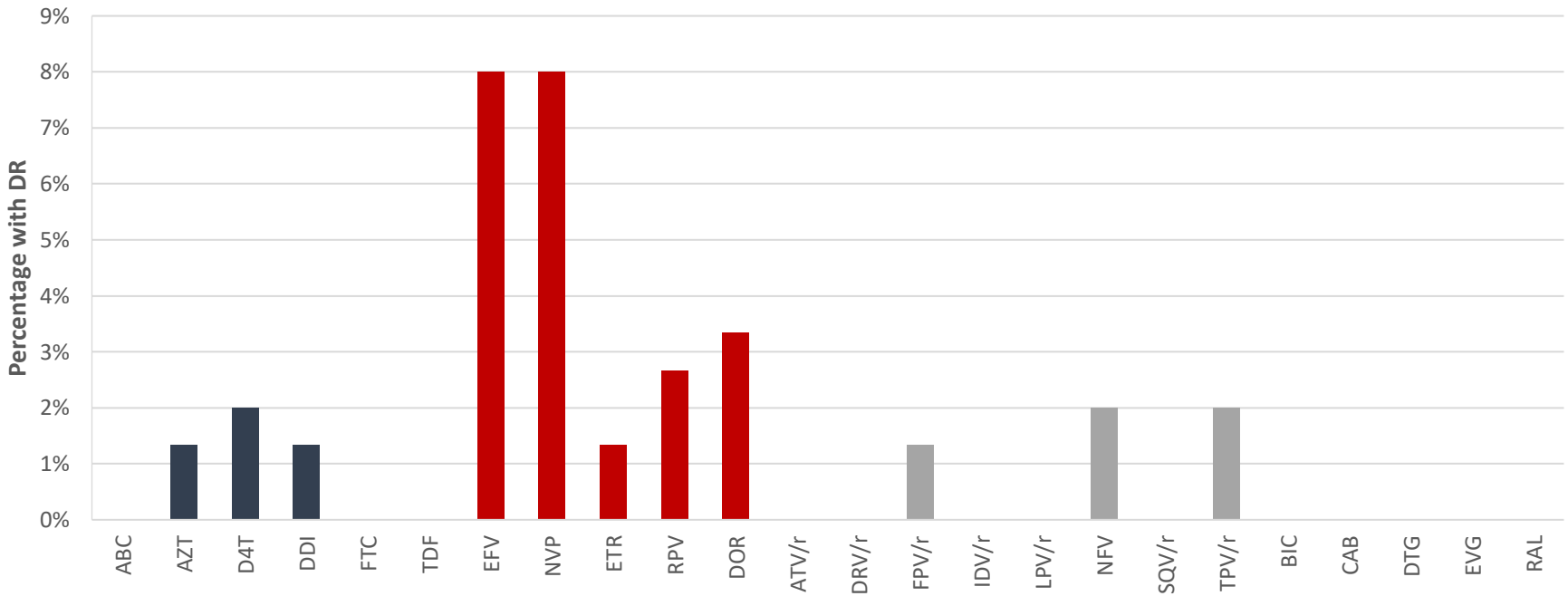
Figure 3. Prevalence of pretreatment HIV drug resistance by drug class among ART initiators, Sri Lanka 2021



	EFV or NVP	Any NNRTI	Any NRTI	NRTI or EFV/NVP	NRTI and EFV/NVP	ATV/r, DRV/r, or LPV/r	Any boosted PI	Any PI/r or RTI*	Any INI
HIVDR	8.0%	8.0%	2.7%	10.0%	0.7%	0.0%	2.7%	10.0%	0.0%

NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase; PI = protease inhibitor; INI = integrase inhibitor; ATV/r = ritonavir-boosted atazanavir; DRV/r = ritonavir-boosted darunavir; LPV/r = ritonavir-boosted lopinavir

Figure 4. Prevalence of pretreatment HIV drug resistance by drug among ART initiators, Sri Lanka 2021



ABC: abacavir; d4T: stavudine; ddI: didanosine; 3TC/FTC: lamivudine/emtricitabine; TDF: tenofovir; ZDV: zidovudine; EFV: efavirenz; ETV: etravirine; NVP: nevirapine; RPV: rilpivirine; ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; FPV/r: fosamprenavir/ritonavir; IDV/r: indinavir/ritonavir; LPV/r: lopinavir/ritonavir; NFV: nelfinavir; SQV/r: saquinavir/ritonavir; TPV/r: tipranavir/ritonavir; BIC: bictegravir; CAB: cabotegravir; DTG: dolutegravir; EVG: elvitegravir; RAL: raltegravir

5. Discussion

The prevalence of pretreatment HIV drug resistance to EFV or NVP was near borderline (8.4%) at the WHO recommended cut-off of 10% that necessitates moving away from EFV-based regimen. However, the prevalence of PDR to EFV/NVP had exceeded 10% in some sub-populations. Among those initiating treatment with prior ARV exposure, PDR to EFV/NVP was much higher at 24%. This group represents about 18% of all patients initiating treatment. PDR to EFV/NVP was also above 10% among women (14.1%). Overall, these findings suggest accelerating the adoption of WHO and Sri Lanka's 2020 recommendations to scale-up DTG-based therapy so as to minimize the impact of PDR on patient outcomes and ensure the country's attainment of the global targets on viral suppression[15,16]. If rapid transition is not feasible, the use of HIVDR testing on patients initiating or re-initiating treatment coupled with screening of patients with prior ARV exposure[16] will be critical to ensure that patients are initiated on optimal ARV regimens. It is worth noting that 67% of those with PDR to EFV/NVP were planned to be initiated on a regimen that they were already resistant to thus highlighting the interim need to use DR test to guide use of optimal treatment before wide access of DTG in all patients.

The high-level of patients re-initiating treatment after disengagement from care, highlights the need to strengthen systems to minimize attrition from care by implementing vigorous local retention strategies. Moreover since patients re-engaging in care are likely to have poor treatment outcomes[5,17], there is need for close monitoring of this group including addressing the factors associated with the initial default from care[18]. Contrary to previous reports, was the high level of PDR among heterosexuals as compared to men who have sex with men which may potentially be due to the high proportion of persons reporting having prior ARV exposure in this group[19]. This highlights the need to not only focus on key populations but also on the general population.

We observed a low prevalence of NRTI resistance as well as resistance to the 2nd generation NNRTIs. These findings give reassurance for potential efficacy of Truvada (TDF+FTC) based pre-exposure prophylaxis as it becomes rolled-out among key populations in Sri Lanka[20].

Nearly 1 in every 3 patients starting treatment had advanced disease with CD4 counts of <200cells/ µl. This observation is alarming, as patients with advanced disease have an increased risk of developing AIDS disease and death. Moreover, patients initiating treatment with low CD4 counts are less likely to achieve optimal immune recovery even while on treatment predisposing them to risk of long-term AIDS and non-AIDS complications, and death [6–9]. This highlights for an urgent need to strengthen and innovate strategies for HIV diagnosis and linkage to care and treatment, including self-testing and assisted partner notification, to increase the rates of early diagnosis of HIV infection and rapid treatment initiation. Moreover there is the need to accelerate the implementation of WHO and Sri Lanka's on advanced disease guidelines, a package of screening, prophylaxis, rapid ART initiation and intensified adherence interventions, to help reduce morbidity and mortality[21].

Overall, our observation for high-level of PDR to EFV/NVP in sub-populations such as women and those initiating treatment with prior ARV exposure, calls for accelerated transition to TLD in line with the current Sri Lanka's guideline. If rapid transition is not feasible, the use of PDR genotyping testing, coupled with screening of patients with prior ARV exposure would be a suitable alternative in the interim.

6. CONCLUSIONS

6.1 PDR prevalence to EFV/NVP was at 8.4%, i.e. at near borderline of the 10% threshold recommended by WHO to trigger a national response to the high-levels of NNRTI PDR. However, the levels of PDR to EFV/NVP were higher in sub-populations such as women (14.1%) and those reporting prior ARV exposure (24.4%).

6.2 Persons initiating ART with prior ARV exposure were 4x more likely to have PDR to EFV/NVP compared to those reporting being ARV naïve (odds ratio 4.6, 95% CI: 1.3–16.6, *p=0.021*).

6.3 A high proportion (29.1% (95%CI 20.0-38.3) of PLHIV initiated ART with a CD4 count <200 cells/mm^3.

6.4 Nearly 1 in every 5 patients initiating treatment reported having been exposed to ARVs, all of whom had been exposed to ARVs for treatment.

7. RECOMENDATIONS

7.1 Borderline level of pretreatment drug resistance in the overall population suggests the need to fast track transition to DTG-based ART among patients initiating treatment as per the current treatment guidelines in Sri Lanka

7.2 High levels of PDR to EFV/NVP in women and among those initiating treatment with prior ARV exposure further highlights the need for using pretreatment drug resistance testing as an interim strategy pending wide-scale rollout of DTG-based therapy. In addition, screening for patients with prior ARV exposure to be prioritized for DTG based therapy could be an alternative strategy.

7.3 The high proportion of PLHIV initiating ART with a CD4 count <200 cells/mm^3 suggest an urgent need to strengthen and innovate strategies for HIV diagnosis and linkage to care and treatment, including self-testing and assisted partner notification, to increase the rates of early diagnosis of HIV infection and rapid treatment initiation. In addition, this calls for the adoption of WHO comprehensive guidance on screening and treatment of patients with advanced disease to ensure better treatment outcomes.

7.4 High levels of patients initiating treatment with prior exposure to ART, suggest the need to strengthen systems for retention as well as close monitoring of this sub-set of patients including addressing the factors associated with the initial default from care

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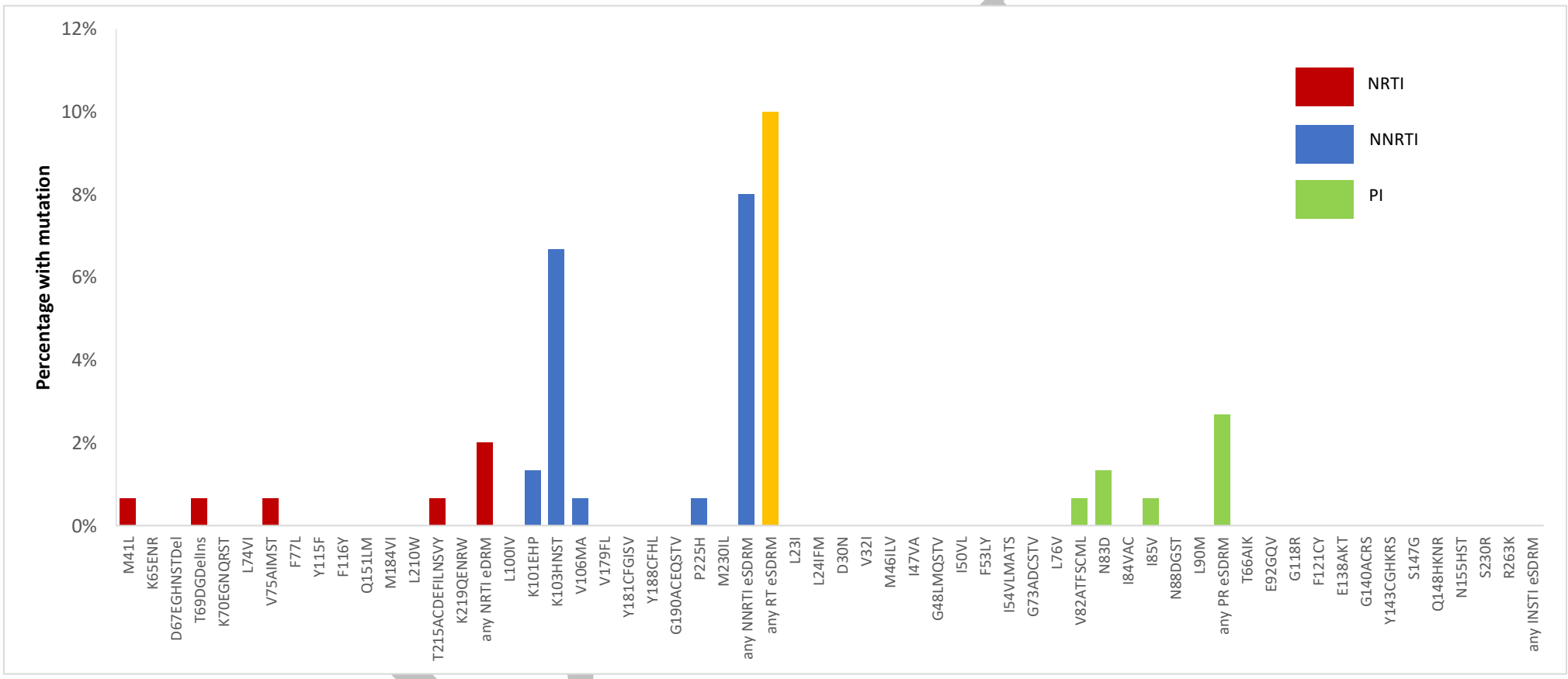
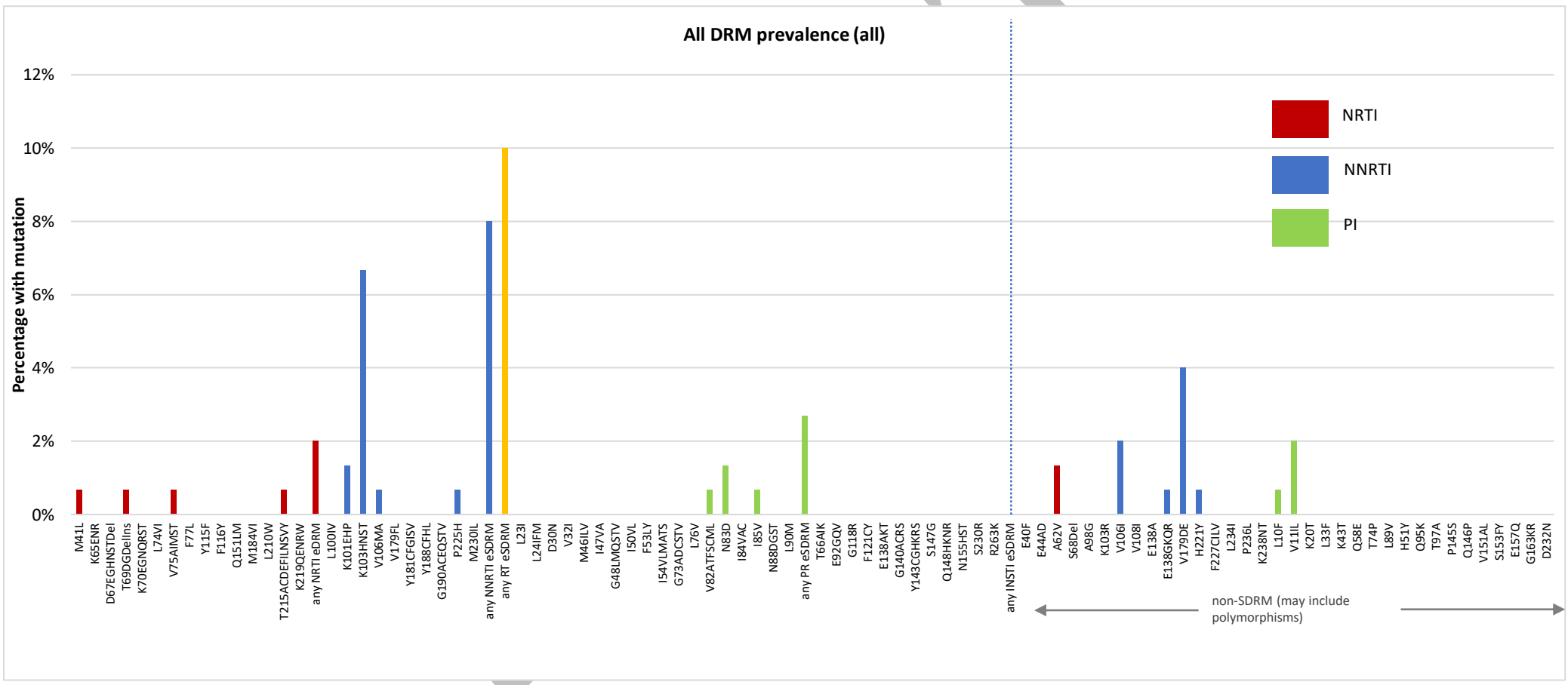
Annex 1 Fig 5: Drug resistance mutation patterns in patients initiating ART in Sri Lanka 2021



Unweighted proportions of sequences with Surveillance Drug Resistance Mutations (SDRM) as defined in Bennett et al 2009[22], plus other rare variants at the same positions that are not polymorphic, and other HIVDR-associated resistance mutations that have non-zero penalty scores in the Stanford HIVdb algorithm.

Annex 2 Fig 6: Drug resistance mutation patterns and polymorphisms in patients initiating ART in Sri Lanka 2021



Unweighted proportions of sequences with Surveillance Drug Resistance Mutations (SDRM) as defined in Bennett et al 2009[22], plus other rare variants at the same positions that are not polymorphic, and other HIVDR-associated resistance mutations that have non-zero penalty scores in the Stanford HIVdb algorithm.

Annex 3 Fig 7 HIV subtype distribution in patients initiating ART in Sri Lanka 2021