INFREQUENT DETECTION OF EMERGENT HIV DRUG RESISTANCE IN LOW VIRAL LOAD SPECIMENS

0575

Hanwei Sudderuddin[1,2], Walter Scott[1], Charlotte Beelen[1], Anh Le[1], Jenny Li[1], Wendy Zhang[1], Tetyana Kalynyak[1], Rob Hollebakken[1], Amanda Granados[1], Sakshi Khanna[1], Weiyan Dong[1], Viviane D. Lima[1,2], Julio Montaner[1,2], Chanson J. Brumme[1,2]

[1]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada, [2]Faculty of Medicine, University of British Columbia, Vancouver, Canada

ADDITIONAL KEY INFORMATION
Hanwei Sudderuddin; hsudderuddin@bccfe.ca
Dr. Chanson Brumme; cbrumme@bccfe.ca

BACKGROUND

- Treatment guidelines recommend genotypic HIV drug resistance testing (DRT) prior to treatment initiation and at virologic failure.
- While many DR assays are validated for samples with plasma viral loads (VL)>1000 HIV RNA c/mL, the BC Centre for Excellence in HIV/AIDS (BC-CfE) is accredited to test samples with VL>250 c/mL; low viral load (LVL) samples with VL of 50–250 c/mL are tested under a research-use-only protocol.
- LVL DRT is resource-intensive and the clinical relevance of results is unclear. We therefore investigated the frequency of and clinical factors associated with newly emergent or evolving DR in LVL samples.

METHODS

- A retrospective analysis of physician-requested LVL DRT from the BC-CfE's Drug Treatment Program database was performed. HIV Protease-RT and Integrase sequences from LVL samples were compared against all prior resistance genotypes from the same participants to identify newly emergent or evolving resistance. HIV DR was interpreted using the Stanford HIVdb v9.1 resistance interpretation algorithm.
- Univariable and multivariable analyses were performed to identify sociodemographic and clinical factors associated with newly emergent or evolving low viral load drug resistance.

RESULTS

- A total of 44,006 Protease-RT DRT were performed between 1999-2022, of which 2971 (6.8%) were on LVL samples. Testing was successful for 1576 (53.0%) LVL samples with VL<250 c/mL compared to 81.4% and 94.4% of samples with VL 250-999 and VL ≥1000 c/mL, respectively (p<0.001).
- Of the LVL DR tests,1424 (47.9%) tests were from 1026 participants with prior DRT (median 1, Q1-Q3 1–1 test/participant).
- LVL samples were collected a median 13.7 months (Q1-Q3 3.6-49.3) after a previous DRT on a sample with VL ≥250 c/mL.
- Resistance mutations were detected in 47 of 137 (34.3%) LVL samples from participants without prior DRT. Of these, NRTI, NNRTI and PI resistance was observed in 55%, 30% and 9.0%, respectively.
- Newly emergent or evolving resistance was detected less frequently in LVL samples than in samples with VL 250-999 c/mL (7.2% vs 10.5%, p = 0.0035).

Newly emergent or evolving drug resistance is detected infrequently in samples with VL <250 HIV RNA copies/mL. Resistance in LVL specimens is associated with PLWH who are younger, for whom a substantial amount of time has elapsed between resistance tests and who were receiving NNRTI- or PI-based cART at the time of testing. Resistance testing of LVL specimens should be performed if resistance testing has not been previously performed.

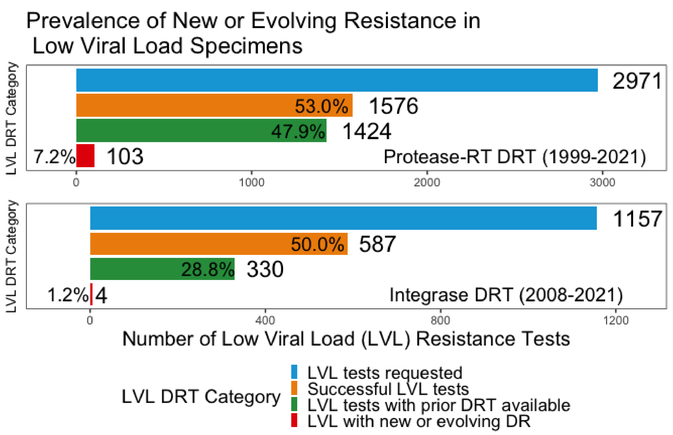


Figure 2. A total of 103 cases of new or evolving Protease-RT resistance and 4 cases of Integrase were identified from 1424 (7.2%) and 587 (1.2%) successfully tested LVL specimens with prior DRT, respectively. Resistance to NRTI, NNRTI, PI and INSTI was inferred using Stanford HIVdb (v9.1) and categorized as Susceptible (HIVdb score ≤14), Intermediate (score 15-59) or High-Level Resistance (score ≥60). New resistance was defined as detection of Intermediate- or High-level resistance in individuals with prior Susceptible HIV. Evolving resistance was defined as a change from Intermediate to High-Level resistance.

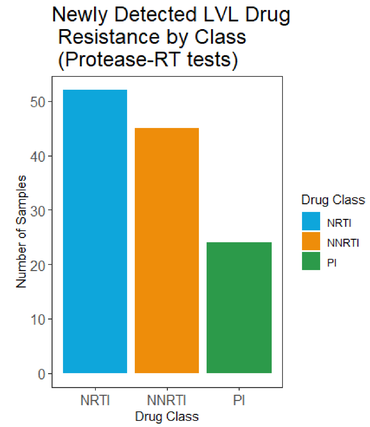


Figure 3. Newly emergent or evolving resistance was identified primarily in the NRTI and NNRTI drug classes. Newly observed resistance was primarily to a single drug class. Of the 103 samples with resistance, multi-class drug resistance was observed in 16 cases (15.5%): 9 NRTI+NNRTI, 3 NRTI+PI and 4 NNRTI+PI.

Table 1. Clinical and sociodemographic factors significantly associated with newly emergent or evolving LVL HIV drug resistance; multivariable GEE logistic regression model

Variable	Median [IQR] n	Unadjusted OR	p-value	Adjusted OR	p-value
Age (per 10-year increment)	49 [41-55]	0.86 (0.72-1.03)	0.099	**0.74 (0.60-0.90)**	**0.002**
Sex at birth					
Female	n=224	1.00			
Male	n=801	0.91 (0.56-1.49)	0.72		
Year of ARV Initiation (per 10-year increment)	2005 [1997-2011]	0.70 (0.53-0.93)	0.012	0.74 (0.52-1.05)	0.089
Months between resistance tests (per month increment)	13.7 [3.6-49.3]	1.01 (1.00-1.01)	<0.001	**1.01 (1.01-1.02)**	**<0.001**
Risk Group					
MSM	n=431	1.00			
IDU	n=336	1.05 (0.64-1.70)	0.86		
Other	n=7	1.10 (0.53-2.29)	0.81		
Unknown	n=156	1.00 (0.53-1.89)	0.1		
Number of prior DRT	4 [2-8]	0.96 (0.93-1.00)	0.048		
Sample Viral Load	2.26 [2.12-2.34]	3.36 (0.95-11.8)	0.059		
Viral Load Category					
Blip	n=467	1.00			
LLV	n=546	0.74 (0.48-1.13)	0.16		
Declining	n=411	0.43 (0.25-0.75)	0.003		
CD4 count (per 100 cells/mm^3 increment)	420 [260-620]	1.02 (0.96-1.09)	0.49		
Number of VL >250 c/mL between resistance tests	1 [1-3]	1.02 (0.98-1.05)	0.36		
Regimen at Collection Date (non-backbone class)					
INSTI	n=244	1.00		1.00	
NNRTI	n=151	4.4 (1.9-10.4)	<0.001	**4.2 (1.7-10.5)**	**0.002**
PI	n=688	2.2 (1.03-4.8)	0.043	**2.5 (1.03-5.8)**	**0.042**
2+ classes	n=231	1.5 (0.56-4.2)	0.41	1.6 (0.52-4.8)	0.43

A multivariable GEE logistic model adjusting for sociodemographic and clinical factors suggests that newly emergent or evolving HIV drug resistance detected in LVL specimens is associated with: younger age at time of testing, NNRTI- or PI-based cART and increased time elapsed between resistance tests. Viral Load Category: LVL samples tested for drug resistance were grouped according to the context of viral load results immediately prior to the tested specimen: "Blip" = previous VL <50 c/mL, "LLV" = ≥2 consecutive VL with VL 50-250 c/mL, "Declining" = previous VL ≥ 250 and current VL 50-250 c/mL.

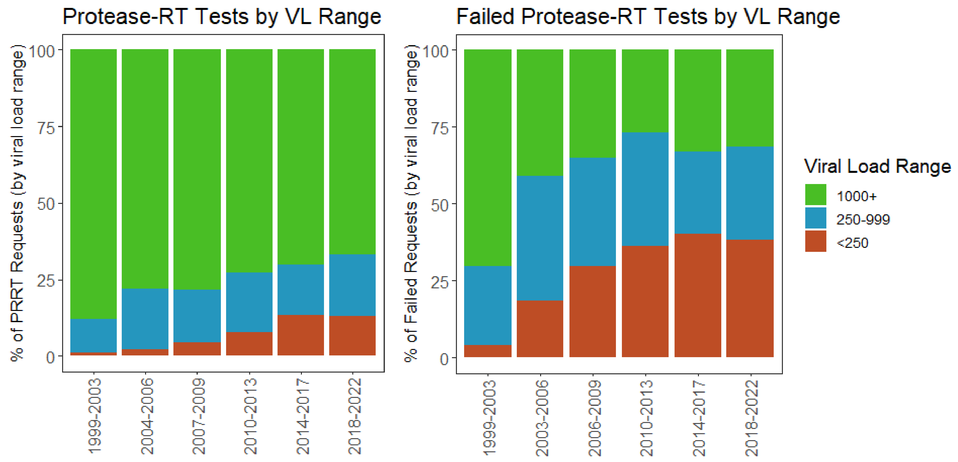


Figure 1a. The number of low viral load resistance tests comprise an increasing proportion of all resistance tests requested in British Columbia, Canada (~11%, in 2018-2022), but are still a minority of all resistance tests requested.

Figure 1b. DRT of low viral load specimens is more resource-intensive than for samples of higher VL. DRT on LVL specimens accounts for a disproportionate fraction (~37.5 % in 2018-2022) of failed resistance tests. This trend is increasing over time as demand for DRT on LVL specimens increases.

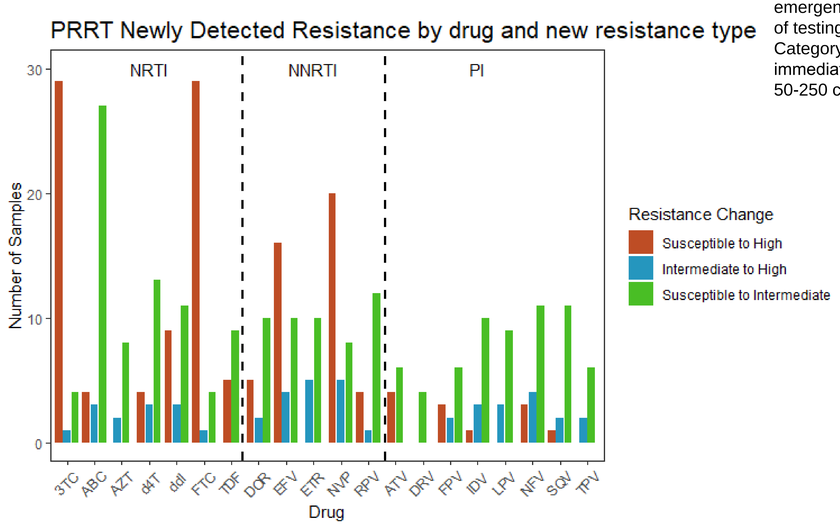


Figure 4. Detection of new or evolving resistance to individual ARVs. High-level resistance was most frequently detected to the NRTIs lamivudine (3TC) and emtricitabine (FTC) and to the first-generation NNRTIs nevirapine (NVP) and efavirenz (EFV). New or evolving high-level PI resistance was infrequent but was observed most commonly for atazanavir (ATV).

CONCLUSIONS

- New or evolving Protease-RT resistance is detected less frequently in specimens with VL 50–250 c/mL compared to samples with VL 250–999 c/mL (7.2% vs. 10.5%, p= 0.0035).
- Newly detected emergent or evolving resistance in low viral load specimens was primarily detected in the NRTI and NNRTI drug classes.
- Given the resource-intensive nature of LVL DRT, LVL DRT may be most suitable for younger PLWH, PLWH for whom a substantial amount of time has elapsed between DRT tests and for PLWH on NNRTI- or PI-based cART.
- Resistance testing of LVL specimens may be appropriate for PLWH for whom prior resistance testing results are not available; resistance to one or more classes was detected in 34.3% of such cases.

ACKNOWLEGEMENTS

We gratefully acknowledge the Clinical Genotyping Program, Drug Treatment Program, and BC-CfE Drug Treatment Program participants, without whom our research would not be possible.