Low Level HIV Viremia and Drug Resistance Testing

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Background:

The impact of low level HIV viremia (LLV; defined here as 50-1000 copies/ml) on HIV resistance is poorly defined, as most clinical resistance assays are not performed below 1000 HIV copies/ml. We explore data from British Columbia, Canada where measurements below this level can be requested.

Methods:

•The proportion of successful tests using an in-house assay using 500 uL of input plasma was examined as a function of viral load in 4893 total attempted assays.

•To examine HIV evolution and LLV, analyses were restricted to ART-naive patients achieving undetectable viral loads and rebounding between 50 and <1000 copies without a previous blip (N=212).

•Fisher's exact test or Pearson's chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables were used.

Results:

• 4304 of 4893 low-level viremia (LLV) assays (88%) attempted produced sequences (Table 1). Successful genotypes were obtained more frequently at higher viral load strata and these these higher viral load samples tended to have more observed sequence mixtures (i.e. >1 variant).

• Previously treatment naïve patients experiencing LLV had reasonably high CD4 counts (median 415 cells/mm^3) and low plasma viral loads at rebound (median 374 copies/mL) (Table 2).

• Overall, 16 patients of the 212 patients (8%) had resistance before therapy (baseline) (Table 3).

• Resistance at baseline was more common in men (p=0.02).

• Of those without baseline resistance (N=196), 38 patients (19%) evolved resistance to any class of medication at follow up with LLV, a median of 6.9 months (interquartile range 3.3–18) later. Of these patients, the most common resistance was to nRTIs (N=28; 14%) and/or NNRTIs (N=18; 9%). Only 2 cases (1%) of emerging PI mutations arose, both in patients taking nelfinavir, despite 67% of patients receiving a PI.

• The most common emerging mutations at LLV were M184V/I (9.4%V, 3.3%I), K103N (5.2%), T215 revertants (3.8%) & M41L (3.3%) (Figure 1).

• Patients on different antiretroviral regimens with no baseline resistance had different rates of resistance at LLV – ordered by increasing rates: 2nRTI + PI boosted (16.7), 2nRTI + PI unboosted (17.4), 2nRTI + 1 NNRTI (18), other ≥4 drugs (26.7) and other ≤3 drugs (38.5).

• Of 29 patients on the same who maintained low level viremia at a subsequent visit, there was no evidence of additional resistance to a new class of antiretrovirals

• There were marginally significant differences in the LLV viral load strata between the patients who evolved resistance and those who did not (median 472 vs 369c/mL, p-value=0.067). Others patient characteristics were not associated with resistance (p-value ≥ 0.1)

Table 1. Success at genotyping of low-level viremia samples

Input Viral Load (cop/mL)	50 - 249	250 - 499	500 - 749	750 - 999
Theoretical Input Copies	1.7 - 8.3	8.3 - 16.6	16.7 - 24.9	25 - 33.3
Attempted (N)	754	2043	1212	884
Successful (N)	567	1820	1118	798
% Successful	75	89	92	90
% Any mixtures	35	53	64	71
Average mixtures	3	6	9	12

Table 2. Patient characteristics at low-level viremia

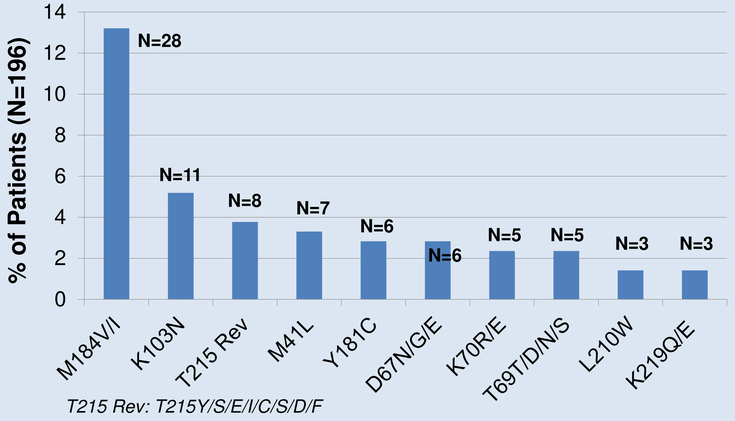
Characteristics at LLV	Category	n (%)
Gender (male)		162 (76%)
Age (Median years, IQR)		44 (37-49)
CD4 cells/mm^3 at LLV (Median, IQR) (N=202)		415 (260-580)
HIV-RNA copies/ml at LLV (Median, IQR)		374 (267-559)
Hepatitis C antibody positive (n=206)		90 (44%)
Risk group (N=162)	IDU	95 (59%)
	MSM	62 (38%)
	Heterosexual sex	83 (51%)
	Blood	2 (1%)
	Other	5 (3%)
Ethnicity (N=139)	White	92(66%)
	Aboriginal	34 (24%)
	Hispanic	11 (8%)
	Asian	9 (6%)
	Black	4 (3%)
Regimen at LLV (N=212)	2 nRTI + boosted PI	81 (38%)
	2 nRTI + unboosted PI	50 (24%)
	2 nRTI + NNRTI	50 (24%)
	other ≥4 ARVs	17 (8%)
	other ≤3 ARVs	14 (7%)

IDU, intravenous drug use; MSM, Men who have sex with men

Table 3. Genotypic resistance at baseline and LLV

Resistance mutations (N=212) N, (%)	At baseline	At LLV	Subset with no pretreatment resistance (N=196)
PI	5 (2.4)	8 (3.8)	2 (1)
NRTI	5 (2.4)	33 (15.6)	28 (14.3)
NNRTI	12 (5.7)	30 (14.2)	18 (9.2)
PI/NRTI/NNRTI	16 (7.5)	52 (24.5)	38 (19.4)

Figure 1: Most common resistance mutations emerging at LLV in patients with no resistance at baseline



T215 Rev: T215Y/S/E/I/C/S/D/F

Conclusions:

- Routine HIV genotyping of samples with detectable low level viremia can be performed with about 90% success above 250 HIV copies/ml and a reasonable chance of success between 50 and 250 copies.
- The lack of mixtures observed at lowest strata implies that only a single variant is being amplified.
- In participants experiencing their first low level viremia episode, 1 in 5 individuals were found to have new HIV drug resistance mutations, mainly to nRTIs and NNRTIs. The magnitude of viremia seemed marginally related to the evolution of resistance.
- The selection of an additional family drug resistance during the LLV episode on the same regime is not a common event.

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