Virologic Success on INSTI-Based ART Despite Archived INSTI DRMs

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BACKGROUND

In individuals with undetectable or low-level viremia, the assessment of effective ART options usually relies on cumulative historical plasma genotypic resistance testing (GRT). When past plasma GRT data are lacking, peripheral blood mononuclear cell (PBMC) GRT may be an alternative. **However, the clinical significance of drug resistance mutations (DRMs) detected in PBMC GRT remains unclear, since they may reside in defective proviruses**. Little data is available especially for integrase strand transfer inhibitors (INSTIs). This study aims to evaluate the clinical relevance of archived INSTI DRMs in virologically suppressed individuals on INSTI-based regimens.

METHODS

Adult people with HIV (PWH) with a history of HIV-1 integrase PBMC GRT since 01/03/2022 were screened. Inclusion criteria were, at the time of PBMC GRT: (i) being virologically suppressed (viral load < 50 copies/mL), (ii) being on an INSTI-based regimen, (iii) presenting at least one DRM conferring full-class INSTI resistance. Individuals who were switched off INSTI within 1 month of baseline PBMC GRT for any reason were excluded.

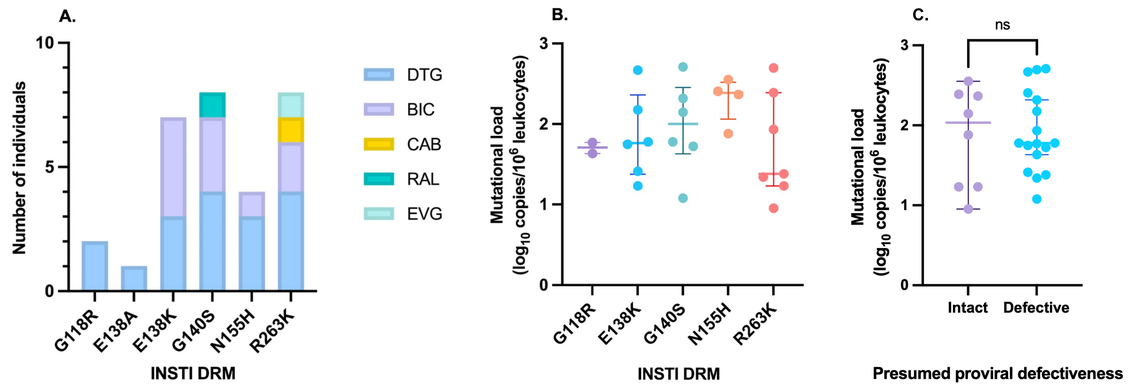
The main outcome was virological failure, defined as having at least two consecutive HIV-1 plasma viral loads over 50 copies/mL. The end of follow-up was either ART switch to a non-INSTI-based regimen or 15/09/2024.

HIV-1 integrase DNA was sequenced using the next generation sequencing Sentosa SQ HIV Genotyping Assay (*Vela Diagnostics*®). HIV-1 integrase RNA was sequenced using either this assay or Sanger sequencing. Genotypic resistance analysis was based on the Stanford HIV Drug Resistance algorithm. Total HIV-1 DNA was quantified with the Generic HIV DNA Cell kit (*Biocentric*®). Mutational load was calculated as the product of DRM frequency and total HIV-1 DNA quantity. Proviral defectiveness was presumed based on the detection of stop codons or G-to-A hypermutations (Los Alamos Hypermut 2 algorithm).

RESULTS

From 883 screened PWH, 26 were included for analysis (sex assigned at birth: 69% male; median age: 53.6 [IQR 40-61.8]; subtype B: 58%). At the time of PBMC GRT, they were successfully treated with regimens containing DTG (n=14), BIC (n=9), CAB (n=1), EVG (n=1) or RAL (n=1). Median total HIV-1 DNA was 2.36 $\log_{10}$ copies/10^6 leukocytes (IQR 2.19-2.65, n=21).

The 6 full-class INSTI DRMs detected on PBMC GRT in our sample were G118R, E138A, E138K, G140S, N155H and R263K. These DRMs were documented 30 times and were distributed across INSTI regimens as shown in Figure A. Variant frequency of DRMs ranged from 5.3% to 100%. Median mutational load was 1.79 $\log_{10}$ copies/10^6 leukocytes (IQR 1.39-2.38). Distribution of mutational loads across DRMs is shown in Figure B.



DRMs were found in presumably defective proviruses in 18 individuals (69%). Mutational loads of DRMs harbored by presumably defective and intact proviruses were not significantly different (p=0.786, Figure C). A history of VF on an INSTI-based regimen was documented for 8 individuals. Half of them had DRMs harbored by presumably intact proviruses. Five participants with a history of VF had previous plasma GRT data available: two of these presented the same DRM(s) as in PBMC GRT. In these two individuals, PBMC DRMs were harbored by presumably intact proviruses.

No virological failure was reported during follow-up (median duration: 202 days [IQR 105-366].

Detection of archived proviral INSTI DRMs does not preclude sustained viral suppression in PWH already suppressed on INSTI-based regimens.

Routine sequencing techniques allowing reliable discrimination of DRMs harbored by defective or intact proviruses are needed.

CONCLUSIONS

No virological failure on an INSTI-based regimen was observed over a 6 months median follow-up in 26 PWH harboring archived INSTI DRMs. While virological suppression on an INSTI-based regimen could suggest that INSTI DRMs should be exclusively found in defective proviruses, we did not identify stop codons and/or hypermutations in about 1/3 of individuals. In addition, there was no significant association between presumed defectiveness of proviruses harboring DRMs and corresponding mutational loads.

Two hypotheses could explain these findings: (i) defectiveness of proviruses could be underestimated by our methods; (ii) presumably intact proviruses harboring DRMs could be transcriptionally silent (“block and lock” state).

The method we used for defectiveness assessment has been previously reported and is commonly used in routine clinical settings. However, it does not allow the joint assessment of proviral defectiveness and DRMs. Methods allowing single-molecule linkage analysis (such as long-read sequencing) could be instrumental for increasing the accuracy of PBMC GRT interpretation.

ADDITIONAL KEY INFORMATION

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