Integrase drug resistance mutations in proviral DNA of HIV-1 Individuals in Puerto Rico

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Background
The Commonwealth of Puerto Rico is among the top ten states and territories having the highest prevalence of HIV infection, rate of HIV diagnosis and highest accumulated cases of Acquired Immune Deficiency Syndrome (AIDS). During the period of 1981 to 2019, approximately 49,791 people had been diagnosed with human immunodeficiency virus type 1 (HIV-1) in PR. Recent studies have shown high prevalence of drug resistance mutations (DRM) to Protease Inhibitors (PIs) and Reverse Transcriptase Inhibitors (RTIs) in PR. Currently, integrase strand transfer inhibitors (INSTIs) are being used as part of first-line ART and as rescue therapy for heavily treated HIV-1 infected patients. Though INSTIs show high genetic barrier to drug resistance, it does occur, and transmission of DR has been reported in ART-naïve patients. As the use of INSTIs increases, including the surveillance of DRM in the integrase gene becomes increasingly more important as part of the clinical management of HIV patients. In PR, integrase inhibitors have been used for several years, however the prevalence of integrase drug resistance mutations has not been determined for DNA integrase sequences of HIV patients.

Methods
A total of 185 integrase sequences comprising the period from 2016 through 2019 were evaluated for the presence of INSTIs DRM. HIV-1 pro-viral DNA and RNA were extracted from whole blood and plasma, respectively. The integrase gene was amplified using our WHO-accredited HIV-1 RNA genotyping protocol and a modified nested PCR for DNA samples. Sequences were obtained using an ABI 3730xl sequencer. Genotypic drug resistance interpretation was performed using the Stanford HIV Drug Resistance Database

Results
Of the 185 proviral DNA integrase sequences we analyzed, six (3.3%) were identified to contain INSTI drug resistance mutations. These six samples corresponded to male individuals, with average age of 42.8 yrs (range 22-62) and an average CD4+ count of 488.16 (range 175-819). In the proviral DNA integrase sequences of these six sequences, we detected several major DRM but no known DR accessory mutations. We also detected other DR mutations or polymorphisms present in the DNA integrase sequence. Comparing the presence of integrase DR mutations in proviral sequences with those from population RNA integrase sequences of the same time period (2016-2019) we found that 4.3% of DNA integrases showed DRMs compared to 7.6% of RNA integrase sequences (n=171).

Conclusions
We found a low frequency of INSTIs drug resistance mutations in the HIV-1 DNA integrase latent reservoir in sequences spanning from 2016 to 2019. However, those resistance mutations were found to provide high to intermediate resistance to INSTIs, and include DRM associated with intermediate resistance to dolutegravir. In this study, we found there was a lower frequency of DR in the proviral DNA integrase when compared to INSTIs drug resistance mutations present in circulating virus for this same time period. The clinical significance and impact of those DRM present in the proviral reservoir remains unclear.