Integrase strand transfer inhibitors (INSTIs) resistance among HIV-1 patients in Malaysia

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Purpose

Raltegravir and Dolutegravir are the two integrase strand transfer inhibitors (INSTIs) available as a first line antiretroviral therapy (ART) in Malaysia. INSTI with a combination with HIV-1 reverse-transcriptase inhibitors are given to HIV-1 infected patients who are not tolerating Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). This study aimed to identify the most common major drug resistance mutation (DRM) towards INSTI and the most predominant HIV-1 subtype for this study population.
Methods and Materials

109 plasma samples from treated HIV-1 adult patients who have demonstrated high level resistance patterns towards first line anti-retroviral therapy (ARV) or are currently treated with INSTI with evidence of virological failure were included in this study. All samples were subjected to the in-house genotyping assay and the integrase region of the \textit{pol} gene were sequenced. Analysed sequenced were submitted to the Stanford HIV-1 Drug Resistance Database to yield associated DRMs and for subtype analysis.
109 plasma samples from treated HIV-1 adult patients who have demonstrated high level resistance patterns towards first line anti-retroviral therapy (ARV) or are currently treated with INSTI with evidence of virological failure were collected from various hospitals in Malaysia.

All plasma samples were subjected to the in-house genotyping assay for integrase. The process included:

- Extraction → Reverse Transcription → Nested PCR → AGE → 1st Purification → Cycle Sequencing → 2nd Purification → Sequencing

Sequencing covers the entire integrase region to encompass all known DRMs. Result submission to Stanford HIV-1 Drug Resistance Database to yield associated DRMs and subtype analysis.

**Fig. 1:** Material and methodology

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Results

HIV-1 viral load of 102 samples ranged from 851- 620,915 copies/mL, while HIV-1 viral load for 6 samples were not stated. Age of patients in the study ranged from 3-71 years old. 73 out of 108 samples were successfully amplified and sequenced. Major DRMs were detected in 19 (18.6%) of patients with the most common DRM detected was Y143C/H/R/Y. The presence of Y143C/H/R/Y had caused a potentially low resistance towards Dolutegravir and high level resistance towards Raltegravir. Other DRMs detected were G140A, Q148R, N155H/N and E138K.

All 3 most commonly reported DRMs which confer resistance to Raltegravir; Y143C/R, N155H and Q148R were identified in this study population. These DRMs represent three different resistance pathways to Raltegravir. In addition, Raltegravir resistance can be further enhanced with the presence of selected accessory mutations, thus its presence needs to be addressed. The percentage of DRMs detected in this study was high which could be due to a low number of samples was tested. Testing more samples for DRMs towards integrase will yield more accurate data for the country. Predominant HIV-1 subtype detected in this study was CRF_01 AE (90.4%).
Images for this section:

**Fig. 2:** Example of chromatogram

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**Fig. 3:** Example of contig map

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Conclusion

The detection of DRMs and the availability of INSTIs susceptibility of the individual patient was crucial in choosing the right treatment in the management of HIV-1 patients. A clearer picture on DRMs and INSTIs susceptibility can be obtained as more patients are tested.
References

2. HIV Stanford Database. https://hivdb.stanford.edu/