Type: Poster Presentation

Final Abstract Number: 42.105
Session: Poster Session II
Date: Friday, March 4, 2016
Time: 12:45-14:15
Room: Hall 3 (Posters & Exhibition)

Archived drug resistance profile among suppressed HIV patients using conventional and sensitive allele specific PCR in Tenofovir experienced patients in South India

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Background: Drug resistance (DR) is one of the major hurdles in HIV treatment. HIV RNA based DR testing is relatively expensive and infeasible compared to DNA based, in setting where transport of specimen to regional/central laboratory is needed. Previous report states concordance between RNA and DNA DR pattern. Patient with suppressed viral load (SVL) may harbor DR, which cannot be detected by conventional DR assay; hence PBMC DNA sequencing and Allele specific PCR (ASPCR) which can quantify minority variants, can predict adherence status and predisposition to failing treatment; which can be managed earlier.

Methods & Materials: We examined reverse transcriptase (RT) sequence in PBMC DNA of patients with SVL for DR using conventional Sanger sequencing and ASPCR for RT mutations K103N and K65R. DR was based in 2014 IAS-USA DR list.

Results: We analyzed n=90 on TDF regimen (82, 1st line and 8, 2nd line), with median age 38 years, n=50 being female; all had subtype C infection and showed monophyletic clustering. Any DR mutations (DRM) were observed in n=12 (13.3%), NRTI DRM in n=8 (8.9%), NNRTI DRM in n=11 (12.2%), and both in n=8 (8.9%). Major NRTI and NNRTI DRM observed was M184I/V (7.8%), K70R (3.3%) and V106A/M (4.4%), K103N (3.3%) respectively. Although, population genotyping shows K65R and K103N DRM in none and 3.3%, respectively. ASPCR result shows 32/30 had >1%, 8/13 had > 5% and 3/ 9 had >10% K65R/K103N, respectively. K65R, and K103N negative by population genotyping and positive (>10%) by ASPCR was observed in 3.3% and 6.7%, respectively. Mutation pattern shows none showed resistance to TDF despite being in that regimen, in contrast resistance for NVP and EFV was observed in 7.8%.

Conclusion: PBMC genotyping among suppressed has shown resistance mutation among 13%, does the mutations observed reflect recent archival is a big question. In this scenario how reliable it is to manage HIV infection among suppressed taking archived DR into consideration, needs to be substantiated. In the other way on considering PBMC DNA as recent archival; based on ASPCR result, the minor proportion of resistant virus corroborates the ongoing minimal viral replication, which is one of the hurdle in HIV cure.

http://dx.doi.org/10.1016/j.ijid.2016.02.573

Type: Poster Presentation

Final Abstract Number: 42.106
Session: Poster Session II
Date: Friday, March 4, 2016
Time: 12:45-14:15
Room: Hall 3 (Posters & Exhibition)

Low virulence of HIV-1 subtype C underlies treatment success despite high baseline viral loads

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Background: High baseline viral load is implicated in rapid disease progression, as is often the case in resource-limited settings. Intriguingly, despite higher baseline viral loads, first-line antiretroviral treatment (ART) of HIV-1C infection in India elicits a response comparable to that of HIV-1B infection in the west. Models of viral dynamics, applied to HIV-1B infection, have shed light on viral decay dynamics and elucidated markers of treatment outcome, although such studies for HIV-1C are lacking. We hypothesized that the HIV-1C strain in India is less virulent than the HIV-1B strain in the west, leading to a favourable treatment response.

Methods & Materials: To test this hypothesis, we measured viral decay dynamics during treatment and analyzed the data using a mathematical model to estimate the within-host basic reproductive ratio, R_0, a quantitative measure of virulence, and the critical efficacy for successful treatment, e_c. Patients were initiated on first-line ART in India and followed for the first 6 months of treatment. Viral load, $CD4^+$ T-cell count, and adherence data were collected at baseline, 4, 12, 16 and 24 weeks following ART initiation. Drug resistance genotyping was done at baseline.

Results: Among 257 patients with complete data (mean age 36.2 years and 60% male), mean baseline viral load was 5.7 $\log_{10}$ copies/mL. At 6 months, 87.5% had undetectable viral load. Sub-optimal adherence (<95%) ($p<0.001$) and primary drug resistance mutations ($p=0.029$) were associated with virological non-response. Our mathematical model, considering the dynamics of productively and long-lived infected cells, provided good fits to the viral load data. We estimated the median R_0 to be 5.3 (IQR: 4.5-7.1), which is significantly smaller ($p=0.001$) than current estimates for HIV-1B (median $R_0 \sim 8$), indicating lower virulence of HIV-1C than HIV-1B. The corresponding e_c for HIV-1C is ~ 0.8, again smaller than that for HIV-1B.

Conclusion: The lower R_0 and e_c imply that responses can be achieved with lower dosages and/or adherence, potentially explaining the favourable treatment response of HIV-1C infection in India despite the high baseline viral loads. The lower virulence of HIV-1C may also underlie its growing global spread.

http://dx.doi.org/10.1016/j.ijid.2016.02.574