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Selection of nonnucleoside reverse transcriptase inhibitor-associated mutations in HIV-1 subtype C: evidence of etravirine cross-resistance

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Summary

Prevalence of etravirine genotypic resistance was assessed among 92 HIV-1C-infected patients failing nevirapine and efavirenz-based regimens from a cohort of 552 Indian patients. Overall prevalence of etravirine cross-resistance identified using the Tibotec weighted score was 41% (31.5% intermediately-resistant and 9.8% fully-resistant). The most frequently described NNRTI-associated mutations included Y181 (35.9%), K101(20.7%), G190(17.4%) and V108 (15.2%). The resistant group demonstrated higher viral load (p=0.01) and longer duration of antiretroviral treatment (p=0.03) compared to the susceptible group.

Keywords

Etravirine cross-resistance; HIV-1 subtype C; NNRTI experience; India

The low genetic barrier to development of resistance to first generation non-nucleoside reverse transcriptase inhibitors (NNRTI) is compounded by cross-resistance across the class which makes sequential therapy with the NNRTIs therapeutically inappropriate. Current first-line NNRTI in most resource-constrained regions includes nevirapine, except in cases of intolerance or potential drug interaction when efavirenz is used [1]. Etravirine, a new generation NNRTI (TMC-125, Intelence, Tibotec Pharmaceuticals Ltd) was approved by US FDA for use in ART-experienced adults with resistance to first-line NNRTIs. Etravirine resistance-associated mutations (RAMs) in reverse transcriptase (RT) gene were identified are as follows; V90I, A98G, L100I, K101E/P/H, V106I, V179D/F, Y181C/I/V, G190A/S, E138A, V179T, and M230L [2–4]. The Tibotec Weighted Score was proposed with 17 etravirine-RAMs and assigned differential weights based upon the impact on clinical response [5]. Alternatively, the Monogram Weighted (MW) Score included 30 etravirine-RAMs based on the genotypic and phenotypic inter-relationship [6]. Etravirine cross-resistance may be influenced by the prevailing HIV-1 subtype [7,8]. With a worldwide prevalence of 50% [9], and prevalence in India of 96%, HIV-1C undoubtedly has a significant impact on the evolution of the HIV epidemic globally. This study reports the

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selection of NNRTI RAMs and etravirine cross-resistance patterns among HIV-1C infected patients failing first-line ART.

Among a total of 552 participants participating in a 2-year longitudinal cohort study [10], 18% (n=101) with detectable viremia were assessed for presence of drug resistance-associated mutations during their baseline visit [11]. Drug resistance genotyping was successfully done from 92 plasma samples from failing patients (viral load >1000 copies/ml) using a validated in-house method [12]. Drug-resistant strains previously reported from India (n=429) from patients failing first-line ART were included as a second group in this study[13–19]. A third group of 1,122 global HIV-1C sequences were obtained from HIVseq Program (http://hivdb.stanford.edu/; accessed 13th August 2010) reported from patients worldwide with a history of treatment of NNRTI drugs. Indian sequences and duplicates were excluded from global subtype C sequences. NNRTI-DRMs in all these sequences were analyzed. Etravirine resistance was evaluated by Tibotec Etravirine Weighted Genotype Score [5]. Statistical analysis was performed in SPSS v11.5.

Plasma virus was successfully genotyped in 92 failing patients; their mean age was 39.6 years (SD 10.2yrs) and 67% were male, similar to the complete cohort. Among the 92 patients, 77% used nevirapine; 12% used efavirenz and 10% changed from an initial nevirapine-based regimen to an efavirenz-based regimen for clinical reasons. The mean duration of nevirapine and efavirenz exposure was 23 and 14 months, respectively.

The overall prevalence of etravirine resistance was 41% (38/92). Single etravirine-RAMs were seen in 13% and two etravirine-RAMs were seen in 33% strains. Eleven percent (10/92) strains harbored three or more etravirine-RAMs. The Tibotec Weighted Score identified 58.7% of the strains to be susceptible to etravirine whereas 31.5% and 9.8% strains displayed intermediate resistance and resistance respectively. Alternative scoring methods showed comparable patterns (39% of strains had an MW score ≥4) indicating that a significant percentage of isolates had reduced efficacy to etravirine.

Genotypic analysis predicted that 41.6% (30/72) of samples from nevirapine-experienced and 9.1%(1/11) from efavirenz-experienced patients were cross-resistant to etravirine. The maximum level of cross-resistance (77.8%, 7/9) was observed in those patients who had exposure of both the drugs. The most frequently described RAMs included amino acid substitutions at positions Y181 (35.9%), K101(20.7%), G190(17.4%) and V108(15.2%).. Similar trends were observed in sequences reported previously from India (n=429); however among global subtype C sequences, K103N was the most frequent RAM (Figure 1).

Compared to patients with susceptible virus, those who harbored etravirine-resistant virus were more likely to have been on ART for a longer duration (p=0.03) and to have higher viral load (p=0.01) (Supplementary digital content 1). There was no significant difference in age, CD4 count, time since diagnosis or self-reported adherence in the last month measured by Visual Analog Scale between the two groups.

Our report highlights the high prevalence of etravirine cross-resistance (41%) among the patients infected with HIV-1C viruses and failing first generation NNRTI-based regimens in India. Etravirine RAMs has also been described in ART-naïve patients from France, Mali and India [20, 21]. Our finding of etravirine resistance is higher than among HIV-infected patients harboring subtype B in UK (11.5%) and Spain (18.7%). A similar study from Thailand found 56% etravirine cross-resistance in HIV-1 CRF01_AE strains [24].

The high prevalence of Y181 and K101 found in our setting is also seen in other places where nevirapine is widely used as first-line NNRTI. Similar trends have been observed in patients with CRF01_AE strains from Thailand (50% Y181C/I/V and 18.7% K101E/H/P)

[24] and UK (17% Y181C in those failing efavirenz and 40.5% Y181C were in those failing nevirapine) [25], thus lending credence to the conclusion that Y181C is particularly selected during prolonged exposure to a failing nevirapine-containing regimen [11].

The association between etravirine resistance and higher viral loads in the study cohort may be reflective of the longer duration on poorly suppressive regimens experienced by these patients [26]. In settings like India where routine viral load monitoring is not a part of standard of care, the second-line antiretroviral therapy regimens have to be designed with caution when including NNRTI drugs. As over 50% of failing isolates are susceptible to etravirine, it can be used as salvage therapy among those patients failing first generation NNRTI-based regimens. Patients with high level of etravirine-RAMs were also more likely to have tenofovir-associated mutations [27] which may raise challenges in designing an effective second-line regimen in resource-constrained settings like India. The presence of cross-resistance also highlights the need for developing effective and sustainable adherence interventions that target local adherence patterns and barriers in order to keep the limited first-line ART agents effective for as long as possible [10].

In summary our study highlights the high level of etravirine cross-resistance in a cohort of ART-experienced patients failing NNRTI-containing first-line therapy in India. The pattern of NNRTI-mutations in nevirapine exposed patients also suggests the possible benefit of reconsidering the use of nevirapine in favor of efavirenz as first-line NNRTI choice in resource-constrained settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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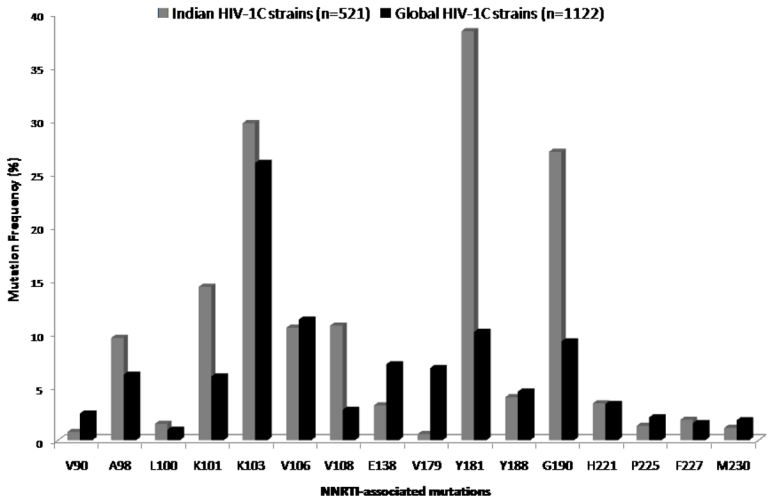

Figure 1. Selection of NNRTI mutations in ART experienced patients harboring HIV-1 subtype C viruses

Higher frequencies of NNRTI drug resistance mutations are present in residues Y181, K101, G190 and V108 in Indian sequences (n=521, 92 primary isolates and 429 previously reported sequences) compared to global subtype C sequences (n=1122) obtained from HIVseq Program from Stanford University HIV Drug resistance database (http://hivdb.stanford.edu/; accessed on 13th August 2010).