BACKGROUND/OBJECTIVE

- Etravirine (ETR) is a second-generation NNRTI that is used as a component of combination antiretroviral therapy (ART) for treatment-experienced persons.
- The extent of cross-resistance between nevirapine (NVP) and efavirenz (EFV) and ETR is not well defined especially in low- and middle-income countries (LMIC) where switches from first-line ART may be delayed.
- To address this gap, the susceptibility to ETR in individuals infected with HIV-1 subtype C experiencing virologic failure while on a first-line NNRTI-containing regimen was investigated.

METHODS

Sample Acquisition
- Residual plasma from samples sent for routine HIV drug resistance testing at LanCt Laboratories, South Africa
- Targeted criteria:
  - Subtype C infection
  - Failing first-line therapy after >6 months of ART
  - Viral load of >10,000 RNA copies/ml
  - Contains ≥ 1 NNRTI mutation in reverse transcriptase (Stanford HIVdb)
- Included N=12 ART-naive controls for calculating composite IC50 for Fold Change (FC) values

Sample Size and Description

<table>
<thead>
<tr>
<th>Subtype C Samples</th>
<th>135 Samples</th>
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<tbody>
<tr>
<td>Extraction Failures</td>
<td>6/135 (4.4%)</td>
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<tr>
<td>PCR Failures</td>
<td>14/135 (10.4%)</td>
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<tr>
<td>Cloning Failures</td>
<td>3/135 (2.2%)</td>
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<tr>
<td>HIV-1 RNA levels Median 20-73 (log) Range 4.01-16.20 (log) (n=135)</td>
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Cloning and Phenotyping
- Extract HIV-1 RNA from donor American
- Generate cDNA & PCR amplify RT full-length sequence (ca 1-568)
- Clone donor full-length HIV-3 RT into viral vector
- Transfer cells with donor-derived viral vector and prepare viral stocks
- Determine viral susceptibility to ETR using TZM-bl cells

Genotype Scoring
- HIVdb vs. ETR weight factors for ETR RNA

Figure 1: (A) Phenotype and (B) genotype cross-resistance to etravirine of plasma-derived HIV-1 subtype C viruses from 100 individuals on four first-line RTKs.

RESULTS

Table 1. The NNRTI mutations L100I, Y181C, M230L and the K65R mutation K65R are associated with ETR Cross-Resistance Phenotype Score.

Table 2. K65R is associated with high ETR phenotypic resistance in (A) HIV-1 subtype C samples and (B) HIV-1 subtype B ETR phenotyping data accessed through the Stanford HIVdb.

Table 3. There was no change in ETR susceptibility in recombinant HIV-1 virus clones containing 65K vs. K65R (site-directed mutation).

Figure 4. The correlation between K65R and ETR phenotypic resistance is related to the total number of NNRTI-resistance associated mutations.

Summary

- The K65R mutation was associated with ETR resistance but reversion to 65K in two samples had no effect on ETR susceptibility, suggesting it may be a marker of resistance rather than a direct cause of resistance.

Conclusions

- Phenotypic cross-resistance to ETR is common in first-line NNRTI-containing ART failure in HIV-1 subtype C from South Africa.
- Genotype-based algorithms differentially classify ETR susceptibility in HIV-1 subtype C.
- Updated weightings of combinations of ETR-associated mutations may be needed to improve genotype prediction of ETR phenotype in HIV subtype C.

REFERENCES


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