Virological Responses to Lamivudine and Emtricitabine in the Dutch ATHENA Cohort.
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Background
Lamivudine and emtricitabine are equally recommended by guidelines with tenofovir and efavirenz, nevirapine, or boosted PI as first-line cART for ART naive HIV-1 patients.

The use of generic lamivudine could replace emtricitabine to constrain costs. The evidence for their clinical equivalence with tenofovir and NNRTIs or boosted PIs in ART naive HIV-1 patients is inconclusive.

The aim of this study was to evaluate the virological responses to lamivudine and emtricitabine in combination with tenofovir and efavirenz, nevirapine, or a boosted PI in the ATHENA cohort.

Methods
Nationwide cohort study between 2002 - 2012 on 6322 ART naive HIV-1 patients without documented baseline resistance.

Clinical endpoints:
1. Virological failure at week 48 and week 240.
2. Time to HIV-RNA <400 c/mL.
3. Time to virological failure after HIV-RNA <400 c/mL.
4. Acquired resistance.

Virological failure was defined as (1) HIV-RNA >400 c/mL at 48±10 weeks, (2) ART switches for failure, (3) death while last HIV-RNA was >400 c/mL. Responses were analyzed by multivariate Cox proportional hazard models.

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lamivudine/tenofovir (n=5452)</th>
<th>Emtricitabine/tenofovir (n=5452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41 (24-68)</td>
<td>43 (24-68)</td>
</tr>
<tr>
<td>Sex</td>
<td>49% (n=2640)</td>
<td>51% (n=2732)</td>
</tr>
<tr>
<td>CDDA</td>
<td>2000 (1000-3000)</td>
<td>2000 (1000-3000)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>90 (10-150)</td>
<td>90 (10-150)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>75 (0-400)</td>
<td>75 (0-400)</td>
</tr>
<tr>
<td>HIV-1 Transmissibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>65% (38-93)</td>
<td>65% (38-93)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>35% (22-49)</td>
<td>35% (22-49)</td>
</tr>
<tr>
<td>Region of origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>175 (95-230)</td>
<td>175 (95-230)</td>
</tr>
<tr>
<td>MSM</td>
<td>66% (33-100)</td>
<td>66% (33-100)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>200 (100-300)</td>
<td>200 (100-300)</td>
</tr>
</tbody>
</table>

Results

Adjusted HR (95%CI) on virological failure with lamivudine compared to emtricitabine was 2.4 (1.43-3.64) with efavirenz, and 2.0 (1.4-3.0) with nevirapine.

Conclusions

With efavirenz or nevirapine, the use of lamivudine instead of emtricitabine in combination with tenofovir for ART naive HIV-1 patients was associated with more virological failure.

With a boosted PI, the use of lamivudine instead of emtricitabine in combination with tenofovir for ART naive HIV-1 patients was not associated with different virological responses.

The evidence for their equal recommendation with tenofovir in NRTI backbones of first-line cART is not based on RCTs that have directly compared lamivudine/tenofovir with emtricitabine/tenofovir. Our results support their equivalence in boosted PI containing cART only.

Our observations warrant a direct randomized blinded comparison of lamivudine with emtricitabine in tenofovir and NNRTI containing cART.