Cross-sectional assessment of virological failure, drug resistance and third-line regimen requirements among patients receiving second-line ART in 3 large HIV-programmes in Kenya, Malawi and Mozambique

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Introduction

Study design

1. Cross-sectional assessment
2. Participant recruitment
3. Viral load measurement (VL)
4. Resistance genotyping
5. ART regimen adaptation based on resistance profile
6. Follow up for 6 months after failure & EAC

Eligibility criteria

Age ≥ 2 years

Results

Participant characteristics at inclusion

<table>
<thead>
<tr>
<th>Study sites</th>
<th>Eligible, N</th>
<th>Included, N</th>
<th>Mean age, year (SD)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>705</td>
<td>355</td>
<td>36.6 (±10.7)</td>
<td>95%</td>
</tr>
<tr>
<td>Malawi</td>
<td>254</td>
<td>342</td>
<td>35.6 (±10.4)</td>
<td>98%</td>
</tr>
<tr>
<td>Mozambique</td>
<td>205</td>
<td>205</td>
<td>36.4 (±10.7)</td>
<td>98%</td>
</tr>
</tbody>
</table>

Viral load at inclusion

<table>
<thead>
<tr>
<th>Study sites</th>
<th>HIV RNA, cps/mL</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>&gt;20000</td>
<td>500 (72%)</td>
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</table>

HIV subtypes

Study sites: Kenya: HIV-1B prevalent; Malawi: HIV-1A prevalent; Mozambique: HIV-1C prevalent.

ART regimen composition for patients with failure (Kenya)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>ART regimen</th>
<th>N (%)</th>
</tr>
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<td>ART regimen</td>
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</tbody>
</table>

Six month follow up VL results after failure (Kenya site)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>6 Month FU - VL available</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
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Discussion

- Overall good virological suppression was achieved on second-line ART, especially in Kenya and Malawi.
- Two-thirds of patients with virological failure required regimen optimization or switch to third-line.
- One third of patients had no major drug resistance - indicating very poor adherence.
- ART Regimen adaptation for patients with failure was through re-cycling of standard of ARTs as well as by use of new generation ARVs.
- Notably higher failure rates found in children and adolescents, highlighting the need for enhanced monitoring.
- Considerable cross-resistance to efavirenz was found.
- Preliminary data indicate good short-term outcomes of patients receiving optimized third-line ART.
- Resistance data were essential to inform ART regimen choice of patients with second-line failure.
- Better access to resistance genotyping and new generation ARVs are urgently needed.

Acknowledgements: We thank the study- and MSF teams in the field sites, the Ministries of Health and the study participants for their support, and SIDACTION for co-funding (A04-120223).

Methods

Study sites

- Kenya: HIV-outpatient clinic in Homa Bay District Hospital
- Malawi: Chiradzulu District, 3 peripheral health centers
- Mozambique: Maputo City, Chaminhau Health District, Alto Mac Rero Referral Health Centre

Sample size: 40-50% of eligible patients per site

Sampling: random (Kenya, Mozambique), convenience (Malawi)

Primary objectives

- To determine the proportion of patients with virological failure
- To describe the drug resistance patterns

Secondary objective

- To assess outcomes at 6 and 12 months after virological failure

Inclusion period: November 2014 - August 2015

HIV viral load in plasma: Kenya and Mozambique: automated real-time PCR using the Cobas Ampliprep/Cobas Taqman HIV-1 test v.2.0 (Roche Diagnostic); Malawi: G2 Generic real-time PCR assay (Bioanalyzer)

HIV-1 resistance genotyping: Subtype determination and resistance was done for patients with VL >500 cps/ml by sequencing protease and part of reverse transcriptase regions with a WHO-acknowledged broadly sensitive in-house assay for HIV-1 non-B strain. Drug resistance scoring was done by applying the Stanford HIVdb Genotypic Resistance Interpretation Algorithm (Version 7.0, last updated 02/27/14).

Definitions:

- Virological failure: VL ≥ 500 cps/mL
- Second-line ART based boosted protease inhibitor (PI) combined with two NRTIs
- Optimized second-line regimen: substitution of one or both NRTIs due to resistance
- Third-line regimen: replacement of the PI due to PI resistance, when or without replacement of NRTI(s)

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Related study

- Malawi: all sequenced strains were subtype C
- Mozambique: 90% were subtype C
- Kenya: were subtype C, most were either A, URFa and/or A2

Results

- The majority were adults aged 34-38 years
- In Kenya and Mozambique all patients received a boosted lopinavir (LPV/r)-regimen
- In Malawi 82% of patients received a boosted atazanavir (ATV/r)-regimen
- Malawian patients on second-line ART at inclusion ranged between 2.2-2.5 years
- Most patients were in overall good clinical condition at inclusion (stage 1H or 2)

Intermediate & high-level resistances by ARV drug

- 12-17% had ≥1000 cps/mL (WHO-recommended virological failure threshold)
- This translates into overall good suppression (<1000 cps/mL, 83% (Kenya), 67% (Malawi), 72% (Mozambique))
- Virological failure was eight times as high among <19 years patients in all sites
- Resistance genotyping was performed on VL ≥500 cps/mL (N=65, N=41, N=61)

ART regimen requirements among patients with failure

- 20-32% of patients with virological failures needed switch to a third-line regimen (major PI resistance)
- 22-32% patients required optimization of their second-line regimen (major NRTI resistance)
- 34-41% were still on an effective regimen
- In Kenya patients with virological failure without major resistance (37%) were changed to a simplified ATV/r-based regimen to support adherence

Six month follow up VL results after failure (Kenya site)

- Overall good virological suppression was achieved on second-line ART, especially in Kenya and Malawi.
- Two-thirds of patients with virological failure required regimen optimization or switch to third-line.
- One third of patients had no major drug resistance - indicating very poor adherence.
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