Pretreatment HIV-1 Drug Resistance and Response to First-line Antiretroviral Treatment in sub-Saharan Africa

The PASER Network

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PASER network: Monitoring cohort

- Prospective, observational cohort at 13 routine ART sites in 6 countries
- Population: Adults initiating 1st-line NNRTI-based ART (n=2733), or switching to 2nd-line bPI-based ART (n=250) in 2007-2009
- Consecutive enrolment of n=240 at each site
- Assessment of HIV-RNA and (if >1000c/ml) population-based pol genotyping
PASER-M patient eligibility criteria

**Inclusion criteria**

- Confirmed HIV-1 infection
- ≥18 years of age
- Eligible for initiation of a first-line ART regimen, or switch from a first-line ART regimen (containing at least three antiretroviral drugs and taken for at least six months) to a second-line ART regimen due to virological, immunological and/or clinical failure
- Signed informed consent for study participation prior to enrolment

**Exclusion criteria**

- Currently taking ART (minimum of 3 drug regimen), if initiating a first-line ART regimen
- Pregnancy at enrolment
- HIV-1/2 dual-infection (in endemic countries only)

**ART, combination antiretroviral therapy**

- Eligibility for ART initiation defined in accordance with national ART guidelines (i.e. advanced immunodeficiency as defined by CD4 cell count <200 or <350 cells/μl, or advanced clinical disease according to WHO clinical stage/CDC classification).
- Specified PASER-M definition: re-initiation of a first-line ART regimen < 30 days after stopping previous first-line ART (previous use of antiretroviral prophylaxis or mono/dual therapy is not an exclusion criterion).
- Exclusion criteria applicable to PASER-M only
Pretherapy HIVDR in ARV-naïve patients by region and drug class  

**PASER-M cohort**

- **2590 participants**
- **2436 pol sequences**
- **139 (5.6%)** with ≥1 DRM
- **112 (81%)** single drug-class
- **104 (75%)** single DRM

**Any DRM:** 5.6%
- **NRTI:** 2.5%
- **NNRTI:** 3.3%
- **NRTI + NNRTI:** 1.2%

**Most common DRMs:**
- K103N, Y181C/I, G190A/S, TAMs, M184V

**Estimated increase since ART rollout**
- **Any DRM:** 38%/yr (13-68) (p=0.001)
- **NNRTI:** 35%/yr (1-81) (p=0.041)

WHO 2009 Surveillance Drug Resistance Mutation list  

Hamers et al. Lancet Inf Dis 2011
Pretherapy HIV VDR

WHO surveys at ART initiation (n=5094, 40 surveys)

Any DRM: 5%
NRTI: 1.4%
NNRTI: 3.7%
NRTI + NNRTI: 0.6%
Pretherapy HIVDR to NNRTI is related to ART coverage

WHO surveys at ART initiation

OR per 10% ART increase: 1.38 (95% CI 1.09–1.75)
TDR (NNRTI) in untreated people is on the rise in East and southern Africa

- 26102 Hiv+ patients from Africa, Asia, Latin America
- Annual increase of TDR in East Africa (29%) and Southern Africa (23%)

Gupta et al. Lancet 2012
### Patient characteristics by pretherapy HIV DR

**PASER-M cohort**

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Overall (n=2579)</th>
<th>No PDR (n=2404)</th>
<th>PDR (n=275)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1493 (58)</td>
<td>1396 (58)</td>
<td>97 (55)</td>
<td>0.494</td>
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<tr>
<td>Age - mean years (SD)</td>
<td>37.8 (9.0)</td>
<td>37.8 (9.0)</td>
<td>37.6 (9.3)</td>
<td>0.736</td>
</tr>
<tr>
<td>Advanced WHO stage (3/4)</td>
<td>1579 (61)</td>
<td>1474 (61)</td>
<td>105 (60)</td>
<td>0.936</td>
</tr>
<tr>
<td>No prior ARV exposure</td>
<td>2442 (95)</td>
<td>2302 (96)</td>
<td>140 (80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CD4 - median cells/μL (IQR)</td>
<td>133 (62-204)</td>
<td>133 (62-204)</td>
<td>129 (53.5-204.5)</td>
<td>0.7148</td>
</tr>
<tr>
<td>HIVRNA- median log₁₀ c/mL (IQR)</td>
<td>5.0 (4.4-5.6)</td>
<td>5.0 (4.5-5.6)</td>
<td>5.2 (4.6-5.7)</td>
<td>0.591</td>
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</tbody>
</table>

**Treatment Distribution**

- AZT 27%
- TDF 34%
- ABC 3%
- d4T 36%
- NVP 40%
- EFV 60%
Pretherapy HI VDR doubles first-year risk of virological failure and acquired HI VDR

**PASER-M cohort**

Multivariate analysis adjusted for sex, age, calendar year, WHO clinical stage, BMI, pretherapy HIV RNA and CD4, prior ARV use, type of NRTI and NNRTI.

Hamers et al. Lancet Inf Dis 2012
Similar findings in a large European cohort collaboration (n=10,056)

Wittkop et al. Lancet Inf Dis 2011

TDR and partially-active ART  HR=3.13 (p<0.0001)
TDR and fully-active ART    HR=1.47 (p=0.12)
Reduced CD4 recovery in patients with pre-therapy HIVDR

**PASER-M cohort**

Linear mixed model (n=2439) adjusted for age, sex, pretreatment CD4 and HIV RNA, subtype, calendar year, NRTI and NNRTI, prior ARV, adherence

Hamers et al. Lancet Inf Dis 2012
Clinical outcomes at 12 months of follow-up

**PASER-M cohort**

<table>
<thead>
<tr>
<th>Location</th>
<th>Still on first-line ART</th>
<th>Discontinued ART</th>
<th>Transferred out</th>
<th>Lost to follow-up</th>
<th>Died</th>
<th>Switched to second-line ART</th>
</tr>
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<tbody>
<tr>
<td>Lusaka#1 (n=116)</td>
<td>82%</td>
<td>&lt;1%</td>
<td>3%</td>
<td>8%</td>
<td>7%</td>
<td>&lt;1%</td>
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<tr>
<td>Lusaka#2 (n=228)</td>
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<td>Lusaka#3 (n=239)</td>
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<td>Pretoria (n=205)</td>
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<td>Johannesburg (n=208)</td>
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<td>White River (n=223)</td>
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<td>Kampala (n=203)</td>
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<td>Fort Portal (n=215)</td>
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<td>Mbale (n=221)</td>
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<td>Mombasa (n=221)</td>
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<td>Nairobi (n=223)</td>
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<td>Harare (n=225)</td>
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<td>Lagos (n=206)</td>
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<td><strong>Total (n=2733)</strong></td>
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</table>

*Hamers et al. Lancet Inf Dis 2012*
HIVDR outcomes in people failing first-line ART at 12 months

**PASER-M cohort**

- **2588** ARV-naïve started first-line ART

- **2128 (82%)** still on 1st-line after 12 months

- **2014 (95%)** HIV RNA
  - 1820 (90%) <400 c/ml
  - 166 (8%) >1000 c/ml

- **142 genotypes**

- **100 (70%)** ≥1 DRM
  - **69 (49%)** dual-class DRMs
  - **2.4 DRM/sequence**
  - **96%** newly acquired

HIVDR defined as ≥1 DRM from IAS-USA list 2010

Hamers et al. CID 2012
Acquired DRMs in people failing ART at 12mo
PASER-M cohort (n=142 genotypes)

DRMs scored using IAS-USA list 2010; Hamers CID 2012
Acquired DRMs in people failing ART at 12mo
PASER-M cohort (n=142 genotypes)

By HIV-1 subtypes

K65R subtype C vs non-C:
17% vs 7%
(p=0.05, adjusted p=0.68)

DRMs scored using IAS-USA list 2010; Hamers et al. CID 2012
Predicted HIV drug-susceptibility in people failing ART at 12mo

**PASER-M cohort**

Sequences with ≥1 DRM, scored using IAS-USA list 2010 (n=100)
Stanford HIVdb algorithm (v 6.1.0)

Hamers et al. CID 2012
Conclusions (1)

- ART scale-up is driving transmitted and pretherapy HIVDR (mostly to NNRTIs) in east and southern Africa
  - Of concern, but not at unexpected rates and levels
  - Uganda: earlier ART rollout, history of mono/dual therapies
  - PASER-M findings corroborated by global data

- Pretherapy HIVDR leads to increased virological failure, further acquisition of DRMs and reduced CD4 recovery, as compared to patients with fully-active regimens
  - Possibility of undisclosed ARV exposure
  - 70% of participants with pretherapy HIVDR started on suboptimal first-line regimen (~5% of total study population)

- Substantial attrition due to mortality and loss to follow-up (15%) in first year of ART
Conclusions (2)

- After first year of first-line ART, 90% viral suppression and 70% of patients failing ART carry ≥1 DRMs (PASER-M and WHO data)
  - Almost all (96%) mutations at failure are newly acquired

- Currently recommended, empirical 2nd-line bPI-based regimens likely to be effective for the majority of patients failing first-line ART
  - Preferential selection of K65R (rather than TAMs) in subtype C after d4t or TDF → ZDV preferred NRTI in 2nd-line ART?

- Need for enhanced HIVDR surveillance and prevention, improved ART program functioning, including access to VL monitoring and 2nd line regimens
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# Transmitted vs pretherapy HIV VDR

<table>
<thead>
<tr>
<th>Target population</th>
<th>Transmitted (TDR)</th>
<th>Pre-therapy (PDR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td>• Recent infection (proxy criteria?)&lt;br&gt;• At HIV diagnosis&lt;br&gt;• VCT and ANC setting</td>
<td>• Chronic infection&lt;br&gt;• At ART initiation&lt;br&gt;• ART sites</td>
</tr>
<tr>
<td><strong>PRO</strong></td>
<td>• True TDR (no prior ARV use)&lt;br&gt;• Epidemiological time trends, success of TDR prevention efforts</td>
<td>• Easy sampling&lt;br&gt;• Inform current ART guidelines (Clinical impact)</td>
</tr>
<tr>
<td><strong>CON</strong></td>
<td>• Difficult sampling, especially in low-prevalence settings</td>
<td>• Possibility of contributing acquired DR (undisclosed prior ARV use)&lt;br&gt;• Reflects DRMs in past&lt;br&gt;• Underestimation due to DRM reversion and diminution</td>
</tr>
</tbody>
</table>
Risk of acquired HIVDR in RLS

- Regimen and drug
  - Low genetic barrier NNRTI
  - Suboptimal regimens (d4T, sdNVP)
  - Drug-drug interactions (TB)
  - Inappropriate prescribing
  - Lack of QA

- Patient
  - Adherence

- Programmatic
  - Human resources
  - Inadequate infrastructure
  - Weak drug supply management
  - Lack of VL monitoring

- Virus
  - Viral genetic diversity?
Differences in approaches to cART provision between resource-limited vs resource-rich countries

<table>
<thead>
<tr>
<th></th>
<th>Resource-limited</th>
<th>Resource-rich</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment model</strong></td>
<td>WHO public-health approach</td>
<td>Individualized patient management</td>
</tr>
<tr>
<td>**Choice of cART</td>
<td>Empiric 1\textsuperscript{st} and 2nd-line Restricted drug options Routine HIVDR</td>
<td>Wide ARV armamentarium Individualized therapies by routine use of HIVDR testing</td>
</tr>
<tr>
<td><strong>regimens</strong></td>
<td>testing not available.</td>
<td></td>
</tr>
<tr>
<td>**Therapeutic</td>
<td>cART failure using clinical and CD4 criteria. pVL testing not generally available.</td>
<td>Close pVL monitoring and timely regimen switching.</td>
</tr>
<tr>
<td><strong>monitoring</strong></td>
<td></td>
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<tr>
<td>**Resources and</td>
<td>Shortage of health professionals, limited training level, inconsistent drug</td>
<td>Specialist care, intensive adherence counselling, continuous availability of</td>
</tr>
<tr>
<td><strong>infrastructure</strong></td>
<td>supply, weak enforcement of quality standards.</td>
<td>drugs.</td>
</tr>
<tr>
<td>**Antiretroviral</td>
<td>The cART roll-out since 2004-2005 employed triple therapy. Widespread use of sd-NVP</td>
<td>Widespread use of sequential mono and dual therapies before 1996.</td>
</tr>
<tr>
<td><strong>history</strong></td>
<td>for PMTCT</td>
<td>Since 1996, triple therapy, individualized regimens and close pVL monitoring.</td>
</tr>
</tbody>
</table>
Baseline study profile

2628 antiretroviral-naive people enrolled from 13 clinical sites

10 with missing data
17 excluded because of protocol violations
7 with previous antiretroviral drug use
5 pregnant at study screening
5 never started antiretroviral therapy

2601 included

96 with viral load <1000 copies per mL
27 with no viral load result available
8 blood specimens missing
16 with failure to amplify
3 results missing

2478 with viral load >1000 copies per mL

18 with failure to amplify
13 with HIV-1 sequence results missing

2447 with successful sequence results, including 150 with one or more drug-resistance mutations

11 excluded because of previous use of antiretroviral drugs after review of antiretroviral drug history

2436 HIV-1 sequences in final analysis from 2590 participants
Hamers et al. Lancet Inf Dis 2012

Study profile pretherapy HIVDR and outcomes
Virological failure and acquired drug-resistance -- other independent predictors

- **Baseline factors:**
  - Previous exposure to ART or PMTCT,
  - High pretreatment VL
  - Young age (for women)
  - Pretreatment CD4 count <50 cells/μL

- **Prospective factors:**
  - No CD4 cell count increase during the first 6 months of ART
  - Suboptimum (<95%) 30 day adherence