Pre treatment HIV-1 Drug Resistance in LMIC

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Transmitted drug resistance (TDR) versus pre-treatment drug resistance (PDR)

- Low ART adherence
- Inadequate drug combination
- Modified pharmacokinetics

Acquired Drug Resistance

Drug Resistant Variant

- Emtricitabine
- Tenofovir
- Efavirenz
Transmitted drug resistance (TDR) versus pre treatment drug resistance (PDR)

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Acquired Drug Resistance

Transmitted or primary Drug Resistance

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- Acquired Drug Resistance
- Transmitted or primary Drug Resistance

*Drug Resistant Variant*
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**Acquired Drug Resistance**

**Transmitted or primary Drug Resistance**

**1st line ART**

Prior exposure

No prior exposure

Drug Resistant Variant
Transmitted drug resistance (TDR) versus pre-treatment drug resistance (PDR)

- Low ART adherence
- Inadequate drug combination
- Modified pharmacokinetics

**Acquired Drug Resistance**

**Transmitted or primary Drug Resistance**

1st line ART
Baseline GRT = PDR

Drug Resistant Variant
PEOPLE STARTING 1st LINE ART (PDR)

Previous exposure to ARV (defaulters re-starting; PrEP, PEP exp; PMTCT)

ARV-naïve (TDR)

20 : 80 in LMIC settings (WHO data)
Why does PDR matter?
PDR increases risk of Virologic Failure

Hamers et al, Lancet Infect Dis, 2012
Also Avila Rios et al, Lancet HIV 2016
Public health impact of unchecked PDR 2016-2030

<table>
<thead>
<tr>
<th>Current level of NNRTI PDR &gt; 10%</th>
<th>AIDS deaths</th>
<th>New infections</th>
<th>ART costs</th>
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<tbody>
<tr>
<td>Percentage attributable to HIVDR</td>
<td>16%</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Amount attributable to HIVDR</td>
<td>890,000</td>
<td>450,000</td>
<td>$6.5 billion</td>
</tr>
</tbody>
</table>

Philips, Bertagnolio et al, *JID 2017*
What is the current state of PDR in LMIC?
National pretreatment HIVDR surveys, 2014-2016 and beyond
**Pretreatment HIVDR to EFV and/or NVP in first-line ART initiators**

- Surveys excluded people starting ART with prior ARV drug exposure.

- Recent infection: Malawi 15%

- 6/11 countries: >10%
- 2/11 countries: >15%

WHO Global Report on HIV Drug Resistance 2017
PDR to EFV/NVP in first-line: naïve vs with previous exposure

Prior exposed to ARV….21.6%  (95% CI 13.8-32.2)
ARV drug naïve ……………8.3%  (95% CI 6-11.4)

p value<0.0001

WHO Global Report on HIV Drug Resistance 2017
PDR to EFV/NVP in first-line ART naive initiators by gender

NNRTI PDR IN ARV DRUG NAIVE INDIVIDUALS

Women 12.2%, 95% CI 9.1-16.3
Men: 6.3%, 95% CI 5.0-8.1

P value < 0.0001.

WHO Global Report on HIV Drug Resistance 2017
NNRTI PDR is increasing over time

- **Southern Africa**: 23% increase in the ESTIMATED INCREMENTAL ANNUAL INCREASE.
- **Western/Central Africa**: 29% increase.
- **Eastern Africa**: 17% increase.
- **Latin America**: 15% increase.
- **Asia**: 11% increase.

**Dataset Information**
- **358 datasets**, comprising **56,044 adults** across **63 countries**; sampled 1993-2016.

**Graphs**
- **Studies**: Numbers vary from 50 to 89.
- **Patients**: Numbers range from 4924 to 16,088.
- **P-value for association**: 0.0000 to 0.0105.

**Citations**
- Gupta, Bertagnolio et al, in revision Lancet Infect Dis.
More modest increases in NRTI resistance

Gupta, Bertagnolio et al, in revision Lancet Infect Dis
Why is prior exposure such an issue?
**Effect of Prior ARV exposure on PDR and VF**

PASER cohort: 13 sites in Kenya (2), Nigeria (1), South-Africa (3), Uganda (3), Zambia (3), Zimbabwe (1)

<table>
<thead>
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<th></th>
<th>N</th>
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<th>P-value</th>
<th>Adjusted OR (95%CI)</th>
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<tbody>
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<tr>
<td>Prior ARV use</td>
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<td>No</td>
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<td>288</td>
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<tr>
<td>Yes</td>
<td>119</td>
<td>39</td>
<td>6.8 (4.3-10.8)</td>
<td>&lt;0.001</td>
<td>7.2 (4.4 -11.7)</td>
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<tr>
<td><strong>Effect of prior ARV use on VF</strong></td>
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<td>Prior ARV use</td>
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<tr>
<td>Yes</td>
<td>83</td>
<td>17</td>
<td>2.5 (1.4-4.3)</td>
<td>0.001</td>
<td>2.7 (1.4-5.2)</td>
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</tbody>
</table>

Adjusted for age, sex, country, calendar year of treatment initiation, NNRTI and NRTI, PDR, pretreatment VL and CD4 cell count, and adherence

Inzaule et al, in preparation
## Prior exposure contributes significantly to PDR

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated levels of drug resistance in 2014-16*</th>
<th>Odds ratio for drug resistance (ARV vs naive)*</th>
<th>Estimated resistance with observed proportion of patients with ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Africa</td>
<td>4</td>
<td>4.99</td>
<td>8.90%</td>
</tr>
<tr>
<td>Latin America</td>
<td>10.1</td>
<td>4.99</td>
<td>8.90%</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>8.8</td>
<td>4.99</td>
<td>8.90%</td>
</tr>
<tr>
<td>Western/Central Africa</td>
<td>10.7</td>
<td>4.99</td>
<td>8.90%</td>
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<tr>
<td>Western/Central Africa</td>
<td>5</td>
<td>4.99</td>
<td>8.90%</td>
</tr>
</tbody>
</table>

Note: Estimated level of transmitted resistance.

unpublished
Inferred prior exposure associated with multiclass resistance following failure of Tdf+NNRTI
How do we deal with prior exposure?
Can we rely on self reported prior exposure?

• M184V/I should not be transmitted in heterosexual transmission due to impaired replication efficiency.

• M184V/I in 7% of those not disclosing prior ARV exposure in meta-analysis compared to 15% in those with prior exposure (P<0.01).

7% still higher than would be expected, raising possibility of undisclosed ART.
Evidence for prior exposure in patients presenting for first line TDF based ART

Derache, Pillay et al, Abstract 43 CROI 2017

Gregson, Gupta et al, Lancet Infect Dis 2017
Minority variants and PDR

Prevalence of PDR by UDS in ANRS 12249 TASP TRIAL

Derache et al, Abstract 43 CROI 2017
Minority variants and PDR

Cozzi Lepri, Metzner et al, JAC 2015
2 fold risk of VF with MV in Europe

Li, Paredes, Kuritzkes et al, JAMA 2011
2-3 fold risk of VF with MV

Zoufaly et al, JAC 2015
No effect of MV on VF in Cameroon
PDR in children
PDR among children is increasing over time

Meta-analysis including 2,617 children from 13 LMIC countries

NNRTI mutations in 9.7% of PMTCT-unexposed children

Boerma et al, J Antimicrob Chemother. 2017
**EFV/NVP PDR in ART naive children < 18 months 2012-2016**
*(national surveys: Mozambique, Swaziland, Uganda, Zimbabwe, South Africa)*

Overall 53% (50-55)

- PMTCT exposure: 56% (51-58)
- Unknown: 33% (23-42)
- No PMCT: 22% (14-29)

Moz=Mozambique; SWZ=Swaziland; UGA=Uganda; ZAF=South Africa; ZIM=Zimbabwe; EFV=efavirenz; NVP=nevirapine; ETR=etravirine; RPV=rilpivirine; AZT=zidovudine; d4T= stavudine; FTC=emtricitabine; TDF=tenofovir

Jordan MR et al. CID 2017
Summary

• PDR is rising globally and exceeding 15% in some countries

• PDR to NNRTI resistance compromises outcomes

• Prior exposure to ART is associated with first line VF
Possible Responses to increasing NNRTI PDR

Early VL testing to detect early VF

Alternative first line, eg DTG. But DTG will have same program issues

Baseline resistance testing to identify those with prior exposure
Near patient for key mutations? See abstracts 18, 21 and 24
NGS at centralized labs? See abstract 19, 20, 23, 25, 27
Traditional Sanger sequencing at centralized labs? See abstract 22
WHO Response to PDR 2017

Are nationally representative PDR data available?

- YES: Implement viral load monitoring; prevent HIVDR emergence and transmission
- NO: Implement nationally representative PDR survey

≥10% PDR to EFV/NVP

- Is it feasible to introduce non-NNRTI first-line ART for ALL starters?
  - YES: Urgently consider using non-NNRTI first-line ART for ALL starters
  - NO: Consider introducing pretreatment HIVDR testing

<10% PDR to EFV/NVP

Prioritize use of non-NNRTI containing first-line ART in people reporting prior exposure to ARV drugs

ART: antiretroviral therapy
ARV: antiretroviral (drug)
EFV/NVP: efavirenz or nevirapine
HIVDR: HIV drug resistance
PDR: pretreatment HIV drug resistance
NNRTI: non-nucleoside reverse-transcriptase inhibitor

Mitigation of HIV DR – focus on ART program functioning

Proportion of clinics monitored achieving target, 2004-2014

- Prescribing Practices: 84.6%
- LTFU at 12 mo: 53%
- Retention on ART 12 mo: 53.8%
- On-time pill pick-up: 58.4%
- On-time appointment keeping: 39.8%
- Drug stock out: 64.3%

Also St Jean, Harrigan et al, HIV Med 2016
Future challenges: NRTI PDR

• So far TAM have been observed as PDR

• PDR with K65R likely to emerge as a public health problem
  - Resulting from prior exposure to TDF or ABC
  - Possibly also as TDR?

Will DTG + TDF +FTC be effective in PDR with K65R +/- M184V/I?
Acknowledgements

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Gregson J, PhD; Tang M, MD; Ndemb N, PhD; Hamers RL, MD PhD; Rhee SY, MD; Marconi VC, MD; Diero L, MD; Brooks K, MD9; Theys K, PhD; Rinke de Wit TF, MD PhD4; Arruda M, Garcia F, MD, Monge S, PhD, Günthard HF, MD, PhD; Hoffmann CJ, MD; Kanki P, MD; Kumarasamy N, MD; Kerschberger B, Mor O, Charpentier C, PhD, Todesco E, PhD; Rokx C, MD, PhD; Gras L, PhD; Halvas EK, PhD; Sunpath H, MD; Di Carlo D, Antinori A, Andreoni M, Latini A, Mussini C, Aghokeng A, PhD; Sonnerborg A, MD, PhD; Neogi U, PhD; Fessels WJ, Agolory S, Yang C, PhD; Blanco JL, MD, PhD; Juma JMc, Smit E, Schmidt D, Lameck D, Watera C, Asio J, Kirungi W, Tostevin A, PhD; PhD El-Hay T, Clumeck N MD, PhD; PhD Goedhals D, MD; van Vuuren C, MD; Bester A, MD; Sabin C, PhD; Mukui I, MD; Santoro MM, PhD; Perno CF, MD, PhD; Hunt G, PhD; Morris L, MD PhD; Camacho R, PhD; de Oliveira T, PhD; Pillay D, MD PhD; Dunn D PhD, Kaleebu P, PhD; Raizes E, MD; Kantor R MD PhD; Shafer RW, PhD; Gupta RK, MD PhD
Long plasma half life of NNRTI leads to monotherapy with treatment interruption
Unchecked PDR will compromise 90-90-90

Emphasizing Viral Suppression Among People Living with HIV

90%

- of people living with HIV know their status
- of people living with HIV who know their status are on treatment
- of people on treatment are virally suppressed
Viral load is not impacted by tenofovir resistance


**K65R+ and K65R- viruses similarly fit in vivo**

K65R+ and K65R- viruses similarly fit in vivo

<table>
<thead>
<tr>
<th>Pos Cons AA</th>
<th>Overall (%Rx) n=1,983</th>
<th>Overall (%Naive) n=50,803</th>
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<td>68 S N</td>
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<td>23.49</td>
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<td>0.96</td>
<td>8.89</td>
<td>9.63</td>
<td>9.83E-89</td>
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Rhee, Gupta, Shafer EBioMedicine 2017

TenoRes Study Group, Lancet Infect Dis 2016
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TABLE 3. Relative Fitness Values (1+s) for Viruses Containing A62V, K65R, and S68G RT Mutations in Direct Competition With WT HIV-1

Svarovskaia et al, JAIDS 2008