Should We Be Worried about HIV Resistance in Prevention Trials?

John W Mellors, MD

MTN Regional Meeting Cape Town, SA
25 Sept 2018
YES
HIV Drug Resistance?

Courtesy Urvi Parikh
• Resistance from ART
  • Resistance from PrEP
  ➢ Solutions needed
ART NOT PrEP Drives Spread of HIV Drug Resistance

Abbas, Mellors
JID 2013
Good News About ART

• Has saved 7-8 million lives
• ~21 million are on it (about 50% of all PLWH)
• Major reductions in MTCT
• NRTIs have residual drug activity despite signature mutations
  – Still inhibit wild-type virus
  – Resistance is relative not absolute
  – Complex resistance interactions, e.g. 184V hypersusceptibility to TNV
  ➢ Surprisingly good efficacy of PI-based 2nd line-ART with recycled NRTI
Not So Good News About ART

- Long-term (4-5 year) suppression rates of 60-85%
  - Worse in children, adolescents, MSM, and post-partum women
  - 80% not suppressed have resistance
  - 15-40% on ART could transmit resistance
- Spotty viral load (HIV RNA) monitoring
- Infrequent resistance testing
- Late switches from failing ART
- Surveillance systems are in arrears
Increase in NNRTI PDR

WHO HIV Drug Resistance Report 2017
WARNING
We’re Using The Same Drugs and Drug Classes for ART and PrEP!

TDF or TAF and 3TC or FTC

EFV and DPV
TLD to the Rescue!
Tenofovir/Lamivudine/Dolutegravir (TLD)

- Better tolerated and higher efficacy than EFV-based regimens (TLE)
  - Little to no transmitted DTG resistance
- PEPFAR rollout/switch starting ($75 per year!)
  - 1st line, 2nd line, beyond
- Cautions
  - TL components overlap with TLE and TNV/FTC for PrEP
  - Double dosing of DTG required with rifampin (Tb)
- ACTG 5381
  - ACTG-PEPFAR Cohort study (N = 1500)
  - TLD for 1st line, 2nd line, 3rd line, and Tb co-infection
  - Adolescents (>10 years) and adults
  - Kenya, Uganda, Zimbabwe, Malawi, SA, and Haiti
Trouble for TLD!
Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception

Stay Tuned!
PrEP Resistance Concerns

• Breakthrough infection and subsequent selection of resistance with continued use of PrEP could:
  – Compromise the effectiveness of 1st-line ART for that individual
  – Result in secondary transmission of drug-resistant HIV

• Efficacy of PrEP could be reduced if:
  – Transmitted variant is from a partner failing ART with virus that is cross-resistant to PrEP, or
  – A partner had acquired PrEP-resistant HIV
Theoretical Infection-Exposure-Resistance Relationships

- Zone of Resistance
- Risk
  - No Drug
  - No Resistance
  - Infection

- No Infection
  - No Resistance

Drug Exposure

Fraction infected or resistant

- Low
- High

HIV infection
Resistant infection

J. Mellors FDA Hearing 2012
Current Status TDF/FTC PrEP and DPV IVR

- Oral PrEP: Truvada (TDF-FTC)
- Vaginal Ring: Dapivirine (DPV IVR) In Regulatory Review
Resistance in Seroconverters in Studies of TDF/FTC PrEP

Randomized Clinical Trials
- FEM-PrEP
- iPrEX
- TDF2
- Partners PrEP
- VOICE

Open-Label and Demo Projects
- HPTN-067
- PROUD
- IPERGAY
- USA DEMO
- iPrEX OLE

Total: 216 seroconverters in 8353 PrEP users
Resistance rates higher in acute infection

Acutely Infected at PrEP initiation

Infected at Follow-Up

% Seroconverters on TDF/FTC PrEP
# 3 REPORTED PrEP Breakthrough TDR Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient</th>
<th>PrEP Duration</th>
<th>Adherence</th>
<th>Resistance</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toronto Case 43yo MSM</td>
<td>&gt;21 months</td>
<td>Pharmacy Records</td>
<td>High: 3TC, FTC, NVP, EVG</td>
<td>Knox et al. NEJM 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TFV levels high</td>
<td>Intermediate: ABC, EFV, ETR, RTG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low: TFV, DTG</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>New York Case 26yo MSM</td>
<td>4 months</td>
<td>TFV and TFV-DP levels in hair and DBS consistent with daily use</td>
<td>K65R+M184V, K103S, E138Q, Y188L</td>
<td>Markowitz et al. JAIDS 2017</td>
</tr>
<tr>
<td>3</td>
<td>North Carolina Case 34yo MSM</td>
<td>Approx 11 months</td>
<td>Adequate</td>
<td>K65R, M184V, K103N</td>
<td>Thaden CROI 2018</td>
</tr>
</tbody>
</table>
JUST IN CASE: MONITORING RESISTANCE from PrEP Roll-Out

Partner with roll-out projects and programs

Collect and test DBS from PrEP seroconverters

Determine frequency of resistance selection in seroconverters

Kenya
South Africa
Zimbabwe
TDF/FTC Resistance Summary

- **Resistance is infrequent (3%)** from use of oral TDF/FTC PrEP if HIV-1 infection is not present at the time PrEP is started.

- **Resistance is more common (41%)** if TDF/FTC PrEP is started during undiagnosed acute HIV-1 infection.

- **Acute HIV-1 infections should be excluded before starting PrEP!**

- **Important to monitor resistance** with PrEP rollout – rates of resistance outside of trial setting unknown.
Use of EFV-based ART in PrEP Seroconverters May Lead to Increase in NNRTI Resistance

Andrew Phillips, unpublished 2018
Resistance Risk with DPV IVR

TRANSMITTED RESISTANCE
Circulating NNRTI resistance could reduce DPV IVR efficacy
(Penrose, et al. AAC 2017)

ACQUIRED RESISTANCE
Selection of DPV resistance could reduce NNRTI-based ART efficacy
(Penrose, et al. JID 2016)

Both would produce an imbalance in resistance of seroconverters between study arms
DPV Activity against NNRTI-resistant variants

In-house population phenotyping using plasma-derived recombinant viruses from donors failing 1st line ART with ≥ 1 ARV mutation & RNA >10,000 c/ml

1. Extract HIV-1 RNA from donor plasma
2. Generate cDNA & PCR amplify RT full-length sequence (aa 1-560)
3. Clone full-length HIV-1 RT into viral vector
4. Transfect cells with plasma-derived viral vector and prepare viral stocks
5. Determine viral susceptibility to DPV in TZM-bl cells
## Dapivirine Cross-Resistance

<table>
<thead>
<tr>
<th>Level of DPV Resistance*</th>
<th># of Samples (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (≥ 10-fold)</td>
<td>79 (77%)</td>
</tr>
<tr>
<td>Intermediate (3 to 9-fold)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Susceptible (≤ 2-fold)</td>
<td>9 (9%)</td>
</tr>
</tbody>
</table>

* All virus were >10-fold resistant to NVP and EFV

- K103N and L100I significantly associated with maximum DPV resistance
Risk of DPV Breakthrough Infection

- Vaginal $C_{\text{day 28}}$ exceeds adjusted $IC_{90}$ of all samples by >23-fold
- Risk of breakthrough is seen in a short window following ring removal;
- 32/102 (31%) viruses exceed $C_{\text{day 31}}$ following ring removal

Same rate of resistance in DPV and PLB arms

168 ASPIRE Seroconverters
165 (98%) Successfully Sequenced

3 HIV RNA <200 c/mL

69 DPV Ring Arm
8 (11.6%) with NNRTI mutations

96 Placebo Ring Arm
10 (10.4%) with NNRTI mutations
Response to 1\textsuperscript{st}-Line ART in Seroconverters from ASPIRE?

<table>
<thead>
<tr>
<th>MTN-015 Study population</th>
<th>All (N=158)</th>
<th>Placebo (N=93)</th>
<th>Dapivirine (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23 (21, 27)</td>
<td>25 (22, 27)</td>
<td>22 (20, 27)</td>
</tr>
<tr>
<td>Clade C virus**</td>
<td>142/155 (92%)</td>
<td>84/92 (91%)</td>
<td>58/63 (92%)</td>
</tr>
<tr>
<td>Initial HIV RNA (log\textsubscript{10} copies/ml)</td>
<td>4.6 (3.9, 5.2)</td>
<td>4.6 (4.0, 5.2)</td>
<td>4.6 (3.6, 5.1)</td>
</tr>
<tr>
<td>Initial CD4 count (cells/mm\textsuperscript{3})</td>
<td>547 (429, 707)</td>
<td>523 (396, 674)</td>
<td>601 (464, 793)</td>
</tr>
<tr>
<td>Median follow up (months)</td>
<td>28.3</td>
<td>29.0</td>
<td>26.7</td>
</tr>
<tr>
<td>Initiated ART</td>
<td>87 (55%)</td>
<td>54 (58%)</td>
<td>33 (51%)</td>
</tr>
<tr>
<td>At least 6 months FU on ART</td>
<td>67/87 (77%)</td>
<td>43/54 (80%)</td>
<td>24/33 (73%)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>14/67 (21%)</td>
<td>10/43 (23%)</td>
<td>4/24 (17%)</td>
</tr>
</tbody>
</table>

*Riddler, et al., In Review*
## Resistance from 1st-line ART failure in seroconverters from ASPIRE

<table>
<thead>
<tr>
<th>Participant</th>
<th>ASPIRE Arm</th>
<th>Initial ART regimen</th>
<th>NNRTI mutations at seroconversion</th>
<th>Mutations at VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DPV</td>
<td>EFV/FTC/TDF</td>
<td>None</td>
<td>K103N</td>
</tr>
<tr>
<td>2</td>
<td>DPV</td>
<td>EFV/FTC/TDF</td>
<td>V108I/V, E138A</td>
<td>E138A</td>
</tr>
<tr>
<td>3</td>
<td>DPV</td>
<td>EFV/FTC/TDF</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>DPV</td>
<td>EFV/FTC/TDF</td>
<td>H221Y</td>
<td>V106M, Y181Y/C, H221Y</td>
</tr>
<tr>
<td>5</td>
<td>Placebo</td>
<td>EFV/FTC/TDF</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Placebo</td>
<td>EFV/3TC/TDF</td>
<td>None</td>
<td>K103N</td>
</tr>
<tr>
<td>7</td>
<td>Placebo</td>
<td>NVP/3TC/d4T</td>
<td>None</td>
<td>G190G/A</td>
</tr>
<tr>
<td>8</td>
<td>Placebo</td>
<td>EFV/3TC/TDF</td>
<td>None</td>
<td>K103K/N</td>
</tr>
<tr>
<td>9</td>
<td>Placebo</td>
<td>NVP/3TC/d4T</td>
<td>None</td>
<td>K103N</td>
</tr>
</tbody>
</table>

_Riddler, et al., In Review_
DPV Resistance Summary

- Overall NNRTI mutation frequency did not differ by ASPIRE arm ($p > 0.05$)
- DPV-associated mutations E138K, L100I or Y181C were not detected
- The polymorphism E138A was the most common mutation amongst seroconverters but its frequency did not differ by arm.

- No obvious difference in response to NNRTI-based 1st-line ART or resistance in DPV vs. Placebo arms of ASPIRE in MTN-015
- NGS Data ongoing – will be presented at tomorrow’s plenary
Yes, we should worry about PrEP resistance...

But more so about resistance to PrEP from ART
What to do?

- Aggressive surveillance
  - ART starts
  - PrEP and ART failures
    - NGS
- Define the HIV RNA (Viral load) cascade
  - Proportion on ART tested
  - Proportion tested suppressed/not suppressed
  - Proportion switched within 3 months
  - Proportion switched that are suppressed/not – 1, 3, 5 years
What to do?

• Assess and improve the VL cascade
  – Quantify drug-resistant viremia AUC
• Plan for the long-term!
  – If TLD plan fails, what next?
  – TAF/FTC/DRV/c?
  – DRV/c/ETV/InSTI?
Conclusions

• HIV drug resistance threatens the ART rollout
  – and PrEP rollout secondarily
• Let’s hope that no additional NTDs appear from TLD
  – Default is starting TLE despite spreading NNRTI resistance
    ▪ May not be good for DPV IVR
  – Need better 2nd line ART options
    ▪ Including those for PrEP failures
• Maintain diligence in monitoring ART failures and PrEP failures for standard and low-frequency resistance in trials
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VOICE Protocol Team
MTN Sites
All Study Participants

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Questions?
HIV Drug Resistance... Not an Iceberg

But caution advised
Resistance from PrEP

• What is known about TDF/FTC Resistance
  – TDF/FTC Resistance from trials
  – Breakthrough cases
  – Monitoring PrEP resistance in rollout

• What is known about DPV Resistance
  – Standard genotyping/NGS/phenotyping

• Concerns
  – Rising NNRTI resistance from treatment and transmission
  – ART driving resistance
  – Hold on dolutegravir means loss of 1st line ART without a good substitute
Things to Worry About

1. Rising NNRTI resistance from treatment and transmission
2. Hold on dolutegravir means loss of 1\textsuperscript{st} line ART without a good substitute
Concerns

- Increasing access to ART
- Very little individualized monitoring – mostly in private sector
- Same drugs used for treatment and prevention
DPV IVR Adherence vs. HIV protection:
Ring data three months prior to detection

<table>
<thead>
<tr>
<th>Proportion of f/u</th>
<th>20%</th>
<th>27%</th>
<th>27%</th>
<th>27%</th>
<th>Placebo 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence /100 p-y (# infections)</td>
<td>4.9 (10)</td>
<td>3.1 (8)</td>
<td>1.9 (5)</td>
<td>0.4 (1)</td>
<td>4.7 (47)</td>
</tr>
</tbody>
</table>

Ref: Brown AIDS 2016 Abst. TUAC0105LB
Transmitted Drug Resistance

Stanford Resistance Database HIV-1 Drug Resistance in ARV-naive Populations
Compendium of published virus sequences from 50,869 persons, 287 studies

Stanford Database 2018