Transmission of Drug Resistance

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Overview

• Definitions and key concepts

• TDR prevalence

• Persistence, transmissibility, and TDR from undiagnosed persons

• Clinical relevance of TDR

• Conclusions
HIV drug resistance (HIVDR)

- Acquired HIVDR (ADR)
  - DR selected in individuals on ART
  - Fitness advantage in the presence of ARVs but often less fit in its absence

- Transmitted HIVDR (TDR)
  - DR in ARV drug-naïve individuals
    - best applied to recently infected individuals
  - Relies on detection of non-polymorphic DRMs, such as the WHO surveillance drug resistance mutations (SDRM) lists

- Pretreatment HIVDR (PDR)
  - HIVDR in individuals initiating ART, may be either transmitted or acquired

Selection of drug-resistant HIV in vivo

Host-related factors
- Viral load
- Immunity
- Genetics
- Adherence

Drug-related factors
- Pharmacokinetics
- Potency
- Penetration

Virus factors
- TDR
- Polymorphisms
- HIV subtype

ART Programme factors
- Human resources
- Infrastructure
- Drug supply
- Routine VL monitoring
- Quality service delivery
- Adherence support

Persistent virus replication

Selection of drug resistance

ARV drug pressure
Daily Production of HIV Mutations in an Untreated HIV-infected Person

- Up to 10 billion new viruses are produced daily\(^1,^2\)
- \(3 \times 10^{-5}\) mutations per site per replication cycle \(^2,^3\)
- 100 million new cells are infected/day
- Mutation rate + viral turnover = a mutation at every position in the HIV genome per day

Emergence and selection of drug-resistant HIV under ARV drug selective pressure

- Drug-resistant mutants are selected (not created) by drug pressure under *incomplete virological suppression*
- Ongoing virus replication under drug pressure leads to the selection of resistance and cross-resistance
- Increasing number of mutations

- Accumulation of mutations on same viral genome
- Resistant mutants often display reduced fitness but compensatory changes emerge over time that partially restore virus
Transmission of drug resistant HIV

- DRM stable after transmission
- Gradual reversion over time, often incomplete
- Persistence as low abundance variants
- Persistence in latently infected cells
South Africa: PDR prevalence over time (ART naive individual); 38 datasets, 6880 sequences (2000-2016)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>1.10 (1.05-1.16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>NNRTI</td>
<td>1.18 (1.13-1.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PI</td>
<td>0.96 (0.89-1.04)</td>
<td>0.3650</td>
</tr>
<tr>
<td>Overall</td>
<td>1.10 (1.06-1.15)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Prevalence of DR mutations in HIV with any drug resistance mutation; N=374

Mutations shown on the horizontal axis include all mutations observed in 1% of the sequences with any drug resistance mutation.

- 278 sequences; 58.2% of sequences with any DRM; 4% of all sequences
- 71 sequences; 14% of sequences with any DRM; 1% of all sequences
- 14 sequences; 3% of sequences with any DRM; 0.2% of all sequences
- PI DRM very rare: 56 sequences (0.9%) with at least 1 PI DRM
Prevalence of DR mutations in HIV with any drug resistance mutation; N=374

<table>
<thead>
<tr>
<th>Mutations (N)</th>
<th>2000-2008</th>
<th>2009-2012</th>
<th>2013-2016</th>
<th>χ² test for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF-associated DRM</td>
<td>0.1% (3/2480)</td>
<td>0.5% (11/2219)</td>
<td>1.1% (23/2181)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>M184V</td>
<td>0.2% (4/2480)</td>
<td>0.9% (20/2219)</td>
<td>2.2% (47/2181)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Chimukangara et al., EClin Med 2019
WHO PDR surveys: DRM prevalence (ARV drug naïve; N=2,905) – surveys 2014-2018

- Cuba
- Eswatini
- Honduras
- Mexico
- Papua New Guinea
- Vietnam

WHO. 2019 Drug Resistance Report
Transmitted INSTI Resistance – Studies

<table>
<thead>
<tr>
<th>Region</th>
<th>Years</th>
<th>#</th>
<th>TDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle</td>
<td>2007-2013</td>
<td>82</td>
<td>0%</td>
</tr>
<tr>
<td>North Carolina</td>
<td>2010-2016</td>
<td>840</td>
<td>0.4%</td>
</tr>
<tr>
<td>CDC (9 jurisdictions)</td>
<td>2010-2014</td>
<td>5,240</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>CDC (23 jurisdictions)</td>
<td>2013-2016</td>
<td>5,571</td>
<td>0.9%</td>
</tr>
<tr>
<td>HPTN 061 (Black MSM)</td>
<td>2009-2011</td>
<td>142</td>
<td>0%</td>
</tr>
<tr>
<td>Florida</td>
<td>2015-2016</td>
<td>1,953</td>
<td>2%</td>
</tr>
<tr>
<td>Washington DC</td>
<td>1999-2014</td>
<td>1,503</td>
<td>0.9%</td>
</tr>
<tr>
<td>Korea</td>
<td>2009-2012</td>
<td>106</td>
<td>0%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>2013-2016</td>
<td>184</td>
<td>0%</td>
</tr>
<tr>
<td>Europe</td>
<td>2006-2007</td>
<td>278</td>
<td>0%</td>
</tr>
<tr>
<td>Spain</td>
<td>2012-2017</td>
<td>1109</td>
<td>0.2%</td>
</tr>
</tbody>
</table>


North Carolina: 17 (2.0%) accessory polymorphisms (L74M, T97A); 3 nonpolymorphic DRMs

CDC 2010-2014: Included only the 5,240 within 3 months of diagnosis

CDC 2013-2016: Increased rates in major metropolitan areas (PR=2.36)

Florida: Uncertain which mutations included

Korea: Stanford CPR tool

Taiwan: Uncertain which mutations evaluated

Europe: IAS-USA 2014 list; no signature INSTI mutations detected but 4% with INSTI associated mutations with HIVdb score ≥10

Spain: IAS-USA list: T66I – 0.1% and G163K – 0.1% (EVG/RAL); no resistance to DTG/BIC; no trend during 6-year study period

Slide courtesy of Bob Shafer
Transmitted integrase inhibitor resistance: key points
N=17,302 InSTI-naïve and 2,450 InSTI-treated

Most major InSTI-resistance mutations almost never occur in InSTI-naive people
- R263K in 0.1% to 0.5%, usually as a mixture

Several accessory resistance mutations (L74M, T97A, and E157Q) occur in ~2% of INSTI-naïve persons

Mutation lists for IN mutations

1Tzou PL. Integrase strand transfer inhibitor resistance mutations for the surveillance of transmitted HIV-1 drug resistance. JAC (In press)
Slide courtesy of Bob Shafer
Persistence, transmissibility, and TDR from undiagnosed persons
Frequency of TDR mutations, by drug class, receding to undetectable on population sequencing; N=75; (total of 195 TDR mutations)

<table>
<thead>
<tr>
<th>Mutation group</th>
<th>Observed data</th>
<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NNRTI</td>
<td>M184V/I</td>
<td>TAMs</td>
<td>T215 Revertants</td>
<td>Other NRTI</td>
<td>PI</td>
</tr>
<tr>
<td>No. baseline mutations (no. patients)</td>
<td>36 (33)</td>
<td>12(12)</td>
<td>54 (29)</td>
<td>15 (15)</td>
<td>9 (5)</td>
<td>69 (31)</td>
</tr>
<tr>
<td>No. replaced by WT (% total mutations)</td>
<td>9 (25%)</td>
<td>9 (75%)</td>
<td>15 (28%)</td>
<td>6 (40%)</td>
<td>1 (11%)</td>
<td>14 (20%)</td>
</tr>
<tr>
<td>Hazard model predictions</td>
<td>Hazard ratio for replacement</td>
<td>Reference</td>
<td>77.5 (14.7-408.2)</td>
<td>2.5 (0.65-9.92)</td>
<td>4.34 (0.76-23.51)</td>
<td>0.39 (0.24-6.33)</td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>&lt;0.001</td>
<td>0.19</td>
<td>0.10</td>
<td>.051</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Jain et al CID 2011
Kaplan-Meier plot - cumulative probability of mutation replacement of transmitted DR variants over time; N=75
Impact of TDR mutations on viral replicative capacity (RC)

- RC measured by p24 expression PBMC
- Site-directed mutants (SDM) HIV-M184V/I/ T with known impact on RC used as controls
- SDM viruses: SDM-L90M – only mutation not to decrease RC compared to WT
- Patient-derived viruses: except for the pM41L variant, all patient derived viruses had a higher RC than the corresponding site-directed mutants

Pingan M et al., Retrovirology 2014
Where does TDR come from?

- Acquired resistance in ART-treated persons is the original source of TDR.

- Rhee et al 2015: 763 genotypes with TDR in sub-Saharan Africa (SSA) and south/southeast Asia (SSEA)\(^1\)
  - Vast majority of sequences genetically dissimilar (5% sequence pairs) – suggesting the majority of in SSA and SSEA arose independently (transmission from people on ART).

\(^1\)Rhee et al 2015 Plos Med
Transmission fitness of drug-resistant HIV - transmission network assessment (1)

- US National HIV Surveillance System: 66,221 persons, 30,196 ART-naive persons; calculation of transmission fitness of 69 DRM

Table 1. Transmission risk factor and subtype for HIV-infected people from twenty-seven U.S. jurisdictions included in this study.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Total Any ART-status n (%)</th>
<th>ART-naïve n (%)</th>
<th>Clustered in network Any ART-status n (%)</th>
<th>ART-naïve n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any ART-status n (%)</td>
<td>ART-naïve n (%)</td>
<td>Clustered in network Any ART-status n (%)</td>
<td>ART-naïve n (%)</td>
</tr>
<tr>
<td>All</td>
<td>66,221 (100%)</td>
<td>30,196 (100%)</td>
<td>21,106 (100%)</td>
<td>11,692 (100%)</td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>33,680 (50.9%)</td>
<td>17,150 (56.8%)</td>
<td>14,341 (67.9%)</td>
<td>8,421 (72.0%)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>20,473 (30.9%)</td>
<td>9,946 (32.9%)</td>
<td>4,484 (21.3%)</td>
<td>2,336 (20.0%)</td>
</tr>
<tr>
<td>PWID</td>
<td>10,844 (16.4%)</td>
<td>2,810 (9.3%)</td>
<td>2,133 (10.1%)</td>
<td>869 (7.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>1,224 (1.8%)</td>
<td>290 (1.0%)</td>
<td>148 (0.7%)</td>
<td>66 (0.6%)</td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>64,781 (97.8%)</td>
<td>29,489 (97.7%)</td>
<td>20,916 (99.1%)</td>
<td>11,607 (99.3%)</td>
</tr>
<tr>
<td>Non-B</td>
<td>1,440 (2.2%)</td>
<td>707 (2.3%)</td>
<td>190 (0.9%)</td>
<td>85 (0.7%)</td>
</tr>
</tbody>
</table>

*Clustered with another ART-naïve individual in network.

*Persons were classified as ART-naïve if they received their first genotype within 3 months of diagnosis and had no evidence of prior ART use.

ART, antiretroviral therapy; MSM, men who have sex with men; PWID, people who inject drugs.

Wertheim JO et al., Virus Evolution. 2017
The relative transmission fitness of a DRM in ART-naive persons can be estimated as a proportion:

- Numerator: the frequency of strains with that specific DRM that cluster with other strains with that DRM
- Denominator: the frequency of wild-type strains that cluster with other wild-type strains

Decrease or excess in the proportion of strains clustering is indicative of fewer or greater transmission events, respectively.
Transmission network assessment: summary of fitness

- 24 DRM had clustering frequencies deviating from neutral expectations, most resulting in significant reduction of transmission fitness

- Reduced relative fitness – **substantial reduction in transmissibility**
  - M184V, T215Y, K219Q, K70R

- No impact on fitness
  - M41L, T215D/S/C/V

- Increased fitness – **substantial increase in transmissibility**
  - L90M

- Relative fitness close to 1.0 – **WT-like transmissibility**
  - K103N, K103S, Y181C

- Unproven impact on fitness: K65R, L74V (due to rarity – unable to determine fitness; P=0.205)
Clinical relevance of TDR
PDR associated with increased risk in virological failure among people on EFV based ART

Slide courtesy Silvia Bertagnolio, unpublished data
Impact of NNRTI PDR in people starting EFV-based ART

Compared to people with no PDR, individuals with NNRTI PDR are:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>less likely to achieve viral suppression and maintain it</td>
<td>3.94</td>
<td>1.99-7.78</td>
<td>8</td>
</tr>
<tr>
<td>more likely to switch/discontinue ART</td>
<td>5.00</td>
<td>1.79-14.70</td>
<td>1</td>
</tr>
<tr>
<td>more likely to acquire new HIVDR mutations</td>
<td>2.45</td>
<td>1.70-3.50</td>
<td>2 (+NAMSAL, not included in the meta-analysis)</td>
</tr>
</tbody>
</table>

Slide courtesy Silvia Bertagnolio, unpublished data
Clinical relevance of transmitted NRTI, PI, InSTI resistance

**NRTI TDR:**
- TAMs: Increasingly less clinically relevant
- K65R/M184V: infrequently observed; reduced transmission efficiency; high levels of VL suppression in people with M184V taking DTG

**PI TDR:**
- Most commonly observed PI mutations (M46I/L) – no impact on currently recommended RTV-boosted PIs (ATV/r, LPV/r, DRV/r)
- L90M – predicted low-level resistance to ATV/r, LPV/r

**InSTI TDR:**
- Extremely rare at present in population-based assessments
- Handful of cases reported in literature
- Pretreatment InSTI resistance testing not cost effective and lead to worse outcomes

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1 Aboud et al., LANCET, 2019. 2Varghese V et al., AIDS Hum Retroviruses 2016; 3 Young B et al., Antivir Ther 2011; 4McGee KS et al., OFID 2018; 5Volpe JM et al., J Int Assoc Provid AIDS Care 2015; 6Boyd SD et al Antivir Ther 2011. 7Koullias Y et al., Clin Infect Dis 2017
Summary of key points

- TDR mutations are stable after transmission - gradual reversion over time, often incomplete
- Pre-existing polymorphisms (present in the virus backbone at time of transmission) function as compensatory mutations improving viral replication capacity

- Prevalence of NNRTI and NRTI TDR has increased in recent years, particularly in LMIC
- Commonly observed NRTI TDR mutations (M184V, T215Y, K219Q, K70R) confer decreased replication capacity and thus are less transmissible
- Commonly observed NNRTI mutations have fitness comparable to WT (K103N/S, Y181C); some PI mutations (L90M) are more fit than WT
  - Explains their higher prevalence in population studies and persistence in transmission clusters
Conclusions

- Global guidelines recommend use of a dolutegravir (DTG)-containing regimen in first-line
  - NNRTI TDR no impact
  - K65R/M184V (fitness disadvantage and infrequently observed)
    - M184V alone unlikely to impact viral suppression outcomes
    - K65R and or K65R + M184V – impact on viral suppression outcomes, less certain
  - InSTI TDR very, very rare at present (no impact on DTG at population level)

- Maximizing population VL suppression will minimize emergence of acquired resistance and its subsequent transmission (TDR)
  - Surveillance of acquired HIVDR will signal future TDR

- Surveillance of HIVDR in people with newly diagnosed HIV (including those with exposure to TDF-containing PrEP) may help inform future HIV treatment recommendations
Acknowledgements

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