HIV replication: principles and prevention

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CLINICAL DATA DURING SIXTEEN WEEKS OF INH THERAPY

INH SUSCEPTIBILITY OF ISOLATES FROM PATIENTS WITH PULMONARY TB TREATED WITH INH MONOTHERAPY

PERCENTAGE OF CASES

WEEKS OF TREATMENT

## PREEXISTENCE OF DRUG RESISTANT MUTANTS OF TB

<table>
<thead>
<tr>
<th>Number of plates</th>
<th>Inoculum* per plate</th>
<th>Drug conc.</th>
<th>Colonies per plate (actual)</th>
<th>Prevalence of resistance mutants</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>$5 \times 10^6$</td>
<td>INH† 1.0</td>
<td>99,101, 106,107</td>
<td>1 in 5 $\times 10^4$</td>
</tr>
<tr>
<td>4</td>
<td>$5 \times 10^7$</td>
<td>SM‡ 2.0</td>
<td>55, 59, 64,70</td>
<td>1 in 1 $\times 10^6$</td>
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<tr>
<td>100</td>
<td>$1 \times 10^8$</td>
<td>INH 1.0</td>
<td>No growth</td>
<td>&lt;1 in 1 $\times 10^{10}$</td>
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<tr>
<td></td>
<td></td>
<td>SM 2.0</td>
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</table>

* Number of viable, bacterial units from a seven to 10 day old vigorously growing, well dispersed *H37Rv* culture in liquid medium (ST).

† Isoniazid

‡ Streptomycin

Cohn et al, J Clin Invest 38:1349, 1959
HIV-1 Drug Resistance is the RESULT and the CAUSE of drug failure

- **RESULT:** Emergence of drug-resistant virus is an inevitable consequence of the failure to fully suppress HIV-1 (HCV, HBV, influenza virus, TB, etc) replication with antimicrobial therapy.

- **CAUSE:** Drug resistance is a major factor contributing to the failure of antiretroviral therapy.
Diversity of RNA Virus Populations

- RNA viruses constitute a *quasispecies*.
- Genetically distinct viral variants evolve from an initial monoclonal or oligoclonal virus inoculum.
- Variants are generated due to error-prone nature of RT.
Drug-Resistant Mutants Preexist in Untreated Patients

- The HIV genome contains $10^4$ nucleotides.
- The mutation rate of HIV is $\sim 3 \times 10^{-5}$ nucleotides/replication cycle.
- $\sim 10^{11}$ virions are generated by $10^7 - 10^8$ rounds of replication each day. Thus every possible mutant is generated daily with high level ongoing replication.
Rapid Turnover of Viral Quasispecies

- Most of the virus population in plasma is cleared and replaced each day.
- Rapid turnover allows rapid emergence of drug-resistant variants under selective pressure.
- Resistant variants may be replaced by residual wild-type virus if selective pressure is removed.
- Resting latently infected cells may continue to harbor drug-resistant provirus.
HIV drug resistance is generated by one of two major mechanisms

- Acquired drug resistance following non-suppressive treatment (secondary resistance)

- Transmitted drug resistance (TDR) (primary resistance)

(PDR combines both TDR and resistance acquired from previous treatment, disclosed or not, after infection)

- Both mechanisms are too prevalent.
- Prevention strategies for these two mechanisms are completely different.
AZT Susceptibility of Sequential Isolates of HIV-1 From a Patient Administered AZT

Larder, Darby and Richman, Science 1989; 243:1731.
HCSUS: Prevalence of HIV Drug Resistance

- HCSUS population
  - Representative as possible to all HIV-positive persons receiving medical care in early 1996
  - 1080 samples with HIV RNA >500 copies/mL
- Resistance more common
  - Lowest CD4 count nadir
  - Higher HIV RNA
  - More access to care
- Resistance less common
  - Patients cared for by the most experienced providers

Richman et al, AIDS 18:1393, 2004
Transmission of Drug-Resistant HIV in Treatment-Naïve Patients


IC$_{50}$ >10-fold increase via PhenoSense HIV (ViroLogic)

Phenotypic Resistance (% patients)

- NNRTI
- PI
- NRTI

<table>
<thead>
<tr>
<th>Year</th>
<th>Number (n)</th>
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<td>1999</td>
<td>90</td>
</tr>
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<td>2000</td>
<td>23</td>
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New detection of drug resistance

Year of ART initiation:
- <1999
- 1999-2006
- ≥2007

New detection of three-class resistance

Scherrer et al, CID, 2016
Slow resistance development and transmission in resource-rich settings

In the 7 years after the introduction of unboosted PIs, PI/r, and NNRTIs, 18.2 times (1543 of 5923), 5.7 times (482 of 5332), and 7.2 times (609 of 4347) more patients did not respond to the respective ART. The median PVL after first exposure to INSTIs, after treatment failure during INSTI receipt, and after detection of INSTI resistance in the 7 years after introduction of the first INSTI was much lower, compared with the median PVL after introduction of other drug classes (Figure 1 and Supplementary Appendix 3 and 4).

DISCUSSION

Seven years after introduction of INSTIs in Switzerland, no transmission of major INSTI resistance mutations was detected by our study. The major reason for this unexpected absence of INSTI transmission is most likely the very low transmission potential in the SHCS. Treatment-naive patients had no transmission potential of INSTI resistance because of lacking INSTI resistance mutations, and the number of treatment failures during INSTI receipt remained remarkably low. Thus, the PVL of patients who experienced a virological failure during INSTI receipt or who carried viruses with INSTI resistance mutations was very low. To put these findings in a historical context was even more impressive. The transmission potential of resistance mutations remained very low after the introduction of INSTI as compared to the time after introduction of PIs and NNRTIs. Despite these very encouraging and unexpected findings, the transmission of INSTI resistance most likely cannot be avoided. Boyd et al postulated that it is only a matter of time until the prevalence of transmitted drug resistance affecting INSTIs is reaching higher levels. However, we demonstrated that the transmission of drug resistance affecting a new class can be minimized. The Swiss setting cannot be compared to other settings (eg, those with limited access to viral load monitoring or no available second-line and third-line therapies). In these settings, patients may continue to receive failing regimens and may accumulate more drug resistance mutations. These patients have a high transmission potential and might also accumulate secondary mutations. Such strains might be transmitted and fixed in the population and might lead to major public health issues in the future.

Minor mutations were more frequently seen in non-B subtype infections, but they probably do not have an impact on the treatment outcome, as has been shown for minor PI mutations. The sample size was too small to analyze specific pattern among non-B subtypes. To our knowledge, this is the largest study to assess the transmission of INSTI resistance in a highly representative population. Owing to the similar history of drug approval and Figure 1.

A – D, Population viral load (PVL) of patients treated with integrase strand transfer inhibitor (INSTIs; A), nonnucleoside reverse transcriptase inhibitors (NNRTIs; B), unboosted protease inhibitors (PIs; C), and ritonavir-boosted PI (PI/r; D) in the 7 years after introduction of each drug class. The areas represent the PVL after first exposure to the specific drug class (light gray) and the PVL after virological failure of the specific drug class.

Abbreviation: HIV-1, human immunodeficiency virus type 1.
How did this reduction of resistance in resource-rich countries with more expanded treatment happen?

- Better drugs
  - More potent and better half-lives (TDF/FTC, better PIs, integrase inhibitors)
  - More tolerable and less toxic (thymidine analogues are history)
  - Fixed dose combinations

- Better monitoring of failure and then use of drug resistance testing and better drugs for treatment failure
Pretreatment HIV Drug Resistance to Nonnucleoside Reverse Transcriptase Inhibitors in 11 Countries.

Shown are the percentages of people tested who had resistance to efavirenz or nevirapine. Error bars denote 95% confidence intervals. Data are from the World Health Organization.1
Cost of continuing a regimen failing as defined by virologic criteria

- CNA3005: ZDV/3TC/ABC vs. ZDV/3TC/IDV
- "First genotype" performed at time of rebound
- "Last genotype" performed prior to changing ART
- Early breakthrough with wild type or M184V
- Increasing NRTI mutations associated with cross-resistance to all RTIs

Melby T, et al. 8th CROI; 2001; Chicago, Ill. Abstract 448
Rapid accumulation of DRMs when first-line ART is continued despite virological failure

Longitudinal genotyping analysis at first detection of VF (t1) and 6-12 months after (t2)

Steep increase in TAMs (+250%) and K65R (+100%) NNRTI susceptibility is already lost at first detection of VF Precedes WHO-defined failure criteria

Barth et al. Antiviral Therapy 2012
Prevention of acquired drug resistance requires addressing the causes

- The patient
  - adherence
- The prescribing care provider
  - selecting an optimal regimen
  - counseling the patient
- The drugs
  - Potency
  - tolerability
  - Pharmacokinetics
- The healthcare delivery system
  - Provide viral load monitoring with prompt turnaround and threshold <100 copies/mL
  - Provide assays for drug resistance (or drug levels).
  - Avoid stockouts
Measures are still needed to preserve the integrase class over time

- Low level viremia ≠ treatment success
  - High threshold may be even more dangerous with DTG, since viruses resistant to DTG are often not very fit and viral load may remain low
- Delayed response to viral rebound puts individuals and society at risk
- Use tools (like viral load monitoring and objective adherence assessment) to generate insight in virological failure
Measures are still needed to preserve the integrase class over time - 2

- Avoid adding 1 new drug to a failing regimen
  - What is the risk of a switch from a failing regimen with TLE to TLD?
  - Surveillance in those who start DTG with unsuppressed viral load should be promptly initiated if resistance testing is not applied at switch
The principles of HIV drug resistance are well established (Darwinian evolution).

The mistakes and lessons learned in the developed world have been recapitulated in low and middle income countries.

Prevention of further increases in drug resistance

- Better regimens (TLD/TFD)
- Avoid stockouts
- Monitor viral load with prompt access to results
- If and when available, access drug resistance tests and drug levels
- Interventions to improve adherence and reduced risk behaviors