Antiretroviral Prophylaxis and HIV Drug Resistance

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Outline

• Two minutes on terminology
• Origins of HIV drug resistance
• Lessons learned from ART
• Do these apply to ARP?
  • Yes, but…
• Other relevant considerations
Two Minutes on Terminology

“Microbicides” mean different things to different people:

- Kills all microbes (i.e., bleach)
- Kills some microbes including HIV
- Only blocks HIV replication (i.e. ARV)
- Anything put into the vagina or rectum
Prevention with Antiretrovirals

• ARV treatment of infected persons (ART)
  ▪ prevent horizontal transmission
  ▪ prevent vertical transmission (pMTCT)

• ARV prophylaxis (ARP) of uninfected persons
  ▪ prevent horizontal transmission (M ⇔ F; M ⇔ M)
  ▪ prevent vertical transmission (pMTCT)

• ARP approaches
  ▪ Mucosal (topical) or systemic (oral, SC, IM) or both
  ▪ Pre- or post-exposure or both
The Ideal ARV for Prevention

- Potent, specific HIV inhibitor
- Acts pre-integration (no provirus formation)
- High mucosal and submucosal exposure
- One dose daily – or less
- Well tolerated, safe for long term use
  - including pregnancy and breastfeeding!
- Gender neutral (empowers women and men)
- Not used for therapy - preserves treatment options!
- Affordable: drug and monitoring costs
Origins of HIV Drug Resistance

- Large, diverse population of HIV variants within a chronically infected individual
  - High viral replication: $\sim 10^{11}$ virions produced per day
  - sloppy RT: $\sim 3$ errors per 100,000 bases copied
  - RT doesn’t correct its errors
  - No two genomes are the same!
  - Differ on average by one base out of $\sim 10,000$
HIV variants in one plasma sample
(*Gag-pol* single genome sequences)
Billions of mutants produced daily!
Origins of HIV Drug Resistance

• For many ARV, a single nucleotide change results in resistance:
  - TNV (K65R): AAA to AGA
  - FTC (M184V): ATG to GTG
  - EFV (K103N): AAA to AAC

• With $10^{11}$ genomes produced daily:
  - All possible single mutants produced daily
  - Double mutants may also exist
  - Triple mutants probably do not

  $P = 10^{-12} (10^{-4} \times 10^{-4} \times 10^{-4}) < 10^{11}$ genomes/day
Lessons Learned from ART

• Resistant variants are rapidly selected by monotherapy with drugs for which 1 mutation confers resistance
Appearance of 3TC-Resistant Mutations in Treated Patients

Schuurman et al, JID 1995; 171:1411

Wild type at codon 184

RNA Copies/ml

Weeks after start of 3TC
Lessons Learned from ART

- Resistant variants are rapidly selected by monotherapy with drugs for which 1 mutation confers resistance
- Incomplete suppression of viral replication results in accumulation of multiple mutations, more resistance and broader cross-resistance
Accumulation of Multiple Mutations in HIV RT

<table>
<thead>
<tr>
<th>AZT, IC_{50} (μM)</th>
<th>Passage Number</th>
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<tbody>
<tr>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
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<tr>
<td>1000</td>
<td>4</td>
</tr>
<tr>
<td>WT</td>
<td>5</td>
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</table>

- 67N/70R/215I/371V/509L
- 67N/70R/215F/371V/509L
- 67N/70R/371V/509L
- 67N/70R
Lessons Learned from ART

• Resistant variants are rapidly selected by monotherapy with drugs for which 1 mutation confers resistance

• Incomplete suppression of viral replication results in accumulation of multiple mutations, greater resistance and broader cross-resistance

• HIV proteins are amazingly flexible
  - Preserved function despite many substitutions
  - e.g., >25% of 99 amino acids in Protease can vary
Protease Mutations Associated with Reduced Susceptibility to Lopinavir
Principles of Successful ART

• Cover all pre-existing mutants
  ▪ Single and double drug-resistant mutants

• Suppress new cycles of HIV replication
  ▪ Plasma HIV RNA < 50 copies/ml

• Generally requires 3 potent drugs
  ▪ With non-overlapping resistance mutations
ART MANTRA

No Replication = No Resistance
Caveats

• Not all three drug combinations are the same
  - TNV + 3TC + ABC $\Rightarrow$ rapid virologic failure in >50%
    » Single mutant (M184V) affects two drugs: 3TC/ABC
    » Failure virus has M184V ± K65R
  - TNV + 3TC + EFV $\Rightarrow$ 75% long-term success
    » No single mutant affects more than one drug
    » M184V increases sensitivity to TNV!

• Can get away with 2 drugs requiring >2 mutations for viral escape
  - LPV/r + EFV = TNV/3TC/EFV (Riddler ACTG 5142)

• Choose combinations wisely
  - Consult your local resistance expert 😊
Relevant for ARP?

• Yes, but…. *Warning, Entering Data Poor Zone*
  - Size and diversity of virus population in genital secretions is tiny compared with that in an infected individual
    » 10^4-10^6 vs 10^{11} genomes
    » Infectious titer probably much lower
    » Probability of pre-existing resistant mutant is low
  - One drug may suffice (TNV in trials)
    » Unless source of infection has resistance to that drug!
  - One drug requiring > 1 resistance mutation or 2 drugs with non-overlapping resistance mutations might be better

• Initial emphasis should be on potency and exposure at the site of infection to maximize efficacy….
ARP MANTRA

No Infection = No Resistance!
## ARP Efficacy vs. Resistance

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Seroincidence</th>
<th>Efficacy of ARP</th>
<th>% Resistant w/ ARP Failure</th>
<th>Individuals with Resistance</th>
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<tbody>
<tr>
<td>100,000</td>
<td>5%</td>
<td>30%</td>
<td>50%</td>
<td>1750</td>
</tr>
<tr>
<td>100,000</td>
<td>5%</td>
<td>60%</td>
<td>50%</td>
<td>1000</td>
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<td>95%</td>
<td>50%</td>
<td>125</td>
</tr>
<tr>
<td>100,000</td>
<td>5%</td>
<td>99%</td>
<td>50%</td>
<td>25</td>
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Other Relevant Issues

- Individuals who are put on ARP with undiagnosed HIV infection will develop resistance
  - Unless APR is equivalent to ART (impractical)
- Individuals who become infected on ARP will likely develop resistance unless it is stopped promptly
  - Impact of resistance on future response to ART?
- Ideally, agents used for ARP and ART will not overlap
  - Not possible today…a goal for the future
Questions?