ARV Resistance and Microbicide Research

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Outline

• Origins of HIV-1 drug resistance
• Mechanisms of RTI action and resistance
• Clinical pathogenesis & consequences
• Review of key scenarios
• Implications for MTN trials
Origins of HIV-1 Drug Resistance

- High viral replication (~$10^{11}$ virions/day)
  - Error prone RT ($3 \times 10^{-5}$/bp/cycle)
- All single & many double mutants likely pre-exist
  - Rapidly selected by monotherapy or dual therapy with drugs for which 1-2 mutations confer resistance
- Multiple mutations are selected and accumulate with continued viral replication during therapy
  - Resistance/cross-resistance to multiple drugs
Origins of HIV-1 Drug Resistance (con’t)

• Recombination between resistant variants
  ▪ Speeds accumulation of mutations on the same genome

• HIV-1 target flexibility
  ▪ Preserved function despite many substitutions
  ▪ e.g., >25% of 99 amino acids in PR can vary
No ARV is Resistance Proof!
# Approved Antiretroviral Drugs 2007

<table>
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<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>FI</th>
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<tr>
<td>zidovudine</td>
<td>nevirapine</td>
<td>ritonavir</td>
<td>enfurvitide</td>
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<td>didanosine</td>
<td>delavirdine</td>
<td>indinavir</td>
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<td>zalcitabine</td>
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<td>darunavir/r</td>
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Nucleoside and Nucleotide RTIs (NRTI)

- Zidovudine (AZT)
- Stavudine (d4T)
- Zalcitabine (ddC)
- Lamivudine (3TC)
- Tenofovir (TDF)
- Didanosine (ddI)
- Abacavir (ABC)
- Emtricitabine (FTC)
NRTI – Mechanism of Action

AZT (Zidovudine)

Intracellular metabolism

AZT-TP
NRTI – Mechanism of Action

AZT (Zidovudine) → Intracellular metabolism → AZT-TP → Incorporation by HIV RT

Viral RNA/DNA → Nascent DNA → Competition!
NRTI – Mechanism of Action

AZT (Zidovudine)

Intracellular metabolism

AZT-TP

Incorporation by HIV RT

Competition!

Viral RNA/DNA

Nascent DNA

Incorporation by HIV RT

Competition!
NRTI – Mechanism of Action

AZT (Zidovudine)
Intracellular metabolism
AZT-TP
Incorporation by HIV RT
dTTP
Competition!

Viral RNA/DNA
Nascent DNA
Chain-termination

Incorporation by HIV RT

Intracellular metabolism

NRTI – Mechanism of Action
Molecular Mechanisms of NRTI Resistance

1. Discrimination:
   Resistance mutations enable HIV-1 RT to preferentially incorporate the natural dNTP substrate over the NRTI-TP
   **Mutations:** K65R, K70E, L74V, M184V, Q151M

2. Excision:
   Resistance mutations facilitate excision or removal of the chain-terminating NRTI-MP from the 3’-terminus of the primer
   **Mutations:** TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219Q)
Nonnucleoside RTIs (NNRTI)

Nevirapine (Viramune)

Efavirenz (Sustiva)

Delavirdine (Rescriptor)
NNRTI – Mechanism of Action

RT → RT-T/P

T/P

dNTP → RT-T/P-dNTP

Chemical Catalysis

RT-T/P_{+1} - PPi

PPi

RT-T/P_{+1}
NNRTI – Mechanism of Action

NNRTI

NNRTI-RT

T/P

NNRTI-RT-T/P

dNTP

NNRTI-RT-T/P-dNTP

Inhibition of phosphodiester bond formation

Spence et al. 1995. Science 267:988
Resistance mutations, such as K103N and Y181C, affect the association and dissociation constants of the NNRTI-RT binding interaction.

Limited Inherent Potency of the Regimen
- Single/dual drug therapy

Suboptimal Drug Exposure
- Incomplete Adherence
- Unfavorable PK (or antagonism)
- Resistant virus (de novo or transmitted)

Incomplete Inhibition of Viral Replication

Selection of Pre-existing Mutants
Evolution of New Mutants

Reduction in Drug Susceptibility

Limit Current/Future Treatment Options
Fitness vs. Drug Resistance: Trade-off for Survival

• Drug-resistant variants are less fit than wildtype when drug is absent
  ▪ Leads to decay of resistant variants when drug is removed

• Drug-resistant variants are more fit than wildtype when drug is present
  ▪ Fitness advantage leads to emergence of the resistant variant

• Example
  ▪ K65R: 3-10 fold resistance
  ▪ 50% fitness of wildtype when drug is absent
Review of Key Scenarios

Chronic HIV-1 infection exposed to oral ARV PrEP?
Pre-existing Mutant at ~0.01%

Limit of Detection for Std Genotype
Monotherapy Selects Pre-existing Mutant

% Mutant

Time (Months)

1 2 3 4 5 6 7 8 9 10 11 12

123456789 1 0 1 1 1 2

Detected by Standard Genotype
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

M184V

M184I
Chronic HIV-1 infection exposed to oral ARV PrEP

- Rapid selection of resistant variants is likely with a single or dual ARV PrEP
  - Potential for horizontal or vertical transmission
- Resistant variants will likely decline in frequency with drug removal
  - May persist for NNRTI
- Impact on response to subsequent therapy unclear!
Re-selection of “Low Frequency” Mutant

% Mutant

Time (Months)

1 2 3 4 5 6 7 8 9 10 11 12
Review of Key Scenarios

Chronic HIV-1 infection exposed to topical PrEP?
Chronic HIV-1 infection exposed to topical ARV PrEP

- Local selection of resistant variants is likely with a single drug
  - Potential for systemic dissemination
  - Potential for horizontal or vertical transmission
  - May persist for certain drugs – NNRTI
- Systemic selection will depend on drug exposure
  - If low exposure likely to be a minor resistant population and not detected by standard genotype methods
- Impact on response to subsequent therapy unclear
Review of Key Scenarios

Acute HIV-1 infection on to oral or topical ARV PrEP
Acute HIV-1 infection on oral or topical ARV PrEP

- For NRTI PrEP, SIV/macaque studies show that initial breakthrough infection is wildtype! (unprotected cells)
  - Resistant virus will be selected with continued PrEP but not if PrEP is stopped in time
  - Should revert to wildtype with PrEP discontinuation unless transmitted virus was drug-resistant (no wildtype)
- Breakthrough infection of topical PrEP is likely to be wildtype with systemic dissemination related to systemic exposure
  - Risk of horizontal or vertical transmission of resistant virus if PrEP is continued
Implications for MTN Trials

• Avoid inadvertent exposure of those with chronic HIV-1 infection to topical or oral ARV PrEP
  - Resistance selection is very likely
  - Subsequent transmission is possible
  - Could affect subsequent treatment response

• Detect acute HIV-1 infection on PrEP trials ASAP
  - Avoid selection of ARV-resistant virus
  - Could be transmitted
  - Could affect subsequent treatment response

• Study subsequent response to therapy carefully (MTN-015)
Discussion?