Key Factors: The Virus, Patient, and Drugs

**Virus**
- Replication
- Mutations & Resistance
- Latent Reservoirs
- Tissue Compartments

**Patient**
- Adherence
- Toxicities
- Quality of Life
- Comorbidities
- Psychosocial Issues

**Drugs**
- Potency
- Tolerability
- Convenience
- Pharmacokinetics
- Resistance Profile
HIV Life Cycle - In Search of Drug Targets
A Closer Look at Reverse Transcription


"Template"

Reverse Transcriptase

dNTP’s

dGTP, dCTP, dATP, dTTP


"Template"

Transfer RNA "Primer"

Viral DNA

Transfer RNA "Primer"

- RNA-Directed Polymerase Activity
A Closer Look at Reverse Transcription


← T–C–G–A–A–C–G–G–A–A–C–U–C ←

Reverse Transcriptase

Viral DNA

Transfer RNA

“Primer”

• RNase H Activity


← T–C–G–A–A–C–G–G–A–A–C–U–C ←

Viral DNA

Transfer RNA

“Primer”
A Closer Look at Reverse Transcription

Viral RNA → C-G-C


Reverse Transcriptase

• DNA-Directed Polymerase Activity


Viral DNA
Nucleotide Analogs

Anatomy of a dNTP

Triphosphate
Sugar
Base
Nucleotide Analogs

Triphosphate

MODIFIED Sugar

Base
Mechanism of Competitive Reverse Transcriptase (RT) Inhibition

nucleotide analogs are incorporated into DNA and work through the process of chain termination

Incorporation into DNA leads to chain termination
Nucleotide Analogs

Can not get into cells

Nucleoside Analog (no Phosphate)

Transport/Diffusion into Cells

Cellular Enzymes

Triphosphate

MODIFIED Sugar

Base
NRTIs = Nucleoside reverse transcriptase inhibitors
NtRTIs = Nucleotide reverse transcriptase inhibitors
Reverse Transcriptase Inhibition

Chain-Terminated (Dead-end) Product
Selectivity?

HIV-Infected Cell

DNA Synthesis (Reverse Transcriptase)

Viral Replication

NRTI or NtRTI

Uninfected Host Cell

DNA Synthesis (Pol-gamma - mitochondria)

Cell Growth and Metabolism

Active Triphosphate Form
Examples of Clinically Useful Anti-HIV NRTIs and NtRTIs

- ZDV  Zidovudine (1987)
- ddI  Didanosine (1991)
- ddC  Zalcitabine (1992)
- d4T  Stavudine (1994)
- 3TC Lamivudine (1995)
- Abacavir (Ziagen) - (1998)
- Tenofovir disoproxil (Viread) – (2001)
## Characteristics of Approved NRTIs/NtRTIs

<table>
<thead>
<tr>
<th></th>
<th>ZDV</th>
<th>ddl</th>
<th>ddC</th>
<th>d4T</th>
<th>3TC</th>
<th>ABC</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum half-life (h)</td>
<td>1.1</td>
<td>1.6</td>
<td>1.2</td>
<td>1.0</td>
<td>3-6</td>
<td>1.5</td>
<td>17</td>
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<tr>
<td>Intracellular half-life (h)</td>
<td>3</td>
<td>25-40</td>
<td>3</td>
<td>3.5</td>
<td>12</td>
<td>3.3</td>
<td>10-50</td>
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<tr>
<td>Oral bioavailability (%)</td>
<td>60</td>
<td>30-40</td>
<td>85</td>
<td>86</td>
<td>86</td>
<td>83</td>
<td>25-39</td>
</tr>
</tbody>
</table>

DHHS Guidelines.
# NRTIs/NtRTIs: Drug-specific Toxicities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV</td>
<td>Nausea; abdominal discomfort; headache; insomnia; myopathy; anemia; neutropenia</td>
</tr>
<tr>
<td>3TC</td>
<td>Toxicity uncommon</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Hypersensitivity reaction; occasional GI toxicity</td>
</tr>
<tr>
<td>ddl</td>
<td>Peripheral neuropathy; pancreatitis; GI toxicity (with original buffered formulation)</td>
</tr>
<tr>
<td>d4T</td>
<td>Peripheral neuropathy; ascending motor weakness; greatest mitochondrial toxicity</td>
</tr>
<tr>
<td>ddC</td>
<td>Peripheral neuropathy; oral ulcers</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>Flatulence</td>
</tr>
</tbody>
</table>
HIV Infection

Critical Insights from HIV RNA Quantification Studies

CD4+ Cells (cells per mm³)

0 2 4 6 8 10 weeks

10⁷ HIV RNA (copies per mL plasma)

10²

10¹⁰ Virions / Day
~180 generations/Yr

“Latent Period”
RESISTANCE

$10^{10}$ replications/day $\times 10^{-5}$ mutations per nucleotide per replication $\times 10^4$ nucleotides/genome $= 10^9$ mutants a day!

RESISTANCE is due to Mutation

Mutations (Resistance) can Happen BEFORE Drug Therapy
- Drugs Select for Mutant Virus

Mutations (Resistance) can Happen DURING Drug Therapy
- If replication is not inhibited completely
Resistance

AZT

- Correlation with Stage, CD4, duration
  - e.g. After 1 year monotherapy in AIDS -> 90% resistance vs 30% in asymptomatic
- Specific mutations in Reverse Transcriptase not only in dNTP binding site, but also in primer-template binding site
  - 1/3 high-level resistance
- New infections with resistant strains on the rise
Resistance

Develops quickly with monotherapy

Cross resistance:

- ddl resistant strains - cross resistant to ddC, D4T, 3TC
- D4T resistant strains - cross resistant to ddl, ddC, 3TC etc.

Abacavir resistant strains resistant to ddl, ddC but increased sensitivity to AZT

Similarly, 3TC can cause AZT-resistant strains to become more sensitive.
Reverse Transcriptase Resistance to NRTIs

Mutant RT

NTRI-TP

Mutant RT

- Decreased Binding
- Primer Unblocking

Chain-Terminated (Dead-end) Product
Primer Unblocking (PUB)

The pyrophospholytic (i.e., reverse incorporation) removal of chain-terminating NRTIs

B. Mutations in the Reverse Transcriptase (RT) Gene Selected by RT Inhibitors

Nucleoside RT Inhibitors

Zidovudine

Didanosine

Zalcitabine

Lamivudine

Stavudine

Abacavir

Multinucleoside Resistance
## Mechanisms of Resistance to Nucleosides

<table>
<thead>
<tr>
<th></th>
<th>Type No. 1</th>
<th>Type No. 2</th>
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<td><strong>Codons</strong></td>
<td>65,74,151,184</td>
<td>41,67,70,210,215,219</td>
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<tr>
<td><strong>Mechanism</strong></td>
<td>Inhibitory competition</td>
<td>Pyrophosphorolysis</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Single or multiple drugs</td>
<td>Multiple drugs</td>
</tr>
<tr>
<td><strong>Fitness</strong></td>
<td>Reduced</td>
<td>Small or negligible change</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>All NRTIs</td>
<td>AZT &gt; all other NRTIs</td>
</tr>
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</table>
Nucleoside Reverse Transcriptase Inhibitors
NRTI Incorporation

NRTI resistance mutations may indirectly alter the positioning of conserved residues involved in catalysis (e.g., Y183, D185, and D186) resulting in alterations in the rate of polymerization or pyrophosphorolysis.

Combinations of Nucleoside Analogs

ddI + AZT - More effective than AZT alone in delaying progression and death in initial to late stage HIV disease.

Slower onset of resistance

Cumulative, not synergistic, toxicities
Rethinking the Role of NRTIs

- Current patterns of use largely reflect custom and convenience
  - AZT/3TC
  - d4T/3TC
  - d4T/ddI

- Emerging concerns of toxicity and resistance have altered patterns of use

- New drugs and new data support new options

¹ Kuritzkes, D. IAC Barcelona July 2002
Nucleoside Analogs - In Development

FTC (Coviracil, emtricitabine) - 3TC (Lamivudine) analog with increased potency, but similar resistance profile. In Phase III clinical trials.
DAPD - novel nucleoside analog with unique resistance profile. In Phase I/II clinical trials.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI’s)

Results of Random Screening Efforts
Many different compounds found (over 30 separate classes)
Specific for HIV-1
Unique Mechanism
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI’s)

Nevirapine (Viramune) - 1996
Delaviridine (Rescriptor) - 1997
Efavirenz (Sustiva) - 1998
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI’s) - Side Effects

Nevirapine (Viramune) - Only in Combination with other agents
Mild to severe rash, fever, nausea
Induces metabolism of protease inhibitors
Twice a day dosing

Delaviridine (Rescriptor) - Only in Combination with other agents
Mild to severe rash, fever, nausea
Inhibits metabolism of protease inhibitors
Interactions with nucleoside analogs
Three-times daily dosing

Efavirenz (Sustiva) - Only in Combination with other agents
Mild rash, Dizziness
Induces metabolism of protease inhibitors
Once-a-day dosing
Nonnucleoside RT Inhibitors - Resistance
HIV Protease Inhibitors

HIV Protease: An Autocatalytic Enzyme

gag-pol polyprotein (contains the protease)

protease

Other HIV proteins (RT, IN, gp120, p24, etc)
Protease Inhibitors - Lead Compounds

Hypertensive Cascade:

Angiotensinogen

\[ \text{Renin} \rightarrow \text{Angiotensin I} \]

\[ \text{Angiotensin-Converting Enzyme (ACE)} \]

\[ \text{Angiotensin II} \]

(Increases Blood Pressure)

Similar to HIV Protease
Protease Inhibitors
Protease Inhibitors
Protease Inhibitors
Protease Inhibitors

- Indinavir (Crixivan) (1996)
- Saquinavir (Fortovase) (1995-1997)
- Nelfinavir (Viracept) (1997)
- Amprenavir (Agenerase) (1999)
- Kaletra (ritonavir + lopinavir) (2000)
Protease Inhibitors - Side Effects

- **Indinavir (Crixivan)** - Must be taken before meals
effects metabolism of other drugs
crystalizes in urine
- **Saquinavir (Fortovase)** - metabolism interactions
gastrointestinal disturbances
- **Ritonavir (Norvir)** - inhibits metabolism of many drugs
numbness, gastrointestinal disturbances
- **Nelfinavir (Viracept)** - gastrointestinal disturbances
  effects metabolism of other drugs
- **Amprenavire (Agenerase)** - gastrointestinal disturbances,
rash, hyperglycemia, hemolytic anemia
Protease Inhibitors - Resistance

A. Mutations in the Protease Gene Selected by Protease Inhibitors

Protease Inhibitors

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<tr>
<th>Indinavir</th>
<th>L</th>
<th>K</th>
<th>L</th>
<th>V</th>
<th>M</th>
<th>I</th>
<th>L</th>
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<th>A</th>
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<th>M</th>
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</table>
HIV Protease Inhibitors in Development

Major problems with existing drugs:

**Pharmacokinetics** - drugs are eliminated quickly, primarily via metabolism. Requires multiple or restrictive dosing.

**Inhibition** or extensive metabolism by cytochrome enzymes

**Hyperlipidemia** - Current drugs can exacerbate HIV-related elevation in lipid levels in certain patients
HIV Protease Inhibitors in Development

• Atazanavir - Phase 2.
  superior Pharmacokinetics
  once daily dosing w/out CYP3A4
  blockade w/ ritonovir
  - beneficial to patients with
    hyperlipidemia-related toxicities to
    other protease inhibitors.
HIV Protease Inhibitors in Development

• Tipranivir - Phase 2.
  Active against HIV strains resistant to other protease inhibitors.
  - requires ritonavir boosting for pharmacokinetics.
Triple-Drug Cocktails

- AZT + 3TC + (indinavir or ritonavir)
- AZT + ddC + saquinavir
- Sustiva + AZT + 3TC (Current standard)

* Time-to-Treatment-Failure FDA standard

Lower viral load (RNA copies / mL plasma) to undetectable levels
(From 200,000 - 1,000,000 copies / mL to less than 50)

For up to 1 year in 90% of patients

Lower rate of progression to AIDS
Triple-Drug Cocktails

Resistance (increased viral load) does eventually develop in some patients

However, cessation of therapy causes rapid onset of symptoms

Even in face of increased viral load, continued therapy helps
Quadruple Drug Therapy

Protease inhibitor + NNRTI + two nucleoside analogs

Trials are on-going

Highly Active AntiRetroviral Therapy - ART
short-hand for triple/quad therapy
Deaths Due to HIV/AIDS, 1987-2000

Trends in Age-Adjusted* Rate of Death due to HIV Infection, USA, 1987-2000

*Using the year 2000 US standard population.
†Preliminary mortality data for 2000

Note: For comparison with data for 1999-2000, data for 1987-1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
Hit Hard. Hit Early?

- “Hit hard, hit early” was common strategy at beginning of combination therapy
  — Based on potential for eradication
- Today, eradication seems unlikely with current drugs
  — Long-term use of ARVs can lead to toxicities and resistance
- Today’s questions
  — When to start?
  — What to start with?
When to Start: HIV-specific Labs

- CD4 count
- HIV RNA

Time

Cells/mm³

Copies/mL

0

0

15,000

30,000

45,000

60,000

75,000

90,000
### What to Start with: Common ART Options

<table>
<thead>
<tr>
<th>Type</th>
<th>Combination</th>
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<tbody>
<tr>
<td>PI-based</td>
<td>NRTI + NRTI + PI</td>
</tr>
<tr>
<td>Double/Boosted PI</td>
<td>NRTI + NRTI + PI + PI</td>
</tr>
<tr>
<td>NNRTI-based</td>
<td>NRTI + NRTI + NNRTI</td>
</tr>
<tr>
<td>Triple NRTI</td>
<td>NRTI + NRTI + NRTI</td>
</tr>
<tr>
<td>NRTI-sparing</td>
<td>PI + NNRTI</td>
</tr>
</tbody>
</table>
Impact of Directly Observed Therapy (DOT) on Viral Load

Retrospective review of 100 ART-naïve patients on 3- or 4-drug HAART under DOT in prison or self-administered therapy (SAT) in trial unit

ART=antiretroviral therapy.
Fischl M, et al. Presented at: 8th CROI; February 6-7, 2001; Chicago, Ill.
<table>
<thead>
<tr>
<th>Event</th>
<th>Associated Drug Class(es)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis/hepatic steatosis</td>
<td>NRTIs</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>NNRTIs, PIs, NRTIs (hepatic steatosis)</td>
</tr>
<tr>
<td>Insulin resistance/hyperglycemia</td>
<td>PIs</td>
</tr>
<tr>
<td>Fat accumulation</td>
<td>PIs</td>
</tr>
<tr>
<td>Lipoatrophy</td>
<td>NRTIs</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Primarily PIs, but also NNRTIs (esp. EFV) and NRTIs (esp. d4T)</td>
</tr>
<tr>
<td>Increased bleeding in hemophiliacs</td>
<td>PIs</td>
</tr>
<tr>
<td>Osteonecrosis, osteopenia</td>
<td>HAART or HIV itself</td>
</tr>
<tr>
<td>Skin rash</td>
<td>NNRTIs</td>
</tr>
</tbody>
</table>
Changing Needs in ARV Drugs

- Past needs
  - Antiviral efficacy
  - More choices for all stages of therapy

- Today’s needs
  - Potency and durability
  - Improved pharmacokinetics
  - Greater tolerability
  - Minimal (or no) long-term toxicities
  - Unique resistance profile
  - New targets
  - Convenient dosing