Antivirals

Lecture 20
Biology 3310/4310
Virology
Spring 2019

You can’t go back and you can’t stand still.
If the thunder don’t get you, then the
lightning will.
JERRY GARCIA
The Wheel (lyrics by Robert Hunter)
Vaccines can prevent viral disease

- But they have modest or no therapeutic effect if an individual is already infected (exception?)
- Our second arm of antiviral defense is antivirals
- Can stop infection once it has started
Despite 50 years of research, our arsenal of antiviral drugs remains dangerously small

Only about 100 antiviral drugs are available on the US market

Most against HIV, HCV, herpesviruses - Persistent infections
Why are there so few antiviral drugs?

- Compounds interfering with virus growth can adversely affect the host cell
  - Side effects are common (unacceptable)
  - Every step in viral life cycle engages host functions

- Some medically important viruses can’t be propagated, have no animal model, or are dangerous
  - HBV, HPV
  - Smallpox - there are two in the US
  - Ebolavirus, Lassa virus
An unappreciated third reason may be the most important

- A compound must block virus replication completely! It must be potent.

- Many standard pharmaceuticals can be effective if enzyme activity is partially blocked.

- Partial inhibition is not acceptable for an antiviral drug - resistant mutants will arise.

- Makes drug discovery expensive.
Another serious problem for antiviral discovery: 
*Many acute infections are of short duration*

- By the time the patient feels ill, it is too late to impact clinical disease
- Antiviral drugs for these viruses must be given early in infection or *prophylactically* to populations at risk
  - *Safety issues; giving drugs to healthy people not wise (exception: PrEP)*
- No broad-spectrum antiviral agents are currently available
- Lack of rapid diagnostic reagents has hampered development of antiviral drugs
Antiviral history

- The first modest search for antiviral drugs occurred in the early 1950s
  - Chemists looked at derivatives of the sulfonamide antibiotics
  - Synthesis of thiosemicarbazones active against poxviruses
  - Smallpox was still a major threat after WWII

- 1960s and 1970s: “blind screening” programs to find chemicals with antiviral activity
  - Spurred on by successes in the treatment of bacterial infections with antibiotics
Blind screening

- No attempt to focus discovery on a virus or a virus-specific mechanism
- Random chemicals and natural product mixtures tested for ability to block replication of a variety of viruses in cell culture systems
- **Hits**, compounds or mixtures that block *in vitro* viral replication; purified and fractions tested in various cell culture and animal models for safety and efficacy
- Promising molecules called **leads** were modified systematically by medicinal chemists
  - *To reduce toxicity, increase solubility and bioavailability*
  - *To improve other pharmacokinetic properties*
Thousands of molecules were made and screened before a specific antiviral was even tested in humans

- Considerable effort, very little success
- One exception: Symmetrel (amantadine)
  - Approved late 1960s for treatment of influenza A virus infections
  - One of three drugs now available for influenza
- Mechanism of action was often unknown or speculative
  - Mechanism of action of Symmetrel deduced early 1990s
Antiviral discovery today

- Recombinant DNA technology & sophisticated chemistry make targeted discovery possible
- Essential viral genes cloned, expressed in genetically tractable organisms, purified, analyzed in atomic detail
- Life cycles of most viruses known, targets for intervention can be generalized
- Modern technology allows inhibitors to be found even for viruses that cannot be propagated in cell culture
- Blind screening procedures are dead
<table>
<thead>
<tr>
<th>Function</th>
<th>Lead compound or example</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attachment</td>
<td>Peptide analogs of attachment protein</td>
<td>HIV</td>
</tr>
<tr>
<td>Penetration and uncoating</td>
<td>Dextran sulfate, heparin</td>
<td>HIV, herpes simplex virus</td>
</tr>
<tr>
<td>mRNA synthesis</td>
<td>Interferon</td>
<td>Hepatitis A, B, and C viruses; papillomavirus</td>
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<tr>
<td></td>
<td>Antisense oligonucleotides</td>
<td>Papillomavirus, human cytomegalovirus</td>
</tr>
<tr>
<td>Protein synthesis/Initiation</td>
<td>Interferon</td>
<td>Hepatitis A, B, and C viruses; papillomavirus</td>
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<tr>
<td>DNA/RNA replication</td>
<td>Nucleoside, nonnucleoside analogs</td>
<td>Herpesviruses, HIV, hepatitis B and C virus</td>
</tr>
<tr>
<td>Assembly</td>
<td>Peptidomimetics</td>
<td>HIV, herpes simplex virus</td>
</tr>
</tbody>
</table>
The path of drug discovery

Proof of principle

- Will the compound get to the right place in the body at the right concentration? (bioavailability)
- Will the compound persist in the body long enough to be effective? (pharmacokinetics)
- Will the compound be safe? (toxicity and specificity)
Significant hurdles stand in the way of finding effective antiviral drugs

It is not unusual for the cost to bring an antiviral drug to market to exceed $100-200 million dollars!
From drug discovery to the clinic

- Discovery/Synthesis
- Preclinical
- Phase I
- Phase II
- Phase III
- FDA review
- Ongoing Safety Surveillance
- Phase IV
Mechanism-based screens

Diagram showing a mechanism involving cleavage site, DRUG, protease, soluble peptide, and insoluble peptide. A graph illustrates the fluorescence intensity of the soluble peptide over time.
Cell-based screen

Active tetracycline efflux protein; insertion of protease site has no effect

Tetracycline-resistant bacteria

Outside cell

Inside cell

Engineered HIV protease site

HIV protease

Copproduction of HIV protease leads to inactivation of the tetracycline efflux protein

Tetracycline-sensitive bacteria

Outside cell

Inside cell

Inactive tetracycline efflux protein

Tetracycline-resistant bacteria

Outside cell

Inside cell

Active tetracycline efflux protein

Addition of a protease inhibitor blocks cleavage, leaving an active tetracycline efflux protein

No colonies

Many colonies

Principles of Virology, ASM Press
Antiviral screening

- High-throughput: 10,000 compounds/day
- Chemical libraries
- Natural products
- Combinatorial chemistry
- Structure-based design
- *In silico* screening
High throughput screening

Microtiter plates with 96, 384 and 1536 wells
We have many antibiotics, but fewer antivirals. What is a reason for the difference?

A. Robotic screening is slow
B. There are few serious viral infections
C. Resistance is a problem
D. Antivirals must be potent
E. All of the above
Resistance to antiviral drugs

- Resistance to any antiviral drug must be anticipated
  - Viruses replicate efficiently
  - Modest to high mutation frequencies
- Special concern during extended therapy for chronic infections (HIV, HBV, HCV)
- Viral mutants resistant to every antiviral drug in arsenal have been detected
- Disconcerting because antiviral arsenal is small
Dangers of drug resistance

- Patient cannot be treated with same drug
- If no other drug is available, infection cannot be stopped
- Genetic analysis of resistance provides insight into antiviral mechanism
- May reveal new strategies to reduce or circumvent problem
Mechanisms of drug resistance

- RNA viruses: error prone RNA polymerase, no correction mechanism
- One misincorporation in $10^4 - 10^5$ nucleotides polymerized ($10^6$ greater than host DNA genome)
- In RNA viral genome of 10 kb, this frequency leads to one mutation in 1-10 genomes
Mechanisms of drug resistance

- DNA viruses: most DNA polymerases can excise and replace misincorporated nucleotides
- DNA viruses evolve more slowly than RNA viruses because they have less diversity
Acyclovir, a highly effective, anti-herpes simplex virus drug

A prodrug; a nucleoside analog

Many antiviral compounds are nucleoside and nucleotide analogs
Acyclovir mechanism of action

ACV → HSV-1 TK → ACV-MP → GMP kinase → ACV-DP → NDP kinase → ACV-TP → Viral DNA polymerase → DNA
Improving acyclovir

- Valacyclovir (valtrex), an L-valyl ester derivative of acyclovir, has markedly improved bioavailability

- Ester is taken up after oral administration, acyclovir is released when the ester is cleaved by cellular enzymes
Acyclovir-resistant HSV

- Arise spontaneously during virus replication
- Some mutants cannot phosphorylate the pro-drug
  - *Mutations are in viral thymidine kinase gene*
- Some mutants cannot incorporate phosphorylated drug into DNA
  - *Mutations are in viral DNA polymerase gene*
Symmetrel (Amantadine)

- Interacts with influenza viral M2 protein (ion channel)
- Blocks entry of protons into virion, prevents uncoating
Go to:

b.socrative.com/login/student
room number: virus

Resistance to which antiviral would involve amino acid changes in a viral enzyme?

A. Acyclovir
B. Amantadine
C. add another one in 2019
D. Penicillin
E. All of the above
Influenza virus NA inhibitors

Influenza virus NA inhibitors

- Designed to mimic natural ligand, sialic acid
- Closer inhibitor to natural compound, less likely target can change to avoid binding drug while maintaining viable function
How inhibitors of NA (Tamiflu, Relenza) work
### Neuraminidase Inhibitor Resistance Testing Results on Samples Collected Since October 1, 2018

<table>
<thead>
<tr>
<th>Type/Subtype or Lineage</th>
<th>Inhibition of Neuraminidase Activity by Antiviral Drug</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oseltamivir</td>
<td>Peramivir</td>
</tr>
<tr>
<td></td>
<td>Virus Tested (n)</td>
<td>Reduced, Number (%)</td>
</tr>
<tr>
<td>Total Viruses</td>
<td>1,812</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>A(H1N1)pdm09</td>
<td>923</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>A(H3N2)</td>
<td>669</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>B/Victoria</td>
<td>105</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>B/Yamagata</td>
<td>115</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Circulating H1N1 and H3N2 viruses are largely resistant to Adamantanes, not recommended for use

http://www.cdc.gov/flu/weekly/index.htm
Baloxavir: A new influenza virus antiviral

- Approved by FDA October 2018 for treatment of acute uncomplicated influenza in people 12 years of age and older who have been symptomatic for no more than 48 hours
- Inhibitor of influenza endonuclease
WIN compounds
Inhibitors of picornavirus uncoating

**Table 1. In Vitro Antiviral Activity**

<table>
<thead>
<tr>
<th>Structure</th>
<th>MIC (µg/ml) equine rhinovirus</th>
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</thead>
<tbody>
<tr>
<td>COOC₂H₅</td>
<td>12-6</td>
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<tr>
<td>CN</td>
<td>Inactive</td>
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</table>

**Table 2. In Vitro Antiviral Activity**

<table>
<thead>
<tr>
<th>Structure</th>
<th>MIC (µg/ml) equine rhinovirus</th>
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<tbody>
<tr>
<td>COOC₂H₅</td>
<td>12-6</td>
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<td>O</td>
<td>12-6</td>
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**Table 3. In Vitro Antiviral Activity**

<table>
<thead>
<tr>
<th>n</th>
<th>MIC (µg/ml), equine rhinovirus</th>
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<tbody>
<tr>
<td>3</td>
<td>Inactive</td>
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<tr>
<td>4</td>
<td>25-6</td>
</tr>
<tr>
<td>5</td>
<td>25-82</td>
</tr>
<tr>
<td>6</td>
<td>6-3</td>
</tr>
<tr>
<td>7</td>
<td>12-6</td>
</tr>
<tr>
<td>8</td>
<td>6-3</td>
</tr>
<tr>
<td>9</td>
<td>Inactive</td>
</tr>
<tr>
<td>10</td>
<td>25-12</td>
</tr>
</tbody>
</table>
HCV drugs

Virology Lectures 2019 • Prof. Vincent Racaniello • Columbia University

Principles of Virology, ASM Press
# HCV antiviral drugs

<table>
<thead>
<tr>
<th>Target</th>
<th>Generic name</th>
<th>Brand name</th>
<th>Developer</th>
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</thead>
<tbody>
<tr>
<td>Polymerase (NS5B)</td>
<td>Sofosbuvir</td>
<td>Sovaldi</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Nucleoside</td>
<td>Mericitabine</td>
<td></td>
<td>Roche</td>
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<tr>
<td>Nonnucleoside</td>
<td>Deleobuvir</td>
<td></td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td></td>
<td>ABT-333</td>
<td></td>
<td>Abbott</td>
</tr>
<tr>
<td>RNA binding (NS5A)</td>
<td>Ledipasvir</td>
<td></td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir</td>
<td></td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td></td>
<td>ABT-267</td>
<td></td>
<td>Abbott</td>
</tr>
<tr>
<td>Protease (NS3/4A)</td>
<td>Telaprevir</td>
<td>Incivek</td>
<td>Vertex/Johnson &amp; Johnson</td>
</tr>
<tr>
<td></td>
<td>Boceprevir</td>
<td>VICTRELIS</td>
<td>Merck</td>
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<tr>
<td></td>
<td>Simeprevir</td>
<td></td>
<td>Janssen/Tibotec/Medivir</td>
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<tr>
<td></td>
<td>Faldaprevir</td>
<td></td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td></td>
<td>Vaniprevir</td>
<td></td>
<td>Merck</td>
</tr>
<tr>
<td></td>
<td>Samatasvir</td>
<td></td>
<td>Idexx</td>
</tr>
<tr>
<td>Combinations</td>
<td>Sofosbuvir + ledipasvir</td>
<td></td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td></td>
<td>Faldaprevir + deleobuvir</td>
<td></td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td></td>
<td>Simeprevir + samatasvir + TMC647055/r</td>
<td></td>
<td>Janssen</td>
</tr>
<tr>
<td></td>
<td>ABT-450/r + ABT-267 and ABT-333</td>
<td></td>
<td>Abbott</td>
</tr>
<tr>
<td></td>
<td>MK-8742 + MK-5172</td>
<td></td>
<td>Merck</td>
</tr>
</tbody>
</table>
Are broad spectrum antivirals possible? LJ001

<table>
<thead>
<tr>
<th>Virus</th>
<th>Family</th>
<th>Genotype</th>
<th>Envelope</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola</td>
<td>Filoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Marburg</td>
<td>Filoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Influenza A</td>
<td>Orthomyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>Junin</td>
<td>Arenaviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Rift Valley fever</td>
<td>Bunyaviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>LaCrosse</td>
<td>Bunyaviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>Nipah</td>
<td>Paramyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Omsk hemorrhagic fever</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>RSV</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>++</td>
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<td>PIV-5</td>
<td>Paramyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
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<td>HPIV-3</td>
<td>Paramyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
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<td>Newcastle disease</td>
<td>Paramyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
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<tr>
<td>HIV-1, *</td>
<td>Retroviridae</td>
<td>ssRNA(-)RT</td>
<td>Y</td>
<td>++</td>
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<tr>
<td>Murine leukemia</td>
<td>Retroviridae</td>
<td>ssRNA(-)RT</td>
<td>Y</td>
<td>+++</td>
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<tr>
<td>Yellow fever</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>West Nile</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>Vesicular stomatitis</td>
<td>Rhabdoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
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<tr>
<td>Cowpox</td>
<td>Poxviridae</td>
<td>dsDNA</td>
<td>Y</td>
<td>+</td>
</tr>
<tr>
<td>Vaccinia</td>
<td>Poxviridae</td>
<td>dsDNA</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Adenoviridae</td>
<td>dsDNA</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Coxsackie B</td>
<td>Picornaviridae</td>
<td>ssRNA(+)</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Reovirus</td>
<td>Reoviridae</td>
<td>dsRNA</td>
<td>N</td>
<td>-</td>
</tr>
</tbody>
</table>

LJ1001, a broad spectrum antiviral
Favipiravir

- Broad-spectrum inhibitor of RNA viruses
- Target: RdRp
- (+) RNA: WNV, YFV, ZIKV, WEEV, CHIKV, picornaviruses, norovirus
- (-) RNA: Lassa virus, EBOV, Rabies virus, measles virus, Pichinde, Junin, Rift Valley fever virus, Hantaviruses, Respiratory syncytial virus, parainfluenza virus
Favipiravir modes of inhibition

Inhibition of RdRp

Replication

Chain termination

Lethal mutagenesis

Incorporation in viral RNA

Favipiravir-RTP

Favipiravir

https://doi.org/10.1016/j.antiviral.2018.03.003
Targets for intervention: HIV replication
The problem with AIDS therapy: relentless viral replication for years
Azido-deoxythymididine (AZT) - first HIV drug

- Initially discovered during screens for anti-tumor cell compounds
- Phosphorylated to active form by cellular kinases
- Chain terminator
- Not good substrate for most cellular polymerases, better for HIV RT
AZT

- Substantial side effects (unlike acyclovir)
- Can be given orally, is absorbed rapidly, but half-life is ~1 hr (degraded by liver enzymes)
- Consequently patients dosed 2-3x daily
- Short half-life, multiple dose regimen problematic: resistant mutants will be selected
Resistance to AZT

- Mutants resistant to AZT arose immediately after drug was licensed
- Single aa changes at one of four sites in RT
- Altered RT do not bind phosphorylated AZT
- New nucleoside analogs developed: Didanosine (ddl), Zalcitabine (ddC), Stavudine (d4T), Lamivudine (3TC)
- This lead to combination therapy, use of two antiviral drugs to combat resistance
- Mutants resistant to two drugs arose <1 yr
Non-nucleoside RT inhibitors (NNRTI)

- Nevirapine (Viramune)
- Delavirdine
- Efavirenz

11-cyclopropyl-4-methyl-5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one
Resistance to NNRTIs

- Resistant mutants are selected rapidly
- Amino acid substitutions in any of seven residues that line binding sites on enzyme confer resistance
- Cannot be used alone for treatment of AIDS
- Now used largely in combination therapy
Antiviral drugs that target HIV protease

HIV protease absolutely required for production of infectious virions
Antiviral drugs that target HIV protease

*Key finding:* HIV protease recognizes and cleaves small synthetic peptides

**A** Natural substrate of the HIV-1 protease

**B** Saquinavir

**C** Darunavir

Peptidomimetic
IN inhibitors

(A) Viral integrase

(B) Raltegravir

(C) Elvitegravir

(D) Dolutegravir

http://cmr.asm.org/content/29/3/695.full  Principles of Virology, ASM Press
Maraviroc: CCR5 inhibitor

(B) Maraviroc

(C) CCR5 coreceptor

High affinity

Very low affinity

MVC Bound to CCR5

gp120 binding site on CCR5

Binding site Disrupted by MVC
Go to:

b.socrative.com/login
room number: virus

Which of the following HIV antivirals inhibits the earliest stage of infection?

A. Nucleoside inhibitors
B. NNRTIs
C. CCR5 inhibitors
D. Integrase inhibitors
E. Fusion inhibitors
Combination therapy

- HAART: HIV can be treated as a chronic disease
- Target different mechanisms
- One pill containing three inhibitors
- Does not cure infection! Latent reservoir remains
Mathematics of drug resistance

- Assume one mutation needed for drug resistance
- Mutation rate 1 every $10^4$ bases polymerized
- Each base is substituted in every $10^4$ viruses
- Each person makes $10^{10}$ new viruses/day
- $10^{10}/10^4 = 10^6$ viruses will be produced each day with resistance to one drug
Mathematics of drug resistance

- Developing resistance to two drugs: \(10^4 \times 10^4 = 10^8\)
- \(10^{10}/10^8 = 100\) viruses resistant to two drugs per day
- Resistance to three drugs: \(10^4 \times 10^4 \times 10^4 = 10^{12}\) viruses needed
- Remember replication is suppressed by drugs
### Nucleoside reverse transcriptase inhibitors (NRTIs)

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name(s)</th>
<th>Manufacturer name</th>
<th>Approval date</th>
<th>Time to approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrovir</td>
<td>Zidovudine, didanosine, AZT, ddC</td>
<td>GlaxoSmithKline (original sponsor Burroughs-Wellcome)</td>
<td>19 March 1987</td>
<td>3.5 months</td>
</tr>
<tr>
<td>Videx</td>
<td>Lamivudine, 3TC</td>
<td>GlaxoSmithKline</td>
<td>27 September 1997</td>
<td>3.9 months</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Lamivudine and zidovudine</td>
<td>GlaxoSmithKline</td>
<td>17 December 1998</td>
<td>5.8 months</td>
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<tr>
<td>Zalcitabine</td>
<td>3TC</td>
<td>GlaxoSmithKline</td>
<td>31 October 2000</td>
<td>9 months</td>
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<tr>
<td>Zepatine</td>
<td>Abacavir, didanosine, ddC</td>
<td>GlaxoSmithKline</td>
<td>14 November 2000</td>
<td>10.9 months</td>
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<tr>
<td>Viread</td>
<td>Tenofovir disoproxil fumarate, TDF</td>
<td>Gilead Sciences</td>
<td>26 October 2001</td>
<td>5.9 months</td>
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<tr>
<td>Emtriva</td>
<td>Emtricitabine, FTC</td>
<td>Gilead Sciences</td>
<td>62 July 2003</td>
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<tr>
<td>Epivir</td>
<td>Emtricitabine, FTC</td>
<td>Gilead Sciences</td>
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<tr>
<td>Epivir</td>
<td>Emtricitabine, FTC</td>
<td>Gilead Sciences</td>
<td>02 August 2004</td>
<td>10 months</td>
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<td>Truvada</td>
<td>Tenofovir disoproxil fumarate and emtricitabine</td>
<td>Gilead Sciences</td>
<td>02 August 2004</td>
<td>5 months</td>
</tr>
</tbody>
</table>

### Nonnucleoside reverse transcriptase inhibitors (NNRTIs)

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name(s)</th>
<th>Manufacturer name</th>
<th>Approval date</th>
<th>Time to approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viramune</td>
<td>Nevirapine, NVP</td>
<td>Boehringer Ingelheim</td>
<td>21 June 1996</td>
<td>3.9 months</td>
</tr>
<tr>
<td>Rescriptor</td>
<td>Delavirdine, DUV</td>
<td>Pfizer</td>
<td>4 April 1997</td>
<td>8.7 months</td>
</tr>
<tr>
<td>Sustiva</td>
<td>Efavirenz, EVF</td>
<td>GlaxoSmithKline</td>
<td>17 September 1998</td>
<td>3.2 months</td>
</tr>
<tr>
<td>Intecerine</td>
<td>Etravirine</td>
<td>Tibotec Therapeutics</td>
<td>18 January 2005</td>
<td>6 months</td>
</tr>
</tbody>
</table>

### Protease inhibitors (PIs)

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name(s)</th>
<th>Manufacturer name</th>
<th>Approval date</th>
<th>Time to approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir</td>
<td>Saquinavir mesylate, SQV</td>
<td>Hoffmann-La Roche</td>
<td>6 December 1995</td>
<td>3.2 months</td>
</tr>
<tr>
<td>Norvir</td>
<td>Ritonavir, RTV</td>
<td>Abbott Laboratories</td>
<td>1 March 1996</td>
<td>2.3 months</td>
</tr>
<tr>
<td>Crixivan</td>
<td>Indinavir, IDV</td>
<td>Merck</td>
<td>13 March 1996</td>
<td>1.4 months</td>
</tr>
<tr>
<td>Viracept</td>
<td>Nelfinavir mesylate, NFV</td>
<td>Asoorun Pharmaceuticals</td>
<td>14 March 1997</td>
<td>2.8 months</td>
</tr>
<tr>
<td>Fortovase</td>
<td>Saquinavir (no longer marketed)</td>
<td>Hoffmann-La Roche</td>
<td>7 November 1997</td>
<td>5.9 months</td>
</tr>
<tr>
<td>Agenerase</td>
<td>Amprenavir, APV</td>
<td>GlaxoSmithKline</td>
<td>15 April 1999</td>
<td>6 months</td>
</tr>
<tr>
<td>Kaletra</td>
<td>Indinavir and ritonavir, LPV/RTV</td>
<td>Abbott Laboratories</td>
<td>15 September 2000</td>
<td>3.5 months</td>
</tr>
<tr>
<td>Reyataz</td>
<td>Atazanavir sulfate, ATV</td>
<td>Bristol-Myers Squibb</td>
<td>20 June 2003</td>
<td>6 months</td>
</tr>
<tr>
<td>Lexiva</td>
<td>fosamprenavir calcium, FOS-APV</td>
<td>GlaxoSmithKline</td>
<td>20 October 2003</td>
<td>10 months</td>
</tr>
<tr>
<td>Apliserv</td>
<td>Tipranavir, TPV</td>
<td>Boehringer Ingelheim</td>
<td>22 June 2005</td>
<td>6 months</td>
</tr>
<tr>
<td>Prezista</td>
<td>Darunavir</td>
<td>Tibotec, Inc.</td>
<td>23 June 2006</td>
<td>6 months</td>
</tr>
</tbody>
</table>

### Fusion inhibitors

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name(s)</th>
<th>Manufacturer name</th>
<th>Approval date</th>
<th>Time to approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuzeon</td>
<td>Enfuvirtide, T-20</td>
<td>Hoffmann-La Roche and Trimeris</td>
<td>13 March 2003</td>
<td>6 months</td>
</tr>
</tbody>
</table>

### Entry inhibitors—CCR5 co-receptor antagonists

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name(s)</th>
<th>Manufacturer name</th>
<th>Approval date</th>
<th>Time to approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selzentry</td>
<td>Maraviroc</td>
<td>Pfizer</td>
<td>06 August 2007</td>
<td>8 months</td>
</tr>
</tbody>
</table>

### HIV integrase strand transfer inhibitors

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name(s)</th>
<th>Manufacturer name</th>
<th>Approval date</th>
<th>Time to approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isentress</td>
<td>Raltegravir</td>
<td>Merck &amp; Co., Inc.</td>
<td>12 October 2007</td>
<td>6 months</td>
</tr>
</tbody>
</table>

### Multi-class combination products

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name(s)</th>
<th>Manufacturer name</th>
<th>Approval date</th>
<th>Time to approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla</td>
<td>Efavirenz, emtricitabine and tenofovir disoproxil fumarate</td>
<td>Bristol-Myers Squibb and Gilead Sciences</td>
<td>12 July 2006</td>
<td>2.8 months</td>
</tr>
</tbody>
</table>

Some can be used to treat HBV (RT inhibitors)
ART saves lives
Pre-exposure prophylaxis (PrEP vs PEP)

- Daily double therapy (tenofovir and emtricitabine) for those at high risk for HIV infection
- Reduces risk of sexual transmission of HIV-1 by >90%
- Reduces risk of transmission by IVDU by >70%
With this number of genomes, it is highly probable that HIV genomes exist that are resistant to every one of the antiviral drugs that we have now, or EVER WILL HAVE!
Next time: Evolution