Though the doctors treated him, let his blood, and gave him medications to drink, he nevertheless recovered.

*Leo Tolstoy*
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 60 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.
Antiviral drugs by virus and target
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
The path of drug discovery

- 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!
From drug discovery to the clinic

Safety is the overriding concern

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

Safety (20-80 subjects)
Efficacy (100-300 subjects)
Efficacy, side effects, superiority (100-1000s subjects)
Mechanism-based screens

**Diagram:**
- **Cleavage site**
- **DRUG**
- **Protease**
- **Soluble**
- **Insoluble**

**Graph:**
- **Fluorescence intensity of soluble peptide**
- **Time (minutes)**
Cell-based screen

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

Engineered HIV protease site

HIV protease

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

Inactive tetracycline efflux protein

Tetracycline-sensitive bacteria

Outside cell

Inside cell

Outside cell

Inside cell

No colonies

Many colonies

Active tetracycline efflux protein

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

Tetracycline-resistant bacteria
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
Nidoviral genomes encode a proofreading exonuclease
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
Entry Inhibitor
Symmetrel (Amantadine)

- Interacts with influenza viral M2 protein (ion channel)
- Blocks entry of protons into virion, prevents uncoating
Maraviroc: CCR5 inhibitor

A

\[
\begin{align*}
\text{F} & \quad \text{F} \\
\text{HN} & \quad \text{N} \\
\text{CH}_3 & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{CH}_3 & \\
\end{align*}
\]

B

C

CD4 CCR5

Maraviroc bound to CCR5
Polymerase Inhibitors

Acyclovir, a highly effective, anti-herpes simplex virus drug

A prodrug; a nucleoside analog

Many antiviral compounds are nucleoside (no P) and nucleotide (1-3 P) analogs
Acyclovir mechanism of action

ACV → ACV-MP → ACV-DP → ACV-TP
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*
Azido-deoxythymididine (AZT) - first HIV-1 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-1 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 HIV-1 RT inhibitors (NNRTI)

- Nevirapine (Viramune)
- Delavirdine (Rescriptor)
- Efavirenz (Sustiva)
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
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. Penicillin
D. All of the above
Hepatitis C virus RNA polymerase inhibitor

Hepatitis C virus RNA polymerase inhibitor

Nucleoside

Nucleoside kinase

Nucleoside monophosphate

Nucleotidyl and nucleoside diphosphate kinase

Active triphosphate

Fast

Cellular enzymes

Sofosbuvir (a prodrug)

$1000 per pill
12 week treatment = $84,000
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
Protease Inhibitors

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

*Development of Ritonavir, a peptidomimetic*

**A**

Pol substrate

**B**

Model of transition state

**C**

A-74702

**D**

Ritonavir

**E**

Principles of Virology, ASM Press
Hepatitis C virus protease inhibitor

HCV polyprotein

Virus capsid and envelope proteins

Non-structural, replication complex

HCV RNA genome

C E1 E2 p7 NS2 NS3 NS4A NS4B NS5A NS5B

Telaprevir
Influenza virus NA inhibitors

*Sialic acid (N-acetyl neuraminic acid)*

*A*  

*B*  

*C*  

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
Neuraminidase Inhibitor Resistance Testing Results on Samples Collected Since September 2019

<table>
<thead>
<tr>
<th>Antiviral Medication</th>
<th>Total Viruses*</th>
<th>A/H1</th>
<th>A/H3</th>
<th>B/Victoria</th>
<th>B/Yamagata</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>Viruses Tested</td>
<td>2,433</td>
<td>885</td>
<td>502</td>
<td>954</td>
</tr>
<tr>
<td></td>
<td>Reduced Inhibition</td>
<td>1 (0.04%)</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Highly Reduced Inhibition</td>
<td>4 (0.2%)</td>
<td>4 (0.5%)</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
</tr>
<tr>
<td>Peramivir</td>
<td>Viruses Tested</td>
<td>2,433</td>
<td>885</td>
<td>502</td>
<td>954</td>
</tr>
<tr>
<td></td>
<td>Reduced Inhibition</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
</tr>
<tr>
<td></td>
<td>Highly Reduced Inhibition</td>
<td>5 (0.2%)</td>
<td>4 (0.5%)</td>
<td>(0.0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Viruses Tested</td>
<td>2,433</td>
<td>885</td>
<td>502</td>
<td>954</td>
</tr>
<tr>
<td></td>
<td>Reduced Inhibition</td>
<td>2 (0.1%)</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td></td>
<td>Highly Reduced Inhibition</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
</tr>
<tr>
<td>PA Endonuclease Inhibitor</td>
<td>Baloxavir</td>
<td>Viruses Tested</td>
<td>2,541</td>
<td>884</td>
<td>584</td>
</tr>
<tr>
<td></td>
<td>Reduced Susceptibility</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
</tr>
</tbody>
</table>

Circulating H1N1 and H3N2 viruses are largely resistant to Adamantanes, not recommended for use.
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
Are broad spectrum antivirals possible? LJ001

<table>
<thead>
<tr>
<th>Virus</th>
<th>Family</th>
<th>Genome Type</th>
<th>Envelope (yes/no)</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola^L (cat A)</td>
<td>Filoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Marburg^L (cat A)</td>
<td>Filoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Influenza A^L (cat A)</td>
<td>Orthomyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>Junin^L (cat A)</td>
<td>Arenaviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Rift Valley fever^L (cat A)</td>
<td>Bunyaviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>LaCrosse^L (cat B)</td>
<td>Bunyaviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Nipah^L,^P (cat C)</td>
<td>Paramyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Omsk hemorrhagic fever^L (cat C)</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>BSBE^L (cat C)</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>PIV-5^L</td>
<td>Paramyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>MPIV-3^L</td>
<td>Paramyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Newcastle disease^L,^P</td>
<td>Paramyxoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>HIV-1^L,^P</td>
<td>Retroviridae</td>
<td>ssRNA(-)RT</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Murine leukemia^L</td>
<td>Retroviridae</td>
<td>ssRNA(-)RT</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Yellow fever^L</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>Hepatitis C^L</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>West Nile^L</td>
<td>Flaviviridae</td>
<td>ssRNA(+)</td>
<td>Y</td>
<td>+++</td>
</tr>
<tr>
<td>Vesicular stomatitis^L,^P</td>
<td>Rhabdoviridae</td>
<td>ssRNA(-)</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Cowpox^L</td>
<td>Poxviridae</td>
<td>dsDNA</td>
<td>Y</td>
<td>+</td>
</tr>
<tr>
<td>Vaccinia^L</td>
<td>Poxviridae</td>
<td>dsDNA</td>
<td>Y</td>
<td>++</td>
</tr>
<tr>
<td>Adenovirus^L,^P</td>
<td>Adenoviridae</td>
<td>dsDNA</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Coxsackie B^V,^V</td>
<td>Picornaviridae</td>
<td>ssRNA(+)</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Reovirus^L</td>
<td>Reoviridae</td>
<td>dsRNA</td>
<td>N</td>
<td>-</td>
</tr>
</tbody>
</table>

LJ1001, a broad spectrum antiviral
Favipiravir (Avigan)

- Broad-spectrum inhibitor of RNA viruses
- Target: RdRp, a nucleoside analog
- (+) 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
- Licensed in Japan to treat influenza

https://doi.org/10.1016/j.antiviral.2018.03.003
Cidofovir (Vistide)

- Broad-spectrum inhibitor of DNA viruses (adenovirus, poxvirus, herpes simplex virus, polyomavirus, papillomavirus)
- Acyclic cytosine phosphonate
- Phosphate group makes it a mimic of deoxycytidine monophosphate
- Diphosphorylated by host cell enzymes
- Diphosphorylated form has higher affinity for viral DNA polymerases than host, a property of acyclic nucleotide analogues
SARS-CoV-2 antivirals under evaluation

- Camostat mesylate - inhibitor of TMPRSS2 protease
- Chloroquine - raises endosomal pH
- Remdesivir, Favipiravir - nucleotide/side analogs
- Lopinavir, Ritonavir, Darunavir - HIV-1 protease inhibitors
- 79 trials at clinicaltrials.gov
Two Stories of Antiviral Success

Combination Therapy for AIDS and Hepatitis C

Key to drug development: Life-long persistent infections
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
<table>
<thead>
<tr>
<th>Target</th>
<th>Generic name</th>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reverse transcriptase</td>
<td>Zidovudine (AZT)</td>
<td>Retrovir</td>
<td>GlaxoSmithKline</td>
<td>1987</td>
</tr>
<tr>
<td>Nucleos(t)ide inhibitors</td>
<td>Didanosine (ddI)</td>
<td>Videx</td>
<td>Bristol-Myers Squibb</td>
<td>1991</td>
</tr>
<tr>
<td></td>
<td>Zalcitabine (ddC)</td>
<td>Hivid</td>
<td>Hoffmann-La Roche</td>
<td>1992</td>
</tr>
<tr>
<td></td>
<td>stavudine (d4T)</td>
<td>Zerit</td>
<td>Bristol-Myers Squibb</td>
<td>1994</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Epivir</td>
<td>GlaxoSmithKline</td>
<td></td>
<td>1995</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Ziagen</td>
<td>GlaxoSmithKline</td>
<td></td>
<td>1998</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>Viread</td>
<td>Gilead Sciences</td>
<td></td>
<td>2001</td>
</tr>
<tr>
<td>Emeritabivirine (FTC)</td>
<td>Emerita</td>
<td>Bristol-Myers Squibb</td>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Neoxonucleoside inhibitors</td>
<td>Nevirapine (NNP)</td>
<td>Vitromune</td>
<td>Roche</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td>Delavirdine (D LV)</td>
<td>Rescriptor</td>
<td>Pfizer</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>Efavirenz (EFV)</td>
<td>Sustiva</td>
<td>DuPont</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td>Etravirine (ETR)</td>
<td>Intelence</td>
<td>Tibotec</td>
<td>2008</td>
</tr>
<tr>
<td>Protease</td>
<td>Saguinavir (SQV)</td>
<td>Invirase</td>
<td>Hoffmann-La Roche</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Ritonavir (RTV)</td>
<td>Norvir</td>
<td>Abbott</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td>Indinavir (IDV)</td>
<td>Crixivan</td>
<td>Merck</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir (NTV)</td>
<td>Viracept</td>
<td>Agouron</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>Amprenavir (APV)</td>
<td>Agenerase</td>
<td>GlaxoSmithKline</td>
<td>1999</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/RTV</td>
<td>Kaletra</td>
<td>Abbott</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Atazanavir (ATV)</td>
<td>Revataz</td>
<td>Bristol-Myers Squibb</td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td>fosamprenavir (FPV)</td>
<td>Lexia</td>
<td>ViV</td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td>Tipranavir (TPV)</td>
<td>Aptivir</td>
<td>Boehringer Ingelheim</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>Darunavir (DRV)</td>
<td>Prezista</td>
<td>Tibotec</td>
<td>2006</td>
</tr>
<tr>
<td>Integrase</td>
<td>Raltegravir (RAL)</td>
<td>Isentress</td>
<td>Merck</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir (FVG)</td>
<td>Vitekta</td>
<td>Gilead Sciences</td>
<td>2012</td>
</tr>
<tr>
<td>Entry</td>
<td>Enfuvirtide (T20)</td>
<td>Fuzeon</td>
<td>Genentech</td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td>Maraviroc (MVC)</td>
<td>Selatrol</td>
<td>Pfizer</td>
<td>2007</td>
</tr>
<tr>
<td>Combinations</td>
<td>3TC/3TC/AZT</td>
<td>Complivir</td>
<td>ViV</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>ABC/3TC/AZT</td>
<td>Triளirvi</td>
<td>ViV</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC</td>
<td>Truvada</td>
<td>Gilead Sciences</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>DRV/CoBicistat (CORE)</td>
<td>Prezobix</td>
<td>Janssen</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC/EFV</td>
<td>Atripla</td>
<td>Bristol-Myers Squibb/Gilead Sciences</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC/EFV/RPV</td>
<td>Complera</td>
<td>Gilead Sciences</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC/EVG/COBI</td>
<td>Stelbild</td>
<td>Gilead Sciences</td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td>DTG/ABC/3TC</td>
<td>Trismaq</td>
<td>Gilead Sciences</td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>RAL/3TC</td>
<td>Dutreba</td>
<td>Merck</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>ATV/COBI</td>
<td>Erovaz</td>
<td>ViV</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>TAF/COBI/FTC/EVG</td>
<td>Genvoya</td>
<td>Gilead Sciences</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>TAF/RPV/FTC</td>
<td>Odefsey</td>
<td>Gilead Sciences</td>
<td>2016</td>
</tr>
<tr>
<td></td>
<td>TAF/FTC</td>
<td>Descovy</td>
<td>Gilead Sciences</td>
<td>2016</td>
</tr>
<tr>
<td></td>
<td>DTG/RPV</td>
<td>Julaqa</td>
<td>ViV</td>
<td>2017</td>
</tr>
<tr>
<td></td>
<td>Bicitravir/FTC/TAF</td>
<td>Biktary</td>
<td>Gilead Sciences</td>
<td>2018</td>
</tr>
</tbody>
</table>
ART saves lives

![Graph A: Actual and projected numbers of people receiving antiretroviral therapy (ART) by region from 2003 to 2018.](image)

![Graph B: Comparison of HIV/AIDS-related deaths averted due to antiretroviral therapy (ART) vs. actual HIV/AIDS-related deaths.](image)

Children acquiring HIV infection (1996-2016)

New HIV infections

New HIV infections averted due to PMTCT

Number of people dying of AIDS-related causes:

- HIV/AIDS-related deaths averted due to antiretroviral therapy (ART)
- HIV/AIDS-related deaths

10 million total adult deaths averted
Pre-exposure prophylaxis (PrEP vs PEP)

- Daily double therapy (tenofovir and emtricitabine) for those at high risk for HIV-1 infection
- Reduces risk of sexual transmission of HIV-1 by >90%
- Reduces risk of transmission by IVDU by >70%
Decreasing length of treatment regimens for hepatitis C

- Before 2013: Pegylated IFNα + ribavirin
- 2013–2015: Boceprevir + pegylated IFNα + ribavirin, Telaprevir + pegylated IFNα + ribavirin
- 2015–2016: Ombitasvir/paritaprevir/ritonavir/daclatasvir, Ledipasvir/sofosbuvir
- After 2016: Grazoprevir/elbasvir, Glecaprevir/pibrentasvir, Velpatasvir/sofosbuvir

Graph showing the comparison of treatment lengths with the orange bar representing the longest treatment and the blue bar representing the shortest treatment.
There are $10^{16}$ HIV genomes on the planet today

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