HIV, HBV, HCV
Virology

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• Many similarities
• Several fundamental differences
• High-level replication: HIV $10^{10}$, HBV $10^{11}$, HCV $10^{12}$ particles/day
• Rapid clearance of newly produced virus
• High mutation rate → quasispecies
• Some mutations detrimental, some allow escape
Antiviral resistance

- Drug resistant variants are produced spontaneously during virus replication
  - Single, double, and even triple mutants emerge daily in untreated patients – persistence as replicating variants directly related to the fitness cost of the mutations
  - “Tolerance” for mutations is HCV > HIV > HBV
Emergence & evolution of HIV drug resistance

Single mutant → Double mutant → Triple mutant
Virus without resistance mutations

Virus with resistance mutations

Virus with resistance and compensatory mutations

Compensatory mutations
HCV genetic variability

NS3: 42% of amino acid conserved among all genotypes

NS5A: 46% of amino acid conserved among all genotypes

NS5B: 55% of amino acid conserved among all genotypes
# HIV

| RNA virus | • Chronic infection  
|-----------|---------------------|  
|           | • Without treatment, most people develop AIDS and die within ~10 years (7.5 to 11.6)\textsuperscript{1,2}  
|           | • Non-AIDS HIV-related disease  
| Latent reservoir as integrated provirus  
| Antiviral therapy controls but does not eradicate HIV  
| Life-long therapy required to suppress virus replication  
| PrEP and PEP  

The HIV virology timeline

- HIV-1 isolated
- HIV-1 genome sequenced
- HIV replicates at high levels throughout the infection
- Plasma HIV RNA ('viral load') suppression as goal of therapy
- Highly active antiretroviral therapy
- HIV replication causes disease through immune activation & inflammation
- HIV eradication research

Timeline:
- 1982
- 1985
- 1991
- 1995
- 1996
- 2009
- 2010
Primary HIV infection

• Encompasses the first **6 months** after infection
• Presents symptomatically in **23-92%** of individuals\(^1\)-\(^14\)
  – *Usually clinically mild, temporary and self-limited*
• Characterised by **high levels of virus replication**\(^15\)
• High risk of onward **transmission**
  – *Can contribute to >50% of all transmissions within focussed epidemics*\(^16\)
  – *Exacerbated by concomitant acquisition of STIs*\(^17\)
• Viral dissemination and establishment of long-lived **viral reservoir** occurs rapidly after HIV acquisition\(^18\)-\(^21\)

*STIs = Sexually Transmitted Infections*
HIV replication

Attachment

Fusion

Release of RNA

Reverse transcription

Integration

Transcription

Assembly

Maturation & budding
Mechanisms of HIV genetic evolution

1. Errors by viral reverse transcriptase
   - \( \sim 1 \) mis-incorporation per genome round

2. Errors by cellular RNA polymerase II

3. APOBEC-driven G \( \rightarrow \) A hypermutation
   - Deamination of cytosine residues in nascent DNA

4. Recombination between HIV strains
HIV replication resumes if therapy is stopped

- Antiretroviral therapy cannot achieve HIV eradication
- After stopping therapy HIV replication resumes to pre-treatment levels
- A few exceptions exist
HIV DNA forms

Host cell

Nucleus

HIV RNA

Linear HIV DNA

Integration

Host DNA

Proviral DNA

HIV RNA

2-LTRc

1-LTRc
Effect of fully suppressive ART on markers of HIV persistence

Mean difference per 10 years of suppressive ART

- Integrated HIV-1 DNA
- Total HIV-1 DNA
- 2-LTRc DNA
- Residual plasma HIV-1 RNA

log-transformed variables

Ruggiero. EBiomed 2015
Targets of therapy

- Attachment
- Fusion
- Release of RNA

- CCR5 antagonists
- Protease inhibitors
- RT inhibitors
- Integrase inhibitors
- Fusion inhibitors

- Reverse transcription
- Integration
- Transcription
- Maturation & budding
Maturation & budding

Polyprotein

Protease

Cleaved Proteins

Ribosome

Viral mRNA

HIV Structural Proteins
- HIV Reverse transcriptase/Polymerase

Two mechanisms of inhibition
- Competitive – NRTIs
- Allosteric – NNRTIs
DNA chain terminated

Template strand

Primer strand

NRTI

DNA chain terminated

5'
Mechanisms of NRTI resistance

- T215Y (AZT, ABC, ddl, d4T, TDF)
- M184V (3TC, FTC)
Mechanisms of NRTI resistance

- T215Y
- M184V

**Antagonised by M184V**
Replicative capacity ("fitness") of integrase resistant mutants

![Bar chart showing replicative capacity of integrase resistant mutants.](image)
Codon usage at integrase position 140 in B vs. non-B subtypes
# HCV

| RNA virus | \- Chronic infection \(\sim 75-80\%\)  \\
|          | \- Cirrhosis (41\% over 30 years), hepatocellular carcinoma  \\
|          | \- Extra-hepatic disease increasingly recognised\(^1,2\)  \\
|          | \- No stable or latent reservoir  \\
|          | \- Simple life cycle  \\
|          | \- Curable with antiviral therapy |

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![Hepatitis C Virus](image)
HCV replication

- Receptor binding and endocytosis
- Fusion and uncoating
- Transport and release
- Virion assembly
- Translation and polyprotein processing
- RNA replication

Antiviral targets & drug classes

**NS5A Inhibitors**
- Ledipasvir
- Daclatasvir
- Ombitasvir
- Elbasvir
- Velpatasvir

**NS5B Polymerase Inhibitors**
- Nucleoside/nucleotide analogues: Sofosbuvir
- Non-nucleoside analogues: Dasabuvir

**NS3 Protease Inhibitors**
- Telaprevir
- Boceprevir
- Simeprevir
- Paritaprevir/ritonavir
- Grazoprevir
Efficacy of antiviral therapy: Overview

SVR rates in patients **without** cirrhosis
*(NB: no head-to-head studies)*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gt 1/4</td>
<td>PI + SOF</td>
<td>97</td>
</tr>
<tr>
<td>Gt 1/4</td>
<td>DCV + SOF</td>
<td>97</td>
</tr>
<tr>
<td>Gt 1/4</td>
<td>SOF/LDV</td>
<td>99</td>
</tr>
<tr>
<td>Gt 1/4</td>
<td>PI/r/NS5A + NS5B +/- RBV</td>
<td>96</td>
</tr>
<tr>
<td>Gt 2</td>
<td>SOF + RBV</td>
<td>97</td>
</tr>
<tr>
<td>Gt 3</td>
<td>DCV + SOF</td>
<td>96</td>
</tr>
</tbody>
</table>

**SVR** = Sustained Virological Response; Gt = Genotype; PI = protease Inhibitor (r = ritonavir); SOF = sofosbuvir; DCV = daclatasvir; LDV = ledipasvir; RBV = ribavirin

Risk of re-infection after SVR\(^1\)

- **Low risk**
  - 43 studies
  - \(N = 9,419\)
  - Avg. FU = 4.1±2.1y
- **High risk (IDUs/prisoners)**
  - 16 studies
  - \(N = 819\)
  - Avg. FU = 2.9±1.6y
- **HIV/HCV co-infected**
  - 7 studies
  - \(N = 833\)
  - Avg. FU = 3.1±1.2 years

Relapse of IDU predicts risk of re-infection\(^2\)

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## Characteristics of current DAAs

<table>
<thead>
<tr>
<th>DAA Class</th>
<th>Potency</th>
<th>BL RAS</th>
<th>TE RAS</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3 Protease</td>
<td>+++ to ++++</td>
<td>Relatively common</td>
<td>Highly common</td>
<td>Simeprevir, Paritaprevir, Grazoprevir</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NS5B Polymerase</td>
<td>++ to ++++</td>
<td>Rare</td>
<td>Rare to uncommon</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>NS5B Polymerase</td>
<td>++ to +++</td>
<td>Common</td>
<td>Highly common</td>
<td>Dasabuvir</td>
</tr>
<tr>
<td>Non-NA</td>
<td></td>
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</tr>
<tr>
<td>NS5A</td>
<td>++++</td>
<td>Common</td>
<td>Highly common</td>
<td>Ledipasvir, Daclatasvir, Ombitasvir, Elbasvir</td>
</tr>
</tbody>
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BL = Baseline; TE = Treatment-Emergent; RAS = Resistance-Associated Substitutions
NA = Nucleoside / Nucleotide Analogue; Non-NA = Non-Nucleoside Analogue
# HBV

<table>
<thead>
<tr>
<th>DNA virus</th>
<th>Vaccine</th>
<th>Persistence as cccDNA, may integrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic infection in &gt;90% children, &lt;5% adults</td>
<td>• Cirrhosis (~30%)</td>
<td>• Several replicative states</td>
</tr>
<tr>
<td>• Hepatocellular carcinoma (with/without cirrhosis)</td>
<td>• Extra-hepatic disease</td>
<td>• Antiviral therapy not always required, controls but does not eradicate HBV, probably life-long</td>
</tr>
</tbody>
</table>

- Antivirals work as PrEP
HBV replication
HBV drug targets

Nucleoside and nucleotide analogues
- Lamivudine*
- Adefovir
- Entecavir*
- Telbivudine
- Tenofovir*
- Emtricitabine*
Incidence of HBV drug resistance

Years 1-5; first-line therapy

LAM = Lamivudine
ADV = Adefovir
LdT = Telbivudine
ETV = Entecavir
TDF = Tenofovir
Drug resistance with HIV, HBV, HCV

- Drug-resistant mutants emerge “spontaneously” during virus replication
- Tolerance for mutation is HCV > HIV > HBV
- Virus replication under drug pressure drives expansion of the mutants – *Natural evolution ➔ increasing resistance & fitness*
- If therapy is stopped, drug susceptible virus tends to outgrow resistant mutants selected by therapy – *mutants persist as enriched minority species*
- Mutants are archived in HIV DNA provirus and HBV cccDNA
- No archive for HCV
The barrier to resistance is expression of multiple interacting factors

- Virus sequence
- Phenotypic effect of individual mutations
- No. of mutations required to reduce drug susceptibility
- Fitness cost of the mutation
- Ease of emergence of compensatory adjustments

- Drug potency
- Mode of interaction between drug and target
- Drug concentration
- Drug combination
- Antagonism or synergism between resistance pathways

- Viral load
- Host genetics
- Host immune function
- Reservoirs of replications
- Disease stage

More than the sum of each drug in a regimen
Your turn 😊
Which of the following correctly describes HIV?

1. RNA virus, high replication during AIDS phase only
2. RNA virus, high replication, stable genetic make-up
3. RNA virus, high replication, rapid genetic evolution
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Which of the following correctly describes HBV?

1. HBV polymerase lacks reverse transcriptase activity

2. The genomic structure favours rapid emergence of resistance

3. Resistance is less of a problem with 3rd gen drugs
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Which of the following correctly describes HCV?

1. Resistance is created by suboptimal therapy
2. Resistance is selected by suboptimal therapy
3. Resistance is archived in the nucleus of hepatocytes
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HIV tropism defined by co-receptor use

Naive CD4 cells
- Must be activated to memory phenotype to become target of R5

Memory CD4 cells
- Activated to memory phenotype

Macrophages
- Activated to memory phenotype

CD4
- Activated to memory phenotype

CXCR4
- Activated to memory phenotype

CCR5
- Activated to memory phenotype

Esté Lancet 2007