Treatment of respiratory virus infection
Influenza A & B
Respiratory Syncytial Virus (RSV)
Influenza A-virus

Endosome

Viral channel protein

Inhibition of uncoating

Amantadine

$\text{NH}_2$
Amantadine and Rimantadine

• Use is limited to Influenza A infection.

• Very effective in preventing infection if used at the time of/or prior to- exposure to the virus.
Side Effects of Amantadine and Rimantadine

- Amantadine crosses the BBB, so, can cause CNS side effects, such as ataxia and dizziness, and was found useful in the treatment of parkinsonism.

- Rimantadine produces few CNS effects because it does not penetrate the blood brain barrier.

- Both should be used with caution in pregnant and nursing women.

- Drug Interactions??
Neuroaminidase Inhibitors

Oseltamivir (Tamiflu): oral
Zanamivir (Relenza): inhalation

Mechanism of action
• Viral neuraminidase catalyzes cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids, a process necessary for release of virus from host cell surfaces.

• Neuraminidase inhibitors thus prevent release of virions from infected cell
Neuroaminidase inhibitors

• Limit the severity and spread of viral infections.
• Useful for combating influenza infection:

Side effects
Nausea and vomiting (Oseltamivir).
Exacerbation of reactive airway disease (Zanamivir).
Ribavirin

• An antimetabolite which inhibits influenza RNA polymerase non-competitively *in vitro*, but poorly in vivo.

• An aerosol form is used against RSV (respiratory syncytial virus).
• Intravenously, it is useful against Lassa fever.

• Can cause anemia due to hemolysis and bone marrow suppression.
Fig. 2: An algorithm for the treatment of acute influenza-like illness (ILI). *Influenza virus outbreak confirmed by public health authorities.+Antiviral agent selected from inactivated influenza vaccine, oseltamivir or zanamivir.\n
**Instructions\n
- Amantadine: 100 mg bid for 5 days if patient < 65 years, 100 mg once daily for 5 days if patient ≥ 65 years. Check serum creatinine.
- Oseltamivir: 75 mg orally bid for 5 days.
- Zanamivir: 10 mg inhaled bid for 5 days.
Antiretroviral agents

Six classes are available nowadays.
Should be used in combinations.
HAART

- **Highly active anti-retroviral therapies**
- Combination therapies (triple drug cocktail) can reduce viral.
- Examples:
  - NNRTI-Based Regimens (1-NNRTI + 2NRTIs)
  - PI-Based Regimens (1 or 2 PIs + 2 NRTIs)
- There will be problems of compliance with all of these complicated drug regimens.
- Non-compliance with therapy leads to resistance of the virus.
**HIV Life Cycle**

**Step 1: Fusion**
HIV attaches to T-cell surface receptors to gain entry into the cell.

**Step 2: Transcription**
Reverse transcriptase converts viral RNA to DNA.

**Step 3: Integration**
HIV uses the integrase enzyme to insert the new viral DNA into the host cell's DNA.

**Step 4: Cleavage**
Cleavage occurs to cut up the long chains of HIV subunits.

**Step 5: Packaging and Budding**
Packaging and budding of new HIV virions.
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

• Considered the “backbone” of antiretroviral therapy.
• Used in combination with other NRTIs or other classes.
• Act by competitive inhibition of HIV-1 reverse transcriptase; incorporation into the growing viral DNA chain causes premature chain termination due to inhibition of binding with the incoming nucleotide.
• Require intracytoplasmic activation by phosphorylation to the triphosphate form.
• Cause mitochondrial toxicity, lactic acidosis, hepatic toxicity, dyslipidemia, and insulin resistance.
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

- Zidovudine (AZT, 1987).
- Abacavir.
- Didanosine.
- Lamivudine.
- Tenofovir.
Zidovudin (AZT)

- A potent antagonist of reverse transcriptase. It is a chain terminator.

- Cellular enzymes phosphorylate AZT to the triphosphate form which can inhibit RT and causes chain termination.

- Widely used in the treatment of AIDS (its only clinical use).

- Bone marrow suppressant, causes severe anaemia and leukopenia with high doses.

- Headache is also common.
Didanosine (Dideoxyinosine)

- Didanosine acts as chain terminator and inhibitor of reverse transcriptase.
- Phosphorylated to the active metabolite of dideoxyadenosine triphosphate
- Used in AIDS (second approved drug).
- Given orally.
- Toxicity includes pancreatitis, peripheral neuropathy, GI disturbances, bone marrow depression.
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Bind directly HIV-1 reverse transcriptase resulting in allosteric inhibition of RNA and DNA dependent DNA polymerase activity.
- Do not compete with nucleotide triphosphate.
- Do not require phosphorylation to be active.
- Cause GI intolerance and skin rash.
- Metabolized by the CYP450 enzyme system.
Nonnucleoside Transcriptase Inhibitors (NRTIs)

- Delavirdine.
- Etravirine.
- Nevirapine.
Protease Inhibitors

- Prevent the processing of viral proteins into functional conformations, resulting in the production of immature, noninfectious viral particles.
- Do not require intracellular activation.
- Cause nausea, diarrhea, and dyslipidemia and prolonged QT interval.
- **Buffalo hump**: redistribution of body fat resulting in central obesity, peripheral and facial wasting and cushingoid appearance.
Retrovirus --- HIV

GAG/POL polyprotein

- GAG
- Integrase
- Polymerase
- Protease
Anti-Viral Chemotherapy

Protease folds and cuts itself free
Protease cuts at a site between the integrase and polymerase
Retrovirus --- HIV

GAG

Integrase

polymerase
Protease Inhibitors

- Indinavir
- Ritonavir.
- Darunavir.
- Lopinavir.

- They are orally active, side effects include GI disturbances and hyperglycemia, interact with cytochrome P450.
Entry Inhibitors

- Peptides derived from gp41 which can block the interaction of gp41 with cell membrane proteins during fusion.
  - Enfuvirtide.
  - Maraviroc.
Integrase Strand Transfer Inhibitors

• Bind the viral integrase enzyme essential for replication of HIV-1 and HIV-2.
• This inhibits strand transfer, thus interfering with the integration of HIV DNA into the chromosome of the host cells.
• Dolutegravir.
• Elvitegravir.
• Raltegravir.
Antihepatitis Agents

- **Interferon Alfa (2a, 2b):**

  Is a host cytokine that exerts complex antiviral, immunomodulatory, and antiproliferative actions. Induces intracellular signals after binding to specific membrane receptors resulting in inhibition of viral penetration, translation, protein processing, maturation, and release as well as enhanced phagocytic activity of macrophages.
THE ROAD TO A CURE

1980s
HEP C DISCOVERY
The virus can't be identified yet, but it is described as non-A, non-B hepatitis

1970s
PEG-IFN & RIBAVIRIN
The use of pegylated interferon and ribavirin combo increased the cure rate to almost 60%

2000s
HEP C DETECTION
The virus can be discovered in the blood. First ineffective treatments with interferon are attempted

2011
BOCEPREVIR & TELAPREVIR
The first antivirals were combined with interferon-ribavirin combo. The success rates improved to 70%, but the side effects were horrible

2014
HARVONI® & VIEKIRA Pak®
The first single-pill treatment regimens were invented. Hepatitis C can now be cured with up to 98% efficiency, and without ribavirin

2015
TECHNIVIE® & DAKLINZA®
Harder-to-treat genotypes 3 and 4 can now be cured with up to 100% success rates, too

2016
ZEPATIER® & EPCLUSA®
The first oral pan-genotypic regimen was approved. Patients in the most rural areas can now be treated

by cure-hepc.com
Antihepatitis Agents

Interferon Alfa(2a, 2b):
Pegylated Interferon Alfa(2a, 2b):

Effective against both HBV and HCV.
Given S.C. or I.M.
Pegylated Interferon Alfa is longer acting (once weekly).
Can cause flu–like syndrome (headache, fever, chills, myalgia, and malaise) 6 hours after administration but resolves after continued treatment.
Antihepatitis (HBV) Agents

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs):

- Lamivudine.
- Adefovir.
- Dipivoxil.
- Tenofovir.
- Entecavir.
- Telbivudine.

Approved for HBV infection.
Have better tolerability and response than interferons.
Have anti-HIV activity.
Antihepatitis (HCV) Agents

Polymerase inhibitors:
  - Sofosbuvir

Protease inhibitors
  - Boceprevir
  - Simeprevir
  - Telaprevir.

Ribavirin