Lecture 2: INFECTIOUS PHARMACOLOGY PART 2: ANTIVIRAL & ANTIPARASITIC AGENTS

Legend

SECTION HEADER | Sub-topics | Important information
Concepts/topics | Drugs | Nursing capsules

See glossary of abbreviations at the end of the document

ANTIFUNGALS (chp. 92)

⇨ Amphotericin B, Azoles, Flucytosine, Griseofulvin, Nystatin
- We target something that fungus have, that bacteria don't. If you give abx to virus infection, you won't kill the virus and you might even create resistance. Important to identify the pathogen.

Classes of Systemic Antifungal Drugs

Drug Class	Mechanism of Action	Class Members
Polyene antibiotics	Bind to ergosterol and disrupt the fungal cell membrane	Amphotericin B
Azoles	Inhibit synthesis of ergosterol and disrupt the fungal cell membrane	Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole Isavuconazole
Echinocandins	Inhibit synthesis of beta-1,3-D-glucan and disrupt the fungal cell wall	Anidulafungin Caspofungin Micafungin
Pyrimidine analogs	Disrupt synthesis of RNA and DNA	Flucytosine

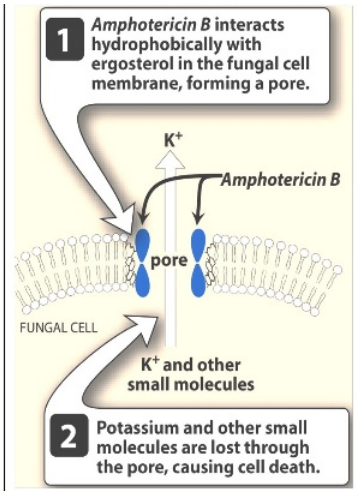
Drugs for systemic mycoses

- Mycoses scientific term for mushroom/fungus
- Systemic mycoses TX = DIFFICULT
  - High resistance
  - Prolonged therapy
  - Increased toxicity
  - Most fungal infections are pretty local so fairly easy to treat. Systemic are very difficult to treat. Fungus are really resistant, they divide more slowly than bacteria, but more resistant and harder to kill.
- Opportunistic VS. Non-opportunistic
  - Opportunistic: Fungus who are harmless and can only infect when immunocompromised (immune system is down) ex. fighting another infection, AIDS, cancer tx... They are not strong enough to overcome the immune system.
  - Non-opportunistic: mushroom that are strong enough that even when fully capable of defending yourself, they are strong enough to overcome those body defenses and cause severe infections.

Drugs of Choice for Systemic Mycoses

Infection	Causative Organism	Drugs of Choice	Alternative Drugs
Aspergillosis	*Aspergillus* species	Voriconazole	Amphotericin B, itraconazole, posaconazole, caspofungin, micafungin, isavuconazole
Blastomycosis	*Blastomyces dermatitidis*	Amphotericin B *or* itraconazole	No alternative recommended
Candidiasis	*Candida* species	Caspofungin *or* fluconazole	Amphotericin B, itraconazole, voriconazole, caspofungin
Coccidioidomycosis	*Coccidioides immitis*	Amphotericin B *or* fluconazole	Itraconazole, ketoconazole
Cryptococcosis Chronic suppression	*Cryptococcus neoformans*	Amphotericin B ± flucytosine	Itraconazole
		Fluconazole	Amphotericin B
Histoplasmosis Chronic suppression	*Histoplasma capsulatum*	Amphotericin B *or* itraconazole	Fluconazole, ketoconazole
		Itraconazole	Amphotericin B
Mucormycosis	*Mucor* species	Amphotericin B	No alternative recommended
Paracoccidioidomycosis	*Paracoccidioides brasiliensis*	Amphotericin B *or* itraconazole	Ketoconazole
Sporotrichosis	*Sporothrix schenckii*	Amphotericin B *or* itraconazole	Fluconazole

Amphotericin B



MOA

- Interacts with ergosterol in the fungal cell membrane, forming a pore. K+ and other small molecules are last through the pore, causing cell death (see image).
  - Inhibits formation of the fungal cell membrane. It interacts will with molecule called Ergosterol (important). It doesn't work on bacteria bcs they don't have ergosterol on their membrane. By creating pores (preventing membrane from closing properly, it allows for Ca^{2+} and other molecules to leak out. It's like a fungus cell bleeding out.

Uses

- Treatment of choice for progressive and systemic mycoses
- High toxicity : Infusion reaction & renal damage
  - Very toxic to us as well, will cause severe AE: renal damage, infusion rx
  - Binds also to cholesterol in host cell membrane

- Lipid-based formulation: ↓ toxicity but ↑↑ $$$
    - Lipid based formulation ↓ toxicity so protects those organs (Kidneys) but very costly
- Very poor GI absorption bcs huge polar molecule → Must be given IV
- Unknown excretion → very long half-life (It was detected in patient more than 1 year after tx)

Adverse reactions and Interactions

- Toxicity is almost certain with IV Amphotericin B → advise pt, so they expect these AE

1) Nephrotoxicity
- Renal impairment in almost all patients
- Minimize via 1L saline injection on admin days
    - To try to dilute it
- Kidney function tests every 3-4 days

2) Infusion Reactions
- Release of pro-inflammatory cytokines
- Frequent fever + nausea + headaches
- Sx occur few hours post-admin
- Aspirin can ↓ reaction but ↑ nephrotoxicity
    - Infusion rx: very certain, most likely, minimize by giving aspirin (bcs inflammatory process), but aspirin emphasize nephrotoxicity, so fix a problem to create another one...
- Glucocorticoid for extreme cases → Immunocompromised ↑ mycotic infections
    - Give in severe inflammation reaction, but drawback: if you give glucocorticoids to suppress immune response, you actually make the pt more susceptible to the initial infection.

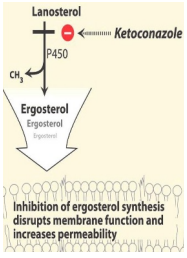
Other ADRs:

- Hypokalemia
- Bone marrow suppression anemia

Drug Interactions:

- Potentiation of other Nephrotoxic Drugs
- Potentiation of Flucytosine → Can ↓Amphotericin B dose → ↓ Toxicity
    - Flucytosine (another fungal drug) = beneficial interaction. Decrease the dose of amphotericin B to reduce toxicity. Using 2 drugs together you can minimize dosage of amphotericin B. You're trading the very severe toxicity of amphotericin B, for the much less severe toxicity of Flucytosine.

Azoles: Itraconazole/Ketoconazole



- Every drug that ends with –azole is part of this group
- Alternative to Amphotericin B = Less toxicity + Available PO

MoA:

- Interacts with ergosterol. Inhibits ergosterol synthesis
    - Instead of opening cell membrane, it inhibits synthesis of ergosterol. Without ergosterol, the fungus can't make more cell membrane so can't reproduce.
    - It's a cell membrane inhibitor, similar to penicillin, but now you're attacking cell membrane in fungus, instead of cell wall in bacteria.
- Broad-spectrum against systemic & superficial mycoses

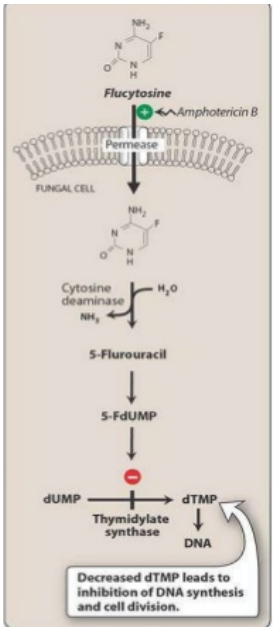
Serious ADRs:

- Cardiac Suppressions → ↓ Inotropic action
    - Decrease inotropic action (↓ strength of contraction) SV down, CO down
- Hepatotoxicity → Uncertain risk, but caution is advised
- **Drawback:** CYP3A4 inhibition → Frequent interactions
    - Ex.: Digoxin, Warfarin = very narrow therapeutic window

Other interactions:

- ↑ pH = ↓ Absorption
    - Increase pH = means more alkaline = tends to decrease absorption of food and other drugs
    - Ex.: Proton-pump inhibitors & H2-Antogonists

Flucytosine



MOA (not so much affecting cell membrane)

- Amphotericin B ↑ Flucytosine entry into fungal cells
    - Remember: combine amphotericin B with Flucytosine to decrease toxicity of amphotericin B
    - Amphotericin B (gentlemen opening door) creates pores in membrane, it allows flucytosine go in the cell. = beneficial interaction
    - Always combined to ↓ resistance development
- Prodrug activated by cytosolic **Cytosine Deaminase (CD)**
    - Once flucytosine is inside the cell, it has to be activate by CD (it's prodrug bcs not active on its own). Once activated it will decrease the synthesis of DNA molecule = you inhibit reproduction of fungus
    - CD is absent from mammalian cells → Theoretically harmless
- Narrow-spectrum: Useful vs. serious *Candida* species & *C.neoformans*
    - Narrow spectrum unlike 2 others previous drugs

Side note: Ergosterol

- Ergosterol = necessary part of cell membrane. –erol = cholesterol, in human cell membrane cholesterol for stability purposes. Fungus just replaces cholesterol with ergosterol. Same purpose.

ADRs:

- Bone Marrow suppression → Reversible thrombocytopenia & neutropenia
- Hepatotoxicity → Mild & reversible / Serious liver damage = rare

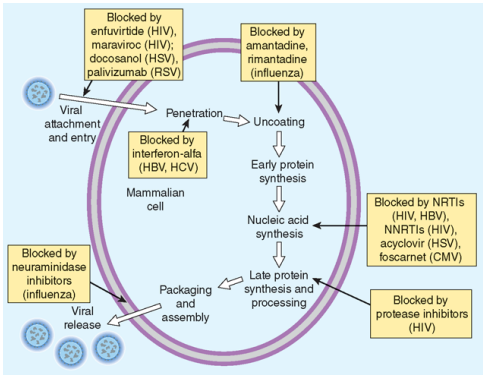
Interactions:

- Amphotericin B nephrotoxicity → ↓ Flucytosine renal excretion
- Inhibition of P450 enzymes → Antidysrhythmic drugs have therapeutic window, likely to change ECG

ANTIVIRAL DRUGS (chp 93-94)

⇨ Herpes Virus Agents, Hepatitis B&C tx, Anti-influenza agents , Antiretroviral Agents , HIV mgmt

Antiviral drug mechanism overview



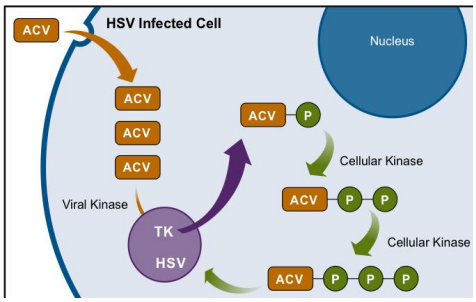
1. Viral attachment and entry
2. Penetration (get inside)
3. Uncoating (Put genetic material inside our material)
4. Early protein synthesis (DNA machinery just copies everything, including virus material, bcs we can't recognize the difference. We multiply more viruses)
5. Nucleic acid synthesis
6. Late protein synthesis and processing
7. Packaging and assembly (Viruses reassemble together)
8. Viral release (Viruses burst out of our cells)
    - By bursting out it kills our cells = pokes holes outside our membrane
    - Now instead of one virus, you have several hundreds that spread out to other cells and repeat the process (multiply, multiply, kill our cells) = viral infection

<u>Strategy</u>

- So we need to block any of these steps.
- Good strategies, 2 drugs that will target different steps to prevent resistance if target the same step
- Differences: some of the steps are more crucial to some viruses than others.
    - That's why the **Neuraminidase inhibitor** (drugs that prevent viruses of getting out of our cells) more commonly used in the influenza virus. Some drugs are reserved to some viruses bcs they work better for them. **Protease inhibitor** best for HIV. .

A lot of viral drugs are prodrugs, they need to be activated!

Acyclovir (ACV)



- 1st choice drug against Varicella-Zoster (VZV) & Herpes Virus (HSV)
    - Ex.: Cold sores / Shingles
    - Most Cytomegalovirus (CMV) strands are resistant
- Admin: Topical, PO & IV
- Renal elimination (↓ dosage if renal impaired)

<u>MoA</u>

- Inhibition of DNA replication
    - See diagram. Drugs gets inside the cell. Needs to be activated (prodrug). They get activated through triphosphorylation.
    - 3 Ps= 3 phosphate groups = attach these groups, when 3 attached now the drug is active. If one or two Ps attached , still not active
    - First P added to ACV is done by viral kinase. ACV has a greater affinity for the viral kinase in first step than it has on our own kinase. If your drugs goes in one of your cell that is not infected by a virus, it is unlikely to get activated bcs of that first step (first P). When there's a virus inside that cell, it's likely to get that first P. Once you get that first P, then the other 2Ps are added by our own enzymes.
        - Viral = from the virus / Kinase = kind of enzyme that adds phosphate groups.
    - Bcs that first P is added by the virus, it's a good thing to prevent toxicity. We wouldn't want our drug to be activated in a healthy cell. We just want the drug to kill the cells that are infected. We do have a bit of toxicity, bcs sometimes it can get activated by our healthy cell

    - Mimics DNA molecule, and will bind to the elongated DNA. But bcs its not a real DNA molecule, it will stop the process. Will prevent replication of virus/ inhibition of DNA replication.
    - Recap: the virus needs to put in its DNA into our cell in order to make more. Doing so, the virus dies, but it's a sacrifice, bcs our machinery will replicate more viruses. However, with this drug, the virus sacrifices itself, but we don't allow the DNA to be recomposed into other viruses. That's how we end up killing the virus.

- Prodrug: Selectivity for viral kinases → ↓ Toxicity

ADRs

- Very well tolerated PO and Topical
    - Over the counter drugs bcs very well tolerated
    - Risk of nephrotoxicity with IV admin
    - Neurologic toxicity in renal impaired without dose adjustments

Ganciclovir

Mechanism of Action:

- Identical to Acyclovir, but more toxic

Therapeutic Use:

- Cytomegalovirus (CMV) infections in immunocompromised hosts only
    - Acyclovir was overused to treat CMV, so now CMV resistant. Need to give ganciclovir instead.
    - Immune functional you can use weaker drugs, and then let immune system take over and win. But when you're immunocompromised, you need to kill the big bugs, you will have more collateral damage
- Prevention & Treatment (ex.: AIDS & organ-transplant patients)
- High relapse risk → Lifelong therapy

Kinetics:

- Low oral bioavailability / Renal elimination → ↓ dosage if renal impaired

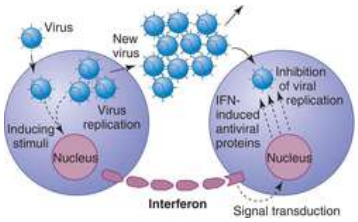
Adverse Effects

- Granulocytopenia & Thrombocytopenia:
    - IV admin or Zidovudine therapy = ↑ risk
    - Minimize via G-CSF administration
    - Monitor neutrophil & platelet count
- Reproductive Toxcity:
    - Embryogenic & Teratogenic
    - Avoid pregnancy up to 90 days post-Tx
    - Also affects male spermatogenesis

Chronic hepatitic C therapy

- New goal: Cure the Infection!
    - Recent switch in hep C paradigm. Before mostly try to minimize sx, contain infection but now curing the infection
- Sustained virologic response (SVR) = Elimination of hep C virus (HCV RNA)
    - Test: Blood sample to look for presence or absence of HCV RNA
    - Cure = SVR at 12 or 24 weeks (=absence of HCV RNA)
- Old Regimen: Interferon-alfa + Ribavirin → higher toxicity & less efficacy
- New regimen: Direct-acting antivirals (DAAs) → Lower toxicity + Higher efficacy
    - NS3/4A Protease Inhibitors (PIs)
    - NS5A inhibitors
    - NS5B nucleoside polymerase inhibitors (NPIs)
    - NS5B non-nucleoside polymerase inhibitors (NNPIs)

Interferon Alfa (INF-A)



- Interferons = Immunomodulatory molecules
    - Cytokines released by immune cell, release when immune rx. It's an immunomodulatory molecule.
- Administration: Subcut
    - Acid in stomach degrades it
- Conventional formulation: Short $T_{1/2}$ → Admin 3x/week
- Long-acting formulation: Short $T_{1/2}$ → Admin 1x/week
    - Higher efficacy = Higher blood levels in between dose, but more risk of ADV so risk/benefit ratio

Actions:

1. Block viral entry
2. Block mRNA synthesis = prevents reproduction
3. Block viral assembly & release

Efficacy

- 30-40% normalize their 1-year HCV-RNA
    - This drug can't cure the HCV but it can't stop propagation and limit the damage
- Relapse rate is high
    - Relapse rate is high, if stop medication, it comes back and worse
- SVR only in 5-15% of patients

Adverse Effects: High Toxicity

- Flu-like syndrome: Most common (50%!!) → Tylenol can minimize
- Neuropsychiatric effects: Ex.: Depression
    - Will need to reduce dosage, but by ↓ the dosage, increase risk of relapse (not ideal drug)
- Many Others

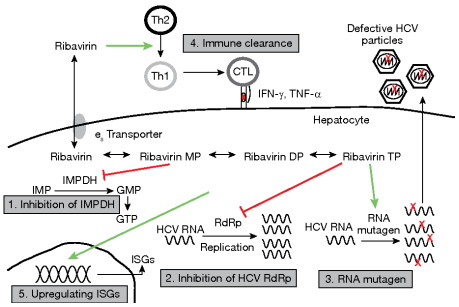
Ribavirin

MOA

- Many actions but mostly at inhibiting the replication/assembly of virus.

Uses and kinetics

- Always combined to IFN-Alfa. Never give this drug alone, bcs can be more harmful.
- Kinetics: PO available / $T_{1/2} \approx$ 6-12 days
- Nucleoside analog with various actions



Main Toxicities:

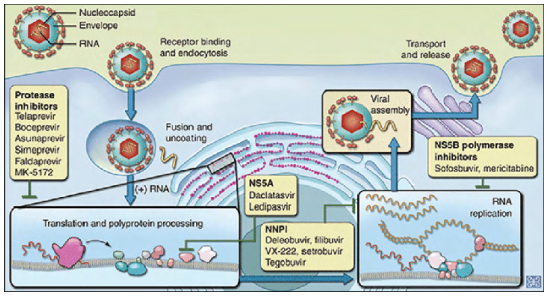
1. Hemolytic Anemia
   a. 10-13% of patients
   b. Onset ≈ 1-2 weeks
   c. Monitor Hb
2. Fetal Injury
   a. Fetal deaths & malformations
   b. Contraindicated during pregnancy
   c. Mandatory to use 2 contraceptive methods

ISGs = Interferon-stimulated genes

Newer drugs for Hep C mgmt...

Protease inhibitor: Simeprevir

- Pro (protein) + ease (enzyme that breaks down)
  - Protease that breaks down other proteins and we want to inhibit this bcs protease are important for viral replication process. Once virus puts genetical inside us and we replicate virus, it makes a huge protein, protease needs to chop them at right places to create subparts to then assemble together. By inhibiting protease = remains one huge protein that doesn't assemble anything concrete.
  - We prevent the assembly of virus
- Always used in combination with other Anti-HCV drugs



Main ADRs:

- Hepatotoxicity
- Photosensitivity / Severe rashes
  - Severe rashes if exposed to sunlight. Cover coats, sunglasses. Any sunray in the skin can trigger reaction. Stay indoors during course of tx

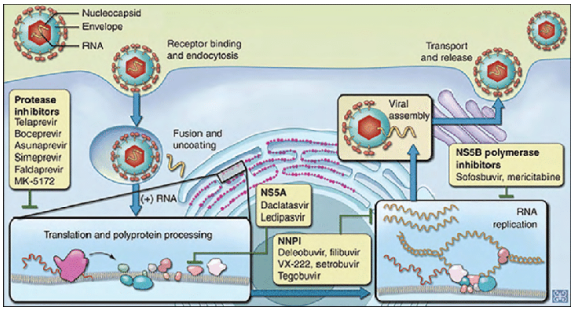
Kinetics:

- PO available
- CYP3A4 metabolism
- Elimination via feces
- Half-life ≈ 41h

Interactions:

- Potential interactions with CYP3A4 inducers/inhibitors (ex.: Statins, Benzodiazepines)

NS5A Inhibitors: Daclatasivir



- Combined with NS5B inhibitors to Inhibit HCV-RNA replication & viral assembly
- NS5A and NS5b are 2 steps in the viral assembly
    - NS5A and B, 2 steps, the result will be the same. If becomes resistant to step 1, step 2 kills it. Best to combine.

Most common ADRs

- Headache + Fatigue
    - Well tolerated

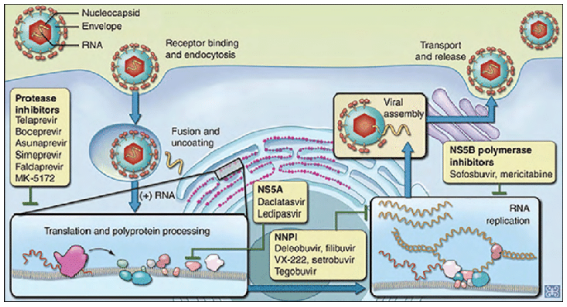
Kinetics:

- PO available
- CYP3A4 metabolism
- Elimination via feces

Interactions

- Potential interactions with CYP3A4 inducers/inhibitors (ex.: St-John's Worth; Phenytoin)

NS5B inhibitor: Sofosbuvir



- Prodrug → Inhibits the viral polymerase NS5B

Most common ADRs

- Headache + Fatigue

Kinetics:

- PO available
- Substrate of P-Glycoprotein Elimination via urine
- Not metabolized by CYP3A4, good alternative

Interactions

- Potential interactions with P-glycoproteins inducers
    - Substrate of P-Glycoprotien (pump that pushes foreign molecules out of cells, but also drugs) = likely to have failed tx if active P-glyco or if drug decrease the efficacy of P-glyco
- inhibitors (ex.: St-John's Worth)

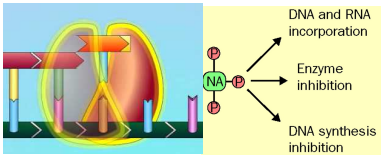
ns5a ns5b and protease inhibitors have less toxicity and more efficacy, more likelihood of getting to that SVR/the cure of HCV.

Chronic Hepatitis B therapy

- **Interferon-Alfa** also used for HBV therapy
    - **interferon alfa** is better for **nucleoside analogs** for efficacy but more toxic and more $. If its mild case use safest one.
- Other options: **Nucleoside Analogs**
    - 1 new drug to add to this regimen of hepB
    - IFN-α > Nucleoside analogs for efficacy but more $$ and toxic
    - High relapse rate with Nucleoside Analogs → Monitor post-Tx

Current guideline recommendations:

- Tx only high-risk patients → Moderate/advanced hepatic fibrosis
    - Hep B a bit less severe and serious than hep C. Moderate + advance= tx, if mild or early on = don't treat (risk/benefit ratio)
- Reduces risks of toxicity, cost & resistance development
    - Pt's case needs to worsen before we can treat the pt.



Nucleoside analogs: Lamivudine

MOA

- Prodrug → Tri-phosphorylation (similar **acyclovir**) → Polymerase + DNA synthesis inhibition
- Needs to go through tri-phosphorylation. Then has 3 effects:
    a) DNA and RNA incorporation to block elongation of those molecules to stop replication
    b) Enzyme inhibition involved in replication
    c) DNA synthesis inhibition
- Selective for viral kinase, which explains why smaller toxicity for human healthy cells.
- Good efficacy but high relapse & resistance development

ADRs:

- No more toxicity than placebo in clinical trials
    - Doesn't mean has no toxicity, but it goes as low as it gets.
- Rare serious effects: Pancreatitis / Lactic acidosis

Kinetics:

- PO available: good advantage over **Interferon alpha (**SC)
- Renal excretion → Watch renal impairment

Side note: Prodrugs

Is happening wherever the infection is (hepatic cell, kidney cell, eye cell) any cell that's infected. Not just happening in the liver (prodrug). Prodrug that are activated on site. Go where it has to go, then activated, then act. Other prodrugs activated in liver first, then goes where it's supposed to go.

INFLUENZA VIRUS

Review

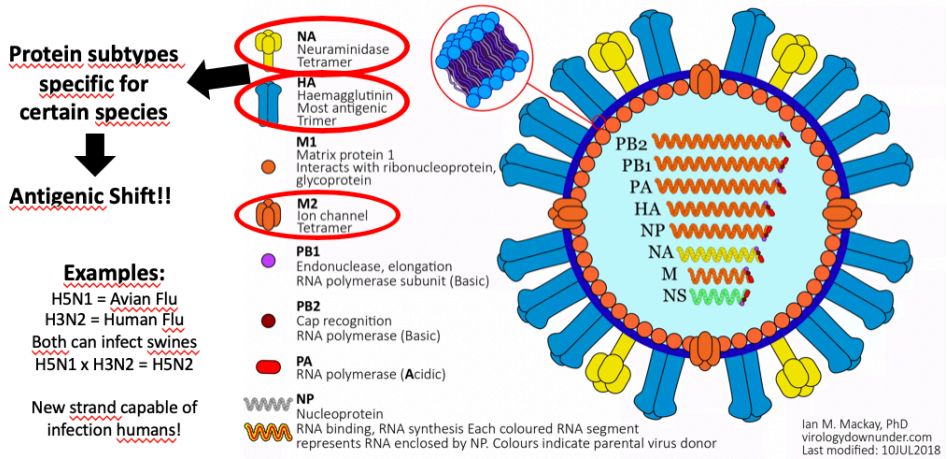
3 parts of influenza virus we can target with drugs

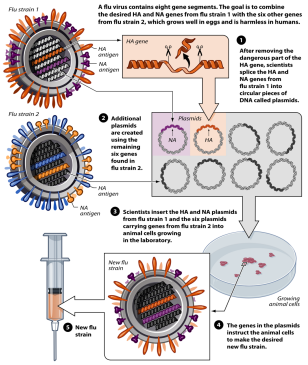
1) NA (yellow): surface molecule: neuraminidase tetramer
2) HA (blue): surface molecule: haemagglutinin most antigenic trimer
3) M2 (orange)::Ion channel tetramer

- Surface molecules (NA and HA) = give the name ex. H1N1, H3N2
- Different strands = molecules have mutated into different version

We can attack those 2 surface molecules OR we can attack the M2 channels.

- M2 channels located on surface = hydrogen channels (H+) = measure acidity
    - Once virus gets inside the cell, the inside of cell has different pH than outside. The M2 channels feel the change in pH (bcs H+ ions move, d/t gradient change). That's how the virus knows it's inside the cells. That's when it uncoats and put its genetic material and replicates. By blocking those channels, prevent the virus from knowing where it is. Trick the virus that it's always outside the cell.
- Antigen shift and drift. Avian flu (H5N1) + Human flu (H3N2) both are specific to species because of the N. N anchors the virus to different places. N1 attaches to bird (avian), N2 attaches to humans. But N1 and N2 can both attach to swine (pig) bcs pigs have both receptors. If N1 and N2 attach on swine, the viruses can mix, exchange material. Now creates H5N2. H5N2 can target humans bcs of N2. We can't defend ourselves against H5N2, bcs we don't have antibody for H5, only for H3. H5N2 can be very virulent and powerful against humans.





Influenza Vaccine

- HA & NA from harmful flu virus inserted within a modified harmless flu virus vector
    - Take H5 in avian flu and insert it in weak virus material. The virus is weaken so can't divide. Our immune system is exposed to this H5 w/o being at risk of killing us. Develop Ab against it. Problem is: HA, NA keep mutated with time
- Annual vaccine is for top 3 or 4 most likely seasonal strands
- Inactivated or live-attenuated or recombinant vaccines
    - Type depends on age of recipient
    - Efficacy of live-attenuated on decline
- Efficacy: age + health of recipient + actual seasonal strands

ADRs:

- Very rare and mild consistent with other vaccines
- Link with Guillain-Barré Syndrome (GBS)
    - 1 in a million chance < risk from severe influenza
    - Higher risk of getting GBS if you have influenza, then by getting your flu shot
- Precautions: Allergic reactions & ill patients

Nursing Capsule: influenza vaccine

Who should be vaccinated?

- Everyone 6 months+
- Especially patients at risk of influenza complications (ex.: elderly, immunocompromised, etc.)
- Healthcare practitioners…YES YOU GUYS ☺!!

Who should not be vaccinated?

- Only if history of severe anaphylaxis
- Immunocompromised or pregnant women
    - Live-attenuated vaccine (weak virus, but still alive, so be more careful)

When should it be administered?

- Flu season peaks in January or February
    - October or November = Best / Late as April can still be good

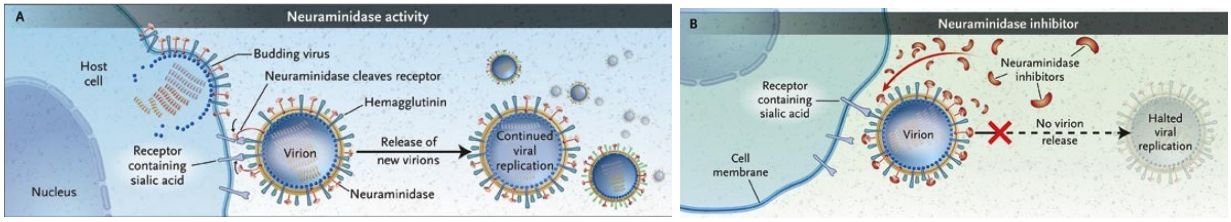
Neuraminidase inhibitor: Oseltamivir

MOA

- Neuraminidase inh (NA= yellow surface molecule)
    - Necessary for the attachment of virus to get incorporated into our cell. By blocking this, you prevent the infection of further cells. Doesn't kill the virus that have already infected you, prevents things of getting worse. Reduce sx significantly so good to take when you have the flu, but know, you will still get sx.
- Useful treatment AND prophylaxis (not as good as vaccine!) against most Influenza strands
- Resistance development = rare
- Prodrug PO available → Hepatic activation → Renal elimination → $T_{1/2} \approx$ 6-10h

ADRs:

- Most common = **Nausea + vomiting** / Serious but rare: **Anaphylaxis**
- Can ↓ live-vaccine efficacy **→ Discontinue before flu shot**
    - Should have vaccine first. If want extra protection you can take the drug, letting time for vaccine to have its effect.



HIV

Overview

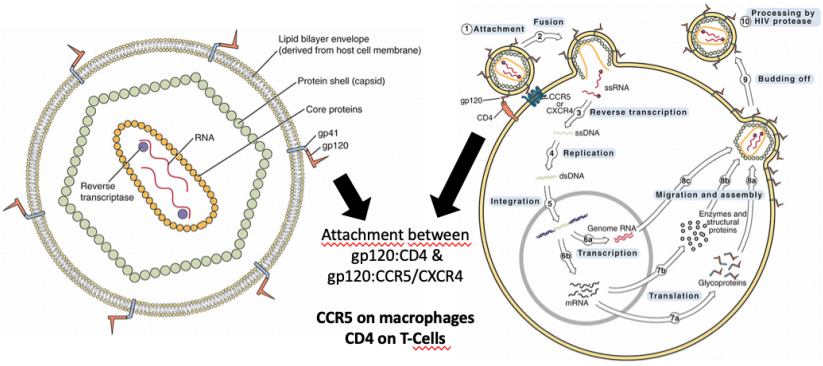
- HIV is a retrovirus, as opposed to the other viruses. It doesn't have DNA, it has RNA. Has to go through reverse transcription step. Dumps RNA inside us and it has an enzyme specific to the virus
- Transcription is to get DNA into RNA. Reverse transcription is to get RNA into DNA.
- Needs to take to its RNA and remake DNA from reverse transcription. Takes that DNA and puts it inside us. Then the DNA is replicated. It gets reassembles, bursts out and kills other cells.
- Bcs it has this specific step (reverse transcription) that we don't, we can target the reverse transcriptase (enzyme that does this step)
- Bcs it affects our T-cells (immune cells), the HIV makes us weaker and immunocompromised when infecting us
    - Like aliens invading us, they start by killing all the policemen first.
- Molecule GP41 and GP120 are on the virus, necessary to attach to CD4 or CCR5. That's why they only affect our t-cells and macrophages, bcs those are the only molecules that express CD4 and CCR5.

<u>Typical HIV clinical course</u>

- Rapid replication rate
- Reverse transcriptase high error rate
- Rapid mutation
- Drug resistance
- Antiretroviral tx borrows similar strategy as for TB tx

<u>HIV steps (see image)</u>

1. Attachment
2. Fusion
3. Reverse transcription
4. Replication
5. Integration:
6. Transcription
7. Translation
8. Migration and assembly
9. Budding off
10. Processing by HIV protease

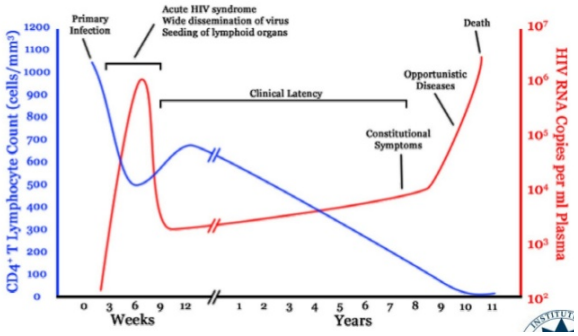


<u>Graph</u>

Red = number of HIV copies (how much virus u have)

Blue = amount of CD4 t-cells u have

More virus u have to more it kills T-cell = inversely proportional



- Once you get infected (day =0) sharp decline in t-cell , rapid replication of virus → Fast initial sx
- Immune cells gets destroyed rapidly, immune system realizes under attack, so starts defending itself a bit. Immune system regains a bit control, so virus drops and immune T-cell goes up.
- Clinical latency = virus being sneaky and kills T-Cell one at a time. You see a very gradual increase of virus and slow decrease in T-cell. Can last almost a decade. The individual can be fairly healthy. Doesn't impair their life so much.
- Later on, once it gets below a certain point, virus killed enough T-cell, virus outnumbers T-cell, so very sharp increase of virus, will finish its job.
- During that time = ↑ opportunistic disease.
    - The virus does not want to kill the host, it needs the host to survive. Fungus and bacteria are alive and don't need the host to live. So what kills you, is bacteria and fungus infections

Resistance

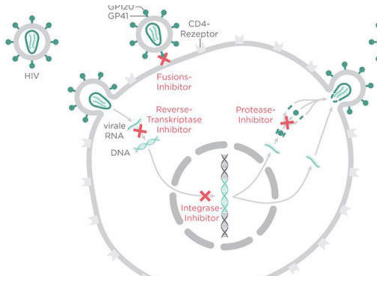
- Rapid resistance (mutation) develops quickly and overtime
- Prevent resistance : Using a lot of drugs + Never a drug alone

Antiretroviral drugs

- NRTI and NNRTI = similar. They block reverse transcription, very similar. Chemically different molecule but it's the same thing
- Integrase inhibitors = act on step 5: integration of viral DNA in our own DNA
    - Protease inhibitors = prevent chopping of virus
- CCR5 antagonists block the entry
- Fusion inhibitors block step2: prevent from dumping material inside us.

Drug Interaction Warning

- P450 induction/inhibition
- Additive ADRs (liver toxicity mostly)
    - Need to combine them, so they can work better, but when combine, additive ADR, + toxicity
- Interactions with antimicrobial Rx



NRTI Inhibitor: Abacavir

MOA

- Most efficient drug for retrotherapy
- Action: Prevent base addition by reverse transcriptase → Inhibit Replication
- Prodrug: Requires tri-phosphorylation
- Not use it alone, but u will have it as part of initial regimen. Pretty good med

ADR

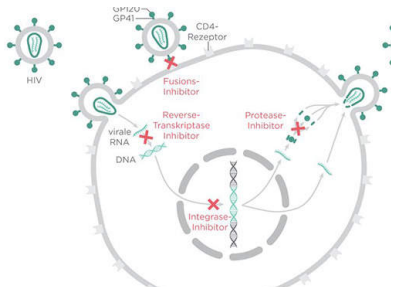
General ADR

- Mitochondrial toxicity-associated Lactic Acidosis and Hepatic Steatosis (Hepatic accumulation of fat molecule)

Specific ADR

- Hypersensitivity Reactions → Screen for HLA-B*5701
    - HLA B*5701 this is specific for abacavir. Do a genetic test to look for presence/absence of this gene. The gene is related to this immune cell. With this version, almost certain to have allergic reaction. It's a minority but if they do have that, u can't use this drug.
- Alcohol competes for Phase II enzymes → ↑ Abacavir concentration

Admin Route	PO
Half-Life (Serum)	1.5-2h
Half-Life (Intracellular)	12-26h
Metabolism	Phase II Enzymes
Excretion	Urine



NNRTIs: Efavirenz

MOA

- Chemically different but same as abacavir
- Action**:** Changes shape of Reverse Transcriptase binding site → Inhibit Replication
    - Blocks the reverse transcription
- **Only NNRTI recommended as 1st-line Tx → Useful for patients with CNS complications**

ADR

- CNS Adverse Effects: Very common (50%!!) → Usually ↓ over time
- Other Adverse Effects: severe rash / teratogenic / liver damage in hepatitis patients
- Discontinue if: hallucinations / severe acute depression / severe rash / hepatotoxicity
    - BBB crossing bcs CNS effects (other meds usually don't)
    - Bcs these effects are not worth it. You can switch medication to prevent these ADR

Interactions

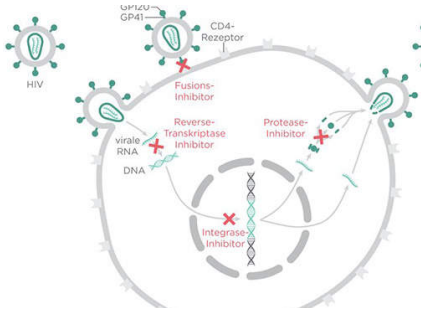
- Interactions: CYP3A4 & 2B6 inducer
    - Complex interactions
    - Ex.: ↓ Hormonal contraceptive efficacy
- CYP2C9 & 2C19 inhibitor → Ex.: ↓ Warfarin metabolism

Admin Route	PO
Distribution	BBB X-ing
Half-Life (Serum)	≈ 40h (Once daily dose)
Metabolism	CYP3A4 / 2B6 2C9 / 2C19
Excretion	Feces

Protease inhibitors

MOA

- Action: Block viral enzyme activity → Inhibit Viral assembly/maturation
    - Acting towards the last few steps. Prevent virus from getting assembled. So many medications, choose your drug from trial and error, look at cost, if it acts well on patient. Very efficient class.
- Very efficient antiviral Rx → Never use alone to avoid Resistance
    - Abacavir mix with protease inhibitor = good start



Prototype: Darunavir Efficient vs. PI-resistant HIV strands	
Admin Route	PO
Half-Life (Serum)	≈ 15h (with ritonavir)
Metabolism	CYP3A4
Excretion	Feces

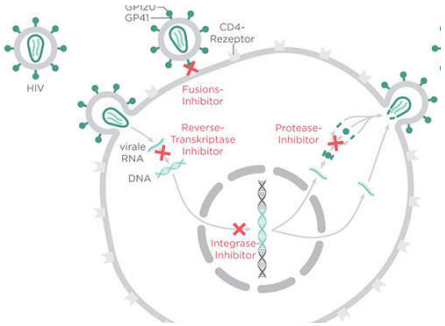
Main Adverse Effects:

- Hyperglycemia/Diabetes → Monitor & Manage
  - ↑ risk of diabetes. Push them over the line if pre-diabetic.
- Lipodystrophy → Cushing syndrome-like Sx without hormonal imbalance

Interactions

- Interactions**:** PIs (Protease inhibitors) can inhibit CYP450 enzymes
- *Ritonavir boosting* = Combine PIs to ↑ Activity/↓ Dosage
  - Ritonavir boosting = another drug that is not very efficient as antiviral drug but it interacts with CYP450 to decrease metabolism of protease inhibitor. If you give them together (PI + ritonavir), it boosts activity of PIs. By doing that you can decrease the dose of PIs (↓ toxicity).
  - Usually we keep this combination for severe, bcs more expensive.

Integrase inhibitors: Raltegravir



MOA

- Action: Block integration of viral genes into host DNA → Inhibit viral replication
  - Integrase inhibitor. Prevents integration of viral DNA into our own.
- Better than **Efavirenz** or most PIs → However resistance development is very likely
  - If it wasn't for resistant development it would be the best drug

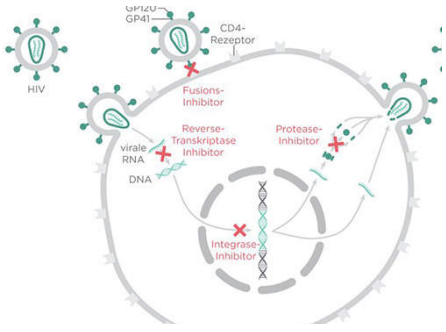
ADR

- Very well tolerated
- ↑ Liver enzymes / rare insomnia or headache or severe rash

Interactions

- Much less than other anti-HIV Rx (not metabolised by P450 enzymes so less interactions)

Admin Route	PO
Half-Life (Serum)	≈ 9h
Metabolism	Glucuronidation (Phase II)
Excretion	Feces



HIV Fusion inhibitors: Enfuvirtide (aka T-20)

MOA

- Action: Binds to GP41→ Inhibits viral envelope fusion & viral entry
  - It acts at the fusion steps. Once the virus binds to the reception, it has to fuse to cell membrane. So inhibit that fusion (doesn't prevent binding, just prevents fusion)
  - Binds to GP41 (looks like a spike), once it binds to that receptors, prevents GP41 from making a hole to fuse in it. Prevents boring.
- Effective but very expensive & inconvenient to admin (2x Subcut/day) → Used as last resorts
  - Twice a day SC, pts can't bring that at home
- Resistance develops due to GP41 mutations → Use in combination

ADR

- Injection-site reactions in 98% of cases
    - Almost certain u get an AE
- ↑ risks of Pneumonia & Hypersensitivity Reactions (ex.: GBS or glomerulonephritis)
- If other drugs fail, u can use it, but not super optimal

Interactions

- So far no significant interactions reported

Admin Route	Subcut
Half-Life (Serum)	≈ 3-4.5h
Metabolism	Hepatic & Renal peptidases
Excretion	Unknown!!

CCR5 Antagonists: Maraviroc

MOA

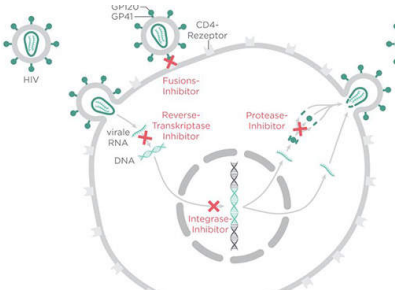
- Action: Prevents co-binding of HIV to CCR5 → Inhibit CCR5 tropic (60% of HIV) viral entry
    - CCR5: receptor the virus binds to
    - Blocks that receptor so the virus has no place to dock.
    - Pretty effective for CCR5 TROPIC version (which is 60% of cases) for 40% this drug will be ineffective. Others binds to CD4, not CCR5. If you have a version that binds to CD4 it will bypass your drug.
    - So take a sample to check what version it is CD4 or CCR5
- Used in drug-resistant patients & against CCR5 tropic strains only
- Resistance develops due to gp41 mutations → Use in combination

ADR

- Mild discomfort
- Rare liver injuries & cardiovascular events

Interactions

- With all major inducers/inhibitors of CYP3A4



Admin Route	PO
Half-Life (Serum)	≈ 14-18h
Metabolism	CYP3A family
Excretion	Feces

Nursing Capsule – HIV management: Antiretroviral therapy (ART)

CD4 T-Cell Counts	Immunocompetence marker: Healthy range ≈ 800-1200 Guides initiation/modification to the regimen Elevation post-Initiation indicates efficient ART
Viral Load (Plasma HIV RNA)	Best clinical outcome predictor Viral Load > 100,000 = Poor prognosis ART Goal: ↓ Viral Load as much as possible Minimum reached ≈ 4-5 months post-ART
HIV Drug Resistance	Genotypic vs. Phenotypic Assays Expensive, long & low-reliability **Useful when:** progression is slow / pregnant women / failure of initial ART
HLA-B*5701 Screening	**Positive test = allergy to abacavir**
CCR5 Tropism	**Positive test = Can use CCR5 antagonist Maraviroc**

- Important lab tests (3 first tests are necessary, 2 last are optional) to help decide the course of tx
- CD4 T-cell
    - Immunocompetence (indicates blue line: T-cell)
    - Below 800 something going on, below 300-400 super incompetent
- Plasma Hiv RNA (viral load) = red line: how much virus material is there
    - If above 100 000 poor prognosis, infection too advance or propagation a greater speed than anticipated
- HIV drug resistant
    - Genotypic: version/type of protein the virus is expressing
    - Phenotypic: what do they look like
    - Similar result but difference is where you're looking: are you looking at the actual protein or at the gene coding for these protein
    - Useful to do if improvement of the pt following tx is slow
    - Useful if failure of initial ART: is it failing bcs pt is not responsive to those drugs specifically or is pt resistant to these drugs
- HLA-B
    - Optional test: If using abacavir
- CCR5
    - Optional test: If want to use antagonist maraviroc

<u>Adolescents/Adult patients</u>

****Treat with ART REGARDLESS of clinical phase or CD4 count****

CANNOT Cure AIDS/HIV → Always dormant virions in memory T-Cells

5 Basic Goals of ART:

1) Maximal + Long-term suppression of viral load
2) Restoration/Preservation of immune functions
3) Improved Quality of Life
4) Reduction of HIV-related morbidities/mortality
5) HIV Transmission Prevention

Initiation

- Recommendations: 3 drugs from 2 different classes
- Best initial regimens based on safety, efficacy & tolerability = 2 **NRTIs** + 1 **Integrase Inhibitor**
    - Exact drug used: Choice depends on lab test (ex.: HLA-B*5701)
- Only use 2 out of 6 classes → Prevents resistance to other classes for later use
- Monitoring milestones: 10-fold ↓ in viral load at 8 weeks / Undetectable at 4-6 months
    - To confirm efficacy of tx, you want to decrease significantly viral load at around 8 weeks. If it doesn't, you should maybe consider changing the drugs

Changing the Regimen: Tx Failure OR Drug Toxicity

- Tx Failure: Disease progression or constant CD4 ↓ or insufficient viral load decrease
    - Change ALL Rx in regimen → Newer Rx (Integrase & Fusion inhibitors) are preferred
- Solution based on cause of failure: Ex: Resistance / Poor adherence / Poor kinetics
- Toxicity: Change only the problematic Rx for another one of the same class
    - If toxicity: easier to spot which drug is the problem, if depression, most likely 1 drug with that side effect with BBB

Promoting Strict Adherence ↑ Efficacy + ↓ Resistance

- Education + social support + HCP collaboration + Extensive patient monitoring
- Lifelong therapy

Specific populations

Infants/Children

- Accelerated clinical course (graph) → treat ASAP bcs won't have 10Y of clinical latency, maybe 1 Y
- Similar therapeutic regimen and goals
- Initiate therapy ASAP
- Monitor FREQUENTLY
- ↑ risk of Toxicity & Opportunistic Infections

Pregnant Patients

- Tx Benefits usually > Risks of fetal harm
- ART protects mother + ↓ fetal transmission risk
- Avoid Efavirenz bcs clear known teratogen
- Monitor mitochondrial toxicity with NRTIs

Preconception Counseling:

- Education on contraception & risks of HIV
    - Possible to have a baby even though you have HIV (give Zidovudine + C-section to reduce risks of transmission)
- Optimize other health status
- Monitor for current opportunistic infections

During labor:

- C-section at 38 weeks recommended
- Zidovudine IV 3h prior → Transmission risk ≈ 0

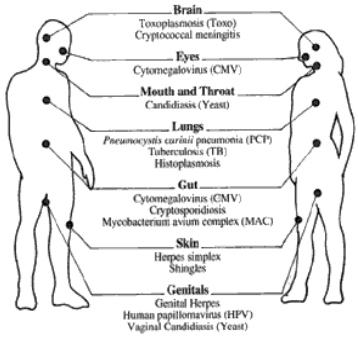
HIV Prevention - Truvada

Pre-exposure Prophylaxis

- **Tenofovir/Emtricitabine** combination (**Truvada**)
    - Combination of 2 anti-viral drugs PO
    - Decrease transmission by 44-73%
    - For the individuals that are sexually active, it does make a big difference. Infected or even if not infected with HIV u can take the pill if u have sex with someone infected with HIV. Also good to decrease viral load
    - Can create a false sense of protection. But most ppl with HIV understand the responsibility they have. Still important to be careful.
- Recommended for High-risk individuals:
    - Known HIV-positive partner
    - Sexually active in a group with high HIV prevalence
    - Injectable drug addiction

Post-exposure Prophylaxis

- When suspected you've been infected or known exposure
- Initiate within 1-2h and no later than 72h
- Regimen = **Truvada + Integrase inhibitor**
- Dosage variations depending on occupational vs. Nonoccupational exposure
- Risk of infection ↓ only → Must get tested for presence of HIV RNA



Opportunistic infection therapy

- Late stage patients
- Main cause of death of HIV patients = opportunistic infections
- Risk ↑ as CD4 count ↓ (especially below 200)
- ART ↓↓ risk of opportunistic infections → ↑ lifespan
    - Main benefit of ART is to decrease risk of opportunistic infections and increase lifespan
    - Table with some of the major opportunistic infections. Review pharm regimen!

Therapy of Major Opportunistic Infections	
Pneumocystis Pneumonia	Trimethoprim + Sulfamethoxazole
Cytomegalovirus Retinitis	Ganciclovir
Tuberculosis	Review TB management in lecture 1
Cryptoccocal Meningitis	Amphotericin B + Flucytosine
Varicella-Zoster Virus	Acyclovir PO or IV
Herpes Simplex Virus	
Candidiasis	PO Itroconazole

HIV Vaccines

Priority Mission to make vaccine

- Prevention = Much cheaper than lifetime ART + ART unavailable in certain regions of the world
    - Much cheaper to prevent further infection than to cure

Obstacles to development

- HIV infects the very cell boosted by vaccines → Could accelerate the spread rather than prevent it
    - Obstacles to development of vaccines. HIV infects the immune cells. You need immune cells for the vaccine to work. You would boost your T-cell with a vaccine, but if you do get the HIV, you'll just have more T-cells to be infected with. It actually accelerates the spread, rather than stopping it.
- Must stimulate BOTH Humoral & Cell-Mediated Immunity
    - Humoral + cell-mediated immunity = activate both pathways.
    - Humoral (Ab pathway) easy part, increase number of Ab. → inactive vaccine
    - Cell-mediated pathway (most important in terms of HIV) u need a live vaccine: would u inject yourself with a live HIV vaccine?

Current Status (850M$ & 30 years later!!)

- 200 Vaccines in Phase I trials
- Only 1 in Phase III
- 3 completed Phase III and data are being analyzed

HIV VACCINE UPDATE: FAILURE...

DRUGS FOR SEXUALLY TRANSMITTED INFECTIONS (ch. 95)

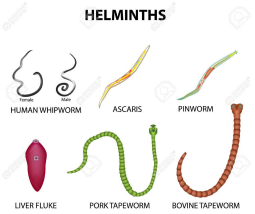
⇨ Chlamydia, Gonorrhea, syphilis, Herpes Simplex

STI incidence

- Chlamydia and syphilis on the rise
- Gonorrhea fairly stable

STI treatments

Chlamydia	**Adults:** Azitrhomycin or Doxycycline → Avoid cyclines in pregnant patients **Infants:** Eryhtromycin **Lymphogranuloma Venereum:** Doxycyline
Gonorrhoea	Rapid resistance development Sulfonamides (30s') → Penicillins (70s') → Cephalosporins (now) **Preferred:** Cefritriaxone IM + Azythromycin PO Doxycycline can replace Azythromycin if allergic
Syphilis	**Primary, secondary or latent**: 1 IM Penicillin G dose **Tertiary or late latent**: Penicillin G IM x3 doses **Neuropyshilis:** IV Penicillin G for 10-14 days Penicillin Allergies: Doxycycline or Ceftriaxone
Herpes Simplex	Sx ↓ only not a cure: Acyclovir or Famciclovir or Valacyclovir Suppressive Tx = Daily Admin vs. Episodic Tx = PRN Valacyclovir can ↓ genital herpes transmission by 50%

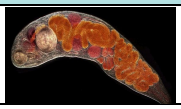


Antihelmintics (ch. 97)

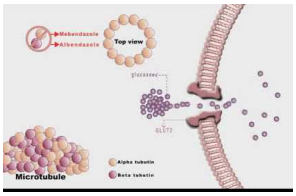
⇨ Helminthic Classification, Mebendazole and albendazole, Pyrantel pamoate and prazinquantel, Diethylcarbamazine and Ivermectin

Helminths

- Helminth = worm
- Not common in developed countries. Most of those = hygiene issues, food, polluted water

Nematodes	Cestodes	Trematodes (flukes)
		
Intestinal or not (lymph, blood) Poor hygiene or sanitation Undercooked meat	Attach to intestines (and eat your food in your GI tract) Undercooked beef, pork or fish	Blood, Liver or Intestinal Flukes Transmitted by insect vectors dirty water

Mebendazole and Albendazole

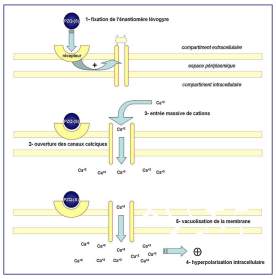


- 2 MOA: Inhibit Glucose intake OR prevent microtubule assembly
  - Pushes the cell away from eachother to create 2 new cell. Only useful for replication, when cell reproduce.
  - Prevents the worm from getting glucose + energy nd prevent from dividing (prevent multiply + living)
- Very Effective against most Nematodes

	Mebendazole	Albendazole
Admin Route	PO	PO
Half-Life	0.5-6h	8-12h
Metabolism	Hepatic	Hepatic
Excretion	Feces	Urine

Toxicity:

- **Mebendazole**: Poor absorption → No ADRs
  - Low toxicity
  - Only works on worms in your intestines, so if worm is in your eyes, mebendazole ineffective
- **Albendazole**: Mild liver impairments & bone marrow suppression
  - Liver function test (LFT) & Blood cell count monitoring



Prazinquantel

- Drug of choice against Cestodes and Flukes

MOA:

- ↑ Calcium influx → Spastic paralysis
  - Opens calcium channels, more calcium goes inside the cell = spastic paralysis
  - Ca2+=propagation of AP, release of NT, muscle contractions
  - Paralyze the worm = abnormal communication in the cell = are washed down in your GI tract
- Disruption of integument → ↑Immune cell efficacy

ADR

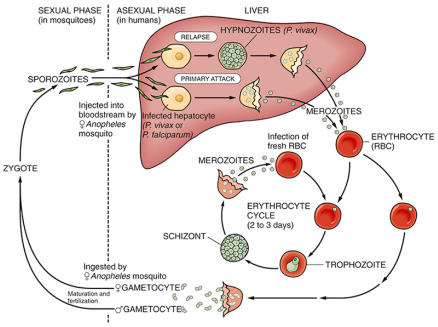
- Well tolerated; Drowsiness → Avoid driving

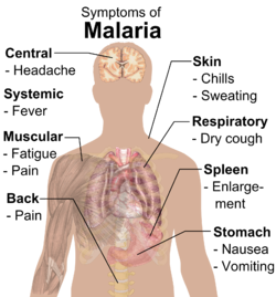
	Prazinquantel
Admin Route	PO
Half-Life	1-1.5h
Metabolism	Hepatic
Excretion	Urine

ANTIMALARIAL AGENTS (chp. 98)

⇨ Malaria Types and Life cycle, Antimalarial Therapy, Chloroquine, Quinine, Artemisinin Derivatives

Malaria types and life cycle Review





- Blood spores = Easy to kill
- Hepatic parasites = Hard to kill
- Sporozoites = Do not respond to current Rx
- Relapse with *P. vivax* due to Hypnozoites hidden in liver
  - 2 types of malaria: Vivax or falciparum
  - The way they behave is different
  - Falciparum = sx more severe, risk of relapse 0
  - Vivax = milder but likely to stick around and hard to remove
  - Vivax has a lot of relapse, bcs a lot of malaria cells stay in the liver, hide in liver. The drugs we use to treat are the malaria cells that attack RBC. When malaria goes in blood, that's when vulnerable to RBC. But the drugs we have, have difficulty to go in liver.
  - Vivax stays in liver and sends a few in the blood, has less sx, when u kill them, just send some more from the liver.

Nursing capsule: Malaria Therapy

Therapeutic Objectives:

- Acute Tx Rx active vs. Erythrocytic parasites
  - The drugs we have to treat are only active when malaria in the blood

    - Is not worth it to treat until you're out of where you got malaria. If you get malaria in a foreign country, monitor the sx for now, once u come back to malaria-free regions, then get rid of it
- Relapse Prevention: Initiate post-departure from malarial region → Target hepatic hypnozoites
- Prophylaxis Before travelling to a malarial region
    - Prevents only blood infection (not hepatic establishment)
    - Prophylaxis: prevent from getting sx, but if u get vivax form, can still get in the liver, will only show up when you stop taking the prophylaxis.

Drug Selection**:** Therapeutic objective + Chloroquine resistance profile

Therapeutic Objective	Chloroquine Sensitive	Chloroquine Resistant
Moderate Attacks	Chloroquine	Artemether/lumefantrine
Severe Attacks	IV Quinidine gluconate	
Relapse prevention	Primaquine (P.vivax only)	
Prophylaxis	Chloroquine	Atovaquone/proguanil

-

- If sensitive to chloroquine, you want to use them, but bcs they are use often, you might be resistant
- Primaquine: targets the ones in the liver.
- Most case u use chloroquine or artemether/lumefantrine

Chloroquine (Best drug for Malaria=1st choice Agent)

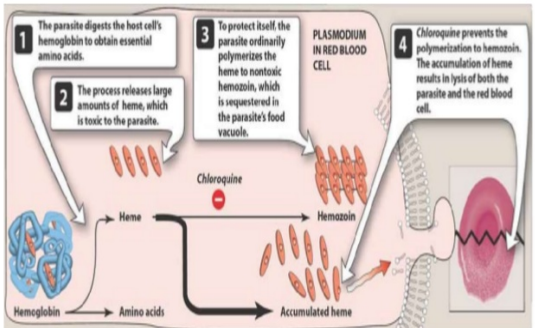
Action

- Prevents polimorization to the form
    - The parasite needs to change its form to get into the blood. This drugs prevents that change.
    - Won't kill the parasite in the liver. Prevents parasite from going from the liver to bloodstream
    - Prevents sx but will need to switch to Primaquine if you want to kill those in the liver
- Might lead to liver damage bcs parasite hide in liver.

Kinetics:

- Excellent PO absorption
- Stored and slow-release from organs
- Once weekly admin (adherence easy)

Mechanism of action



Toxicity: Minimal

- Caution with liver impaired + Some visual disturbances

Primaquine

Therapeutic Usage

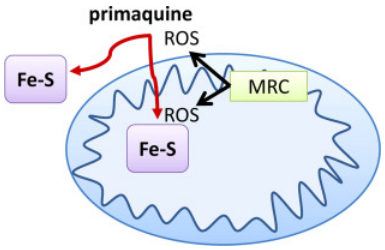
- Relapse Prevention
- Targets P.vivax within the liver

Mechanism of Action

- 2 MOA Inhibit Electron Transport Chain (ETC) + ↑ ROS within parasite mitochondria
    - Inhibits electron transport chain in mitochondria of parasite and increases the production ROS within the parasite mitochondria. Kill them from within.

Kinetics:

- Excellent PO absorption
- Rapid metabolism
- Renal Excretion



Toxicity:

- G6PD-defciency Hemolysis
    - G6PD type of genetic deficiency = likely for hemolysis.
- Screen prior to Tx
- Monitor blood count and urine

Artemether/Lumefantrine

Therapeutic Usage

- Best option against Multidrug Resistant *F.malaria*
- Combination prolong duration → ↓ resistance development
    - 2 separate drug, we combine them bcs synergistic action. Quick effect with one and prolong effect with other (different MOA = synergistic)

Mechanism of Action

- Artemether: Prodrug → Releases ROS species
- Lumefantrine: Works like Chloroquine

Kinetics:

- Artemether: Fast absorption + Short $T_{1/2}$
- Artemether = prodrug
- Lumefantrine: Slow absorption + Long $T_{1/2}$

Toxicity

- QT Prolongation!!!!! (very bad AE)

Interactions:

- CYP3A4 Metabolism
- Lumefantrine inhibits CYP2D6

ECTOPARASITICIDES (ch. 100)

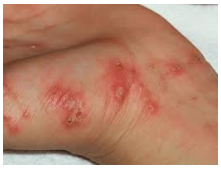
⇨ Lice Infestations, Scabies, Permethrin, Malathion

Lice Infestations

- Tx will be fairly similar
- They don't transmit disease, but skin reaction that's unpleasant, hygiene thing , itching. Not life-threatening.

Head Lice	Human head-to-head transmission only **Tx: OTC 1% permethrin formulations** Remove dead & remaining live lice with comb few days later
Body Lice	Live on clothes and bedding. Only on skin to feed. **Tx: Wash clothes & bedding + apply permethrin or malathion** Combination with trimethoprim/sulfamethoxazole if resistance
Pubic Lice	Sexual intercourse transmission **Tx: 1% permetrhin or 0.5% malathion lotions** Should also wash clothes and bedding at high temperature

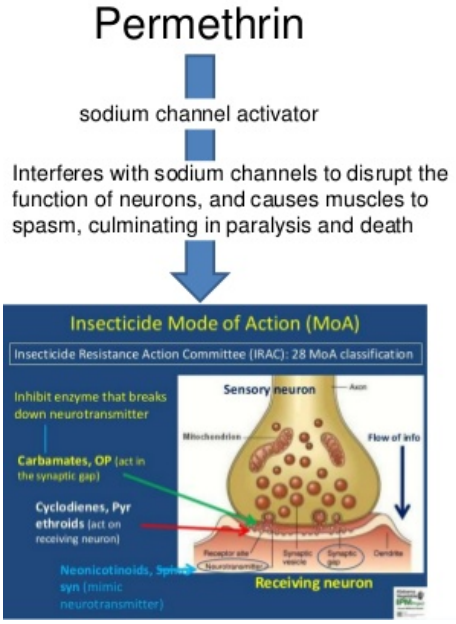
Scabies (mites infestations)



- Lesions caused by females burrowing to lay eggs within skin
- Severe itching + scratching may lead to secondary infections
    - Really hurt. Female have to burrow, eggs grow under your skin.
    - Inflammatory reactions from burrow + eggs
    - Severe itching, open scabs = infection can go in.
- Transmission via intimate contact or infected clothing/bedding

<u>Treatment</u>

- Wash all body with permethrin 5% cream
- Itching persists for a week or 2 post-Tx

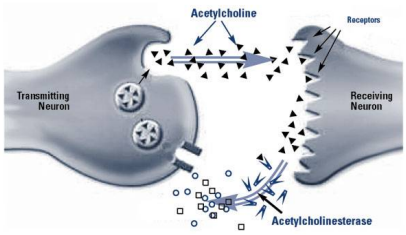


Permethrin

Action & Uses	**Disrupt AP propagation via Na^+ channel activation** **1% Formulation = Best for lice** **5% Formulation = Best for scabies**
Resistance	Inefficient in ≈ 5% of patients for head lice
Kinetics	Topical administration < 2% absorbed quickly eliminated
Adverse Effects	Only mild redness and itching

- Work similar, same end result to impair neuronal communication
- Permethrin: Na+ channel open, sodium comes in, AP triggers. Opening = constantly sending AP. The lice/scabies have so many AP = shaking, or depolarized so nothing happens, paralyze → die

Malathion



Action & Uses	**Organophosphate cholinesterase inhibitor** **Kills lice & Eggs**
Kinetics	Harmless since quickly metabolised
Adverse Effects	Bad smell and mild scalp irritation

- Work similar, same end result to impair neuronal communication
- Malathion = cholinesterase enzyme that breaks down Ach in the synapse. It usually causes contraction. When you block this enzyme, Ach stays there for a long time, excessive contraction, get tired, die.
- Both well tolerated but malathion is more toxic.

Abbreviations

Ab: antibody

Ach: acetylcholine

ADR: adverse reaction

AE: adverse event

Aka: also known as

AP: action potential

ART: antiretroviral therapy

ASAP: as soon as possible

BBB : blood brain barrier

Bcs: because

CO: cardiac output

d/t: due to

GBS: Guillain-Barré Syndrome

GI: gastrointestinal

LFT: liver function test

MOA: mechanism of action

NT: neurotransmitter

PI: protease inhibitors

Ppl: people

Pt: patient

ROS: reactive oxygen species

Rx: reaction or prescription

SV: stroke volume

Sx: symptom

$T_{1/2}$: half-life

TB: tuberculosis

Tx: treatment

VS: versus