Introduction

- A nucleoside to be integrated to DNA, it has to be first Phosphorylated with **three phosphate residues** and then DNA polymerase can integrate them to our DNA.

Treatment of DNA viruses; herpes simplex, cytomegalovirus, varicella-zoster:

Remember these viruses replicate their viral genome through nucleic acid synthesis; in which the nucleic acid of the virus hijacks the cellular machinery for replicating new viral nucleic acids and proteins for the manufacture of new virus particles.

So if we used a drug that is an analog of nucleosides, when they get phosphorylated, they will produce abnormal nucleosides that will prematurely terminate chain through stopping DNA polymerase action and therefore, inhibiting viral replication cycle.

Drugs that act on this pathway are called **anti-metabolites**; they include:

A. **Acyclovir**: **Specific and highest tolerability**!
- This drug is a **guanosine analog**, and its first phosphate group is attached through **thymidine kinase** which is only found in **HSV/ VZV viruses**, this way only infected cells are affected. The remaining 2 phosphate residues are attached by **cellular kinases**.
- It is 30-fold more potent against the **virus** DNA polymerase than the host enzyme that is why its highly tolerable
- Has a short bioavailability so it's given **4 times daily** (**prophylactic use involves giving acyclovir twice**), a derivative called **Valacyclovir** has better bioavailability given **twice daily** (**prophylactic use involves giving valacyclovir once**)
- Used to treat:
  - Herpes simplex infections (genital herpes, and herpes encephalitis) in which it **shortens** duration of symptoms by 2 days.
  - Chickenpox in immune-compromised patients.
  - **Prophylactically in patients treated with immunosuppressant drugs or radiotherapy who are in danger of infection by reactivation of latent virus.**
  - **Prophylactically in patients with frequent recurrences of herpes (more than 3 times/year of oral labialis)**
- Given orally (**prophylactic dose is usually ½ the therapeutic dose**)
- Has minimal SE like: **N/V, diarrhea and headache**, additional SE when given **IV include: Renal** (**prevented by adequate hydration**) and **neurological toxicity + teratogenicity (according to doctor and not according to google):)**

A. **Ganciclovir**: Very potent against all herpes viruses including **CMV**, but has **BAD SE**
- MOA is like acyclovir
- Low oral bioavailability ➔ **given I.V**
- **Drug of choice for CMV infections: retinitis, pneumonia, colitis**
- **SE: it's not selective ➔ bone marrow suppression (leukopenia 40%, thrombocytopenia 20%) and CNS effects (headache, behavioral, psychosis, coma, convulsions), teratogenic.**
  - 1/3 of patients have to stop because of adverse effects

B. **Foscarnet:**
- If we face resistance, then we use our weapon Foscarnet (**which is really potent but has many side effects**)
- MOA: **direct inhibitor of viral DNA polymerase** (very selective unlike ganciclovir))
- Inorganic pyrophosphate analog that directly inhibit DNA polymerase and Reverse Transcriptase
- **Nephrotoxicity** (25%) ➔ most common side effect
- Uses:
  - CMV retinitis and other CMV infections instead of ganciclovir (which may cause bone marrow suppression)
  - H. simplex resistant to Acyclovir & HIV.

Treatment of Influenza A & B, AND Respiratory suncytial virus (RSV)

A. **Oseltamivir (Tami-flu): Neuroaminidase inhibitors**
- MOA: ***inhibit neuraminidase*** which cleaves sialic acid that connects budding virus from cell membrane, thus prevent release of virions.
- Given orally and Early administration is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness.
- Help in 1. Decrease duration 1-2 days, 2. Less symptom severity 3. Less complications in children and adults 4. Once-daily prophylaxis is 70–90% effective disease after exposure in immunocompromised.
- **Side effect: Nausea and Vomiting**

B. **Baloxavir marboxil: Cap-dependent endonuclease inhibitor (new drug)**
- **MOA:** inhibit influenza virus' cap dependent endonuclease activity (cap snatching). Cap snatching: the first 10 to 20 residues of a host cell RNA are removed (snatched) and used as the 5' cap and primer to initiate the synthesis of the nascent viral mRNA.

Treatment of Antiretrovirals (HIV):

First know life cycle on the right, there are drugs that inhibit each step.

Main classes: a. **Nucleoside reverse transcriptase inhibitors (NRTIs) b. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) c. Protease inhibitors (PIs), Others:**

- **Enfuvirtide**: derived from gp41, work by blocking the interaction of gp41 with cell membrane proteins during fusion.
- **Raltegravir**: Integrase Inhibitor, inhibit fusion of viral genes to cell DNA
- **Maraviroc**, it blocks the interaction between chemokine receptor CCR5 and HIV gp120.

Combination therapies (triple drug cocktail, HAART) are very effective and can reduce viral load in the patient below detectable levels implying that HIV replication has ceased. **Examples**: Note 2 NRTI are a must in all regimens (1) NNRTI–Based Regimens (1-NNRTI + 2NRTIs) (2) PI-Based Regimens (1 or 2 PIs + 2 NRTIs). Trouble with these drugs is noncompliance.

NRTI

Azidothymidine

Potent antagonist of reverse transcriptase, It is a chain terminator

Cellular enzyme phosphorylate AZT to the triphosphate form which inhibits RT and causes chain termination

AZT is toxic to bone marrow, cause severe anaemia and leukopenia In patient receiving high dose. Headache is also common

Didanosine

Same MOA

Toxicities are pancreatitis, peripheral neuropathy, GI disturbance, bone marrow depression.

NNRTI

MOA:(1) Bind to viral RT, inducing conformational changes that result in enzyme inhibition

(2) Combination therapy with AZT

(3) Resistance mutations will be at different sites

Nevirapine

Used to blockmother to child transmission (perinatal - breast feeding)

SE: A. CNS effects (e.g. sedation, insomnia, vivid dreams, dizziness, confusion, feeling of "disengagement") B. ***Rash***(in 20%) in first 4-6 weeks, usually mild but is dose-limiting inWhen initiating therapy, gradual dose escalation over 14 days is to decrease the incidence of rash. 7%. W>M.

PI

Inhibit the viral enzyme responsible for cleavage of viral polyprotein into number of essential enxymes.

Examples are : **Saquinavir, and Ritonavir** given orally.

SE: GI disturbances, hyperglycemia, interact with **cytochrome P450** leading to **buffalo hump.**

Non-compliance with PI is the most serious, bc resistance develops!

Anti-Malarial Drugs

Life cycle

➔Sexual cycle: in the mosquito.

➔Asexual cycle: in the human (drugs only work in this cycle). Has 2 phases:

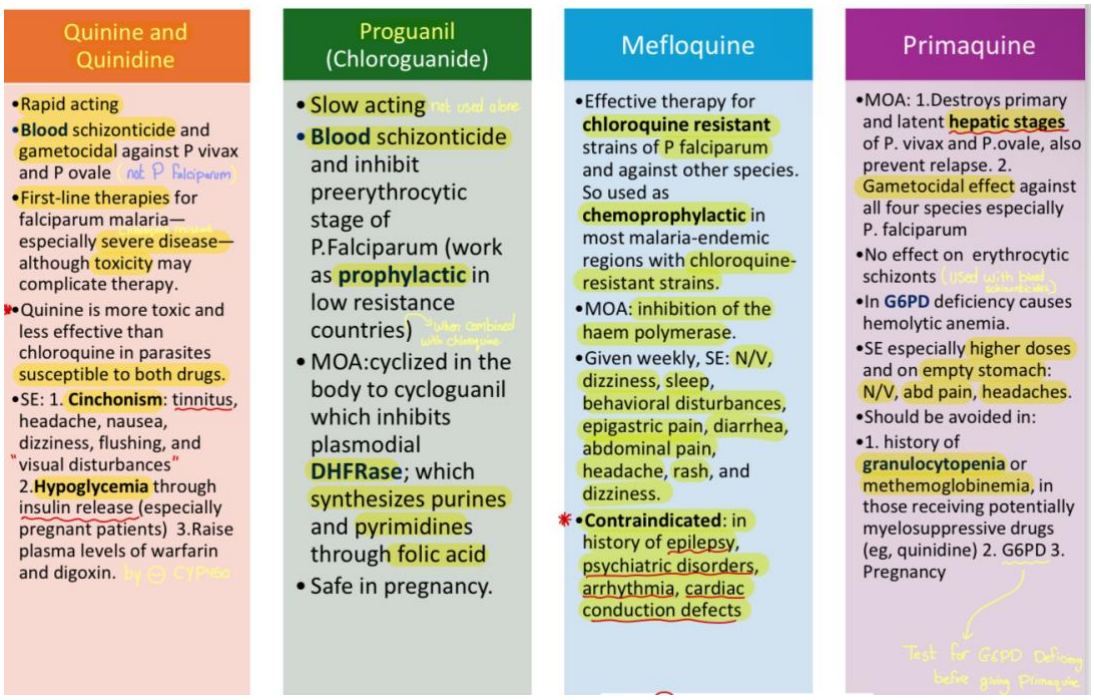
- Exoerythrocytic phase: occurs "outside" the erythrocyte
- Erythrocytic phase: occurs "inside" the erythrocyte.

Anti-malarial agents are classified into:

1. **Tissue schizonticides**: Drugs that eliminate developing or dormant liver forms.
2. **Blood schizonticides**: act on erythrocytic parasites
3. **Gametocides**: kill sexual stages and prevent transmission to mosquitoes

Chloroquine

- Potent **blood schizontocidal** drug effective against all plasmodium species. Used in the treatment of extraintestinal amebiasis too.
- **Mechanism of Action**
  - Enter parasite lysosome and inhibit digestion of hemoglobin thus reduce AA supply
  - **Inhibit haem polymerase**: the enzyme that polymerises toxic free haem to the harmless hemozoin.
- Less effective against vivax malaria, and there is **high rate of resistance worldwide**.
- **Can be given in pregnancy (not teratogenic)**
- SE At high doses: **gastrointestinal upset, pruritus, headaches, and visual disturbances**
- SE At Parenteral administration: **hypotension and cardiac arrhythmia, convulsions**.
- Contraindication: psoriasis or porphyria



Artemisinin derivatives: Artemether /Arteether / **Artesunate** (derived from Artemisia annua – sweet wormwood)

- A potent and rapidly acting **blood schizontocide** and have peroxide configuration – that eventually inhibit haemozoin.
- Always use in combination therapy!
- DOA: short but it reduces parasite burden rapidly

Pyrimethamine-sulphonamide and antibiotics:

- **Pyrimethamine inhibits plasmodial dihydrofolate reductase** at much lower concentrations than those that inhibit the human enzyme
- Tetracycline and doxycycline are active against **erythrocytic schizonts** of all human malaria parasites. They are <u>not</u> active against liver stages. **Doxycycline** is used in the treatment of falciparum malaria in conjunction with **quinine**, allowing a shorter and better tolerated course of that drug.

Iron Deficiency Anemia

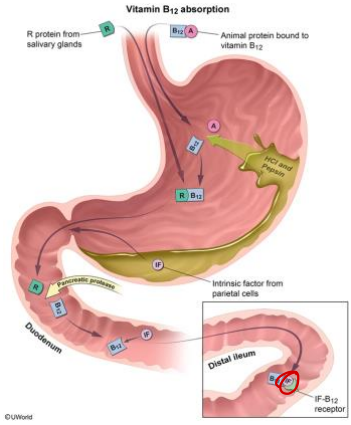
- **Indications for the Use of Iron**
  - Treatment or prevention of iron deficiency anemia.
  - Iron deficiency is commonly seen in populations with <u>increased iron requirements</u>
    - **infants**, especially premature infants; **children** during rapid growth periods.
    - **Pregnant** and **lactating** women
    - **Chronic kidney disease** who lose erythrocytes at a relatively high rate during **hemodialysis** and also form them at a high rate as a result of treatment with the erythrocyte growth factor **erythropoietin**.
  - <u>Inadequate iron absorption</u> can also cause iron deficiency.
    - This is seen frequently after **gastrectomy**
    - **Severe small bowel disease** that results in generalized malabsorption.
- **Oral Iron Preparations:**
  - **ferrous fumarate** contains 33% elemental iron ➔ BEST one
  - **ferrous gluconate** contains 12% iron
  - **ferrous sulfate** contains 20%.
- **Adverse Effects:**
  - Oral iron ➔ 20-25% have GI problems: **nausea, epigastric pain, constipation, abdominal cramps**
  - Patients taking oral iron develop **black stools**.
  - Intramuscular injection ➔ Tissue staining & local pain ➔ IV is preferred.
- Notes:
  - Food decreases absorption by 30 - 50% (preferably taken on empty stomach yet more side effects arise)
  - **Drug interactions: tetracycline and antacids decrease iron absorption.**
  - Treatment with oral iron should be continued for **3–6 months** to replenish iron stores.
- Parenteral Iron (intravenous) should be reserved for
  - Patients with documented iron deficiency, or patients who are unable to tolerate or absorb oral iron
  - patients with extensive chronic anemia who cannot be maintained with oral iron alone. This includes

1. Patients with advanced chronic renal disease requiring hemodialysis and treatment with erythropoietin
2. various post gastrectomy conditions and previous small bowel resection
3. inflammatory bowel disease involving the proximal small bowel
4. malabsorption syndromes.

Adverse effects of intravenous iron dextran therapy include

- **<u>HEADACHE</u>**, light-headedness
- fever, arthralgias, back pain
- flushing, urticaria, bronchospasm, and, rarely, anaphylaxis and death.

Megaloblastic Anemias

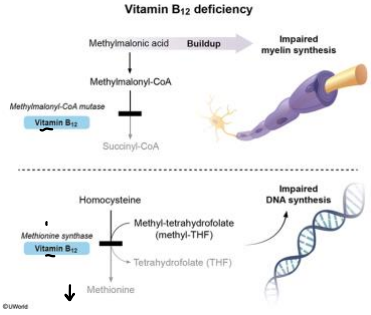


- Bone Marrow disorder caused by defective DNA synthesis.
  - **Vitamin B12 Deficiency**
  - **Folic Acid Deficiency**
- Vitamin B-12 deficiency Anemia may result from:

1. Low oral intake: Deficiency of B12 (strict vegetarians)
2. Impaired absorption (Pernicious anemia) from decreased intrinsic factor (protein secreted by stomach)
3. Gastrectomy
4. malnutrition, RA, thyroid conditions.

- Vitamin B12 is used to treat or prevent deficiency.
- Distinguished from other anemias by its Neurological Syndrome, Delirium, numbness, tingling of hand and feet, loss of fine learned movements, difficulty in walking, bladder and bowel dysfunction.
- Neurologic symptoms (**paresthesias** occur first, then **balance**) in severe deficiency may be irreversible after several months
- Injections only benefit if deficiency

– May need lifelong injections if malabsorption; can not absorb B12/intrinsic factor complex



1. **Folic acid alleviates anemic syndrome but the neurological disorder progresses**.
2. Antagonism of Vit Bp by nitrous oxide (inactivates Vit B12 dependent enzymes) => megaloblastic response, neuropathies

- Vitamin B12 for parenteral injection is available as:
  - Cyanocobalamin
  - Hydroxocobalamin, which is preferred because it is more highly protein-bound and therefore stays longer in the circulation.
- **Initial therapy** should consist of 100–1000 mcg of vitamin B12 intramuscularly daily or every other day for 1–2 weeks to replenish body stores.
- **Maintenance therapy** consists of 100–1000 mcg intramuscularly once a month for life.
  - **If neurologic abnormalities are present, maintenance therapy injections should be given every 1–2 weeks for 6 months before switching to monthly injections.**
- Oral vitamin B12-intrinsic factor mixtures and liver extracts should not be used to treat vitamin B12 deficiency; however, oral doses of 1000 mcg of vitamin B12 daily are usually sufficient to treat patients with **pernicious anemia who refuse or cannot tolerate the injections**.

Megaloblastic Anemia (Folic acid Deficiency)

- Folic Acid (folate, Vitamin B9) found in fresh **green veggies,** yeast, animal proteins but easily destroyed.
- **Anemia may be indistinguishable from B12 deficiency but occurs rapidly.**
- Must evaluate fully before treatment- folate therapy will correct hematological abnormalities but not neurological problems **(make sure patient doesn't have anemia due to B12 Deficiency before treatment)**
- B12 deficiency may **be masked** by folate supplementation.
- because body stores of folates are relatively low (unlike the case of Vitamin B12) and daily requirements high, **folic acid deficiency and megaloblastic anemia can develop within 1–6 months after the intake of folic acid stops**, depending on the patient's nutritional status and the rate of folate utilization.
- Patients with **alcohol dependence** and patients with **liver disease** can develop folic acid deficiency because of **poor diet** and **diminished hepatic storage of folates**.
- Patients who require **renal dialysis** **develop folic acid deficiency** because folates are removed from the plasma during the dialysis procedure.

FOLIC ACID

- **Drug interactions**: In large doses may counteract the effects of anticonvulsants potentially leading to seizures.
- **Adverse reactions**: Erythema, itching, and rash