بسم الله الرحمن الرحيم

Pharmacology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

Final | Lecture 5

Chemotherapy for Leukemia and Lymphoma (Pt.2) & Antiviral (Pt.1)

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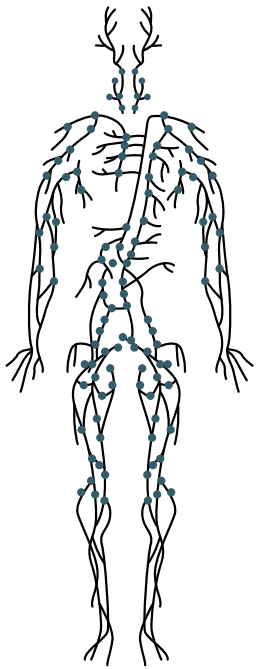


Induction

four to six weeks:

- Vincristine
- Glucocorticoid (prednisone, prednisolone or dexamethasone)
- L-asparaginase

- **Daunorubicin** – like doxorubicin (in adults)
- **If the patient is younger than 1-year, additional drugs are added.**

❖ **Combination therapy:** use drugs with different mechanisms and toxicities to achieve synergism and lower overall side effects.
Minimal regimen: vincristine, glucocorticoid, asparaginase (often expanded to 5 drugs).
In ALL: given stepwise across phases (induction → consolidation → maintenance).

ALL: acute lymphocytic leukemia

Pharmacodynamics of Asparaginase

- The malignant cells are dependent on an exogenous source of asparagine for survival.
- Normal cells, however, are able to synthesize asparagine and thus are affected less by the rapid depletion produced by treatment with the enzyme asparaginase.

❖ **L-asparaginase inhibits protein synthesis by depleting L-asparagine, an amino acid required for the survival of ALL cells.** However, systemic depletion of L-asparagine also affects normal cells, leading to reduced protein synthesis and associated side effects.

L-Asparaginase – Mechanism of Action

- Catalyzes the conversion of L-asparagine to aspartic acid and ammonia.
- Reversal of L-asparagine synthetase activity.
- Results in rapid and complete depletion of L-asparagine.
- Lack of intracellular asparagine results in decrease of protein synthesis and apoptosis.
- Most successful drug in treatment of acute lymphocytic leukemia.

L-Asparaginase – Impaired Protein Synthesis most important side effect.

- Decreased production of insulin
  - Resultant hyperglycemia secondary to hypoinsulinemia
  - Hyperglycemia usually transient and resolves upon discontinuation
    - Blood sugar should be closely monitored and managed through diet or drugs.
- Decreased production of albumin
  - Hypoalbuminemia can be severe resulting in peripheral edema or ascites needing diuretics.
    - Patients with limited hepatic synthetic function may be unable to tolerate the effects of L-asparaginase

L-Asparaginase – Impaired Protein Synthesis

- Decreased production of vitamin K-dependent clotting factors and endogenous anticoagulants such as proteins C and S and antithrombin III
  - Coagulopathies, thrombosis, or bleeding due to impaired protein synthesis may occur depending on the body's response to the drug and individual variability within the population, ultimately requiring condition-specific management such as vitamin K or warfarin therapy.
  - Monitor coagulation parameters during L- asparaginase therapy
  - Use cautiously in patients with a preexisting coagulopathy (e.g. hemophilia) or hepatic disease
  - Intramuscular injections may cause bleeding, bruising, or hematomas due to coagulopathy

L-Asparaginase – Toxicities

- Mild nausea/vomiting
  - Anorexia, abdominal cramps, general malaise, weight loss

❖ **ALL** involves **rapidly dividing cells**. When three **drugs** are combined, ~25% of **bone marrow** is destroyed (20% being **leukemic cells**). The resulting **cell lysis** releases **DNA**, **phosphate**, **potassium**, and **uric acid** into the **blood**, overwhelming the **kidneys** and potentially causing **tumor lysis syndrome**.

- Tumor Lysis Syndrome (TLS)
  - Hyperkalemia, hyperphosphatemia, hyperuricemia hypocalcemia, and decreased urine output
  - Severe renal insufficiency

·**Hyperkalemia:** give insulin → shifts K^+ into cells
·**Hyperphosphatemia:** treat with fluids → ↑ excretion
·**Purines → uric acid (via xanthine oxidase):** give allopurinol
·**Hypocalcemia:** due to phosphate binding Ca^{2+} → give calcium gluconate
·↓ **Urine output:** from uric acid & phosphate crystals → fluids + diuretics → ↑ GFR → prevent renal failure

Don't memorize these details, just know TLS

Vincristine

- **Vincristine** is an **antimitotic drug** that inhibits **mitotic spindle polymerization**. In contrast, **taxoids** (paclitaxel, docetaxel) inhibit **spindle depolymerization** and are more **neurotoxic**.
- Vincristine blocks cells in the **M phase** and is **cell cycle-dependent**, so its effect on **bone marrow** is minimal, making it a **BM-sparing drug** with low **toxicity**.

- Constipation is common during articularly because of the Vincristine.

- Nerve Irritation

Vincristine may cause numbness or tingling in the hands and feet. If this occurs.

- Anything that has to do with the mitotic spindle results in neuropathy.

Glucocorticoids

- They have **inhibitory** effects on **lymphocyte proliferation** and are used in **treating lymphomas and leukemias**.
- **Prednisone** is an example that used to **induce remission** in the treatment of **lymphocytic leukemia** and in the treatment of **Hodgkin and non-Hodgkin lymphoma**.

Steroid Side Effects

- Potential side effects of the steroid prednisone include:
  - Trouble sleeping
  - Increased appetite
  - Fluid retention and swelling
  - Indigestion
  - Restlessness
  - Nervousness
  - Headache
  - Blurred vision
  - Muscle cramps and weakness
  - Increased blood sugar level
  - Bone pain
  - High blood pressure.

❖ **Glucocorticosteroids** have many **side effects** because they alter the expression of about **one-third of a cell's genes**, causing widespread changes in the body. Their main effect is **immunosuppression** (useful in **autoimmune diseases**). In **ALL**, we exploit this effect by using **high doses** to induce **lympholysis**, inhibiting **CD3, CD44, and CD8**, which triggers **apoptosis of lymphocytes**.

Consolidation

- Once normal hematopoiesis is achieved (bone marrow contains **5% or fewer cancer cells**), patients undergo **Consolidation therapy.**
- Common regimens in childhood ALL include:
  1. **Methotrexate with mercaptopurine (antimetabolite)**
  2. **High-dose asparaginase** over an extended period **due to cancer cell resistance**.
  3. **Reinduction treatment** (a repetition of the initial induction therapy in the first few months of remission).

❖ The **cancer cells** that survive **induction** are inherently **resistant**, so we use an **augmented approach**. **Methotrexate** inhibits **dihydrofolate reductase**, depleting **purines**, the precursors for **DNA synthesis**, while **mercaptopurine**, a **faulty purine**, blocks DNA synthesis, arresting cells in the **S phase**. This **targets a common pathway** to enhance the effect (similar to **co-trimoxazole** in bacteria) and ultimately **eliminates all remaining leukemic cells**.

Maintenance

Any surviving cancer cells are targeted.

- Maintenance usually consists of:
  1. Weekly methotrexate
  2. Daily mercaptopurine
- For 2–3 years

❖ **Maintenance therapy** works via the **same mechanism as consolidation** but at **lower doses**. Duration: **2 years for females** and **3 years for males**, since **females generally have stronger immunity**. **Compliance is crucial**, as skipping doses **reduces effectiveness**.

❖ **6MP** and **methotrexate** kill normal cells, causing **bone marrow suppression** and **febrile neutropenia**, whereas **vincristine, asparaginase, and prednisolone** only **arrest bone marrow division** without extensive killing.

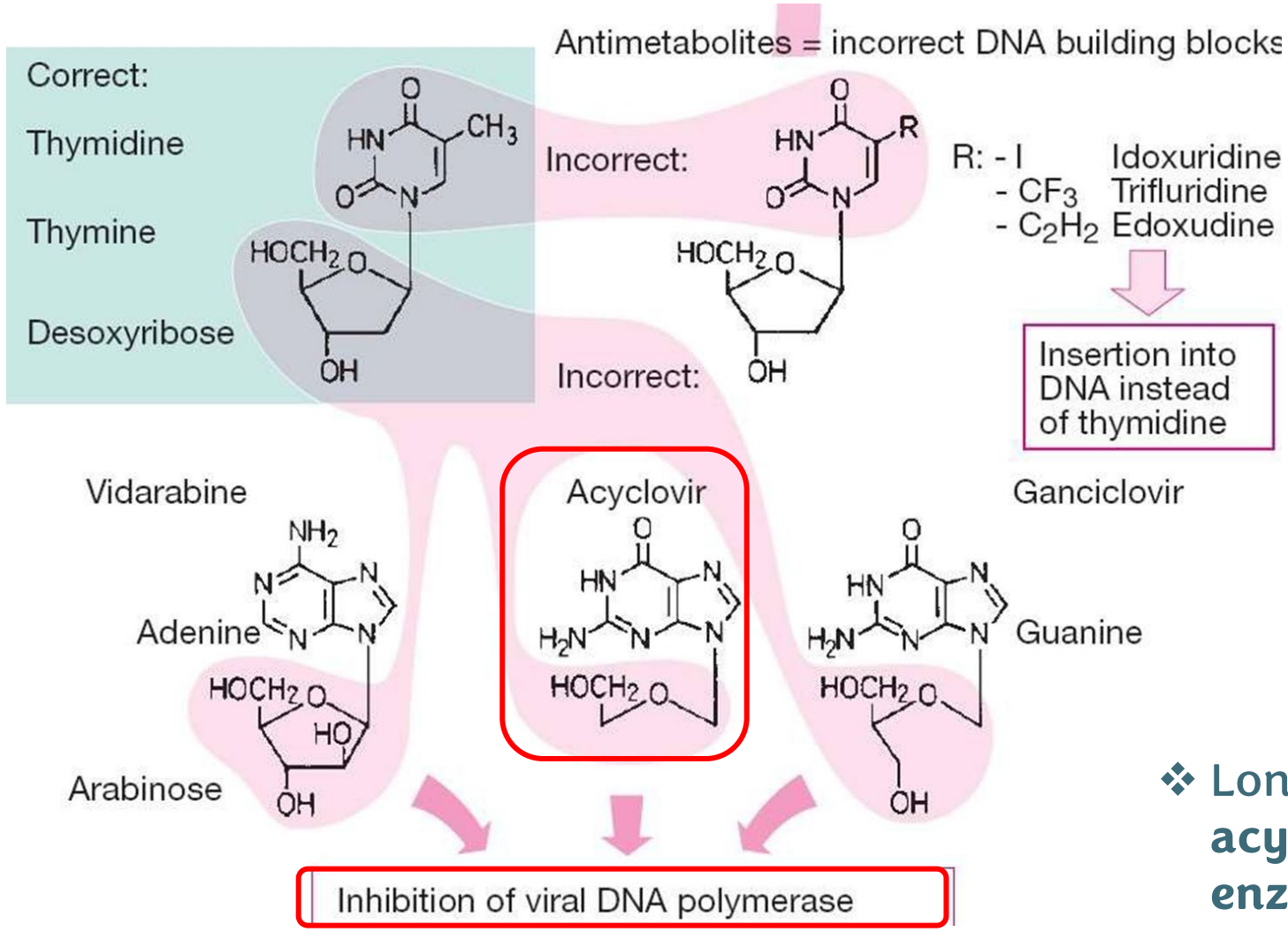
CNS prophylaxis

- Patients with ALL frequently have meningeal leukemia at the time of relapse (50–75% at one year in the absence of CNS prophylaxis), and a few have meningeal disease at diagnosis (<10%).
- **Intrathecal** (methotrexate, cytarabine (**pyrimidine** analog), steroids)
- **And for adults:** high-dose systemic chemotherapy (**methotrexate, cytarabine, L-asparaginase**)
- Some cancer cells escape to the brain, which could be fatal — that's why we use **high-dose chemotherapy** for CNS protection in adults (via blood) or **direct injection into cerebrospinal fluid** in children.

❖ If these methods fail, we proceed to **bone marrow transplantation**, which is **more commonly used in AML therapy**.

Antiviral-(pt.1)

The head of a pin can hold five hundred million rhinoviruses (cause of the common cold). One sneeze can generate an aerosol of enough cold viruses to infect thousands of people!



- Acyclovir is a nucleoside analog resembling the natural nucleosides used by the virus. The viral enzyme **thymidine kinase** has a much higher affinity for acyclovir, phosphorylating it into **acyclovir triphosphate**. This selectivity allows acyclovir to primarily target infected cells, **minimizing side effects**.

- Long story short, the key point is that **acyclovir is activated by a VIRAL enzyme (thymidine kinase)**, not by normal cellular enzymes – **keep this point in mind later when we discuss HIV drugs**.

Acyclovir

and Valacyclovir (pro-drug, better availability)

A Guanine analogue with antiviral for Herpes group only

Acyclovir ——— **AcycloGMP** ——— **AcycloGTP**

(Which is why Acyclovir is effective for HSV with minimal side effects)

Thymidine kinase

Viral 200x affinity of mammalian

Cellular kinases

1. Inhibits viral DNA polymerase selectively
2. Incorporated into DNA and terminates synthesis

Resistance:
1. ↓ activity of thymidine kinase
2. altered DNA polymerase

HSV: herpes simplex virus

(The picture shows the main steps of viral infection in a host cell.)

Viruses hijack the host cell's machinery to make their own proteins. Treating them is difficult because killing infected cells also harms normal ones – unlike bacteria, viruses lack clear structures like a **cell wall** to target.

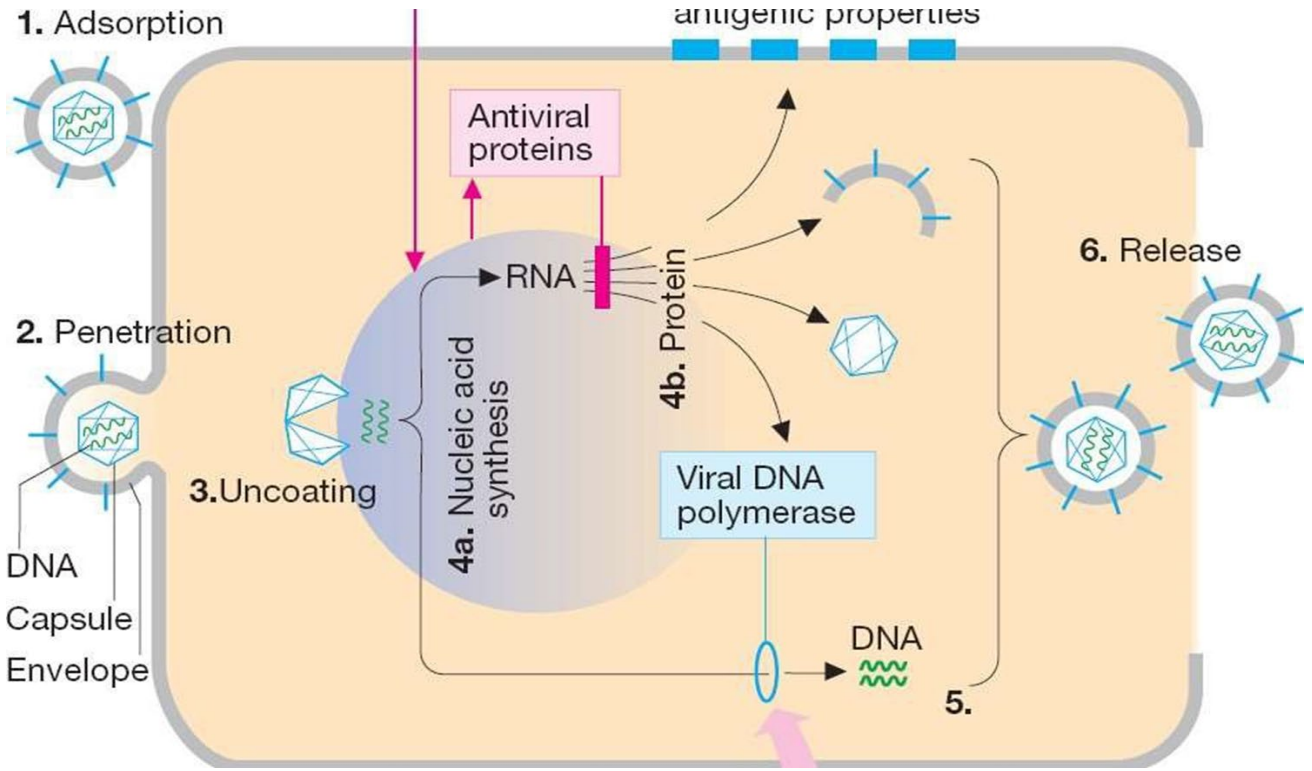
Acyclovir is an exception. It selectively kills **virus-infected cells** by acting as a **false nucleoside**, blocking DNA synthesis – a strategy mainly used against **HSV**.

For **HIV**, we target different viral enzymes instead:

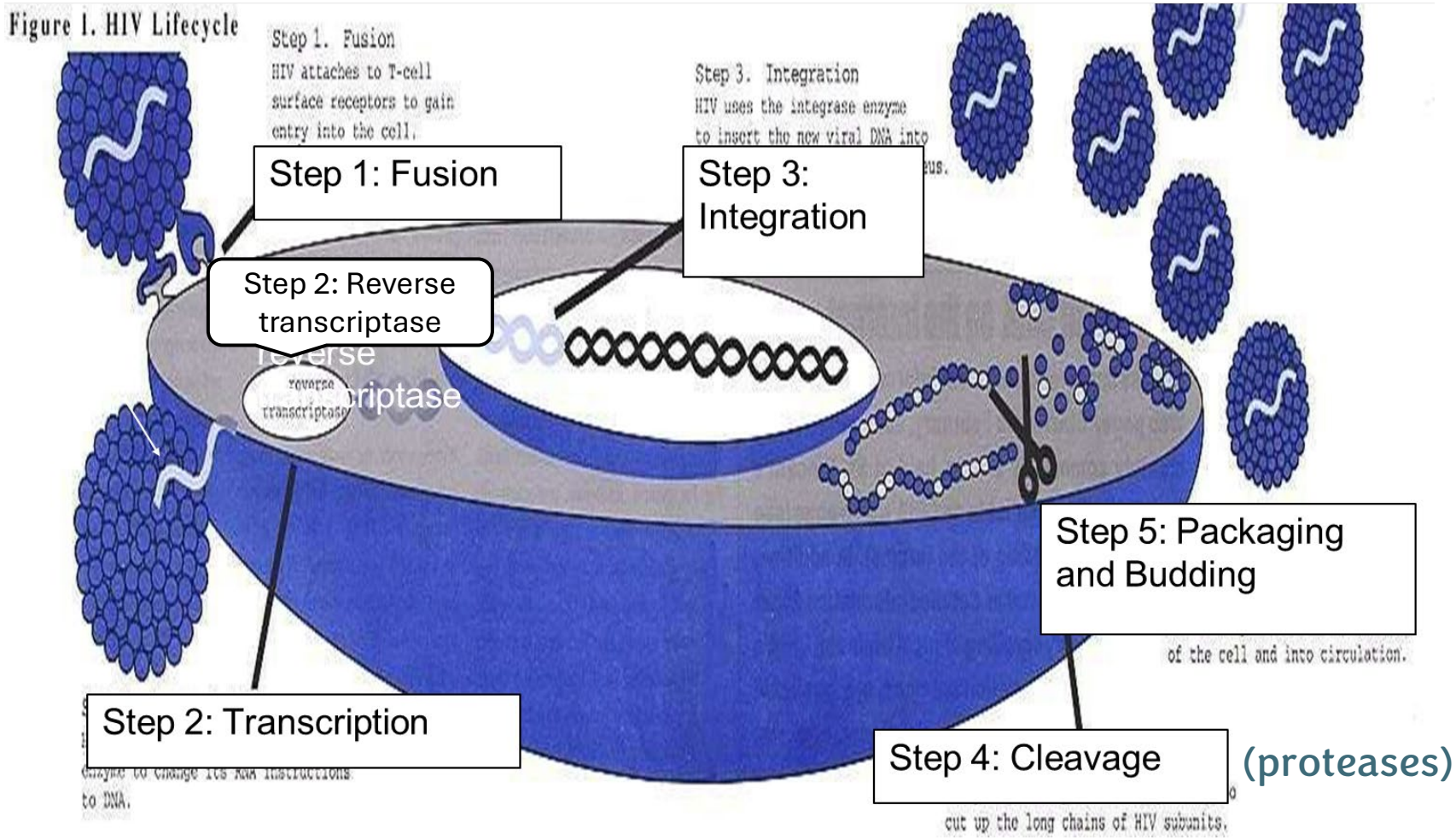
- **Reverse transcriptase** – converts viral RNA to DNA.
- **RNA polymerase** – transcribes viral genes.
- **Integrase** – inserts viral DNA into the host $CD4^+$ DNA.
- **Protease** – helps assemble new viral particles.

So while acyclovir introduces the concept of **selective targeting**, in **HIV** we apply it by focusing on **viral enzymes not found in human cells**.

Knowing the steps can help you understand how drugs inhibit viral replication.



HIV Life Cycle



- The steps of **HIV infection** involve several key stages, and **antiviral therapy** targets each of them. There's also a **transcription step**, where viral **DNA is copied into RNA** using **host RNA polymerase**, not reverse transcriptase.

HIV life cycle

- Step 3 (**integration**) is especially important because once the viral DNA is integrated into the host genome, it **cannot be reversed**. As a result, treatment focuses on **managing the infection** rather than curing it. This is achieved through **HAART (highly active antiretroviral therapy)**, which keeps the viral load low (to be discussed in another lecture).
- In some cases, we may also need to use **less selective drugs**. For all these reasons, **careful management is crucial** in dealing with HIV.
- By using the appropriate drugs, we can **target each of the five steps of the HIV life cycle**.

Azidothymidine (Zidovudin (AZT))

Faulty thymidine

- An old drug
- **It is a potent antagonist of reverse transcriptase, It is a chain terminator** Inhibiting the **conversion of RNA to DNA**.

unlike acyclovir!

- **Cellular enzyme phosphorylate AZT to the triphosphate form which inhibits RT (reverse transcriptase) and causes chain termination.**
- **It is widely used, as it is the only antimetabolite still used in the treatment of AIDS (its only clinical use).**
- **AZT is toxic to bone marrow since it relies on cellular enzymes, causing severe anemia and leukopenia in patients receiving high doses. Headache is also common due to anemia.**

Non-nucleoside Non-competitive RT inhibitors

(1)**bind to viral RT, inducing conformational changes that result in enzyme inhibition**

(2)**Combination therapy with AZT (resistant mutants rapidly emerge, little use in monotherapy)**

(3)**Resistance mutations will be at different sites**

Never use it **alone**, HIV (viruses in general) can easily become **resistant**.

more on that in the following slide.

Examples:

Generic Name	Trade Name	Usual Dose
Nevirapine	Viramune®	200 mg QD x14 days, then 200 mg BID
Delavirdine	Rescriptor®	400 mg TID
Efavirenz	Sustiva™	600 mg QD

RT: Reverse transcriptase

Non-nucleoside Non-competitive RT inhibitors

Nevirapine **Approved for AIDS patients, Good blocker of mother to child transmission (perinatal - breast feeding)**

- **Single dose at delivery reduced HIV transmission by 50%** For the mother
- **Single dose to baby by 72 hours**

NNRTI's: Adverse Effects RASH!!

CNS effects (e.g. sedation, insomnia, vivid dreams, dizziness, confusion, feeling of "disengagement")

- This drug is really effective (50% reduction is considered high). Unfortunately, due to wrong practices in the past (monotherapy) many people developed resistance (the virus became resistant). Hence, we should avoid monotherapy.

Pharmacology Quiz 5

PHARMACOLOGY QUIZ

LECTURE 5

For any feedback, scan the code or click on

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	SLIDE 11	the precursors for **protein synthesis**, while **mercaptopurine**, a **faulty purine**, blocks protein synthesis	the precursors for **DNA synthesis**, while **mercaptopurine**, a **faulty purine**, blocks DNA synthesis
V1 → V2			