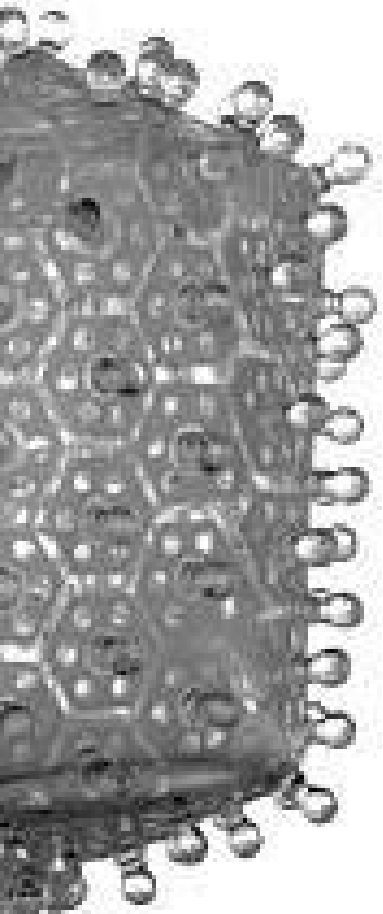

Microbiology

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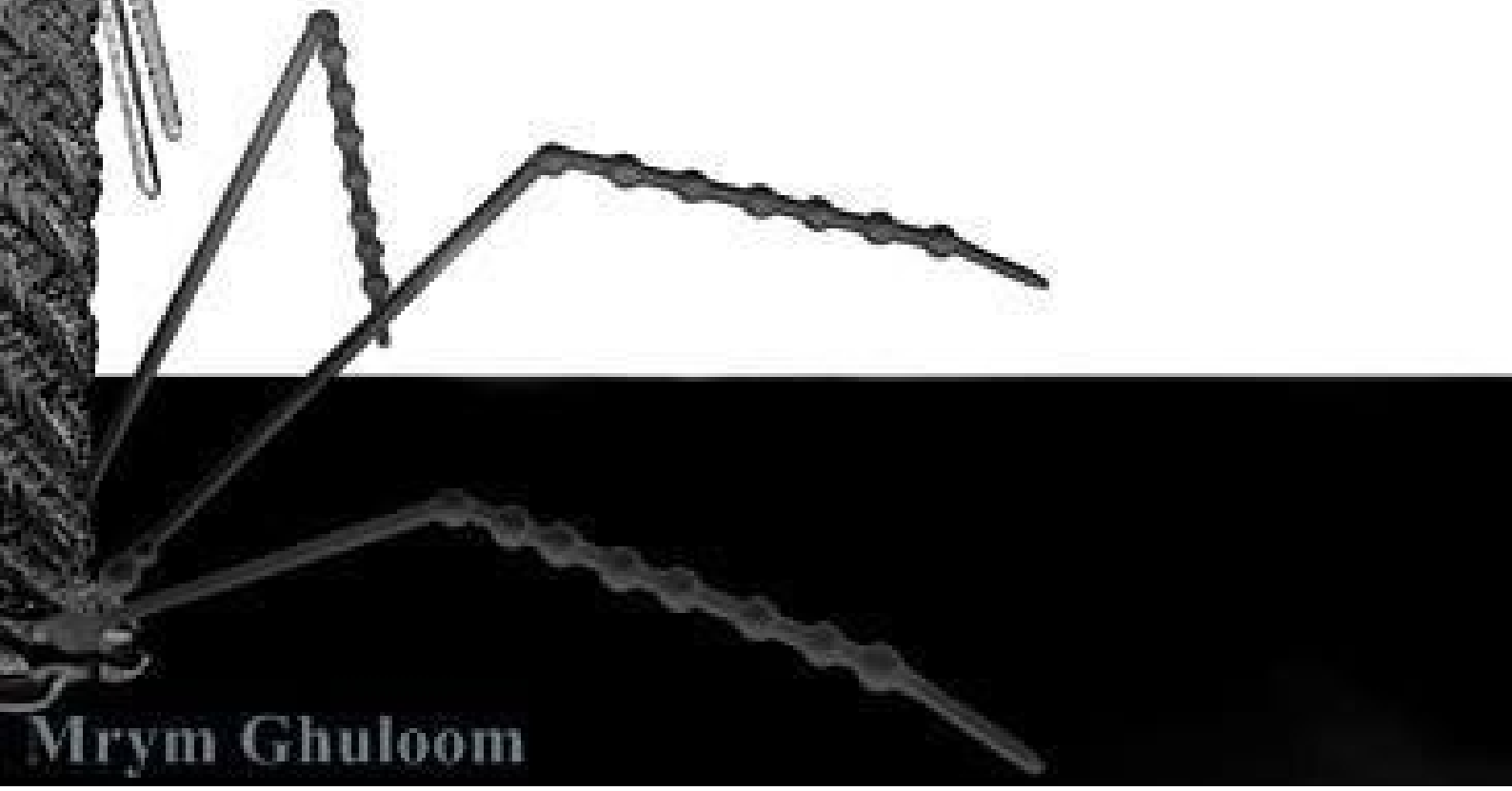

Mrym Ghuloom

Virology – **Antivirals 2**
JU- 2nd Year Medical Students

By

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- HIV
- Hepatitis

- HIV infections
- **1 Nucleoside RT inhibitors (NRTIs)**
- **Mode of action**

- **AZT, Zidovudine,** was the first RT inhibitor to be used for treating HIV infection.

- Like ACV, it must be tri-phosphorylated intracellularly to become active

- potent inhibitor of viral RT and prevents nucleotide chain elongation much in the same manner as ACV.

- The 3 positioning of the azido group of AZT blocks the essential phosphodiester linkage, which would normally enable the next nucleotide to be added to the growing DNA chain.

- AZT triphosphate binds to the viral RT rather than to the cellular DNA polymerase, giving some specificity of action.

- By contrast with ACV, cell enzymes rather than viral enzymes phosphorylate AZT

- The other dideoxynucleosides have a similar mode of action to that of AZT.

- **Clinical application**
- AZT, was shown quite quickly to be effective in prolonging the lives of AIDS patients by about 18 months.

- patients given a drug holiday the immune system rebounded and could be expected to suppress virus (interrupted therapy)

- new drugs can act synergistically with AZT to avoid drug resistance problems and can be used in lower dosages to avoid side-effects.

- Molecules such as **ddi (Didanosine), ddC (Zalcitabine), and 3TC (Lamivudine)** are used in **combination chemotherapy** with AZT plus a viral protease inhibitor.

- This use of a combination of drugs is called HAART (highly active antiretroviral therapy).

- **2 Non-nucleoside RT inhibitors (NNRTIs)**
- E.g nevirapine
- They are powerful RT inhibitors

- drug-resistant HIV mutants appear almost immediately after starting treatment.

- highly selective for HIV-1 and bind tightly to the viral RT close to the polymerase active site, where they distort this region of the viral enzyme.

- They are used in combination with nucleoside and protease inhibitors.

- **3 Protease inhibitors**
- The virus-coded protease cleaves certain HIV structural proteins at the **maturation** stage

- no cleavages – virus is not mature and is not infective.

- At least six new drugs have been found that inhibit HIV protease but not mammalian cell proteases e.g Indinavir.

- They are well tolerated but:
- difficult to manufacture
- patients require large doses
- Drug-resistant mutants are easily selected
- cross-resistance.

- **4 Nucleotide inhibitors**
- tenofovir
- targets the viral reverse transcriptase enzyme and can be used in place of a NRTI
- drug in the HAART scheme.
-
- **5 Fusion inhibitors**
- Enfuvirtide (Fuzeon).
- stop the virus from binding to and entering the cell

- **Combination chemotherapy (HAART):**

- using a **combination** of drugs, e.g. AZT, 3TC, a non-nucleoside analogue, and a protease inhibitor.

- reduce the load to undetectable levels

- Treatment effect monitored by assaying the amount of viral genome in the plasma of the patient—the **viral genome load**.

- expensive
- complicated to monitor

- patients have to take perhaps 15 tablets at specific times each day.

- Default can allow a very rapid rebound of drug-resistant virus,
- Nevertheless, many AIDS patients have benefited from drugs combinations

- **Hepatitis C virus:**

- Persistent infection can lead to chronic liver disease and the virus is the leading cause for liver transplantation in developed nations.

- Pegylated IFN used in combination with ribavirin is the best now

- **Hepatitis B virus**
- Despite the availability of vaccine, 400 million carriers (unvaccinated or unresonsive).

- antivirals - modest success

- patients with active liver disease and low-level viraemia do respond to treatment with IFN-_ given subcutaneously. side-effects of the IFN.

- Nucleoside analogue lamivudine (3TC), are potent and well tolerated inhibitors of HBV.

- The drug acts by inhibiting reverse transcription during the replicative cycle of hepatitis B

- It is effective in patients who fail to respond to IFN and can be given orally.

- It is also used as prophylactic treatment in liver transplants.

- Relapses can occur, when discontinue therapy

  Or with monotherapy.

- A second nucleoside analogue, adefovir, an acyclic analogue of deoxyadenosine monophosphate has also been licensed for chronic hepatitis B patients.

- Treatment of choice uses IFN , which is effective in 20–30% of patients, followed by lamivudine.

END