

# First line ARV Drugs: Mechanism of action, dosage and storage

# Objectives



1. Describe how the different classes of ARVs work
2. Identify the drugs to include in the first-line ARV regimen
3. Discuss the use of these regimens in reference to Nigerian guidelines
4. Discuss dosages and administration of ARVs
5. Discuss storage and availability in country

# Desired Characteristics of a First Line Regimen



- The simplest three-drug combination as the first line therapy. **Simple =**
  - As few pills a day as few times as possible
  - Lower likelihood of side effects
  - High barrier to resistance
  - Scalable / Affordable
  - Practical in the Nigerian Setting
    - for example – not requiring refrigeration
  
- There is no perfect first line regimen.

# What Therapy to Begin With



- At least three antiretrovirals are needed in combination to achieve the following desirable outcomes of antiretroviral therapy:
    - Dramatically reduce viral replication
    - Reduce the risk of resistance and treatment failure
  - Choices\* include
    - Seven nucleoside reverse transcriptase inhibitors (NRTIs)
    - One nucleotide reverse transcriptase inhibitor (NtRTI)
    - Three non-nucleoside reverse transcriptase inhibitors (NNRTIs) and
    - Eight protease inhibitors (PIs)
    - One fusion inhibitor
    - New drugs in development
- \* Most, but not all, of these are available in Nigeria

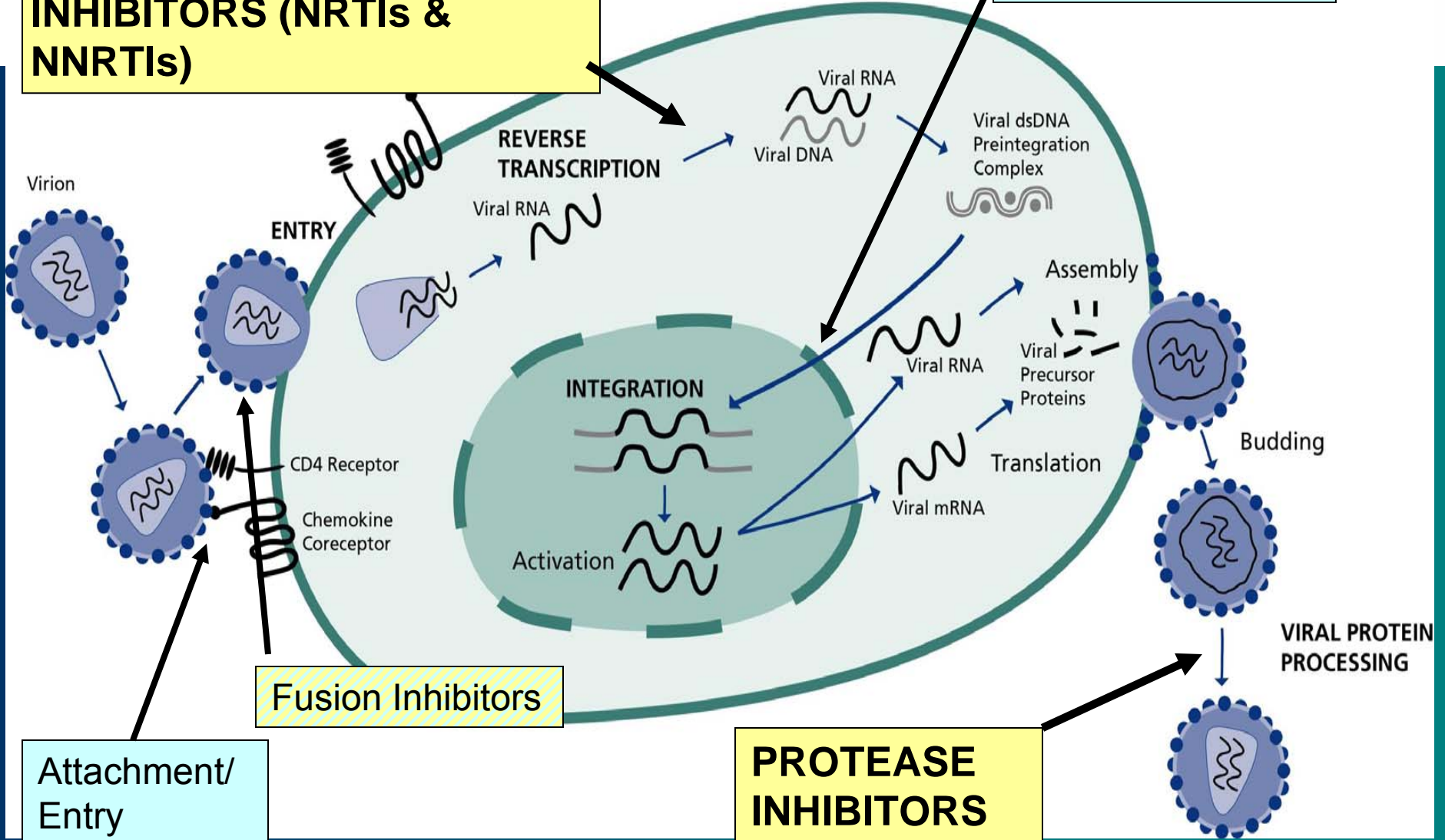
# Antiretroviral therapies: Mode of action



- Antiretroviral drugs (ARVs) act on HIV by interfering with its reproductive cycle.
- The main stages of the cycle where these drugs act to inhibit replication of the virus are:
  - NRTIs and NNRTIs prevent formation of proviral DNA
    - *Mechanism: inhibit reverse transcriptase enzyme*
    - *NRTIs and NNRTIs work by two different mechanisms*
  - PIs inhibit maturation of virion
    - *Mechanism: interrupt the protein processing and virus assembly*
  - Fusion inhibitors prevent attachment of HIV to CD4 cells

**REVERSE TRANSCRIPTASE INHIBITORS (NRTIs & NNRTIs)**

**Integrase inhibitors**



**Fusion Inhibitors**

**Attachment/  
Entry  
Inhibitors**

**PROTEASE  
INHIBITORS**

**HIV DRUG TARGETS: CURRENT AND FUTURE**

# Antiretroviral therapies: Mode of action, continued



- Nucleoside reverse transcriptase inhibitors (NsRTIs) and nucleotide reverse transcriptase inhibitors (NtRTI), or NRTI as a whole group
  - Lead to premature termination of the production of the HIV DNA chain
  - Are competitive inhibitors of reverse transcriptase
  - Are active against both HIV 1 and 2

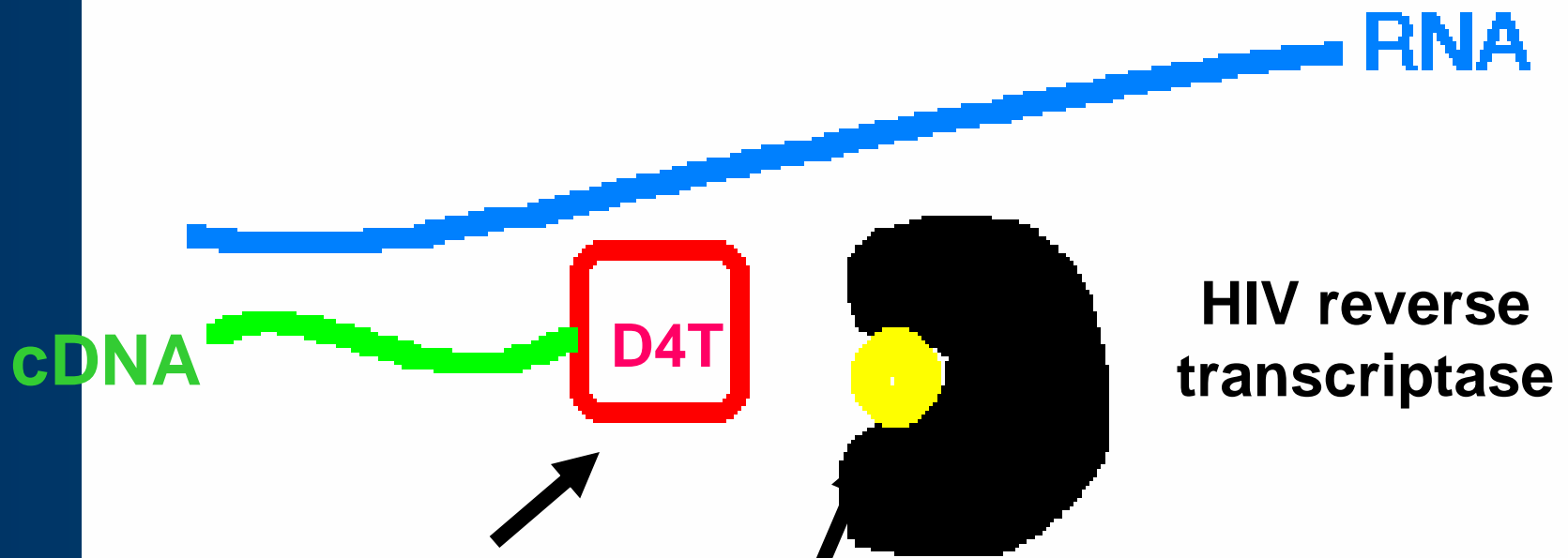
# Non-nucleoside reverse transcriptase inhibitors (NNRTIs)



- NNRTIs work to change the conformation of reverse transcriptase, inhibiting it from functioning properly
  - Non-competitive inhibitors (NRTIs are competitive)
- NNRTIs do not work in HIV-2 and HIV-1 group O infection
- Delavirdine and Nevirapine are antagonistic in action on the HIV reverse transcriptase activity---do not use together
- Interaction with some drugs occurs due to induction and/or inhibition of cytochrome P450 enzymes in liver

# Mechanism of reverse transcriptase inhibitors

**NRTI = Nucleoside reverse transcriptase inhibitor**  
**NNRTI = Non-nucleoside reverse transcriptase inhibitor**



**NRTI (such as d4T) is added onto cDNA chain, blocking further reverse transcription**

**NNRTI (NVP or EFV) Blocks reverse transcriptase by binding at active site**

# Protease Inhibitors (PIs)



- NFV, Nelfinavir (Viracept)
- LPV/r, lopinavir/ritonavir (Kaletra)
- SQV, Saquinavir (Fortovase)
- APV, Amprenavir (Agenerase)
- IDV, Indinavir (Crixivan)
- RTV, Ritonavir (Norvir)
  - As pharmacoenhancer
- Atazanavir (Reyataz)

# Protease inhibitors (PIs)



- HIV protease enzyme
  - cleaves various polyproteins in the process of producing mature infectious virions
- Protease Inhibitors or PIs
  - interfere with the action of HIV protease
  - lead to reduction of the virus in the body
  - reduction is often significant enough to lead to undetectable levels of virus
  - Multiple viral mutations required for resistance

# PIs, continued



- PIs are associated with multiple drug interactions because of their inhibition of cytochrome P450 enzymes

*For example: PIs decrease the metabolism of rifampicin and increase its toxicity*

- Indinavir should be taken with plenty of water to prevent kidney stones
- If a patient develops diabetes during PI treatment, it is best to stop the PIs if there is another alternative

# Nigerian Guidelines Recommended First Line Regimen for Adults/Adolescents



- d4T (stavudine) + 3TC (lamivudine) + {NVP (nevirapine) or EFV (efavirenz)}
- ZDV (zidovudine) + 3TC + {NVP or EFV}
- {TDF (Tenofovir) or ABC (Abacavir)} + {FTC (Emtricitabine) or 3TC} + {NVP or EFV}
- ddl (didanosine) + {3TC or FTC} + {NVP or EFV}

# First Line Regimens for Special Categories of Adults/Adolescents



- Pregnant women or women who are likely to become pregnant whose CD4 count is < 250
  - ZDV (zidovudine) + 3TC (lamivudine) + NVP (nevirapine)
    - May use d4T in place of zidovudine in the case of anaemia
- Increase in risk of hepatotoxicity in women whose CD4 counts are over 250
  - May consider EFV in women whose CD4 counts are above 250 AFTER THE FIRST TRIMESTER
  - May consider using LPV/r or Nelfinavir
- These will be discussed in further detail in a later lecture

# Alternative First Line Regimens for Special Categories of Adults/Adolescents

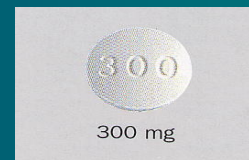
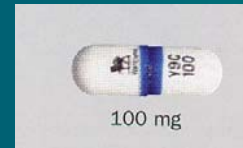


- Patients with HIV and Tuberculosis
  - ZDV (zidovudine) OR TDF (tenofovir) + 3TC (lamivudine) + NVP (nevirapine)
    - (during non-Rifampicin containing continuation phase)
  - ZDV OR d4T + 3TC + EFV (efavirenz)
    - (during Rifampicin containing intensive or continuation phase)

# Zidovudine/Retrovir (AZT, ZDV)



- 100mg capsules
- 300 mg tablet
- 10mg/ml yellow liquid, strawberry flavoured
- Intravenous formulation



# Zidovudine/Retrovir (AZT)



- Was first available antiretroviral medication
- Initially used for cancer but taken off market for that indication (due to toxicity concerns at higher doses than are being used now for ART)
- Adolescent and adult dose
  - 300 mg PO BD

# Zidovudine/Retrovir (AZT)



- Also comes in combination forms
  - *Combivir*
    - \*AZT + 3TC
  - *Trizivir*
    - \*AZT + 3TC +  
ABC

# Zidovudine/Retrovir (AZT)



- Tablets and capsules can be stored at room temperature
- Protect capsules from moisture
- May be taken with or without food

# Tenofovir/Viread(TDF)

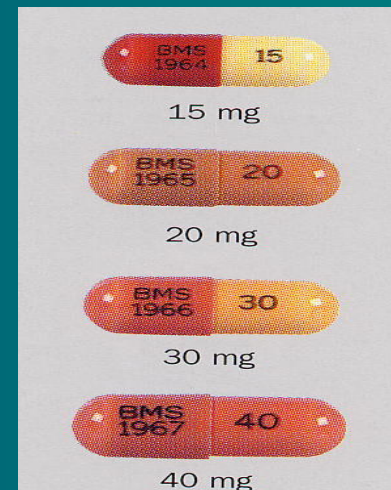


- First nucleotide RTI with durable activity against some nucleoside-resistant strains of HIV
- Favorable safety profile – low incidence of renal failure
- Preferred drug for Hepatitis B virus
- Tenofovir and/or nevirapine may be used in cases of high cholesterol and triglyceride levels
- Dose: 300 mg OD (ONCE A DAY)

# Stavudine/Zerit (d4T)



- Capsules: 15 mg, 20 mg, 30 mg, 40mg
- Solution: 1 mg/ml



# Stavudine/Zerit (d4T)

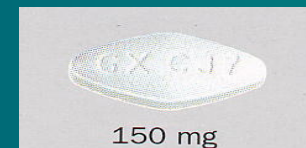


- Can be given with or without food
- Capsules can be opened and sprinkled on mashed potatoes, porridge or other soft foods
- Dose
  - > 60 kg      40 mg bid
  - < 60 kg      30 mg bid

# Lamivudine/Epivir (3TC)



- Tablets: 150 mg, 300mg
- 10 mg/ml clear solution
- Epivir HBV: 5 mg/ml solution , 100 mg tab



# Lamivudine/Epivir (3TC)



- Adolescents/Adults
  - < 50 kg: 2 mg/kg twice daily
  - $\geq$  50 kg: 150 mg twice daily or 300 mg once daily
- Also comes in Combivir and Trizivir

# Lamivudine/Epivir (3TC)



- Can be given with or without food
- Store oral solution at room temperature
- Dosage should be decreased in patients with renal impairment

# Emtricitabine (FTC; Emtriva)



- New reverse transcriptase inhibitor
  - FDA-approved 2003
- Longer  $T_{1/2}$  than lamivudine
- Single, 200mg once daily dose - oral
- Very good side effect profile
- Active against hepatitis B, but not against lamivudine (epivir)-resistant HBV

# Didanosine/Videx/Videx EC (ddI)



- Chewable buffered tablets:
  - 25 mg, 50 mg, 100 mg, 150 mg, 200mg
- 10 mg/ml white suspension
- Videx EC:
  - 125mg, 200mg, 250mg, 400mg
  - Not available in Nigeria



# Didanosine/Videx (ddI)

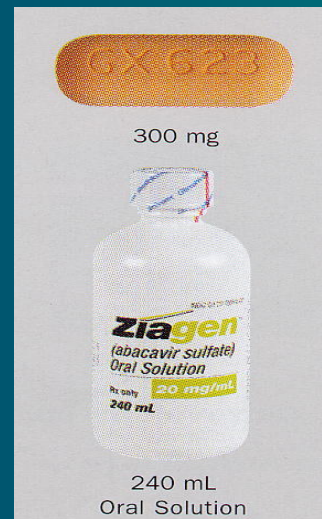


- Adolescent/Adult dosing
  - 400 mg OD if  $\geq 60$  kg
  - 250 mg OD if:
    - \*  $< 60$  kg
    - \* combined with tenofovir (TDF)
- Give on an empty stomach at least 1 hour before or 2 hours after meals
- *Buffered tablets, give 2 tablets to ensure adequate buffering*
  - EXAMPLE: if the dose is 400 mg, give two 200 mg tablets, *NOT* one 400 mg tablet
- Buffered tablets not suitable for once daily dosing except in patients with renal failure

# Abacavir/Ziagen (ABC)



- Tablet: 300 mg
- 20 mg/ml yellow oral solution



# Abacavir/Ziagen (ABC)



- Adolescent/Adult dosing
  - Oral: 300 mg twice daily
- Give with or without food
- Store at room temperature
- Teach the signs and symptoms of hypersensitivity reaction
- Instruct patients/care givers to telephone immediately if rash occurs
- Provide medication guide and warning card
- \$80 per month

# Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)



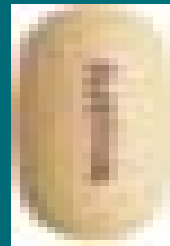
- EFV, Efavirenz (Sustiva) #1
- NVP, Nevirapine (Viramune) #2
- DLV, Delaviridine (Rescriptor)\*

\*Not used in Nigeria (or anywhere else) #536

# Efavirenz/Sustiva (EFV)



- Capsules: 50 mg, 100 mg, 200 mg
- Tablets: 600 mg
- No oral suspension



# Efavirenz/Sustiva (EFV)



- Adolescents and Adults
  - 600 mg once daily
  - Increase to 800 mg once daily if used with rifampicin
- Because of the long half-life of efavirenz, when you discontinue it, continue other antiretroviral medications for three to seven days so as to reduce the likelihood of resistance (NNRTI tail)

# Efavirenz/Sustiva (EFV)

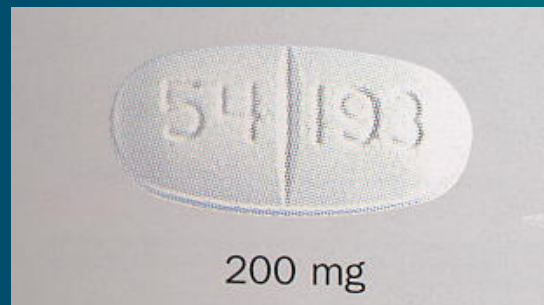


- Can be administered with or without food, but avoid high fat meals
- Capsules can be opened and added to liquids or foods; grape jelly masks the peppery taste well
- Tolerability of CNS side effects can be improved by bedtime dosing

# Nevirapine/Viramune (NVP)



- Oval White tablet 200 mg
- Oral solution 10 mg/ml



# Nevirapine/Viramune (NVP)



- Adolescent/Adult
  - Oral: 200 mg every 12 hours
- INITIATE THERAPY WITH ONCE DAILY DOSING FOR 14 days for ALL patients. If no rash or other problems, then increase to full dose.
- Because of the long half-life of nevirapine, when you discontinue it, continue other antiretroviral medications for three to seven days so as to reduce the likelihood of resistance (NNRTI tail)
- Single dose for Prevention of Mother to Child Transmission