ANTIRETROVIRAL THERAPY

AKSHAY BRIGHT

ROLL NO: 13

GOALS OF ART

- Reduce the viral load to an undetectable level for as long as possible
- Improve the CD4 count to over 200 cells/mm so that severe HIV-related disease is unlikely
- Improve the quantity and quality of life without unacceptable drug toxicity
- Reduce HIV transmission

LIFE CYCLE AND SITE OF ACTION OF ART

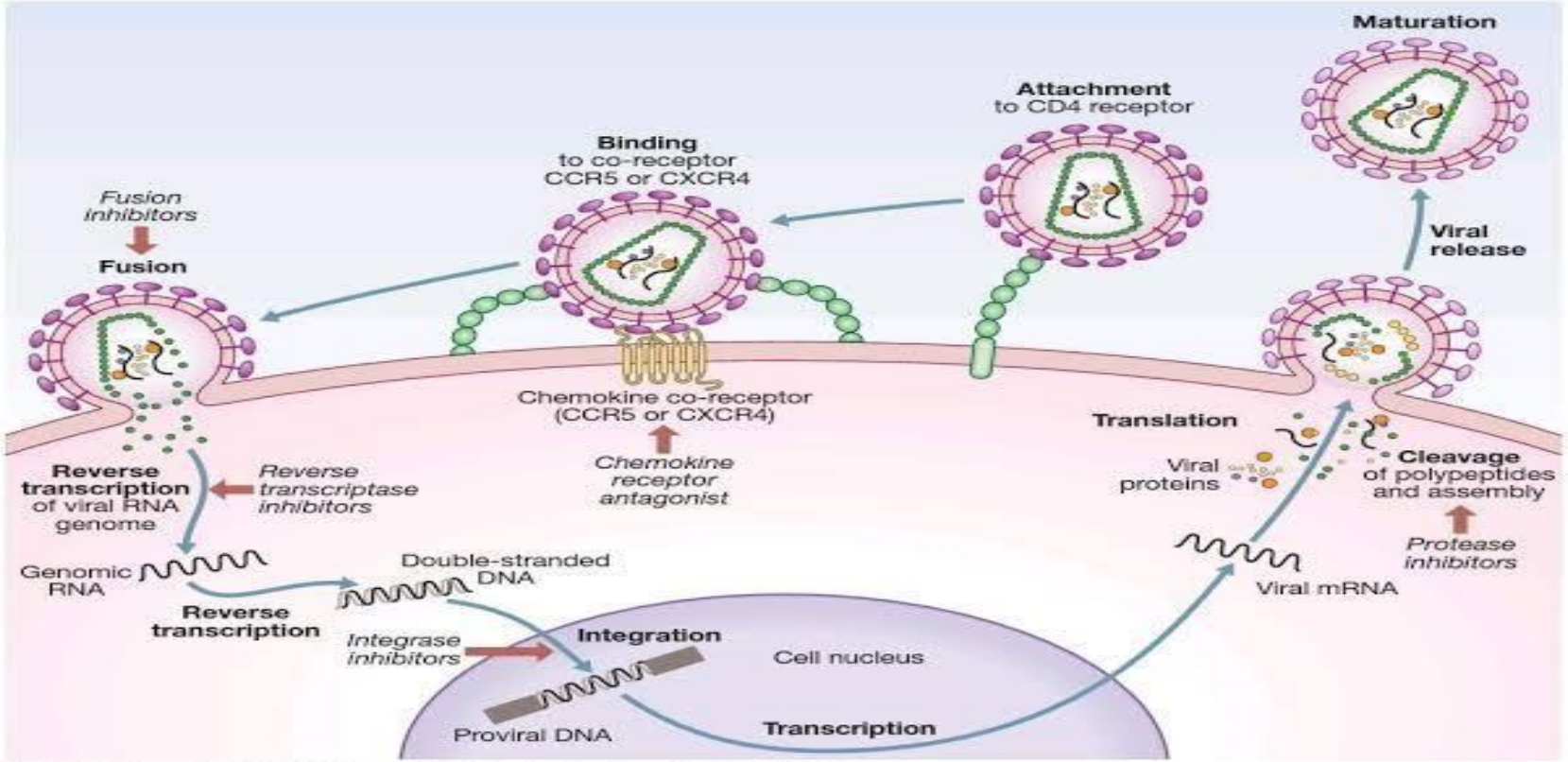

Fig. 12.1 Life cycle of HIV. Red arrows indicate sites of action of antiretroviral drugs.

DRUGS

14.16 Currently preferred antiretroviral drugs

Classes	Drugs
Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir, emtricitabine, lamivudine, tenofovir
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz*, rilpivirine (only if viral load < 100 000)
Protease inhibitors (PIs)	Atazanavir*, darunavir, lopinavir*
Integrase inhibitors	Dolutegravir, bictegravir

*These drugs are no longer recommended as first-line options due to their toxicity.

ANTIRETROVIRAL REGIMENS

- The standard combination antiretroviral regimens are two NRTIs together with an NNRTI, protease inhibitor (PI) or integrase inhibitor.

- The preferred regimen is Tenofovir(TDF, 300mg) + Lamivudine (3TC, 300mg) + Dolutegravir(DTG, 50 mg) as FDC : 1 FDC taken daily
- ABC + 3TC + DTG
- TAF+FTC + BIC

- 2 drug regimen (NRTI + INSTI): 3TC + DTG

LESS PREFERRED REGIMENS:

2 NRTIS + NNRTI:
TAF or TDF + 3TC or FTC + EFV (600 mg)
TDF+3TC+ EFV (400 mg)

2 NRTIS + boosted PI:
TAF or TDF + 3TC or FTC + ATV/r
TAF or TDF + 3TC or FTC + DRV/r

- ABC: Abacavir, 3TC: Lamivudine , DTG: dolutegravir
- TAF : tenofovir alafenamide, TDF : tenofovir disoproxil fumarate
- FTC: Emtricitabine, BIC : Bictegravir

STARTING ART

- ❑ Start ART in all people with confirmed HIV infection, irrespective of CD4 count or clinical status to reduce morbidity & mortality, as well as reducing the risk of transmission.
- ❑ In asymptomatic PLWH, initiating ART on the same day that the diagnosis is confirmed has been shown to improve retention in care.
- ❑ Recognition and management of depression and substance abuse is important.
- ❑ In patients with major opportunistic infections, ART should generally be started within 2 weeks, with two important exceptions:
- ✓ In cryptococcal meningitis, ART should be deferred for 5 weeks,
- ✓ In tuberculosis, ART should be deferred until 8 weeks as earlier initiation increases the risk of IRIS.

MONITORING EFFICACY

VIRAL LOAD

- Baseline should be measured before treatment initiation
- Repeated 4 weeks after starting ART
- Viral load supressed after 6 months
- Repeated 6 or 12 monthly after viral load suppression

CD4 COUNT

- Increases rapidly within the first month
- Gradually increases thereafter
- In the first year, count increases by 100-150 cu/mm3
- Subsequent years, increases by 80 cells/mm3 per annum
- CD4 count is highly variable

ANTIRETROVIRAL RESISTANCE

- Reverse transcription is error-prone, generating many mutations. If the viral load is suppressed on ART, viral replication is suppressed and resistance mutations will not be selected.

- If replication occurs during ART, due to either resistant mutations or suboptimal adherence, mutations associated with resistance to antiretroviral drugs will be selected.

- Antiretroviral drugs differ in their ability to select for HIV resistance mutations. NRTI's/NNRTI's have a low genetic barrier to resistance such that a single mutation will result in resistance.

- PIs and the second-generation integrase inhibitors (bictegravir and dolutegravir) are less prone to resistance, and require multiple mutations to accumulate before the drug's efficacy is lost.

ANTIRETROVIRAL RESISTANCE

- Patients who develop antiretroviral resistance will result in clinical failure if the regimen is not changed, and may transmit resistant virus to others.
- Antiretroviral resistance is assessed by sequencing the relevant viral genes to detect mutations that are known to confer resistance.
- A minimum viral load of 1000 copies/mL (WHO) is required for resistance testing.

ART COMPLICATIONS

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

- IRIS is a common early complication of ART, especially in patients who start ART with CD4 counts below 50 cells/mm 3 .
- IRIS presents either with paradoxical deterioration of an existing opportunistic disease or with the unmasking of a new infection.
- Fever is the most common clinical presentation is often characterized by an exaggerated immune response, with pronounced inflammatory features.

- For example, patients with CMV retinitis developing IRIS on ART develop a uveitis; inflammatory haloes occur around KS lesions.
- Most common disease-causing IRIS – TB
- The management of IRIS is to continue ART and to ensure that the opportunistic disease is adequately treated. Symptomatic treatments are helpful.
- Anti inflammatory therapy with NSAIDs and Glucocorticoids

ANTIRETROVIRAL ADVERSE DRUG REACTIONS

DRUG CLASSES	ADVERSE REACTIONS
Integrase inhibitors	Insomnia , GI symptoms, hyperlipidaemia
NNRTIs	Hypersensitivity rashes Mild neuropsychiatric effects(efavirenz) Hepatotoxicity (Nevirapine)
NRTIs	Nephrotoxicity, Loss of bone mineral density(tenofovir) Rash & peripheral neuropathy (Lamivudine) Skin discolouration in palms & soles (Emtricitabine)
Proteases inhibitors	GI symptoms (nausea, vomiting, & diarrhoea) Dyslipidaemia

HIV AND PREGNANCY

- ART has dramatically reduced the risk of mother-to-child transmission of HIV to less than 1%.
- Screening: All pregnant women should have HIV testing at an early stage in pregnancy.
- All pregnant women with HIV infection regardless of CD4 T cell count should start ART as soon as possible.
- 2 NRTIs+ Integrase inhibitors or PIs preferred
- For women on ART with HIV viral load >1000 copies/mL, IV Zidovudine 2mg/kg at first hour is administered at the onset of labor.

- Caesarean section is associated with a lower risk of mother-to-child transmission than vaginal delivery, but the mode of delivery does not affect transmission risks if the viral load is suppressed on ART
- HIV is also transmitted by breastfeeding.
- There is minimal risk of transmitting HIV by breast feeding in women with a suppressed viral load on ART.
- Providing antiretrovirals to infants (usually nevirapine monotherapy) while they are breastfeeding has been shown to reduce the risk of transmission.
- Infants should be exclusively breastfed for the first 6 months, as mixed feeding (with formula or solids) is associated with a higher risk of transmission.

HIV & TB

- TB is the leading cause of death in patients with HIV as it is most common opportunistic infection.
- Clinical presentation is mostly pulmonary but may also develop extrapulmonary manifestations also.

MANAGEMENT:

- Start ATT first, ART can be started 2-8 weeks later due to risk of developing IRIS
- ART-naïve patient:
  - CD4 counts <50 cells/mm^3: Initiate ART as soon as possible , but within 2 weeks of starting TB treatment
  - CD4 counts ≥50 cells/mm^3: Initiate ART within 8 weeks of starting TB treatment.
- Non-ART-naïve patient:
  ART can be continued as it is, and ATT can be started.

TUBERCULOSIS PREVENTIVE THERAPY

- Either with isoniazid or combinations of rifampicin with isoniazid.
- It is important to rule out active tuberculosis before starting preventive therapy, and symptom screening The usual duration of isoniazid preventive therapy is 6 months.
- Rifampicin or rifapentine combined with isoniazid for 12 weeks.

OPPORTUNISTIC INFECTIONS IN AIDS

Viral

- **Cytomegalovirus (CMV): CMV retinitis.**
- **Human herpes virus 8 (HHV-8): Kaposi's sarcoma.**
- **Human papillomavirus (HPV): Cervical cancer.**
- **Epstein barr virus (EBV): Primary CNS lymphoma.**

Herpes-zoster virus & varicella zoster virus: localised or disseminated

Bacterial

- **Mycobacterium tuberculosis: Pulmonary or extra-pulmonary tuberculosis**
- **Mycobacterium avium complex (MAC): Disseminated infection with multi organ involvement.**

Nocardia: pneumonia, meningitis, disseminated

Salmonella infections: disseminated

Fungal

- Candida: Oropharyngeal and oesophageal candidiasis
- Pneumocystis jirovecii: Pneumonia
- Cryptococcosis: Usually manifests as meningitis
- Histoplasmosis: Disseminated infection

Coccidioidomycosis: Disseminated infection.

Microsporidia: Causes diarrhea.

Protozoal

- Toxoplasma gondii: Toxoplasmosis of brain.
- Cryptosporidiosis: Intestinal infection leading to diarrhea.
- Isosporiasis: Intestinal infection leading to diarrhea

PREVENTION OF OPPORTUNISTIC INFECTIONS

- **Access to safe water-** to prevent cryptosporidiosis, microsporidiosis and cystoisosporiasis
- **Food hygiene-** to prevent salmonella infection and toxoplasma exposure by proper cooking
- **T.B prevention** – by wearing masks, proper ventilation and safe coughing practices
- **Safer sex-** should be practiced among PLWH.
- **Pets**- To prevent toxoplasmosis and cryptosporidiosis, proper handling and handwashing afterwards is important

CO-TRIMOXAZOLE PRIMARY PROPHYLAXIS

- Co-trimoxazole reduces the incidence of several opportunistic infections
- Indications:
  Clinical evidence of immune suppression
  laboratory evidence of immune suppression (CD4 count < 200 cels/mm 3).
- In low-income countries where malaria and/or severe bacterial infections are highly prevalent, the WHO recommends initiating cotrimoxazole regardless of CD4 counts or clinical stage.
- The recommended dose of co-trimoxazole is 960 mg daily.
- Co-trimoxazole prophylaxis can be dis continued when CD4 counts increase to more than 200 cells/mm 3 on ART, except in low-income countries where it should be continued life-long.
- Co-trimoxazole prophylaxis is well tolerated. The most common side-effect is hypersensitivity, causing a maculo-papular rash.
- If co-trimoxazole cannot be tolerated, then dapsone 100 mg daily should be substituted.

PREVENTION OF HIV

14.18 Prevention measures for HIV transmission

Sexual

- Sex education programmes in schools
- Easily accessible voluntary counselling and testing centres
- Promotion of safer sex practices (delaying sexual debut, condom use, fewer sexual partners)
- Effective ART for HIV-infected individuals
- Pre-exposure prophylaxis (PrEP) for high-risk groups
- Male circumcision
- Post-exposure prophylaxis

Parenteral

- Blood product transmission: donor questionnaire, routine screening of donated blood
- Injection drug use: education, needle/syringe exchange, avoidance of 'shooting galleries', methadone maintenance programmes

Perinatal

- Routine 'opt-out' antenatal HIV antibody testing
- Measures to reduce vertical transmission (see text)

Occupational

- Education/training: universal precautions, needlestick injury avoidance
- Post-exposure prophylaxis

PRE-EXPOSURE PROPHYLAXIS

Indications: MSM, heterosexual men & women, IV drug users

Evaluation to be done before PrEP: 4th generation HIV antigen antibody testing, HIV viral load, screening for other STIs, pregnancy test.

PrEP options:

- TDF/FTC (Tenofovir disoproxil/ Emtricitabine)
- TAF/FTC (Tenofovir alafenamide/ Emtricitabine)
- Duration: Daily for 1 month after the last high-risk exposure

Follow up after 1 month & 3 month after starting treatment, and then every 3 months thereafter.

POST EXPOSURE PROPHYLAXIS

- Post-exposure prophylaxis (PEP) is recommended after a potential exposure to HIV after a careful risk assessment, in both occupational and non-occupational settings.
- The first dose should be given as soon as possible.
- The effectiveness of PEP diminishes with time and it is ineffective if given more than 72 hours after exposure.
- Tenofovir together with emtricitabine is the most widely used dual NRTI combination, together with either a PI or an integrase inhibitor depending on ART exposure in the source patient.

POST EXPOSURE PROPHYLAXIS

- Regimen: TDF + FTC + DTG or TDF + FTC + Boosted PI (ATV/r or DRV/r)
  Total duration of PEP: 28 Days

- PEP should not be given if the exposed person is
- HIV-infected.

- HIV antibody testing should be performed 3 months after exposure.

THANK YOU !

REFERENCES:

1. DAVIDSON'S PRINCIPLES AND PRACTICE OF MEDICINE 24TH EDITION
2. ARCHIT BOLOOR