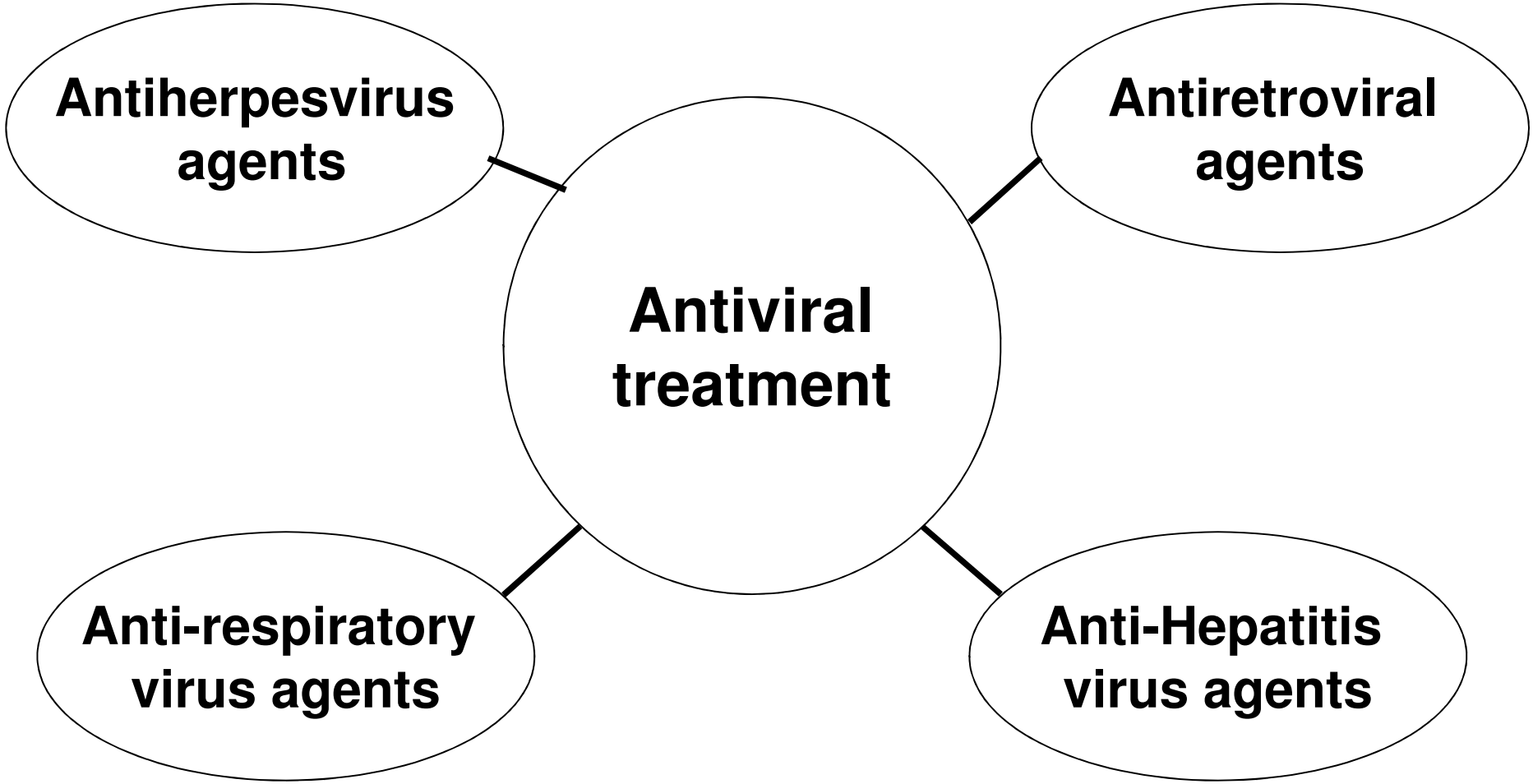
Antiviral Therapy

Antivirals: Classification



- **Herpes simplex virus**
- **Varicella zoster virus**
- **Cytomegalovirus**

Treatment: HSV / VZV

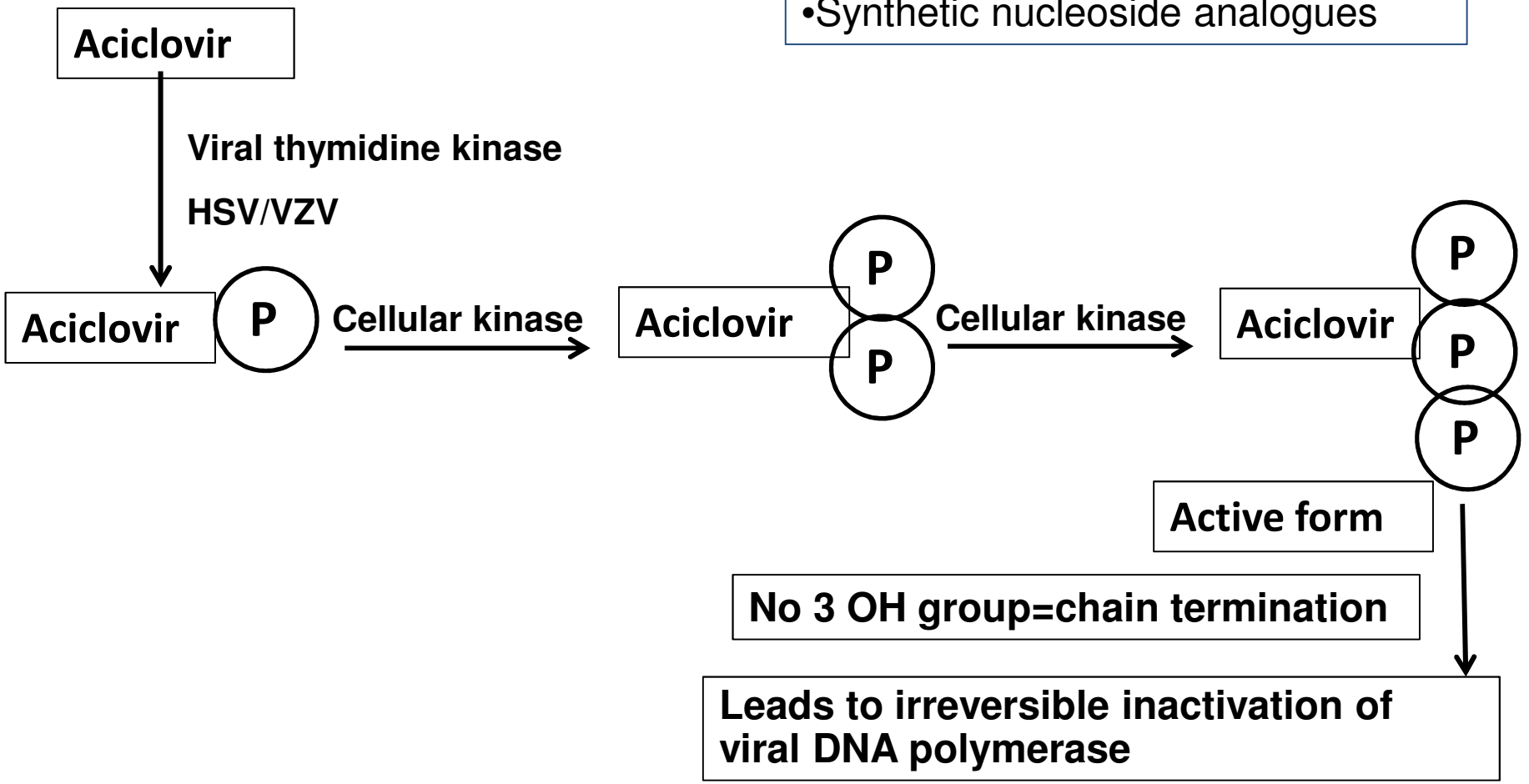
Drug		Active
Aciclovir*	Guanine analogue Topical, oral and IV Well tolerated IV: phlebitis, nephrotoxic if given to fast	HSV/VZV
Valaciclovir*	Prodrug: Aciclovir	HSV/VZV
Penciclovir	Poor bioavailability Topical only: 1% cream	Herpes labialis
Famciclovir*	Prodrug: Penciclovir	HSV/ VZV
Trifluridine*	Topical (eye drops/ cream)	HSV keratitis (2nd line Rx)

***available in SA**

Mechanism of action: Aciclovir

Mechanism of action:

•Synthetic nucleoside analogues



HSV: Aciclovir treatment

- Topical treatment
  - e.g. herpes keratitis
- Oral treatment
  - e.g. herpes labialis, genital HSV
- IV treatment
  - e.g. disseminated, organ involvement (hepatitis, encephalitis), neonatal infection

Varicella: Aciclovir treatment

- Uncomplicated varicella in healthy children < 12 y
  - Treatment only of modest benefit : not routine
- Oral treatment
  - children at increased risk of complicated disease
    - > 12 years old
    - chronic cutaneous or pulmonary disorders
    - taking steroids or salicylates
  - secondary contacts: at increased risk for more severe disease
  - **ALL** adults with varicella (especially pregnant women)
- IV treatment
  - immunosuppressed with complicated or uncomplicated varicella
  - disseminated disease e.g. pneumonia or encephalitis

Zoster: Aciclovir treatment

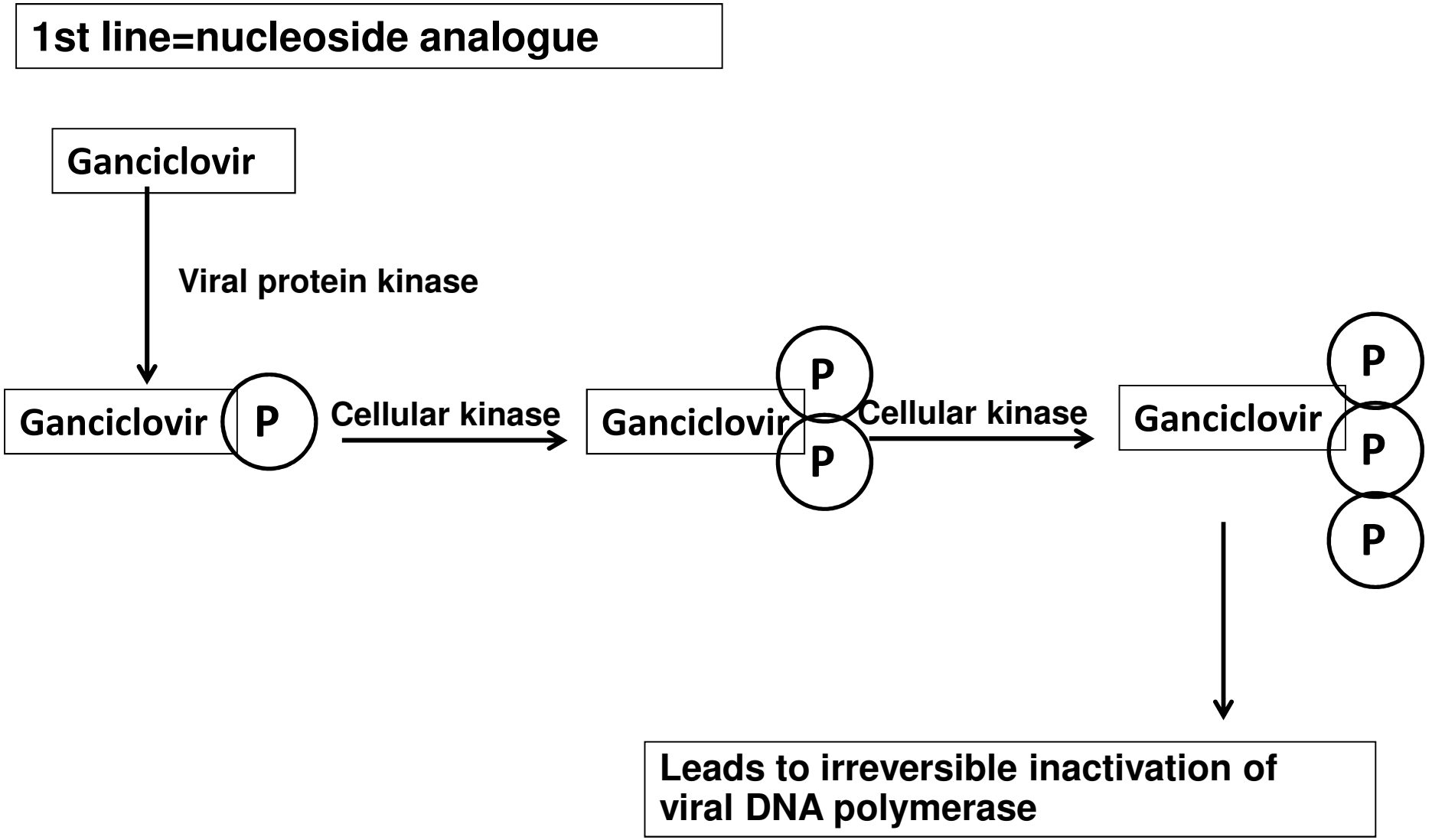
- Initiate treatment within 72h of presentation
- Goals:
  - promote more rapid healing
  - lessen the severity and duration of pain
  - reduce the incidence or severity of post herpetic neuralgia
- Herpes zoster ophthalmicus: needs systemic treatment

CMV treatment

Drug		Active	Side effects
Ganciclovir	100 x > aciclovir activity	CMV	Myelosuppression: neutropenia, plt↓
Valganciclovir	Prodrug: Valganciclovir	CMV	
Cidofovir		CMV	Nephrotoxic
Foscarnet	Organic analogue of inorganic pyrophosphate	CMV, HSV, VZV resistant infections	Nephrotoxic

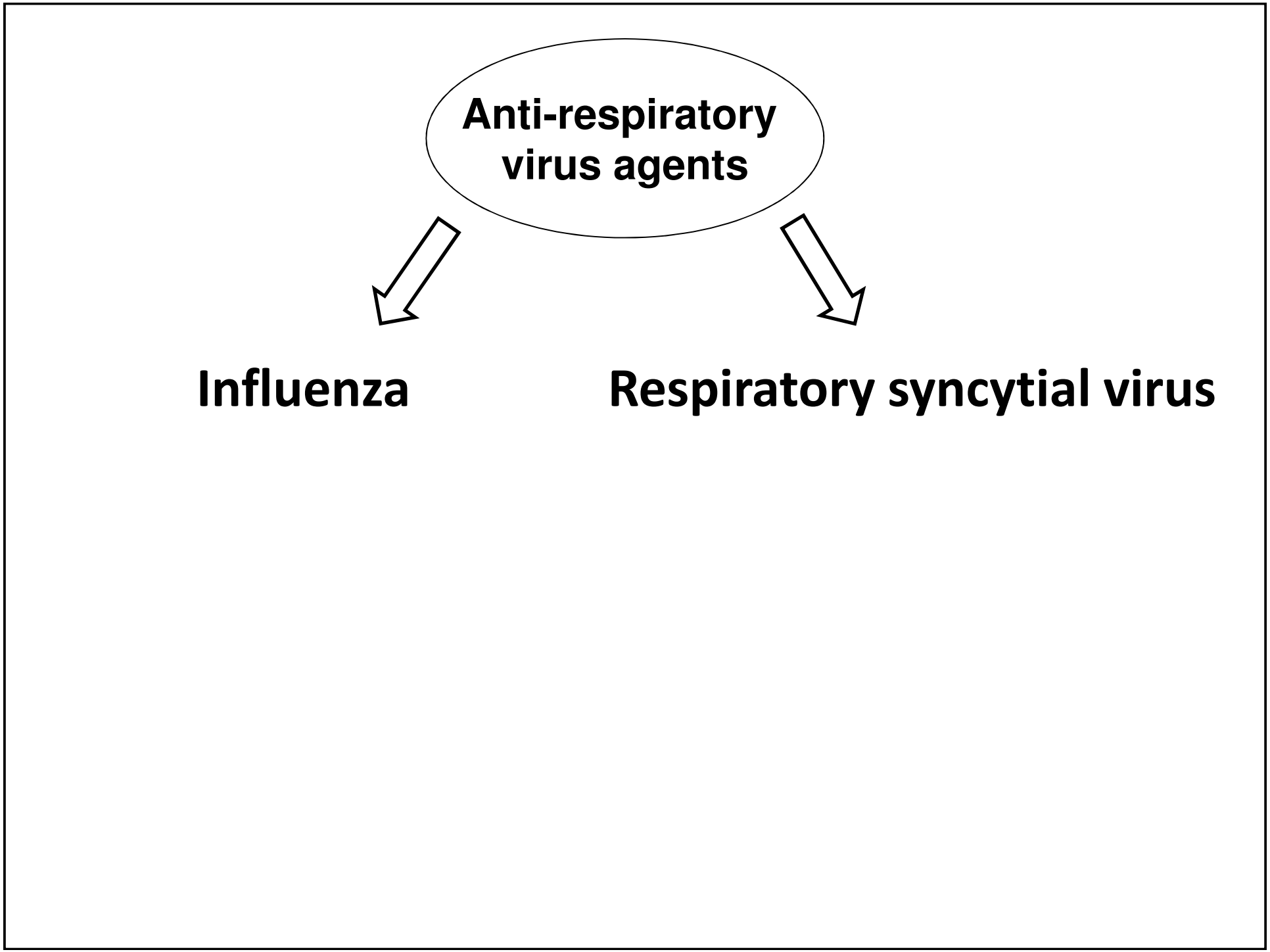
Not in SA

Ganciclovir: Mechanism of action

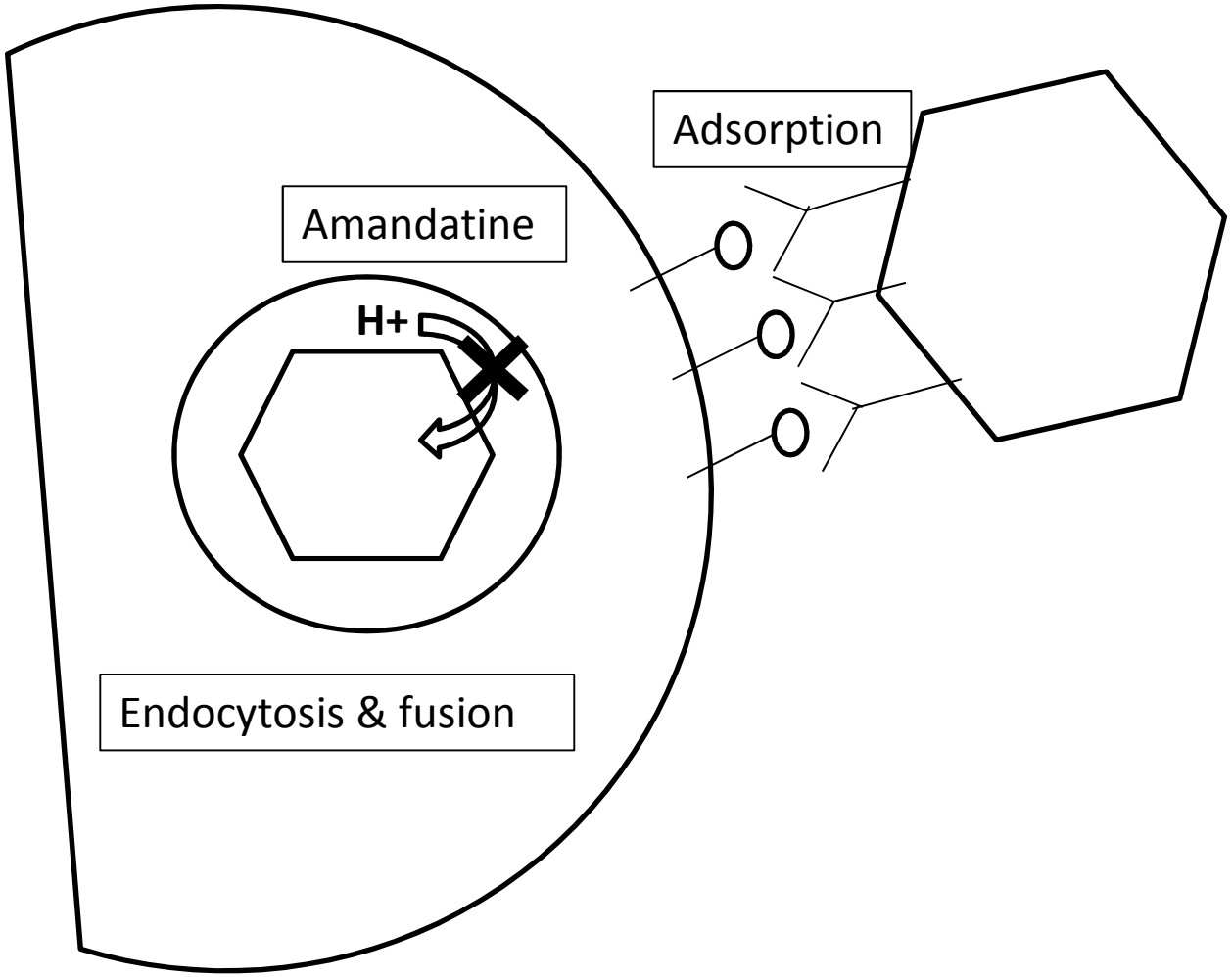


Ganciclovir – indications

- Prevention of CMV disease
  - Transplant recipients
- Treatment of sight- or life-threatening CMV infections in immunocompromised patients
  - CMV retinitis
  - CMV pneumonitis


Anti-respiratory virus agents
Influenza
Respiratory syncytial virus

M2-ion channel inhibitors: Adamantanes



Only influenza A

- e.g. Amantadine
- e.g. Rimantadine

Mechanism: blocks the ion channel of the viral M2 protein→ prevents viral uncoating

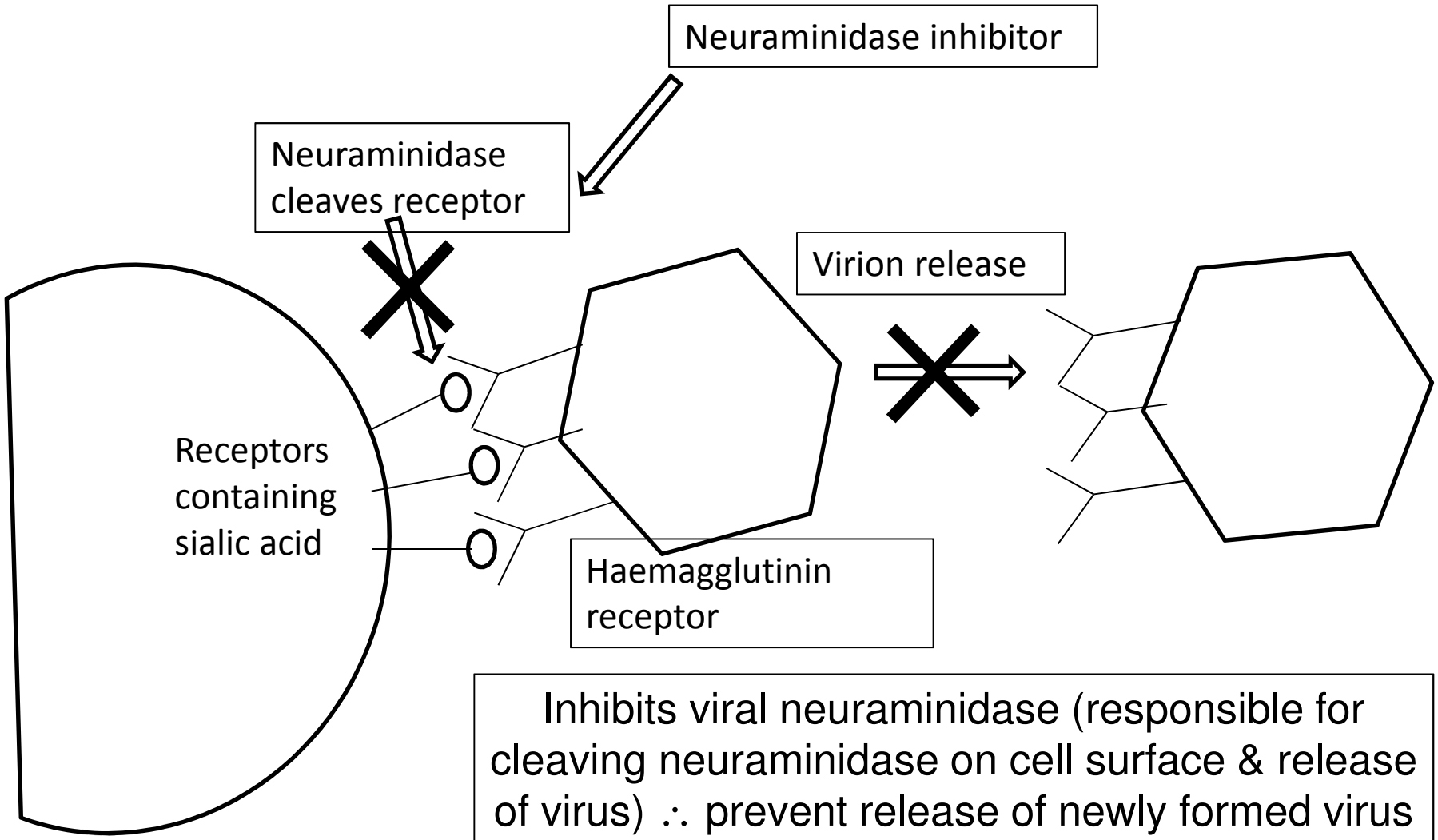
Use limited by increasing resistance

Antivirals used in influenza

2 Types of antivirals

- M2-ion channel inhibitors
- Neuraminidase inhibitor

Neuraminidase inhibitors



Inhibits viral neuraminidase (responsible for cleaving neuraminidase on cell surface & release of virus) ∴ prevent release of newly formed virus from cell surface & limit viral spread

Neuraminidase inhibitors

- Zanamivir (inhalations)
- Oseltamivir (oral)

Prevention is better than cure: Vaccinate

Influenza resistance: October 2012

Influenza	Oseltamivir	Zanamivir	M2 Inhibitors
Pandemic H1N1 2009	Susceptible	Susceptible	Resistant
Seasonal A H3N2	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	No activity

Amantadine and Rimantadine: not recommended currently

SA guidelines: 2013

HEALTHCARE WORKERS HANDBOOK

ON

INFLUENZA

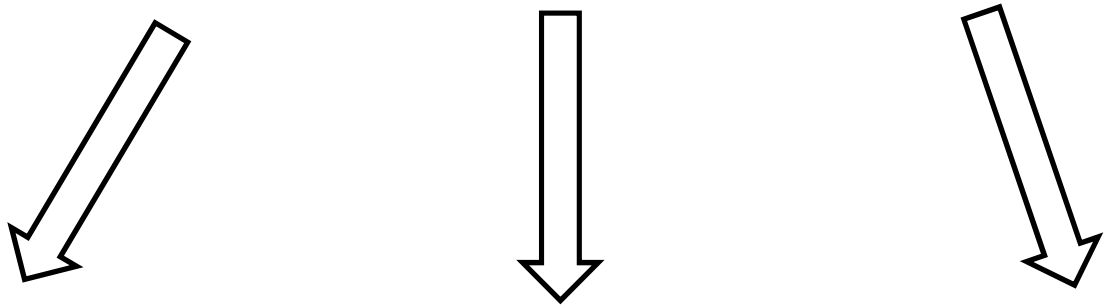
Last updated: April 2013

Handbook: updated yearly (NICD website)

Influenza: Risk factors

- Age
  - infants and young children: <2 years of age
  - Age ≤18 years receiving chronic aspirin
  - Age ≥ 65 years
- Pregnancy
- Chronic diseases eg pulmonary diseases, cardiac diseases, metabolic disorders, renal disease, hepatic disease, certain neurological conditions, neuromuscular etc.
- Immunosuppression e.g. HIV
- Morbid obesity (BMI ≥40)

3 Clinical categories



Influenza like illness (ILI)

Temperature ≥38°C

PLUS 1 or more: sore throat, rhinorrhoea, dry cough, headache, myalgia, malaise, diarrhoea/vomiting

Absence of lower respiratory tract disease signs

Progressive

ILI

PLUS clinical deterioration e.g. shortness of breath, productive cough with bloody or purulent sputum, altered mental state persistence of fever ≥38°C for > 3 days

Complicated/Severe

- Lower respiratory tract disease (e.g. pneumonia)
- Extrapulmonary complications: CNS involvement
- Exacerbation: chronic disease e.g. asthma,
- Other conditions requiring hospital admission e.g. secondary bacterial pneumonia

Category	Treatment
Influenza like illness (uncomplicated)	No risk factors present • Symptomatic treatment eg paracetamol • No routine lab testing Risk factors present • Oseltamivir orally twice per day for 5 days • Consider lab testing
Progressive influenza	• Referral to hospital for supportive care • Oseltamivir: 5 days bd (oral) • Do lab testing
Complicated/Severe influenza	• Referral to hospital for supportive care • Oseltamivir: 5 days bd (oral) • Do lab testing • Antibiotics to cover S. aureus, S. pneumoniae and S. pyogenes (e.g. co-amoxiclav) • Supportive: Oxygen, adequate hydration

- Start oseltamivir within the first 48 hours of symptoms
- Lab testing should NOT delay administration oseltamivir when indicated

Ribavirin: Indications

Hepatitis C virus

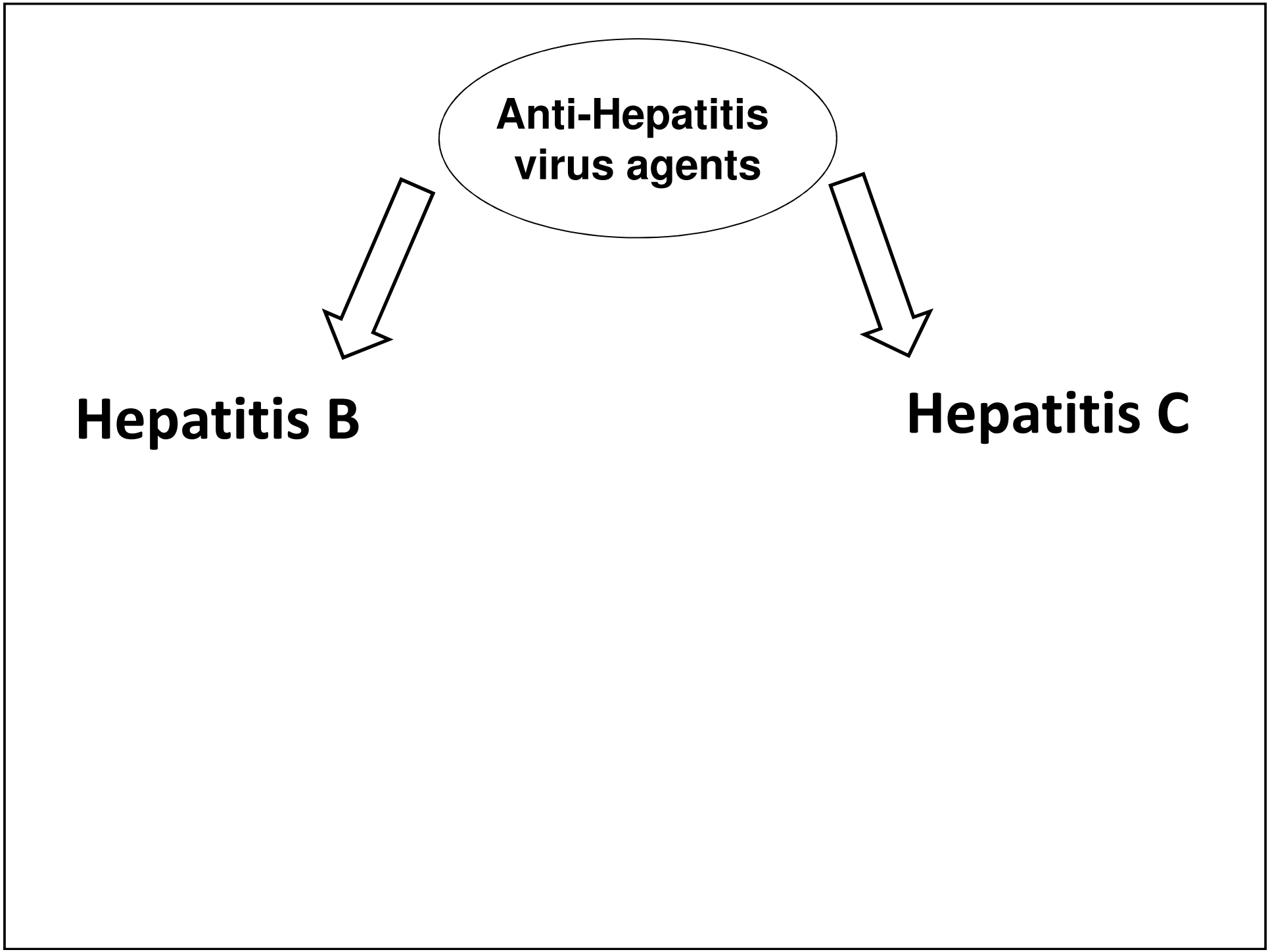
- In combination with pegylated interferon

Respiratory syncytial virus

- Controversial
- Reserved for immunosuppressed patients with severe infection

Certain viral haemorrhagic fevers

- Crimean-Congo Haemorrhagic fever (CCHF)


Anti-Hepatitis virus agents
Hepatitis B
Hepatitis C

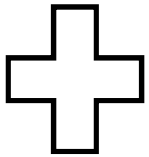
Chronic Hepatitis C

- Objective of treatment
  - To achieve sustained virological response
    - absence of HCV RNA 6 months after the completion of Rx
- Likelihood of sustained virological response
  - Acute hepatitis C: 80-100%
    - With early intervention
  - Chronic hepatitis C
    - Genotype 1: 42-65%
    - Genotypes 2 and 3: 76-88%

Hepatitis C Rx: Adverse events

Peginterferon α-2a:

- Influenza-like symptoms
- Neuropsychiatric side effects
- Haematologic abnormalities
- Induction of autoimmune disorders



Ribavirin

- Haemolytic anaemia
- Teratogenic

Treatment duration depends on the genotype

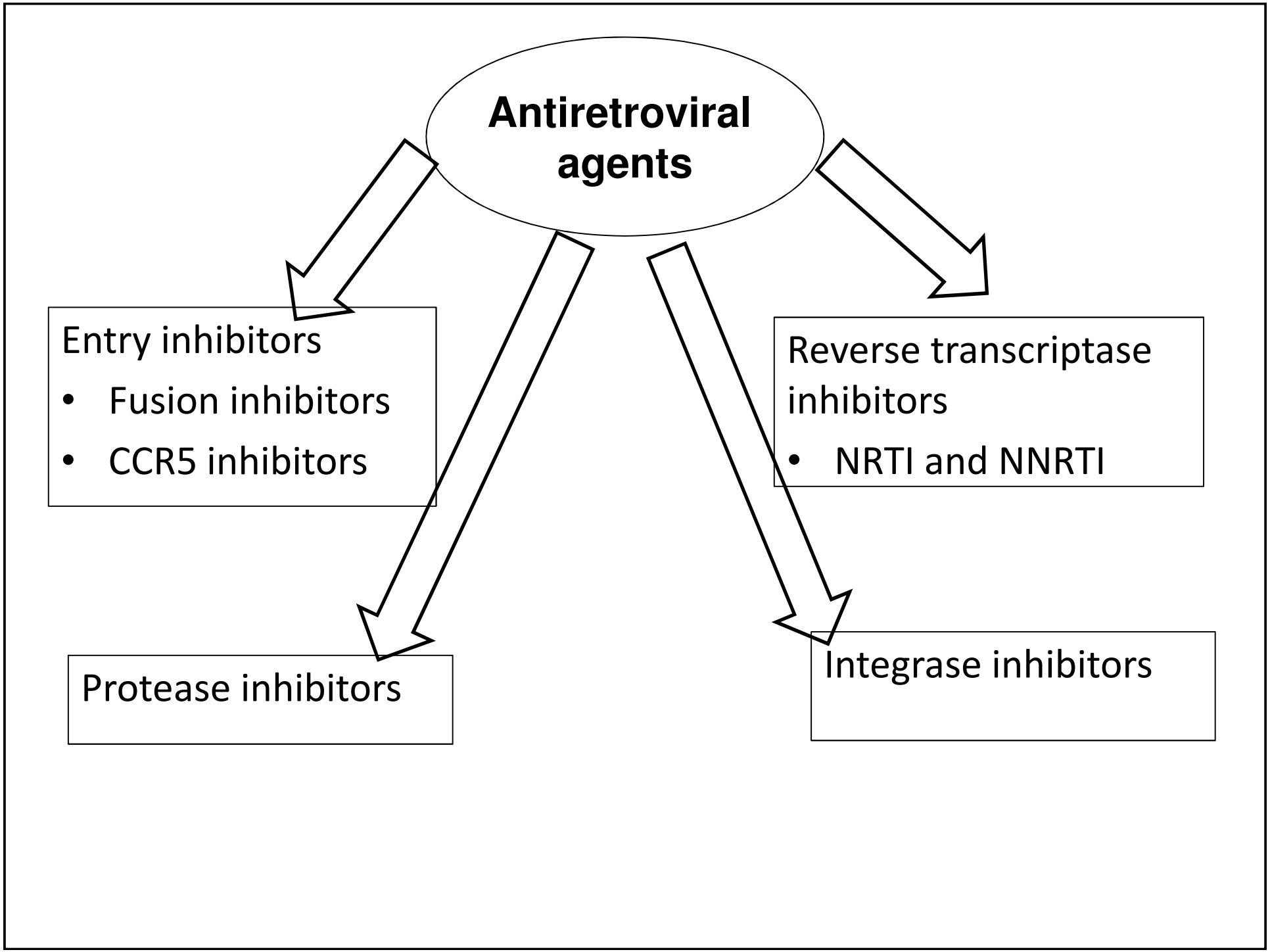
- Gt 1=48w
- Gt 2/3=24w

Chronic Hepatitis B virus (HBV)

- Chronic HBV=Hepatitis B surface antigen positive > 6/12
- Treatment depends on:
  - ALT/AST level: Persistent ↑ AST/ALT
  - Hepatitis B viral load:
    - >20 000 IU if eAg+
    - >2000 IU if eAg-
  - Active histology : severe necro-inflammation on biopsy
- All patients should have an HIV test prior to starting HBV therapy due to some drugs having dual activity against both HIV and HBV

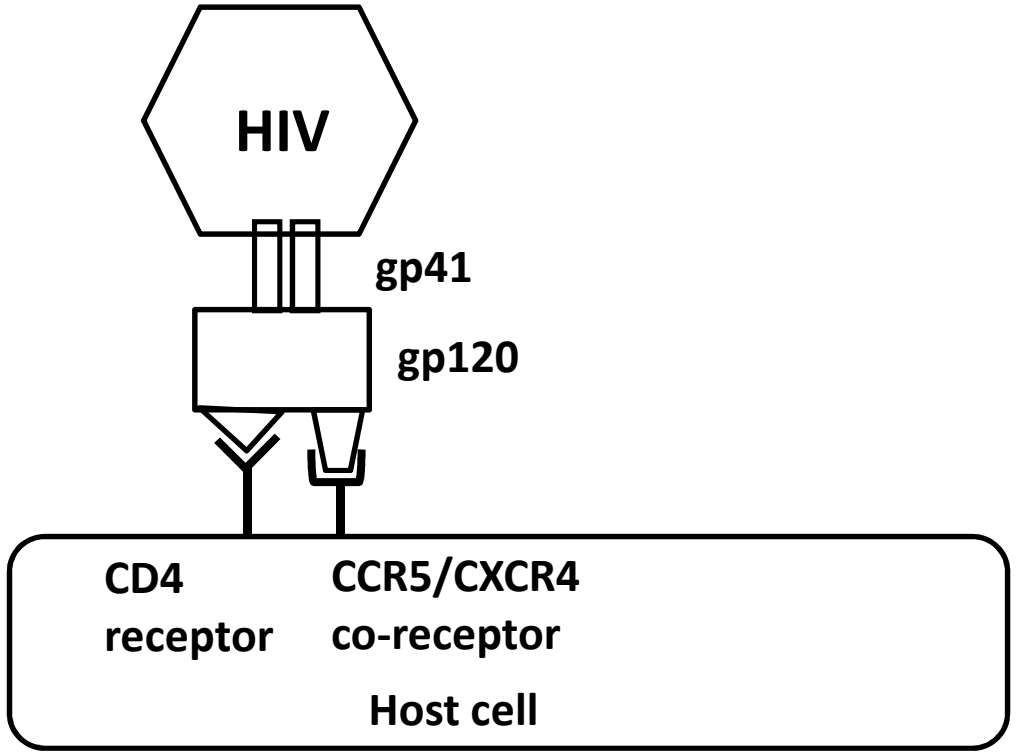
Chronic HBV treatment options

Drug	HIV activity	
Interferon	No	Not in decompensated disease
Entecavir	Possible	Do not use in HIV+ patients
Tenofovir	Yes	Given in combination to Hepatitis B/HIV co infected patients
Lamivudine (3TC) Emtricitabine (FTC)	Yes	


Antiretroviral agents
Entry inhibitors
• Fusion inhibitors
• CCR5 inhibitors
Reverse transcriptase inhibitors
• NRTI and NNRTI
Protease inhibitors
Integrase inhibitors

Entry inhibitors

Enfuvirtide (T-20)	Prevents fusion: interferes with the gp41
Maraviroc	CCR5 antagonist: blocks entry of R5 virus



Nucleoside reverse transcriptase inhibitors (NRTI)

Nucleoside analogues that lack 3’ OH group=Chain termination

Prevents completion of synthesis of the double-stranded viral DNA

Thymidine Analogues

- Stavudine (D4T)
- Zidovudine (AZT)

Cytosine Analogue

- Lamuvidine (3TC)
- Emtricitabine (FTC)

Adenosine Analogue

- Didanosine (DDI)

Guanosine

- Abacavir (ABC)

Possible toxicity/adverse events

AZT: Neutropenia/Anaemia

ABC: Hypersensitivity reaction=never rechallenge

DDI: Lactic acidosis, peripheral neuropathy

D4T: Lactic acidosis, peripheral neuropathy

Nucleotide reverse transcriptase inhibitors (NtRTI)

- Works the same as NRTI's
- E.g. Tenofovir

Nucleoside = sugar +base
Eg Zidovudine

Nucleotide = sugar + base + phosphate
Tenofovir

Possible renal toxicity:

- Check renal function prior to giving TDF=creatinine at baseline, 3,6,12 months, there after every 12 months
- Contraindication to TDF=use AZT

Non-nucleoside reverse transcriptase inhibitors (NNRTI's)

Mechanism of action : binds directly to reverse transcriptase enzyme

1st generation: Efavirenz; Nevirapine
- Low genetic barrier
- Cross-resistance

2nd generation: Etravirine
- Can work with existing resistance to EFV/NVP
- For 3rd line management in resistance by an expert panel

Possible toxicity/adverse events

Nevirapine
- Rash, Stevens-Johnson syndrome
- Hepatotoxicity: CD4>250 in women and CD4>400 in men

Efavirenz
- CNS side effects=not for psychiatric patients and shift workers

Efavirenz: is it safe in pregnancy

- Review of available data provides reassurance that EFV in early pregnancy has not resulted in increased birth defects or other toxicities
- WHO recommends EFV as part of first-line treatment, including pregnant women and those who may become pregnant (June 2012)

Integrase inhibitors

• Mechanism of action: block the integration process that is, the insertion of reverse-transcribed viral DNA into host DNA

•Recommended for 3rd line treatment in cases of resistance by an expert panel only

•E.g. Raltegravir (RGV)

Protease inhibitors (PI's)

- High genetic barrier to resistance
- Inhibit HIV protease enzyme → prevents cleavage of viral polyproteins → immature non-infectious HIV viral particles

Lopinavir/Ritonavir (LPV/r) *Used in 2nd line in adults *Used in 1st or 2nd line in children	Metabolic side effects • Hyperlipidaemia • Hyperglycaemia
Atazanavir/Ritonavir *Used in special cases only	If patient severe dyslipidemia or diarrhea on LPV/r
Darunavir *Used as 3rd line by an expert panel only	2nd generation PI Useful in causes with resistance

South-Africa: 2013 Adult guidelines

- CD4 count <350 cells/mm^3 irrespective of WHO clinical stage

OR

- Irrespective of CD4 count
  - All types of TB
  - HIV positive women who are pregnant or breast feeding

OR

- Patients with Cryptococcus meningitis or TB meningitis (defer ART for 4-6 weeks)
- WHO stage 3 or 4 irrespective of CD4 count

South-Africa: 2013 Adult guidelines

1st line

TDF+FTC/3TC+EFV

All new patients including pregnant women

Fixed drug combination

*Contraindication to:

EFV use NVP

TDF use AZT

TDF &AZT use D4T

Failing

2nd line

AZT+3TC+LPV/r

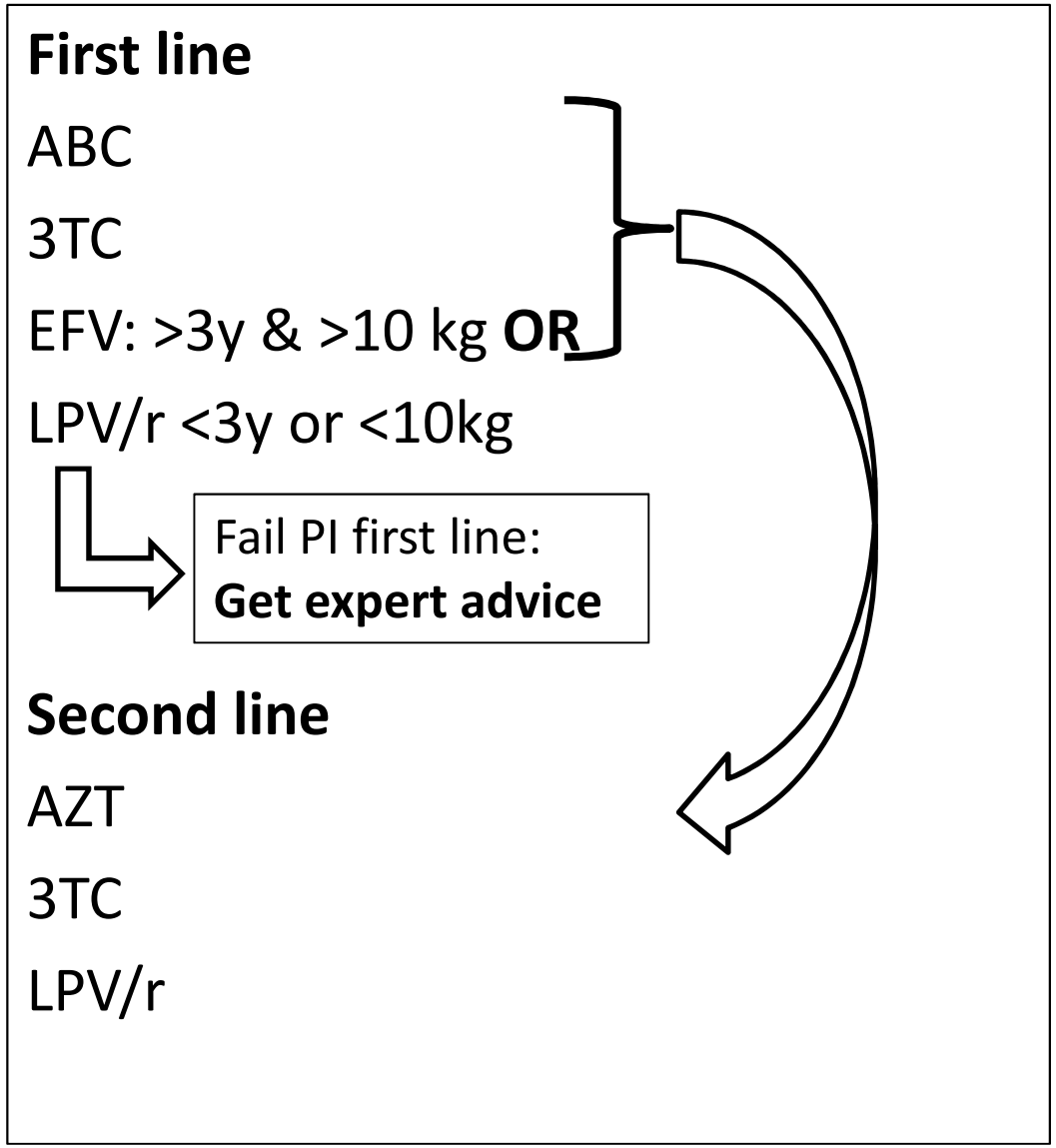
Failing

3rd line

Expert designed regimen that uses resistance testing e.g. Raltegravir/Darunavir/Etravirine

South Africa: 2013 Children guidelines

- All children < 5 years of age, irrespective of CD4
- Children 5-15 years with WHO clinical stage 3 or 4 or CD4 <350 cells/mm^3



Useful resources

Department of Health website:

South African Antiretroviral treatment guidelines 2013:

http://www.doh.gov.za/docs/policy/2013/ART_Treatment_Guidelines_Final_25March2013.pdf

NICD website:

Healthcare workers handbook on influenza: April 2013

http://www.nicd.ac.za/assets/files/Healthcare%20Workers%20Handbook%20on%20Influenza%20in%20SA%20-10%20April%202013final%20_2_.pdf