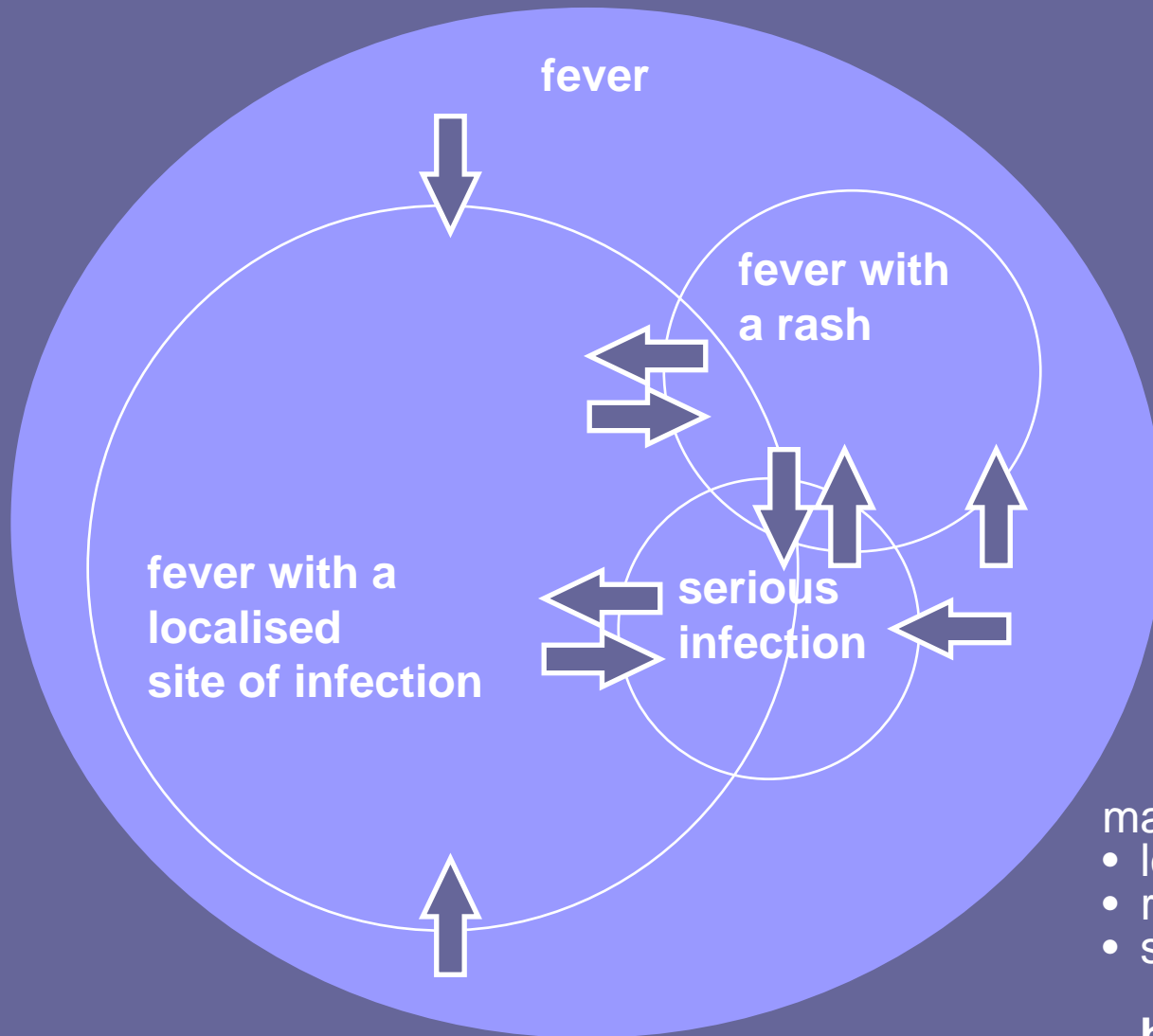


# Viral infections

# Childhood infections



- many infections lack
- localisation
  - rash
  - severe complications

**...but these may evolve**

# Plan:

- Exanthems

- Measles
- Rubella
- Mumps
- Parvovirus

- *Herpesviridae*

- EBV
- CMV
- HHV6
- VZV
- HSV

- Enteroviruses

- Echo
- coxsackie

- Retroviruses

- HIV
- HTLV

- Miscellaneous

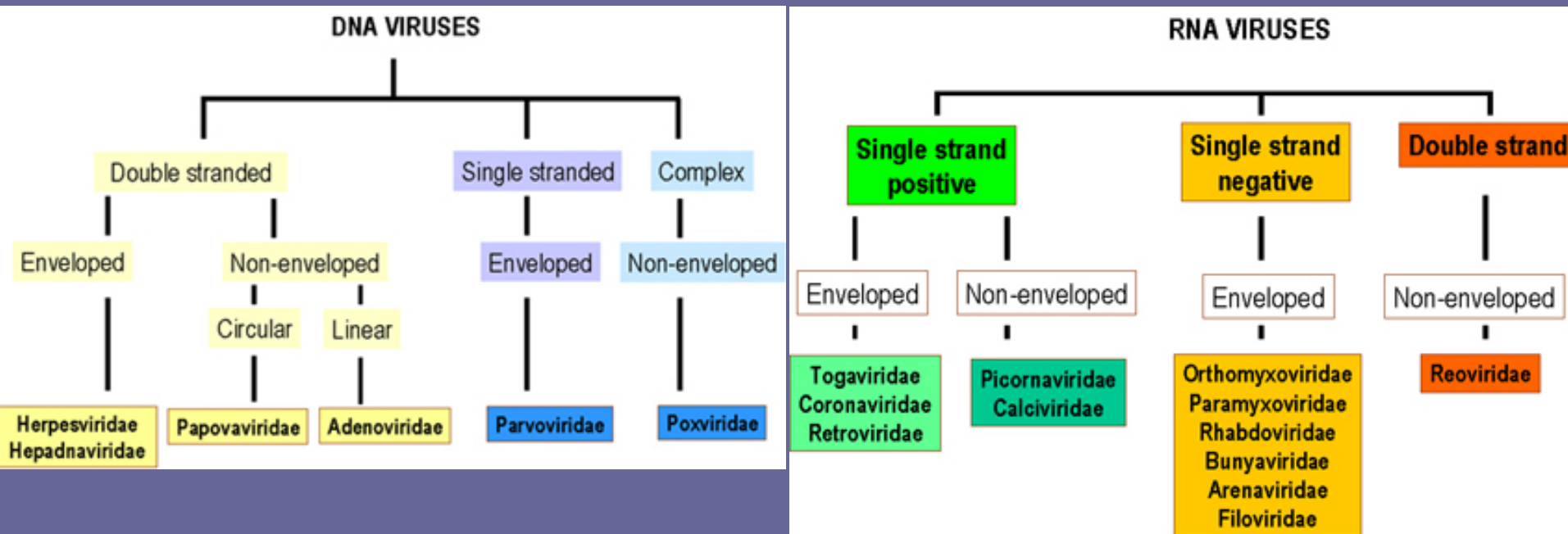
- Molluscum
- HPV
- adeno



**Fever  
with a  
blotchy  
or  
spotty  
rash**

- measles
- rubella
- erythema infectiosum (parvo)
- roseola infantum (HHV6)
  
- scarlet fever
- erythema multiforme
- Kawasaki disease
- systemic JCA (Still's)
- allergy

# Virus classification



# Common viral pathogens in childhood

## (1) DNA viruses

### *typical manifestation*

- Pox viruses
  - molluscum contagiosum      benign skin nodules
- Herpes viruses
  - HSV 1      stomatitis
  - HHV 6      roseola infantum
  - varicella zoster      chickenpox
  - cytomegalovirus      congenital infection
  - Epstein-Barr virus      infectious mononucleosis
- Adenoviruses
  - many serotypes      URTI
- Small DNA viruses
  - parvovirus      erythema infectiosum

# Common viral pathogens (2)

## RNA viruses

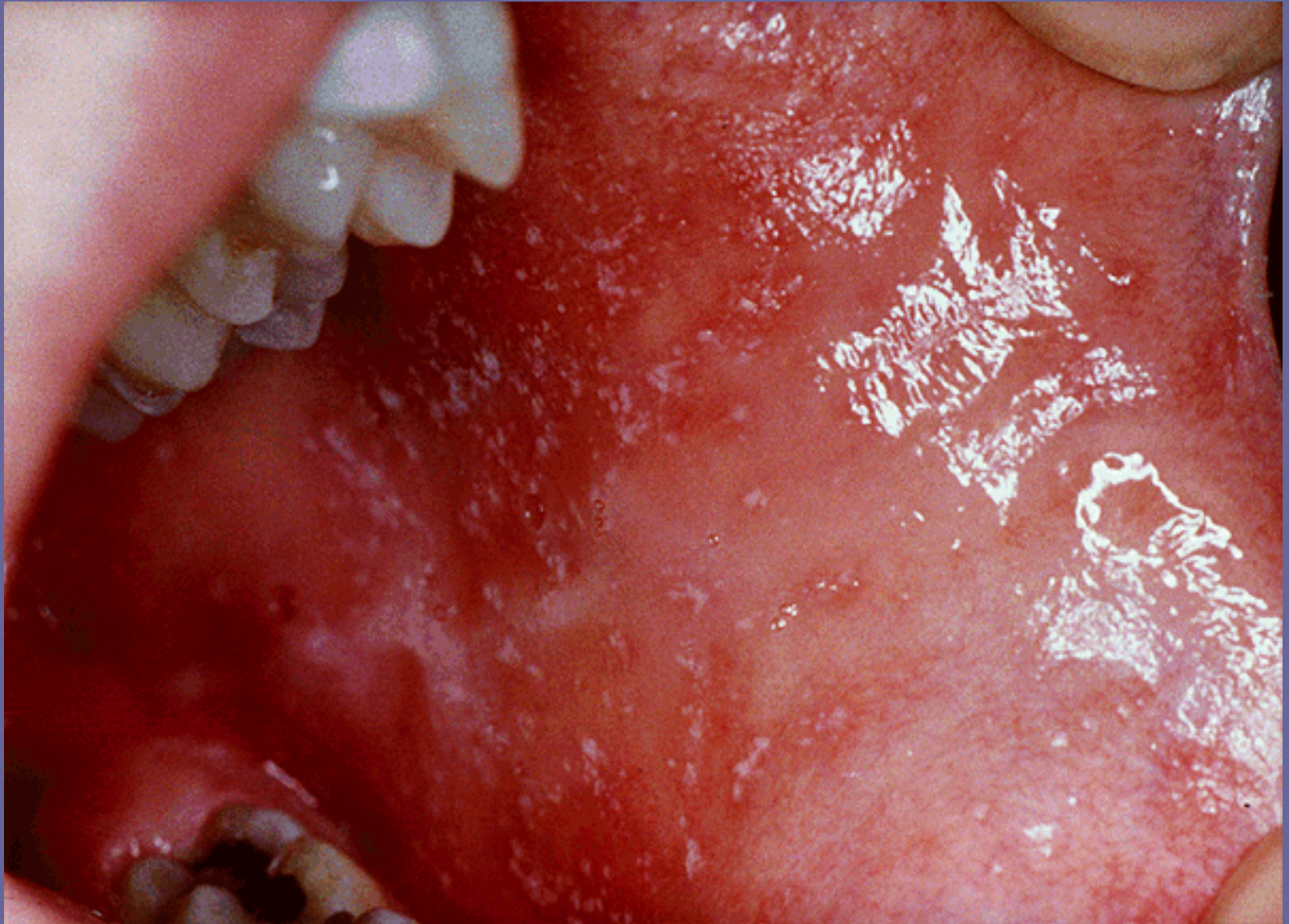
<b>'childhood fevers'</b>	<ul style="list-style-type: none"><li>■ rubeola (<b>measles</b>)</li><li>■ rubella (German measles)</li><li>■ mumps</li></ul>
<b>respiratory infection</b>	<ul style="list-style-type: none"><li>■ rhino</li><li>■ respiratory syncytial virus</li><li>■ influenza</li><li>■ parainfluenza</li></ul>
<b>diarrhoea</b>	<ul style="list-style-type: none"><li>■ rotavirus</li><li>■ Norovirus</li></ul>
<b>enteroviruses</b>	<ul style="list-style-type: none"><li>■ coxsackie</li><li>■ echo</li><li>■ polio</li></ul>
<b>other important viruses</b>	<ul style="list-style-type: none"><li>■ human immunodeficiency virus</li><li>■ dengue</li></ul>





7 year old boy

- cough
- fever
- sore eyes



# Measles

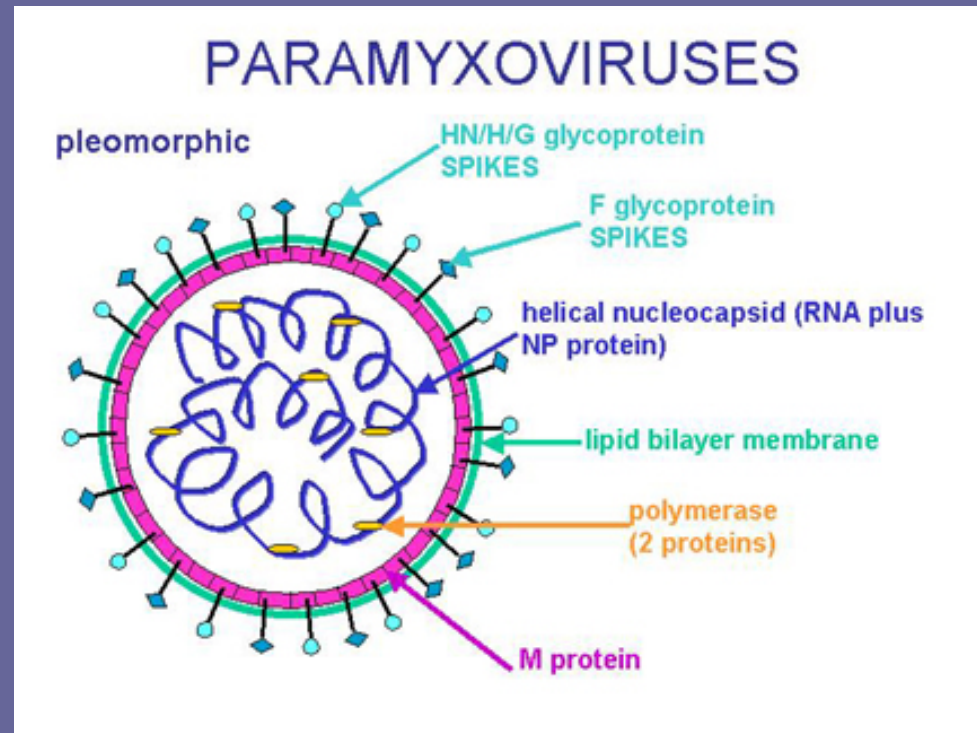
- Highly contagious acute viral illness due to a paramyxovirus and characterise by classic triad:
  - Cough
  - Coryza
  - Conjunctivitis

# Measles: epidemiology

- Endemic worldwide
- Kills ~1 million each year
- 2-3 yearly epidemics in non-vaccinated populations
- Temperate climates max late winter-early spring
- Peak susceptibility infants and y children
  - 40% < 16m

# Measles: aetiology

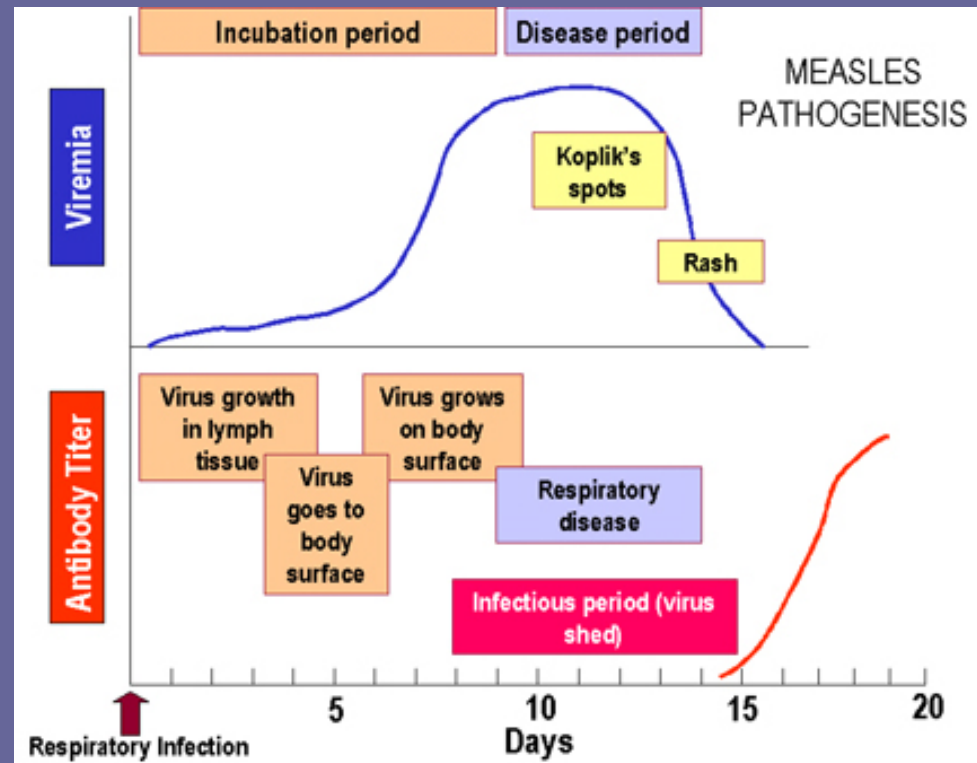
- Paramyxovirus
- ssRNA
- Minor antigenic shifts only seen
- External proteins:
  - H- haemagglutinin
  - F- fusion
  - Envelope proteins



# Measles: pathogenesis

## ● Transmission - aerosolised respiratory secretions

- Max infectivity prodrome to d4 of rash
  - from 7-10 days after contact
- Stable for at least 1hr fomites
- Invades/replicates nasopharynx
  - →spreads to regional lymphatics
  - 2° viraemia d5-7 after exposure (esp PBMCs)
  - Dissem replication d7-14
  - Immunity 15-17 d after exposure





# Measles: common features

## 3-4 days of URTI-like symptoms

- fever, coryza, cough
- conjunctivitis
- lymphadenopathy
- Koplik's spots

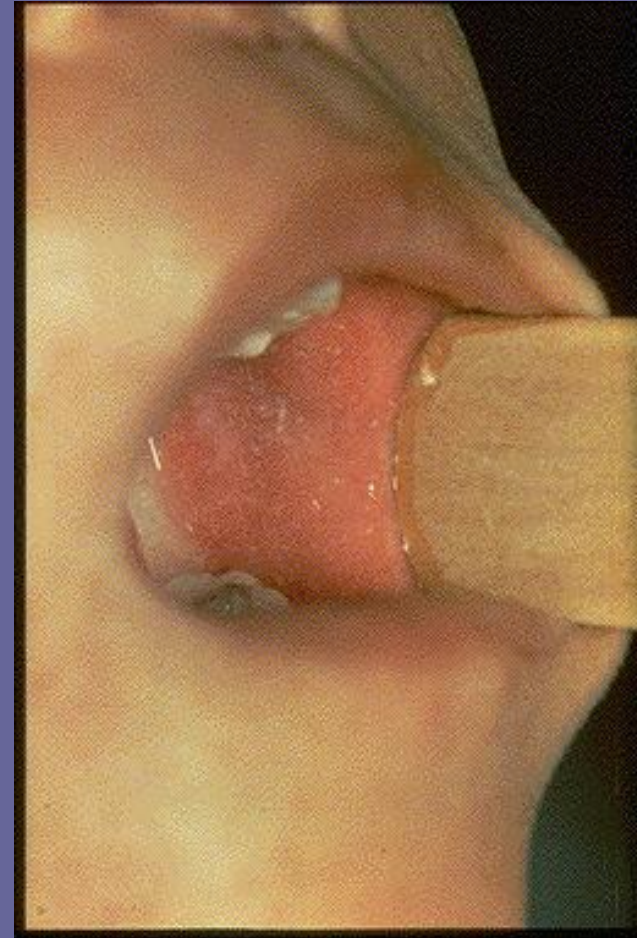
## followed by rash

- florid, blotchy
- starts on head & neck, spreads to whole body

# Measles: clinical picture

## ● Typical:

- Incubate 8-12d
- Prodrome
  - Fever, cough, non-purulent conjunctivitis, coryza
- Koplik's spots within 2-3d
  - Anywhere buccal mucosa
    - Classically opposite lower premolars 12-72hrs
    - Coalesce
- Rash ~14 days after exposure
  - Forehead/post occipital
    - Spreads over 3 days to trunk & extremities
    - Confluent higher up





# Measles



# Measles: exanthematous phase

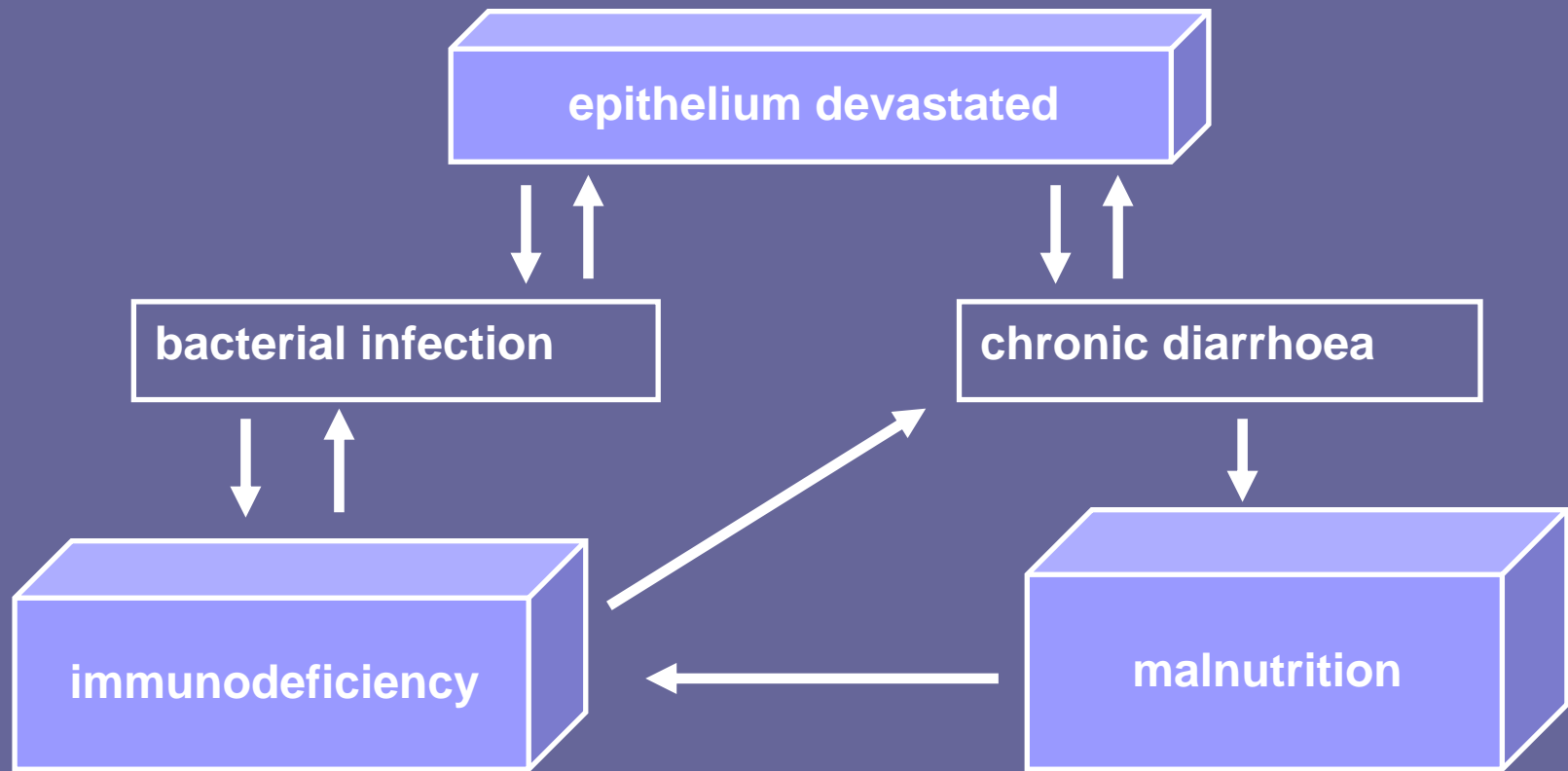
- high fever peaks 2-3 d after rash appears
  - If persisting think 2° bacterial infection
- Occas GI Sx- diarrhoea major Cx in developing countries
- Severe haemorrhagic measles
  - Pneumonia, seizures, DIC, mucosal bleeds
- Can get milder modified measles post exposure if given Ig (longer incub)

# Measles: Cx

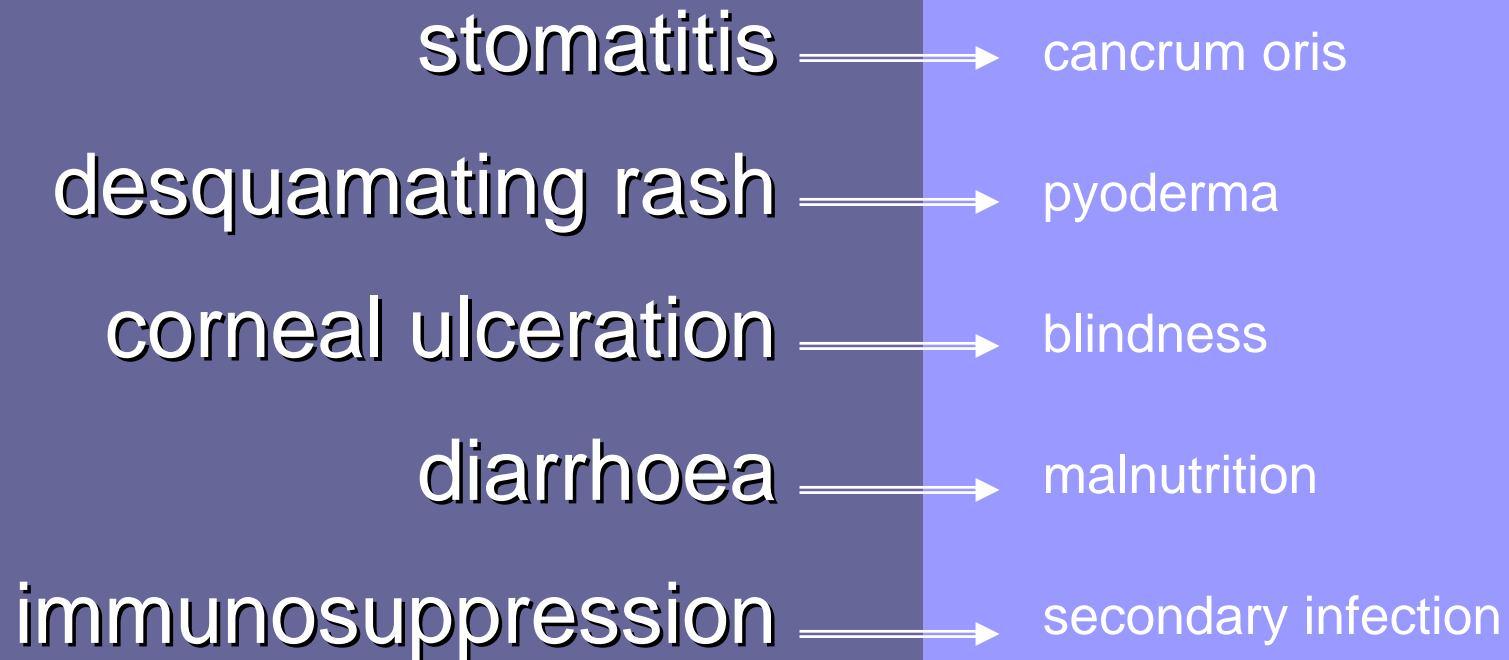
- 1 in 1000 †
  - Usually LRTI (60%) or encephalitis
- stomatitis
- AOM 7-9%
- LRTI – viral extension or bacterial 1-6%
- Developing: mastoiditis, pneumonia, diarrhoea
- Thrombocytopenia, hepatitis, appendicitis etc

# Measles is a major cause of childhood mortality in developing countries

In some parts of Africa the case fatality rate is as high as 30%.



# Measles: complications in the malnourished child



# Measles encephalitis

## Acute:

- 0.1-0.01%
- 2-6 days after rash starts
  - Mild in most, 15% severe, 25% sequelae
- Pleocytosis

## SSPE

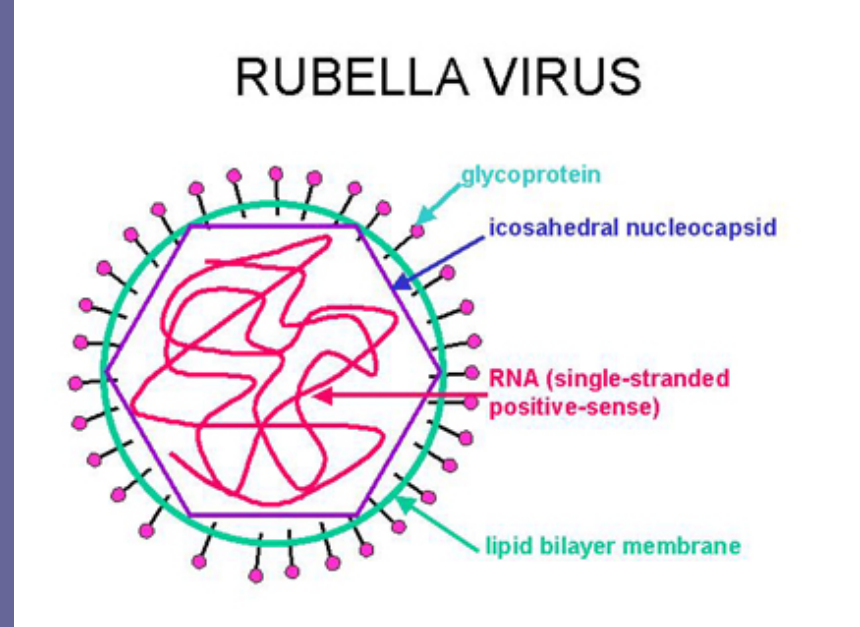
- If wild infection b4 2yo, M>F
- Sx usually ~10 years after infection
- Slow behav and intellectual deterioration
  - Then myoclonic seizures, 6-9 months to death
- EEG: burst suppression

# Measles Mx:

- Vaccine may be protective if within 72 hrs
- Resp isolation until 5 days after rash
- Vitamin A
  - Decreases diarrhoea and pneumonia

# Rubella

- togavirus, ssRNA
- Only one antigenic type
- resp transmission (n-p)
  - Day 3-8 after exposure, lasts 11-14 days
- Active replication throughout body d8-14
- Rare in vaccinated populations
  - Immigrants increased risk incl SEA
- Immunity lifelong- Ab and CMI
  - Reinfection rarely causes cong rubella







# Rubella: common features

generally a mild illness

- fever
- pink macular rash
- generalised lymphadenopathy  
(suboccipital nodes)
- URTI

# Rubella complications

These are rare in children:

- thrombocytopaenia
- encephalitis
- arthritis

Main risks are in first  
3 months of pregnancy:

- abortion
- severe birth defects



## CONGENITAL RUBELLA

- ⑥ deafness
- ⑥ heart defects
- ⑥ mental retardation
- ⑥ cataracts / retinopathy
- ⑥ thrombocytopaenia
- ⑥ hepatosplenomegaly
- ⑥ bony lesions

# Acquired Rubella

- 'Rash and suboccipital lymphadenopathy'
- Prodrome d10-20: fever, eye pain, sore throat, arthralgia
- Rash d14-21: start face, cephalocaudal spread over 24h, fades over 2-3d (m-p, but can vary)
  - Can be pruritic in adults
- Adenopathy- up to 1w before rash
  - Suboccipital and post auricular



# Congenital rubella

## ● Risk inversely related to gestation

- 80% exposed in TM1 have defects
- Almost none after 16/40

## ● Transient:

- Thrombocytopenia, hepatosplenomegaly, IUGR, bone lesions
  - Lymphadenopathy, hepatitis, haemolytic anaemia, pneumonitis, cloudy corneas,

## ● Permanent:

- Deafness, pulmonary stenosis, PDA, VSD, retinopathy, cataract, microphthalmia, UDT, inguinal hernia, IDDM

## ● Delayed:

- SNHL, periph PS, MR, language defects, IDDM, immune complex disease, hypogammaglobulinaemia
  - hypothyroidism

# Congenital rubella



## ● Ix baby

### ■ Excretion

- ceases by 12m in 90%
- Dx cult from n-p, blood

### ■ Serol:

- IgM FPs
  - (Rh factor or maternal IgG)

## ● Ix: Maternal

### ■ EIA IgG,A,M

- Fourfold rise or single IgM
- IgM may not be detectable until 1-2w after rash
- May go 3w after rash

# Parvovirus B19

- Erythema infectiosum, fifth disease
- ssDNA, resp droplet spread
- 50% 2° infection rate in households
- Single type
- Erythrocyte P antigen is receptor for virus
  - Also found in myocardium, endothelium, placenta, megakaryocyte, foetal liver
- Some effects direct, some immune
- Normal kids:
  - (Direct) Mild fever d8, rash d17-18
    - Slapped cheek, spreads extremities lacy reticular
  - (Immune) arthralgia 3w (asymmetrical)



# Parvovirus B19

## ● Normal hosts Cx:

- HSP, vasculitis
- Arthropathy
- Neuropathy, meningitis
- Transient anaemia, thrombocytopaenia, neutropenia

## ● Haemoglobinopathy

- Pure red cell aplasia
- Transient aplastic crisis

## ● Immunosuppressed

- Can affect all haem cell lines

## ● Pregnancy

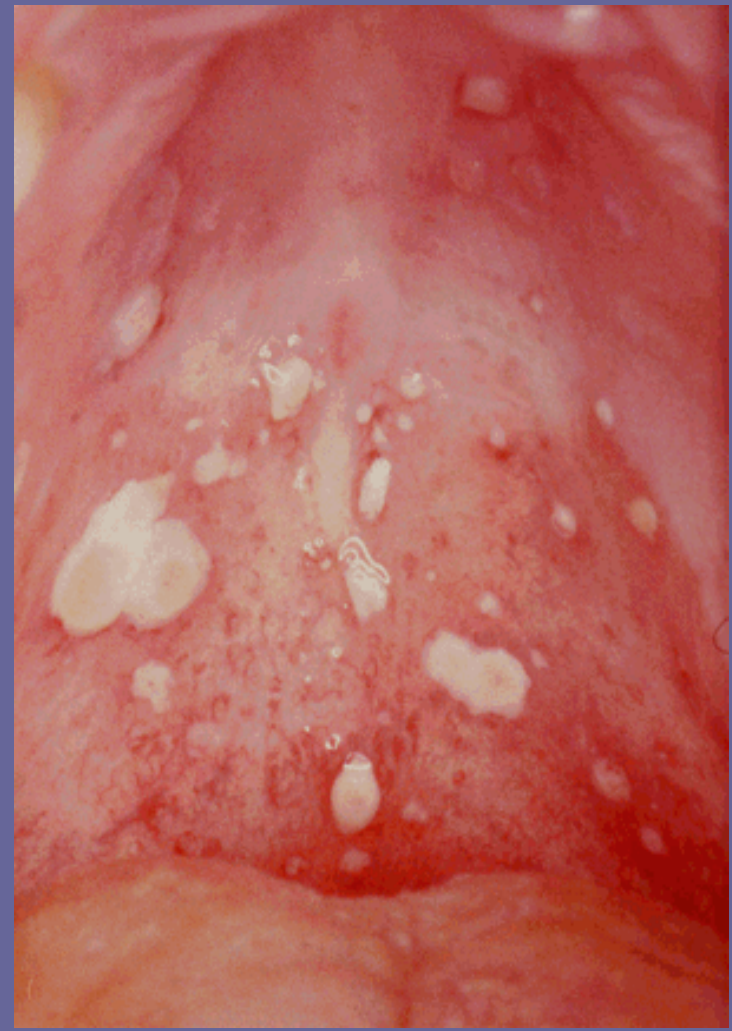
- ~30% foetuses infected
- ~50% women susceptible
- ~6% risk of catching in community outbreak
- Death <10%, mainly TM2
  - Spon abortion
  - Still birth
  - Non-immune hydrops

# Herpesviruses

		Target cell	Latency	Transmission
1	Herpes simplex-1 (HSV-1)	Mucoepithelia	Neuron	Close contact
2	Herpes simplex-2 (HSV-2)	Mucoepithelia	Neuron	Close contact usually sexual
3	Varicella Zoster virus (VSV)	Mucoepithelia	Neuron	Contact or respiratory route
4	Epstein-Barr Virus (EBV)	B lymphocyte, epithelia	B lymphocytes	Saliva
5	Cytomegalovirus (CMV)	Epithelia, monocytes, lymphocytes	Monocytes, lymphocytes and possibly others	Contact, blood transfusions, transplantation, congenital
6	Herpes lymphotropic virus	T lymphocytes and others	T lymphocytes and others	Contact, respiratory route
7	Human herpes virus-7 (HHV-7)	T lymphocytes and others	T lymphocytes and others	Unknown
8	Human herpes virus-8 (HHV-8) Kaposi's sarcoma- associated	Endothelial cells	Unknown	Exchange of body fluids?




5 year old with fever and rash



# Fever with vesicles

- chickenpox
- herpes simplex
- hand, foot and mouth

# Chickenpox common features



incubation  
14 - 16 days

- moderate fever
- crops of vesicles
  - macule > papule > vesicle > scab
  - typically trunk and face more than limbs
  - may occur in mouth
  - sometimes become **bacterially infected**

# Chickenpox: complications

- In normal children Cx rare (apart from 2° infection)
  - encephalitis (espec. cerebellar ataxia)
  - pneumonia (leaving calcifications on CXR)
  - haemorrhagic form
- Can be fatal in immunosuppressed patient
  - prophylaxis with zoster immune globulin (ZIG)
  - treatment with intravenous acyclovir
- Congenital infection
  - risk highest if mother is incubating infection just before or after delivery (transmission rate 25%)
  - give ZIG at birth
- Shingles in elderly and immunosuppressed
- Aspirin + VZV = risk factor Reye's syndrome

# CMV

- dsDNA herpes virus
- Latency: viral genome persists as episomal
- Present all human (only) populations
  - There are non-human CMV species
- No seasonal variation
- Early acquisition developing nations & DCC
  - 50-70% children in DCC infected
- Most common cause congenital infection

# CMV transmission

- Direct or indirect person-to-person contact
- Close or intimate contact with secretions

# CMV transmission

- Direct or indirect person-to-person contact
  - No aerosol spread
- Close or intimate contact with secretions
  - Urine
  - Semen
  - Tears
  - Blood
  - Oropharyngeal secretions
  - Cervicovaginal secretions
  - Breast milk
  - Transplanted organs
- Excretion starts 4-6 wks after infection
  - Persists for months to years
  - Intermittent excretion possible at any time
- May persist on fomites for hours

# CMV risk groups

## ● Occupational

- DCC workers x5-10
- Paed health workers no clear increased risk

## Perinatal CMV

- Perinatal lecture



# Acquired CMV: normal host

- >90% asymptomatic
- IM syndrome
  - Fever up to 2w
  - Abn LFTs (bilirubin usually N)
  - malaise, HA, atypical lymphocytosis
  - Rash (esp after ampicillin)
  - EBV >CMV
    - ✿ Exudative pharyngitis
    - ✿ Hepatomegaly
    - ✿ Splenomegaly
    - ✿ adenopathy

# CMV: immunocompromised host

- Fever
  - Malaise
  - Leukopenia
  - Transaminitis
  - Pneumonitis
  - Retinitis
  - Enterocolitis
  - Encephalitis
  - Polyradiculopathy
  - Graft function deterioration
- Primary  
➤ 4-12 w after Tx
- Reactivation

# CMV Dx

## ● Viral detection

- Tissue culture
- Antigenaemia detection (pp65 and others)\*
- DNA PCR- quantitative\* vs qualitative
- Histology

## ● Serology

- IgG
- IgM
  - (FPs in Rh factor, FNs in immunosuppressed)

# CMV Mx

## ● Treatment

- Ganciclovir (IV/o)
- Foscarnet
- Cidofovir
- Hyperimmune globulin

## ● Prevention

- Hyperimmune globulin
- GCV
- Hygiene
- Donor screening
- Reduce viable leukocytes in blood product

# EBV

- dsDNA, herpesvirus
- Lytic infection in oropharyngeal & salivary cells
- Latent infection in B lymphocytes
- All human populations
- No seasonal variation
- Early acquisition developing world and ?DCC
- Adolescent seroprevalence 40-50%

# EBV pathogenesis

## ● B cells

- Up to 20% infected
- Monoclonal and polyclonal proliferation
- Immortalisation of B cells

## ● Atypical LCs are cytotoxic CD8 positive

- Kill infected B cells
- Outnumber B cells 50:1

# EBV transmission

- Oropharyngeal secretions
  - Low titre even during acute illness
  - No isolation needed in hosp
- Blood products
  - Less common than CMV

# Clinical: acute EBV

- Asymptomatic frequency inverse to age
- IM syndrome
- Neurologic
  - Nerve palsy
  - GBS
  - Meningoencephalitis
  - Transverse myelitis
- ITP



# Mononucleosis syndrome

- Incubation 30-50d
- Fever
- Lymphadenopathy
- Pharyngitis
- Splenomegaly
- Hepatitis – mild
- Rash
  - 15% if no antibiotics
  - 60-80% if beta-lactams
- Pneumonitis
- Neurol
- Myocarditis
- Thrombocytopaenia
- Anaemia
  - Haemolytic
  - Aplasia
- neutropenia

# EBV: immunosuppressed

- X-linked lymphoproliferative syndrome
- Post Tx B cell lymphoproliferative syndrome
- HIV associated
  - Lymphoma
  - Oral Hairy leukoplakia

# EBV cancers

- Burkitt lymphoma- mainly African type
- Nasopharyngeal carcinoma
- Hodgkin's (some)

# EBV Dx

- FBE: platelets (low), WCC (up or down)
  - film: atypical LC
- Heterophile Ab (Paul Bunnell)
  - aggl of sheep/horse RBCs after absorption with guinea pig kidney cells
  - rapid test horse or beef RBCs
  - positivity increases
    - with age (rare<5y)
    - time after Sx onset)
- serology IgG/M VCA
  - also EBNA (6-12w) / EA

# HHV6

- Roseola infantum:
  - virus 1st noted in LC of infant 1988
- infects T lymphocytes, esp activated CD4
- ?latency in macrophages
- 2 types:
  - A- adults- ?role
  - B- roseola and other febrile illnesses

# HHV6

- Worldwide, no seasonal variation
- peak 6-12 months of age
- 6-12m: causes 20% all ED visits
  - 9.7% all ED visits <3 years
- most adults sero+ve
- shed intermittently, often asymptomatic
  - virus present in saliva of healthy adults
    - ?major source
- transplacental possible, BMilk ?not fd

# HHV6 clinically

## ● Immunosuppressed

- BM suppression in BMT & HIV
- interstitial pneumonitis
- renal dysfunction
- skin rash

## ● neurological manifestations

- aseptic meningitis
- FCs
- meningoencephalitis
- ?MS flares

# HHV6 clinically

- High fever 3-5 days
  - 'no focus' often
- irritable
- adenopathy: Cx/occ
- rash- mac-pap
  - 25% during fever
  - most after fever
  - Nagayama's spots
    - red papules buccal mucosa
- Inflamed TMs
- URI Sx
- GI Sx
- bulging AF
- Febrile seizures
  - 15-20%
  - incl recurrent FCs



# HHV6

## Dx:

- Serology
- PCR
  - +ve indicates current or past infection
  - plasma rather than whole blood indicates active

## Rx:

- *in vitro* susceptible to GCV, foscarnet, cidofovir

# HHV7

- Frequent
- older than HHV6
- mild fever, rash etc
- found in breast milk and adult saliva

# HHV8

- Kaposi's sarcoma
  - does occur in childhood in Africa
- ?transmission

# HSV:

- Latency in neuron DRG episome
  - no role in malignancy/transformation
- neurovirulent
- HSV thymidine kinase
  - VZV has, CMV does not
- can affect any organ of body
- worse if T cell abnormality
- ?Ab only important for neonates

# HSV Rx

- Valacyclovir prodrug for ACV
- Famcyclovir also acts TK
- Foscarnet reserved for resistant virus
  - Acts on viral DNA polymerase

# Vertically acquired HIV- NHx

- 20% early progression to AIDS and death in infancy
- 40-50% survived to 10 years without ART

# Scenario: HIV +ve mother

You are called to counsel an HIV positive mother about vertical transmission of HIV

- *What is the transmission risk?*
- *What are the risk factors?*
- *What interventions may reduce risk?*
- *How will you manage and diagnose the baby?*

# HIV: kids aint adults

- VL much higher, esp early
- CD4 counts age dependent
  - Much higher in infancy
  - Use CD4%
- Lifetime of Rx
  - Resistance/options
  - Toxicity



# Vertical Transmission:

- Accounts for >90% paediatric HIV
  - Risk if HIV positive mother
    - Europe ~14%, Africa ~30%
- *In utero* - from 1<sup>st</sup> trimester
- Intrapartum – 50-70% vert t'mission
  - Contact with infected secretion or blood
- Postpartum – 14-29%\*
  - Breastfeeding

# Risk factors for vertical infect<sup>n</sup>:

- Advanced maternal disease/low CD4
- High viral load
- NVD (vs LUSCS)
- ROM > 4 hours
- Bloody delivery
- prematurity
- Breast feeding- esp long term

# What can we do?

## Antenatally:

- Maximise maternal status
  - Health, nutrition
- Diminish viral load, raise CD4 %
  - Maximise anti-retroviral regimen by delivery
- Book for elective LUSCS at 37/40
- Don't breast feed

# Vertical Transmission- Antiretroviral treatment:

## ● ACTG 076

- Maternal zidovudine (ZDV) po from 34/40
- ZDV IV during labour
- Oral ZDV to infant for 1<sup>st</sup> 6 weeks
- Reduced risk from 25.5% to 8.3%

# Vertical Transmission- Antiretroviral treatment:

## HIVNET 012

- Oral nevirapine (NVP) single doses
  - to mother at onset of labour
  - to baby at 48 hours
- vs modified 076 protocol
- Nearly all breast fed, RV at 14-16 w
- Transmission:
  - NVP 13.1%, ZDV 25.1%
- Cost-effective

# Vertical Transmission- management of newborn:

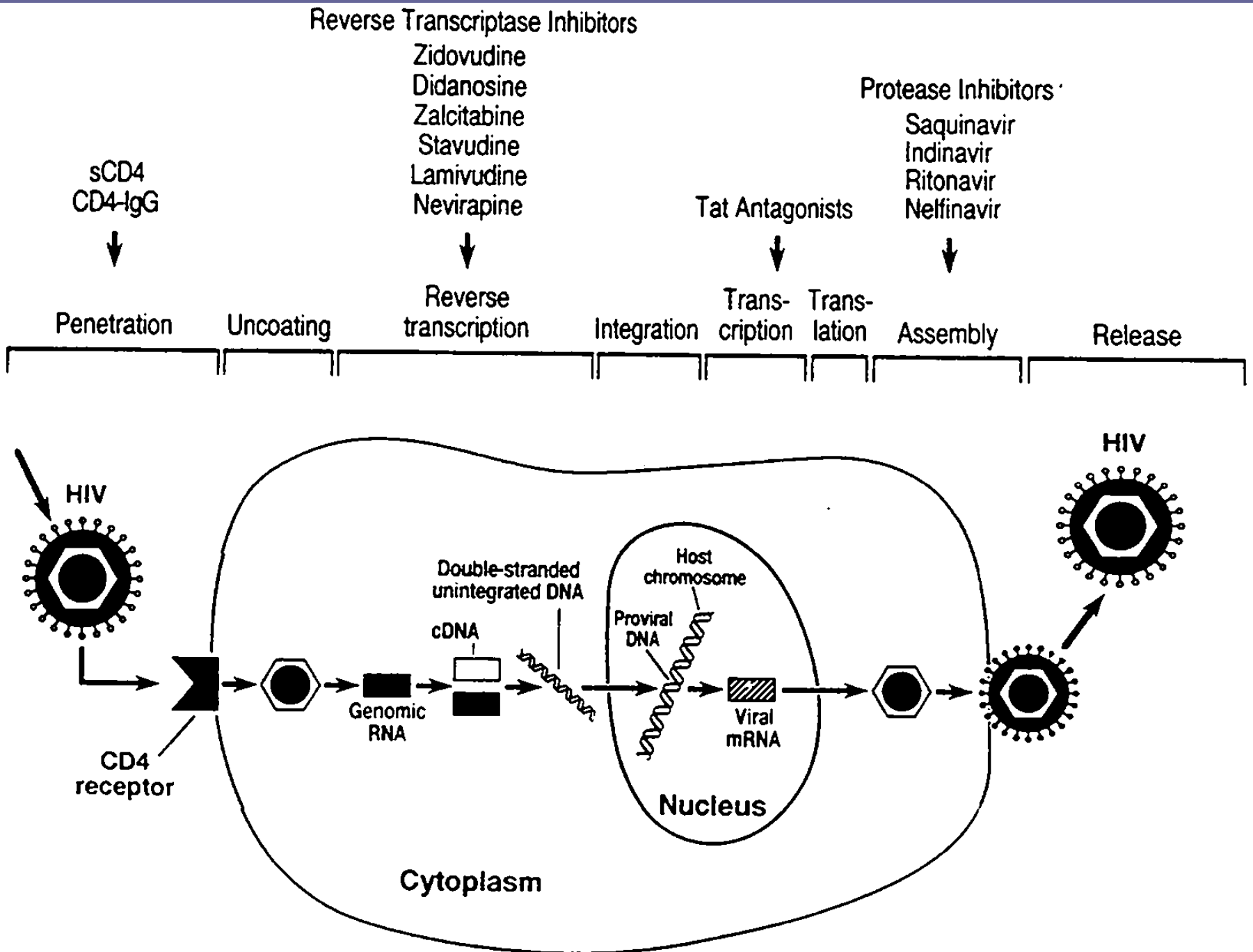
## ● Diagnostic PCR:

- 1<sup>st</sup> at 48 hrs pick up 38%
- 2<sup>nd</sup> at 2-4 weeks pick up 93%
  - IF NEGATIVE HERE:
    - CEASE ANTIRETROVIRALS
    - START SEPTRIN
- 3<sup>rd</sup> at 4 months pick up 99.7%
  - IF NEGATIVE HERE:
    - CEASE SEPTRIN
- 4<sup>th</sup> at 6m

## ● serology at 12, 18 months

# Vertical Transmission- drug management of newborn:

- Usually mother on HAART
- Intrapartum ZDV
- Neonatal ZDV
  - +/- 3TC
  - and NVP (intrapartum and neonatal)
  - and both
  - for 4-6 weeks
- possible maternal viral resistance



Reverse Transcriptase Inhibitors

- Zidovudine
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Nevirapine

Protease Inhibitors

- Saquinavir
- Indinavir
- Ritonavir
- Nelfinavir

Tat Antagonists

sCD4  
CD4-IgG

Penetration

Uncoating

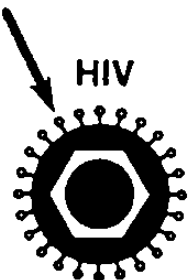
Reverse transcription

Integration

Transcription

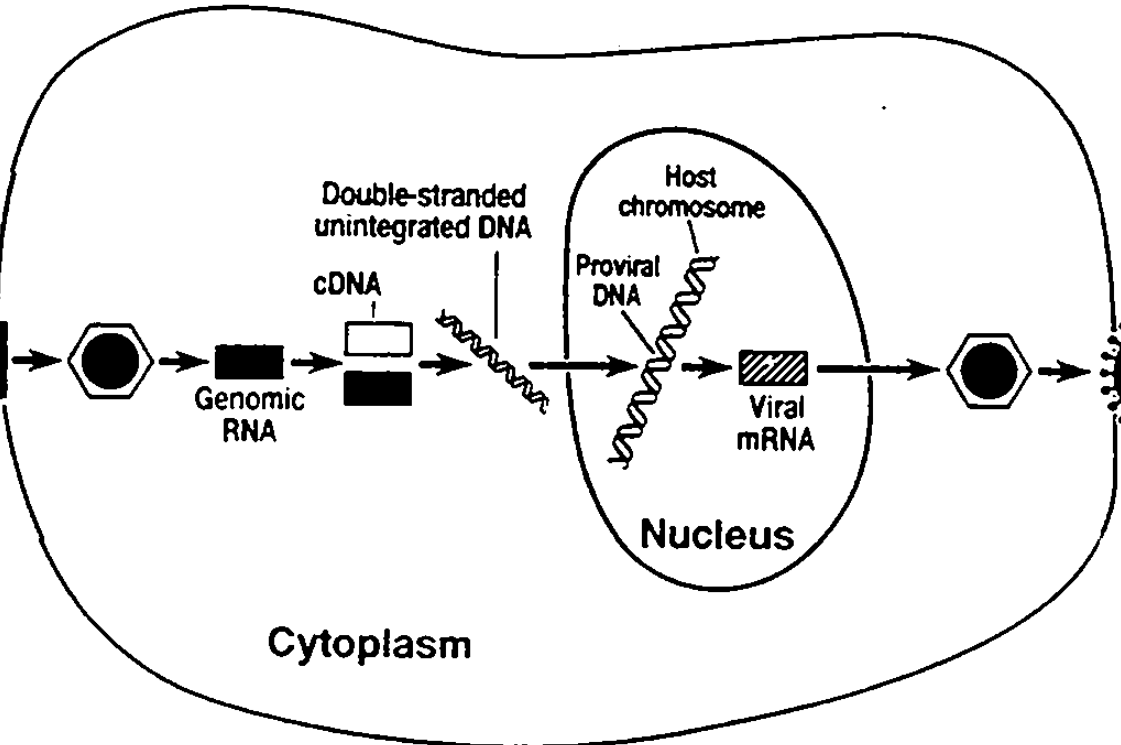
Translation

Release



HIV

CD4 receptor



Cytoplasm

Nucleus

Double-stranded unintegrated DNA

cDNA

Genomic RNA

Host chromosome  
Proviral DNA

Viral mRNA



HIV



# HIV testing

**Serology:** screen with ELISA, confirm with Western blot. OK after 18 months, when maternal Ab waned.

**HIV DNA PCR:** Preferred test to diagnose HIV infection in infants and children younger than 18 months of age; highly sensitive and specific by 2 weeks of age and available; performed on peripheral blood mononuclear cells

**HIV p24 Ag:** Less sensitive, false-positive results during first month of life, variable results; not recommended

**ICD p24 Ag:** Commonly available; negative test result does not rule out infection; not recommended

**HIV culture:** Expensive, not easily available, requires up to 4 wk to do test

**HIV RNA PCR:** Not recommended for routine testing of infants and children younger than 18 months of age because a negative result cannot be used to exclude HIV infection

# Are there risks of therapy?

- ?lactic acidosis/mitochondrial defects
  - relative potency inhibiting mitochondrial gamma DNA polymerase highest for:
    - ddC, followed by didanosine (ddI), stavudine (d4T), 3TC, ZDV and abacavir (ABC)
  - Keep watching this space
  - Adults/older children lipodystrophy synd
- ?preterm- not clear association
  - Raised for combination therapy

# HIV: to treat or not?

## Infants

- Always start if:
  - Stage C
  - CD4 < 20%
  - CD4 rapidly falling and persistent high VL > 10<sup>6</sup>/ml
- Consider in any infected infant

# HIV: to treat or not?

## Children >12m

- Always start if:

- CD4%<15

- Consider if:

- Stage B
- CD4%<20 or VL>10<sup>5</sup>

- Defer if:

- Stage N or A
- CD4%>20
- VL<10<sup>5</sup>

# HIV therapies kids can take

## ● NRTIs

- ZDV, ddl, ddC, d4T, 3TC, ABC

## ● NNRTIs

- Nevirapine NVP, efavirenz EFV, delvaridine DLV

## ● PIs

- Indinavir, ritonavir, saquinavir, nelfinavir, amprenavir, lopinivir/ritonavir

# Topical viruses

- Enterovirus 71
  - HFM, neurological and systemic disease
  - SEA
- Nipah virus Malaysia 1998
  - flying foxes natural host
- SARS
  - coronavirus

# Enteroviruses

- Small RNA viruses (Picornaviruses)
- ssRNA
- Rapid replication in host cell=> cell lysis
- Groups:
  - A1-24
  - B1-6
  - Echoviruses (31)
  - Enteroviruses (types 68-71)
  - Polioviruses (types 1-3)

# Enterovirus disease:

- distinct viruses, diverse array disease
- Summer peak time
- Humans only natural host
- Faeco-oral, resp, mother-infant transmission
  - Faecal shedding ~8w
  - Resp shedding ~1w
- Fomite spread possible
- Incub 3-6d



# Enterovirus manifestations:

- Different tissue tropisms
  - Non-spec febrile illness
  - Resp: URTI....pneumonia
  - CNS disease: aseptic meningitis, encephalitis, paralysis
  - Skin exanthem/enanthem: HFM
    - A16, Echo19, EV71
  - Eye: acute haemorrhagic conjunctivitis
  - Cardiac: myocarditis, pericarditis
    - Coxsackie B1-5
  - GI: V, D, abdominal pain, hepatitis

# EV meningitis

- can be neutrophilia in CSF early
- Many different serotypes possible
- Most in childhood
- Not associated with permanent sequelae
- Daily PCR cost-effective in US studies
- pleconaril

# EV Dx:

## ● Culture:

- Throat, faeces, rectal swab, blood, Bx
- Positive culture from anywhere except faeces diagnostic

## ● PCR

- ?Gold standard

## ● Serology

- Polio mainly