

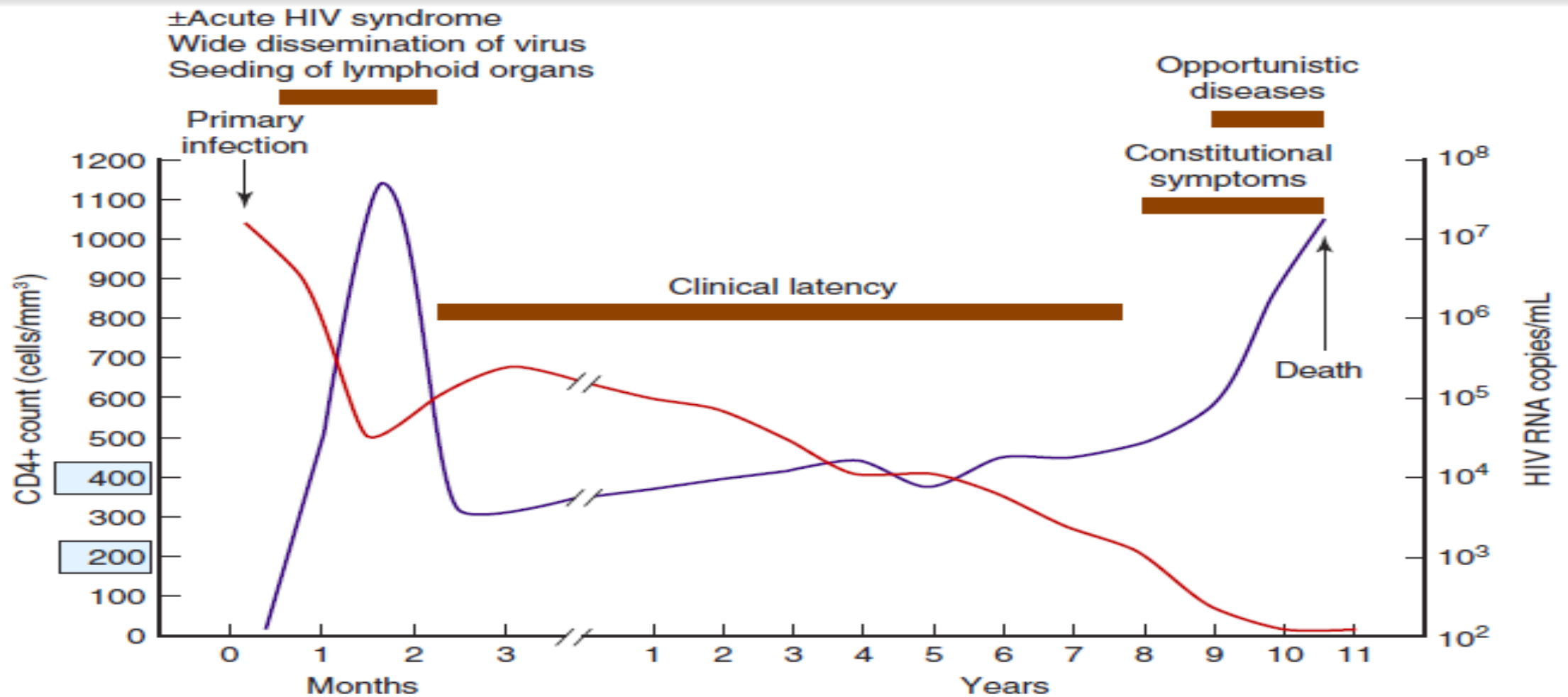


HIV/AIDS 2

A decorative graphic on the left side of the slide. It features a dark grey arrow pointing right at the top, with several thin, curved lines in shades of blue and grey extending downwards and to the right from its base.

Stages of HIV infection

- Acute
- Clinical latency - asymptomatic
- Chronic – symptomatic (including AIDS)



Red line = CD4+ T-lymphocyte count (cells/mm³); blue line = HIV RNA copies/mL plasma.

Blue boxes on vertical CD4+ count axis indicate moderate immunocompromise (< 400 CD4+ cells/mm³) and when AIDS-defining illnesses emerge (< 200 CD4+ cells/mm³).



Acute HIV infection

- ▶ Present in 20-40%, onset in 3-4 weeks after first contact and it takes up to 4 weeks
- ▶ Symptoms – fever, flu-like symptoms or mono-like symptoms (lymphadenopathy, arthralgia, fatigue, exanthemas)
- ▶ Rare – neurologic symptoms (peripheral neuropathies, encephalitis, aseptic meningitis)



Chronic asymptomatic HIV infection (clinical latency)

- ▶ 2-10 years, and depends on different factors
- ✓ Route of transmission and viral load
- ✓ Age at the moment of contact
- ✓ Type of HIV 1/2 - longer for HIV 2
- ✓ Present status – different infections, malnutrition, drug using

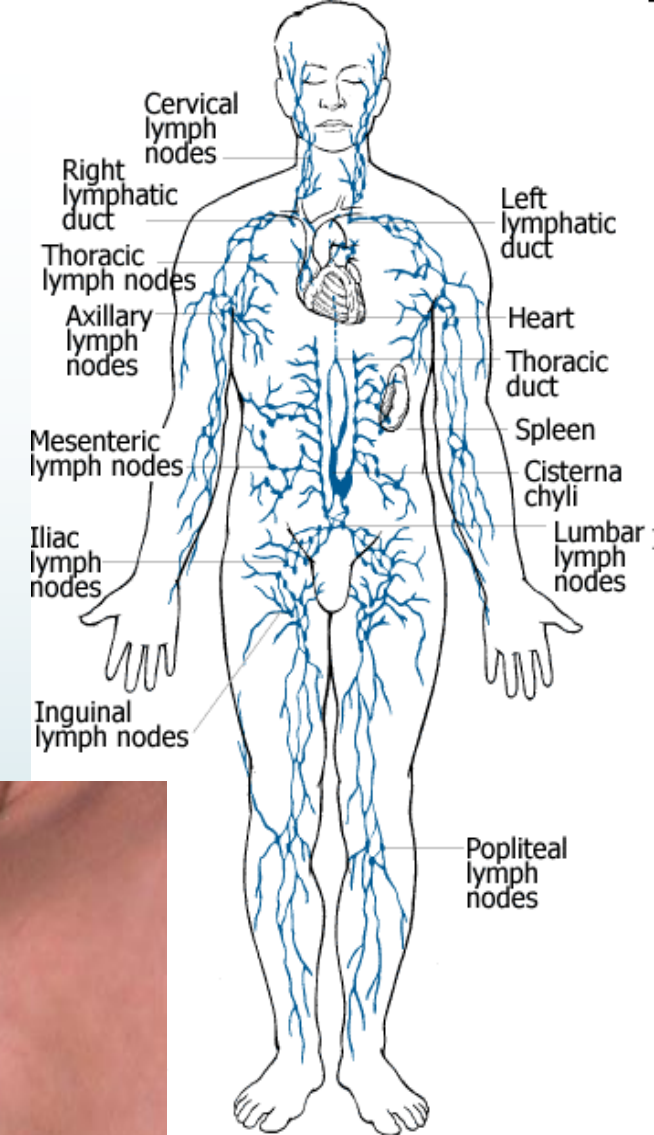
Latency for 1/3 months to 4 years (patient is infectious)

Chronic symptomatic HIV infection

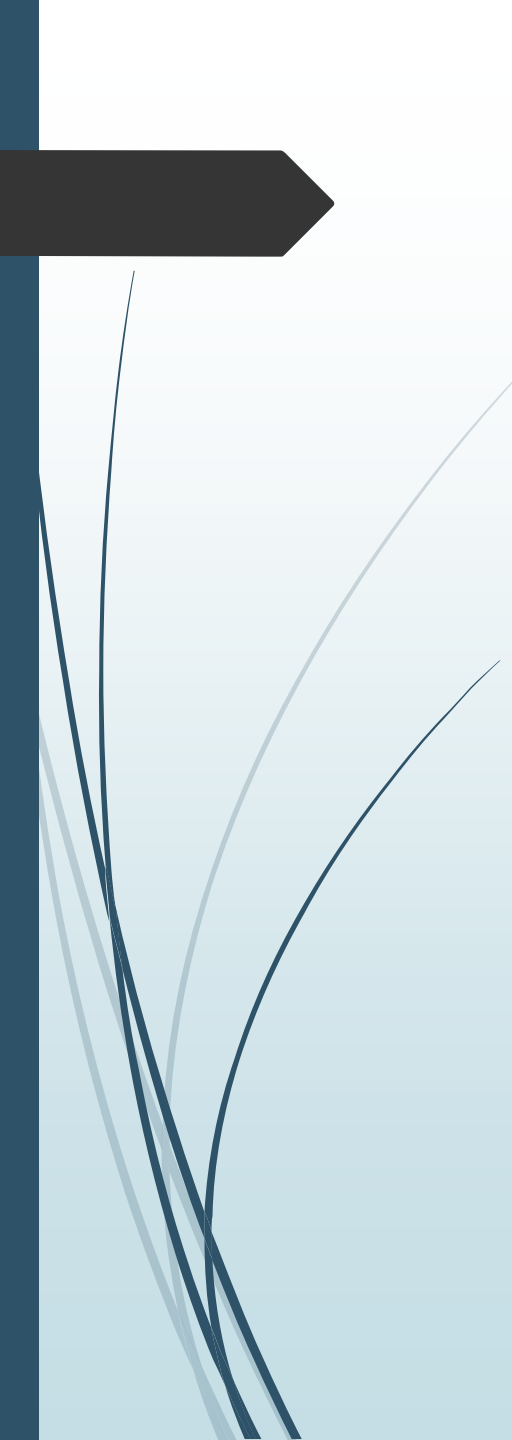
- ▶ Painless generalized persistent lymphadenopathy (2 peripheral groups – most common cervical, axillar, occipital)
- ▶ It contain :
 1. Non – specific symptoms – unknown fever 3-4 weeks, weight loss >10%, persistent diarrhea >1 month; for children - chronic bilateral parotidites, physical retard
 2. Opportunistic infections related to decreasing immunity – respiratory recurrent infections (otitis, sinusitis, pneumonia), oral symptoms (candidiasis, hairy leukoplakia, gingivitis), skin manifestations (herpes simplex, recidivate shingles, molluscum contagiosum, seboreic dermatitis, prurigo etc.)
 3. Suggestive clinical symptoms, specific for HIV (AIDS Related Complex – ARC).

Persistent generalised lymphadenopathy because of HIV

- Larger than 1.5 cm in diameter
- In 2 or more extra inguinal sites
- Of 3 or more months duration
- Non-tender, symmetrical,
- often involve the posterior cervical, axillary, occipital, epitrochlear nodes
- No other cause as HIV



CAUSES OF LYMPHADENOPATHY in HIV

- 
- **Bacterial infection:**
 - pyogenic bacteria
 - syphilis
 - **Mycobacterial:**
 - tuberculosis
 - MAC
 - **Fungal:**
 - histoplasmosis
 - coccidioidomycosis
 - **Chlamydial:**
 - lymphogranuloma venereum
 - **Parasitic:**
 - toxoplasmosis
 - **Viral:**
 - EBV
 - CMV
 - **Malignant disorders of the immune system:**
 - Hodgkin's disease
 - non-Hodgkin's disease
 - other malignancies

Lymphomas that develop in HIV+ patients (LHIV)

- 4-10% of AIDS pts
- 10% of non-Hodgkin lymphomas in US/Europe are AIDS related
- Most common LHIV:
 - diffuse large B cell lymphoma (DLBCL),
 - Burkitt lymphoma,
 - primary effusion lymphoma (PEL),
 - plasmablastic lymphoma
- HIV is NOT directly involved in the malignant transformation of B cells
- several pathogenetic mechanisms:
 - chronic antigen stimulation,
 - genetic abnormalities,
 - cytokine dysregulation,
 - EBV and HHV8
- Lymph node involv.: 1/3 of patients;
- extranodal: GI, CNS, liver, bone marrow
- Aggressive, poor outcome

Mucocutaneous manifestation in HIV infection



3 groups of oral manifestations of AIDS

Group 1 (strongly associated with HIV infection):

1. oral candidosis,
2. hairy leukoplakia,
3. Kaposi sarcoma,
4. linear gingival erythema,
5. necrotizing ulcerative gingivitis,
6. necrotizing ulcerative periodontitis,
7. non-Hodgkin lymphoma.

Group 2

1. atypical ulcers,
2. salivary glands diseases,
3. viral infection such (CMV, HSV, HPV, HZV).

Group 3 (rarer)

1. diffuse osteomyelitis
2. squamous cell carcinoma.

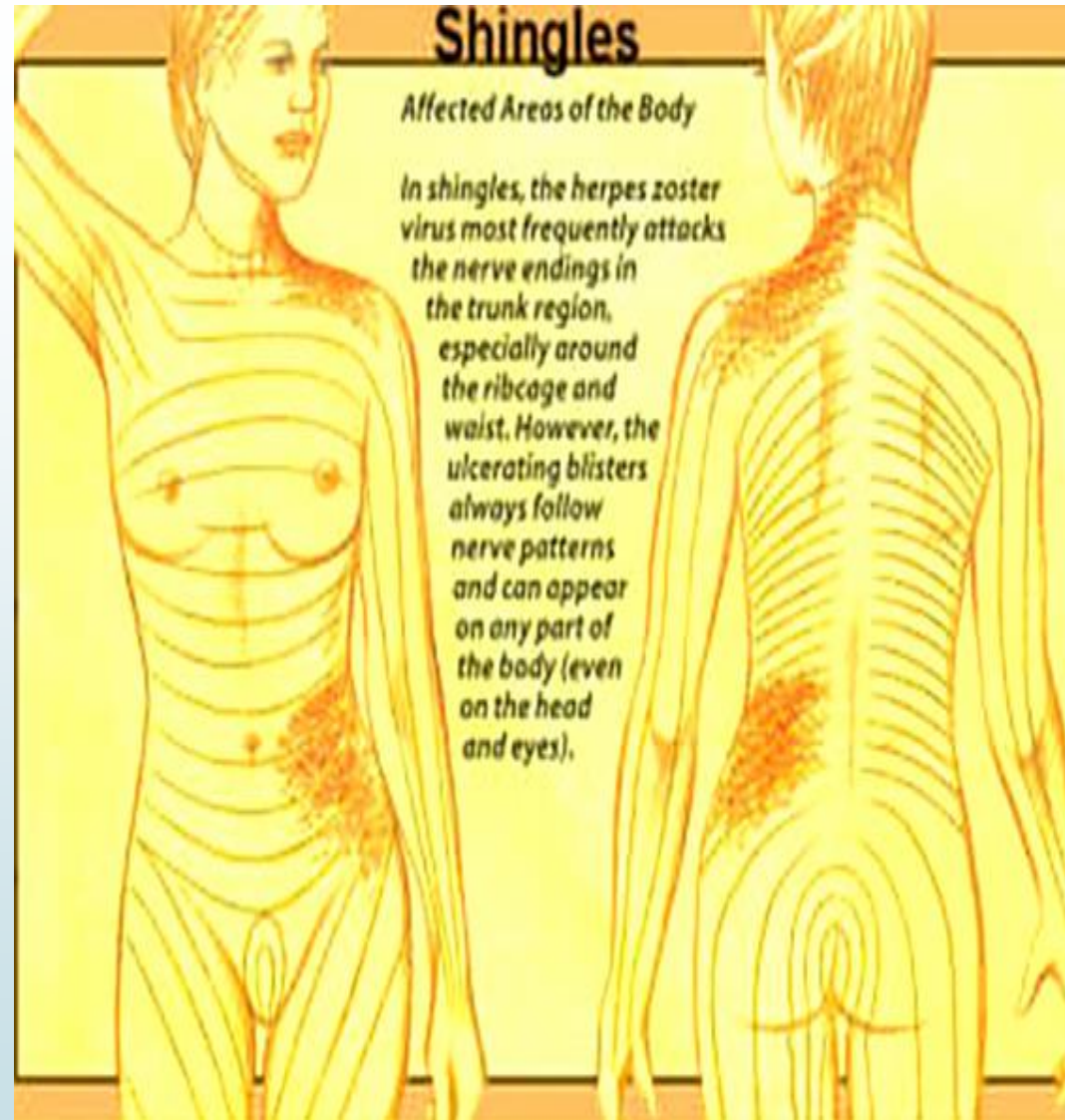
HIV:

HSV infection:

- ▶ chronic >1 mo duration
- ▶ orolabial / genital / anorectal
- ▶ visceral at any site

HZV infection:

- ▶ children / young adults
- ▶ bilateral / multidermatomal
- ▶ repeated / recidivant





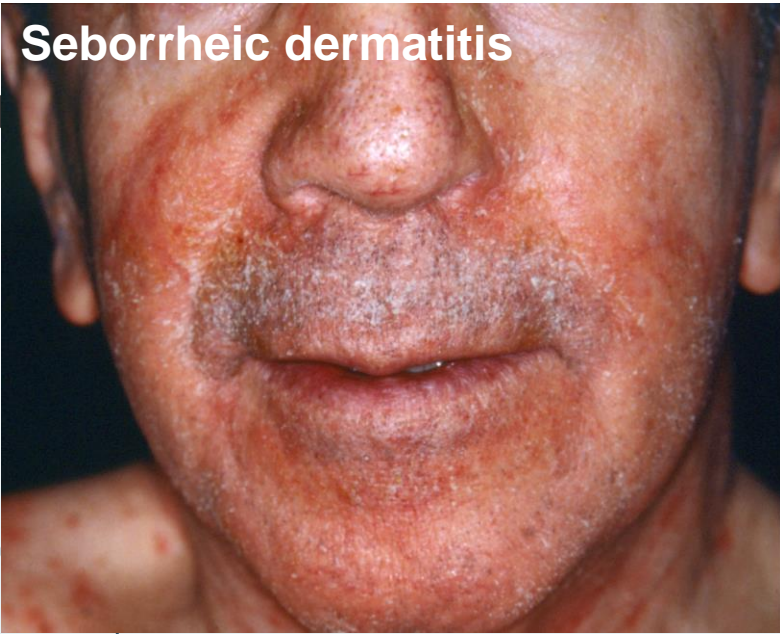


HSV infection:
chronic >1 mo duration
orolabial / genital / anorectal
visceral at any site



Mucocutaneous manifestation, stage II

Seborrheic dermatitis



Seborrheic dermatitis



Onycholysis



Paronychia



Mucocutaneous manifestation, stage II



Angular cheilitis



**Recurrent
oral ulceration ≥ 2 in 6mo**



Persistent or recurring oral candidiasis (stage III)

- associated with more frequent progression to AIDS
- has been also used as a clinical marker to define the severity of HIV infection
- pseudomembranous candidosis usually followed by erythematous candidosis

Pseudomembranous



Erythematous



Acute necrotizing ulcerative gingivitis (stage III)

- ≥ 2 episodes in past 6 mo
- "Chronic" periodontal disease \rightarrow more common and/or more aggressive



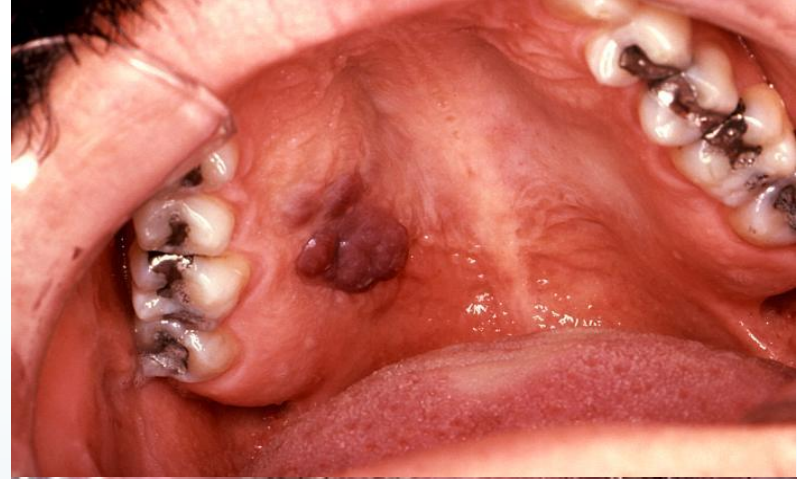
Oral Hairy Leucoplakia (stage III)

- EBV,
- Asymptomatic
- vertically ribbed, keratinized plaques
- along the lateral tongue borders
- Prevalence → 38%
- has no malignant potential
- does not rarely requires treatment



Kaposi sarcoma (stage IV)

- multifocal systemic disease
- originates from the vascular endothelium
- HHV 8
- Sexually, via blood, saliva
- skin, mucous, lymphatic system, viscera, lung & GI
- most commonly: palate & gingivae
- purplish or brown macules and plaques
- May become nodular
- More aggressive
- may ulcerate, cause local tissue destruction
- Treatment:
 - Elimination / reduction of cosmetically unacceptable lesions
 - relief of symptoms caused by visceral involvement.



Molluscum contagiosum

MC virus, DNA, Poxviridae family
replicates in cytoplasm epidermal cells
small papules with central umbilication



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Crusted or "Norwegian" scabies
widespread eczematous eruption,
no characteristic papules and burrows



Pulmonary manifestation in HIV **infection**



Pulmonary manifestation in HIV infection

Pulmonary complications = often initial clinical manifestation HIV inf.

Pneumonia & respiratory failure = most common causes of death in late stages

Based of CD4

- CD >400 : Increase risk of
 - Bactetial infection
 - *Mycobacterium tuberculosis*
- CD4 200-400 : Increase risk for
 - Recurrent bacterial infections
 - *Mycobacterium tuberculosis*
 - Lymphoma and Lymphoproliferative disorders
- CD4 <200 : Increase risk for
 - PCP
 - Disseminated *Mycobacterium tuberculosis*
- CD4 <100 : Increase risk of
 - PCP
 - A typical *Mycobacterium tuberculosis*
 - CMV
 - Kaposi's sarcoma
 - Lymphoma

Bacterial Pneumonias in HIV

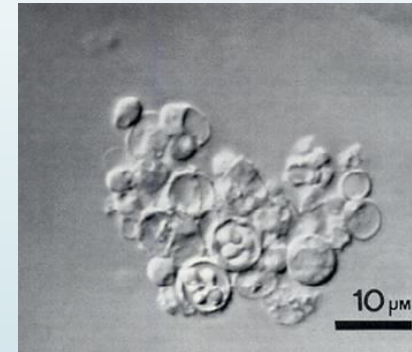
- **suggestive of HIV infection is bac. pneum ≥ 2 episodes in 6 mo**
- most common causes:
 - *Streptococcus pneumoniae*,
 - *Hemophilus influenzae*,
 - *Staph. aureus* (parenchymal necrosis + cavitation commonly seen)
- The signs and symptoms:
 - fever and cough (90%),
 - tachypnea,
 - purulent sputum production,
 - pleuritic chest pain
- Chest x-ray: focal infiltrates
- Response to antimicrobial therapy is generally prompt;
- If no prompt improvement, suggests complications such as:
 - empyema (infected parapneumonic pleural effusion),
 - lung abscess
 - or another opportunistic infection

Pneumocystis Jiroveci Pneumonia (PJP)

- ***Pneumocystis jirovecii*** – in humans / *Pneumocystis carinii* - in the rat host
- ubiquitous fungal organism
- 90% Ab by age 4

- Disease: new acquisition / reactivation of latent,
- risk factors: CD4 <200, oral thrush, recurrent bac pneum., weight loss

- exclusively respiratory system
- **reduce alveolar capillary permeability**
 - impairs O₂ diffusion
 - interstitial fibrosis
 - alterations in expression & activity of surfactants



The symptoms *Pneumocystosis*:

- Typically - gradual onset:
 - Fever (>80%) 2-6 we, usually **low-grade**, fatigue
 - **Nonproductive** cough (95%)
 - **Progressive** dyspnea (95%)
 - Shortness of breath
- **Bilateral basal symmetrical** few fine crackles or wheezes, diffuse dry (cellophane) rales / unremarkable
- In severe disease:
 - tachycardia, tachypnea, cyanosis,
 - **respiratory failure**: nasal flaring, intercostal retractions.
- Acute dyspnea + pleuritic chest pain \approx pneumothorax
- **Uncommon**: productive cough, purulent sputum, rigors, pleuritic chest pain, hemoptysis

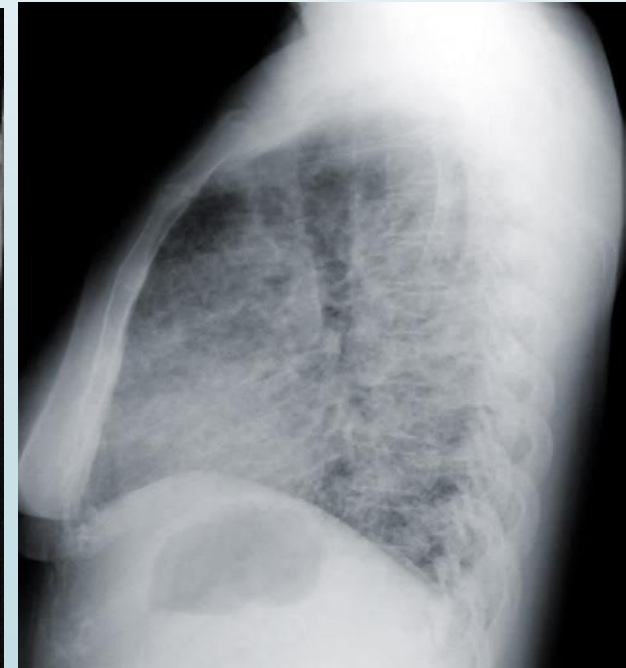
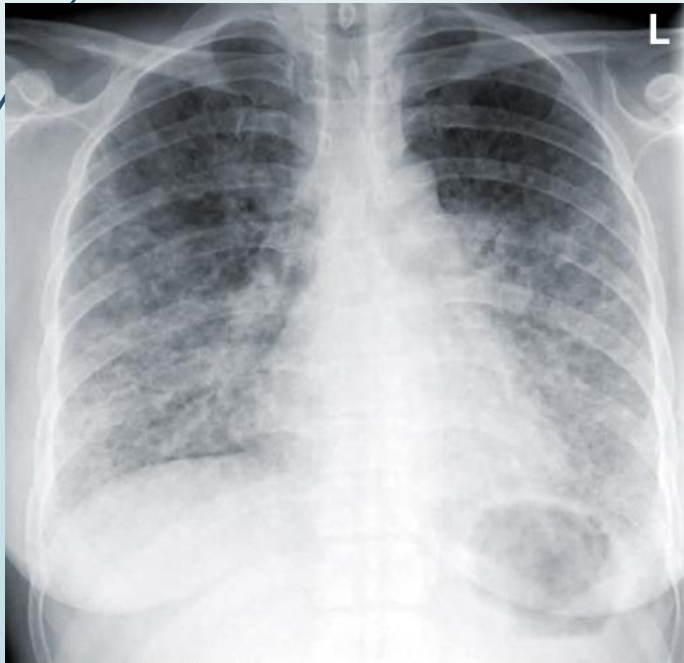


Chest radiography

- ▶ may be N in early mild disease $\approx 20\%$
- ▶ **bilateral, symmetrical**, perihilar, **lower lobe** opacities (in a butterfly pattern)
- ▶ interstitial infiltrates appear as:
 - ▶ finely granular, reticular, or ground glass opacities

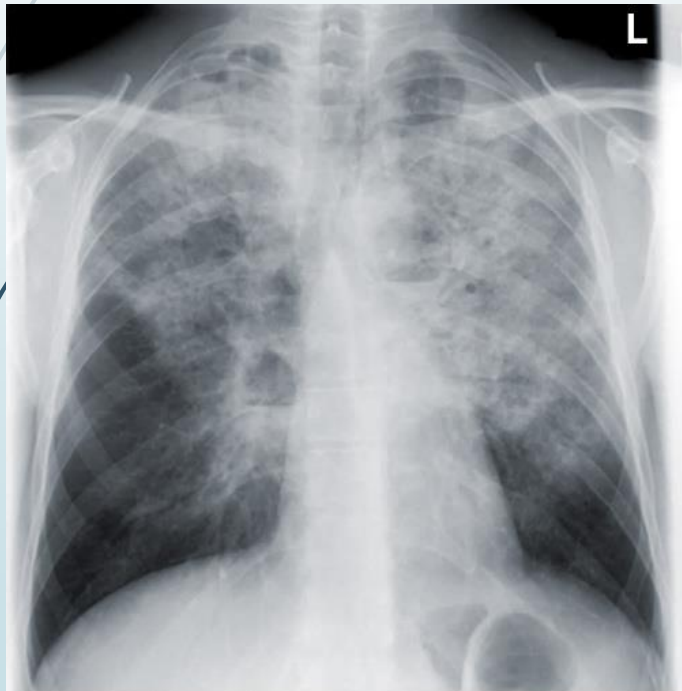
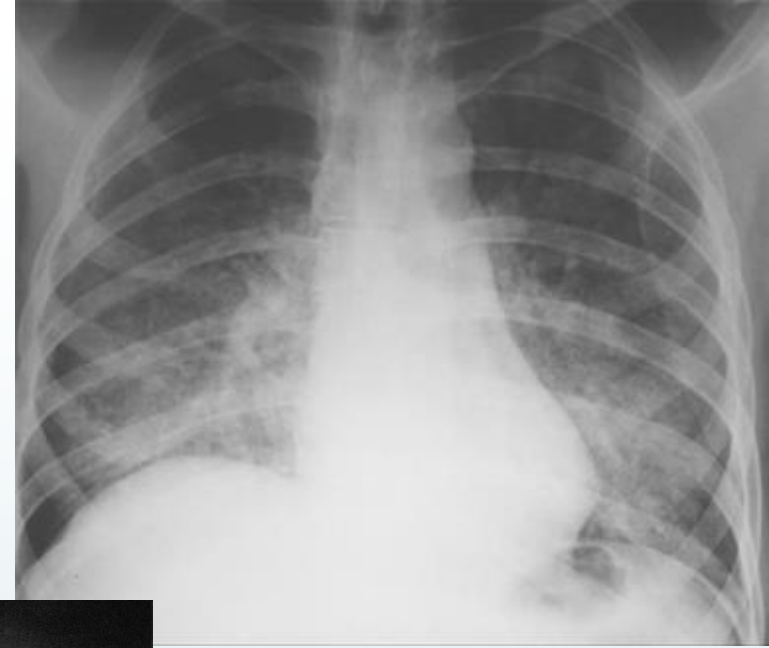
When chest Rx-normal \Rightarrow CT:

extensive ground-glass attenuation or cystic lesions.



Less-common:

- upper lobe predominance
- focal infiltrates, nodules, cystic lesions
- patchy asymmetric infiltrates
- pneumatoceles
- pleural effusions
- intrathoracic adenopathy
- cavitation



PJP is seen as lower lobe alveolar infiltrates

bilateral perihilar opacities and interstitial prominence, as well as multiple hyperlucent cystic lesions, most prominent in the upper lobes.

- Spontaneous pneumothorax 5-10%
- **is virtually diagnostic of PJP**
- is a poor prognostic indicator

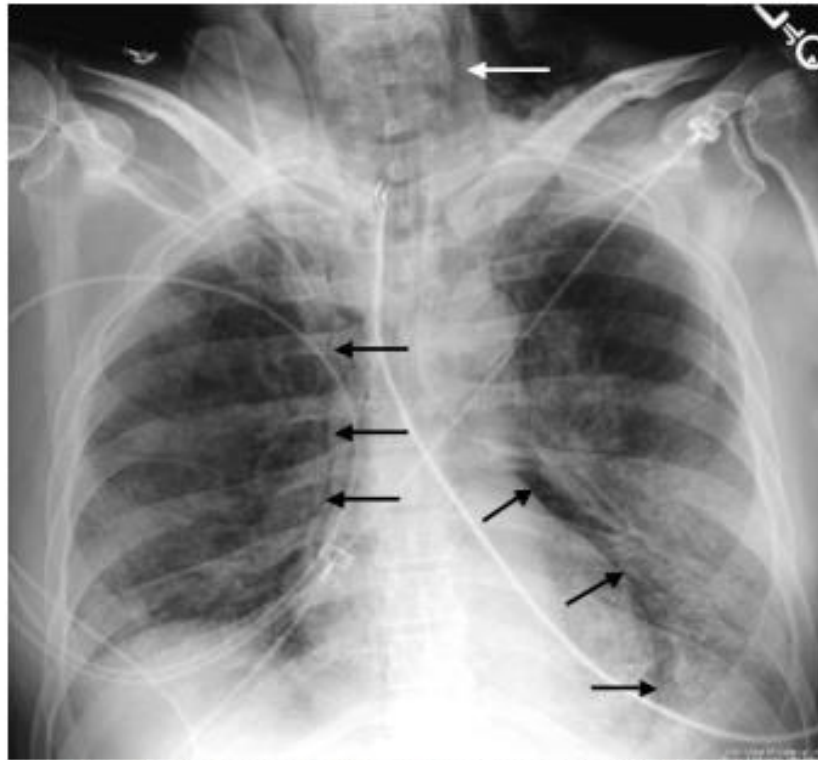


Fig 3: AP chest radiograph reveals pneumomediastinum (long black arrows), subcutaneous emphysema (long white arrow), and bibasilar reticulonodular ground-glass opacities. Note the wide lucency projecting over the left cardiac border consistent with pneumomediastinum (and/or medial pneumothorax?), in contradistinction to Mach effect.

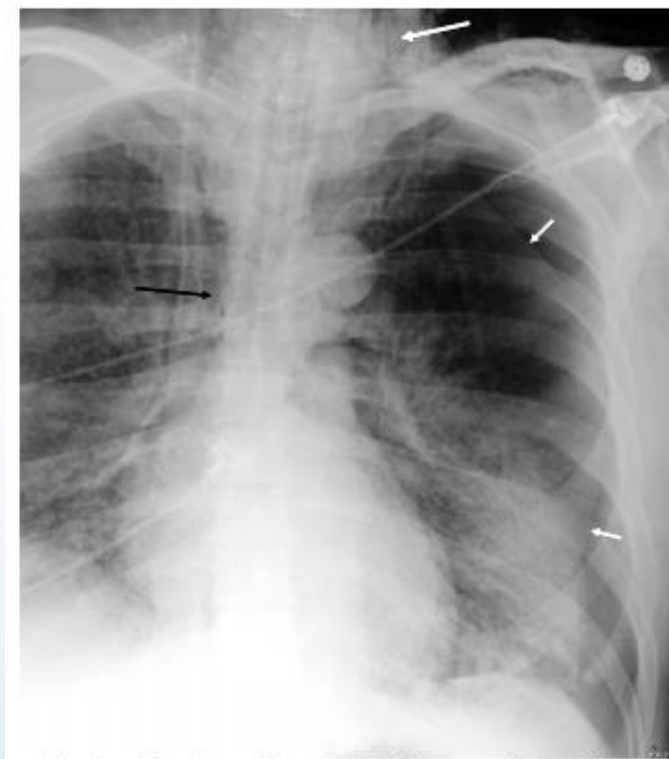
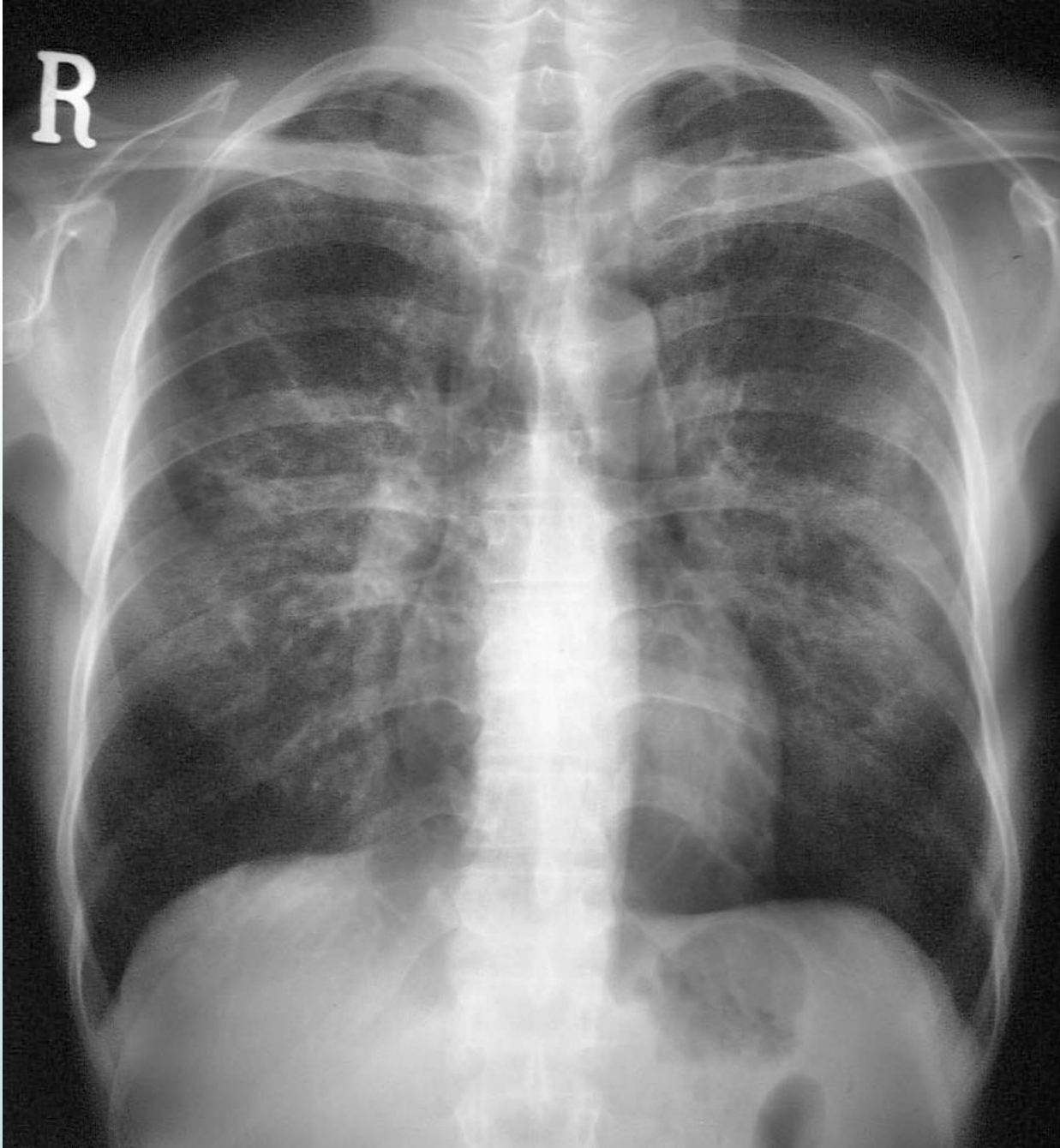


Fig 4: AP chest radiograph reveals pneumothorax (short arrows), pneumomediastinum (long black arrow), subcutaneous emphysema (long white arrow), and bibasilar reticulonodular ground-glass opacities.



Fig 5: Contrast-enhanced axial CT image through mid-lung fields shows persistent pneumomediastinum (short white arrows), persistent left side pneumothorax (long white arrows), right side pleural effusion (black arrows), and ground-glass attenuation with focal consolidations in bilateral lung bases.



Residual interstitial opacities in a patient with a history of *PJP*

R
01 03
01/10/2017
15:06
5079
Chest (an view)





pts CD4 <200 perihilar
ground-glass appearance
in the shape of bats-wings

Pts low CD4 miliary TB
or predominantly middle
& lower lung zone infiltrates
be mistaken for bac.pneum.

Diagnosis

➤ Specimens:

- **induced sputum** with hypertonic saline
- bronchoscopy with BAL (bronchoalveolar lavage)
- transbronchial biopsy
- open lung biopsy 95% to 100%

➤ Stains preferred:

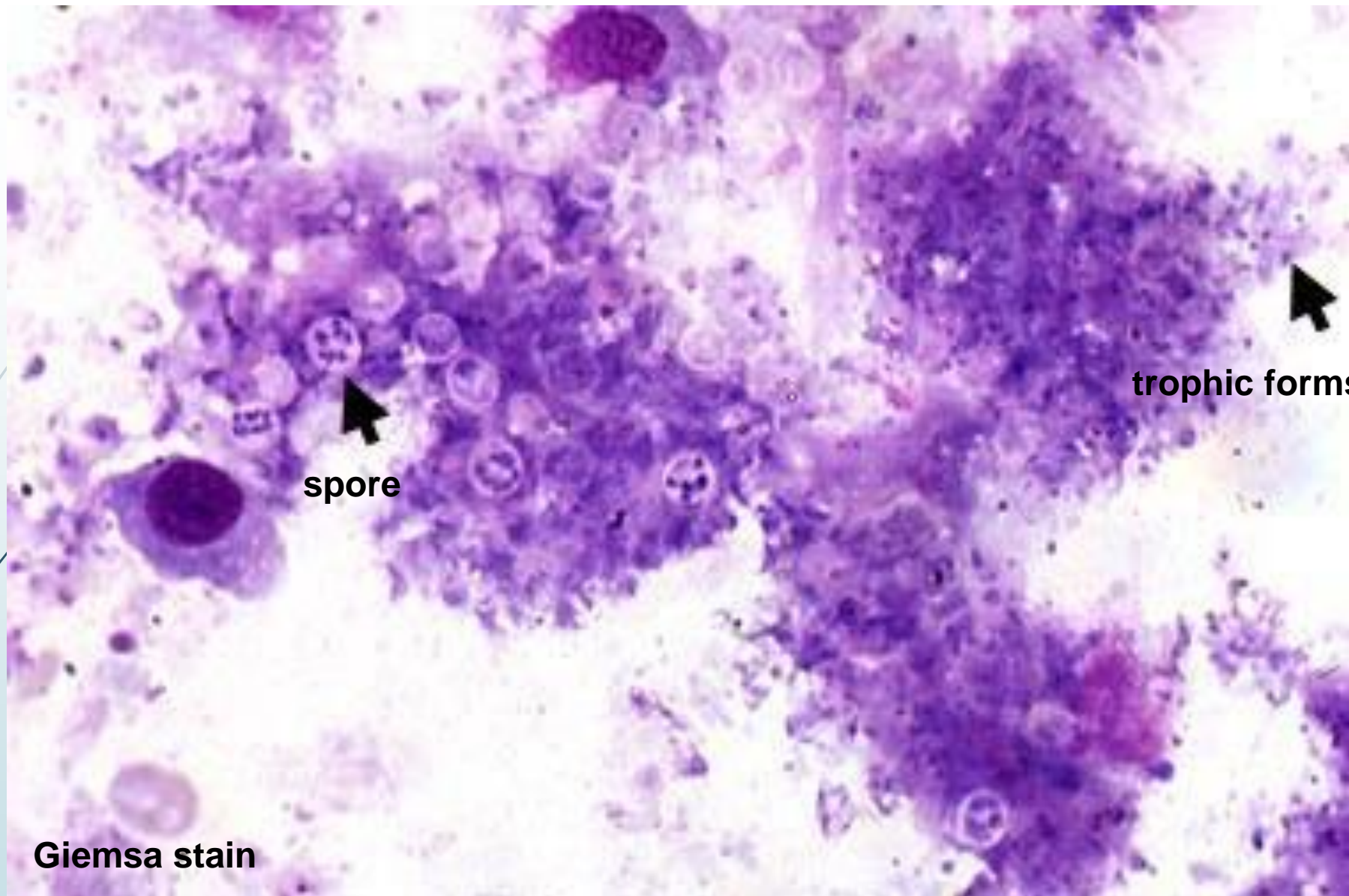
- **Giemsa**
- Toluidine blue
- Methenamine silver

➤ **Culturing yet not possible**

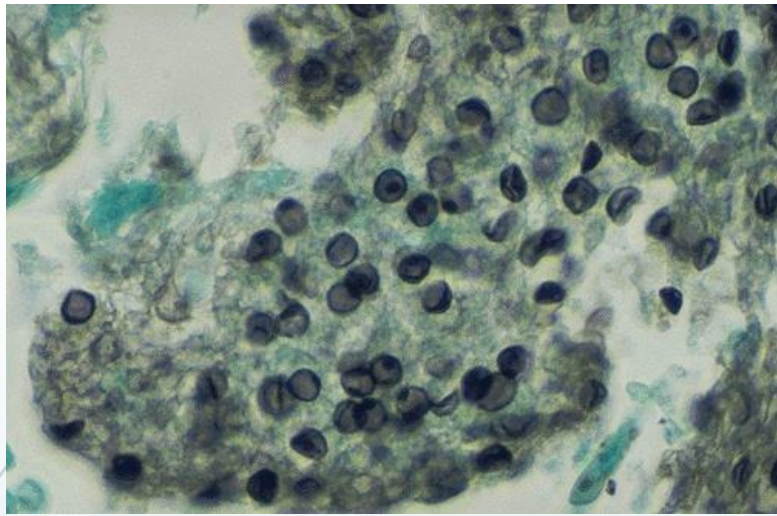
- Rapid method - direct fluorescent method with monoclonal`s
- Serology – to establish prevalence for epidemiology purpose
- PCR – (ability to distinguish colonization from disease is less clear)

➤ **LDH are usually elevated** (>220 U/L) in 90% of pts:

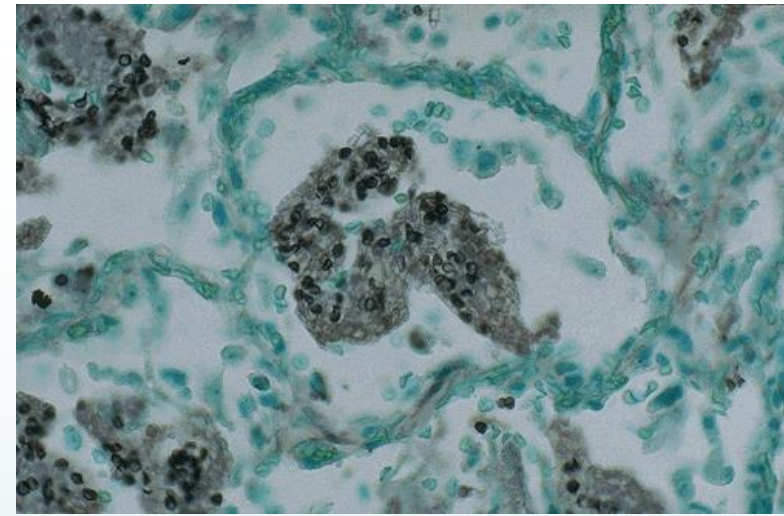
- reflect the degree of lung injury
- elevated LDH may indicate therapy failure



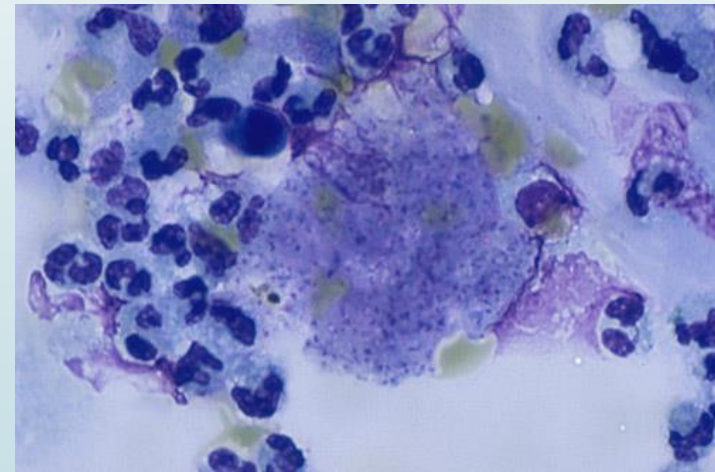
- ✓ **trophic forms** → dot-like nuclei and pale blue cytoplasm (right arrow).
 - ✓ **spore** (formerly cysts) → do not stain, but the **intracystic bodies** (sporozoites) do.
- Two alveolar macrophages indicate the relative sizes of organisms and cells.



With Gomori methenamine silver stain at high magnification, the cysts of PJ in lung have the appearance of crushed ping-pong balls



With Gomori methenamine silver stain, PJ in lung is demonstrated by the appearance of brown to black cysts in the alveolar exudate.



With giemsa stain at high magnification, the faint bluish dot-like intracystic bodies of PJ in lung from a bronchoalveolar

Initial *Pneumocystis* pneumonia therapy

Therapy	Preferred Therapy	Alternative Choices
Oral Therapy	TMP-SMX: 15 mg/kg/d (based on Trimethoprim component) PO in 3-4 divided doses x 21d (typically 2 DS tablets tid to qid)	Trimethoprim: 15 mg/kg/d PO in 3-4 divided doses <i>plus</i> Dapsone: 100 mg PO qd x 21d ----- Clindamycin: 450 mg PO q6h x 21d <i>plus</i> Primaquine: 15 mg base PO qd x 21d ----- Atovaquone Suspension: 750 mg PO bid x 21d
IV Therapy	TMP-SMX: 15mg/kg/d (based on Trimethoprim component) IV divided q6h to q8h x 21d	Clindamycin: 600 mg IV q6h x 21d <i>plus</i> Primaquine: 15 mg base PO qd x 21d ----- Pentamidine: 3 to 4 mg/kg IV qd x 21d ----- Trimetrexate: 45 mg/m ² (1.2 mg/kg) IV qd x 21d <i>plus</i> Leucovorin: 20 mg/m ² IV (or PO) q6h x 24d
Adjunctive Therapy (if pO ₂ < 70 mm Hg) and within 72 hours of starting therapy	Prednisone: 40 mg PO bid x 5d, then 40 mg qd x 5d, then 20 mg qd x 11 days	Methylprednisolone: 30 mg IV bid x 5 days, then 30 mg IV qd x 5 days, then 15 mg IV qd x 11 days

clindamycin plus primaquine was the most effective salvage regimen among patients who failed to respond to initial *Pneumocystis* pneumonia therapy

Pneumocystosis

Primary prophylaxis

- when CD4 <200
- a history of oropharyngeal candidiasis
- Pts receiving pyrimethamine sulfadiazine for suppression of toxo do not require additional prophylaxis for PCP

- **TMP-SMX** 5 mg/kg/day (1 single-strength tab/day / 1 double-strength tab/3xwe)
- **Dapsone** 100mg/day
- **Dapsone** 50mg/day + **pyrimethamine** 50mg/we + **leucovorin** 25 mg/we
- atovaquone

Cotrimoxazole preventive therapy (WHO)

Age	Criteria for initiation	Criteria for discontinuation ^a	Dose of cotrimoxazole
HIV exposed infants	In all, starting at 4–6 weeks after birth	Until the risk of HIV transmission ends or HIV inf. is excluded	
<1 year	In all	Until 5 years of age regardless of CD4% or clinical symptoms (if for PJP / toxo)	
1–5 years	WHO stages 2 - 4 or CD4 <25% or in all (limited health infrastructure)	Never	
≥5 years, including adults	Any WHO stage and CD4 <350 WHO (<200 USA) or WHO 3-4 any CD4	Never or CD4 ≥350 after 6 mo of ART (high bac inf/malaria) or CD4 ≥200 after 6 mo (3 mo USA) of ART (some countries)	>30kg = 960mg/day

Contraindications to CTX preventive therapy:
severe allergy to sulfa; severe liver disease, severe renal disease and G6PD deficiency.

Secondary Prophylaxis to Prevent Recurrence of Disease

Preferred Therapy	Alternative Choices
TMP-SMX: 1 DS qd <i>or</i> TMP-SMX: 1 SS qd	Dapsone: 50 mg bid <i>or</i> Dapsone: 100 mg qd
	Dapsone: 50 mg qd <i>plus</i> Pyrimethamine: 50 mg qweek <i>plus</i> Leucovorin: 25 mg qweek
	Pentamidine (aerosolized): 300 mg qmonth
	Atovaquone Suspension: 1500 mg qd
	TMP-SMX: 1 DS 3x/week

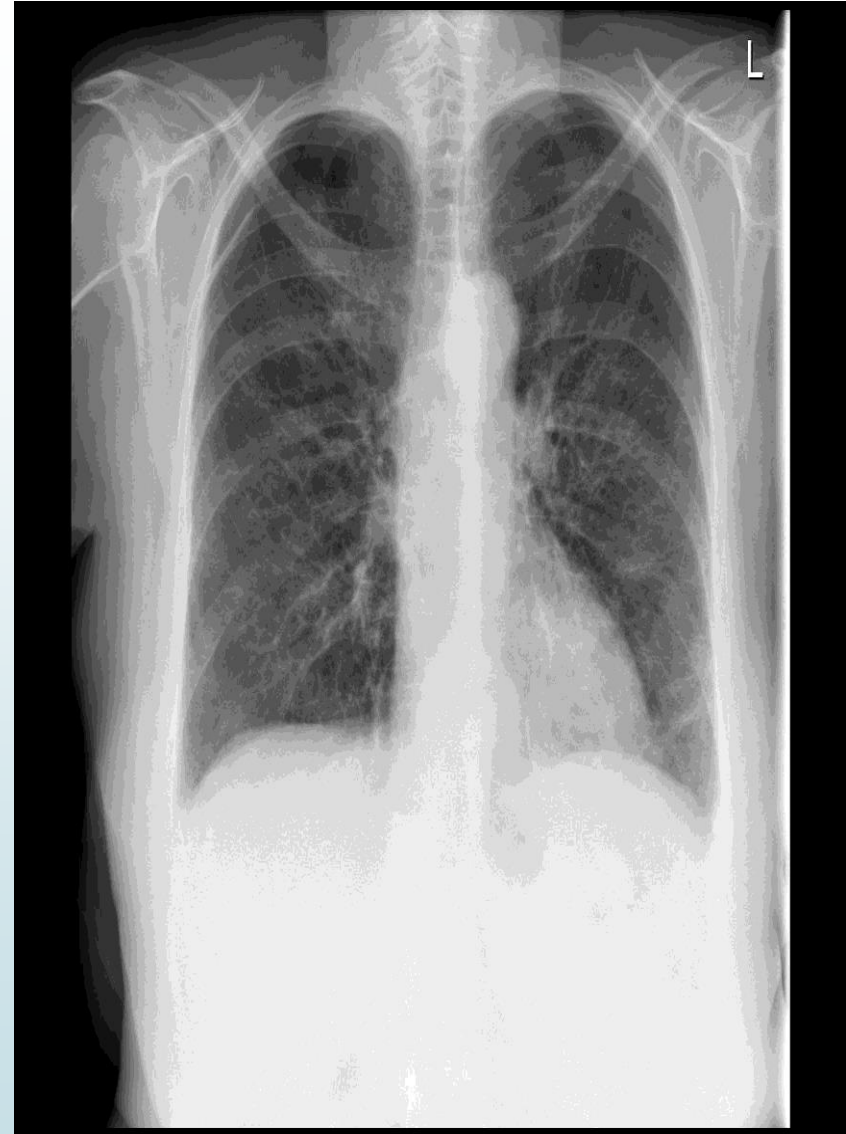
Patients who have responded to HAART & have:

- well controlled HIV RNA levels
 - CD4 >200 cells/mm³ for at least 3 mo
- should discontinue long-term secondary prophylaxis for *PJP*

**Pts who have discontinued secondary prophylaxis and have:
CD4 count < 200 cells/mm³ →
should restart prophylaxis**

LYMPHOID INTERSTITIAL PNEUMONIA

- **children** 30-40%
- lymphoproliferative disorder
- Histologically, diffuse **alveolar infiltration with lymphocytes**
- Pts **may be asymptomatic** or
- insidious onset of respiratory distress
- cough and mild hypoxemia, weight loss.
- chest xR:
 - **bibasilar,**
 - fine **reticular & nodular opacities**
 - an occasional alveolar component
 - **+ mediastinal adenopathy**
- Severe cases: + corticosteroids
- Antiretroviral therapy



HIV wasting syndrome



**involuntary weight loss >10% baseline
body weight**

Unexplained

PLUS EITHER

chronic diarrhoea reported for >1month

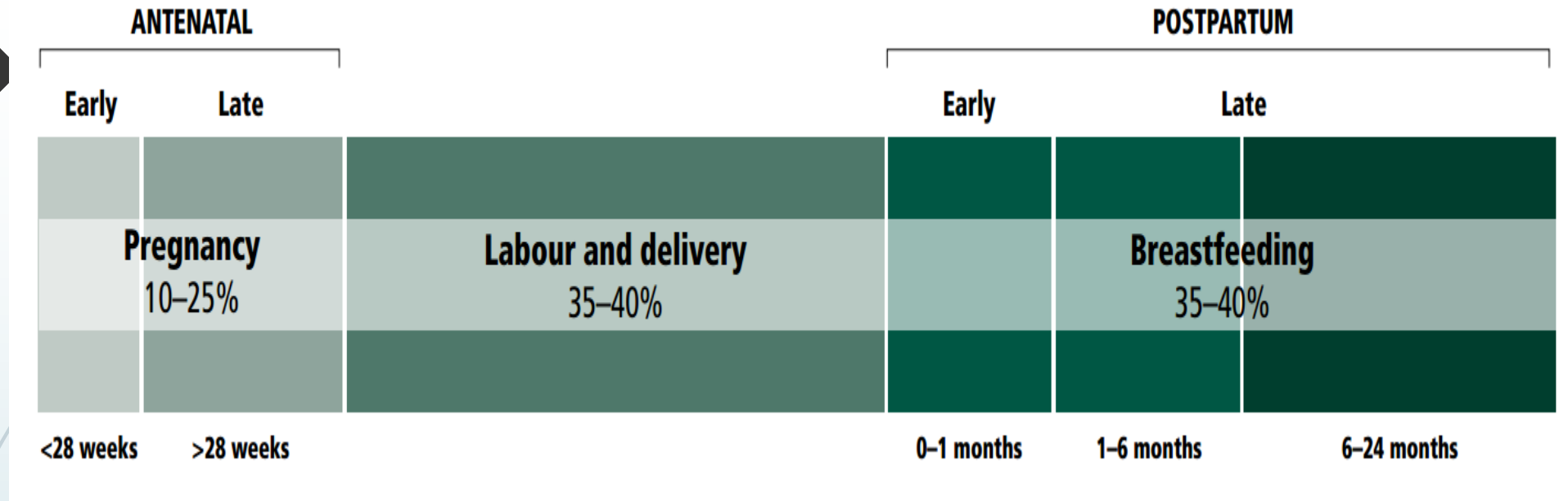
Unexplained

OR

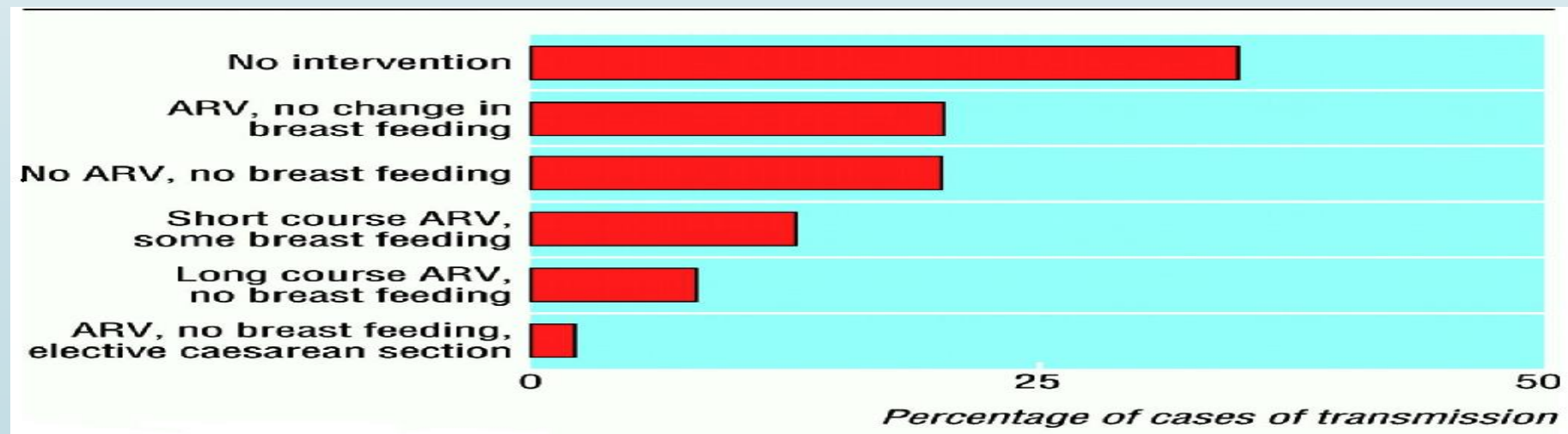
fever or night sweats for >1 month

Unexplained

The risk of HIV mother-to-child transmission



Caesarean section is not recommend VL-HIV<50



Evolution of HIV infection in children

➤ Early infection

➤ Late infection

Average length of life

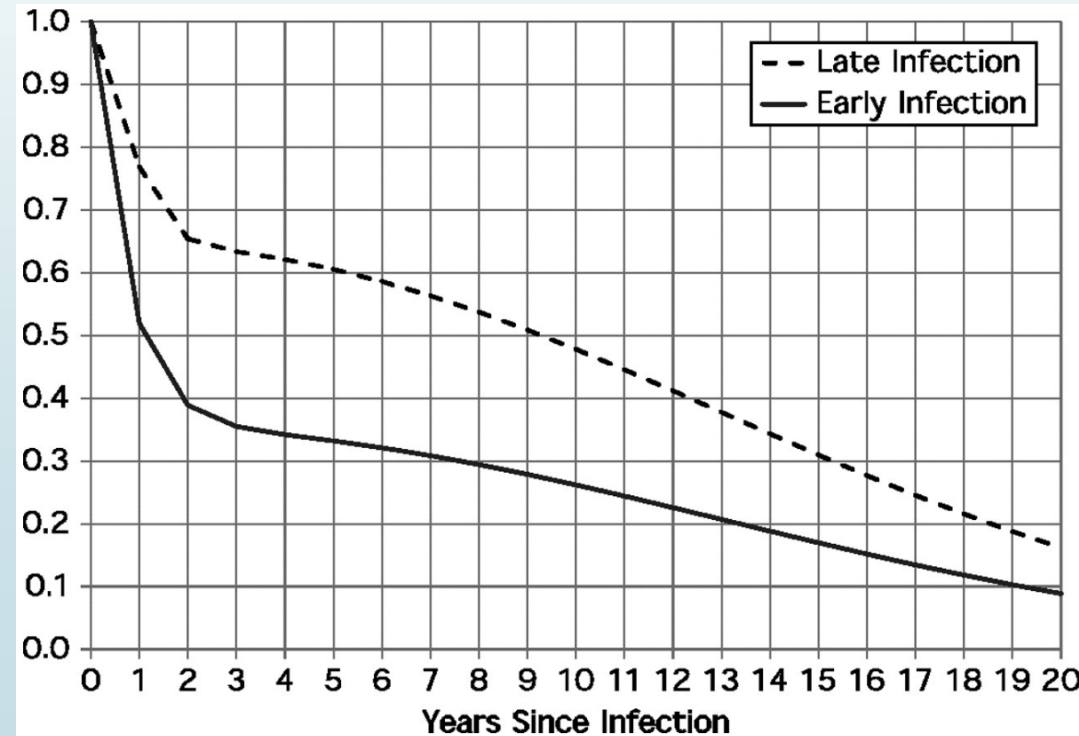
1,1 years

9,4 years

**Median survival time of
about 20 years**

< 9% patients

16% patients



Symptoms of pediatric HIV infection:

- vary by age and individual child,
- the more common symptoms:
 - Unusually frequent / severe / recurrent / not responding to standard treatment
 - bac inf. (otitis media, sinusitis, pneumonia)
 - fungal inf. (candid.)
 - viral infections (HSV, HZV, CMV)
 - **Growth** failure
 - Failure to gain **weight**
 - Failure to reach **developmental** milestones during the expected time frame
 - **Behavioral** abnormalities (in older children), such as loss of concentration and memory

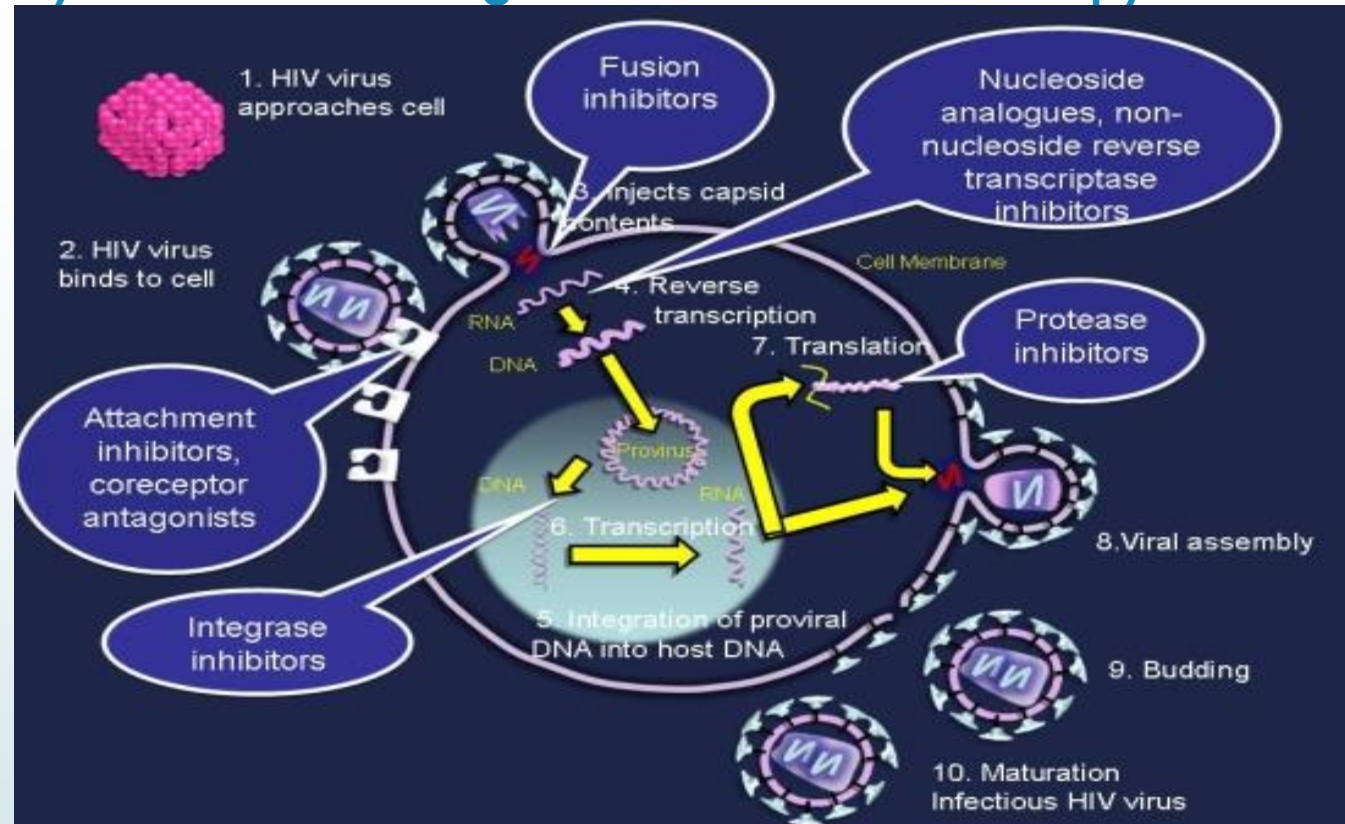
Signs and symptoms of pediatric HIV infection

- Unexplained persistent *hepatosplenomegaly*
- Lineal gingival erythema
- Extensive **wart** virus infection,
- Extensive **molluscum** contagiosum
- Unexplained persistent **parotid** enlargement
- **Unusually frequent / severe / recurrent / not responding** to standard treatment
 - bac inf. (otitis media, sinusitis, bronchitis, pneumonia)
 - fungal inf. (candid.)
 - viral infections (HSV, HZV, CMV)
- Unexplained persistent **diarrhoea** (14 days or more) not responding atment
- **Lymph node tuberculosis**

Signs and symptoms of pediatric HIV infection

- Symptomatic **lymphoid interstitial pneumonitis**
- Chronic HIV-associated lung disease including **brochiectasis**
- Persistent oral **candidiasis** (after first 6–8 weeks of life)
- **CMV inf:** retinitis or another organ, at age older than one month
- **CNS toxo** after one month of life
- Growth/ thrive failure = Documented weight for height or weight for age of more than –3 standard deviations from the mean
- **Developmental delay** (impairment development of expressive language)
- **Behavioral abnormalities** (older children), loss of concentration and memory

The replication cycle of HIV and targets for antiretroviral therapy



First approved to treat HIV	How they attack HIV
1987	NRTIs interfere with the action of an HIV protein called reverse transcriptase, which the virus needs to make new copies of itself.
1997	NNRTIs also stop HIV from replicating within cells by inhibiting the reverse transcriptase protein.
1995	PIs inhibit protease, which is another protein involved in the HIV replication process.
2003	Fusion or entry inhibitors prevent HIV from binding to or entering human immune cells.
2007	Integrase inhibitors interfere with the integrase enzyme, which HIV needs to insert its genetic material into human cells.

CLASSIFICATION OF ANTIRETROVIRALS

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Zidovudine (AZT or ZDV)
- Abacavir (ABC)
- Stavudine (d4T)
- Didanosine (ddI)
- Lamivudine (3TC)
- Emtricitabine (FTC)

Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

- Tenofovir (TDF)

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

(*potential for cross resistance*; skin rash; *HIV2 resistant*)

- Efavirenz (EFV)
- Etravirine (ETV)
- Nevirapine (NVP)
- Rilpivirine (RPV)

CLASSIFICATION OF ANTIRETROVIRALS

Protease Inhibitors (PI) Higher genetic barrier to resistance

- Atazanavir + ritonavir (ATV/r)
- Darunavir + ritonavir (DRV/r)
- Fosamprenavir + ritonavir (FPV)
- Indinavir + ritonavir (IDV)
- Lopinavir/ritonavir (LPV/r)
- Saquinavir + ritonavir (SQV/r)
- Tipranavir (TPV)

HIV integrase strand transfer inhibitors (INSTI)

- Raltegravir (RAL)
- Dolutegravir (DTG)
- Elvitegravir (EVG/c)

Fusion Inhibitors (FI)

- Enfuvirtide (ENF)

Entry Inhibitors - CCR5 co-receptor antagonist)

- Maraviroc (MVC)

Oral pre-exposure prophylaxis of HIV (PrEP)

→ to block the acquisition of HIV

fixed-dose combination of TDF and FTC in a single daily dose

- ▶ serodiscordant heterosexual couples,
- ▶ *men and transgender women who have sex with men,*
- ▶ *high risk heterosexual couples,*
- ▶ *people who inject drugs*
- ▶ **HIV testing** → to confirm pts HIV neg Ab-test within **1 week before PrEP.**
- ▶ Oral rapid tests should not be used.
- ▶ HIV testing should be repeated at least every 3 months
- ▶ Max intracellular concentrations of TFV-DP in blood after ~20 days

Recommended Oral PrEP Medications

Generic Name	Trade Name	Dose	Frequency	Common Side Effects ⁶⁶
Tenofovir disoproxil fumarate (TDF)	Viread	300 mg	Once a day	Nausea, flatulence
Emtricitabine (FTC) ^a	Emtriva	200 mg	Once a day	Rash, headache
TDF + FTC	Truvada	300mg/200 mg	Once a day	—

^aNot recommended alone; only for use in combination with TDF.

Post-exposure prophylaxis (PEP)

for occupational and non-occupational exposure to HIV

→ to reduce the likelihood of acquiring HIV inf. after potential exposure

- Theoretically, PEP might prevent or inhibit systemic inf. by limiting the proliferation of virus in the initial target cells or lymph nodes
- first dose → ideally < 4 hours after the exposure, and no later than 48 hours (EACS) // 72 hours (WHO)
- Duration: 4 weeks
- Choice of PEP drugs should be based on the country's first-line ARVT
- Standard PEP regimen: TDF/FTC (alternative: ZDV/3TC) + LPV/r or + RAL or + DRV/r

Follow-up:

- within 48 hours of exposure: serology: HIV; HBV; HCV; pregnancy test
- Re-evaluation of PEP by HIV expert within 48-72 hours
- Repeat HIV serology after 2 and 4 months

ARV therapy

The goals for treating

- Maximally and durably suppressing viral **replication**
- Potentially reduce the emergence of **viral mutations**
- Reducing HIV-related **mortality and morbidity**
- Restoring and/or preserving **immune** function
- Maintaining in children normal physical growth and **neurocognitive** development

Disadvantages of ARV therapy

- **Adverse** effects on quality of life (toxicities, complex regimens)
- Potential for drug **resistance** (nonadherence, insufficient suppression)

Combination ART **at least 3 drugs** from **at least 2 classes**
recommended for initial treatment

TDF + FTC + DTG

TDF + 3TC + DTG

When to start ART in people living with HIV

ALL HIV infected persons regardless CD4 count and viral load!!!

Conditions Favoring More Urgent Initiation of Therapy:

- **Pregnancy**
- **AIDS**-defining conditions
- **Acute OIs**
- Lower CD4 counts (e.g., <200 cells/mm³)
- HIV acquired **nephropathy**
- **Acute/Early Infection**
 - • HIV/**HBV** coinfection
 - • HIV/**HCV** coinfection
- Rapidly **declining CD4** counts (e.g., >100 cells/mm³ decrease per year)
- **Higher viral loads** (e.g., >100,000 copies/mL)

A combination ART regimen **generally consists of:**

- 2 NRTIs +
 - INSTI I (I line – for initial ARV) or
 - PI (generally boosted with RTV) (II line) or
 - NNRT or

Individualization of ART on the basis of:

- virologic efficacy
- toxicity
- pill burden
- dosing frequency
- drug-drug interaction
- resistance testing results
- comorbidity

Antiretroviral Regimens **Not** Recommended

Monotherapy with NRTI

- Rapid resistance
- Inferior ARV activity

Dual-NRTI regimens

- Rapid resistance
- Inferior ARV activity

Triple-NRTI regimens except for ABC/ZDV/3TC or possibly TDF + ZDV/3TC

- High rate of early virologic nonresponse (ABC/TDF/3TC; TDF/ddI/3TC).

Initial Combination Regimen for ART-naïve Adult HIV-positive Persons

A) Recommended regimens (one of the following to be selected)^{*,**}

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC/DTG ^(i, ii)	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
TDF/FTC ^(iii, iv) + DTG	TDF/FTC 300 ^(viii) /200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd	None	
TDF/FTC/EVG/c ^(iii, iv)	TDF/FTC/EVG/c 300 ^(viii) /200/150/150 mg, 1 tablet qd	With food	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
TDF/FTC ^(iii, iv) + RAL	TDF/FTC 300 ^(viii) /200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
2 NRTIs + NNRTI			
TDF/FTC/RPV ⁽ⁱⁱⁱ⁾	TDF/FTC/RPV 300 ^(viii) /200/25 mg, 1 tablet qd	With food (min 390 Kcal required)	Only if CD4 count >200 cells/ μ L and HIV VL <100,000 copies/mL. PPI contraindicated; H2 antagonists to be taken 12h before or 4h after RPV.
2 NRTIs + PI/r			
TDF/FTC ^(iii, iv) + DRV/r	TDF/FTC 300 ^(viii) /200 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Monitor in persons with a known sulfonamide allergy.



Adherence

→ once-daily fixed-dose

HIV-2 infection www.who.int/hiv/pub/guidelines/arv2013/annexes

HIV-2 is naturally resistant to NNRTIs,

treatment-naive people coinfecting HIV-1 + HIV-2 = treated with three NRTIs:

- TDF + 3TC (or FTC) + AZT
- AZT + 3TC + ABC
- ritonavir-boosted PI (LPV/r or SQV/r, or DRV/r) + two NRTIs.

Drug-resistance testing is recommended:

- acute HIV infection
- ART-naive patients regardless of whether therapy is initiated
- repeat resistance testing before initiation of ART
- virologic failure
- suboptimal suppression of viral load
- pregnant women

What to expect in the first months of ART

- ▶ Clinical & immunological improvement & virological suppression
- ▶ opportunistic inf. and/or **immune reconstitution inflammatory syndrome (IRIS)**
- ▶ early adverse drug reactions (hypersensitivity), especially in the first three months of ART.

ART:

- ▶ significantly decreases mortality overall,
- ▶ but death rates are also highest in the first three mo of ART. (more common when:
 - ▶ severe immunodeficiency
 - ▶ existing coinfections and/or comorbidities,
 - ▶ severely low Hb,
 - ▶ low body mass index
 - ▶ very low CD4 counts

Immune reconstitution inflammatory syndrome (IRIS)

- ▶ associated with immune recovery by a response to ART.
- ▶ 10–30% people; within first 4–8 we of ART
- ▶ may present in two different ways:
 - ▶ **paradoxical IRIS:** opportunistic inf. / tumour (TB, cryptococ, Kaposi's, HZV) diagnosed before ART initially responds to treatment but then deteriorates after ART starts
 - ▶ **unmasking IRIS:** ART triggers disease that is not clinically apparent before ART (exclude new inf.)
- ▶ The main risk factors:
 - ▶ low CD4+ cell count (<50 cells/mm³) at ART initiation,
 - ▶ disseminated opportunistic inf. / tumours
 - ▶ short duration of therapy for opport. inf. before ART starts
- ▶ generally self-limiting, rarely indicated interruption of ART
- ▶ Most important steps to reduce IRIS:
 - ▶ earlier HIV diagnosis
 - ▶ ART before CD4 <200
 - ▶ improved screening for opportunistic infections before ART
 - ▶ optimal management of opportunistic infections before initiating ART.

Monitoring the response to ART and the diagnosis of treatment failure

WHO

- ▶ Viral load measurements = preferred monitoring approach to diagnose and confirm ARV treatment failure

Treatment failure = persistently detectable viral load >1000 copies/ml

(2 consecutive viral load measurements within 3 mo interval, with adherence support) after at least 6 mo of ART

If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure

Pregnant & breastfeeding

- ▶ triple ARVs (ART)
- ▶ initiate ART as lifelong treatment
- ▶ **NO breastfeeding!!!**
- ▶ **When + breastfeeding:**
 - ▶ exclusively breast. first 6 mo → appropriate complementary foods thereafter & breast. first 12 mo.
 - ▶ once-daily fixed-dose of TDF + 3TC (or FTC)+ EFV

Infants of mothers who are receiving ART

- ▶ **If replacement feeding:** 4-6 we NVP (or twice-daily AZT).
- ▶ Breastfeeding: 6 we prophylaxis with daily NVP
- ▶ Prophylaxis → at birth or when HIV exposure is recognized

Treatment of HIV-positive Pregnant Women

Pregnant women should be monitored every month and as close as possible to the predicted delivery date

Criteria for starting ART in pregnant women (see different scenarios)	Same as for non pregnant
Objective of treatment in pregnant women	Full plasma HIV-VL suppression at least by third trimester and specifically at time of delivery
Resistance testing	Same as for non pregnant women, i.e. before starting ART and in case of virological failure
SCENARIO	
1. Women planning to be pregnant while already on ART	1. Maintain ART, unless taking some contra-indicated regimen during pregnancy (ddl + d4T, triple NRTI combinations)
2. Women becoming pregnant while already on ART	2. Maintain ART, unless taking some contra-indicated regimen during pregnancy (ddl + d4T, triple NRTI combinations)
3. Women becoming pregnant while treatment-naïve	3. Starting ART as soon as possible and not later than beginning of 2nd trimester is highly recommended
4. Women whose follow-up starts after week 28 of pregnancy	4. Start ART immediately and consider adding INSTI to obtain rapid HIV-VL decline in case of high HIV-VL
5. Women whose HIV-VL is not undetectable at third trimester	5. Perform resistance testing and consider adding INSTI to obtain rapid HIV-VL decline
Antiretroviral regimen in pregnancy	Same as non pregnant
	NVP not to be initiated but continuation is possible if started before pregnancy
	EFV can be started if other options are not available or suitable. Continuation of EFV is possible if already started before pregnancy
	Among PI/r, prefer LPV/r or ATV/r
Drugs contra-indicated during pregnancy	ddl + d4T, triple NRTI combinations
iv ZDV during labour	Not necessary if HIV-VL < 50 copies/mL
Single dose NVP during labour	Not recommended
Caesarean section	Only if HIV-VL > 50 copies/mL at week 34-36

Table 7.8 Summary of maternal and infant ARV prophylaxis for different clinical scenarios

Scenario	Maternal ARV prophylaxis ^a	Infant ARV prophylaxis ^b	Duration of infant ARV prophylaxis
Mother diagnosed with HIV during pregnancy ^{c,d}	Initiate maternal ART	NVP ^c	6 weeks ^c
Mother diagnosed with HIV during labour or immediately postpartum and plans to breastfeed	Initiate maternal ART	NVP	6 weeks; consider extending this to 12 weeks
Mother diagnosed with HIV during labour or immediately postpartum and plans replacement feeding	Refer mother for HIV care and evaluation for treatment	NVP ^c	6 weeks ^c
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is breastfeeding	Initiate maternal ART	NVP	Perform infant PCR early infant diagnosis test and then immediately initiate 6 weeks of NVP – strongly consider extending this to 12 weeks
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is not breastfeeding	Refer mother for HIV care and evaluation for treatment	No drug	Do HIV PCR test in accordance with national recommendations on early infant diagnosis; no infant ARV prophylaxis; initiate treatment if the infant is infected
Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)	Determine an alternative ARV regimen or solution; counsel regarding continuing ART without interruption	NVP	Until 6 weeks after maternal ART is restarted or until 1 week after breastfeeding has ended

CHILDREN +ART

- ▶ any child <18 mo. presumptive clinical diagnosis of HIV
- ▶ all HIV+ <5 y.o. regardless of clinical stage or CD4 count.
- ▶ >5 y.o ART CD4 ≤ 500 (≤ 350 - strong recomand., regardless of WHO clinical stage).
- ▶ all with severe / advanced sympt. disease (stage 3 or 4)
- ▶ ART should be initiated in infection (*strong recommendation, low-quality evidence*)

Virological Failure

Definition	Confirmed HIV-VL > 50 copies/mL 6 months after starting therapy (initiation or modification) in persons that remain on ART
General measures	Review expected potency of the regimen
	Evaluate adherence, compliance, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues
	Perform resistance testing on failing therapy (usually routinely available for HIV-VL levels > 350-500 copies/mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations
	Tropism testing
	Consider TDM
	Review antiretroviral history
	Identify treatment options, active and potentially active drugs/combinations
Management of virological failure (VF)	If HIV-VL > 50 and < 500-1000 copies/mL
	Check for adherence
	Check HIV-VL 1 to 2 months later
	If genotype not possible, consider changing regimen based on past treatment and resistance history
	If HIV-VL confirmed > 500/1000 copies/mL, change regimen as soon as possible. What to change will depend on the resistance testing results:
	No resistance mutations found: re-check for adherence, perform TDM
	Resistance mutations found: switch to a suppressive regimen based on drug history; multidisciplinary expert discussion advised
	Goal of new regimen: HIV-VL < 400 copies/mL after 3 months, HIV-VL < 50 copies/mL after 6 months

In case of demonstrated resistance mutations	General recommendations:
	Use at least 2 and preferably 3 active drugs in the new regimen (including active drugs from previously used classes)
	Any regimen should use at least 1 fully active PI/r (e.g. DRV/r) plus 1 drug from a class not used previously e.g. fusion, integrase or CCR5 antagonist (if tropism test shows R5 virus only), or 1 NNRTI (e.g. ETV), assessed by genotypic testing
	Defer change if < 2 active drugs available, based on resistance data, except in persons with low CD4 count (< 100 cells/ μ L) or with high risk of clinical deterioration for whom the goal is the preservation of immune function through partial reduction of HIV-VL (> 1*log ₁₀ reduction) by recycling
	If limited options, consider experimental and new drugs, favouring clinical trials (but avoid functional monotherapy)
	Treatment interruption is not recommended
	Consider continuation of 3TC or FTC in particular situations even if documented resistance mutation (M184V/I)
	If many options are available, criteria of preferred choice include: simplicity of the regimen, toxicity risks evaluation, drug-drug interactions, future salvage therapy

Table 7.13 Recommended and desirable laboratory tests at HIV diagnosis and monitoring on ART

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV serology, CD4 cell count TB screening	HBV (HBsAg) serology ^a HCV serology <i>Cryptococcus</i> antigen if CD4 count ≤ 100 cells/mm ³ ^b Screening for sexually transmitted infections Assessment for major noncommunicable chronic diseases and comorbidities ^c
Follow-up before ART	CD4 cell count (every 6–12 months)	
ART initiation	CD4 cell count	Haemoglobin test for AZT ^d Pregnancy test Blood pressure measurement Urine dipsticks for glycosuria and estimated glomerular filtration rate (eGFR) and serum creatinine for TDF ^e Alanine aminotransferase for NVP ^f
Receiving ART	CD4 cell count (every 6 months) HIV viral load (at 6 months after initiating ART and every 12 months thereafter)	Urine dipstick for glycosuria and serum creatinine for TDF ^c
Treatment failure	CD4 cell count HIV viral load	HBV (HBsAg) serology ^a (before switching ARV regimen if this testing was not done or if the result was negative at baseline)

Table 7.14 WHO definitions of clinical, immunological and virological failure for the decision to switch ARV regimens

Failure	Definition	Comments
Clinical failure	Adults and adolescents New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) ^a after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome ^b occurring after initiating ART
	Children New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment	For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure ^a
Immunological failure	Adults and adolescents CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm ³	Without concomitant or recent infection to cause a transient decline in the CD4 cell count A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure (182). The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
	Children Younger than 5 years Persistent CD4 levels below 200 cells/mm ³ or <10% Older than 5 years Persistent CD4 levels below 100 cells/mm ³	

Persons with TB

should be started on standard TB therapy with:

- 2 mo rifampicin/isoniazid/pyrazinamide +/- ethambutol followed by
- 4 months rifampicin/isoniazid
- choice of drugs and length of treatment → susceptibility & site disease

All persons with TB/HIV co-infection should start ART irrespective of CD4

Suggested timing of ART initiation in TB/HIV co-inf according to CD4:

<50 WHO / <100 EU → within 2 we of TB treatment

> 50 WHO / >100 EU → can be deferred until 8-12 we of TB treatment




WHO:

Immediate ART initiation is not recommended in patients with cryptococcal meningitis due to the high risk of immune reconstitution inflammatory syndrome (IRIS)

Among people living with HIV with a recent diagnosis of cryptococcal meningitis, ART

initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy and

- after two to four weeks of induction and consolidation treatment with amphotericin containing regimens combined with flucytosine or fluconazole; or
- after four to six weeks of induction and consolidation treatment with a high-dose oral fluconazole regimen (*conditional recommendation, low-quality evidence*).

A dark grey arrow points to the right at the top left. Below it, several thin, curved lines in shades of blue and grey sweep across the left side of the slide.

Cryptococcus meningitis remains a leading cause of mortality among people with HIV, contributing up to 20% of AIDS-related deaths in low- and middle-income settings, and WHO recommends systematic Cryptococcus antigen screening for everyone with CD4 \leq 100 cells/mm³ and preemptive treatment for those with positive antigen test

WHO recommends providing co-trimoxazole prophylaxis to everyone presenting to care with a CD4 count \leq 200 cells/ mm³ (as well as for those with WHO clinical stage 3 or 4). Co-trimoxazole improves survival by reducing the risk of death from a range of infections, including malaria, severe bacterial infections, Pneumocystis pneumonia and toxoplasmosis

Table 2 - Classification of the oral manifestations of HIV disease in adults

Group 1 lesions strongly associated with HIV infection	Group 2 lesions less commonly associated with HIV infection	Group 3 lesions seen in HIV infection
<p>Candidosis</p> <ul style="list-style-type: none"> • Erythematous • Pseudomembranous 	<p>Bacterial infections</p> <ul style="list-style-type: none"> • Mycobacterium avium-intracellulare • Mycobacterium tuberculosis 	<p>Bacterial infections</p> <ul style="list-style-type: none"> • Actinomyces israelii • Escherichia coli • Klebsiella pneumonia
<p>Hairy leukoplakia</p> <p>Kaposi's sarcoma</p>	<p>Melanotic hyperpigmentation</p> <p>Necrotizing (ulcerative) stomatitis (Figure 5)</p>	<p>Cat-scratch disease</p> <p>Drug-reactions</p> <ul style="list-style-type: none"> • Ulcerative • erythema multiforme • lichenoid • toxic epidermolysis
<p>Non-Hodgkin's lymphoma</p>	<p>Salivary gland diseases</p> <ul style="list-style-type: none"> • Dry mouth due to decreased salivary flow rate • Unilateral or bilateral swelling of major salivary glands 	<p>Epithelioid (bacillary) angiomatosis</p>
<p>Periodontal disease</p> <ul style="list-style-type: none"> • Linear gingival erythema • Necrotizing gingivitis • Necrotizing periodontitis 	<p>Thrombocytopenic purpura</p>	<p>Fungal infections other than candida</p> <ul style="list-style-type: none"> • Cryptococcus neoformans • Geotrichum candidum • Histoplasma capsulatum • Mucoraceae (mucormycosis, zygomycosis) • Aspergillus flavus
	<p>Ulceration NOS (not otherwise specified)</p>	<p>Neurological disturbances</p> <ul style="list-style-type: none"> • Facial palsy • Trigeminal neuralgia
	<p>Viral infections</p> <ul style="list-style-type: none"> • Herpes simplex virus • Human papillomavirus lesions <ul style="list-style-type: none"> ◆ Condyloma acuminatum ◆ Focal epithelial hyperplasia ◆ Verruca vulgaris • Varicella zoster virus <ul style="list-style-type: none"> ◆ Herpes zoster ◆ Varicella 	<p>Viral infections</p> <ul style="list-style-type: none"> • Cytomegalovirus • Molluscum contagiosum

Table 3 - Classification of oral manifestations of pediatric HIV disease

Group 1 lesions commonly associated with pediatric HIV infection	Group 2 lesions less commonly associated with pediatric HIV infection	Group 3 lesions strongly associated with HIV infection but rare in children
Candidosis <ul style="list-style-type: none"> • Erythematous • Pseudomembranous • Angular cheilitis 	Seborrhoeic dermatitis	Neoplasms <ul style="list-style-type: none"> • Kaposi's sarcoma • Non-Hodgkin's lymphoma
Herpes simplex virus infection	Bacterial infections of oral tissues <ul style="list-style-type: none"> • Necrotizing (ulcerative) stomatitis 	Oral hairy leukoplakia
Linear gingival erythema	Periodontal diseases <ul style="list-style-type: none"> • Necrotizing (ulcerative) gingivitis • Necrotizing (ulcerative) periodontitis 	Tuberculosis-related ulcers
Parotid enlargement	Viral infections <ul style="list-style-type: none"> • Cytomegalovirus • Human papilloma virus • Molluscum contagiosum • Varicella-zoster virus <ul style="list-style-type: none"> ◆ Herpes zoster ◆ Varicella 	
Recurrent aphthous ulcers <ul style="list-style-type: none"> • Minor • Major • Herpetiform 	Xerostomia	

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Brand Name	Generic Name	Manufacturer Name*
<u>Combivir</u>	lamivudine and zidovudine	GlaxoSmithKline
<u>Emtriva</u>	emtricitabine, FTC	Gilead Sciences
<u>Epivir</u>	lamivudine, 3TC	GlaxoSmithKline
<u>Epzicom</u>	abacavir and lamivudine	GlaxoSmithKline
<u>Hivid</u>	zalcitabine, dideoxycytidine, ddC (no longer marketed)	Hoffmann-La Roche
<u>Retrovir</u>	zidovudine, azidothymidine, AZT, ZDV	GlaxoSmithKline
<u>Trizivir</u>	abacavir, zidovudine, and lamivudine	GlaxoSmithKline
<u>Truvada</u>	tenofovir disoproxil fumarate and emtricitabine	Gilead Sciences, Inc.
<u>Videx EC</u>	enteric coated didanosine, ddl EC	Bristol Myers-Squibb
<u>Videx</u>	didanosine, dideoxyinosine, ddl	Bristol Myers-Squibb
<u>Viread</u>	tenofovir disoproxil fumarate, TDF	Gilead
<u>Zerit</u>	stavudine, d4T	Bristol Myers-Squibb
<u>Ziagen</u>	abacavir sulfate, ABC	GlaxoSmithKline

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Brand Name	Generic Name	Manufacturer Name*
<u>Edurant</u>	rilpivirine	Tibotec Therapeutics
<u>Intelligence</u>	etravirine	Tibotec Therapeutics
<u>Rescriptor</u>	delavirdine, DLV	Pfizer
<u>Sustiva</u>	efavirenz, EFV	Bristol Myers-Squibb
<u>Viramune</u> (Immediate Release)	nevirapine, NVP	Boehringer Ingelheim
<u>Viramune XR</u> (Extended Release)	nevirapine, NVP	Boehringer Ingelheim

Protease Inhibitors (PIs)

Brand Name	Generic Name	Manufacturer Name*
<u>Agenerase</u>	amprenavir, APV (no longer marketed)	GlaxoSmithKline
<u>Aptivus</u>	tipranavir, TPV	Boehringer Ingelheim
<u>Crixivan</u>	indinavir, IDV,	Merck
<u>Fortovase</u>	saquinavir (no longer marketed)	Hoffmann-La Roche
<u>Invirase</u>	saquinavir mesylate, SQV	Hoffmann-La Roche
<u>Kaletra</u>	lopinavir and ritonavir, LPV/RTV	Abbott Laboratories
<u>Lexiva</u>	Fosamprenavir Calcium, FOS-APV	GlaxoSmithKline
<u>Norvir</u>	ritonavir, RTV	Abbott Laboratories
<u>Prezista</u>	darunavir	Tibotec, Inc.
<u>Reyataz</u>	atazanavir sulfate, ATV	Bristol-Myers Squibb
<u>Viracept</u>	nelfinavir mesylate, NFV	Agouron Pharmaceuticals

Fusion Inhibitors

Brand Name

[Fuzeon](#)

Generic Name

enfuvirtide, T-20

Manufacturer Name

Hoffmann-La Roche & Trimeris

Entry Inhibitors - CCR5 co-receptor antagonist

Brand Name

[Selzentry](#)

Generic Name

maraviroc

Manufacturer Name

Pfizer

HIV integrase strand transfer inhibitors

Brand Name

[Isentress](#)

[Tivicay](#)

Generic Name

raltegravir

dolutegravir

Manufacturer Name

Merck & Co., Inc.

GlaxoSmithKline

Multi-class Combination Products

Brand Name	Generic Name	Manufacturer Name*
<u>Atripla</u>	efavirenz, emtricitabine and tenofovir disoproxil fumarate	Bristol-Myers Squibb and Gilead Sciences
<u>Complera</u>	emtricitabine, rilpivirine, and tenofovir disoproxil fumarate	Gilead Sciences
<u>Stribild</u>	elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate	Gilead Sciences