



HIV/Aids Training

Module 2

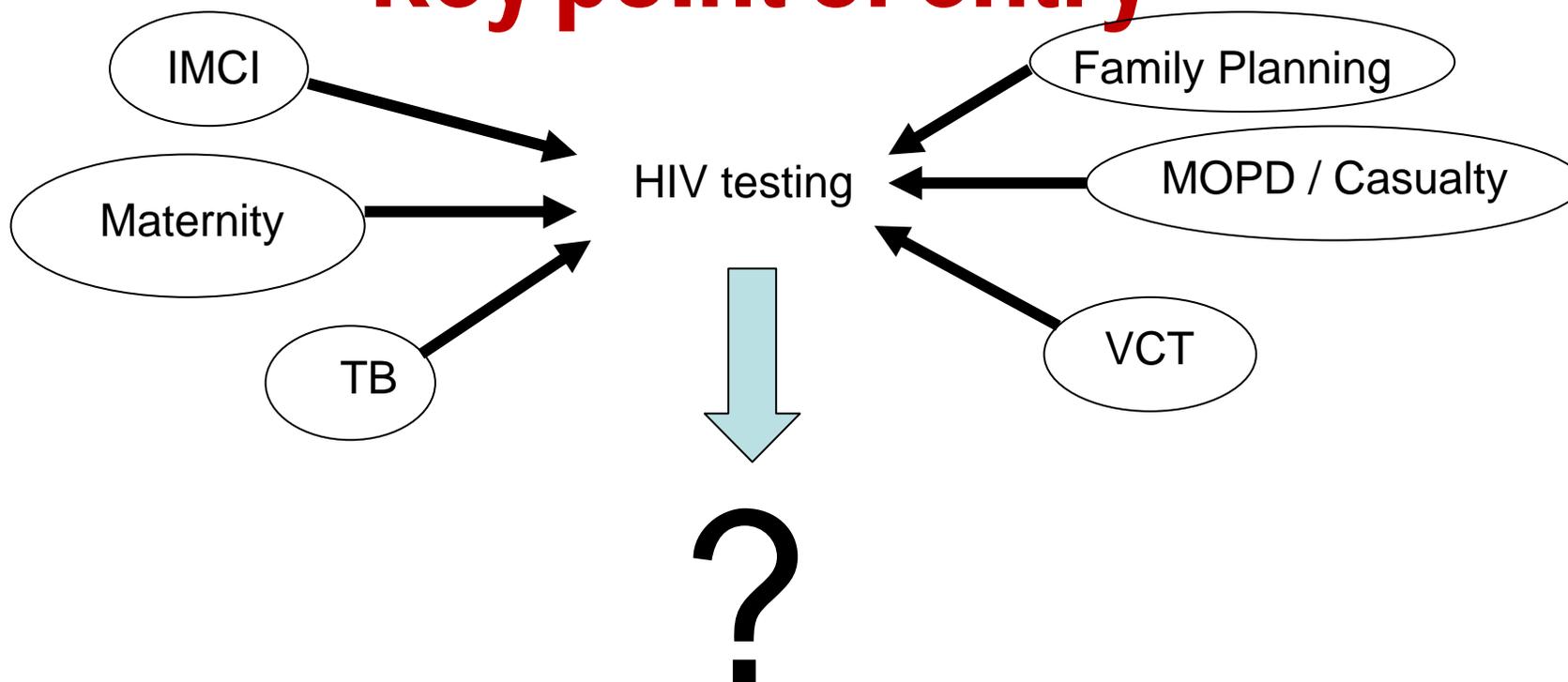
Diagnosing; Clinical Staging and
Opportunistic Infections
June 2008

Adapted from and thanks to:

Foundation for Professional Development; Ashraf Grimwood; GF Jooste meetings; Prof Gary Maartens lectures; PATA conference; MIC and Department of Pharmacology UCT



Key point of entry



Although the findings from this study are generally similar to those from the 2002 survey, it is interesting to note the significant increase in testing among respondents aged 15 years and older from a national average of 19.8% in 2002 to 30.5% in this study. Similar improvements are also evident among those who were HIV positive (36.5%) than among those who were HIV negative as was also the case in the 2002 survey (23.1% versus 18.2% respectively)

SA National Survey, 2005

Variable	Previously tested for HIV*
	%
Sex	
Male	26.4
Female	30.9
Marital status	
Married	39.1
Unmarried	25.5
Locality type	
Urban formal	40.4
Urban informal	29.2
Rural informal	19.3
Rural formal	21.0

SA National Survey, 2005

Table 3.54: HIV test history among respondents 15 years and older (n = 11 838), South Africa 2005

Variable	Previously tested for HIV*	HIV status found in this study	
	%	HIV+ %	HIV- %
Age group			
15–24	20.8	33.8	18.3
25–49	43.4	37.6	44.8
50+	17.7	35.1	18.5

Average = 30.3 % (less one third) have tested

Voluntary Counselling and Testing

- 1.7 million people have accessed the government's VCT programme in 2006 (more than the previous year)
- 35% of those tested were found to be HIV +
- 4172 VCT service points are operational in both medical and non-medical sites in 9 Provinces (R26 million spent annually on all Provinces for VCT) - Nov 2006

Routine in USA since 1999 in several states and opt-out for pregnant women → universal cover
Also at ANC in UK and Canada. Botswana has opt out approach

Introduction - HIV TESTING

- USA 1 to 1.2 million HIV+ and 25 % unaware of their status (transmission risk high)
- 40% receive their diagnosis < 12 months before developing AIDS
- EARLY diagnosis important
- 22 September 2006 USA revised HIV testing as a normal part of medical practice unless patient declines ie opts out screening
- written consent now NOT required

362 ARV sites
SAMJ April 2008

Sub-Saharan Africa

- 24.5 million HIV+ and <10% aware of their status Int J STD AIDS 2001 (Rwanda)
- Botswana initiated opt-out in 2004
- 4 types of testing recognised by WHO:
 - VCT
 - diagnostic testing of those with S & S of HIV disease
 - screening of blood products for transfusion
 - Health care provider testing

ATTIC = AIDS Training Information and Counselling Centre

Pre-test counselling

- **Confidentiality!**
- **Definitions HIV/AIDS**
- **Transmission**
- **Risk factors**
- **Meaning of results**
- **Implications of test**
- **“Window period”**
- **Procedure**
- **When results available**
- **How to ↓ risk and protect sexual partners**
- **Possible reaction to results**
- **Social support**
- **Return appointment**
- **No blood/organ donation**

“ It is never too early to start counselling”

**INFECTIOUS DISEASES CLINIC
COUNSELLING 1**

1. General information about transmission of HIV test general knowledge.

2. Counsellor must confirm that patients understand why they are here at the clinic.
2.1 Mention that patient are here for possible starting of ART.

3. Give information regarding clinic and procedures as well as clinic hours.

4. What does the HIV virus do?

5. What is the difference between HIV & Aids?

6. What is my CD4 count?

7. What is the CD4 function in my body?

8. What do you understand by viral load?

9. Disclosure issues:

10. Explain necessity of treatment supporter
Identify and bring with next visit.
No treatment supporter > no ART

11. Socio-economic in household
Alcohol and drug abuse habits
Depression/Psychiatry problems
Marital/sexual habits
Religion/Traditional healer

12. Grains

13. Family planning methods

14. Support groups

15. General comments

COMPLETED BY:

COUNSELLING 2

1. Questionnaire regarding counselling, according to patients' feedback, weaker areas must be identified and concentrated upon.

2. What is ART?

3. What does ART do? Important to stress suppresses the virus, but does not kill it. CD4 goes \uparrow viral load \downarrow .

4. Explain how to take ART

- 4.1 Importance of taking medication with discipline what will happen with CD4. VL if ART not taken correctly. Explain possibilities of resistance.

- 4.2 What to do if vomiting.

- 4.3 Skip doses.

- 4.4 Eating habits and availability of food (*most ART does not need full stomach*).

- 4.5 Discuss treatment plan.

5. When can you stop taking ART?

6. How regular will I see a doctor?

7. Day hospital there for minor ailments.

8. Do you believe ART will work?

9. Show them what is ART and differentiate between bactrim and vitamins.

10. Bactrim count to be done.
Always bring all your containers even though empty.

11. General comments:

COUNSELLING 3

1. What is the side-effects of ARV minor S/E, Major S/E
Patient to contact clinic if occur
(Make sure patient has contact numbers)

2. Does patient recognise ARV tablets and know their names?

3. Precise times to take ARV's and confirmation of treatment plan?

4. If treatment supporter there – make sure he/she has the same information regarding 1, 2, 3.

5. If patient going on leave for > 1 month, they must inform the clinic so that arrangements for enough ARV's can be made for that time.

6. Don't share your tablets with others.

7. If you have to go to other pharmacist/doctors they must be inform that you are on ARV's.

8. Effects of alcohol with ARV's.

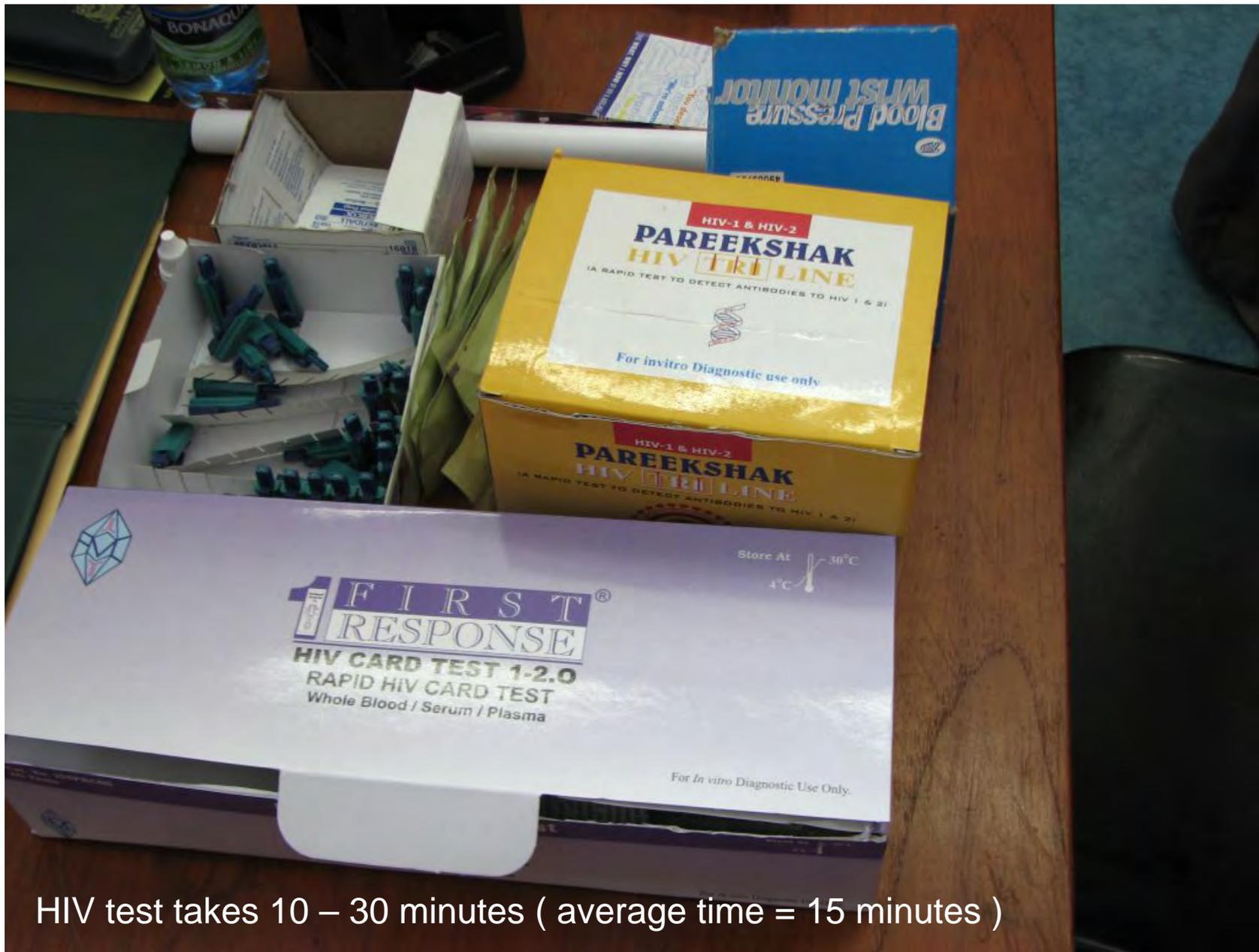
9. Individualisation of medicine use, e.g. patient working shifts/overtime.

10. If patient does not turn up for clinic visits, what must we do?

11. Lifelong decision, patient wants to stop need to inform us.

12. Support group.

13. General comments:



HIV test takes 10 – 30 minutes (average time = 15 minutes)

In KZN, *3D Broline* used for screening and “ *Sensa*” used for confirmatory test.

www.avert.org

VCT became available in Port Sudan Sudan in 2006

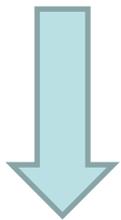
CHOICE ?

Patient = vulnerable

Medical staff = "powerful position"

Mandatory
HIV
testing

Voluntary
HIV
testing



PIT



VCT

ETHICS

ETHICS

- Do only good
- Do not harm
- Patient has the right to choose (patient autonomy – respect)
- Public health consideration (look at society at large)

VCT in 2008

- Policy guidelines for HIV voluntary counselling and testing recently published
- released from National Department of Health (NDoH) on **23 June 2008** supports National Strategic Plan (NSP) 2007 to 2011
- VCT established in SA in 1999 (53 sites after first year; one in each district)
- currently > 4100 VCT points in SA
- in 2007, there are 7000 lay counsellors providing counselling services (3000 in 2005)

VCT

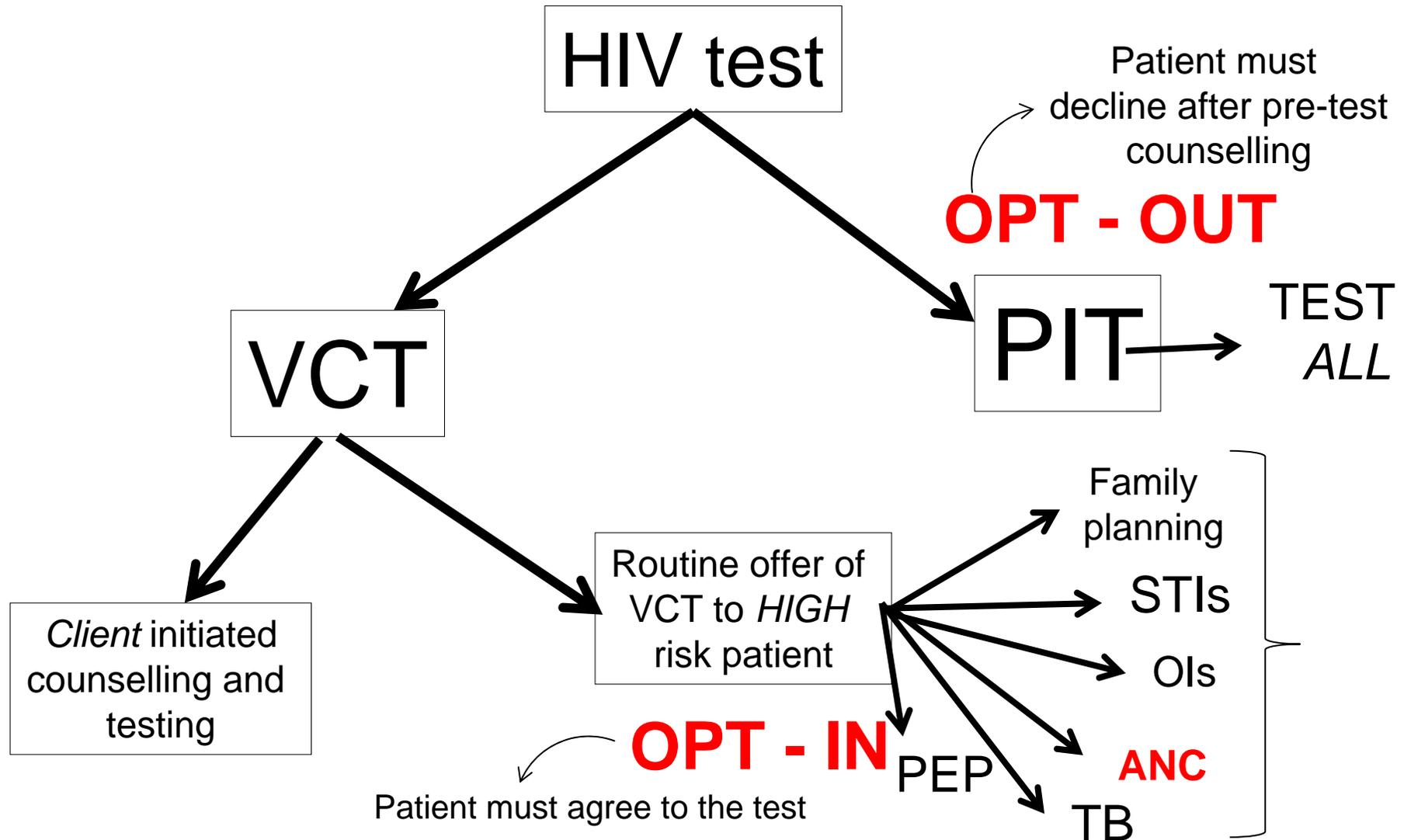
- from 2004 to 2006, \pm 5 million people utilised VCT, while 4 million were tested (20% declined ?)
- approximately 20% of the South African population have received HIV testing*
- NSP aims for an increase in the number of people in South Africa to know their status to 70%

HSRC July 2008 (personal communication)

Definitions

- child = all individuals under the age of *12 years*
- VCT = voluntary counselling and testing
- PITC = provider initiated *testing* and counselling
- PICT = provider initiated counselling and testing

Types of HIV testing



Age of HIV testing

- a child may be tested if he/she has sufficient maturity to understand and parent/caregiver has knowledge of the test
- *otherwise*, a parent/Provincial Head of Social Development/designated Child Protection Unit/Superintendent of a hospital or Children's Court

under the age
of 12 years

Laboratory Diagnosis

- Pre- and post-test counseling
- Detection of:
 - Antibodies
 - p24 antigen
 - viral nucleic acid (PCR)
 - virus by isolation from cell culture
- Typically ELISA (diagnosis)
- Western Blott, PCR (confirmation)
- Dried spot test

Window Period

- Time delay between infection and positive diagnostic tests

Assay	Days to Positivity (\pm)
1 st generation ELISA (Lysate)	42
3 rd generation ELISA (sandwich recombinant and synthetic peptides)	23
p24 antigen assays	16
4 th generation ELISA (+p24)	16
DNA PCR (proviral DNA)	16
RNA PCR (HIV-1 RNA)	11

- Implication: Diagnostics negative however highly infectious

Post-test counselling

- Significance of either a +/- result
- If negative - retest in 3 months
- If positive - explain infected and infectious
- Routes of transmission and prevention
- Pt's comprehension and significance
- Who he/she wishes to tell about result
- Notify sexual partners
- Social support
- Explain progression
- Availability of care programs
- Medical follow-up



EDTA (**purple top**) tube for CD4 count and viral load collection

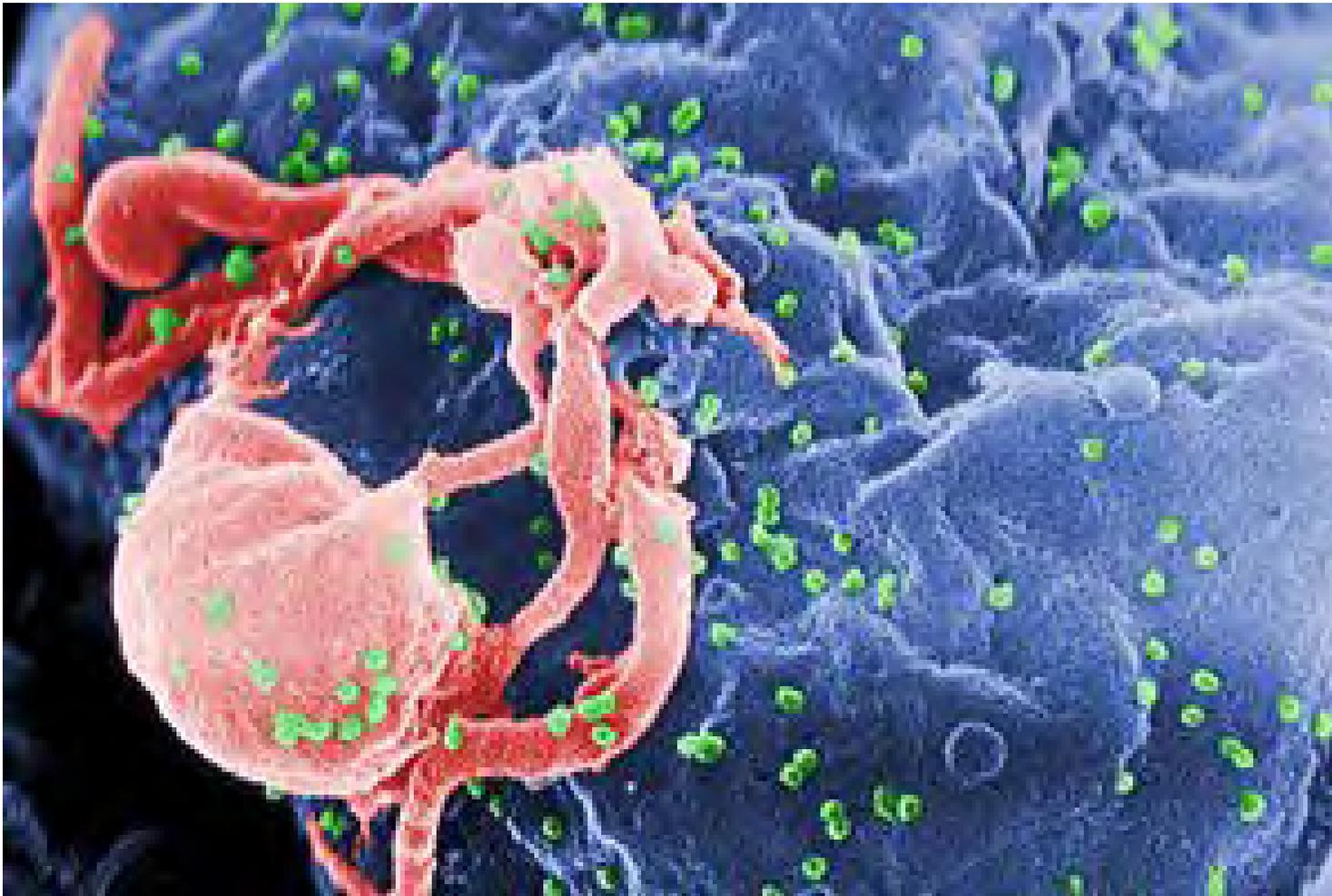
The CD System: 'cluster of differentiation'
Caligaris-Cappio F. *Lancet* 2001;358:49-54

**CD molecules are not merely
'markers'
that differentiate cells,
they have specific functions**

**the T cell and B cell receptors
are involved in
signal transduction.**

**Events occurring on
the surface
of the cell are relayed
into the cell
by means of these receptors**

- **CD classification system:**
www.hlda.org
- **Originally used to define T lymphocyte subsets but now applied to *all blood cells***
- **CD4 = helper T cells or T4 cells**
- **CD8 = cytotoxic/suppressor T cells**
- **CD3 = the T cell receptor, a general marker for all T cells**



Scanning electron micrograph of HIV-1 budding from lymphocyte



CD4 CELL COUNT



- **CD4 is a molecule primarily on the surface of T lymphocytes and is the main receptor for HIV infection**
- **progressive loss of CD4 cells is the cardinal manifestation of the effects of HIV infection**
- **is used to determine the *stage of disease* of the infected individual.**
- **criterion for starting ARV's - *less than 200*.**
- **PGWC protocol: performed *every 6 months* (pre ARV's and routine monitoring on ARV's)**



CD4 cell count (cells/mm³)

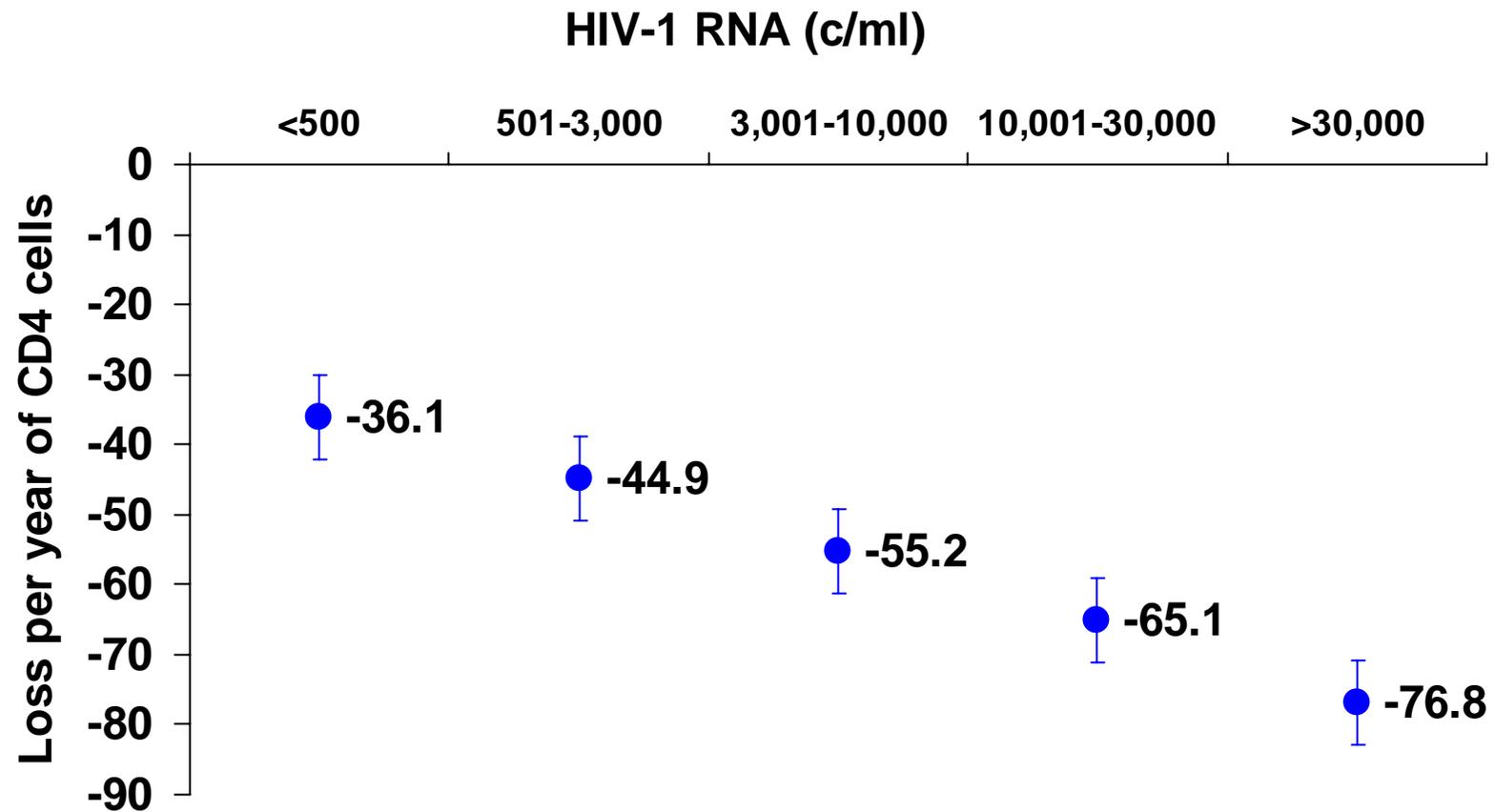
- Reflects degree of immune suppression

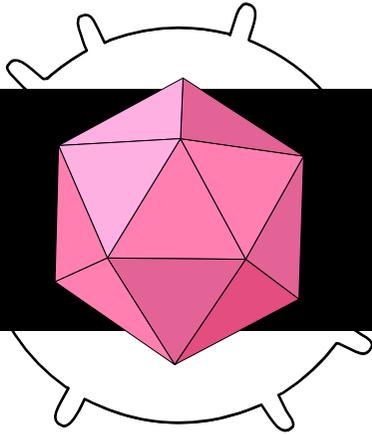
>500/mm³	Not significant immunosuppression
350 – 499/mm³	Mild immunosuppression
200 – 349/mm³	Advanced immunosuppression
<200/mm³	Severe immunosuppression

CD4 count recovery

- CD4 count rises rapidly within 4 weeks on starting HAART; then more gradually
- the average rise in CD4 is about 150 in the first year; thereafter about 80 cells/mm³
- this is extremely variable
- in about 10 – 20% of patients, the CD4 count fails to rise despite suppressed VL; do *not* change the HAART regime

Loss of CD4⁺ Cells/Year

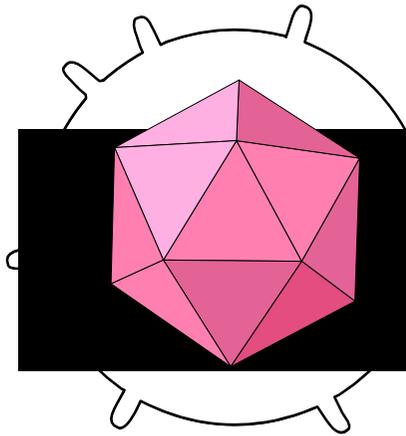




VIRAL LOAD

- Measures the amount of HIV in the blood.
- Indicates how fast the virus is replicating.
- Several techniques available – copies/ml.
- Use same technique for follow up VL's!!
- 5000-10000 copies/ml = low level of replication.
- May be millions/ml in early and late infection





VIRAL LOAD

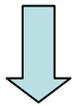
- Useful for monitoring the response to ARV's (and in some situations deciding when to initiate).
- Monitoring as per National guidelines is every 6 months
- Used to determine prognosis in terms of likely progression to AIDS
- CD4 counts drop more rapidly in patients with high VL's



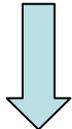
Venesection of monitoring bloods

- important to have correct timing every 6 months eg start date: January 2008

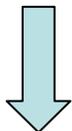
January 2008



July 2008



January 2009
1st Anniversary



July 2009



January 2009
2nd anniversary



for the
rest of
the
patient's
life

Note: If the patient is on leave, one can do the bloods a month earlier or later, but next must be done on DUE DATE

Follow-up of abnormal V/L

- all new lab results from the NHLS must be checked by the doctor
- patients with abnormal results must be recalled and *cause** identified
- **MUST** act within 3 - 6 months (do not ignore or put result away in file)
- ignoring an abnormal V/L may compromise future ARV treatment options

* usually poor adherence at 6 months

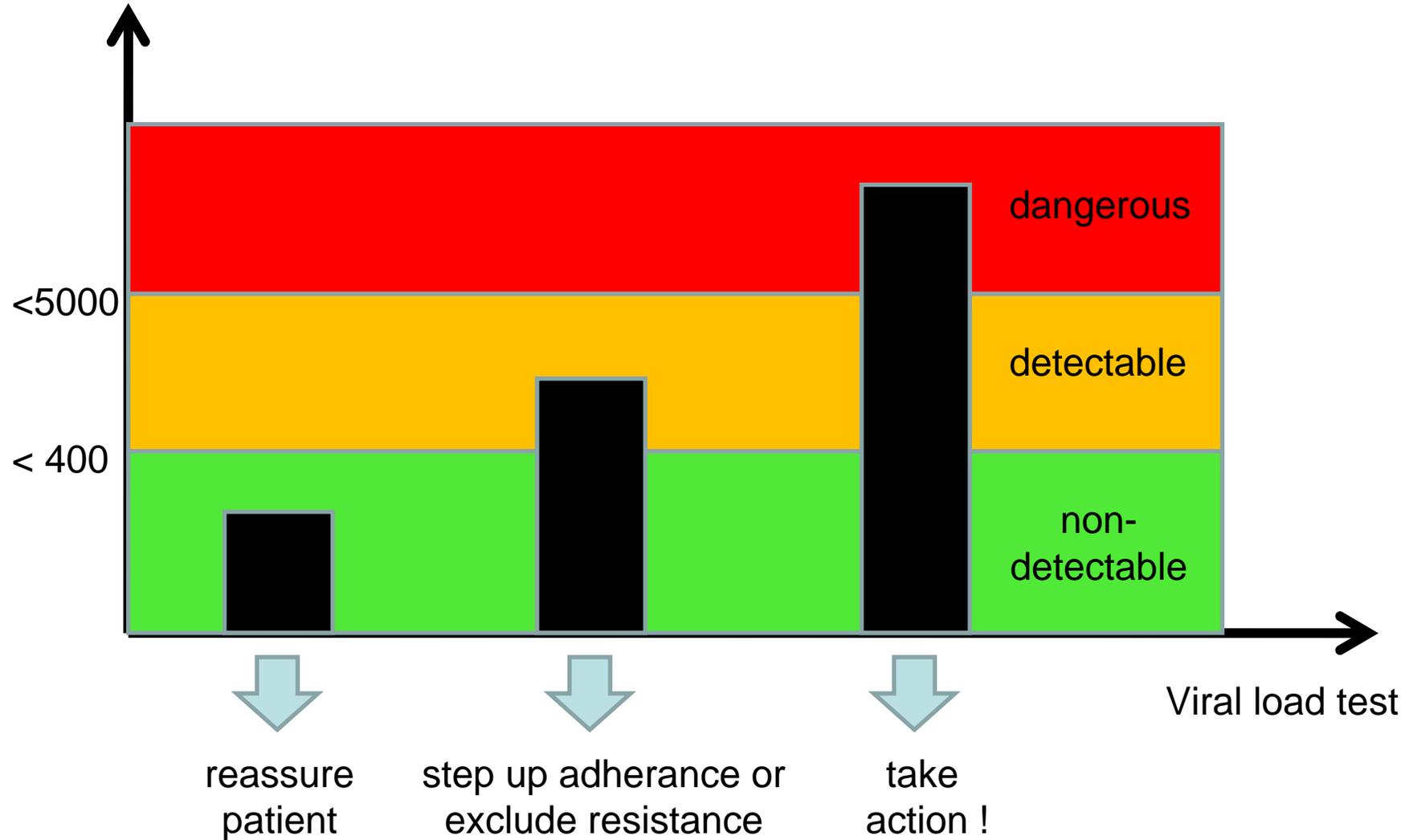
Viral load



- V/L **never** returns to zero
- ARV's cannot cure but they can control the HIV infection ie suppress viral replication
- tell the patient the virus " goes to sleep in the body "
- it will always remain slightly above zero as long as the patient takes the ARV's

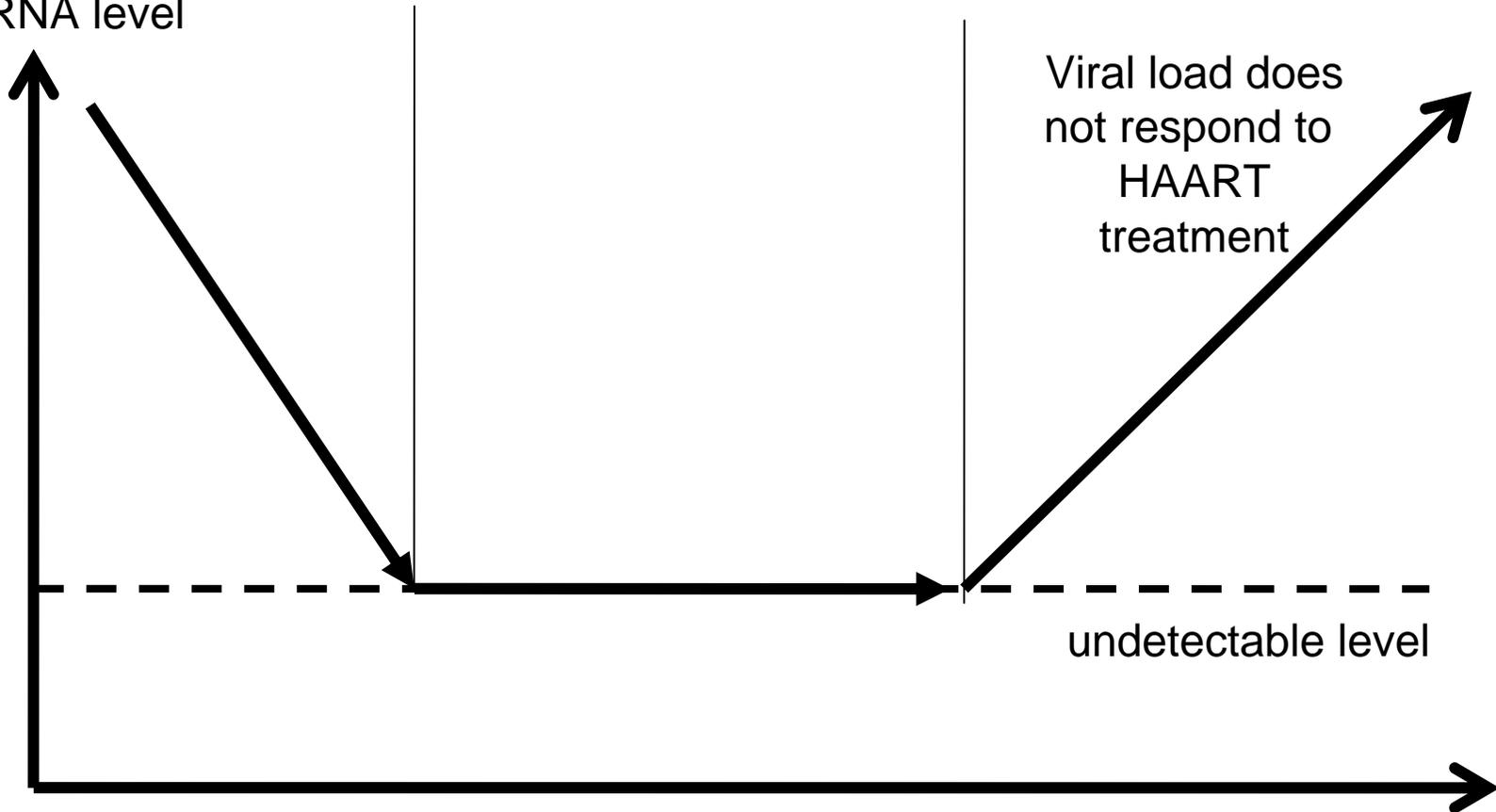
Viral load

copies per ml
HIV RNA level



Viral load

copies per ml
HIV RNA level



Viral load
responds to
HAART treatment

successful HAART
treatment

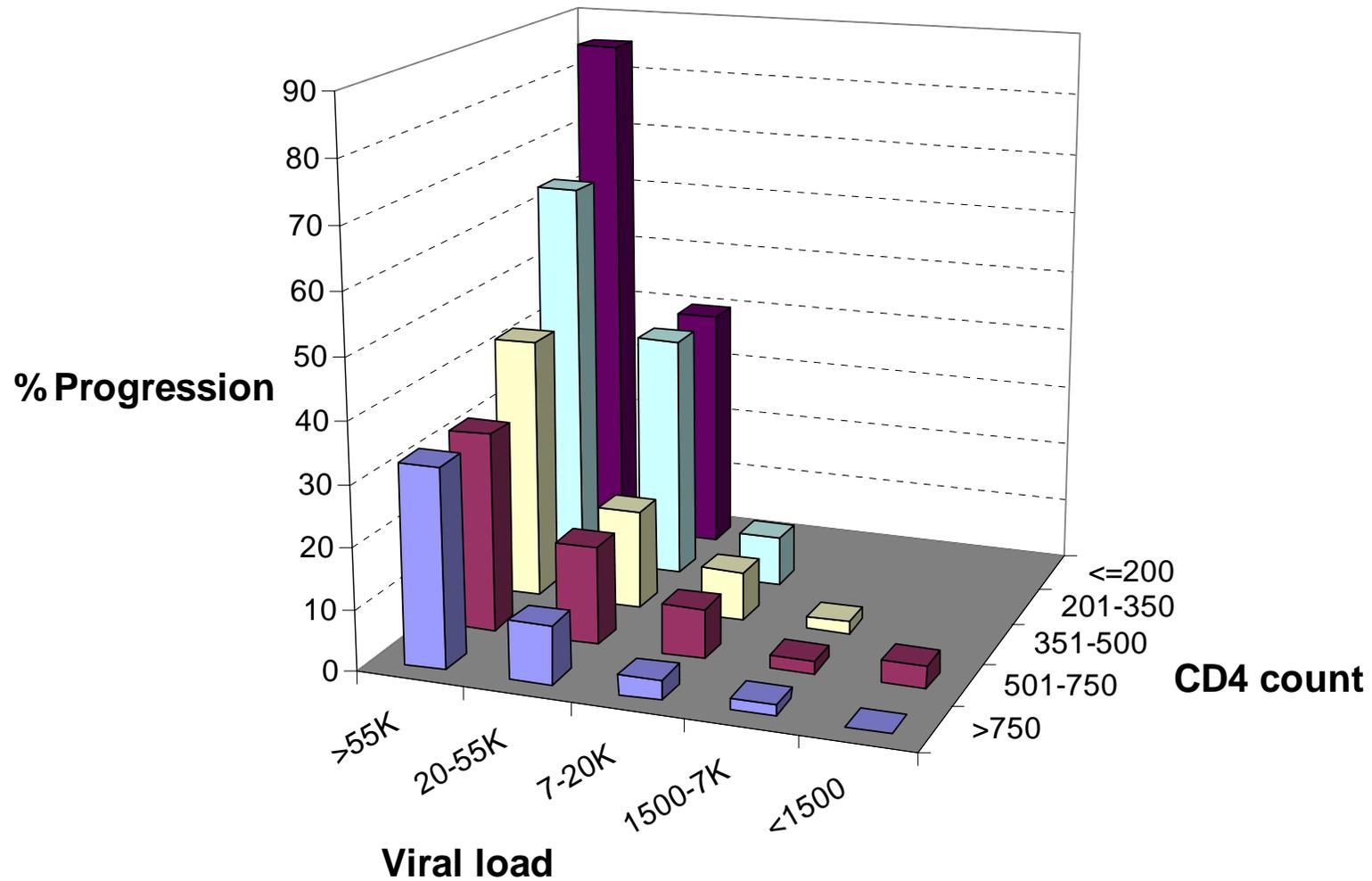
time

Viral load results

Acceptable	Unacceptable
L.D.L = lower than OK detectable	40 000
Undetectable OK	5643
Less < than 400 OK	456
< 50 OK	4 million
< 25 (lab has a VERYsensitive test) OK	any result more than 400
325 OK	5040

Viral load helps predict prognosis

Likelihood of developing AIDS within 3 years



Adapted from Mellors et al. Ann Intern Med 1997; 126: 946

Factors affecting CD4 & VL

1. Intercurrent or recent infection within the last 2-4 weeks
2. Recent vaccination within 2-4 weeks
3. Intercurrent immunosuppression (steroids)
4. Diurnal variation – less apparent in AIDS
5. Sequential use of different assays
Wait at least 4 weeks post complicating factor prior to doing test!!



Viral load (copies/ml blood)

- May be expressed as an absolute number (copies/ml) or as a logarithm (\log_{10})
- Reflects rate of clinical deterioration

> 100 000 copies	Fast progression to AIDS
< 10 000 copies	Slow progression to AIDS

THEORY

PRACTICE





The Blood tests – viral load

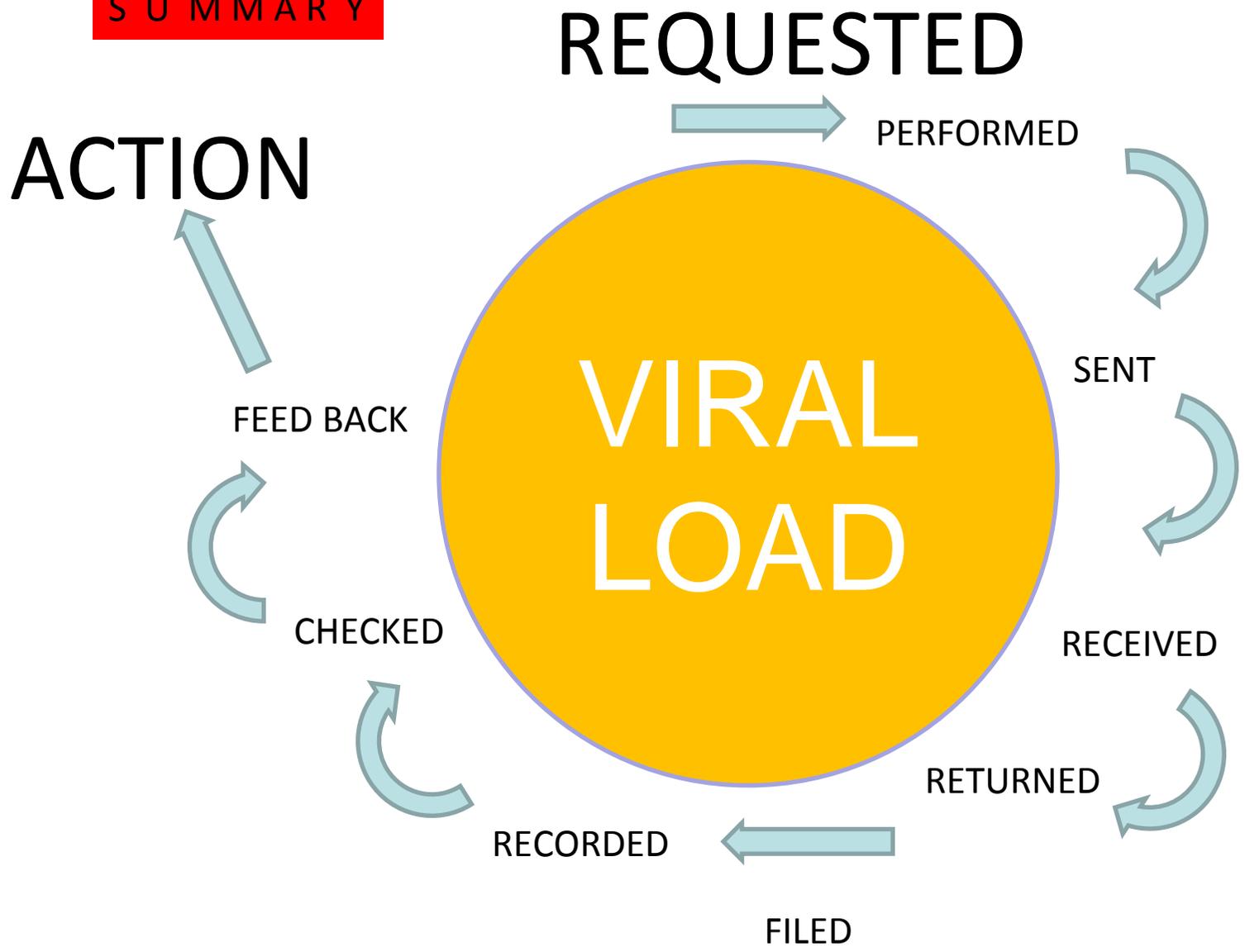
- Must ensure that the test is first *requested* - **Dr**
- Must ensure that someone *does* the test – **Sr**
– done correctly
- Must ensure that the test is *sent* to the lab -
labelling
- Must ensure that the test is *received* by the lab -
- courier
- Must ensure that the test result is *returned* to
the ARV site – **lab form information**



The Blood tests – viral load

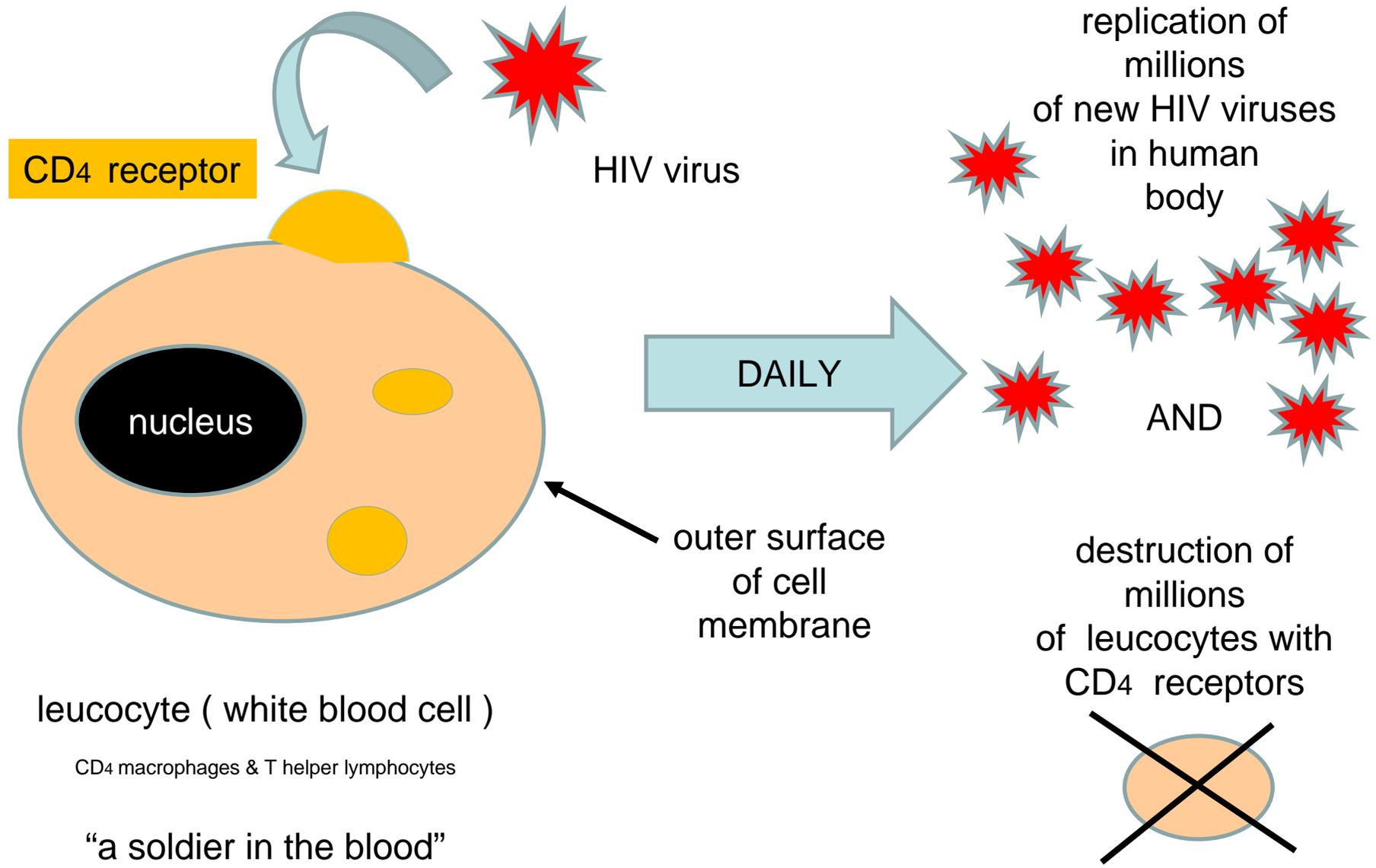
- Must ensure that the result is put into the patients file – *filing system*; big clinics, large numbers
- Ensure results are *recorded* in patient's flow chart - *documentation*
- Must ensure that the results are *checked* by the ARV team – *doctors and sisters*
- Ensure results are *fed back* to the patient
- Ensure that the results are *acted upon*

S U M M A R Y

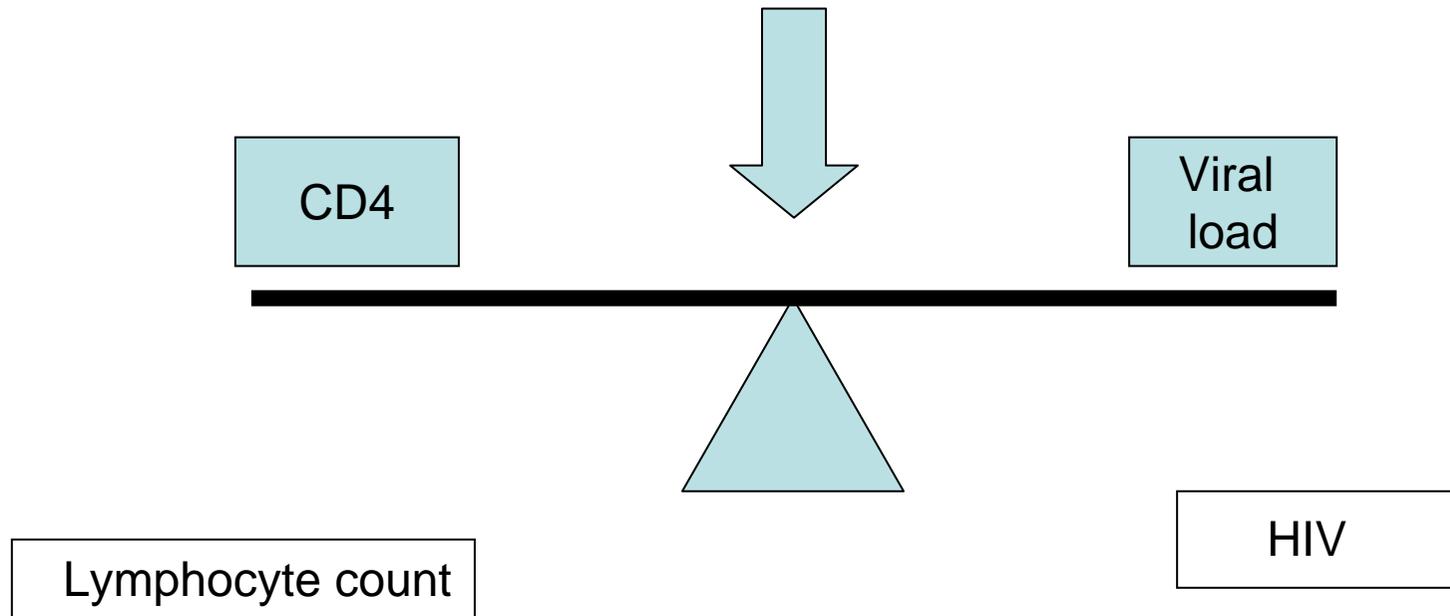




HIV virus and target cell



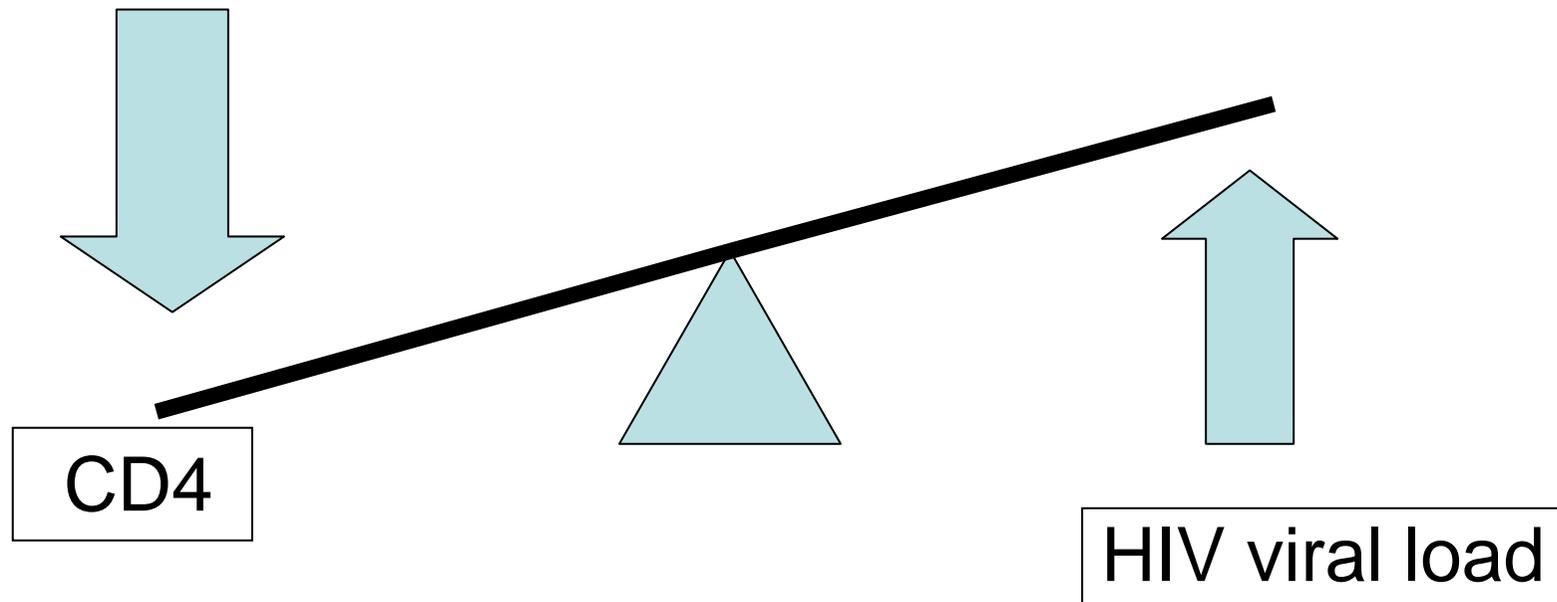
Balance between CD4 and viral load



Normal reference range = **500 to 2010** (NHLS)

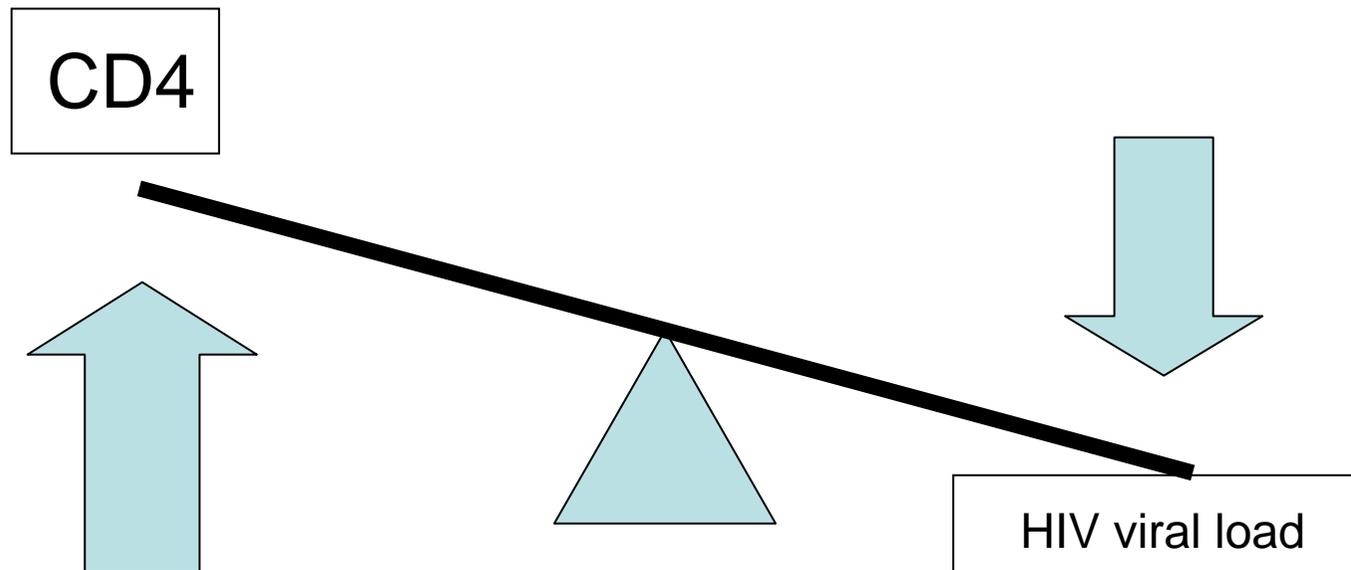
NHLS = National Health Laboratory Services

Natural HIV disease progression

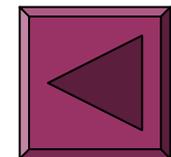
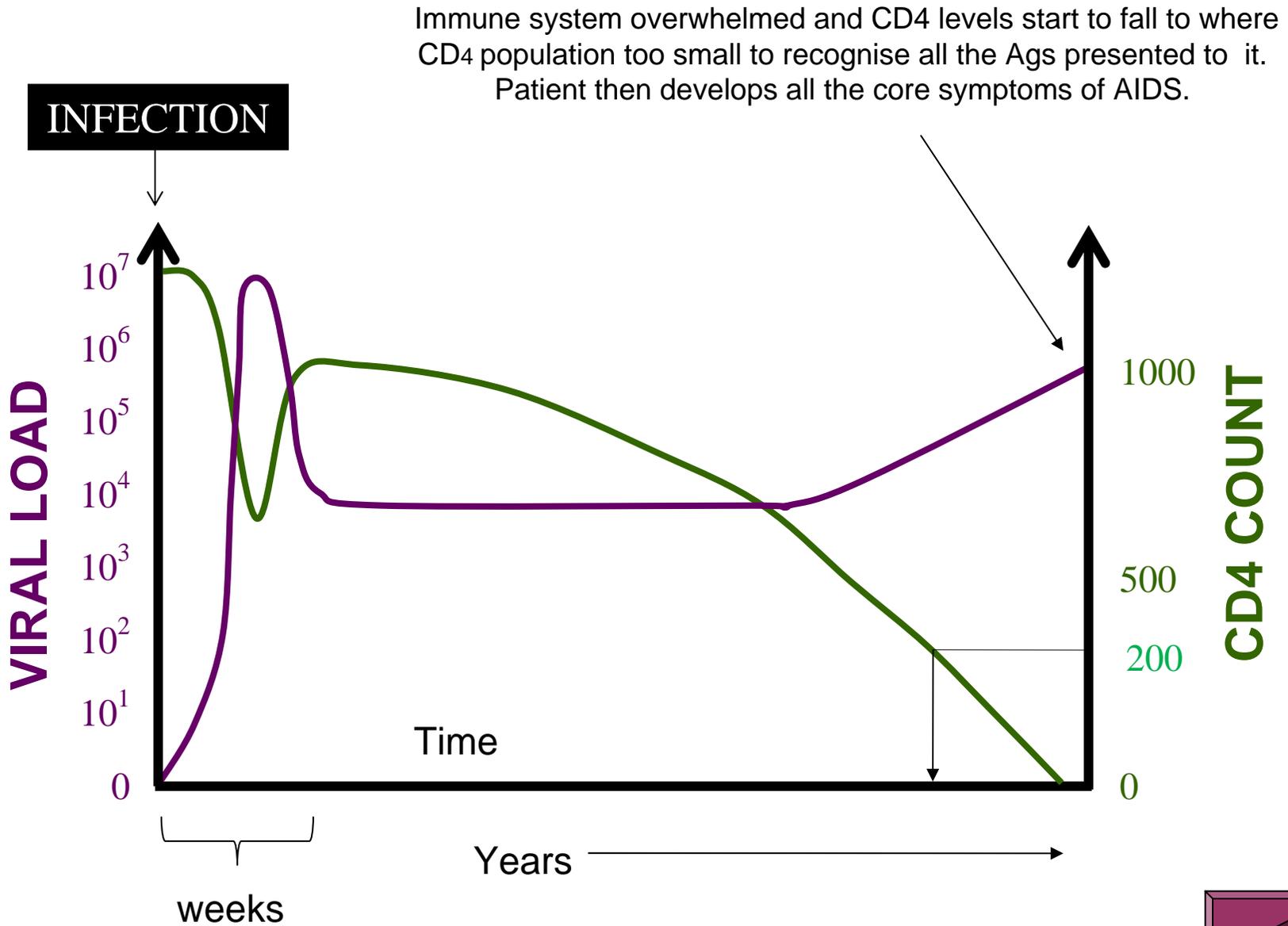


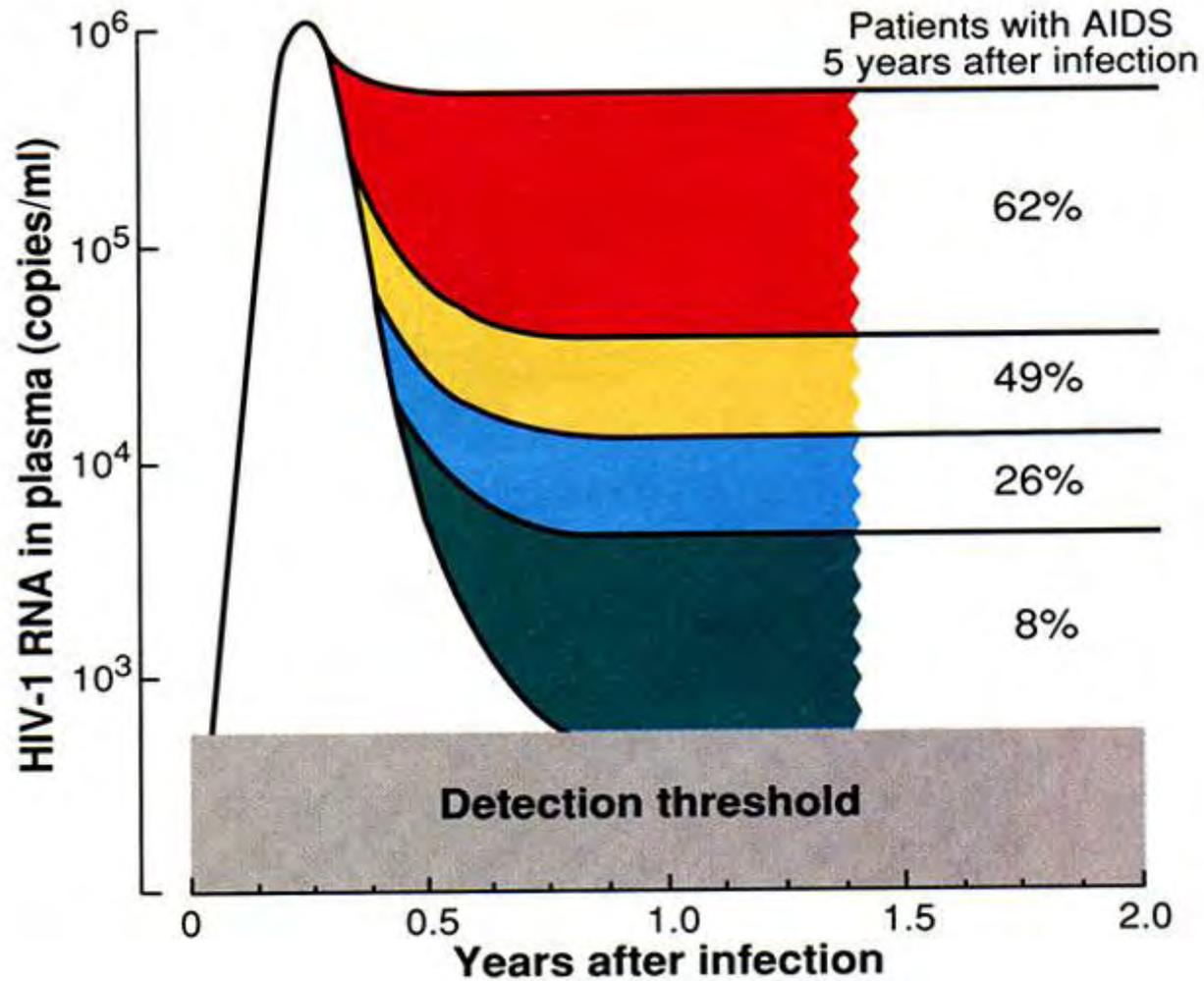
Uncontrolled viral replication – in absence of ARV's or resistance has developed or poor adherence

Patient on ARV's with good adherence



Viral load remains “undetectable” and CD4 continues to rise, patient not at risk of developing opportunistic infections





Viral 'Set Point' and risk of progression to AIDS

Ho DD, *Science* 1996; 272:1124-5



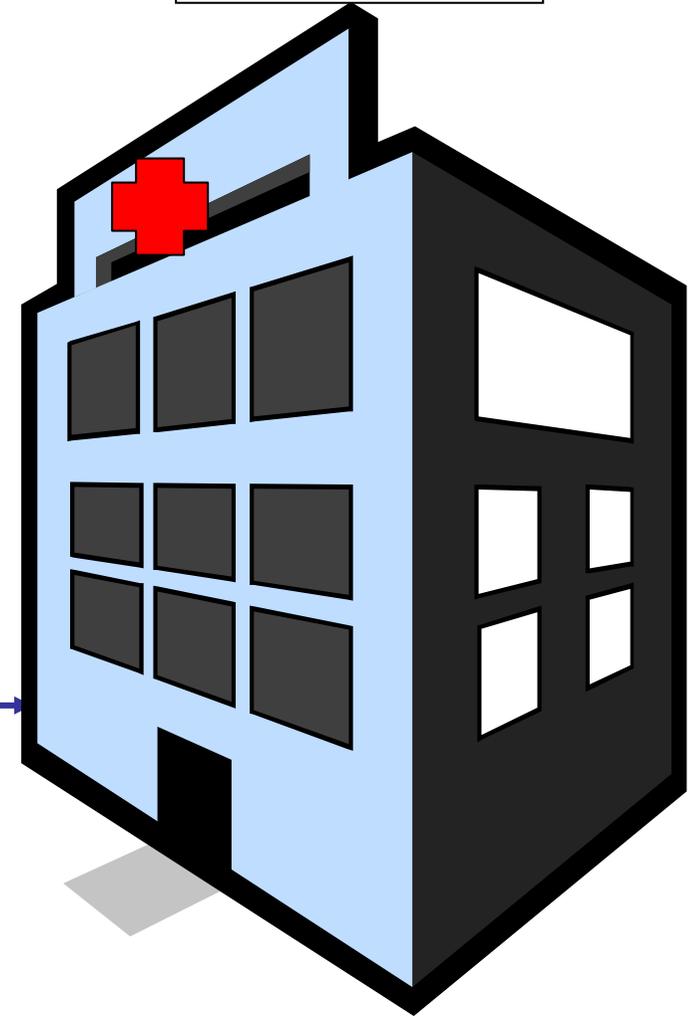
Natural Progression

AIDS

Viral load = speed



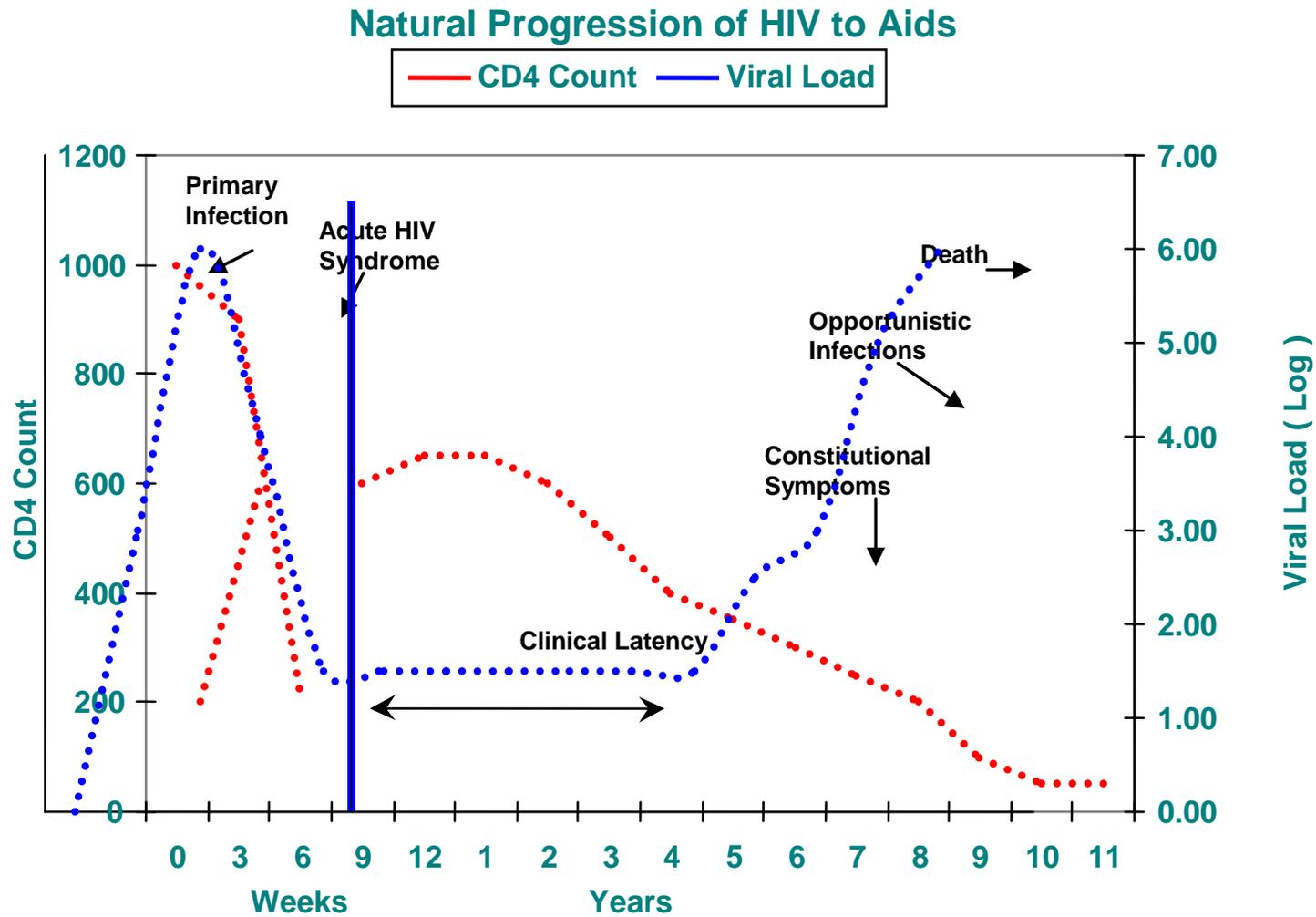
CD4 count = distance

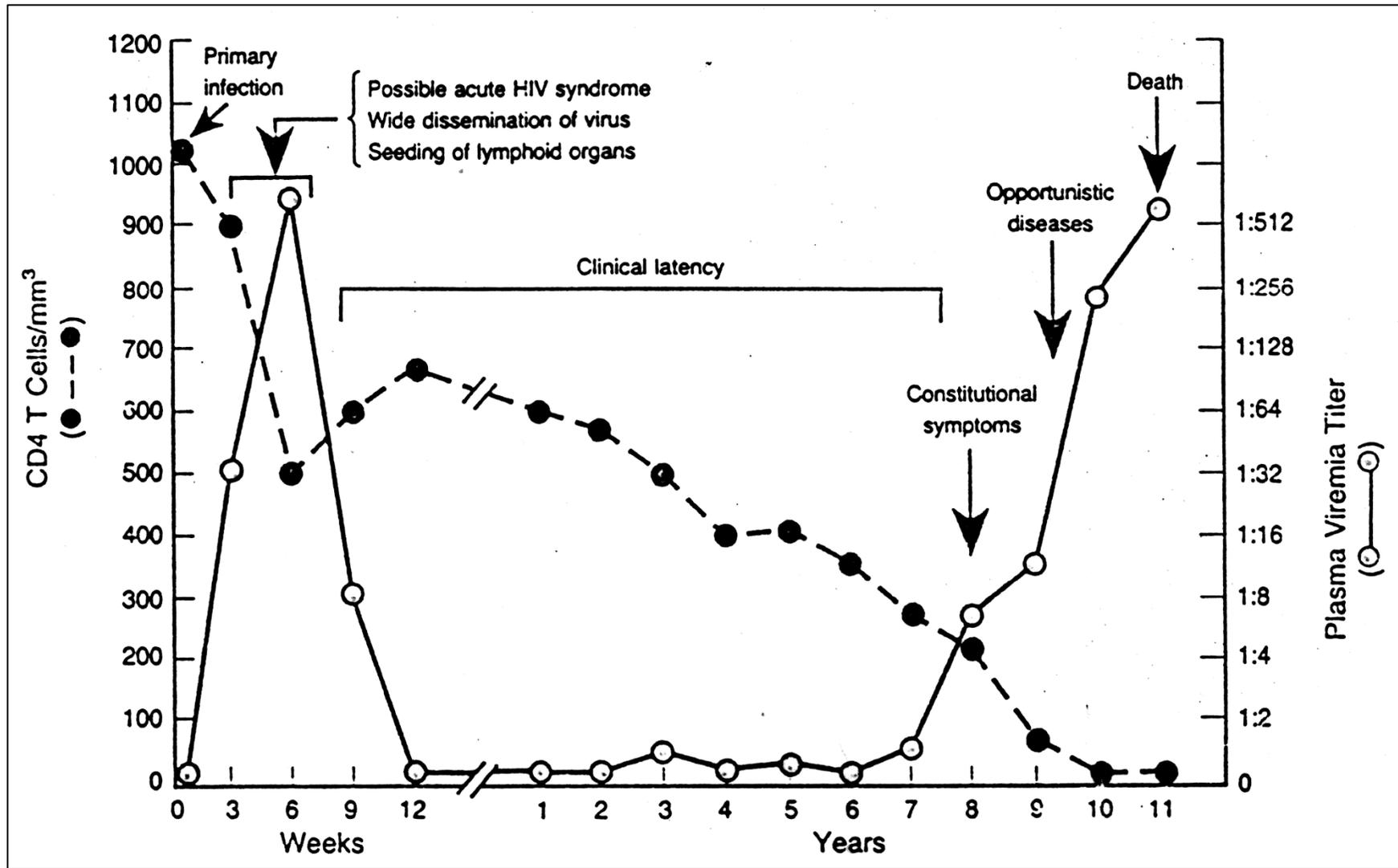




CD₄ cell and virus

Natural progression of HIV to AIDS

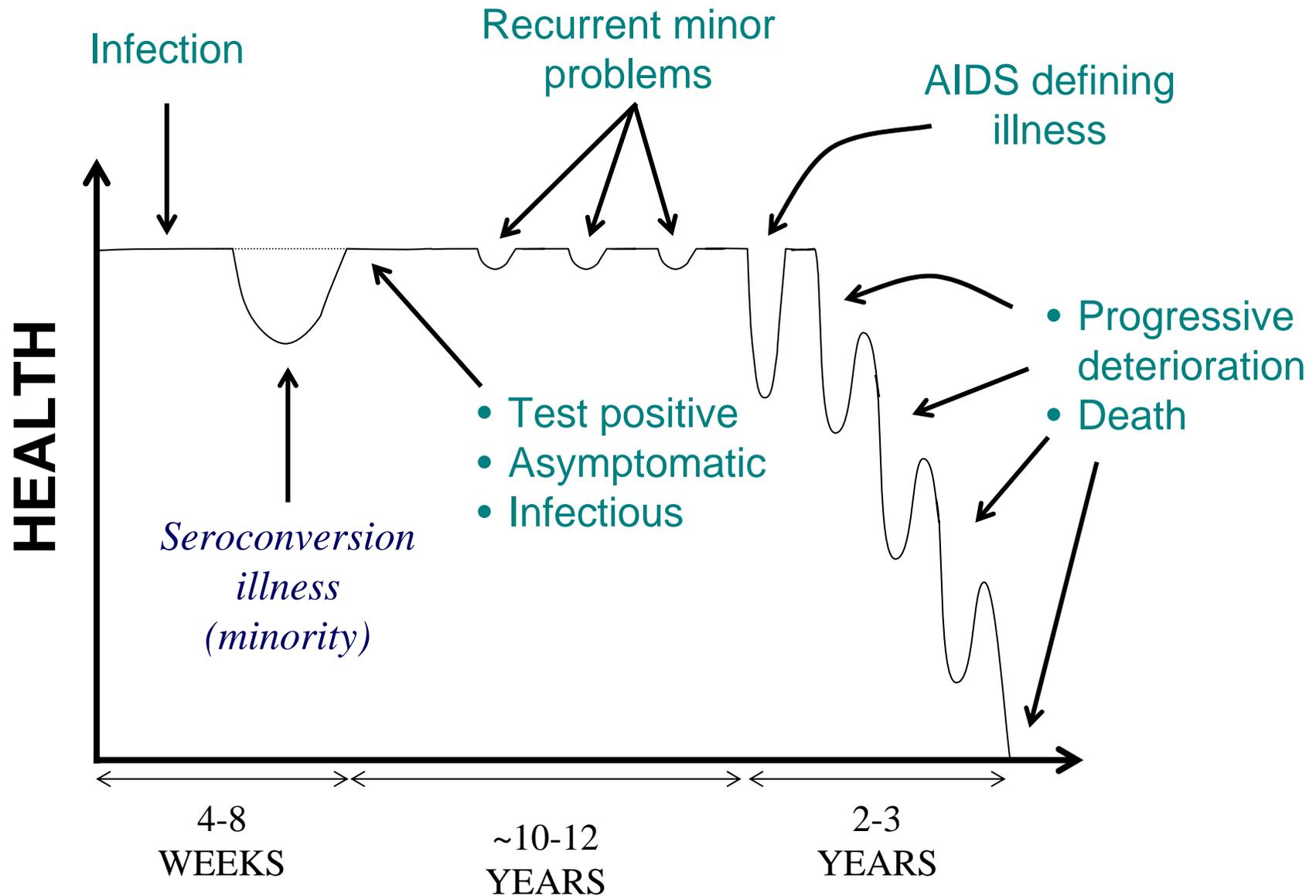




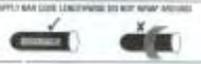
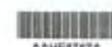
The typical course of HIV infection. Pantaleo G, Graziosi C, Fauci AS. The Immunopathogenesis of HIV Infection. NEJM 1993;328:327-336



Clinical course of HIV infection



Specific NHLS
form for CD4's
and VL,
PCR

HOSPITAL/CLINIC		HEALTH CARE WORKER NAME	
WARD		SIGNATURE	
ATTACH PATIENT LABEL HERE PLEASE			
HOSPITAL/CLINIC NUMBER		TEL. NO.	
SURNAME		FAX NO.	
FIRST NAMES		PRACTICE NO.	
ADDRESS		ADDRESS	
DATE OF BIRTH		GENDER	
		ETHNIC GROUP	
SPECIMEN TYPE		APPLIES TO PRIVATE PATIENTS ONLY	
DATE TAKEN		ACCOUNT TO: PRINCIPAL MEMBER	
TIME TAKEN		MID AID NAME	
HOSP. CLASS		MID AID NO.	
HEALTH DISTRICT		DISP CODE	
RESP. CODE		MEMBER ADDRESS	
PROJECT ACCOUNT STAMP		MEMBER TEL. (H)	
ZARV 7		(W)	
		ICD10 CODE(S)	
CLINICAL INFORMATION			
COMPREHENSIVE CARE, TREATMENT AND MANAGEMENT PROGRAMME SPECIFIC TESTS			
<input type="checkbox"/> CD4 (PLG)	<input type="checkbox"/> Viral Load	<input type="checkbox"/> Hepatitis B sAg	<input type="checkbox"/> Lactate (on ice)
<input type="checkbox"/> HIV PCR	<input type="checkbox"/> FBC & DIFF	<input type="checkbox"/> ALT	<input type="checkbox"/> Cryptosporidium
<input type="checkbox"/> HIV RNA (ELISA)	<input type="checkbox"/> U & E	<input type="checkbox"/> AET	<input type="checkbox"/> Isospora belli
<input type="checkbox"/> HIV RAPID	<input type="checkbox"/> Cholesterol	<input type="checkbox"/> Triglyceride	<input type="checkbox"/> Cryptococcus
			<input type="checkbox"/> Penicopysis (proved)
			<input type="checkbox"/> TB Direct (AFB)
			<input type="checkbox"/> TB Culture
			<input type="checkbox"/> TB Sens
			OTHER TESTS:
THE FOLLOWING DETAILS MUST BE COMPLETED		PLEASE NOTE	
ID Number: <input type="text"/>		Please note that this form must be used in compliance with your provincial treatment guidelines and financial protocols.	
Current HIV Programme Status (Please tick only one): PMTCT <input type="checkbox"/> Patient on PMTCT programme NEW <input type="checkbox"/> Has just enrolled in HIV care, first ever HIV related blood tests TFI <input type="checkbox"/> Previous CD4 elsewhere, first follow-up here, not yet on ART FU <input type="checkbox"/> Previous CD4 here, testing as part of follow-up care, not yet on ART CARV <input type="checkbox"/> Currently on the antiretrovirals marked alongside Has started ART, but was not on ART at the time of these tests due to: TGM <input type="checkbox"/> Toxicity AG <input type="checkbox"/> Non-Compliance VF <input type="checkbox"/> Virological Failure OTHER <input type="checkbox"/> Other		Current treatment <input type="checkbox"/> 3HI <input type="checkbox"/> 3TC <input type="checkbox"/> EFV <input type="checkbox"/> AZT <input type="checkbox"/> ddI <input type="checkbox"/> NVP <input type="checkbox"/> ABC <input type="checkbox"/> KLT <input type="checkbox"/> TDF <input type="checkbox"/> BQV Other ARV: <input type="checkbox"/> RTV <input type="checkbox"/> Co-trimoxazole <input type="checkbox"/> Flucanazole <input type="checkbox"/> INI <input type="checkbox"/> RI Other drugs: _____	
Additional HIV Programme Status: Patient is about to start ART and these are baseline tests: NA <input type="checkbox"/> Naive EKPP <input type="checkbox"/> PMTCT EKPA <input type="checkbox"/> Treatment experienced		 AAHE5767A  AAHE5767A  AAHE5767A  AAHE5767A  AAHE5767A  AAHE5767A	
Has this patient been transferred in from another program, e.g. TSCF?		YES NO	
Months since first enrolling on ART at this facility (irrespective of stops and restarts)		8 12 18 24 Other	

**KZN PROVINCIAL LABORATORY SERVICES
ARV VIROLOGY REQUEST FORM**

STICK BARCODE HERE

PATIENT DETAILS

SURNAME											NAME										
AGE		GENDER	M	F	ID #																
ARV SITE																					
ANC SITE											PMTCT #										
PREVIOUS SPECIMEN #																					

CLINICAL DETAILS

AIDS DEFINING CONDITION																																					
PREVIOUS CD-4 Count																					Cells/ul	DATE:															
PREVIOUS Viral Load																														Copies/ml	DATE:						
ARV HISTORY (DETAILS OF PAST AND CURRENT ARV)																																					

TESTS REQUIRED (PLEASE TICK APPROPRIATE BLOCK)

Time Collected				H				Date Collected																												
CD-4 Count	Screening			6 mths				Every 6 mths																												Other (Reason)
Viral Load	Baseline			6 mths				Every 6 mths																												Other (Reason)
HIV DNA PCR (CHILDREN 6 WEEKS TO 15 MONTHS ONLY)																																				

CLINICIAN DETAILS

NAME											SIGNATURE											TEL #																			
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SAMPLES WILL NOT BE PROCESSED IF ANY INFORMATION IS MISSING.

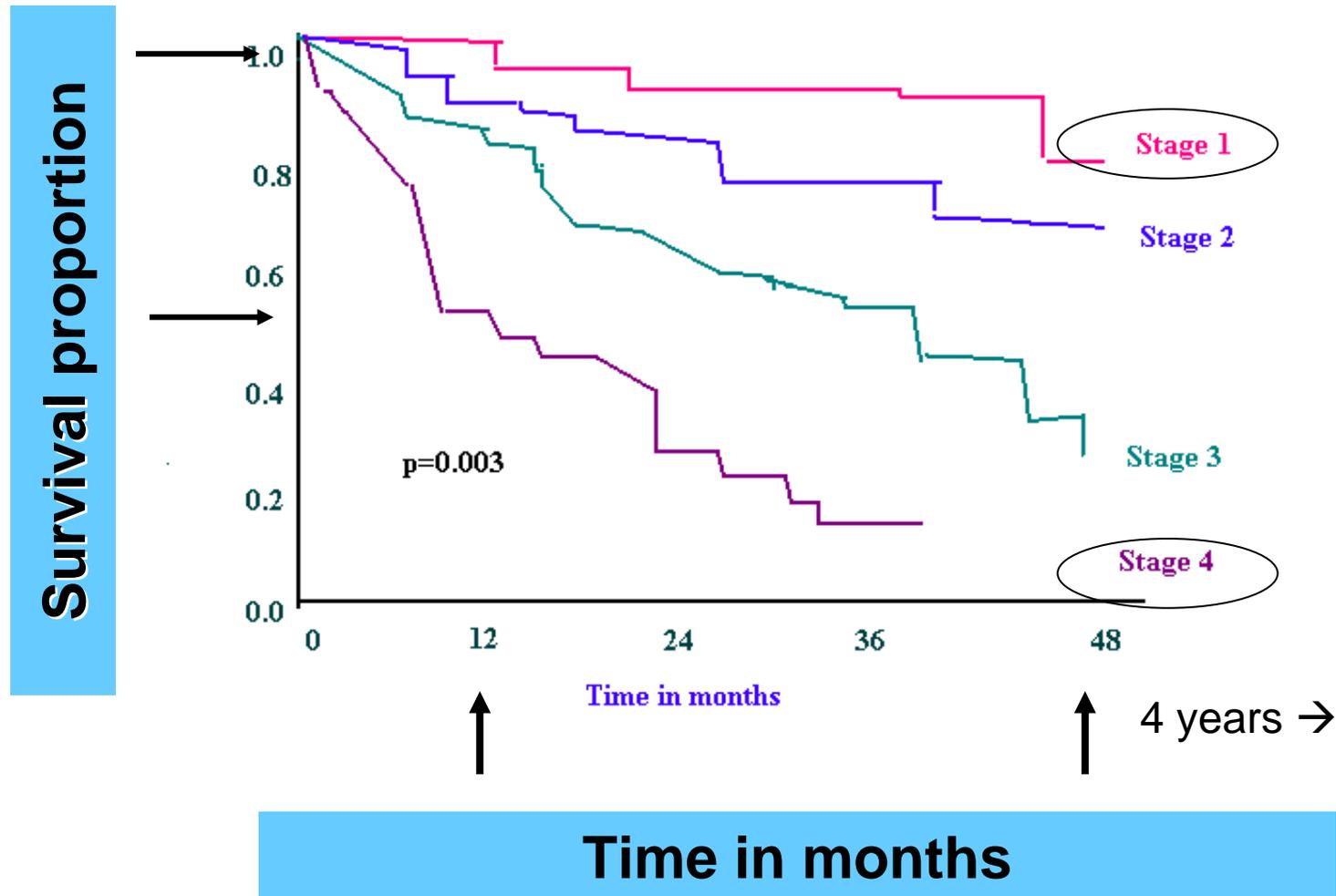




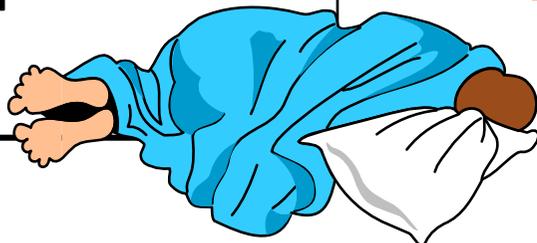
WHO clinical staging system

- developed in 1990, updated 1994
- emphasis on clinical parameters to help guide decision making
- designed for resource poor settings with limited access to laboratory tests
- has proved pragmatic and useful at both primary and referral level
- recognised the relentless progression of HIV infection and did not allow for reversal or improvement
- confusion with disease classification system of CDC in the USA (CD4 and clinical) – designed for surveillance purposes

Mortality according to WHO stage



WHO Clinical Stage	Associated conditions
Acute sero-conversion illness	Asymptomatic <i>or</i> Mononucleosis-like illness
1 Better prognosis	Asymptomatic
2	
3	
4 Poor prognosis	AIDS indicator diseases



Primary HIV infection

Acute HIV-1 infection/Acute sero-conversion illness

- frequency of symptomatic disease is uncertain - ?
40-90%
- acute mononucleosis-like syndrome 2-6 weeks after exposure
- presumed diagnosis “viral illness”
- most distinguishing feature: RASH
- painful anogenital ulcers
- clinical illness may last 2-4 weeks
- majority do not seek medical attention

Acute sero-conversion illness

- during the acute HIV infection, the viral load is very high
- the risk for transmission of the virus is also HIGH especially during :
 - breast feeding
 - unprotected intercourse
 - unborn foetus (pregnant mothers)

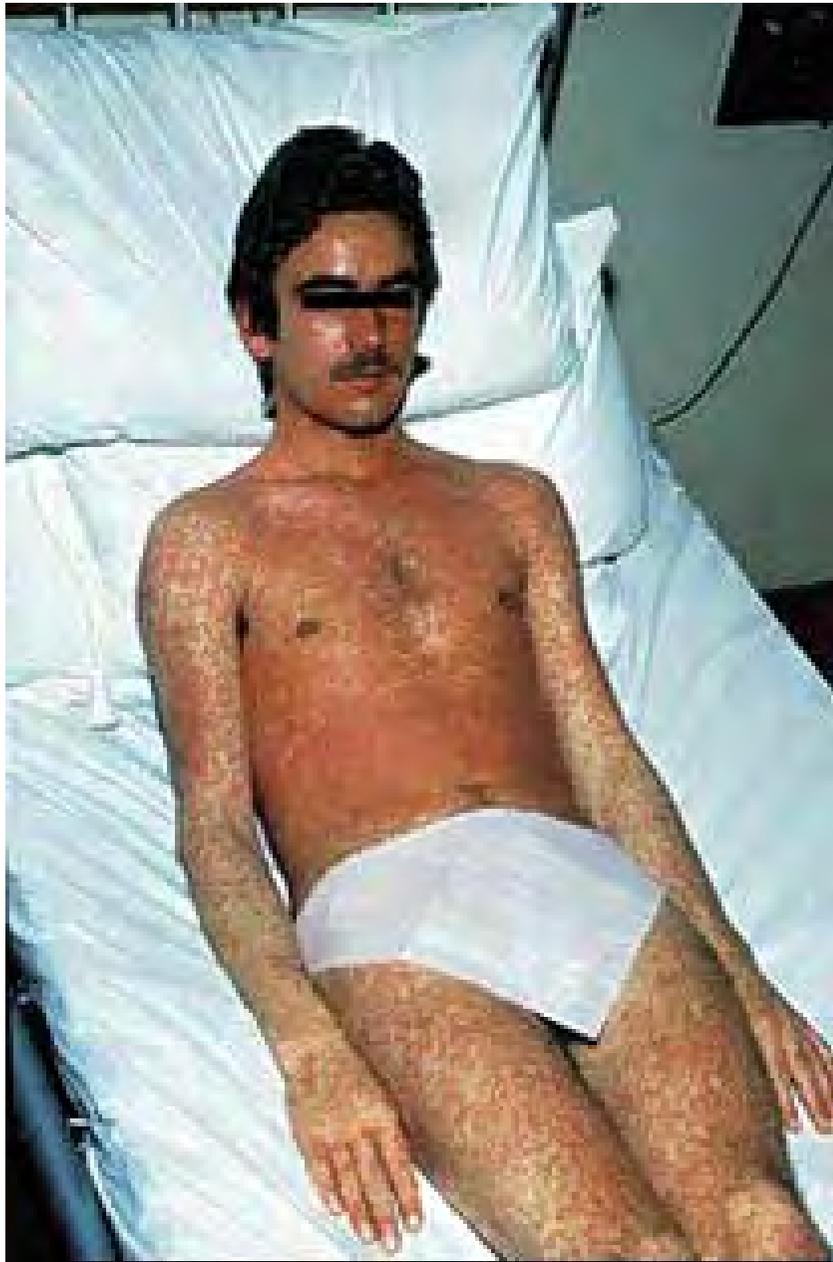
Acute infection may be masked in testing

- almost 1:40 of those who tested HIV negative in a large clinic cohort in Lilongwe, Malawi turned out to have acute HIV infection that was too recent to be detected by rapid antibody testing*
- missing the diagnosis carries important consequences, stress the “**window period**” to every patient

*Journal of Infectious Diseases, 2007 ; 1450 patients over 21 months

Primary HIV Infection

FEVER 95%	MYALGIAS 54%	HEPATO- SPLENOMEGALY 14%
ADENOPATHY 74%	DIARRHOEA 32%	WEIGHT LOSS 13%
PHARYNGITIS 70%	HEADACHE 32%	THRUSH 12%
RASH* 70%	NAUSEA & VOMITTING 27%	NEUROLOGICAL SYMPTOMS# 12%





Summary of Staging

Stage 1

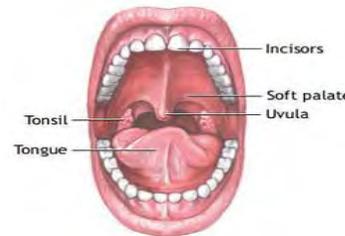
- “*well*” patient

URTIs = *upper* respiratory tract infections

Stage 2

- *URTIs*
- *muco-cutaneous lesions*

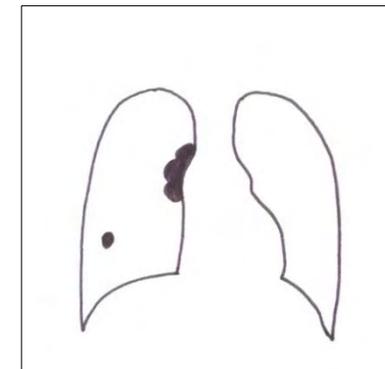
mucous membranes



Stage 3

- *LRTIs*

skin rashes



Stage 4

- *AIDS defining illnesses*; rare and unusual diseases

LRTIs = lower respiratory tract infections

Clinical Stage 1

- Laboratory: CD4⁺ count \approx 500 cells/mm³
- asymptomatic
- Persistent Generalised Lymphadenopathy (PGL)
 - non tender lymphadenopathy >1cm in 2 or more non-contiguous sites, excluding inguinal nodes
 - no known cause
- Performance Scale 1: normal activity

85% chance of surviving for 2 years

Clinical Stage 2

- Laboratory: CD4⁺ count \approx 350 cells/mm³
- minor constitutional symptoms
 - myalgias
 - arthralgias
 - fatigue
 - low-grade fever
- and / or performance scale 2: symptomatic; normal activity
- 75% chance of surviving for 2 years

Stage 2

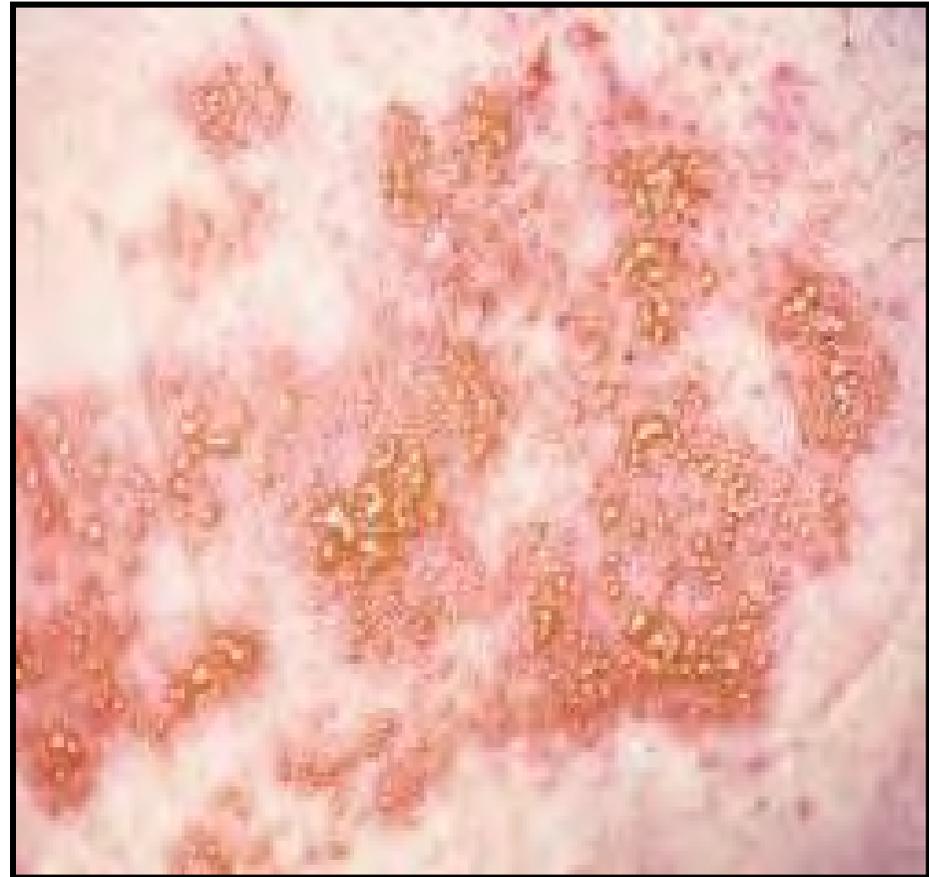
1. Moderate unexplained weight loss (<10%)
2. Recurrent presumed bacterial URTI (2/more in one six month period)
 - sinusitis
 - otitis Media
 - pharyngitis
 - bronchitis
3. Herpes Zoster
 - current or in last 2 years
 - severe or frequently recurrent HZ usually associated with more advanced stage
4. Angular cheilitis
5. Recurring oral ulcerations (aphthous ulceration)
 - 2 or more times in 6 months
 - halo of inflammation + yellow-grey pseudomembrane
6. Papular pruritic eruptions
 - exclude scabies and insect bites
7. Seborrhoeic dermatitis
 - itchy, scaly affects scalp, face, upper trunk and perineum
8. Fungal nail infection fingers
 - paronychia and/or onycholysis



Rash begins as raised red lesions



Later forms fluid-filled vesicles which later rupture (itchy) and forms a crust









Right lumbar dermatome



RIGHT
side only

UNILATERAL
dermatome

Herpes Zoster (Ophthalmicus - eye involvement)



Naso-ciliary nerve affected – lesion on tip of the nose – eye invariably involved
Eye lid oedema.

HZ
affecting
the eye



Dr D Spencer " The Clinical Practice of HIV Medicine " p41

● ● ● | **Herpes Zoster**



fluid-filled vesicles



Herpes Zoster

- Herpes Zoster – 20% of HIV-infected who are sero-positive for VZV.
- recurrences common – multi-dermatomal
- dissemination may occur, but is rare.
- diagnosis: clinical
- ophthalmic zoster is common – if the tip of the nose is involved, then the disease is sight-threatening and needs ophthalmological referral (Hutchison's sign)

Herpes Zoster

- Treatment
 - Rash
 - Calamine lotion daily
 - Secondary infection
 - Anti-*Staphylococcal* antibiotics - oral
 - Viral infection
 - Acyclovir 800mg 5x/day for 7-10 days or until no new vesicles appear
 - Pain
 - Mild – Paracetamol + Codeine/NSAID's
 - Tricyclic antidepressants for post herpetic neuralgia – amitriptyline [Trepilene®] start with 10-25mg nocte and slowly increase to 75-150 mg per day
 - Severe – Opioids





Lesions in different ages and stages

Papular Pruritic Eruption (PPE)



Commonest skin rash noted in HIV positive patients

PPE Treatment

- mild topical steroids [Hydrocortisone: Mylocort ® Biocort ®]
- potent topical steroids [Betamethasone: Betnovate® Lenovate ®]
- treat any secondary infection with oral antibiotics
- antipruritic and sedating antihistamine: Promethazine [Phenergan ®] Chlorpheniramine
- [Allergex ®]
- ARVs
- resolves slowly and often leaves hyper-pigmentation and scarring





Seborrhoeic dermatitis





Seborrhoeic Dermatitis Treatment

- potent topical steroid
- wean to lower strength asap
- treat any secondary infection
- anti-dandruff shampoo ie selenium [Selsun®]
- if no response, give a trial of topical antifungal [clotrimazole: Canestan®] or fluconazole [Diflucan®] orally





Molluscum Contagiosum

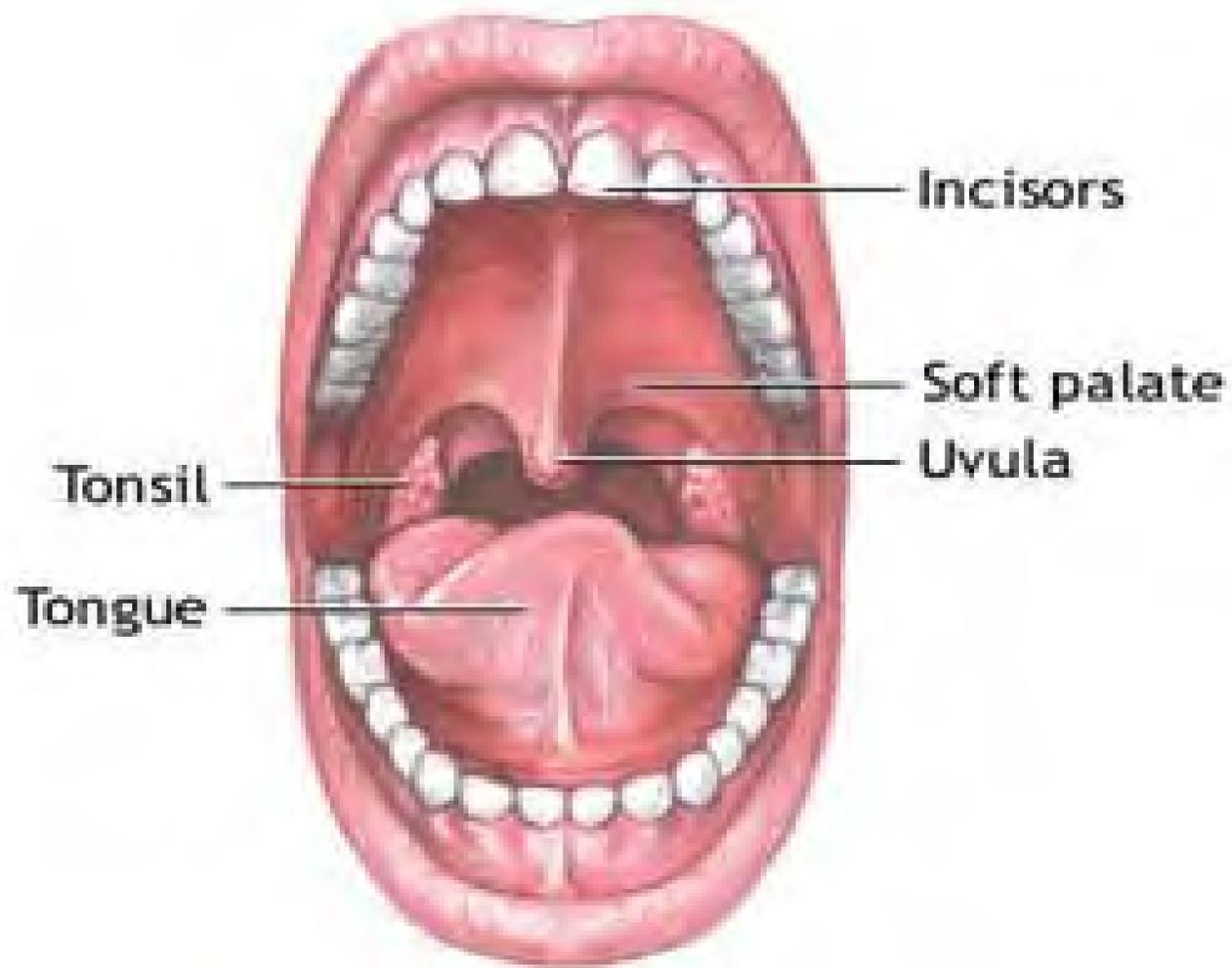


Molluscum Contagiosum

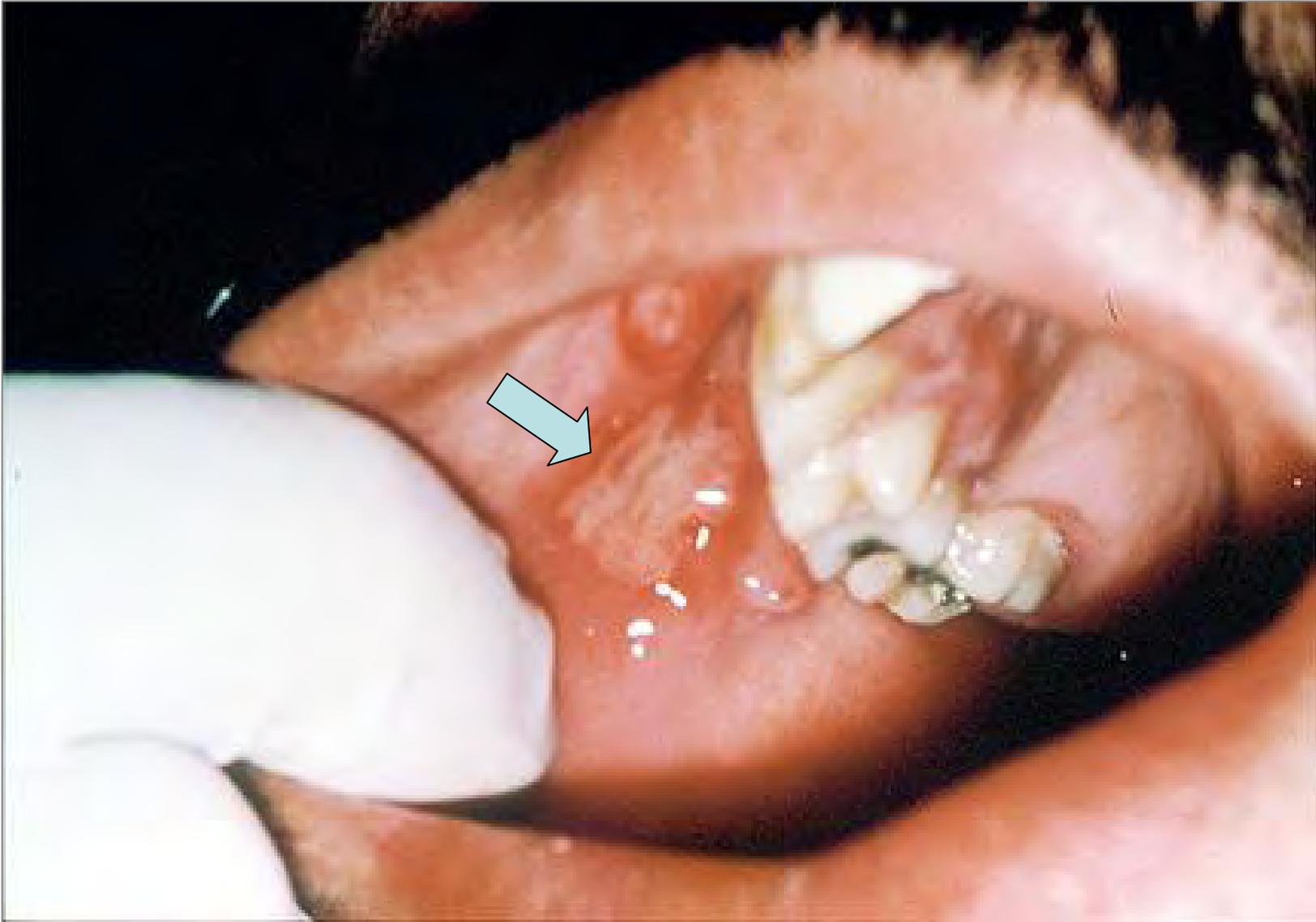
- **Caused by a poxvirus**
- **Spread via direct contact**
- **Appears as a skin-colored, smooth, waxy papule with central umbilicus**
- **Lesions are typically seen on the trunk
however, molluscum contagiosum is frequently
seen on the face of HIV seropositive individuals.**

Management of MC

- topical liquid nitrogen
- Imiquimod *Aldara*® - topical immunotherapy cream not available in public sector, expensive
- local destructive methods - curettage
- lesions recur
- HAART has been associated with disappearance of lesions



Aphthous ulcers



Note: Gloves and a strong light, good oral examination



Re-occurring oral ulceration – mastication difficult and painful



Clinical Stage 3

- (Laboratory: CD4⁺ count \approx 200 cells/mm³)
- Severe unexplained weight loss (>10%)
- Unexplained chronic diarrhoea for > 1 month
- Unexplained persistent fever (intermittent/constant for > 1 month)

30% chance of surviving for 2 years

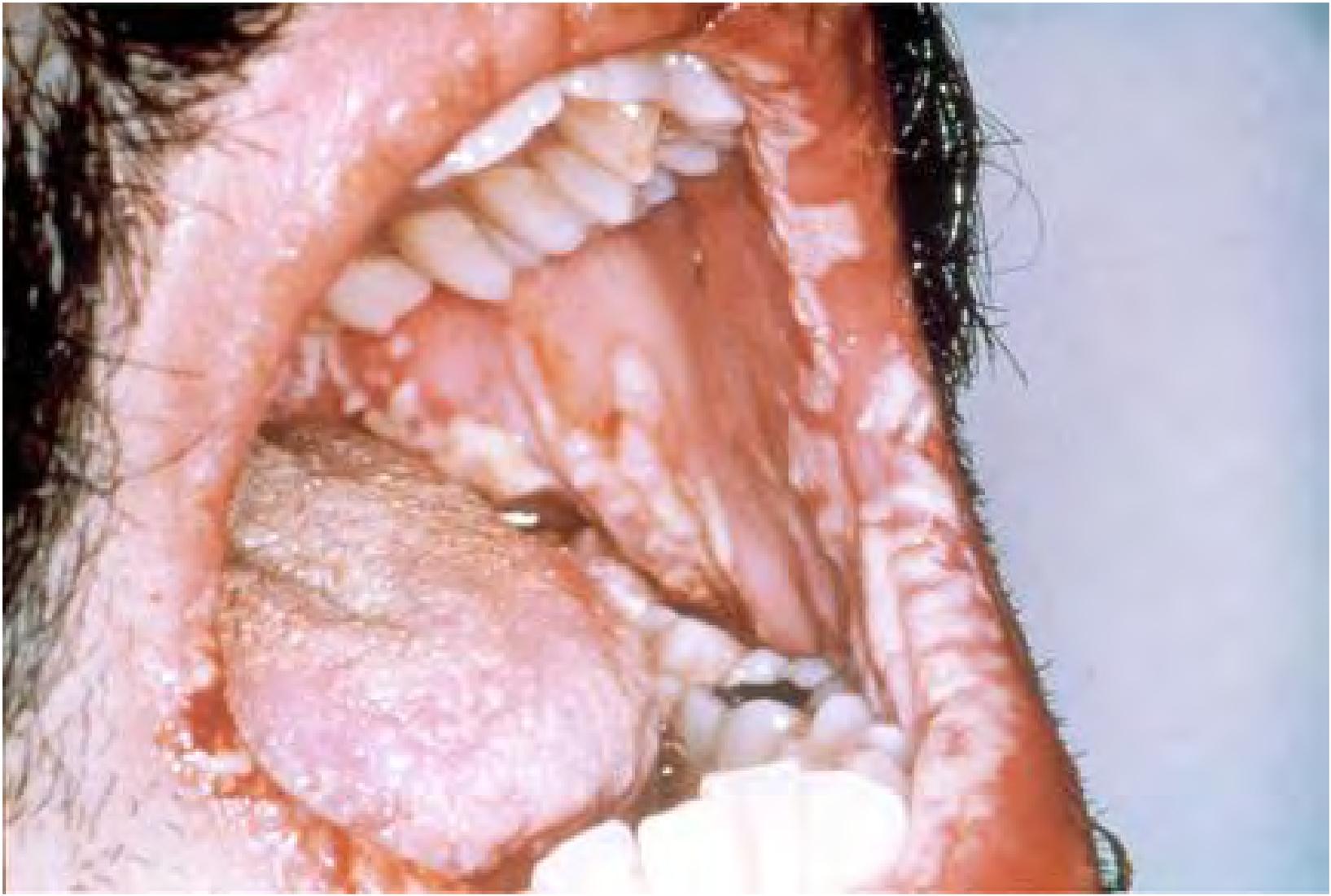
Stage 3

1. Severe unexplained weight loss (>10%)
2. Unexplained chronic diarrhoea for > 1 month
 - loose/watery stools 3/more times per day
3. Unexplained persistent fever (intermittent/constant for > 1 month)
 - no response to A/B or anti malarials
 - no other foci or disease known
4. Oral candidiasis
 - can scrape off – underlying erythema (bleeds)
5. Oral hairy leucoplakia
 - bilateral and cannot scrape off
6. Pulmonary TB
 - current or in last two years
 - sputum smear positive/negative

Stage 3

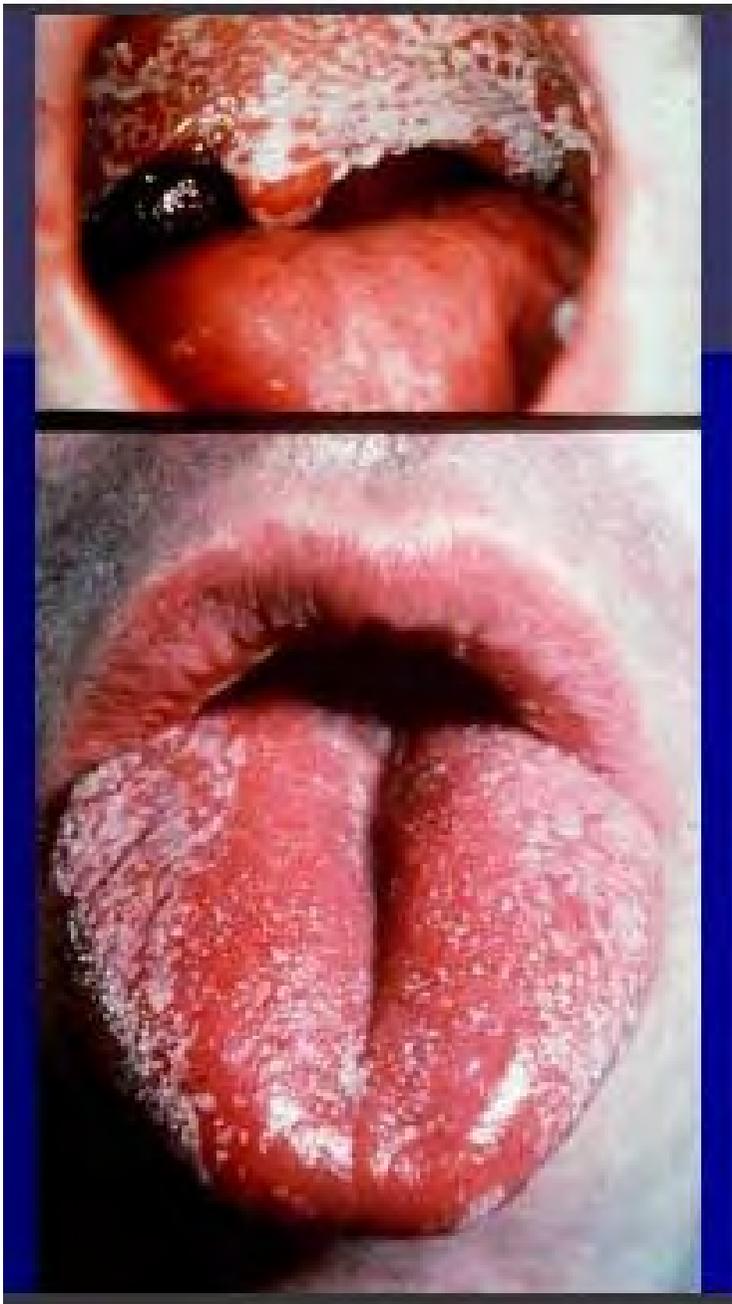
7. Severe presumed bacterial infection
 - pneumonia, Meningitis, Empyema, pyomyositis, bone/joint infection, bacteraemia
8. Acute necrotising ulcerative gingivitis
9. Unexplained anaemia for > 1 month
 - (<8g/dl)
10. Unexplained neutropenia > 1 month
 - (<1000/mm³)
11. Unexplained thrombocytopenia > 1 month
 - (<50 000/mm³)





Oral Candidiasis





Oral Candidiasis

- Pseudomembranous
- Erythematous
- Hyperplastic
- accompanying angular cheilitis



NB : Inspect mouth and mucous membranes thoroughly (good light and spatula or gloves)

Management

- **Mild “thrush”:** oral nystatin drops 1 ml 6 hourly. After meals - swill around mouth for 5 minutes.
- **Moderate or no response to nystatin:** amphotericin lozenges (Fungizone®)
- **Severe: not responding to above:** Fluconazole (Diflucan®) 200mg daily for minimum 7 days.



Oral Hairy Leukoplakia



Oral Hairy Leukoplakia

- Caused by Epstein-Barr Virus (EBV)
- White, velvety sometimes corrugated plaque-like clinical appearance on the lateral border of tongue
- Histopathology must demonstrate intracellular EBV for definitive

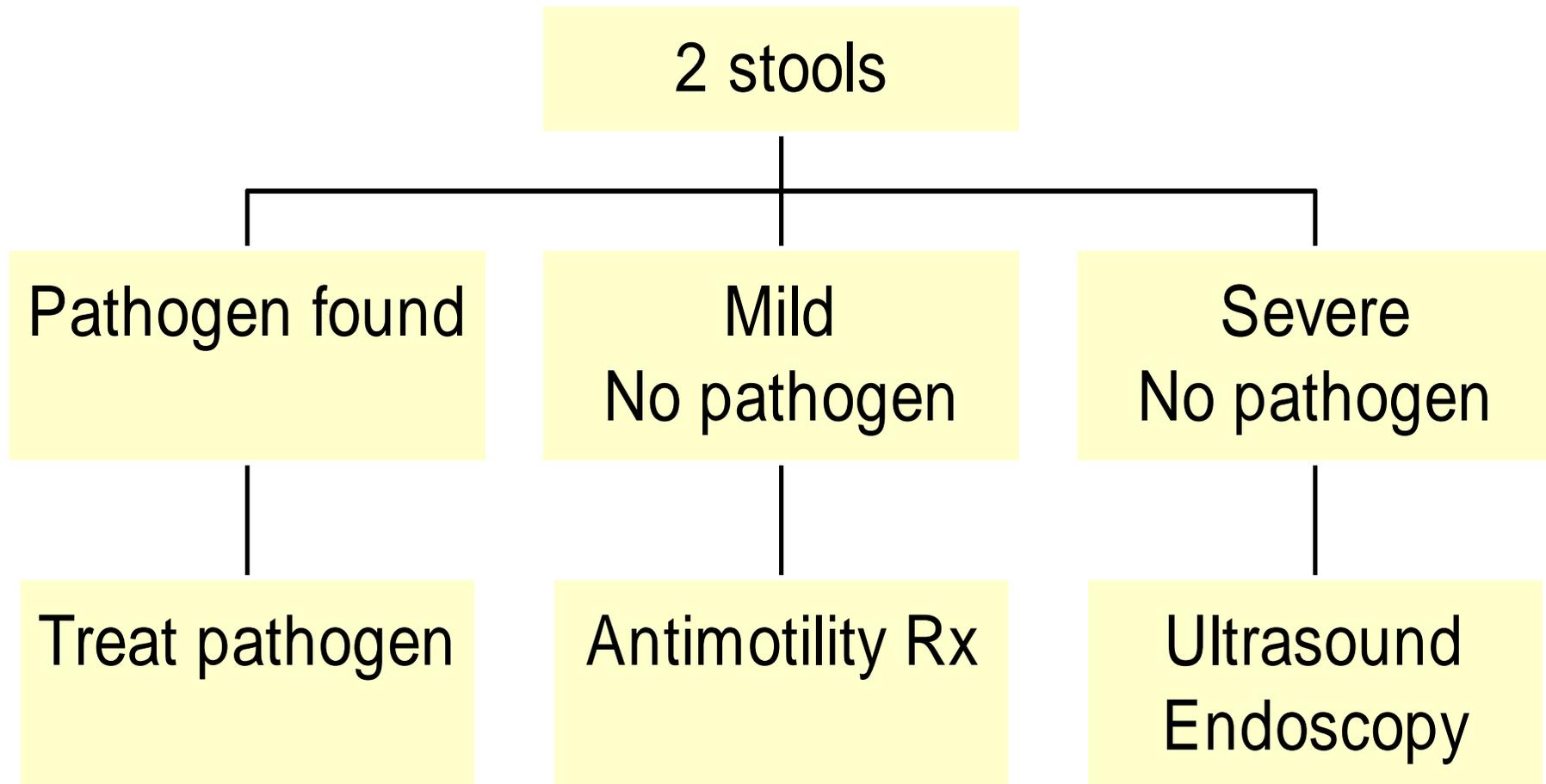
Oral hairy leucoplakia

- Treatment:
 - **No treatment is warranted – except for cosmetic reasons**
 - **Use of Acyclovir or topical Podophyllum resin has been reported to provide relief**
 - **Regular brushing of affected area**
 - **HAART**

HIV+ Diarrhoea in HIV positive patients

- oral rehydration as first priority
- acute: empiric Ciprofloxacin 500mg 12 hourly for 3 to 7 days if fever or blood or mucus in stool, otherwise loperamide
- chronic: no specific therapy for cryptosporidiosis (ARV's), but try loperamide/codeine, Isospora Belli responds to Cotrimoxazole 2 tablets 6 hourly for 10 days, Microsporidiosis – Albendazole?

Approach to chronic diarrhoea



AN APPROACH

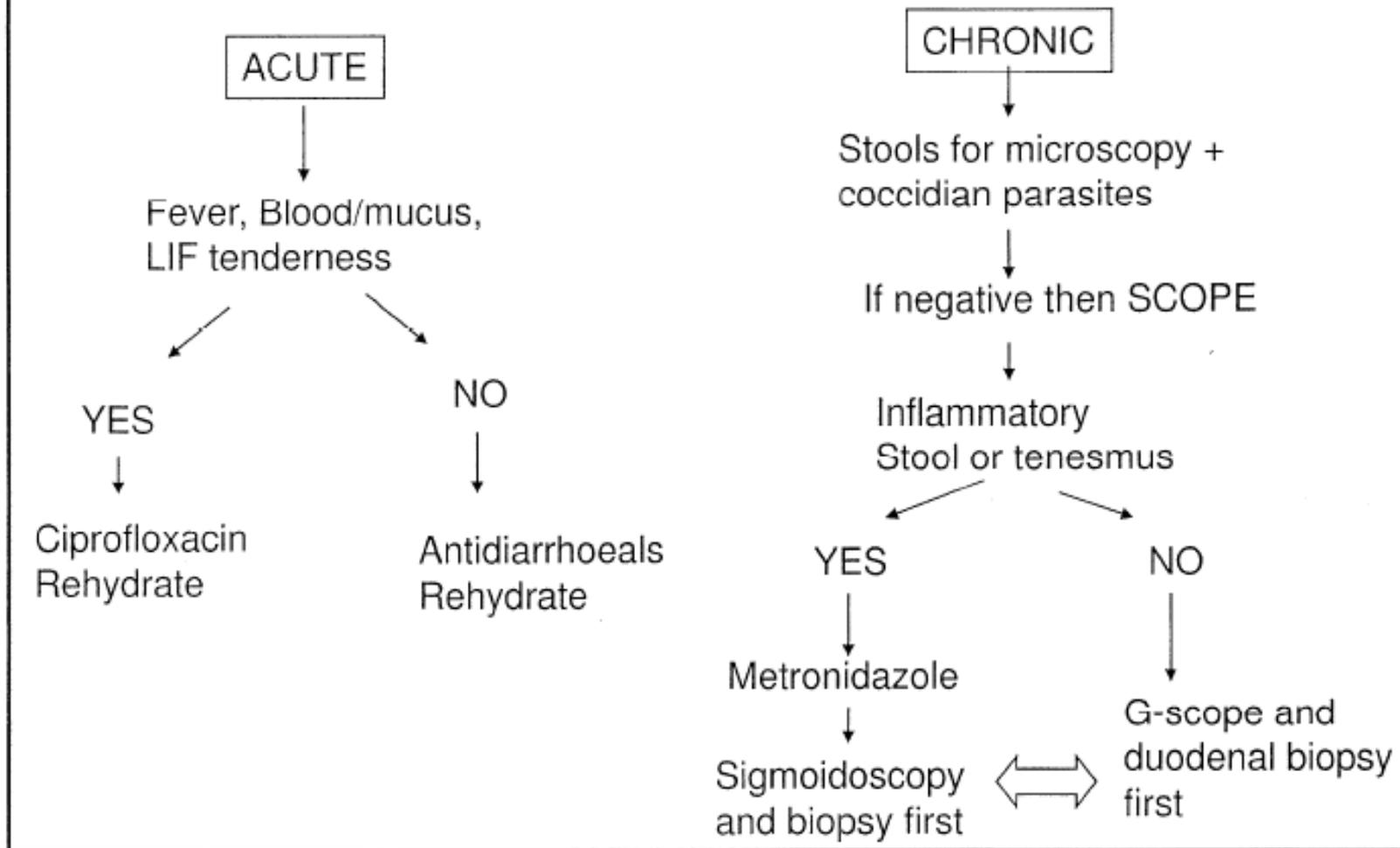


Fig. 2. Algorithm for investigation of diarrhoea.

Table IV. Causes of diarrhoea in HIV-infected patients

Acute (<2 weeks)

- Viral
- Bacterial (*Salmonella*, *Shigella*, *Campylobacter*, *E. coli*, *Clostridium difficile*)
- Early phase of chronic causes

Chronic (>2 weeks)

- *Isospora*
 - *Cryptosporidium*
 - *Microsporidium*
 - Amoebiasis
 - *Giardia*
 - CMV
 - *Mycobacterium avium* complex (MAC)
 - TB
 - Kaposi's sarcoma
 - Intestinal atrophy
 - HIV itself
- } opportunistic infections – Stage IV

Bacterial pneumonia in HIV

- **10 to 100 x fold increased incidence**
- **increased risk with lower CD4 count**
- **usual organisms** in 40 to 75% of cases:
 - ***Streptococcus pneumoniae*** 20-40-70%
 - ***Haemophilus influenzae*** 10-15-5%
 - ***Staphylococcus aureus* (?)** } 5%
 - ***Klebsiella* spp** }

Pneumonia prevention during HIV

Daniel R Feikin, Charles Feldman, Anne Schuchat, and Edward N Janoff



Clinical Stage 4

- Laboratory: CD4⁺ count < 200 cells/mm³
- Performance scale 4: bed-ridden > 50% of the day during last month
- HIV wasting syndrome
 - Unexplained weight loss >10% and visible thinning of face, waist & extremities
 - plus either
 - unexplained chronic diarrhoea (>1 month)
 - or
 - unexplained prolonged/ intermittent fever (>1 month)
- 15% chance of survival for 2 years

Stage 4 - AIDS defining illnesses

1. HIV wasting syndrome
 - Unexplained weight loss >10% and visible thinning of face, waist & extremities

plus

 - Either unexplained chronic diarrhoea (>1 month) **or**
 - Unexplained prolonged/intermittent fever (>1 month)

2. Pneumocystis jirovecii pneumonia [PCP]
 - With or without laboratory confirmation

3. Recurrent severe/radiological pneumonia
 - 2/more episodes in one year

4. Chronic herpes simplex
 - Oral, genital or anorectal for > 1month
 - Visceral of any duration

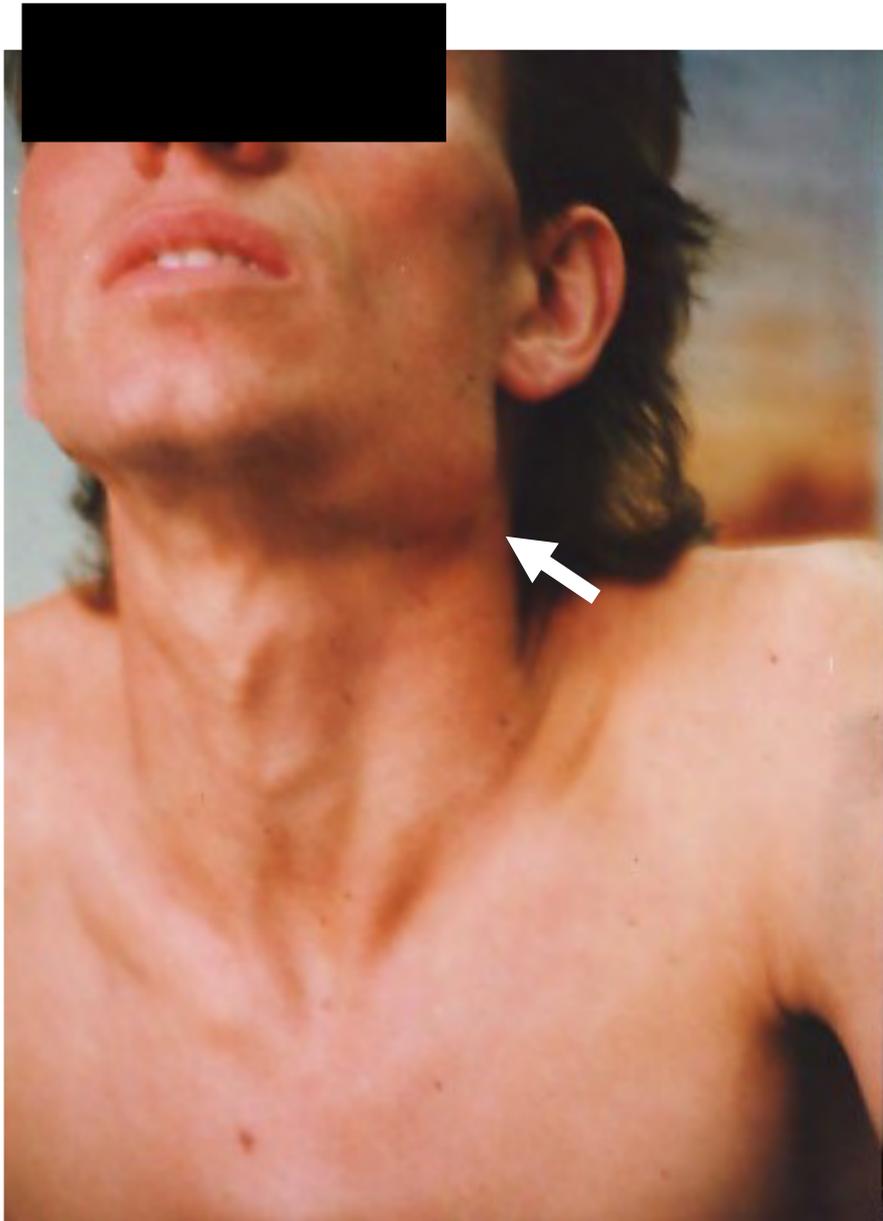


5. Oesophageal candidiasis
 - With/without oral candida

6. Extrapulmonary/Disseminated TB (ETB)

7. **Kaposi's sarcoma [KS]**





Stage 4

8. **CMV** retinitis or a organ other than the liver, spleen or lymph nodes

- May diagnose retinitis clinically, needs to confirm other sites



9. **CNS toxoplasmosis**

10. **Cryptococcal** meningitis / other extrapulmonary cryptococcal disease

11. HIV encephalopathy

- Confirm clinical findings and exclude other conditions

12. Disseminated **non-TB *Mycobacterium*** infection

- Always confirm with culture

13. Progressive multifocal leuco-encephalopathy [PML]

- Progressive focal neurological signs without headache or fever
- Always confirm with CT/MRI. Viral PCR for JC virus

14. **Candidiasis** of trachea, bronchi or lungs

15. **Cryptosporidiosis**

- With diarrhoea for > 1 month
- Confirm with modified ZN stain on stool sample



Stage 4

16. Isosporiasis
 - indistinguishable from cryptosporidiosis
 - responds to high dose cotrimoxazole

17. Any disseminated mycosis
 - Histoplasmosis, penicilliosis

18. Recurrent non-typhoidal salmonella septicaemia
 - 2/more in the last year
 - confirmed by blood culture

19. **Lymphoma**
 - cerebral
 - B-cel non-Hodgkin

20. **Invasive cervical carcinoma**
 - not carcinoma in-situ

21. Visceral leishmaniasis



NEOPLASIA

Additional Criteria for initiation of ART

1. Auto-immune haemolytic anaemia
 2. HIV-associated Idiopathic Thrombocytopaenic Purpura (ITP)
 3. HIV associated nephropathy
 4. HIV-associated cardiomyopathy (CMO)
 5. Thrombotic thrombocytopaenic purpura (TTP)
 6. Severe HIV neuropathy or HIV myelopathy
 7. Refractory aphthous ulceration
- } recently added to WHO Stage 4

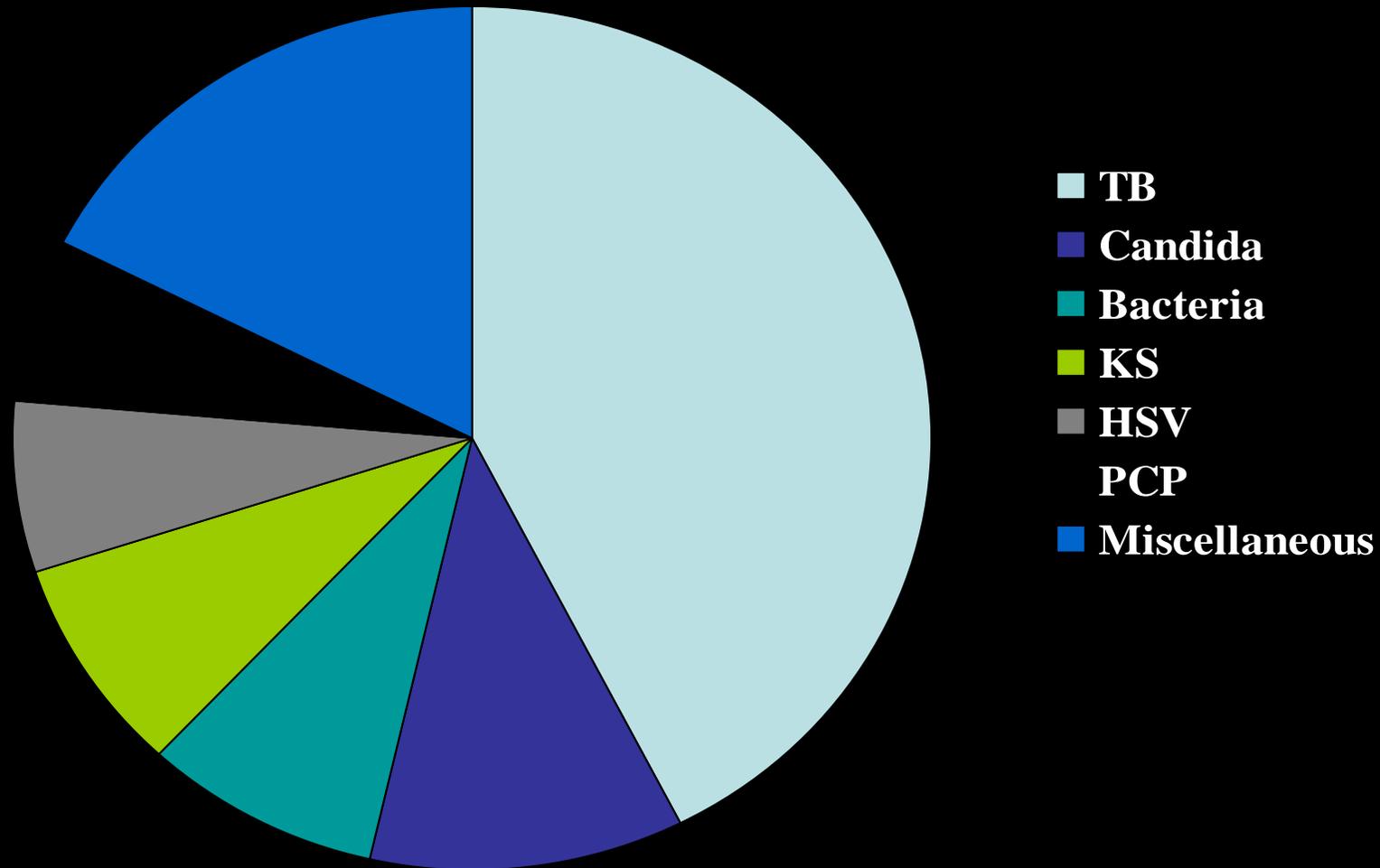
Additional Criteria for initiation of ART

8. All malignancies (unless early malignancy that is surgically resectable with low relapse risk)
9. MDR-TB (after adherence and assessment has been done and patient is seen to be suitable candidate)
10. HIV-associated vasculopathy
11. Diffuse infiltrative syndrome (DILS) with severe symptoms
12. Acute or chronic inflammatory demyelinating polyneuropathy (AIDP/CIDP) non-responsive to immuno-modulatory therapy

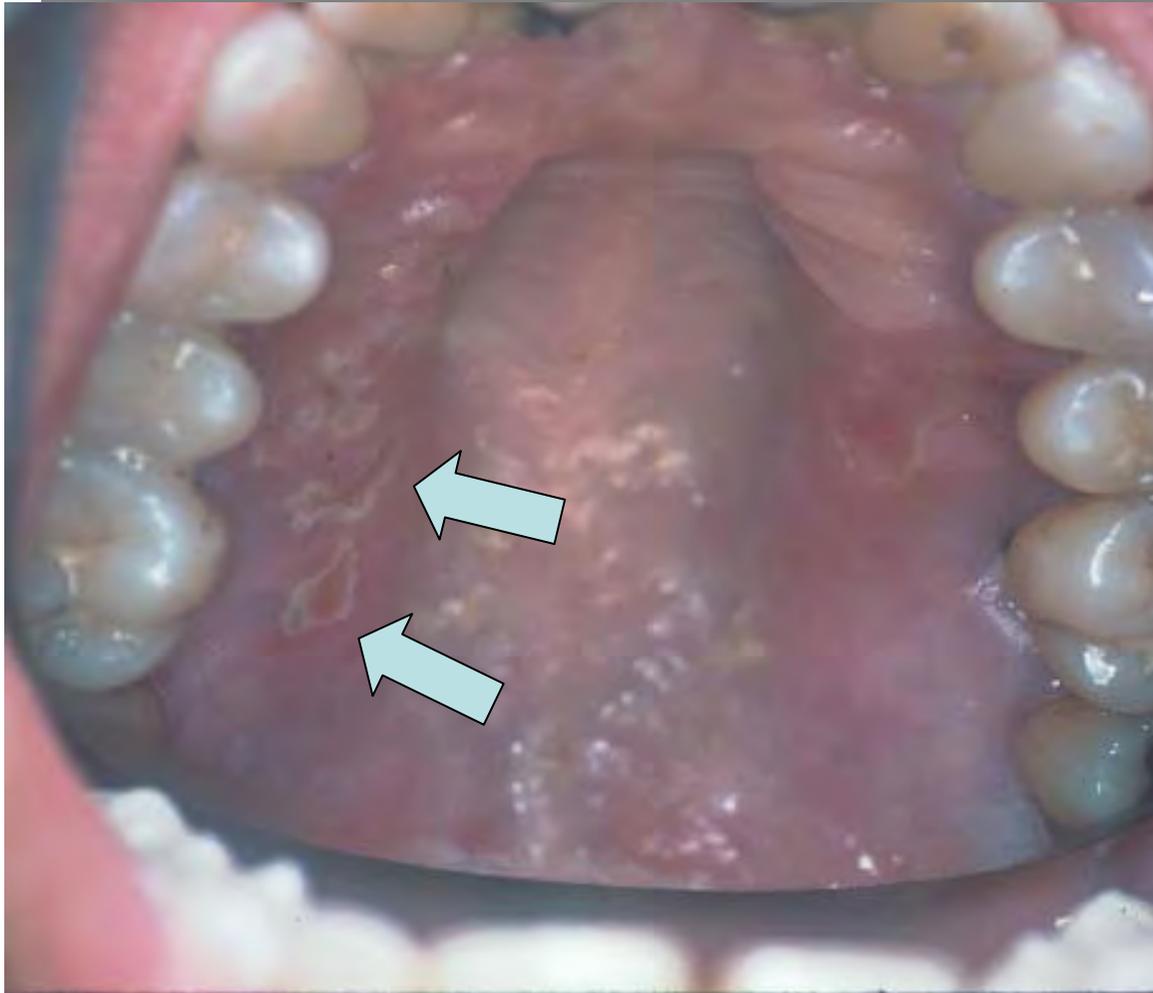
HIV - associated nephropathy HIVAN

- in 1980's, HIVAN was an uncommon cause of end-stage renal disease (ESRD)
- with improved survival, HIVAN became the most rapidly increasing cause for ESRD in USA
- 90% patients black (racial prediliction) with a male preponderance
- USA incidence of HIVAN 3.5 – 12% has led to an unprecedneted burden of chronic kidney disease in Africa

OIs in Cape Town



Herpes Simplex Virus 1 and 2



VI Meeks, DDS, U Md Dental School

Herpes Simplex 1 and 2

Intra-orally, usually found on tissue bound to bone, e.g. hard palate
Herpetic lesion lasting longer than 30 days is an AIDS defining lesion

Mucocutaneous viral lesions

Herpes Simplex Virus 1 and 2 (HSV-1,2)



VI Meeks, DDS, U Md Dental School

- Vesicular lesions which rupture becoming painful, irregular ulcerations;
- HSV-1 (oral; perioral) and HSV-2 (genital) infection clinically identical



Dr D Spencer " The Clinical Practice of HIV Medicine " p35



Herpes Simplex Virus 1 and 2

TREATMENT only if severe and start within 72 hrs:

- acyclovir 400 - 800mg 5x/day for 7-10 days or until no new lesions appear
- treat secondary infection appropriately

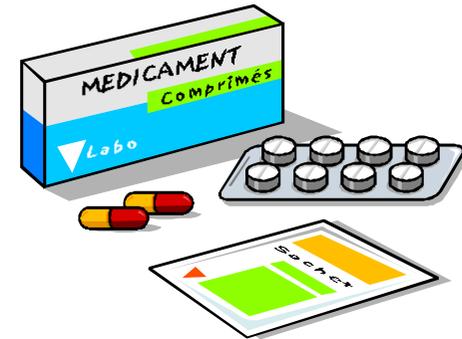
Oesophageal Candidiasis

- **80% of patients with AIDS**
- **symptoms:**
 - **odynophagia, dysphagia**
 - **retrosternal chest pain and regurgitation.**
 - **oropharyngeal Candidiasis often present**
 - **these features are sufficient for a presumptive diagnosis and therefore justify empirical oral antifungal therapy**

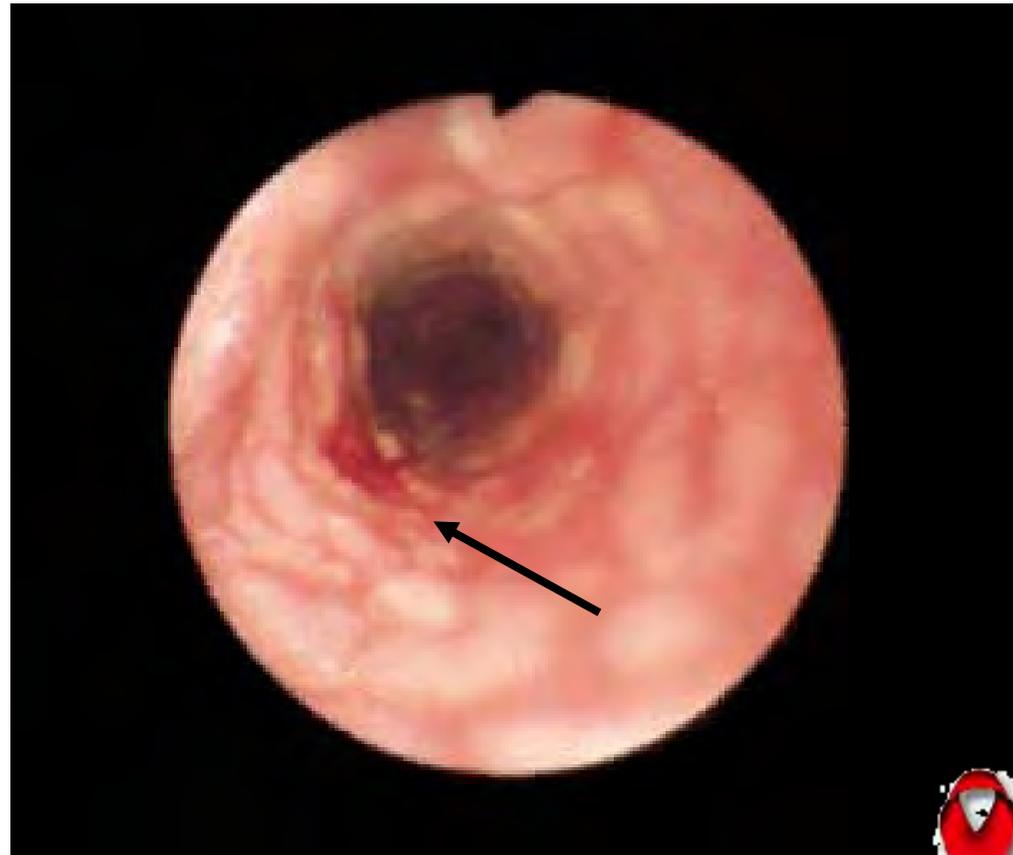


Oesophageal Candidiasis OC

- topical therapy NOT adequate for OC
- Azoles:
 - fluconazole *Diflucan*®
 - itraconazole *Sporonox*®
 - ketoconazole *Nizora*®]
- fluconazole 200mg daily - freely available from pharmacist who records in register
- should be given for 14 days
- iv amphotericin B for severe cases or where patient is unable to swallow.



Oesophageal Candidiasis



HIV - Dementia

- HIV infection is associated with CNS disease such as HIV-associated dementia (HAD) also known as AIDS dementia complex (ADC) or HIV encephalopathy and
- HIV-associated minor cognitive/motor disorder (MCMD)

Pathogenesis of HAD

- exact mechanisms by which HIV causes damage unclear
- changes in immune and inflammatory activity appear to underlie toxicity
- HIV easily crosses the BBB via infected monocytes
- virus in the brain initiates an inflammatory cascade that results in neuro-pathological changes and neuro-degeneration

BBB = blood-brain barrier

likes “ nerves “

HIV-associated dementia

- HIV is a *neurotropic* virus
- occurs in *advanced* stages or in *severe* immuno-suppression
- forgetfulness, slowing of responses and difficulty multi-tasking occur early
- cortical function relatively well preserved
- exclude other causes for memory loss such as vitamin B12 deficiency, metabolic conditions, adverse drug interactions

Clinical features of HIV-associated dementia

Cluster of symptoms	Presentation
Neurological	Motor symptoms - weakness, altered fine motor skills (handwriting), unsteady gait, tremor, visuo-spatial memory & coordinating difficulties, impaired verbal memory (word-finding), impaired attention & concentration, mental slowing
Psychiatric	Psychomotor retardation (slowed speech), personality changes (aggression, suspicion), social withdrawal, apathy, irritability, depression, mania, psychotic symptoms (paranoia), anxiety, obsessive or panic symptoms



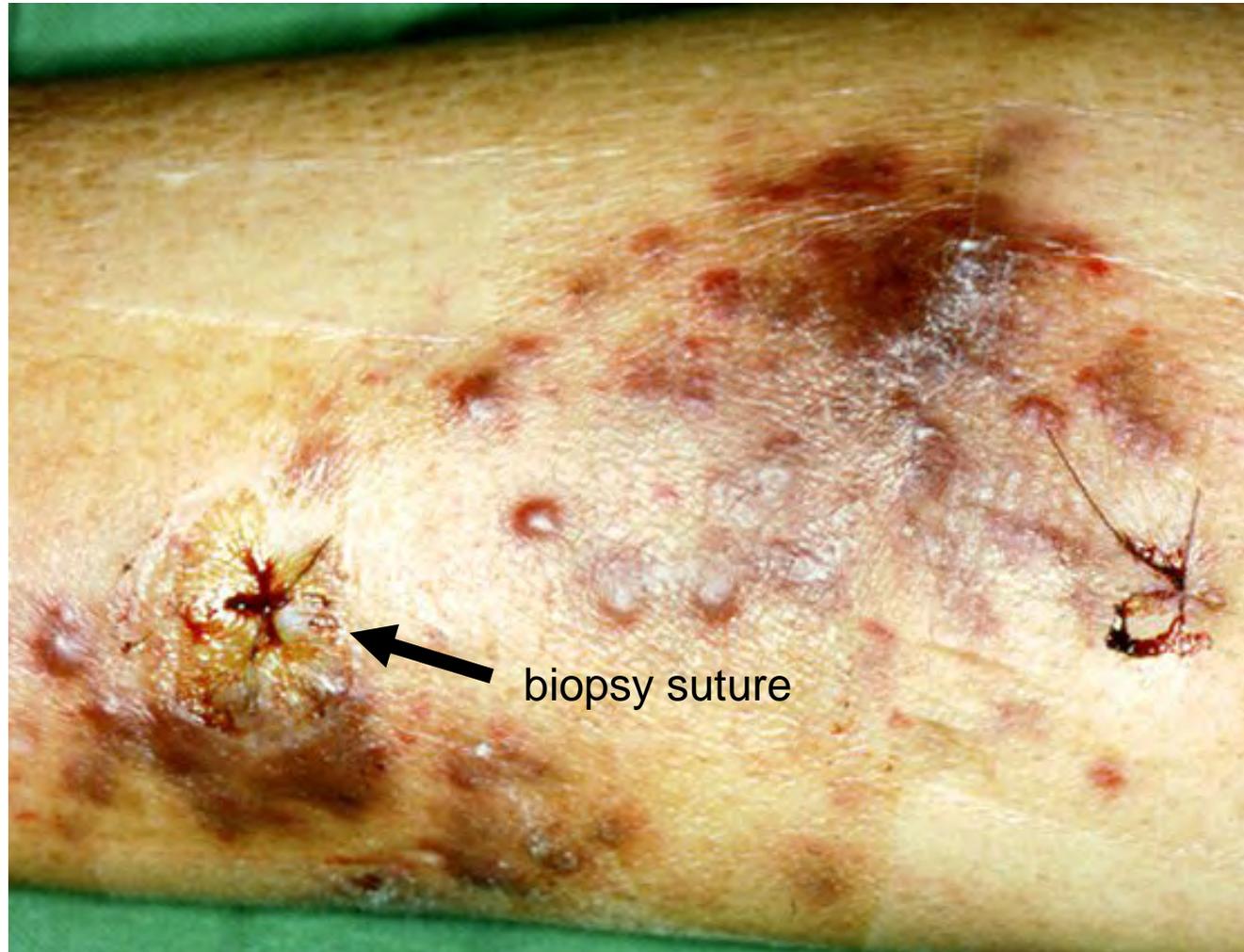
Blood or bruise-coloured skin lesions (flat plaques or nodules)



Different sizes and shapes



KAPOSI'S SARCOMA



KAPOSI SARCOMA

- *early* lesions may be very subtle suggestive of a bruise or pigmented callous starting in the head or neck area, upper torso or lower extremities
- as they *grow* they form flat patches, or raised, round or oval nodules
- if pressed, these lesions do not become as pale (as a bruise would)
- with time, they progress and ulcerate

K.S.

- lesions can occur ANYWHERE on the body
 - face, hands, anorectal or genital regions
 - mucous membranes (around eye or inside mouth [20%])
 - lymph nodes, lungs or G.I.T.
 - common on feet and limbs
- often there is swelling at the edges of the lesions at which point the lesions start to become painful

Background

- most common HIV-related cancer – 13% of people with AIDS (liver and prostate cancer 2nd and 3rd)
- aggressive – AIDS associated or “epidemic” KS
- caused by human herpes virus -8 (HHV-8)
- KS uncommon in patients who do not acquire HIV sexually
- male = female





Clinical picture – Oral KS

- 10-15% of KS patients
- hard palate typical site
- problems with swallow and mastication
- increased risk of visceral KS

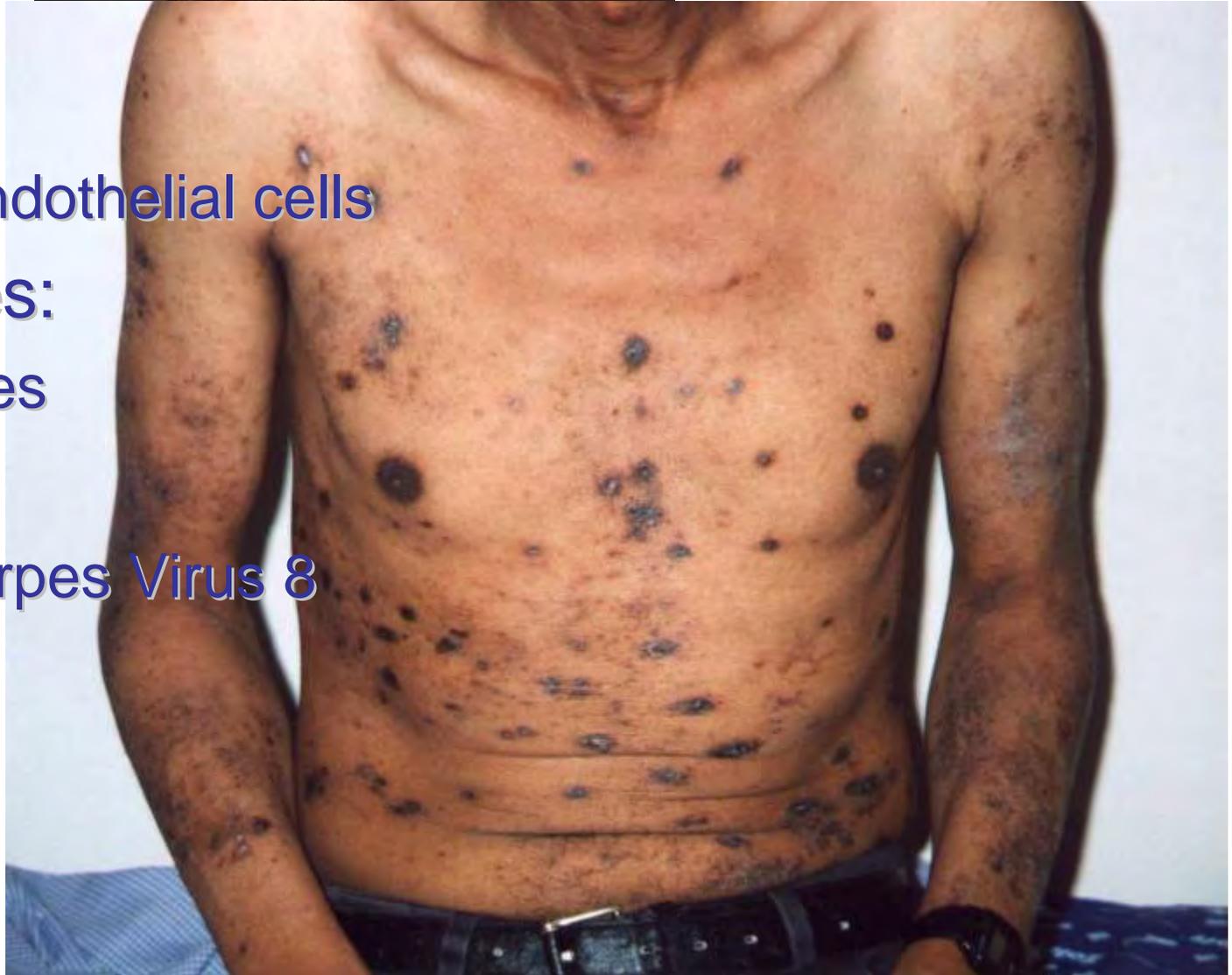


Clinical picture

- manifests differently from immune competent individuals
- typically multi-focal with widespread lesions involving the skin and mucous membranes of the mouth, and spreading to lymph nodes, GIT, lungs and other visceral organs is common.

KAPOSI'S SARCOMA

- derived:
 - capillary endothelial cells
- metastasises:
 - lymph nodes
- HHV8
 - Human Herpes Virus 8





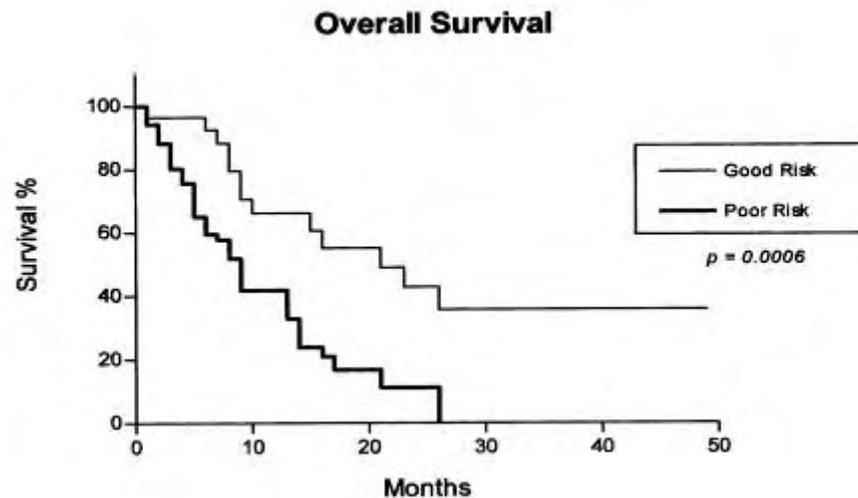
KAPOSI'S SARCOMA





KAPOSI'S SARCOMA

- survival remains poor
- most series: overall survival 17 months
- KS and ART:
 - 49 months v.s. 12 months without ART
- chemotherapy and ART associated with a reduced risk of death and an increased survival

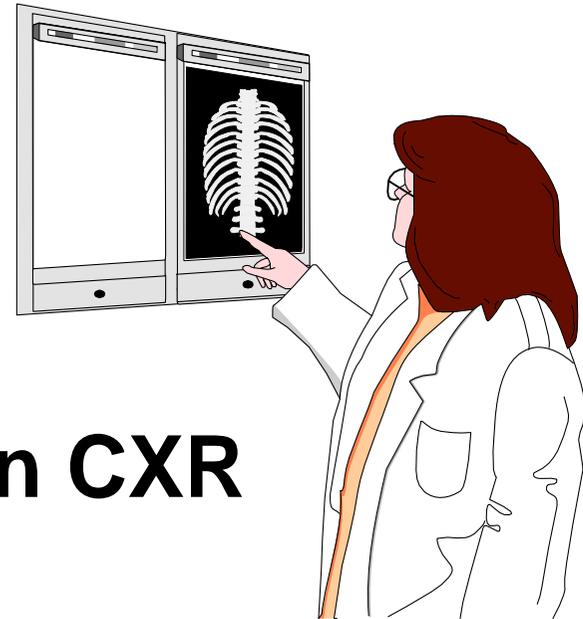


***Pneumocystis jirovecii* pneumonia (PCP)**

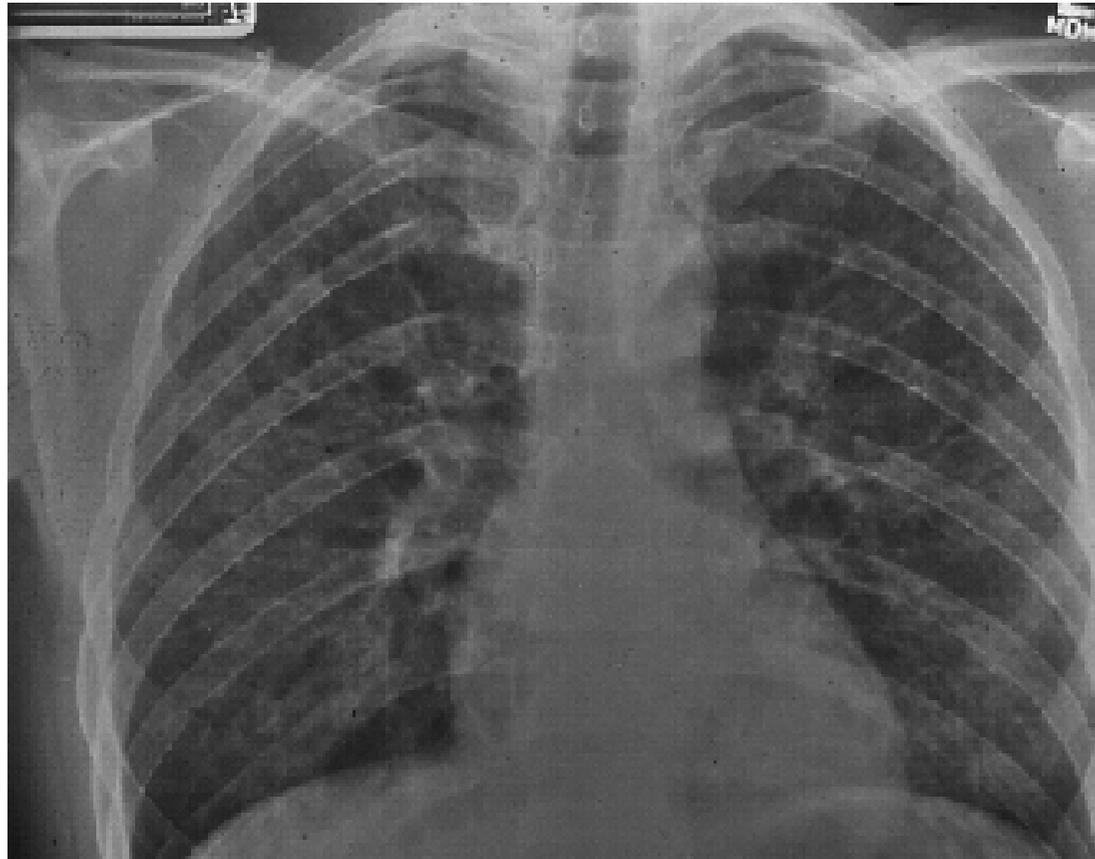
- **less common in sub-Saharan Africa**
- **single-celled organism previously classified as a protozoan**
- **ubiquitous in environment and infects most people sub-clinically during childhood via the respiratory route.**
- **HIV infected individuals are particularly susceptible when CD4⁺ count falls below 200 cells/mm³**

Pneumocystis jeroveci pneumonia

- presents *sub-acutely for weeks*
- progressive *dyspnoea*
- *dry cough*
- *fever*
- “ground glass” pattern on CXR
- serum LDH > 1000
- hypoxemia or desaturation on effort

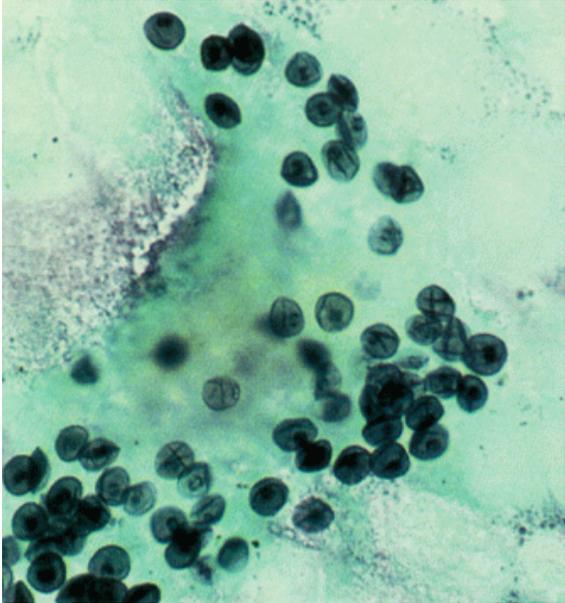
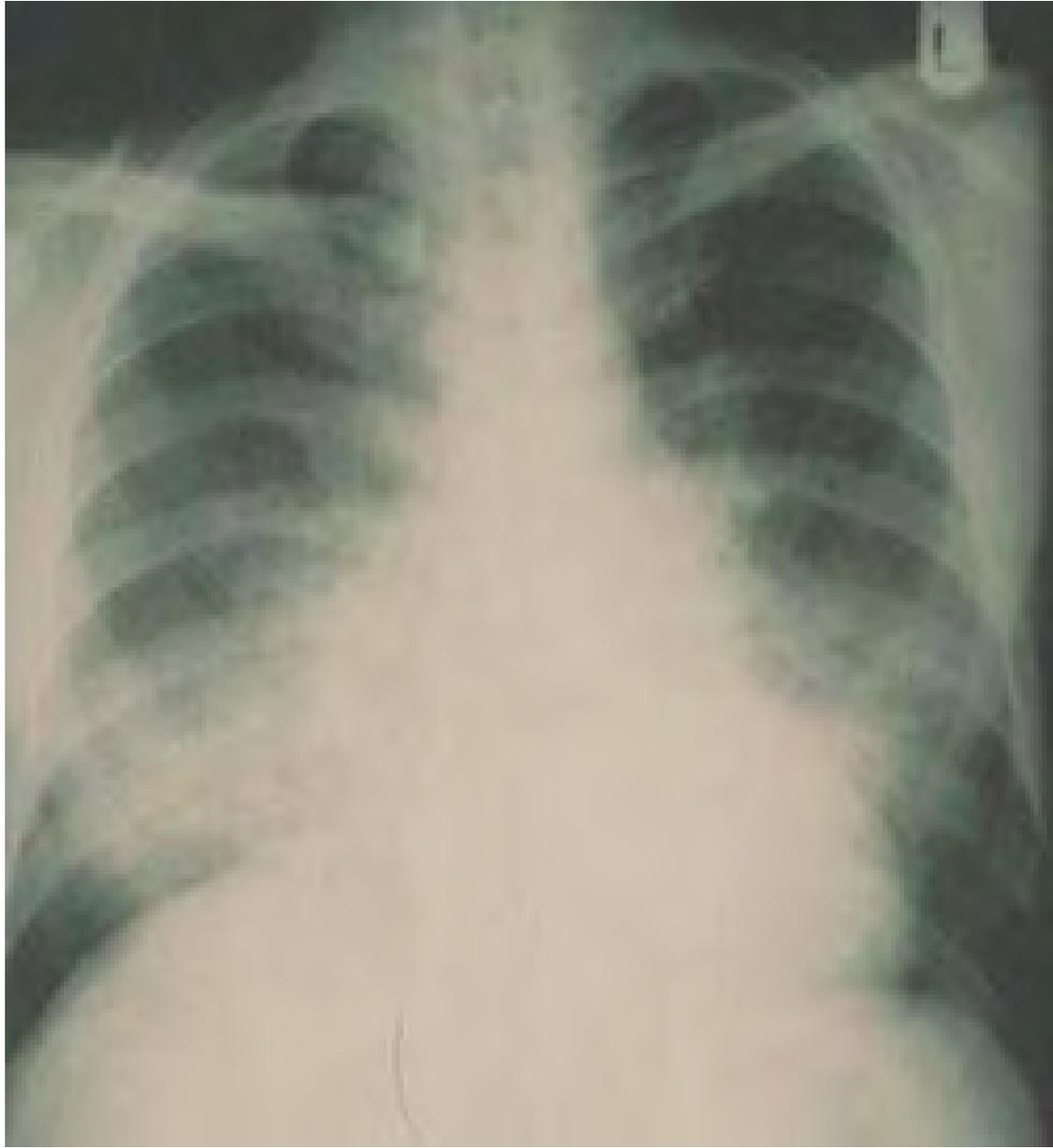


PCP



Pneumocystis carinii pneumonia in patient with AIDS Chest radiograph shows diffuse ground glass opacification without air bronchograms and without obliteration of the pulmonary vessels. Courtesy of Paul Stark, MD.





Pneumocystis jirovecii pneumonia

TREATMENT

- **empirical therapy often necessary...**
- **first-line treatment: TMP-SMX (Bactrim®)**
- **high doses: 480mg per every 4-5kg body weight given 6-8hourly for 14-21days.**
- **adjunctive corticosteroids** (Prednisone 40mg 12hourly for 5 days – taper rapidly) **in patients who are hypoxic and hospitalised**
 - **no benefit after 72hrs or when taken for mild disease**

Pneumocystis jirovecii pneumonia

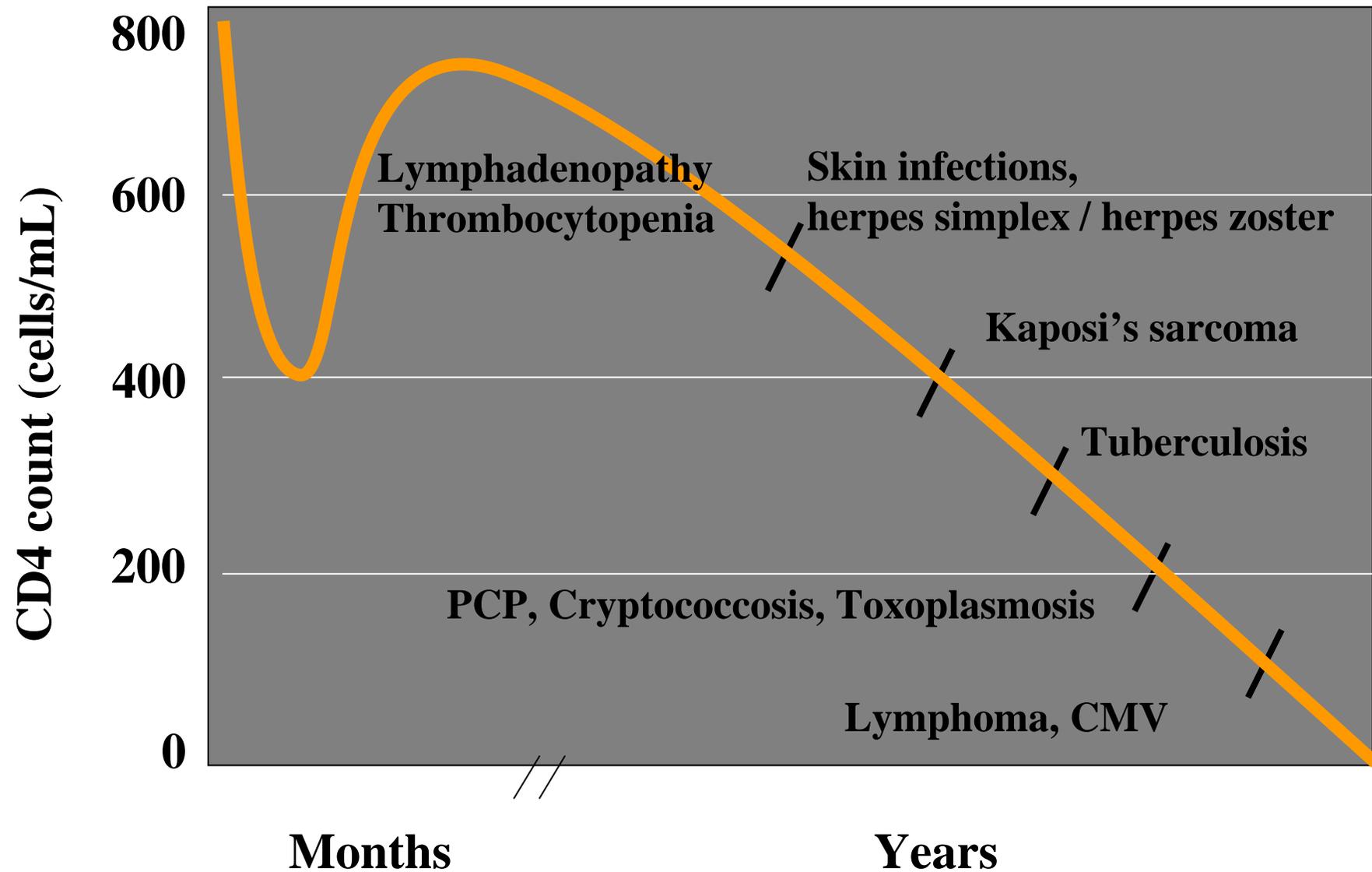
PROPHYLAXIS/MAINTENANCE

- **daily dose of 160mg TMP + 800mg SMX is the most effective prophylactic regimen.**
- **lower doses is probably as effective and are better tolerated.**



Prophylaxis against *P. carinii* can safely be discontinued in patients on highly active antiretroviral therapy if their CD4 count has risen to >200 cells/mm³ for 6 months

Opportunistic Disease Thresholds with declining CD₄ Counts



CD4+ count (cells/mm ³)	Infectious	Non-infectious
> 500	Vaginal candidiasis	Persistent generalized lymphadenopathy Guillain-Barré syndrome Bell's palsy Aseptic meningitis Parotidomegaly Kaposi's sarcoma
200 – 500	Pulmonary tuberculosis Pneumonia (bacterial) Herpes zoster Oral candidiasis Oral hairy leukoplakia Oesophageal candidiasis	Cervical intraepithelial neoplasia Cervical cancer Mononeuritis multiplex Idiopathic thrombocytopenic purpura Hodgkin's lymphoma Lymphocytic interstitial pneumonitis Kaposi's sarcoma
50 – 200	Extrapulmonary tuberculosis <i>Pneumocystis carinii</i> pneumonia Cryptococcal meningitis Toxoplasmosis Cryptosporidiosis (chronic) Microsporidiosis Histoplasmosis (disseminated) Chronic herpes simplex ulcers Septicaemia (non-typhoidal salmonella)	Wasting Anaemia Peripheral neuropathy HIV-associated dementia Non-hodgkins lymphoma Cardiomyopathy Vacuolar myelopathy Kaposi's sarcoma
< 50	Cytomegalovirus (disseminated) <i>Mycobacterium avium</i> complex (disseminated)	Kaposi's sarcoma

Prophylaxis

cotrimoxazole 960mg daily

- clinically WHO stage 3 or stage 4
- laboratory CD4 < 200



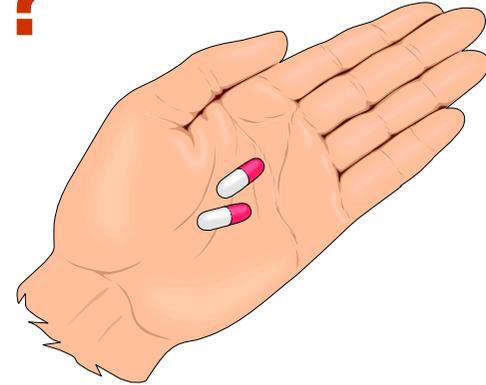
Infections prevented by cotrimoxazole

- PCP
- Bacterial pneumonia
- Bacteraemia
- Toxoplasmosis
- Isosporiasis / Cyclosporiasis



Who should get Bactrim prophylaxis?

- **CD4 count < 200**
- **co-existent TB**
- **AIDS defining illness (irrespective of CD4 count)**
- **unexplained weight loss**
- **chronic diarrhoea**
- **oral hairy leukoplakia**
- **oral thrush**



Cotrimoxazole hypersensitivity

- permanently discontinue if severe :

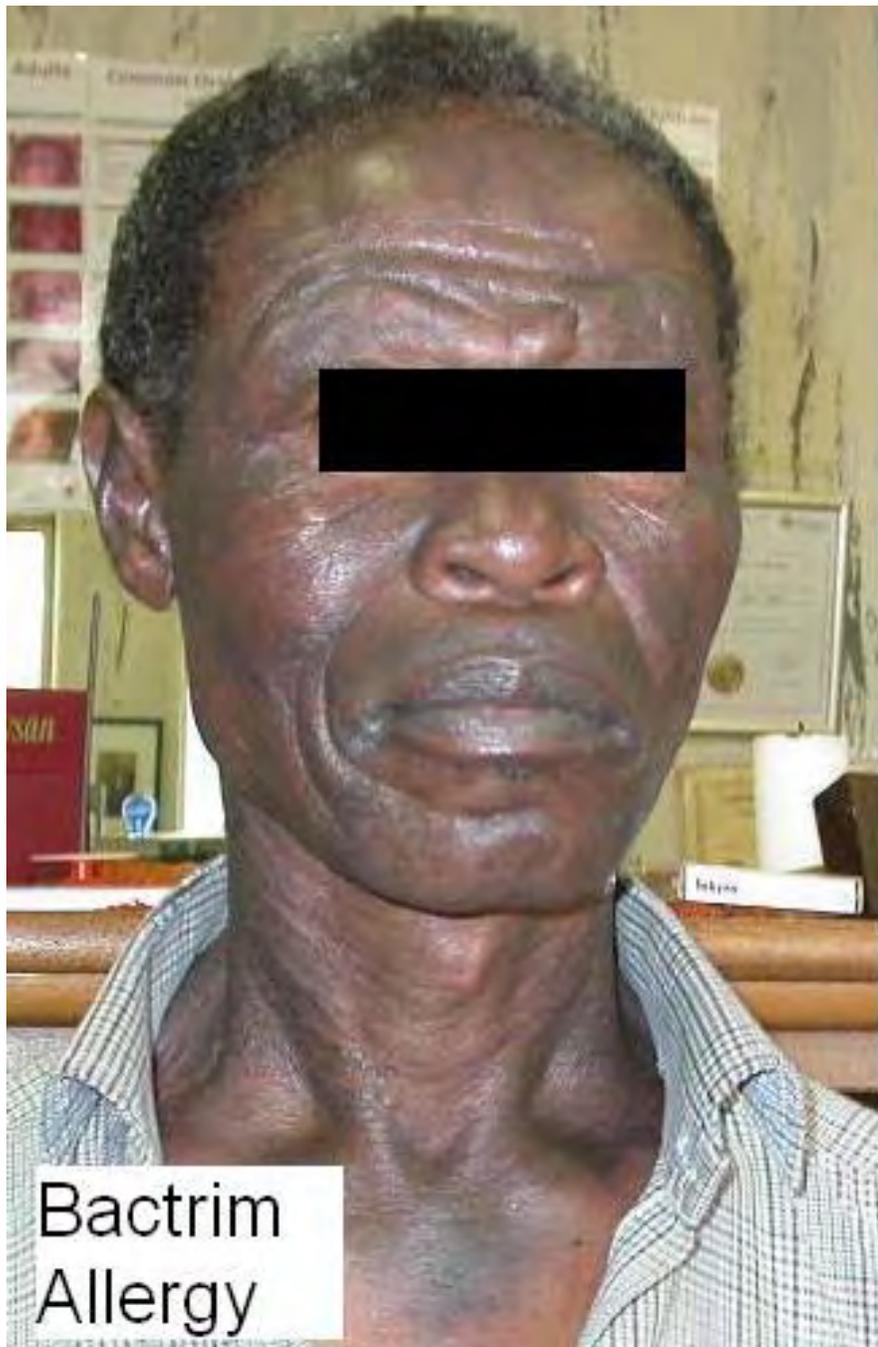
Stevens-Johnson syndrome

Fixed drug eruption

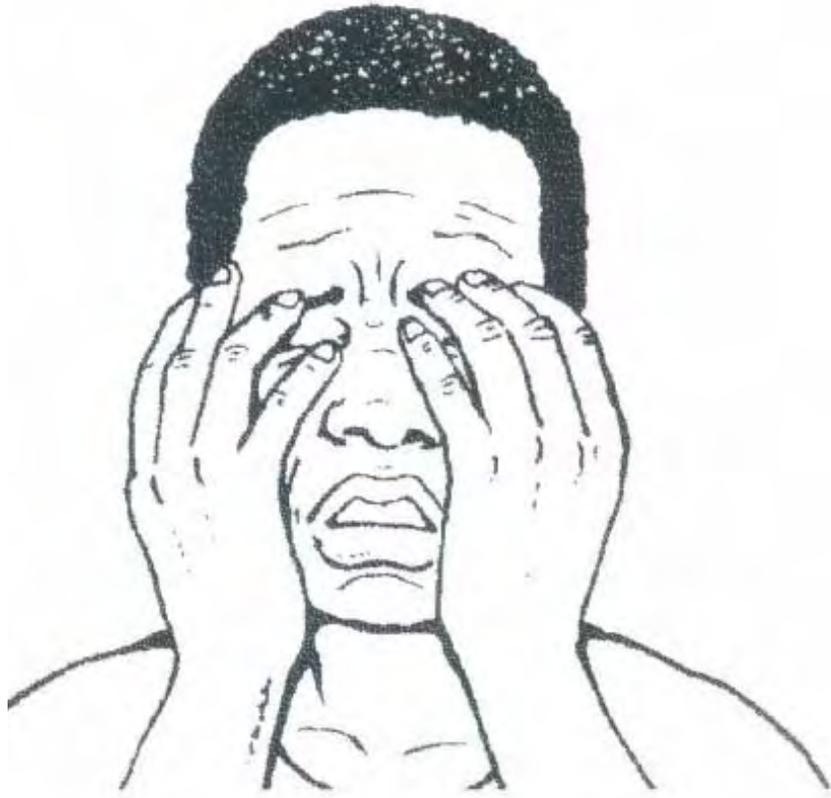


- antihistamines and/or steroids & continue
- discontinue & desensitise later under antihistamine cover
- **Dapsone** 100mg daily if rash recurs (unless Stevens-Johnson)

J Infect Dis. 2001;184:992-7.

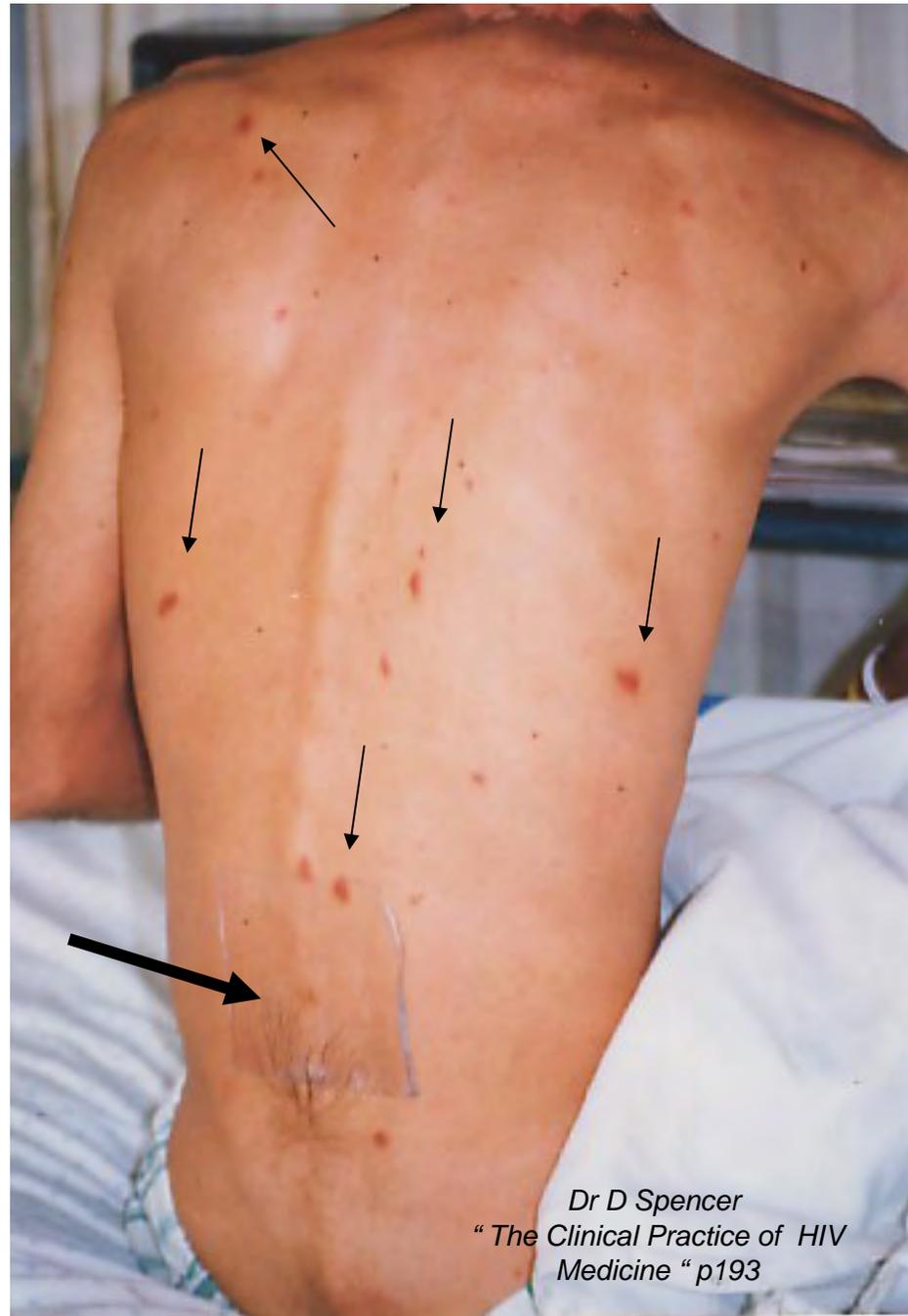


Bactrim
Allergy



Headache ?

Photophobia ?

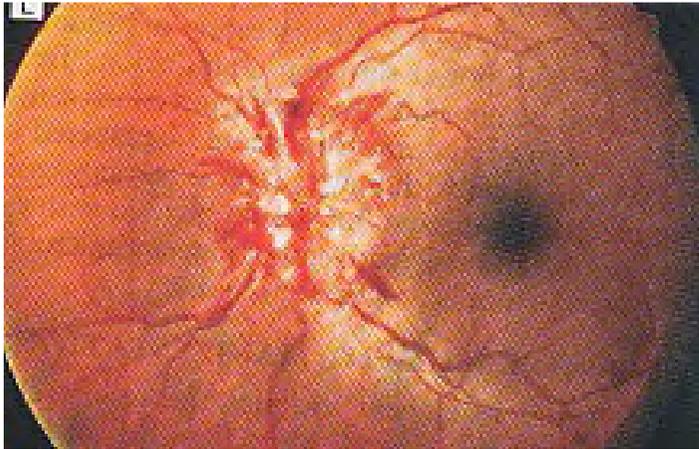


*Dr D Spencer
"The Clinical Practice of HIV
Medicine" p193*

Cryptococcal meningitis

Symptoms and signs

Headache, fever, nausea and vomiting, somnolence and confusion. Coma. Focal signs including a 6th cranial nerve palsy described in up to 20% in some series. Neck stiffness and the classical signs of Kernig and Brudzinski are frequently absent.



Papilloedema of
the eye: raised
intracranial pressure
in cryptococcal
meningitis

Cryptococcal meningitis

Diagnosis

CSF: opening pressure and total protein increased, glucose low – low normal, cells are mainly lymphocytes, India-ink stain positive and the cryptococcal latex agglutination test (CLAT) is positive.

Additional measures: detection of fungus in blood; CT Scan of the Brain: meningeal enhancement, cerebral oedema, mass lesions occasionally, hydrocephalus.

Cryptococcal meningitis

Treatment

Induction phase:

- Poor prognostic indicators
 - IV amphotericin B 0.7mg/kg/day x 14 days
 - 5-Flucytosine (5FC) 100mg/kg daily po x 14 days if available
- The remainder
 - IV fluconazole 800 mg loading dose followed by IV 400 mg daily x 2 days
followed by 400 mg daily po x 8 weeks

Cryptococcal meningitis

Maintenance therapy:

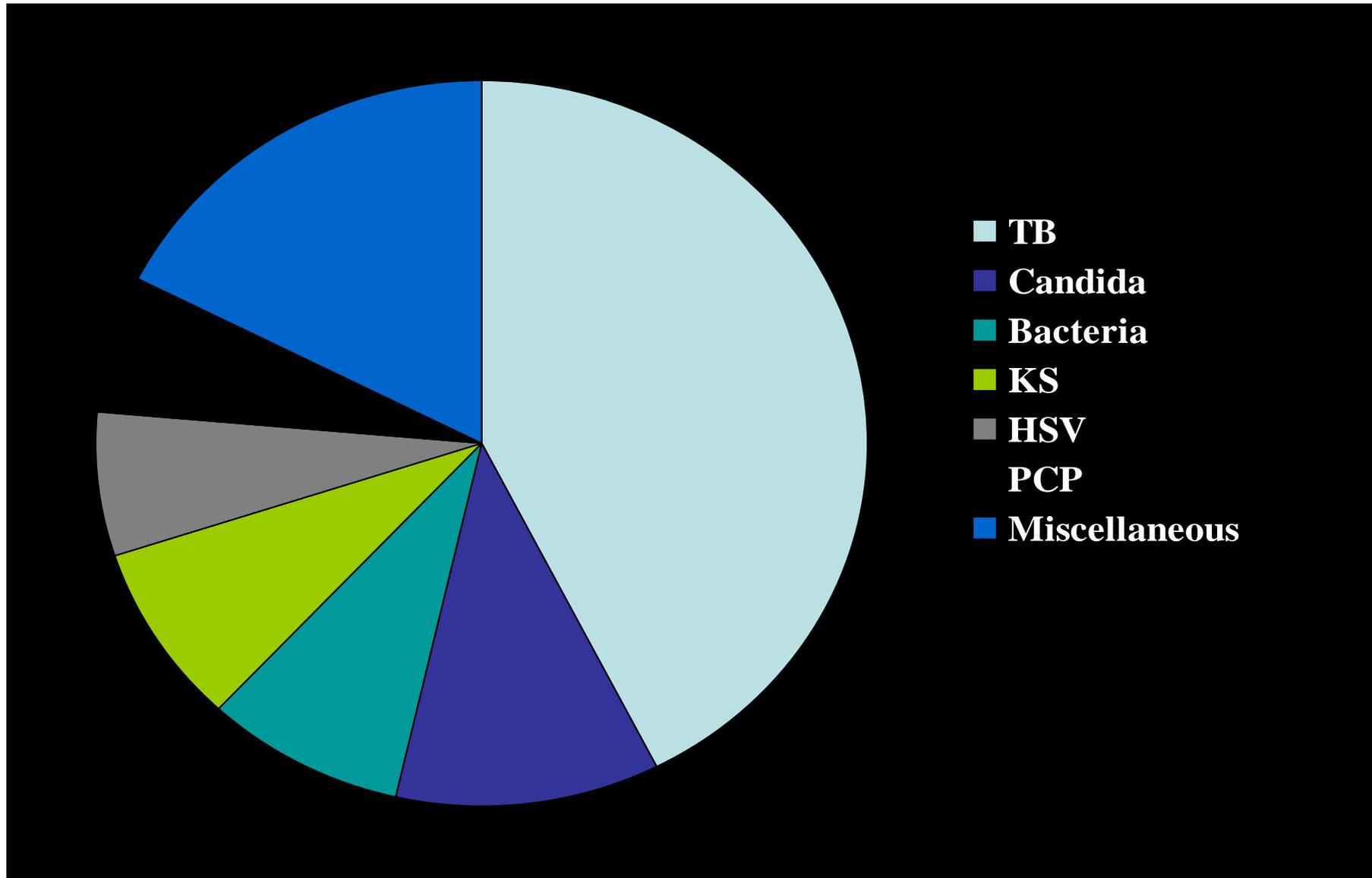
- fluconazole 200mg daily po until the CD4 sustained above 200.
- repeat lumbar puncture (therapeutic taps) may be necessary after treatment of CM due to raised intracranial CSF pressures.
- HAART

Tuberculosis (TB) and HIV/AIDS

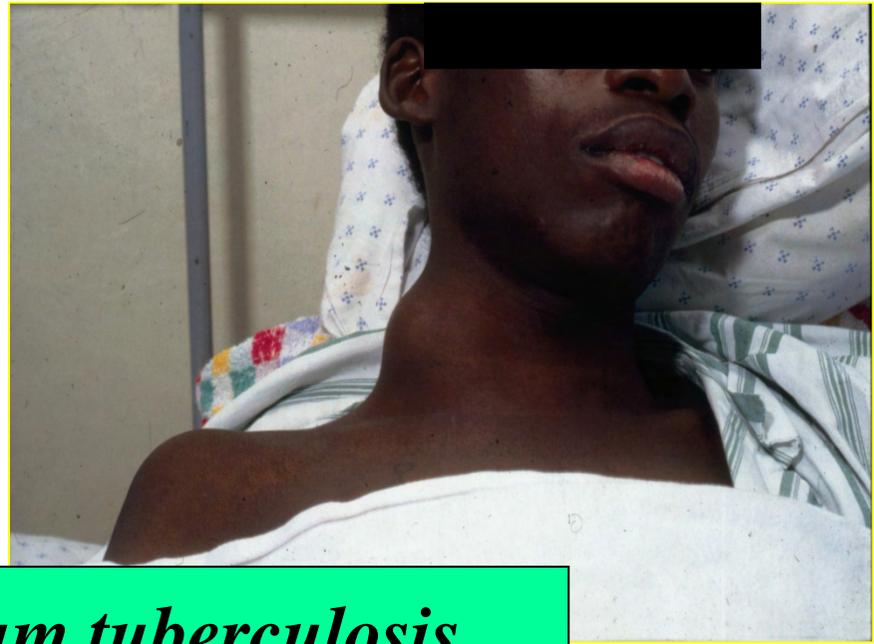
Co-morbidities
“The terrible twins”



OIs in Cape Town



Erythema Nodosum



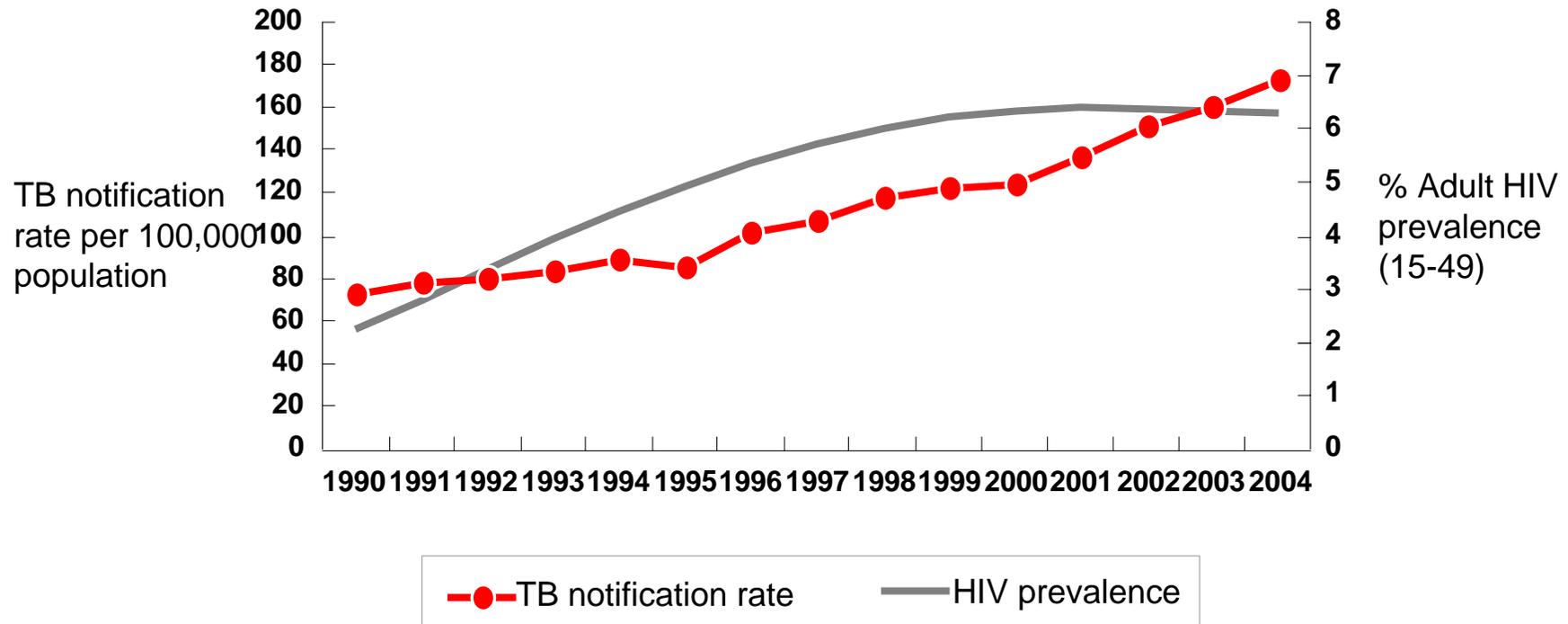
Mycobacterium tuberculosis



Mycobacterium tuberculosis



TB notification rate in 20 African countries* versus HIV prevalence in sub-Saharan Africa, 1990–2004



- **Consistently reporting each year:** Algeria, Angola, Botswana, Cameroon, Comoros, Congo, Côte d'Ivoire, Democratic Republic of Congo, Ghana, Guinea, Kenya, Malawi, Mauritius, Mozambique, Nigeria, Senegal, South Africa, Uganda, United Republic of Tanzania, Zimbabwe

Table I. HIV-associated TB symptoms and signs

Symptoms	Signs	if < 45 years, start TB treatment
Weight loss >5% over preceding 4 weeks	Consolidation	
Chronic cough with or without sputum production or haemoptysis	Pleural effusion	←
Drenching night sweats	Pericardial effusion	
Fevers and chills	Lymph node enlargement	
Dyspnoea	Ascites	
Chest pain during coughing	Signs of meningitis (requires urgent referral)	
Fatigue		
Asymmetrical lymph node swelling		
Abdominal swelling		
Headache		

WC disease burden

- WC 2nd highest burden of TB cases in South Africa 1030 / 100 000 developing the disease every year
- KZN highest 1076 / 100 000
- in 2007, 348 MDR cases diagnosed and 73 XDR in WC (of which 26 died)
- XDR is incurable, patients kept in Brooklyn Chest Hospital special unit in WC

Management

- as diseases, both have many similarities but they also have many differences
- both are a huge burden on the DoH medical services
- spread easily with-in the community TB >>HIV
→ follow-up on defaulters important
- both need poly-pharmacy ie multiple drugs
- (HAART *triple* therapy and Rifafour)
- both can lead to drug resistance, contact tracers needed (P.A.'s or CHW's)

Management

- both have standardised treatment regimes
- ARV's 1a, 1b, 2
- both require treatment DAILY
- TB has Reg I - 6 months
Reg II – 8 months



- Resistance can emerge to drugs of both diseases due to non-compliance
- (TB medication in South Africa used to be Monday to Friday)

Table II. Diagnostic considerations in TB patients deteriorating on TB therapy

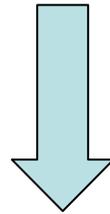
Possible diagnosis	Action
Non-adherence to TB therapy	Check TB clinic card and contact TB clinic
Secondary infection, either focal (e.g. pulmonary) or systemic (e.g. non-typhoid salmonellosis)	Treat for bacterial pneumonia or pneumocystis as appropriate, and consider admission for intravenous third-generation antibiotics (avoid quinolones)
Multidrug-resistant TB (MDR TB)	Send off good clinical specimens for TB culture and drug susceptibility testing
Fungal infections	Look for skin lesions to biopsy, send away blood for cryptococcal agglutination test and consider lumbar puncture, bone marrow biopsy and liver biopsy
Kaposi's sarcoma and lymphoma	Look for skin lesions, enlarging lymph nodes (including in the chest and abdomen) and hepatosplenomegaly; refer for biopsy

Diagnosis of TB

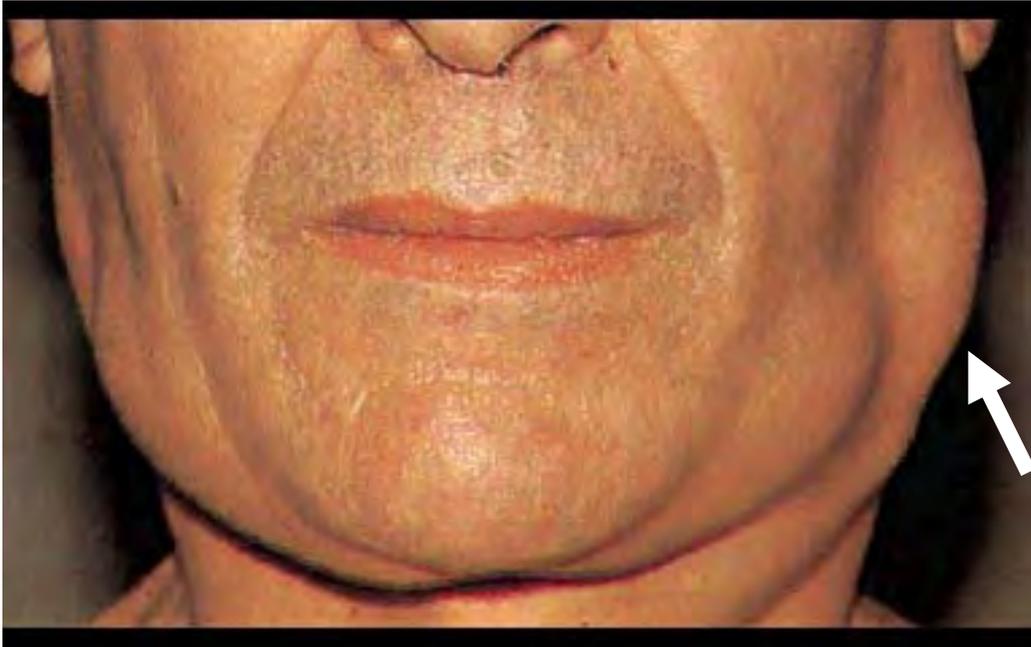
- HIV negative patients do not always have positive smears for TB bacilli
- HIV positive are MORE likely to have a *smear negative* test in the face of TB infection
- it may be necessary to treat a patient for TB without laboratory confirmatory evidence → *empirical treatment*
- trial of antibiotics may be tried
- defer ARVs – watch weight and clinical

TB diagnosis

“ the sister at the clinic did a TB spit (sputum) test and told me that I do not have a TB “



“The test has come back negative so we cannot prove you have TB but you may still have the infection – further tests will be needed.....”



Extrapulmonary TB



Protocol for diagnosing TB in HIV

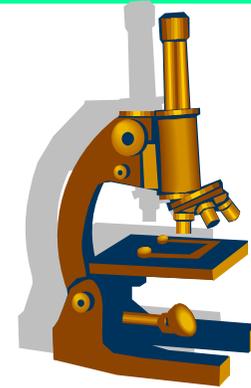
2 sputum *positive* → treat as TB

1 sputum *positive* and 1 negative:

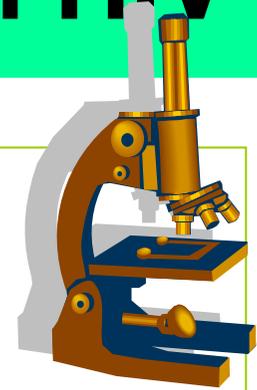
- if patient HIV positive, treat as TB
- if patient HIV negative or unknown, send off a 3rd sputum for AFB and culture, get CXR, check for symptoms of severe disease (weight loss, ↑ RR)

Both sputum negative:

- if HIV positive or unknown, send off 3rd for AFB and culture, get CXR, check for S&S



Protocol for diagnosing TB in HIV



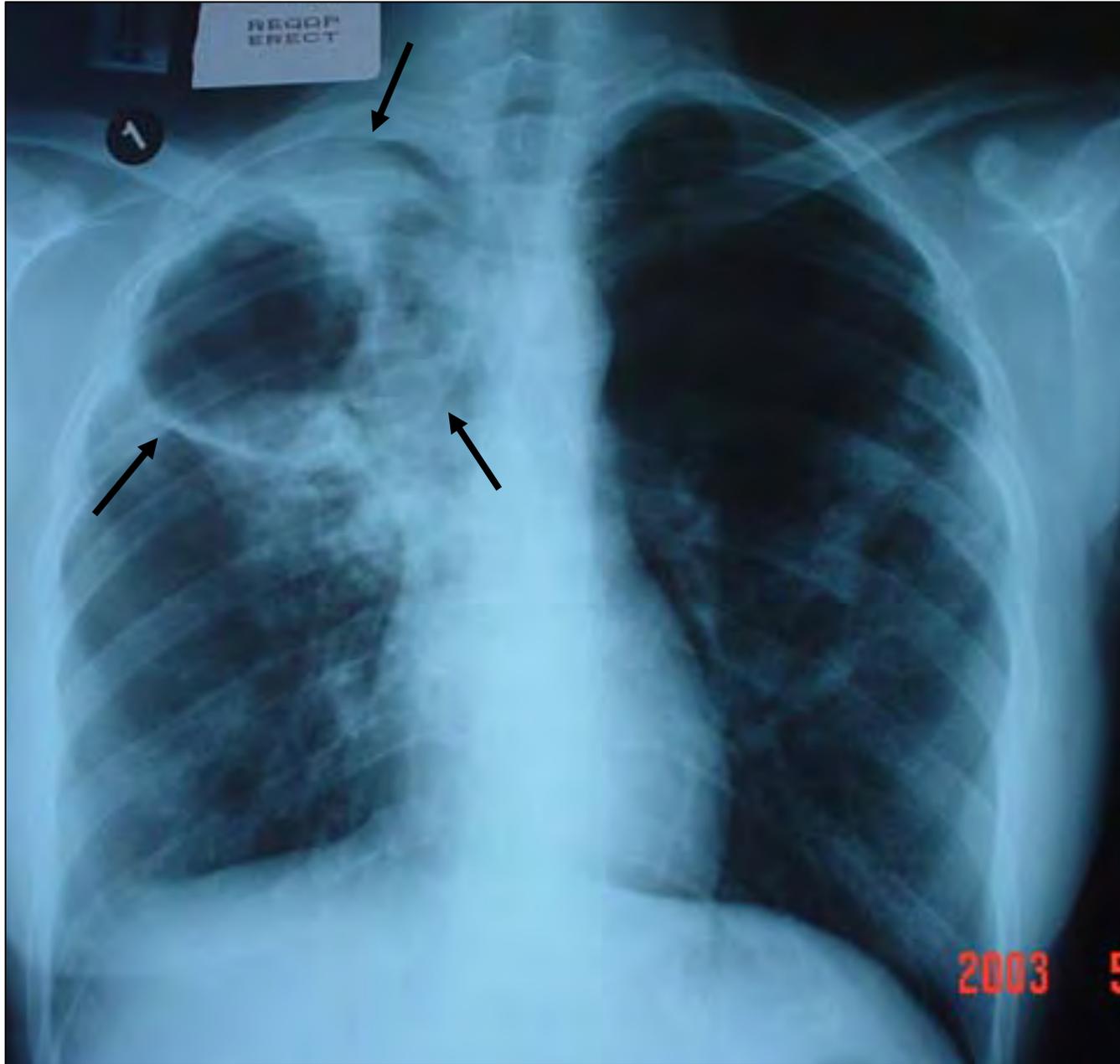
- if 3rd sputum positive for TB (AFB or culture positive), treat as TB
- if 3rd sputum AFB negative, check CXR for evidence of TB, check for MDR if a re-treatment case, screen household contacts, watch weight, check *CRP* (a marker of non-specific inflammation), note response to antibiotics

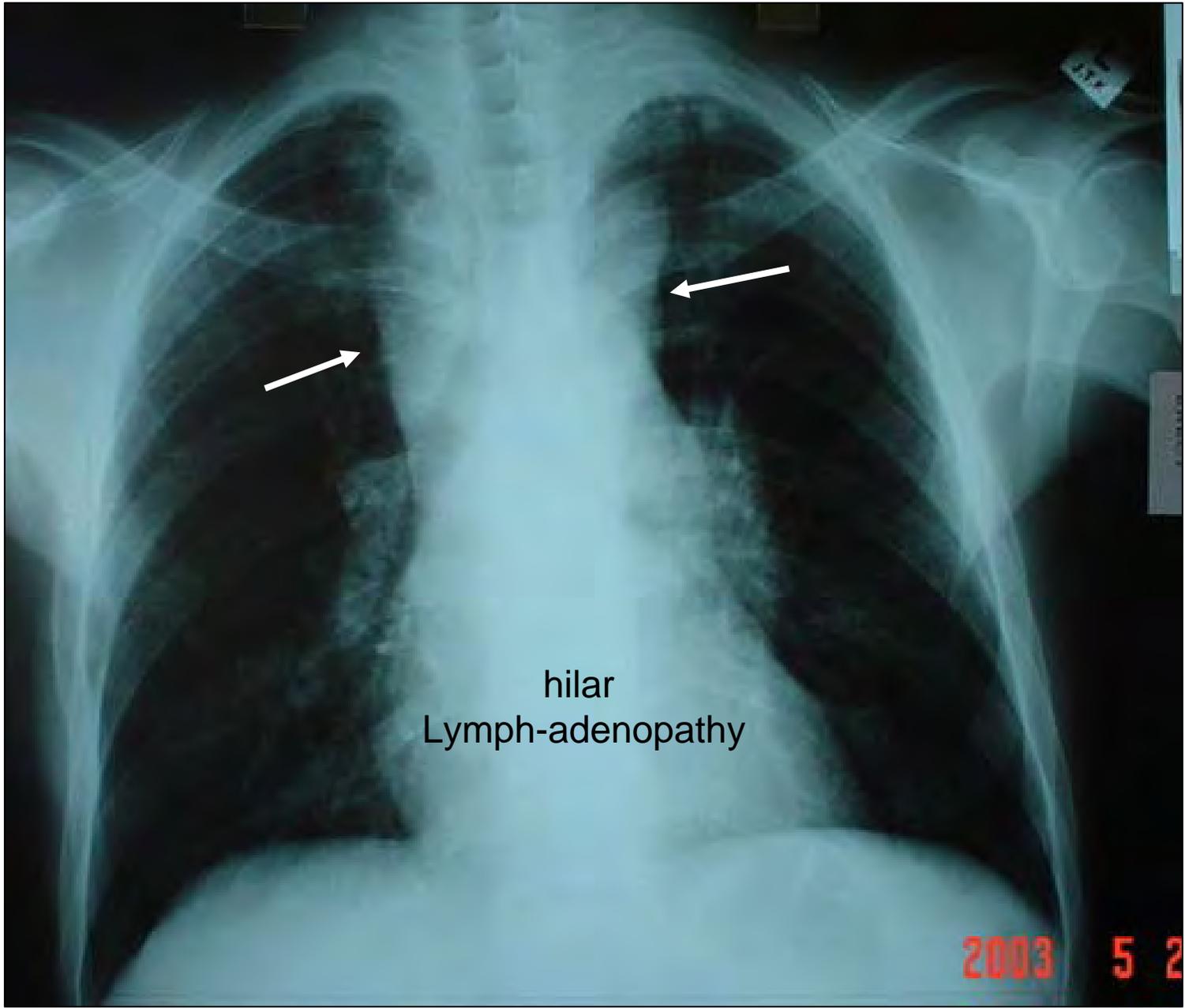
“C” reactive protein (CRP)

- a *non-specific* marker of inflammation
- it is *raised* in any infection eg pneumonia
- normal 0 – 20 (depending on laboratory reference range)
- if elevated, maintain a high clinical suspicion of TB especially if supportive evidence (history, symptoms an signs)
- particularly useful if smear **NEGATIVE** and CXR unhelpful

Common CXR findings in TB/HIV

- **Cavitation**
- **Focal infiltrates in upper and hilar regions**
- **Hilar adenopathy**
- **Pleural or pericardial effusions**





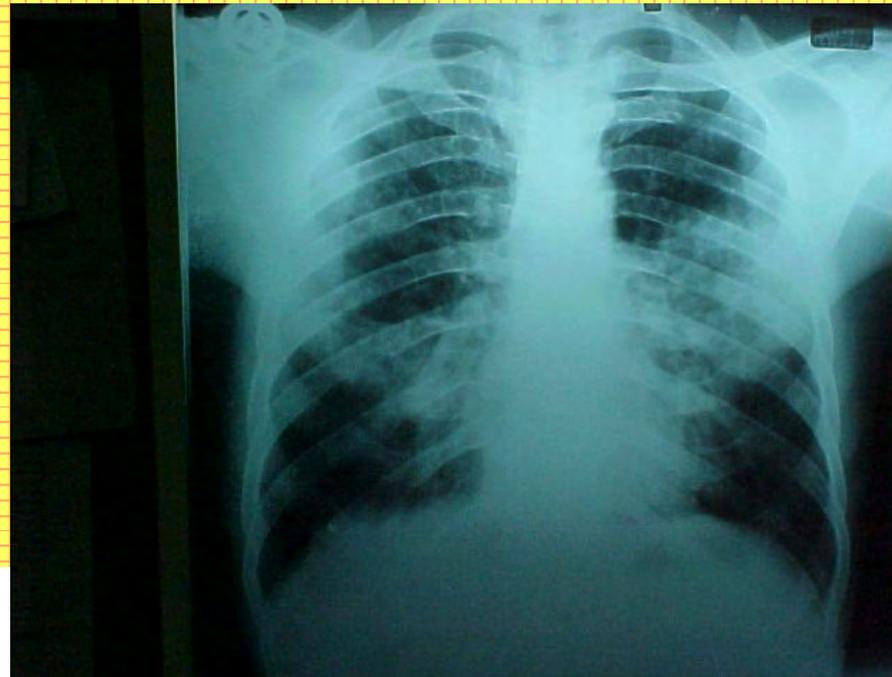
hilar
Lymph-adenopathy

2003 5 2

Tuberculosis and HIV in 2007. Diagnosis and Management.

Dave Spencer Kimera Consultants 2007

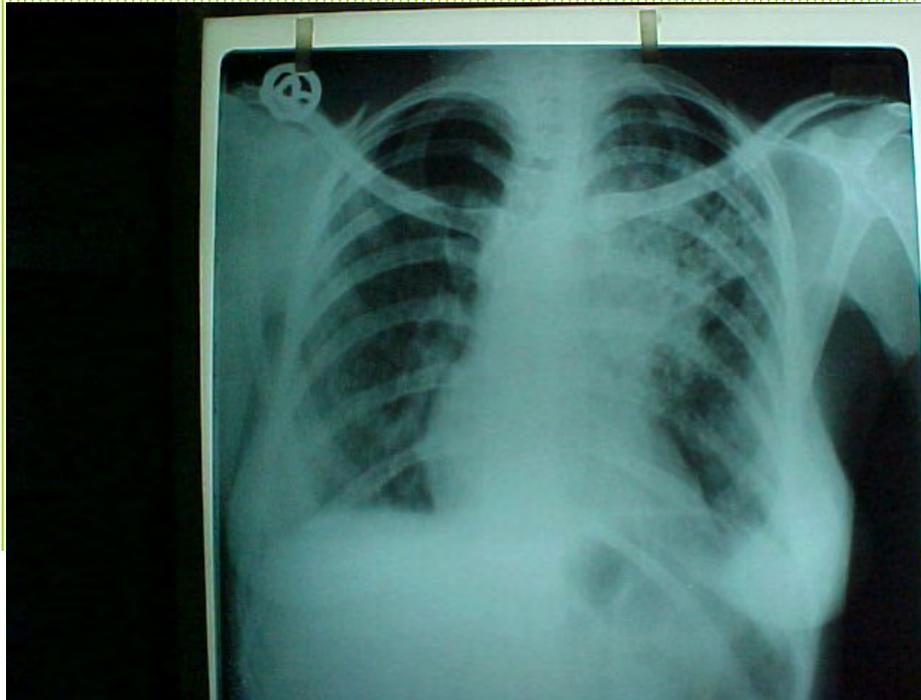
HIV and TB. Radiography



Tuberculosis and HIV in 2007. Diagnosis and Management.

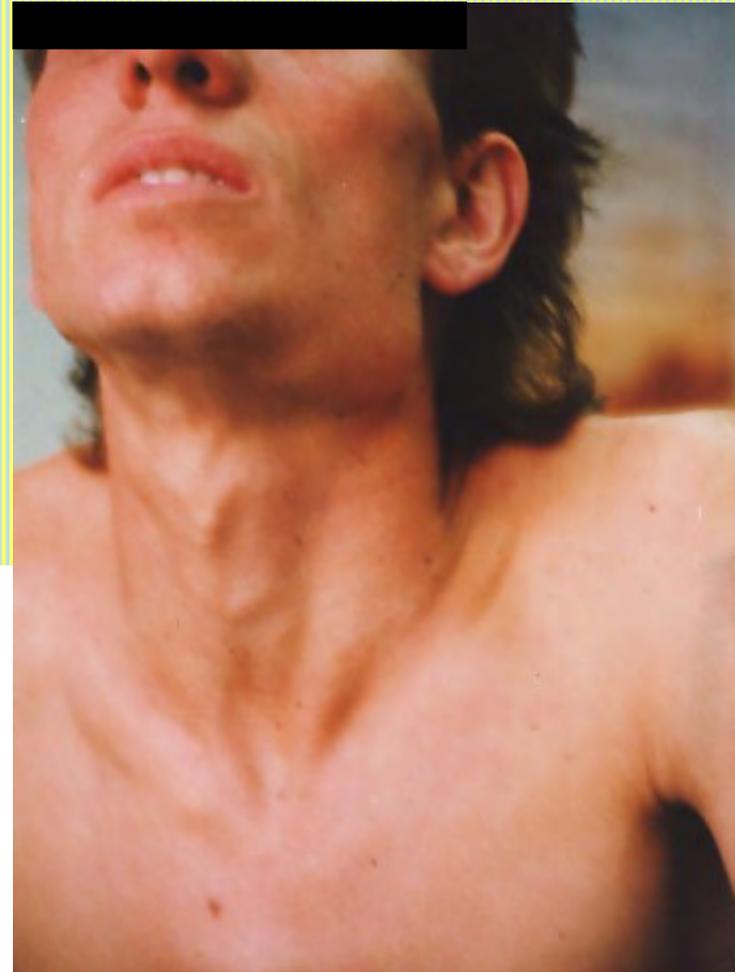
Dave Spencer Kimera Consultants 2007

HIV and TB. Radiography



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Dave Spencer Kimera Consultants 2007

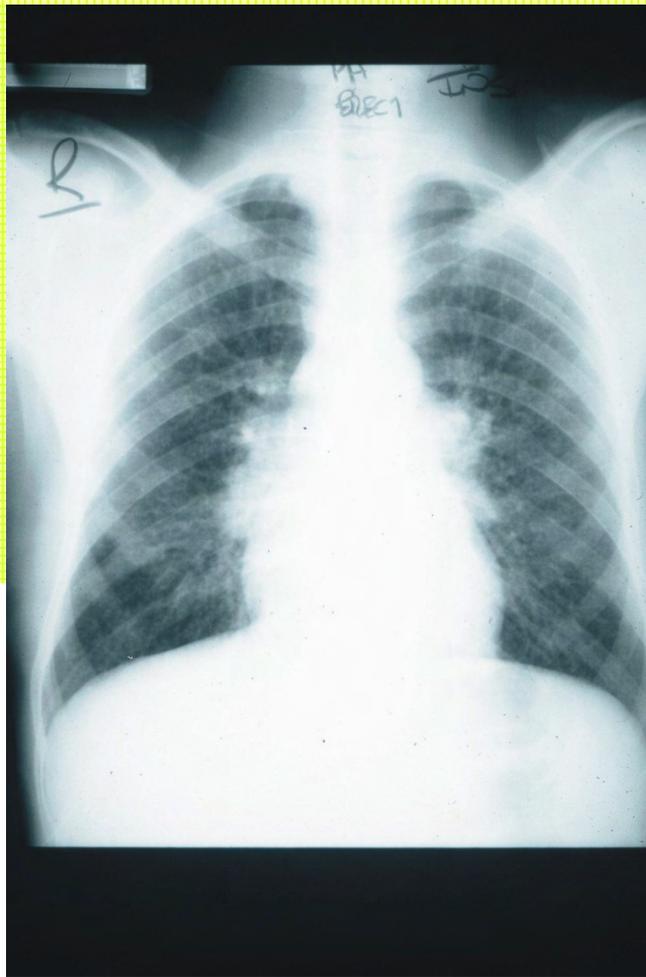
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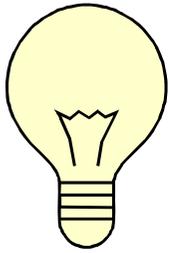
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HIV and TB. Radiography

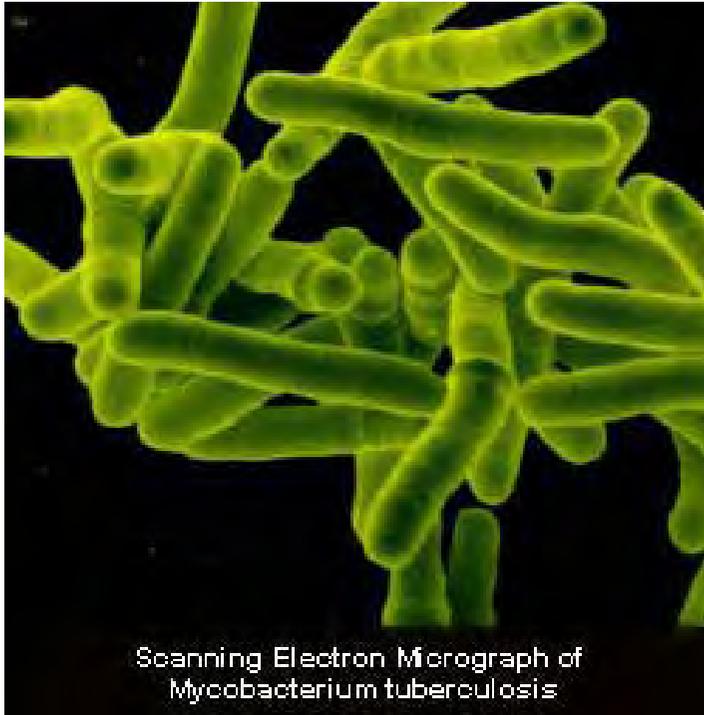


Treatment of TB in HIV+ patients

- as for any TB patient, DOT is highly recommended
- sputum conversion rates and cure rates are not significantly different between HIV+ and HIV-negative TB patients treated with rifampicin-based regimens
- HIV positive TB patients are more likely:
 - to develop side effects from TB treatment
 - and have 3 - 6 fold higher mortality

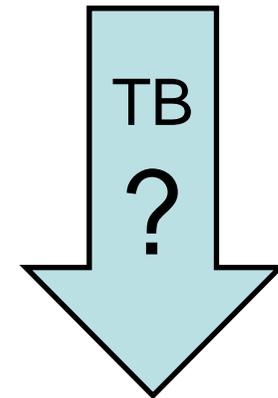


TUBERCULOSIS (TB)



Algorithm for the diagnosis of TB in ambulatory HIV infected patients

- WHO guidelines
www.who.int/tb/publications/who_tbm_tbr_2004_329/en/index.html
- all patients too ill to receive out-patient TB treatment need to be admitted
- referral is also indicated for patients who are not clinically improving or are deteriorating



Diagnosis of TB

- danger signs include:
 - respiratory rate > 30 / minute
 - fever > 39°C
 - pulse rate > 120/min
 - patient unable to walk unaided
 - AFB positive = at least one positive
 - AFB negative = two or more negative smears
- URGENT admission

AFB = acid fast (TB) bacilli

PCP = *Pneumocystis carinii* or *Pneumocystis jirovecii* pneumonia

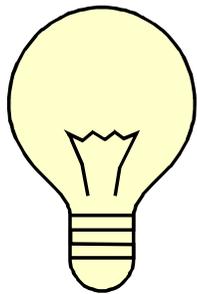
1. Find the source
2. TB is a family disease (ask about contacts OR family members with symptoms IF undiagnosed)
3. Test all for HIV
 - a compromised immune system dramatically ↑ *risk of disease progression* following TB infection
 - HIV is the commonest cause of disease progression (other factors include malnutrition, cigarette smoking, alcohol and/or substance abuse and diabetes)
 - risk of TB increases with decreasing CD4 count
 - TB is the commonest O.I.

4. Smear negative patient can infect

- smear negative NEVER excludes TB
- consider extra-pulmonary TB (EPTB)
- sputum test is not a useful test in small children (use nebs &/or gastric washings)
- use CXR and TB culture in adults with persistent symptoms or suspicious symptoms
- symptomatic children < 5 years (especially < 2 years) and who have a TB contact = TB

5. Do not use a poor chest X-ray or rely too much on a chest X-ray
6. May start treatment prior to having conclusive evidence but **MUST** send off for TB culture to confirm retrospectively
7. Don't rush to treat in a stable patient
8. Do not be bullied into treating by an irate G.P.
9. Follow-up is a useful diagnostic tool
10. Take a chest X-ray on completion of TB treatment in HIV + patients

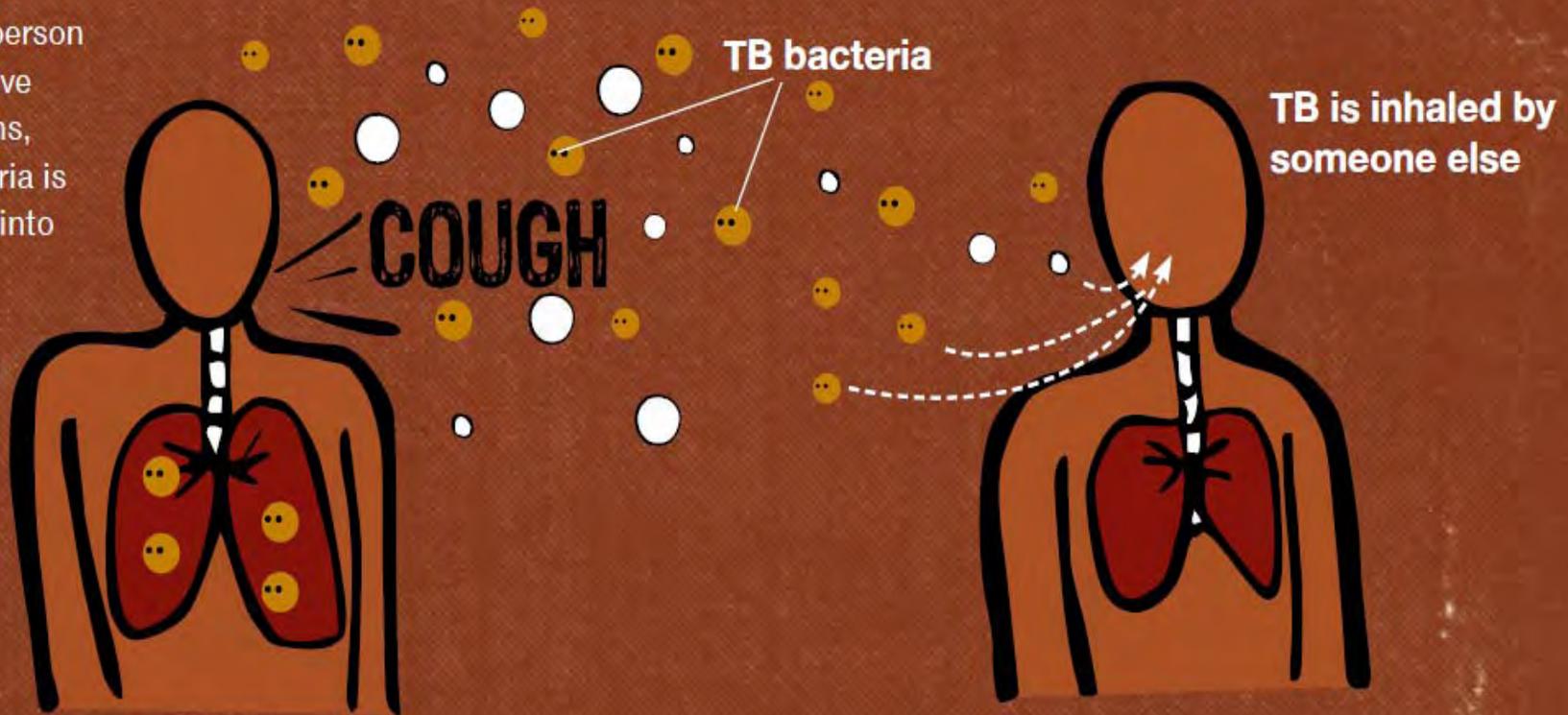
11. TB pleural effusion can be treated without further investigation in the right clinical setting (< 35 years age)



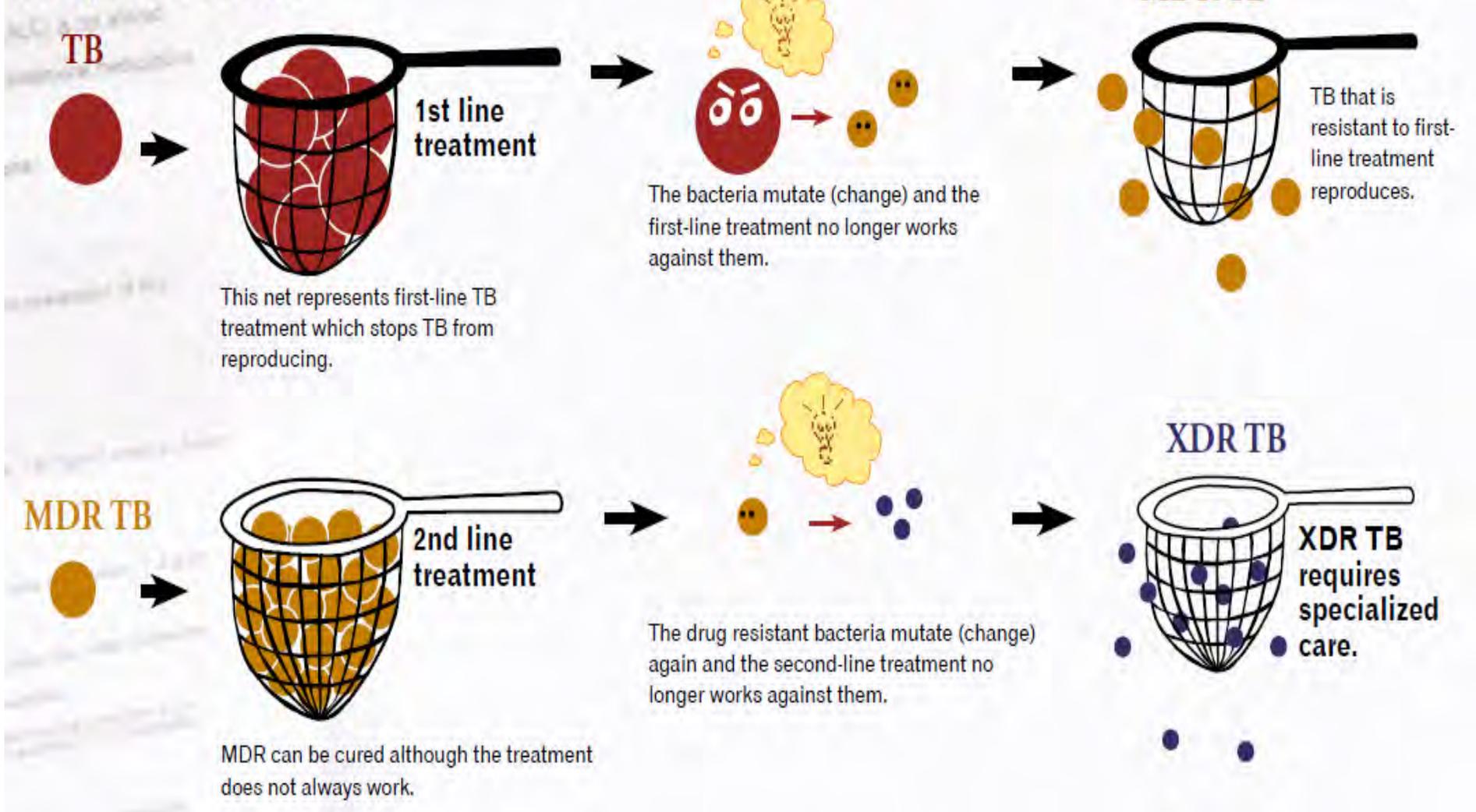


TB passes from one person to the other through the air.

When a person with active TB coughs, TB bacteria is released into the air



1. Acquired resistance



Tuberculosis – 8 points

1. TB is caused by *Mycobacterium tuberculosis* – inhaled as a small aerosol droplet

- only a small minority of people infected with TB ever develop TB (<10% lifetime risk in immune competent individuals → 3% overall)
- an HIV+ patient has 10% risk per annum for every year positive
- e.g. if positive for 5 years → 50% risk of developing TB

* **VENTILATION** * = Infection control



Open the windows in taxis.



Clinic windows should be open.

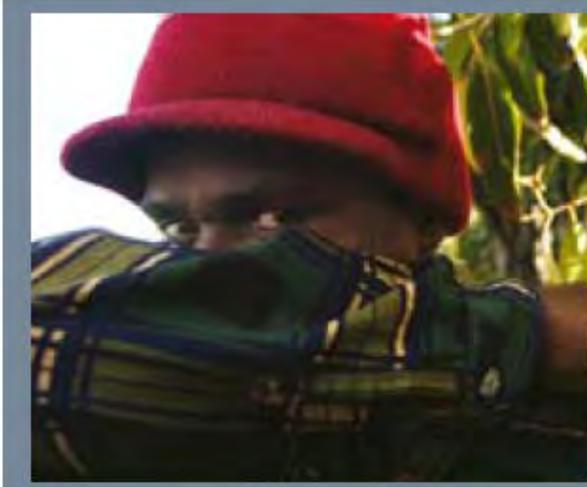


A health worker wearing an N-95 respirator.



The Ubuntu Clinic in Khayelitsha has fans and good air flow.

Cover your mouth when you cough:



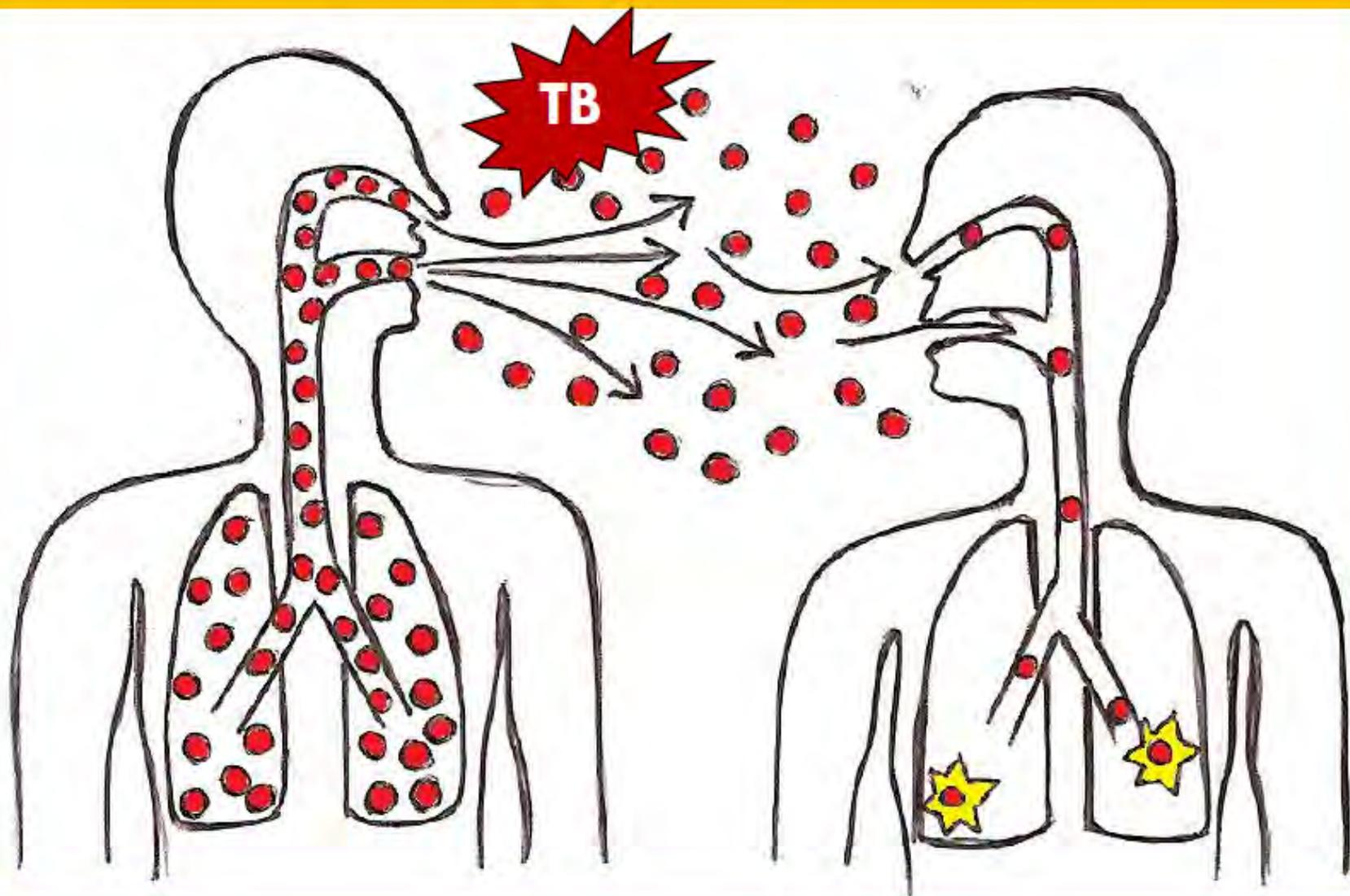
with your elbow;



with a tissue;



wear a mask.

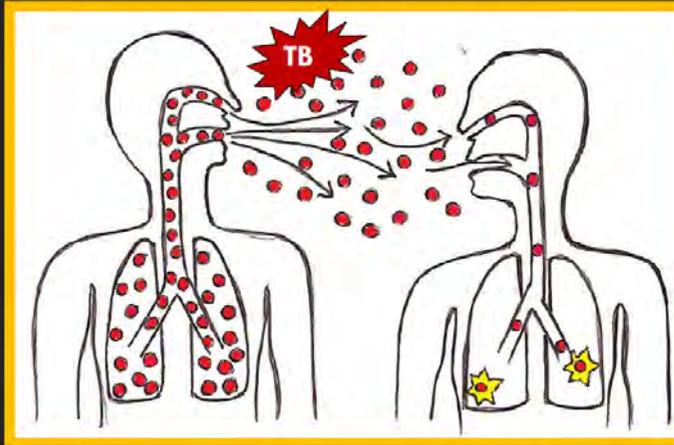




Collecting Sputum

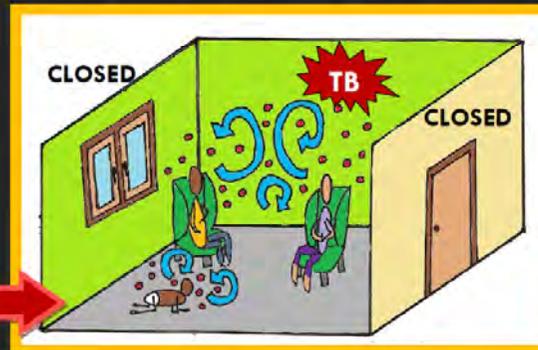


OPEN THE WINDOWS!



TB is spread in the air when someone with TB coughs, sneezes, spits or talks

When doors and windows are closed, the TB bacteria stay inside the house

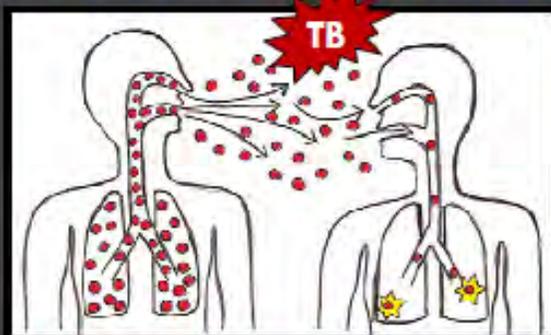


When doors and windows are open, clean air blows the TB bacteria outside



TB

INFECTION CONTROL



TB is caused by bacteria. These bacteria are spread in the air to other people when someone with TB coughs, sneezes, spits or talks.

YOU CAN PROTECT YOURSELF AND OTHERS FROM GETTING TB

COUGH HYGIENE

It is important to cover your mouth and nose when you cough. There are three ways to do this.



Use your inner arm



Use a tissue



Use a surgical mask

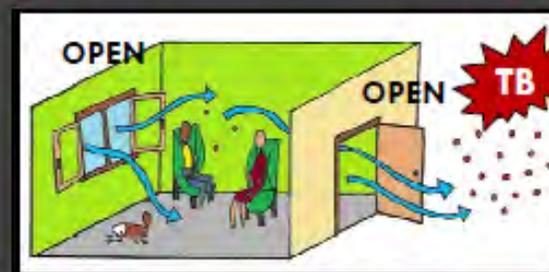


Do not spit in public

OPEN THE WINDOW



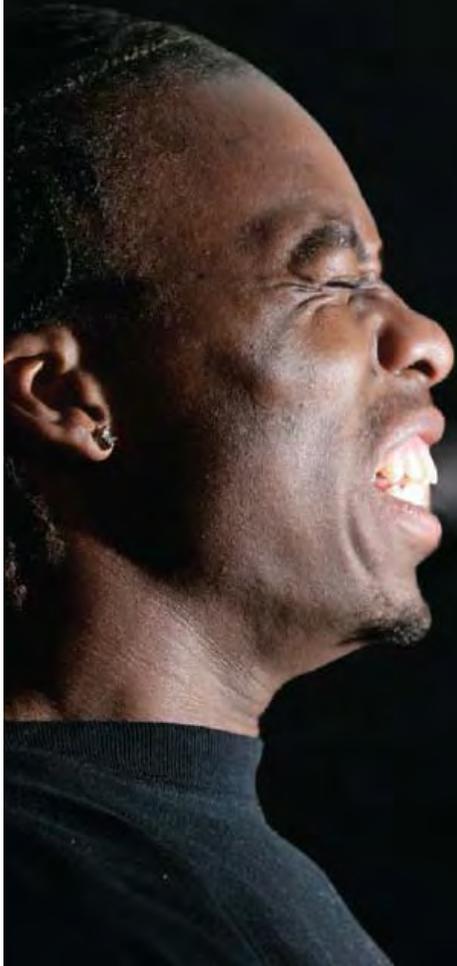
When doors and windows are closed, the TB bacteria stay inside the house



When doors and windows are open, clean air blows the TB bacteria outside

**FOR MORE INFORMATION:
MSF – Site B Khayelitsha (021) 364 5490**

Cough Hygiene



Cover your mouth and nose when you cough. There are three ways of doing this:

Use your upper arm



Use a tissue

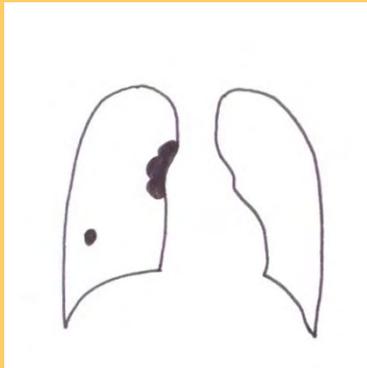


Use a surgical mask



If you have any more questions, please do not hesitate to contact the MSF Infection Control Practitioner:
Tel: 021 364 5490 (office) or 0784 908 102 (mobile) or email: msfb-khayelitsha-ic@msf.org.za

Tuberculosis. The Pre-HIV era



Majority infected
in childhood.
Some manifest
with **Primary TB**



Latent TB
(Majority)



10% reactivate
with PTB in
adulthood

Tuberculosis

2. Smear positive sputum cases are most infectious

- high priority in the community as they pose the highest transmission risk
- smear negative sputum are also infectious, but less so – probably posing 10 – 30% of the transmission risk compared to smear +
- the ‘cumulative sum’ of risk from smear negative may be higher when you have fewer smear positives among all the cases in the community
- children are less infectious (pauci-bacillary disease) but adolescent children > 10 years of age frequently develop smear+ sputum disease and are as infectious as adults

Tuberculosis

3. Provide preventative chemotherapy to high risk individuals (HIV+ and young children < 5 years if high risk of exposure

- INH (Isoniazid) safe and effective but compliance and resistance (areas where (R) > 10%) concerns
- Neonatal BCG offers some protection against diss. TB in children < 3 years but poses risk of disseminated BCG disease if HIV+ → ultimate risk : benefit remains uncertain

* KZN gives INH and Rifampicin for 3 months

* BCG = *Bacillus Calmette Guerette*

Tuberculosis in Children

4. Childhood TB mainly involve the intra-thoracic lymph nodes and airways

- children < 3 years vulnerable to develop disseminated disease and TB meningitis (TBM)

Manifest as :

a) Intra-thoracic – manifestations include uncomplicated lymph node disease, complicated lymph node disease with airway involvement , pleural effusion, pericardial effusion, adult type disease and disseminated miliary disease

Tuberculosis

5. Adult TB mainly involves the upper lobes (apices) with cavities

- adult TB also represents a diverse spectrum of disease
- a) Intra-thoracic manifestation include adult-type with or without cavities. Less frequently lymph node disease, pleural effusion, pericardial effusion and disseminated (miliary disease)
- b) Extra-thoracic – great mimicker with “atypical disease “– any site (brain, joint, skin, spine)

TB medication and ARVs

1. HIV+ and CD4 > 200 = start TB treatment and repeat CD4 count in 6 months
2. HIV+ and CD4 50 – 200 = start TB treatment and then add ARV's after 2 months
3. HIV+ and CD4 < 50 = start TB treatment and start HAART after 2 – 4 weeks
(check patient tolerating TB treatment) - follow up weekly

TB medication and ARVs

4. Patient started on ARV's and then TB discovered (culture or positive sputum)

Do not stop ARV's. Start TB treatment and monitor patient CAREFULLY for drug interactions and side effects.

Tuberculosis Drugs

- *Rifafour* (Aventis) had 2 year tender, now changed to *Rimstar* (Sandoz)
- from September 2007 till August 2009:

- ***Rimstar*** 4-FDC (Sandoz) 28 tablets with 14 per blister pack or 100 lose per bottle, used for intensive phase 150 / 75 / 400 / 275 R36/month

R H PZA ETHAM

- ***Rimactizid*** 2 drugs (there is also a double strength for *heavier* patients)

- R 150 / H 75

- R 400 for 6 months adult

- -----
- ***Rimcure Paed*** 3-FDC (Sandoz) – cream soda flavour

- ***Rimactizid*** (Sandoz) – spearmint flavour

- R300 for 6 months child

R = rifampicin H = isoniazid

Dissolves easily in a
teaspoon (5ml) of water

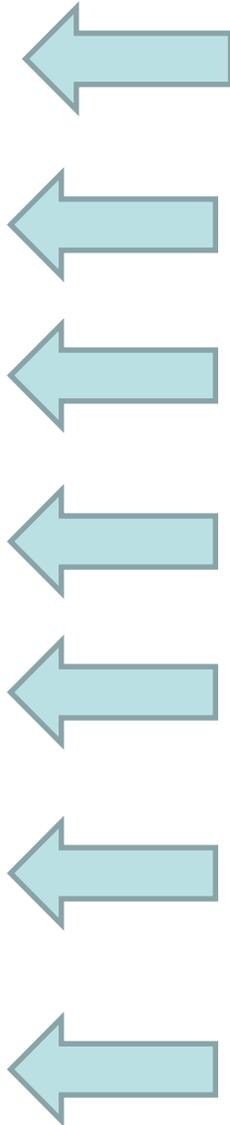
MPL

ANTIB-4 and
EBSAR (2 drugs)

TB Treatment

- Regimen 1:
 - Intensive Phase: 2 months
 - RIFAFOUR / RIMSTAR
 - Rifampicin + isoniazid + pyrazinamide + ethambutol combination tablet: 150;75;400;275mg

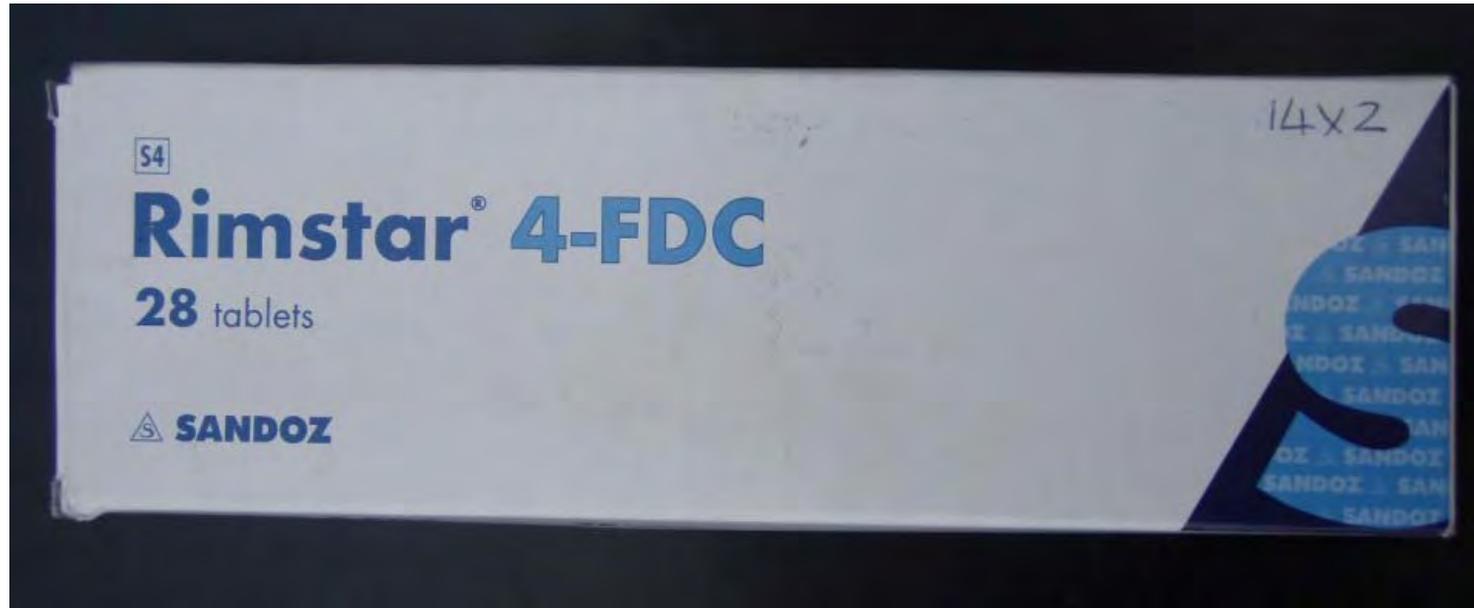
Weight [kg]	No of Tablets
30 - 37kg	2
38 - 54kg	3
55 - 70kg	4
> 71kg	5



SEVEN days per week
since ± September 2007,
officially
1 March 2008 in Western
Cape

Overall TB cure rate in South Africa
currently stands at 57 %

Fixed Drug Combination – 4 drugs



R = rifampicin

H = isoniazid

P = pyrazinamide

E = ethambutol



TB Treatment

- Regimen 1

- Continuation Phase: 4 months

- RIFINAH / RIMACTAZID

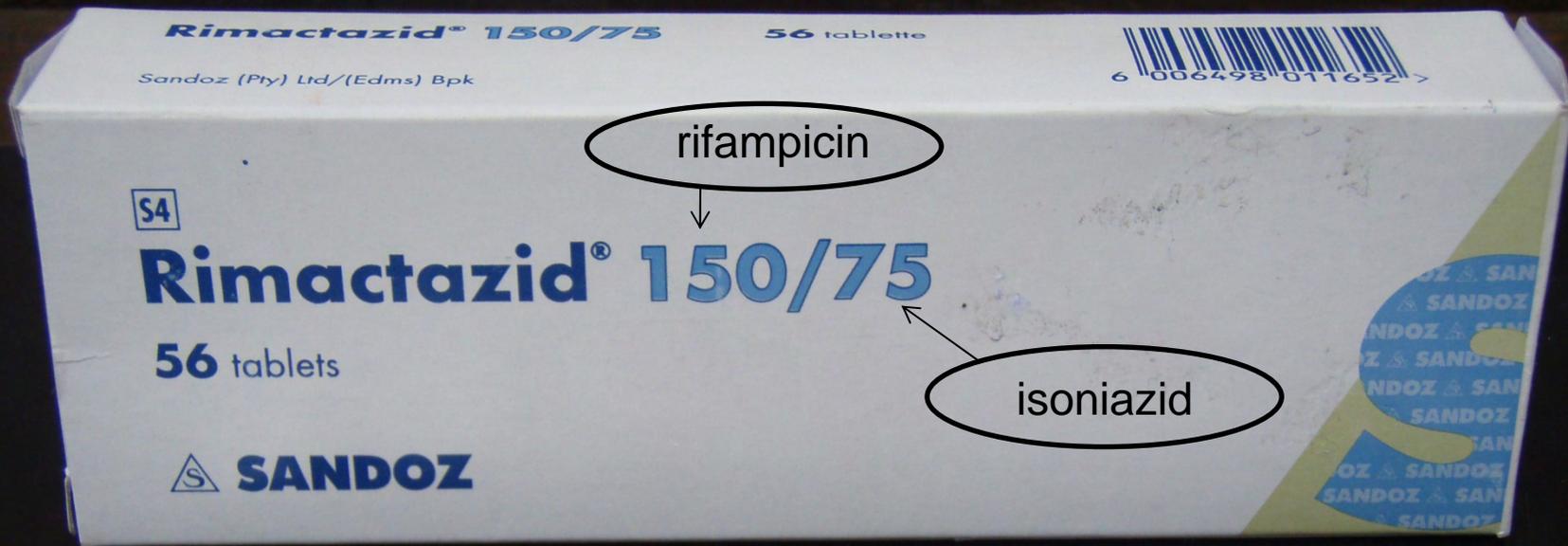
- Rifampicin + Isoniazid combination

Aventis

Rolab

Weight [kg]	No of Tablets
30 - 37kg	2 x 150/75mg
38 - 54kg	3 x 150/75mg
55 - 70kg	2 x 300/150mg
> 71kg	2 x 300/150mg





Adult TB – continuation or maintenance phase

TB Treatment

- Regimen 2
 - Intensive Phase = 3 months:
 - Regimen 1 + Streptomycin 40 injections daily Monday to Friday
 - 7 days per week
 - Month 3: Streptomycin stopped

Weight [kg]	Streptomycin
30 - 37kg	500mg
38 - 54kg	750mg
55 - 70kg	1000mg
> 71kg	1000mg

- NOT to be given:
 - during pregnancy
 - > 65 years of age
 - children [only under specialist advice]

TB Treatment

- Regimen 2
 - Continuation Phase for 5 months = Total of 8 months

Weight	Rif / Ison 150/75mg	Ethambutol	Rif / Ison 300 / 150mg	Ethambutol
30 – 37 kg	2	2		
38 – 54 kg	3	2		
55 – 70 kg			2	3
> 71kg			2	3

Disseminated TB = 9 - 12 months

TB & ARV's – the challenges

- Complex drug-drug interactions
- Increased pill burden
- Shared toxicity
- Paradoxical deterioration of TB due to immune reconstitution
- Most common shared side-effects:
 - Peripheral neuropathies
 - Nausea
 - Rash
 - Hepatitis

NON-HODGKIN'S LYMPHOMA

Clinical picture

- **constitutional symptoms** weight loss, fever, night sweats
- **mass lesions or lymphadenopathy**
- **visceral involvement**
- **rule out OI's as cause of these symptoms**
- **appropriate special investigations** Bone marrow biopsy and/or CT/MRI scan of the brain, chest, abdomen and pelvis
- **Fine Needle Aspirate (F.N.A.) cytology** can support the diagnosis
- **Excision biopsy** recommended to make a definite diagnosis

INVASIVE CERVICAL CARCINOMA

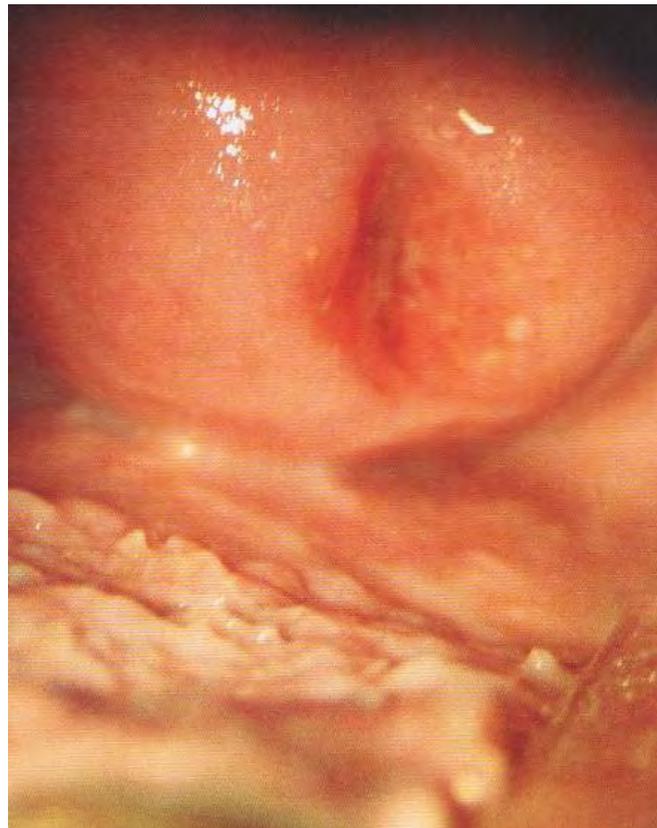
- CIN lesions are more common among HIV infected women and are associated with high or intermediate risk HPV types
- prevalence of HPV infection is higher in HIV infection with most in the severely compromised group – CD4<200



Am J Obstet Gynecol 2001 Mar;184(4):584-590

Cervical cancer (Ca Cx)

- in 1993, CDC included it as an AIDS defining illness
- presents earlier [15 years] than in usual HIV – women
- advanced clinical stage of disease
- there has been an ↑ in background prevalence of cervical cancers in SA



Member State	Children aged 6–59 months who received vitamin A supplementation* (%)	Children aged <5 years (%)				Contraceptive prevalence ^f (%)	Women who have had PAP smear (%)
		Sleeping under insecticide-treated nets	Received any antimalarial treatment for fever	With ARI symptoms taken to facility ^e	With diarrhoea receiving ORT ^e		
	2000–2006	2000–2006				2000–2006	2000–2006
Saint Lucia
Saint Vincent and the Grenadines
Samoa
San Marino
Sao Tome and Principe	...	41.7 ^s	24.7 ^s	29.3	...
Saudi Arabia
Senegal	75.3	7.1 ^w	26.8 ^w	47.2	52.5	11.8	11 ^q
Serbia	41.2	...
Seychelles
Sierra Leone	...	5.3 ^w	51.9 ^w	5.3 ^l	...
Singapore
Slovakia	59 ^q
Slovenia
Solomon Islands
Somalia	...	9.2 ^s	7.9 ^s
South Africa	60.3 ^l	17 ^q
Spain	60 ^q
Sri Lanka	70.0	2 ^q
Sudan	...	0.4 ^s	50.2 ^s	7.6	...
Suriname	...	2.7 ^s	42.1	...

Neoplasia of lower genital tract

- 5 – 6 x ↑ risk of squamous intraepithelial neoplasia compared to HIV- ♀
- HPV overwhelming aetiological factor in Ca Cx
- CD4 < 200 & high V/L result in ↑ likelihood of HPV infection, abn. PAP & squamous intraepithelial lesions (SIL)
- 20% vs. 3-5 % HIV- ♀ will develop SIL on screening
- atypical sq. cells of undetermined significance (ASCUS) also ↑

Screening of Ca Cx

- Ideally a PAP twice in first year after diagnosis → then **annually**
- colposcopy recommended for:
 - single PAP with cytological atypia (ASCUS, low grade SIL or high grade SIL, atypical glandular cells of undetermined significance AGUS)
 - severe inflammation that had not resolved after treatment (*Neisseria gonorrhoeae*, *Chlamydia*, *HSV*, *Trichomonas*)

Human Papilloma Virus (HPV)

- very strong relationship between and the development of cervical dysplasia and cancers
- HPV16 ass. with 50% of all invasive carcinomas HPV18 – 16% and HPV31 – 8%
- there is a need to identify HIGH risk groups eg those who are HIV+, need to follow more closely with regular cytology screening - ANNUAL PAPS

SCREENING INTERVAL OPTIONS FOR HIV NEGATIVE WOMEN

Number of
years
between
Pap smears

1

3

5

10

Total number
of smears
per lifetime

30

10

6

3

Reduction in
cumulative incidence
of cervical cancer (%)

94

91

84

64

= much higher yield
of abnormal PAPs

IRIS

Immune Reconstitution
Inflammatory Syndrome



Definition

- soon after starting ARV's the immune system begins to recover
- the body vigorously starts to fight infections eg TB, CMV
- these infections may have been present before, but because there was a very weak immune system, there were NO signs or symptoms



- once on ARV's, the newly recovering immune system's response to these infections can result in a LARGE inflammatory response with severe symptoms
- this is called IRIS = Immune Inflammatory Response Syndrome
- in SA, this often happens with TB (commonest O.I.)

Symptoms of IRIS

- soon after starting ARV's, the patient can develop symptoms depending on infection:
 - eg TB: fever, weight loss, coughing (and bronchospasm), lymphadenopathy, lung infiltrates on the chest X-ray (“worsening picture”)

Paradoxical worsening of TB

- Well documented.
- More common in HIV-infected patients.
- Typical in large lymph nodes or tuberculomas.
- Temporally related to initiation of ART, especially if commenced within intensive phase of TB treatment.

Mechanism ?

- Host immune response?
 - Increased antigen release – TB therapy
 - Immune reconstitution – ART/HAART
 - In patients who initiate HAART if $CD4^+ < 50$

Other common infections with IRIS

- Herpes Zoster (Shingles) – new attacks
- Herpes simplex – new attacks
- Cytomegalovirus (CMV) – worsening blindness
- Molluscum contagiosum – new inflammation
- PCP
- Cryptococcal meningitis – worsening of headaches
- TB tuberculomas - seizures

Tuberculosis IRIS - definition

If within **3** months of the introduction of HAART there are NEW or recurrent constitutional symptoms (recurring fever) plus NEW or expanding/recurring :

- a) lymph nodes (> 20 mm or > 50% in volume)
- b) TB cold abscess eg paraspinal
- c) intra-cranial tuberculomas ± clinical signs
- d) pulmonary infiltrates on CXR
- e) TB meningitis (exclude bacterial or fungal)
- f) serous effusions (peri-cardial / pleural / ascitic)
- g) hepatitis (on biopsy)
- i) infiltration of bone marrow
- j) TB skin lesion on biopsy



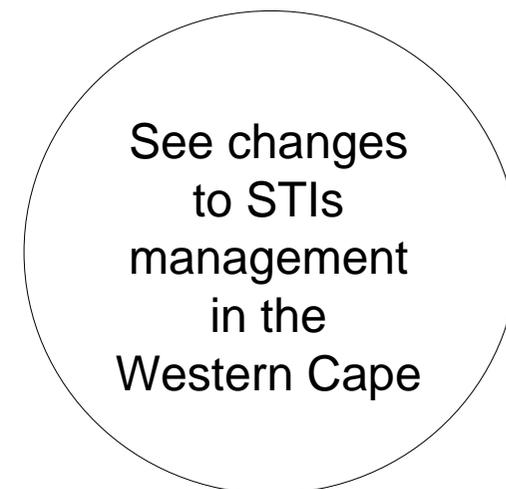
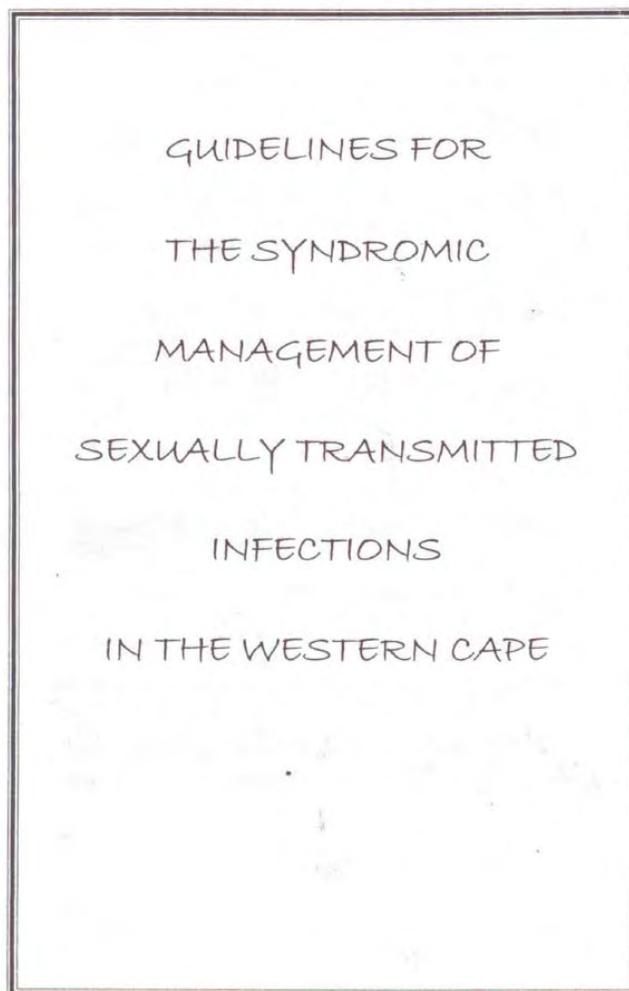
STD's

A SYNDROMIC APPROACH

- infection with *Trichomonas vaginalis* significantly increases a woman's risk of becoming infected*
- it leads to inflammation and results in cells in vagina and cervical mucose being vulnerable to HIV infection
- mucosal haemorrhage damages the natural defences

*Journal of Infectious Diseases, 2007

Treatment of STD's – Sexually Transmitted Diseases (IDC – Infectious Disease Clinic)



City of Cape Town

Code 02 - Vaginal discharge

Take history (including family planning) and examine:

- * ABDOMEN & VAGINA (speculum examination)
- * FP history (NB - Women on oral contraception should take precautions until two weeks following completion of the antibiotics has passed.)
- * URINE + PREGNANCY TEST and PAP SMEAR if indicated.

FOR NON-PREGNANT WOMEN:

IF AT RISK OF STI
(Especially young, sexually active women):

Treat for vaginitis and cervicitis:

Ciprofloxacin 500 mg p o stat
PLUS
Doxycycline 100 mg 12 hrly X
7 days
PLUS
Metronidazole 2 g stat

**IF THERE IS DEFINITELY
NO RISK OF STI ON
HISTORY**

(Especially peri - / post -
menopausal women):

Treat for vaginitis only:

Metronidazole 2 g stat

(consider Metronidazole
400 mg 12 hrly x 7 days if
no response to stat dose)

PLUS

TOPICAL THERAPY FOR CANDIDA IF SUSPECTED (itchy,
white, cheesy discharge) Clotrimazole 500 g
pessary stat OR Clotrimazole 2 tabs PV for 3 nights.

FOR PREGNANT WOMEN:

Metronidazole 2 g stat plus Topical candida therapy (above)

IF AT RISK OF STI:

Treat with: Ceftriaxone 125mg stat imi

PLUS

Erythromycin 500 mg 6 hrly x 7 days

If no response to treatment or a complication of pregnancy
is suspected then refer to MOU

FOR ALL SYNDROME 02 AT RISK OF STI:

take blood for RPR and ask patient to return in one week
Counsel; Compliance; Condom Promotion; Contact Tracing

Golden rules

- remember Co-trimoxazole and Fluconazole prophylaxis is required until CD4 is above 200 (decision is most safely made on a sustained elevation measured on two separate occasions)
- when testing HIV status:
 - 6 weeks to 18 months → PCR
 - birth to 18 months → If an ELISA is done and is positive, repeat at 18 months (maternal antibodies may cause false positives up to 18 months)
 - > 18 months → do ELISA
- remember to repeat 6 weeks after cessation of breast feeding if ELISA negative

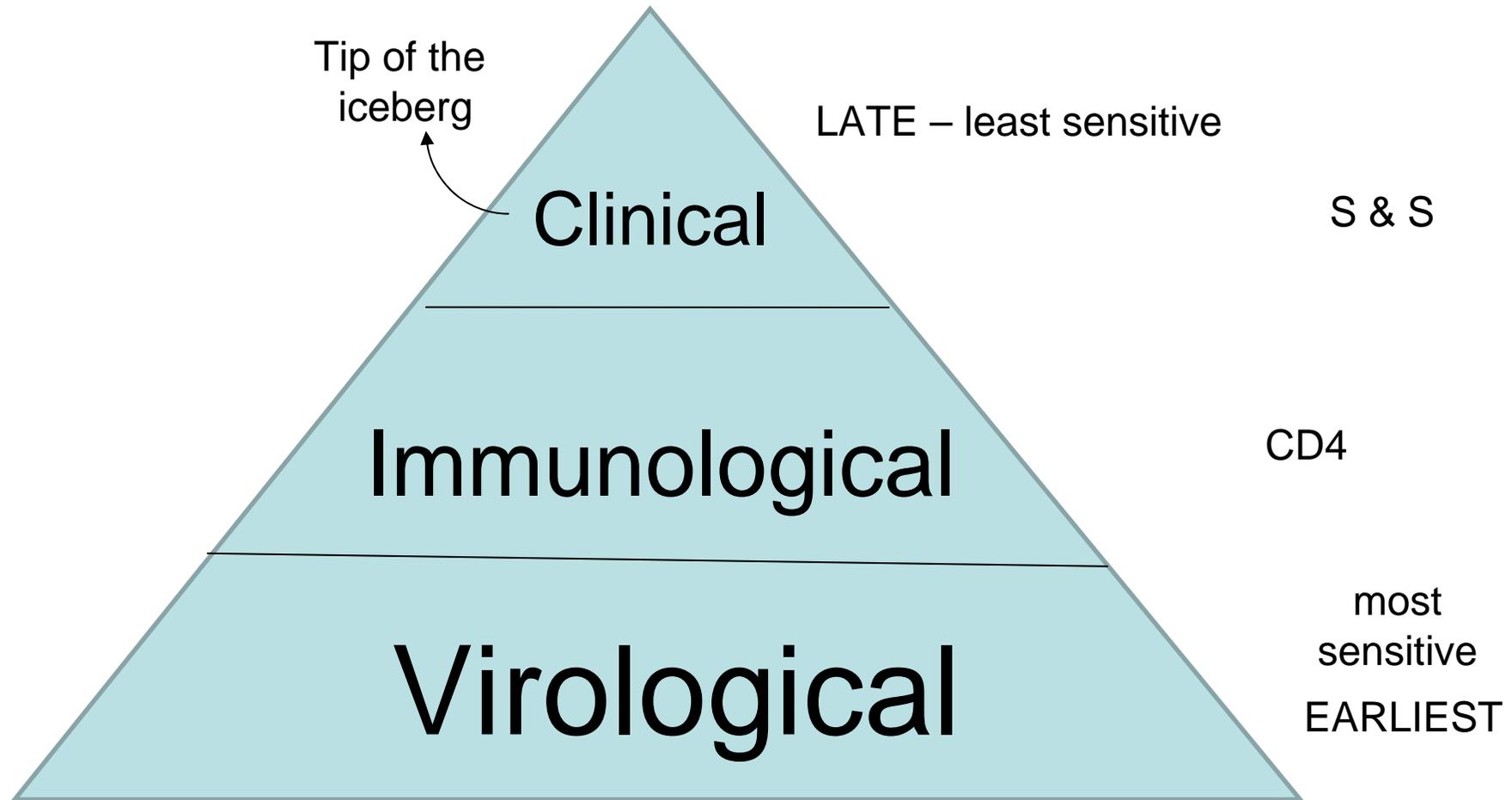
Golden rules

- All infants under 1 year of age should receive Cotrimoxazole [Bactrim] syrup from 6 weeks age till 1 year of age or until HIV status is established (high risk of PCP)
- If allergic: Dapsone – 1mg/kg daily

Approx. Age	Weight	Daily Dose
< 5kg	6 weeks to 2 months	2.5ml
5-9.9kg	2 up to 12 months	5ml
10-14.9kg	12 up to 24 months	7.5ml
15-21.9kg	24 up to 60 months	10ml or 1 tab
>22kg	> 60 months	15ml or 1½ tab

Module 2

Evaluation of HIV patient



Choosing patients for ARVs

Immunology

CD4 counts

where available as an
indicator of immune
status

Clinical

examination to
Stage the patient
based on WHO
classification

Criteria for initiating ARVs

Adults
Adolescents
Pregnant women

CD₄ count
less than
<200
cells/mm³
irrespective
of Stage

OR

WHO Stage 4
AIDS defining
illness,
irrespective of
CD₄ count

Patient expresses willingness and readiness to take ARVs with good adherence