

愛滋病的臨床表徵與伺機感染

Introduction of HIV and AIDS

王甯祺

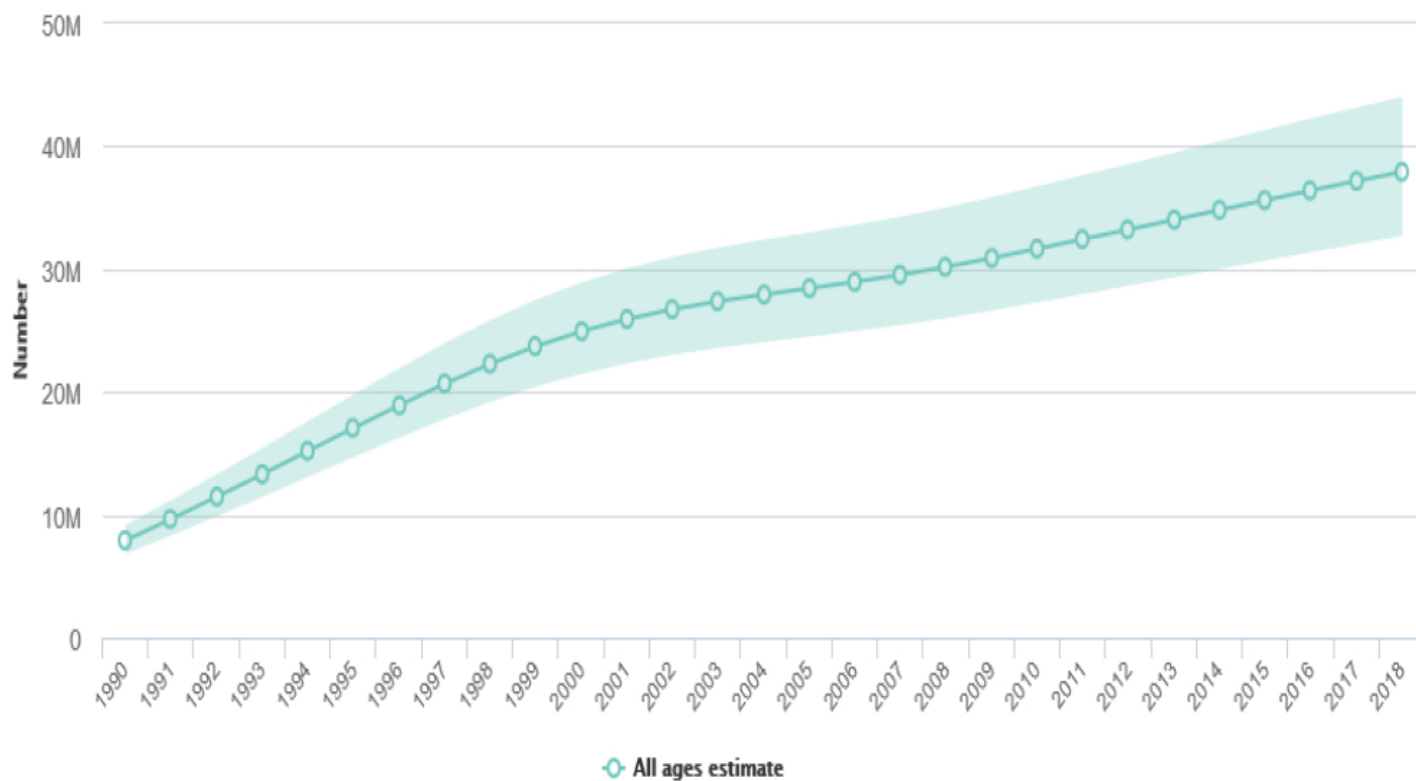
三軍總醫院 感染科

Outline

- HIV virology and epidemiology
- Clinical course of HIV infection
- Diagnosis and management of opportunistic infection and malignancies
- Diagnosis and management of co-infections (STDs and hepatitis)
- Combination antiretroviral therapy

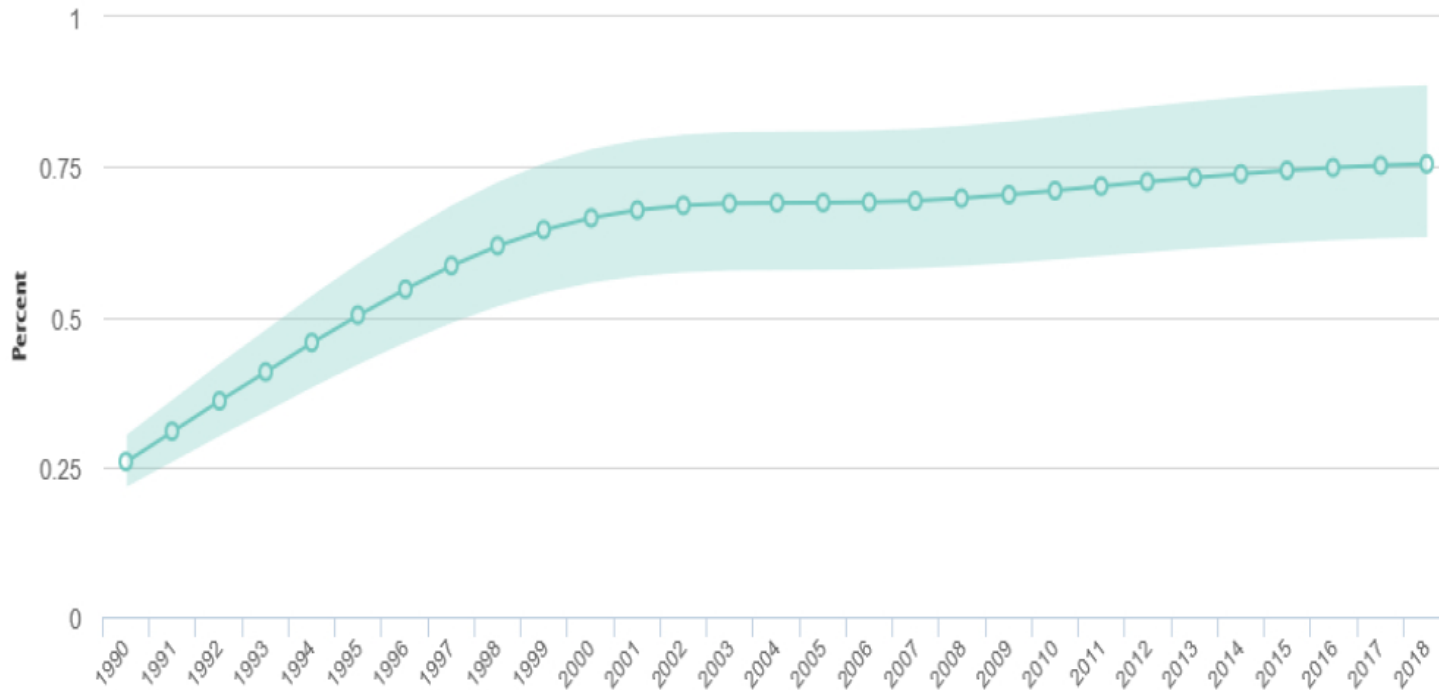
People living with HIV

People living with HIV (all ages)



People living with HIV

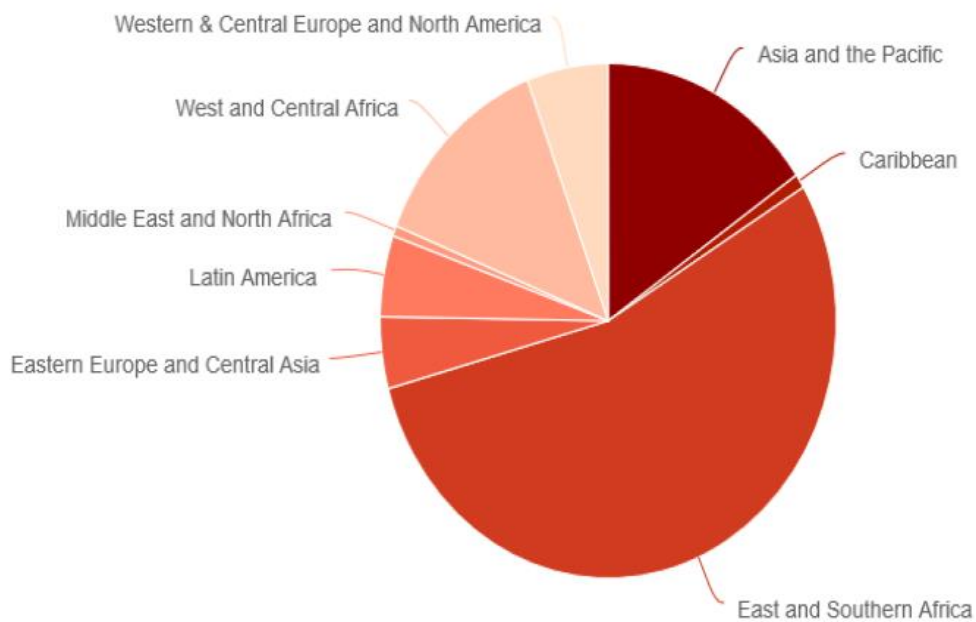
HIV Prevalence among adults (15-49)



Adults (15-49) estimate modelled

People living with HIV

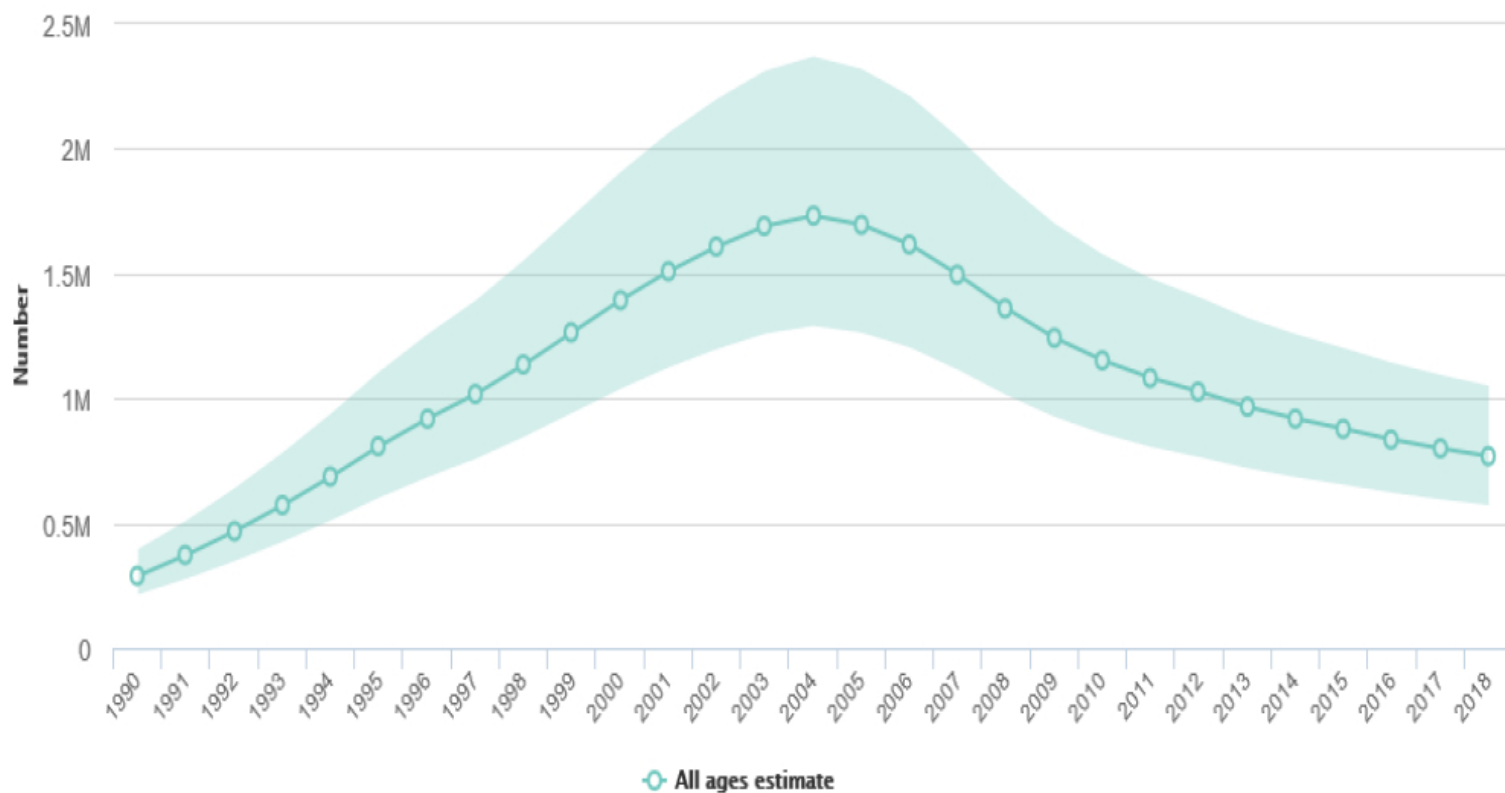
People living with HIV (all ages) - by region



HIV Prevalence among adults (15-49)

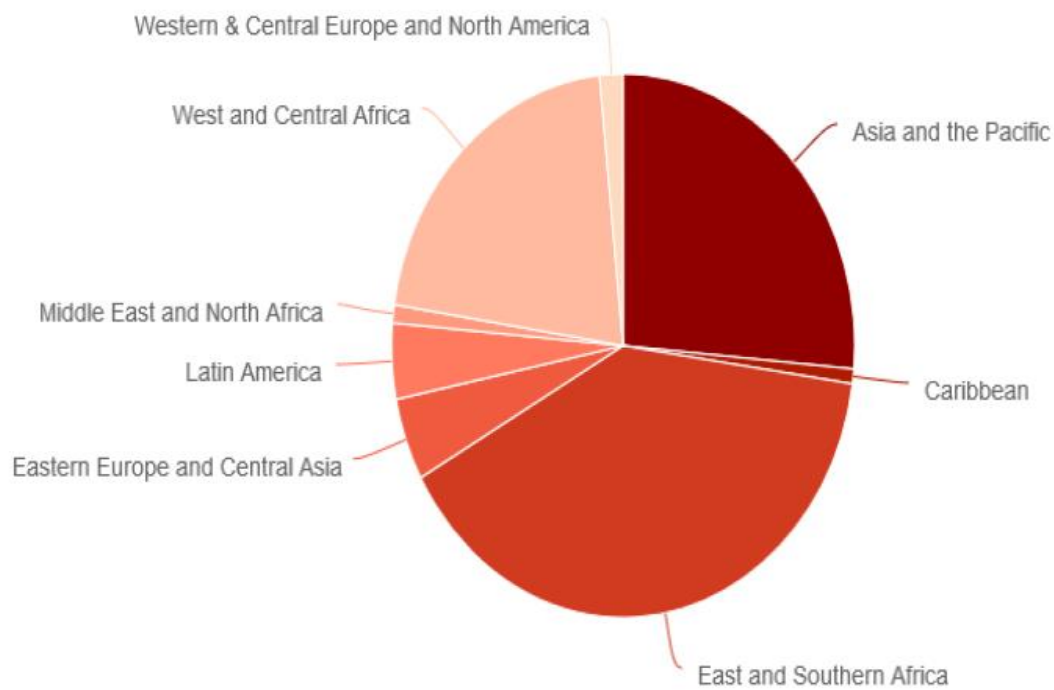
AIDS-related deaths

AIDS-related deaths (all ages)

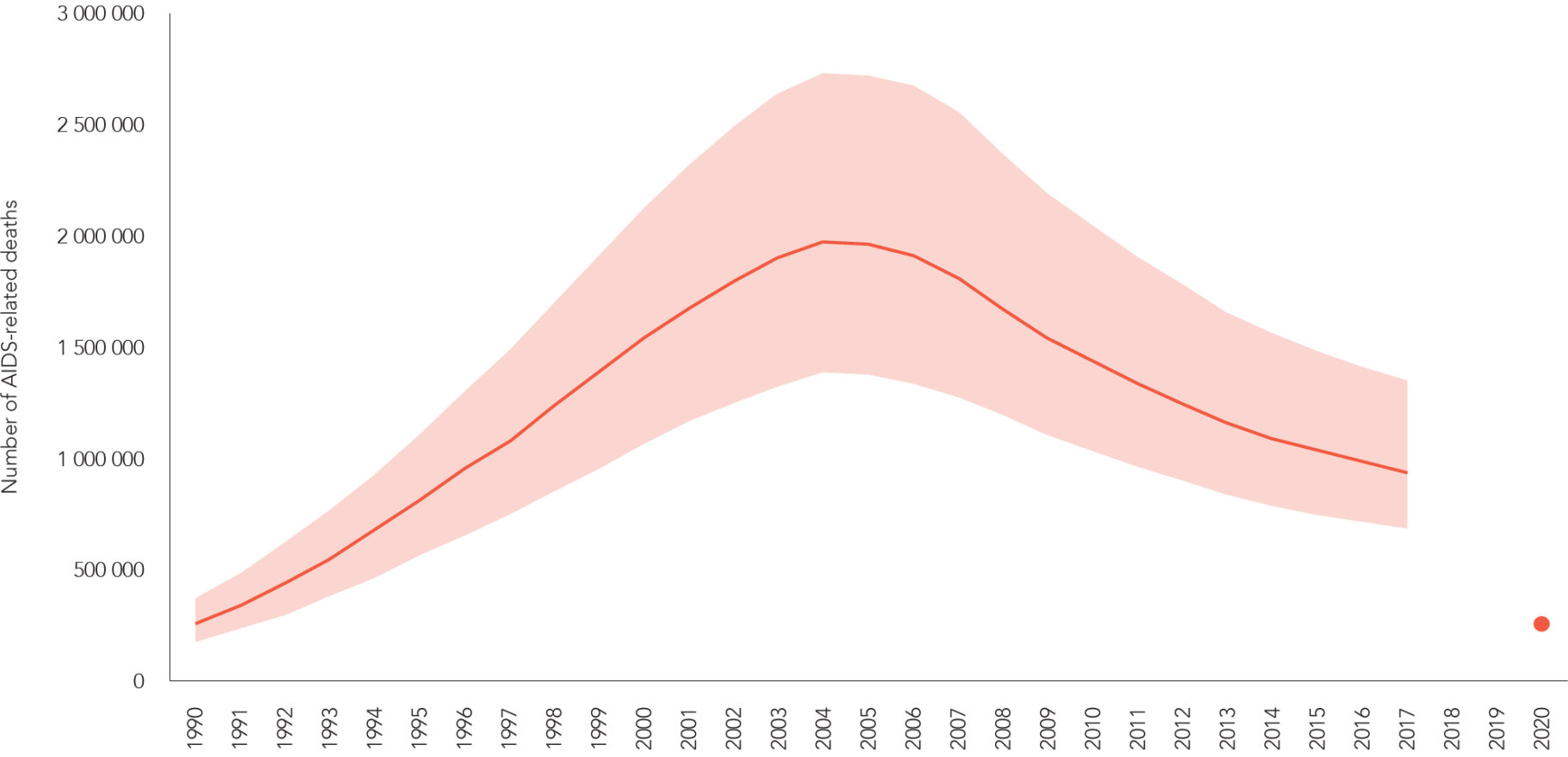


AIDS-related deaths

AIDS-related deaths (all ages) - by region



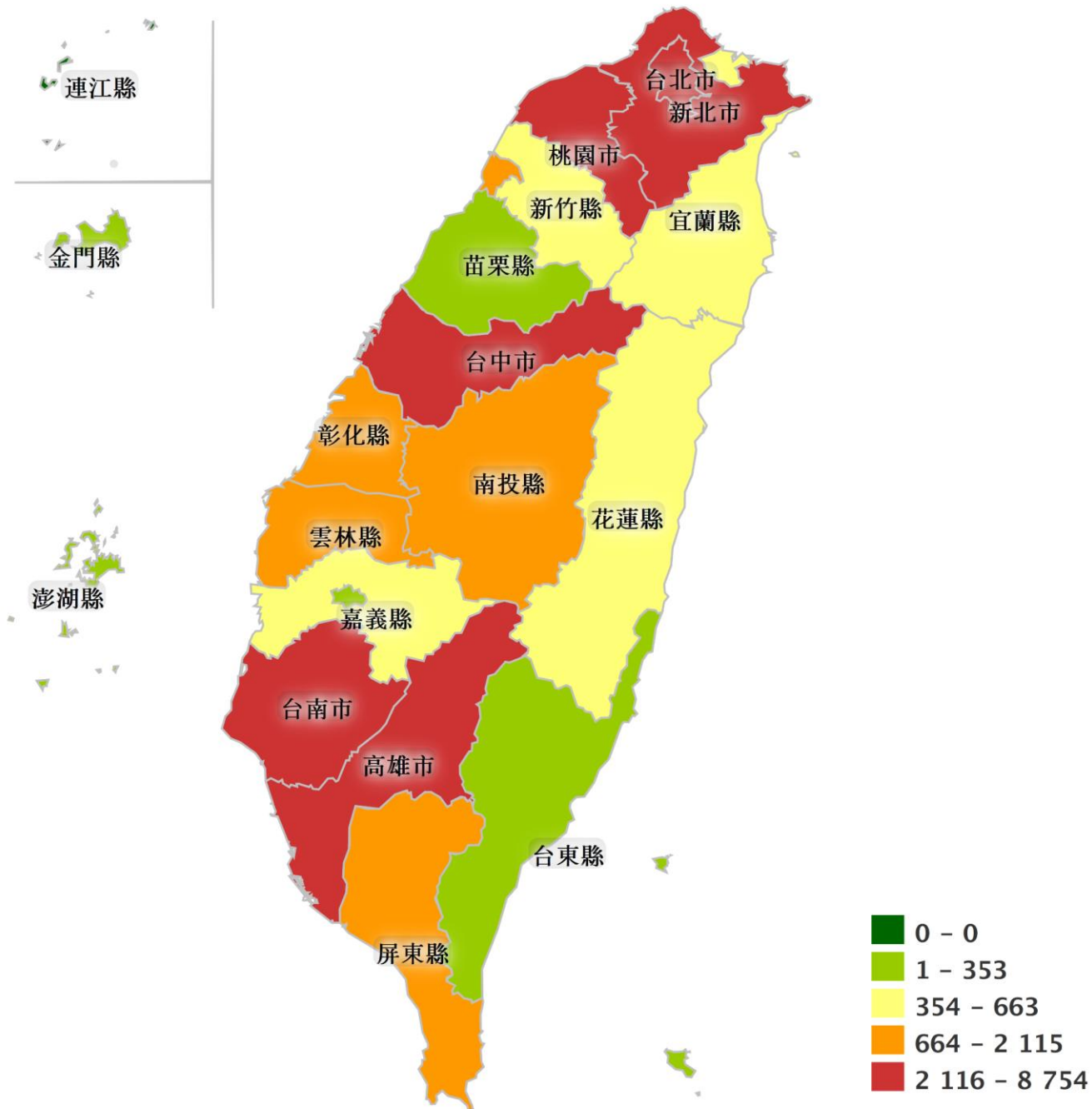
Number of AIDS-related deaths, global, 1990–2017 and 2020 target



— AIDS-related deaths ● Target

Source: UNAIDS 2018 estimates.

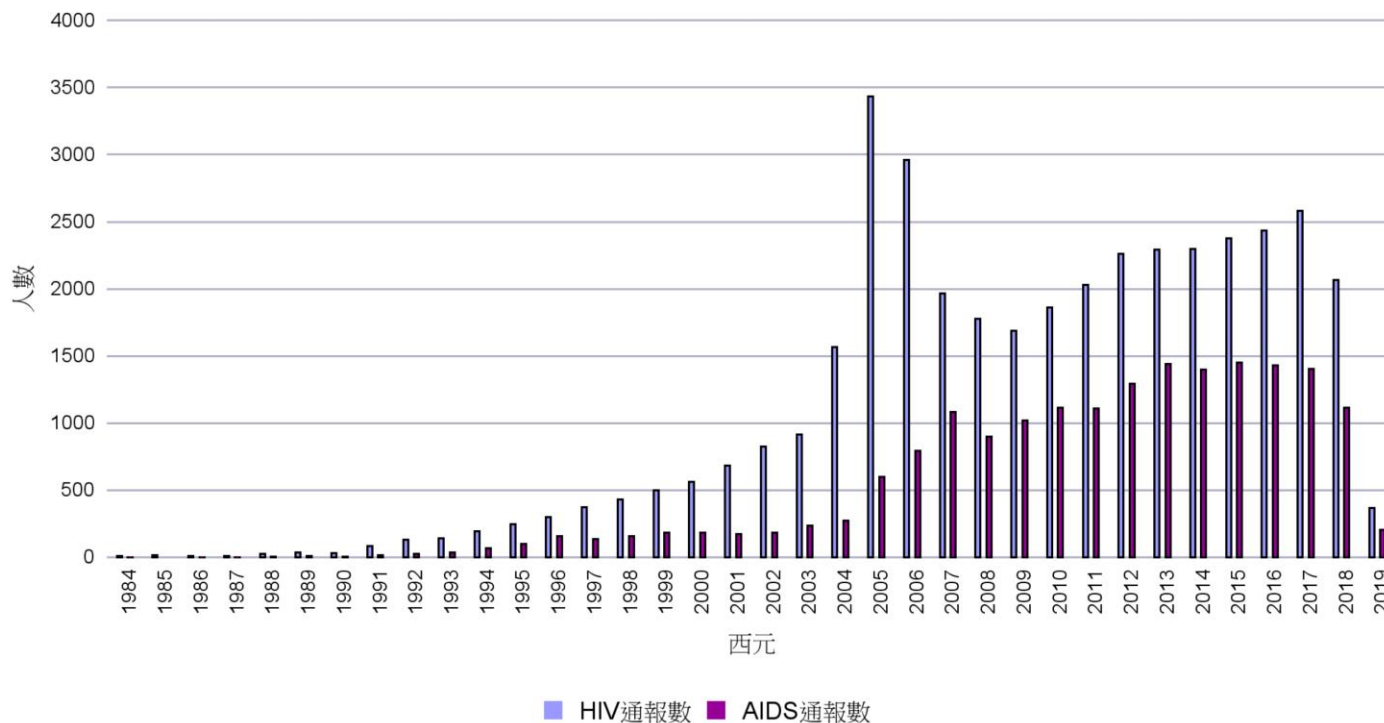
全國HIV感染(含母子垂直感染疑似個案)本國籍地理分佈(1984年-2019年)



本國籍感染人類免疫缺乏病毒發病者年齡別統計表

AIDS診斷年齡	發病者數				
	本月通報數(%)	本年個案數(%)	2018年個案數(%)	2017年個案數(%)	歷年累計個案數(%)
0-4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (0.02%)
5-14	0 (0%)	0 (0%)	0 (0%)	2 (0.14%)	10 (0.06%)
15-24	12 (12%)	21 (10.88%)	122 (11.18%)	197 (14.17%)	2,057 (11.36%)
25-34	38 (38%)	83 (43.01%)	427 (39.14%)	536 (38.56%)	7,090 (39.17%)
35-49	33 (33%)	63 (32.64%)	426 (39.05%)	496 (35.68%)	6,747 (37.27%)
50-64	14 (14%)	24 (12.44%)	102 (9.35%)	133 (9.57%)	1,801 (9.95%)
65以上	3 (3%)	2 (1.04%)	14 (1.28%)	26 (1.87%)	393 (2.17%)
總計	100 (100%)	193 (100%)	1,091 (100%)	1,390 (100%)	18,102 (100%)

本國籍感染人類免疫缺乏病毒者趨勢圖
1984年至2019年2月(依診斷日分析)



本表中

※HIV感染者：指當年通報之HIV新增個案數

※AIDS發病者：指當年通報之AIDS個案（包含前幾年已通報之HIV個案，當時尚未發病者）

診斷年份	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
HIV 通報數	9	14	9	12	21	37	31	78	123	132	160	221	267	341	387	471	526	652	765	860	1520	3377	2915	1929	1738	1641	1793	1968	2220	2243	2234	2326	2394	2512	1992	360
AIDS 通報數	0	0	1	1	2	8	5	13	23	35	64	97	156	136	153	181	180	167	181	235	269	587	787	1070	894	1009	1104	1100	1289	1431	1387	1443	1413	1390	1091	200

90-90-90

■ By 2020, 90% of all people living with HIV will know their HIV status.

■ By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy.

■ By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression.



90%

diagnosed



90%

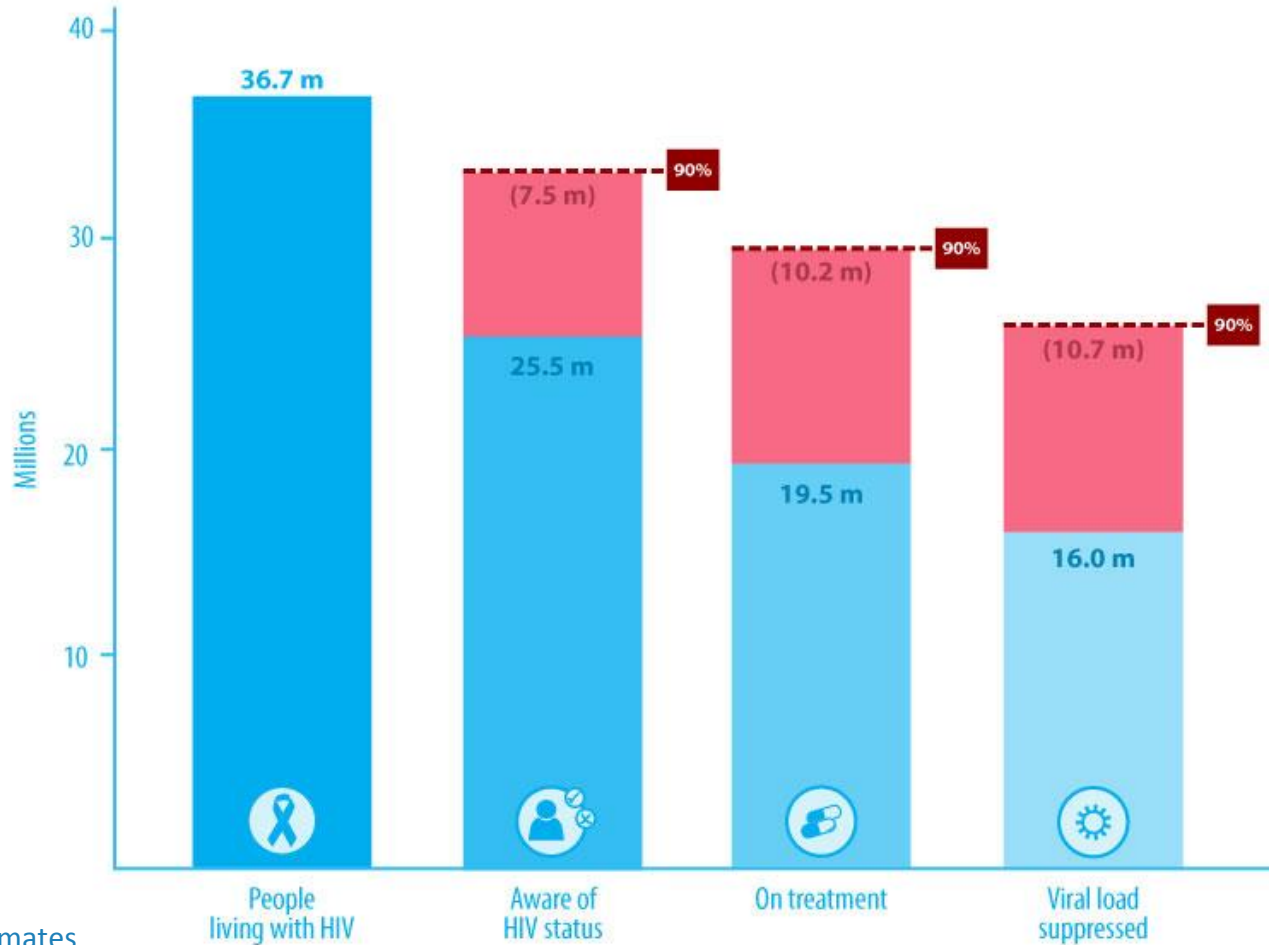
on treatment



90%

virally suppressed

HIV testing and care continuum (2016)



UNAIDS/WHO estimates

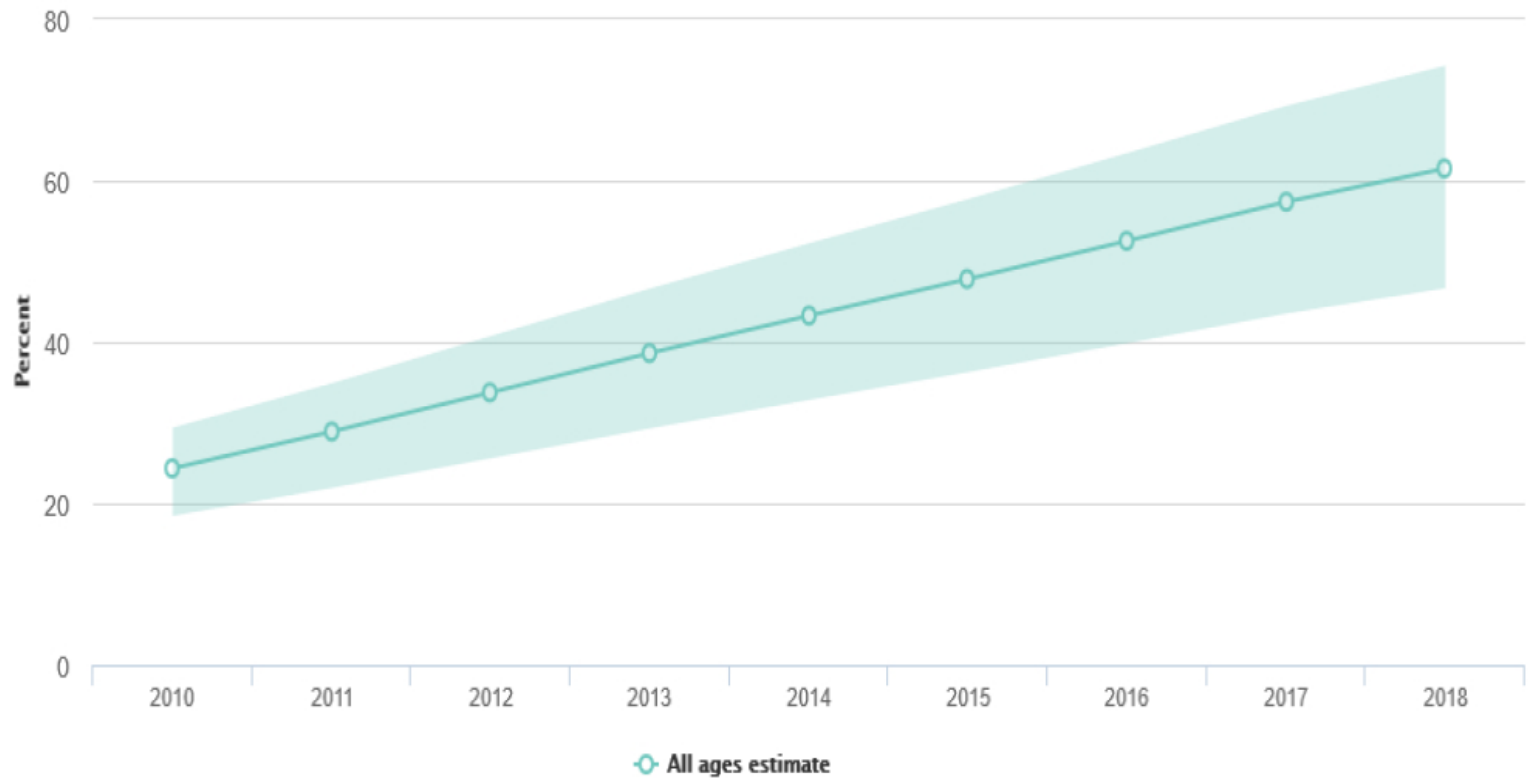
Treatment cascade

Progress towards 90-90-90 target



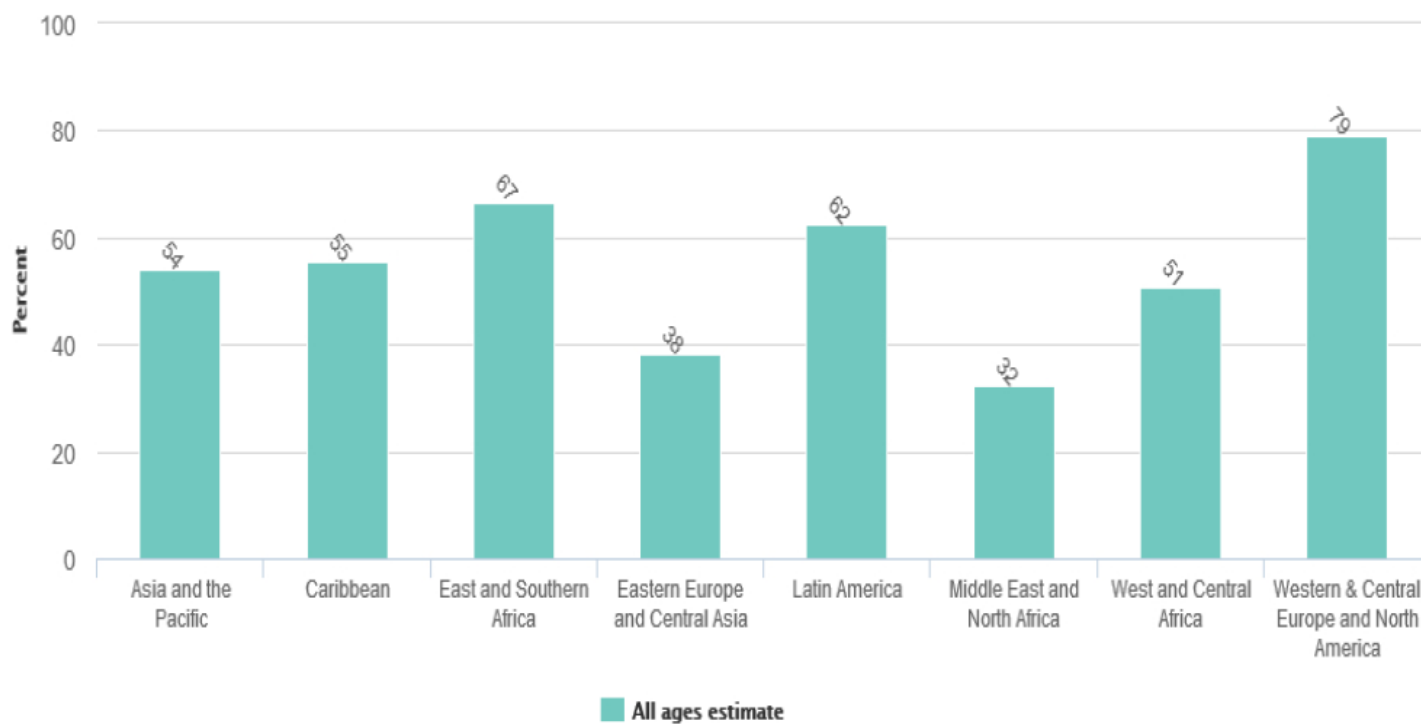
Treatment cascade

Coverage of people receiving ART (all ages)



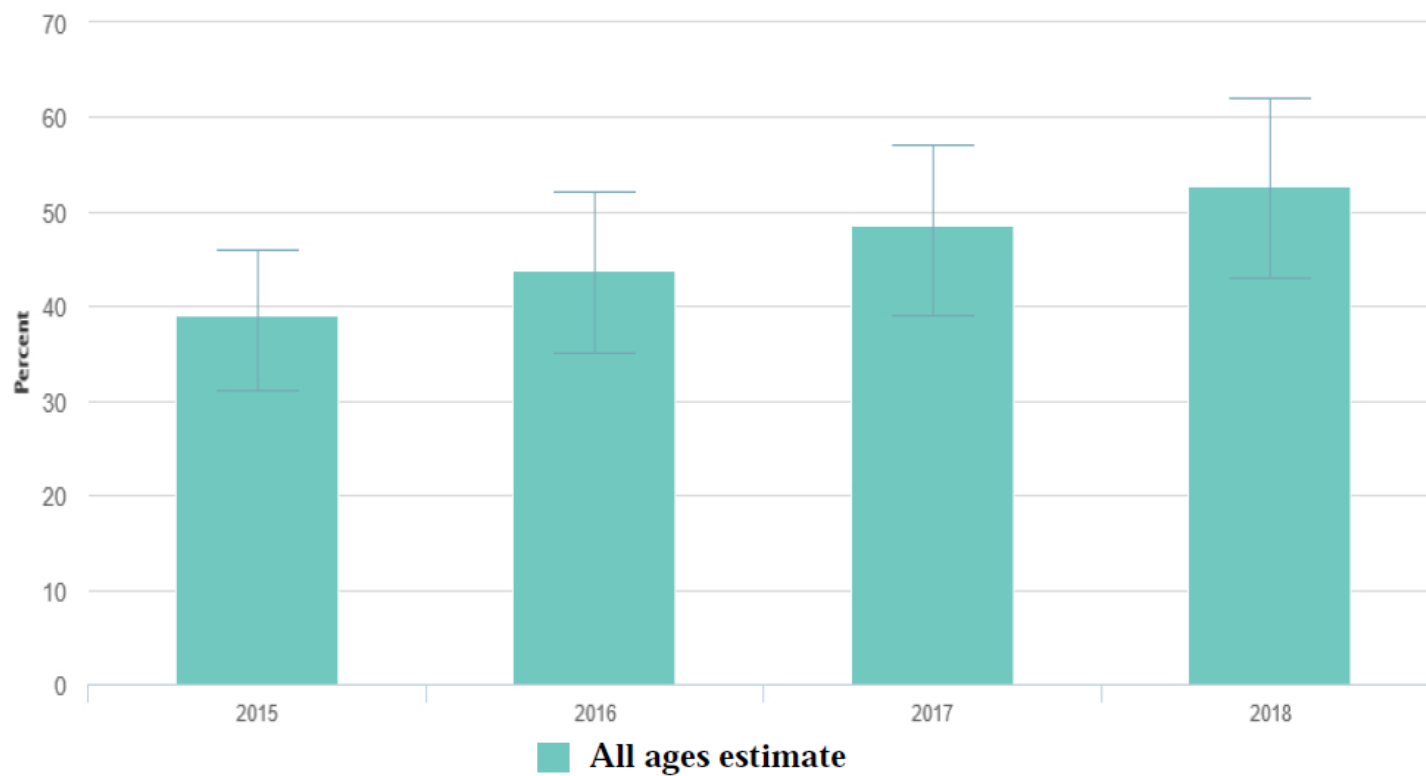
Treatment cascade

Coverage of people receiving ART (all ages) - by region



Treatment cascade

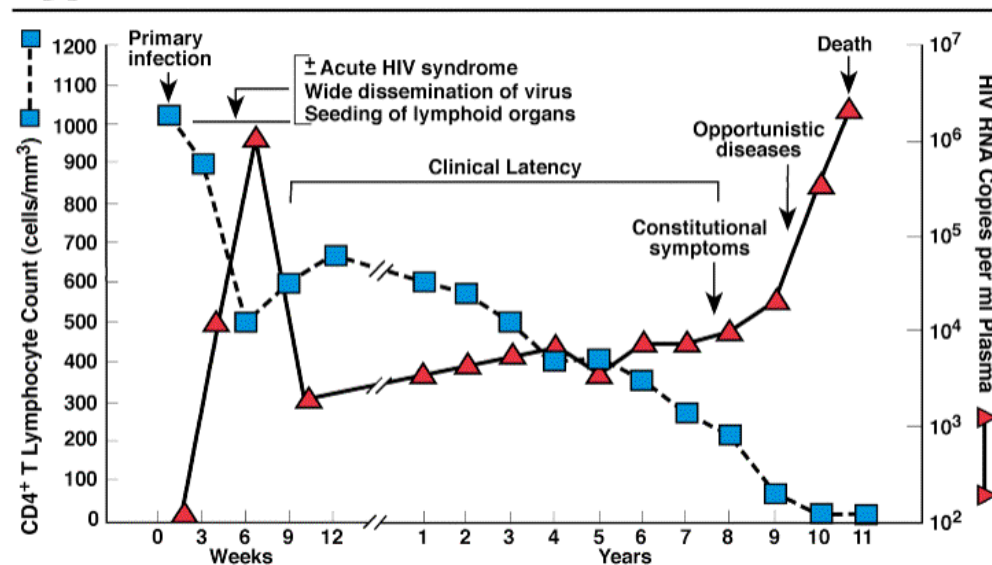
Viral load suppression



愛滋病毒感染後的病症分期

- 急性感染期
 - 不明熱, 皮疹, 全身性淋
- 無症狀期
 - 可能長達5-10年
- 有症狀期
 - 淋巴腺腫, 腹瀉, 盜汗, 癆
 - 口腔與食道念珠菌感染
 - 嚴重的伺機性感染與腫

Typical Course of HIV Infection



Modified From: Fauci, A.S., et al, *Ann. Intern. Med.*, 124:654, 1996

Stages of HIV Disease

Acute/Early Infection:

Following HIV transmission, approximately 50% of individuals will develop a febrile, flu-like illness with some or all of the following conditions:

- Swollen glands
- Oral ulcers
- Sore throat
- Diarrhea
- Rash
- Muscle aches
- Headache
- Nausea or vomiting

Stages of HIV Disease

Intermediate Stage

- T cell destruction by HIV begins to weaken the immune system over time (the immune system “keeps pace” by producing an equivalent amount of CD4 cells).
- If untreated, an 8-10 year period during which an HIV+ individual undergoes a gradual **decline** in immune function and **increase** in HIV viral load.
- *Often no symptoms exhibited during the intermediate disease stage*

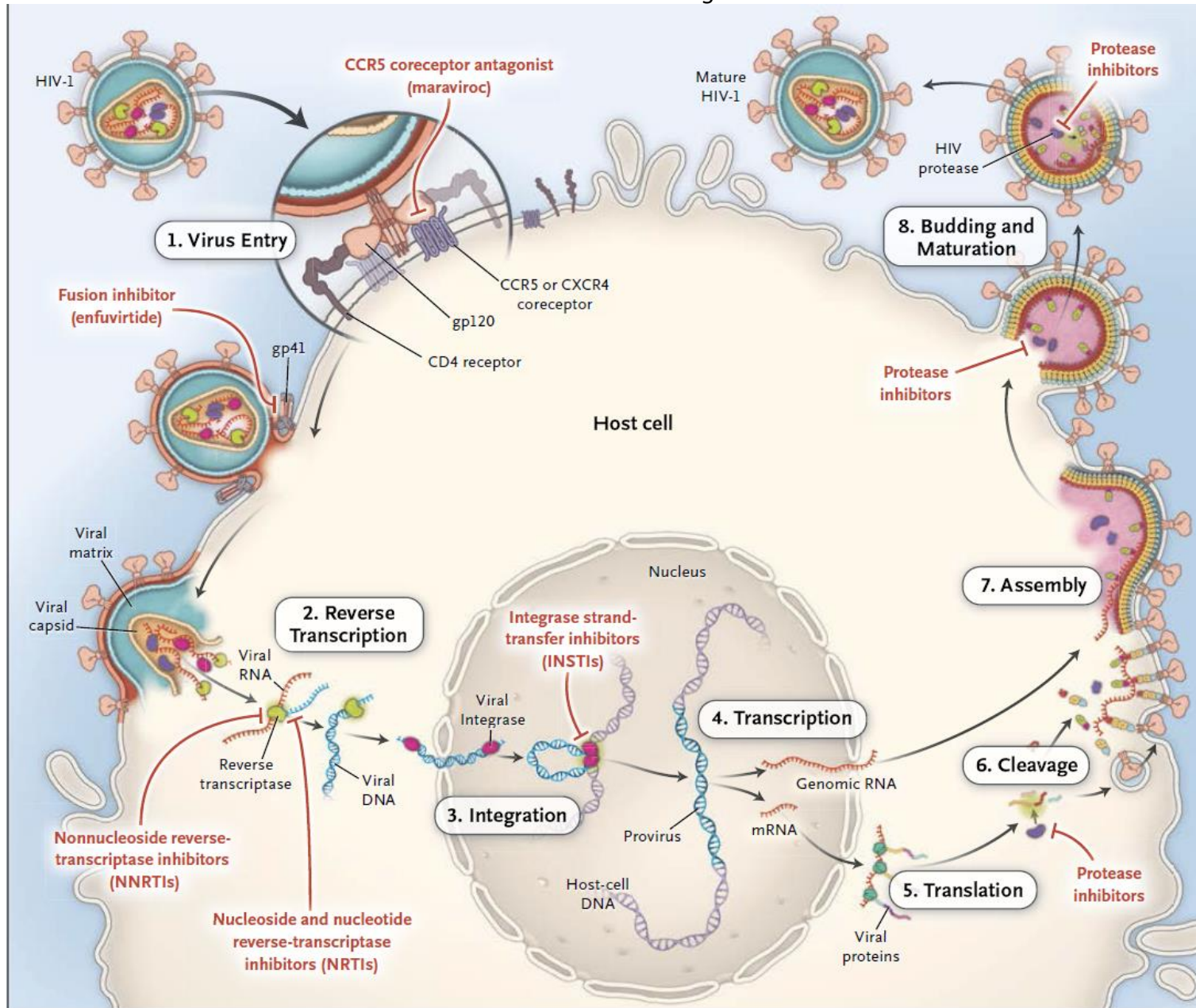
Stages of HIV Disease

Advanced Stage

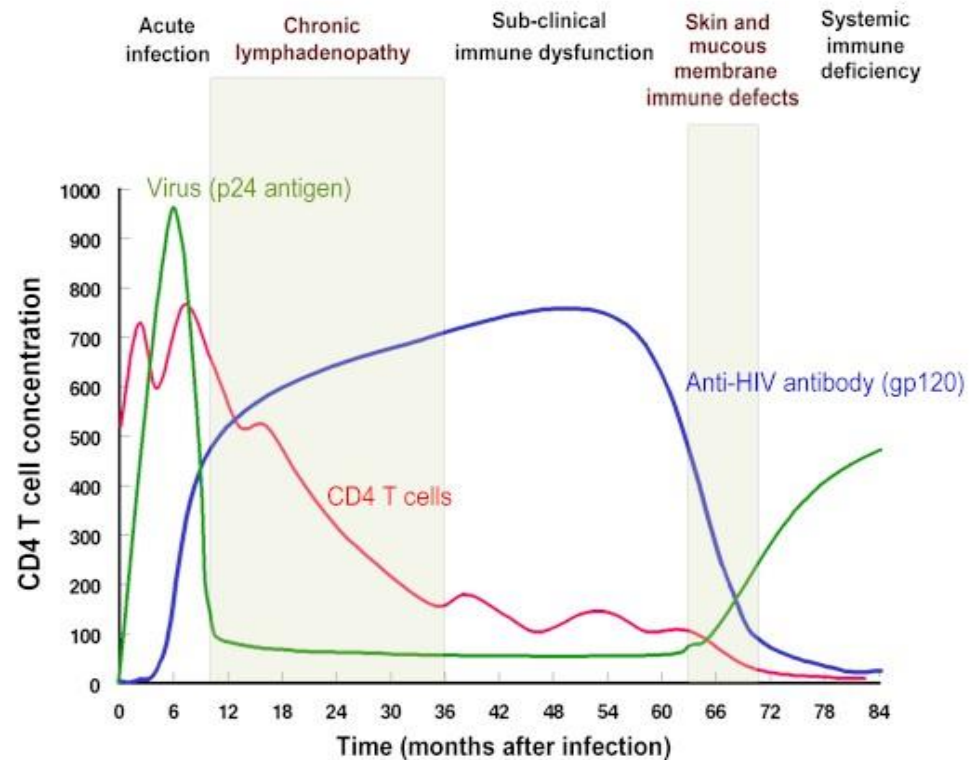
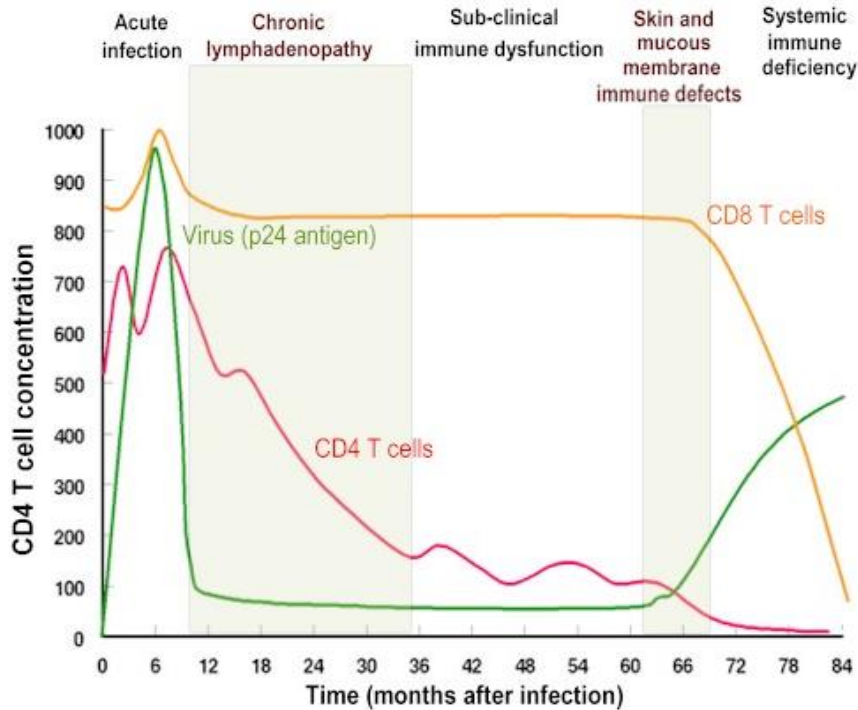
- Untreated, the rapid replication of HIV will deplete the immune system in most people, the patients will lose critical body defenses and can succumb to infections, AIDS and ultimately death.
- Symptomatic HIV can present in a variety of forms.
- Hallmarks of this stage of the disease include:
 - Opportunistic infections or malignancies
 - Rashes
 - Recurrent vaginal candidiasis
 - Herpes zoster
 - Thrush
 - Neuropathy
 - Diarrhea
 - Recurrent infections
 - Cancers
 - Anemia

HIV life cycle and antiretroviral drug targets

Gandhi M and Gandhi R. *N Engl J Med* 2014



Evolution of CD4/CD8 and plasma HIV RNA load of HIV infection

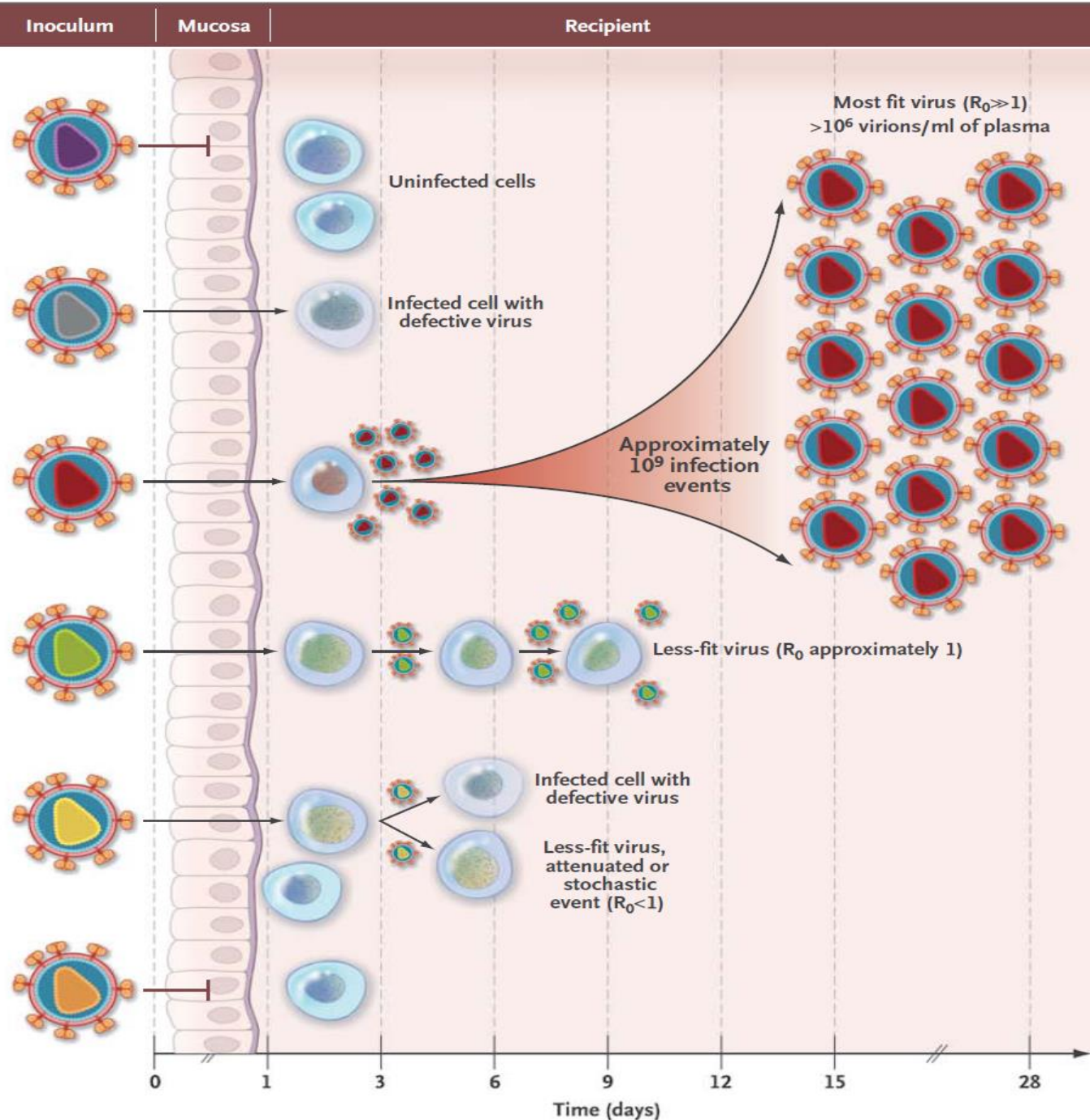


Mode of HIV Transmission

A genetically and phenotypically diverse quasi-species of virus is present in the semen, cervicovaginal secretions, or blood of person with chronic HIV Infection.

But most often, only a single viron or virtually infected cell is transmitted and leads to productive clinical infection.

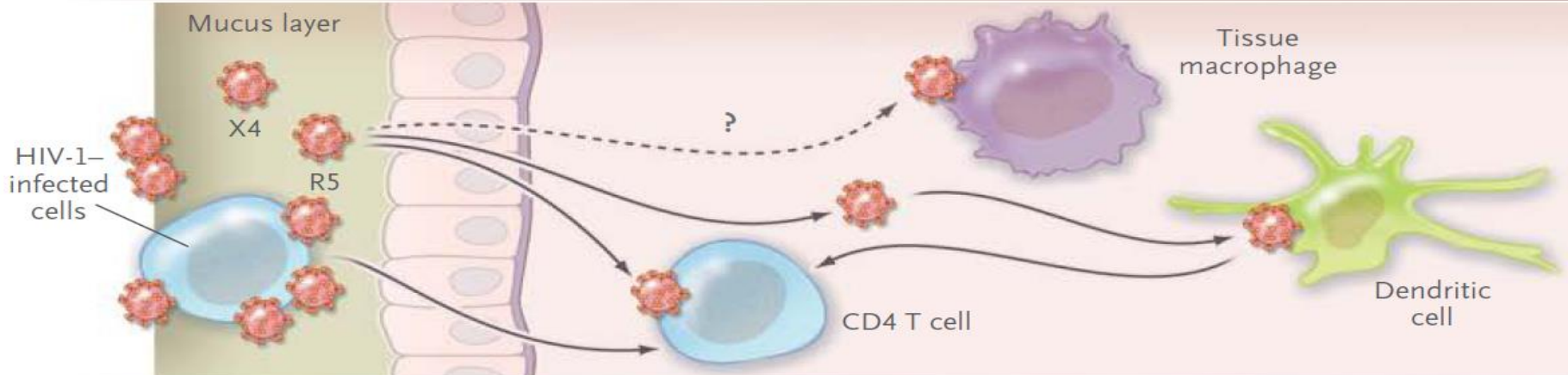
N Engl J Med 2011;364:1943



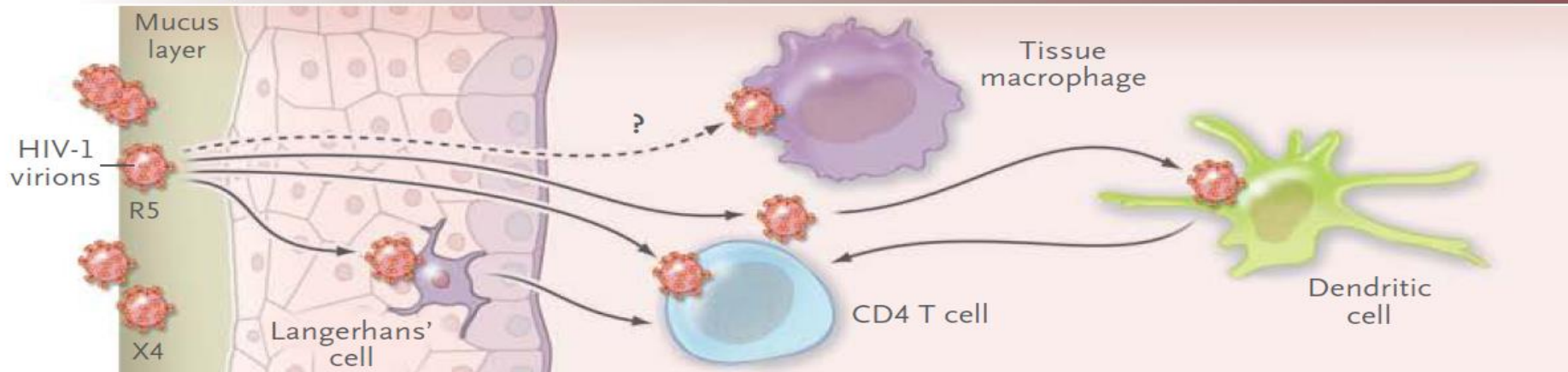
Progression from HIV-1 transmission to productive clinical infection (female)

N Engl J Med 2011;364:1943

Columnar epithelium in rectum and endocervix



Stratified squamous epithelium in vagina and ectocervix



Timing of HIV-1 infection events

Virus or virus-infected cells crossing mucosal barrier

2–6 hours

Local propagation of infection on CD4 T cells

3–6 days

Dissemination into draining lymph nodes

Systemic dissemination

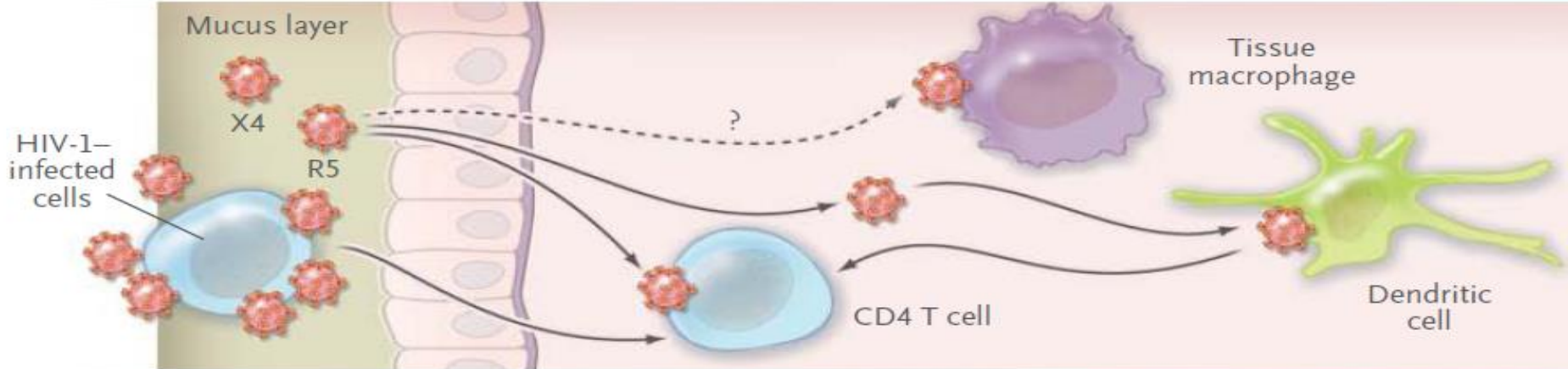
6–25 days

Establishment of CD4 T-cell virus reservoirs (? earlier)

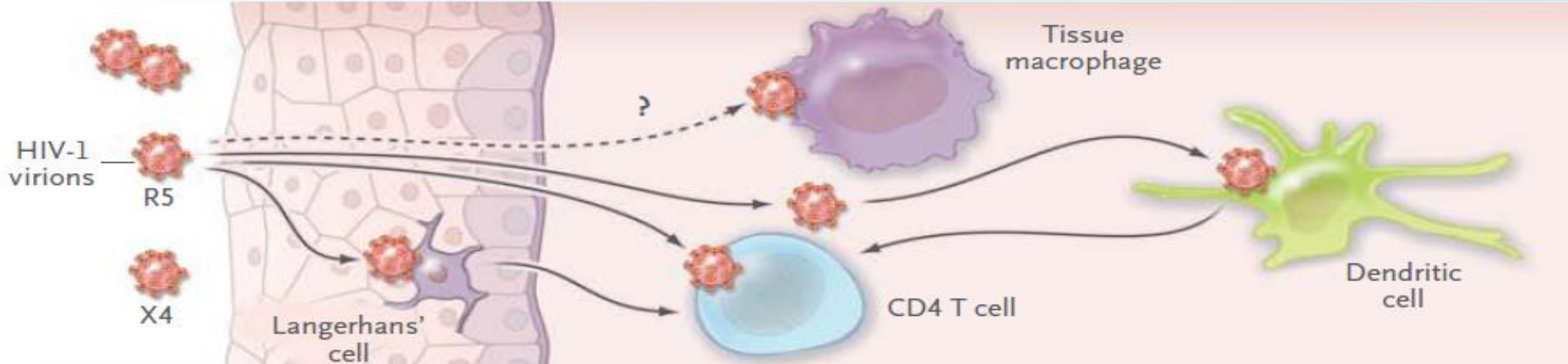
Progression from HIV-1 transmission to productive clinical infection (male)

N Engl J Med 2011;364:1943

Columnar epithelium in rectum



Stratified squamous epithelium of inner side of penile foreskin



Timing of HIV-1 infection events

Virus or virus-infected cells crossing mucosal barrier

2–6 hours

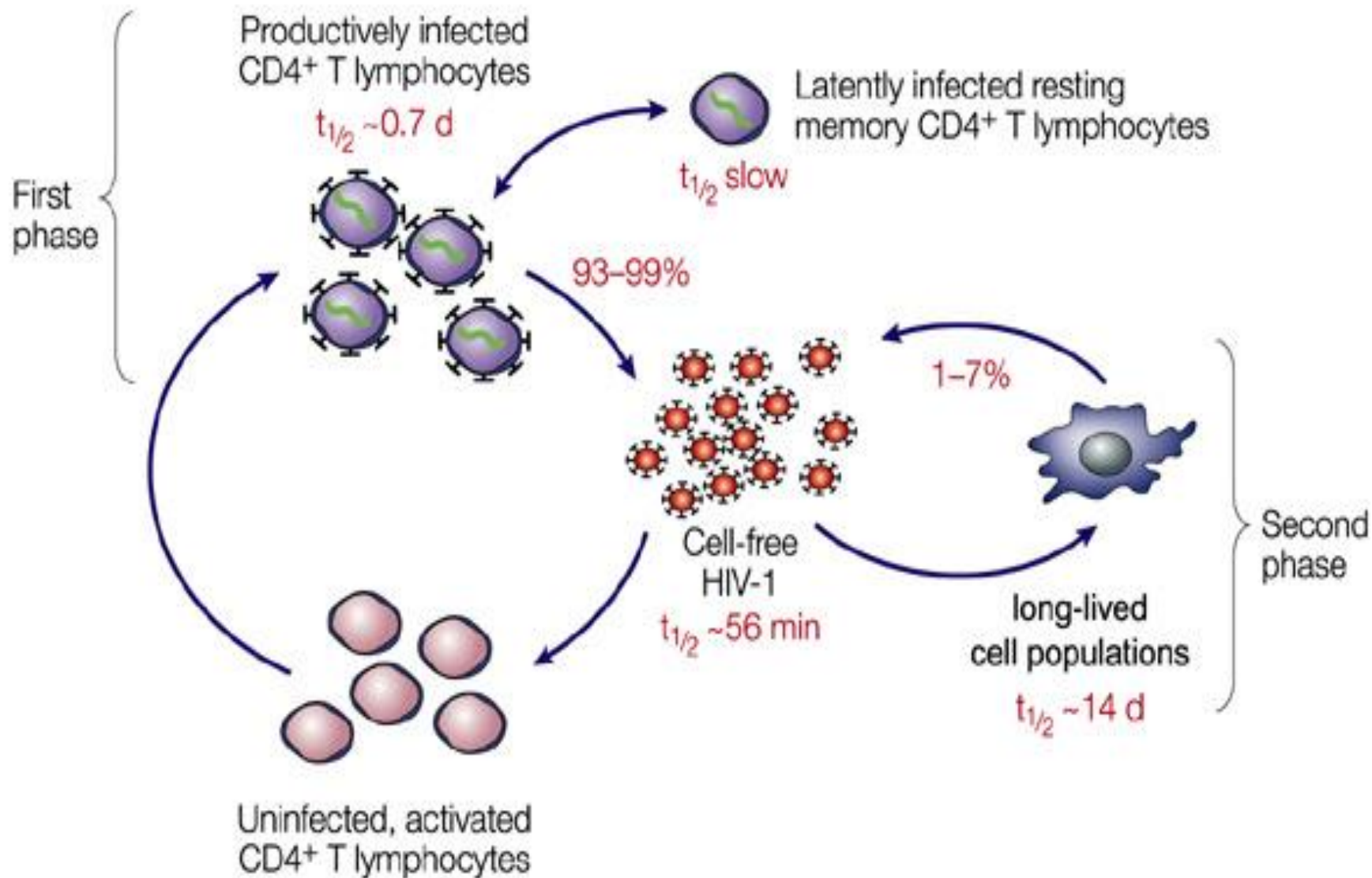
Local propagation of infection on CD4 T cells

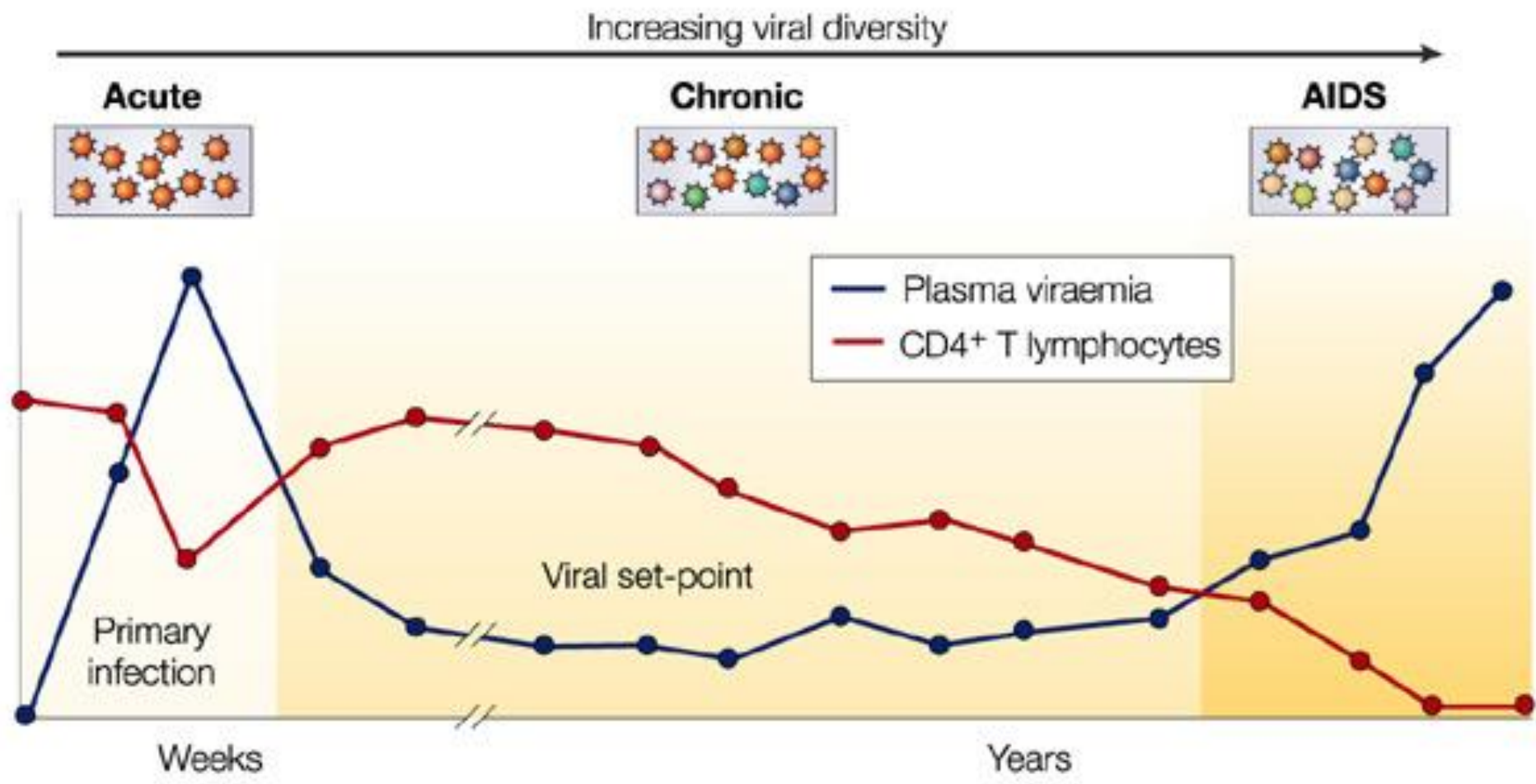
3–6 days

Systemic dissemination

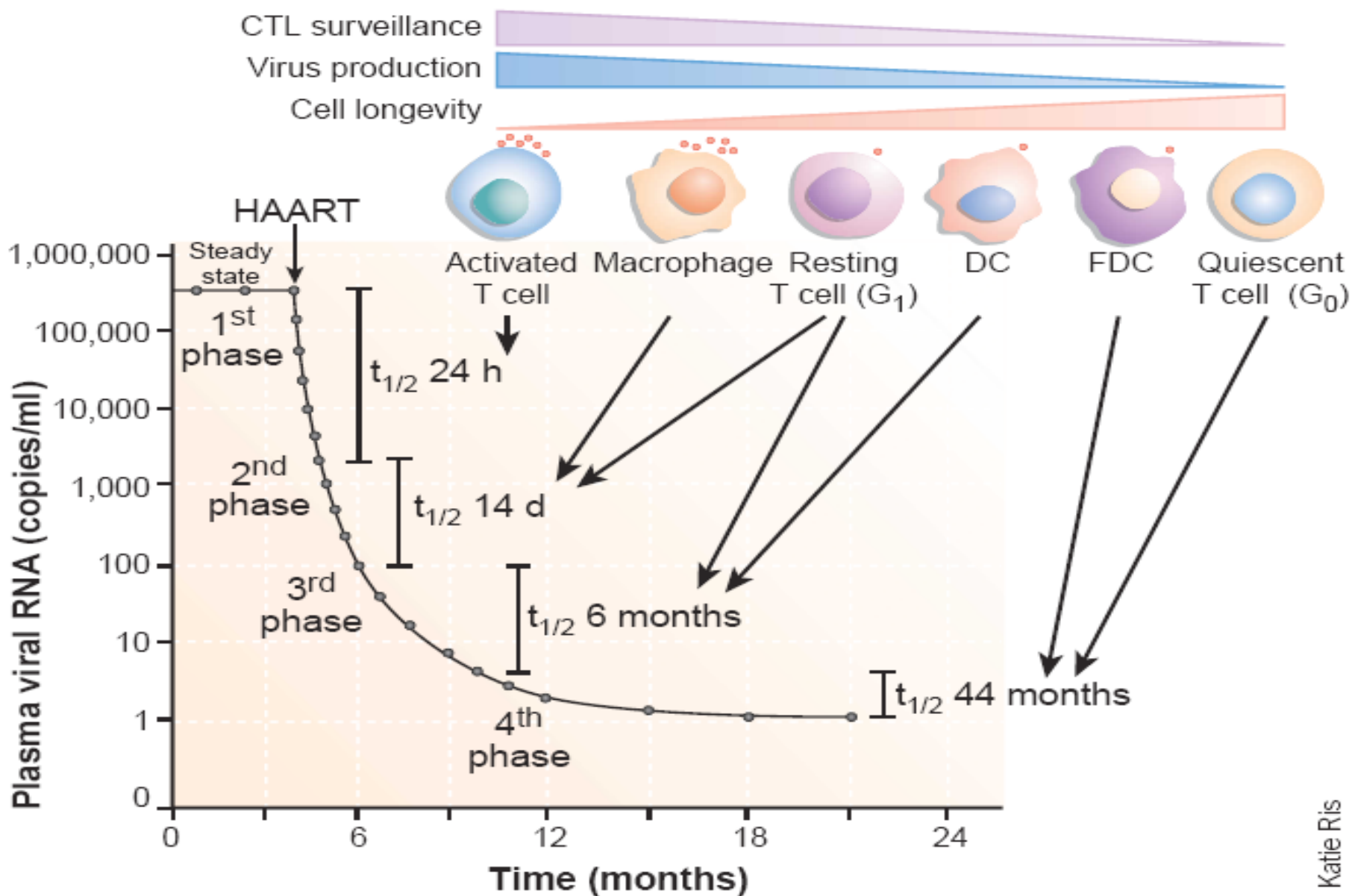
Establishment of CD4 T-cell virus reservoirs (? earlier)







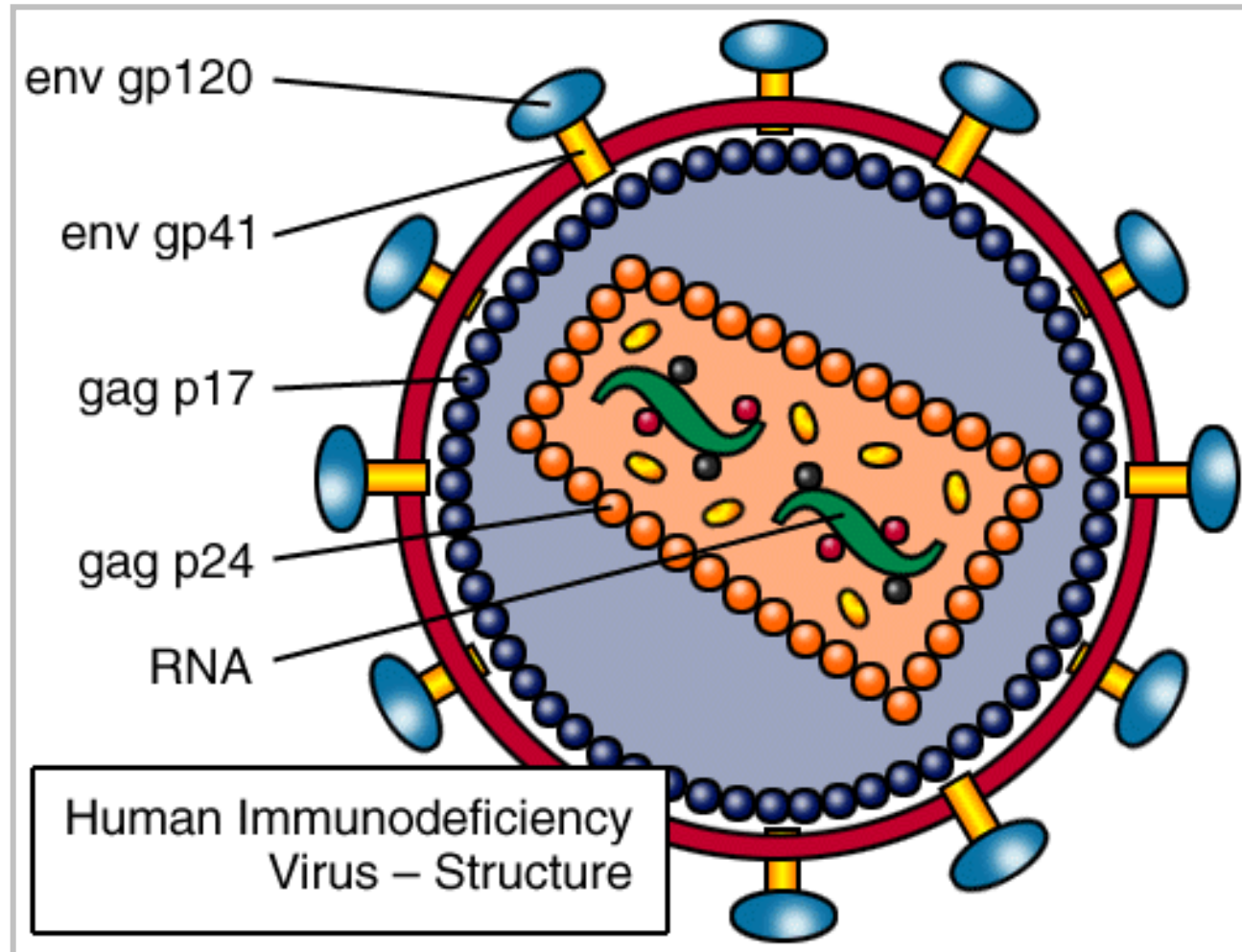
愛滋病毒持續存於人體的原因



Diagnosis of HIV infection

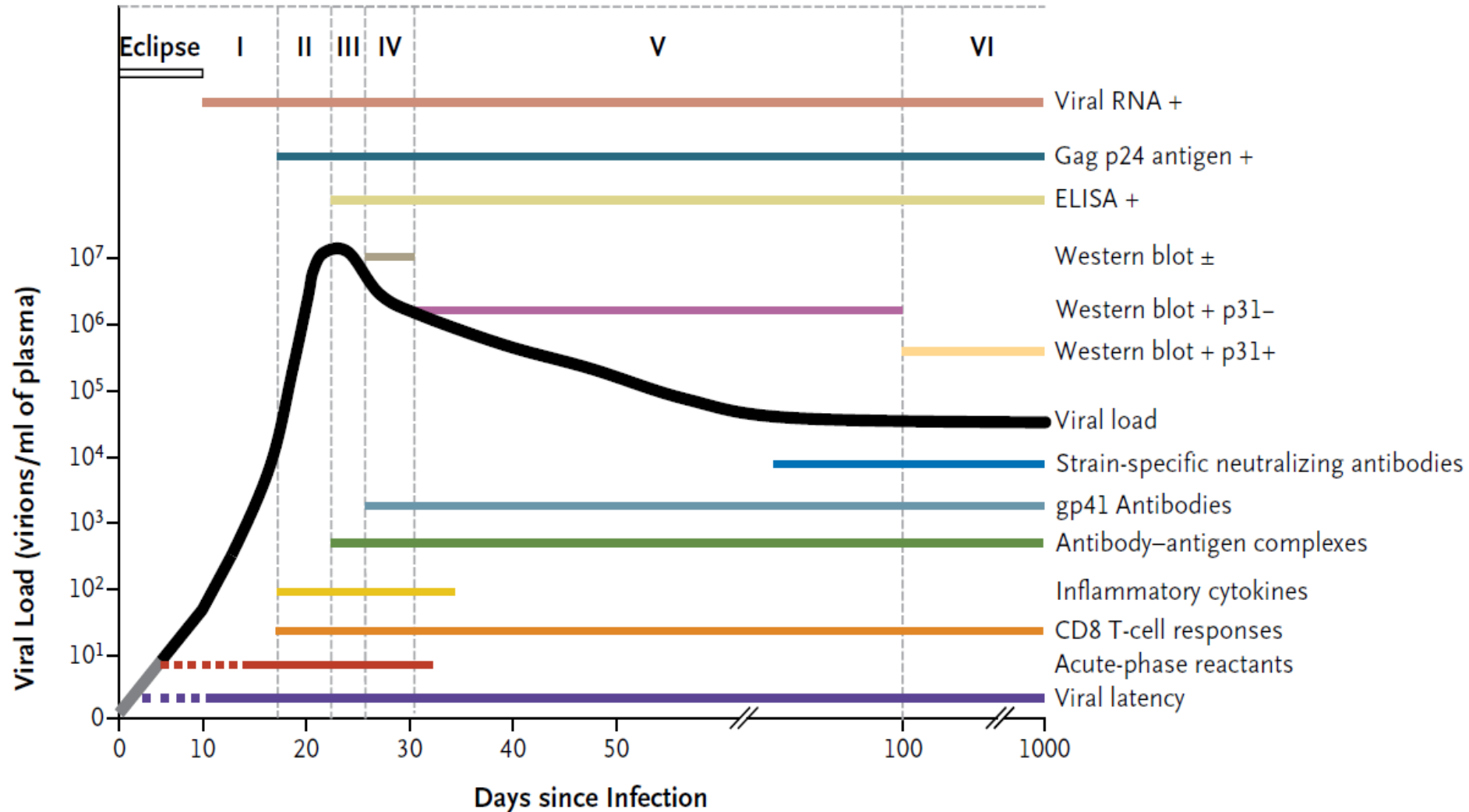
Laboratory Diagnosis of HIV Infection

- Antigen
- Antibody
- Nucleic acid



Natural history and immunopathogenesis of HIV-1 infection

N Engl J Med 2011;364:1943



Enzyme immunoassay (EIA)

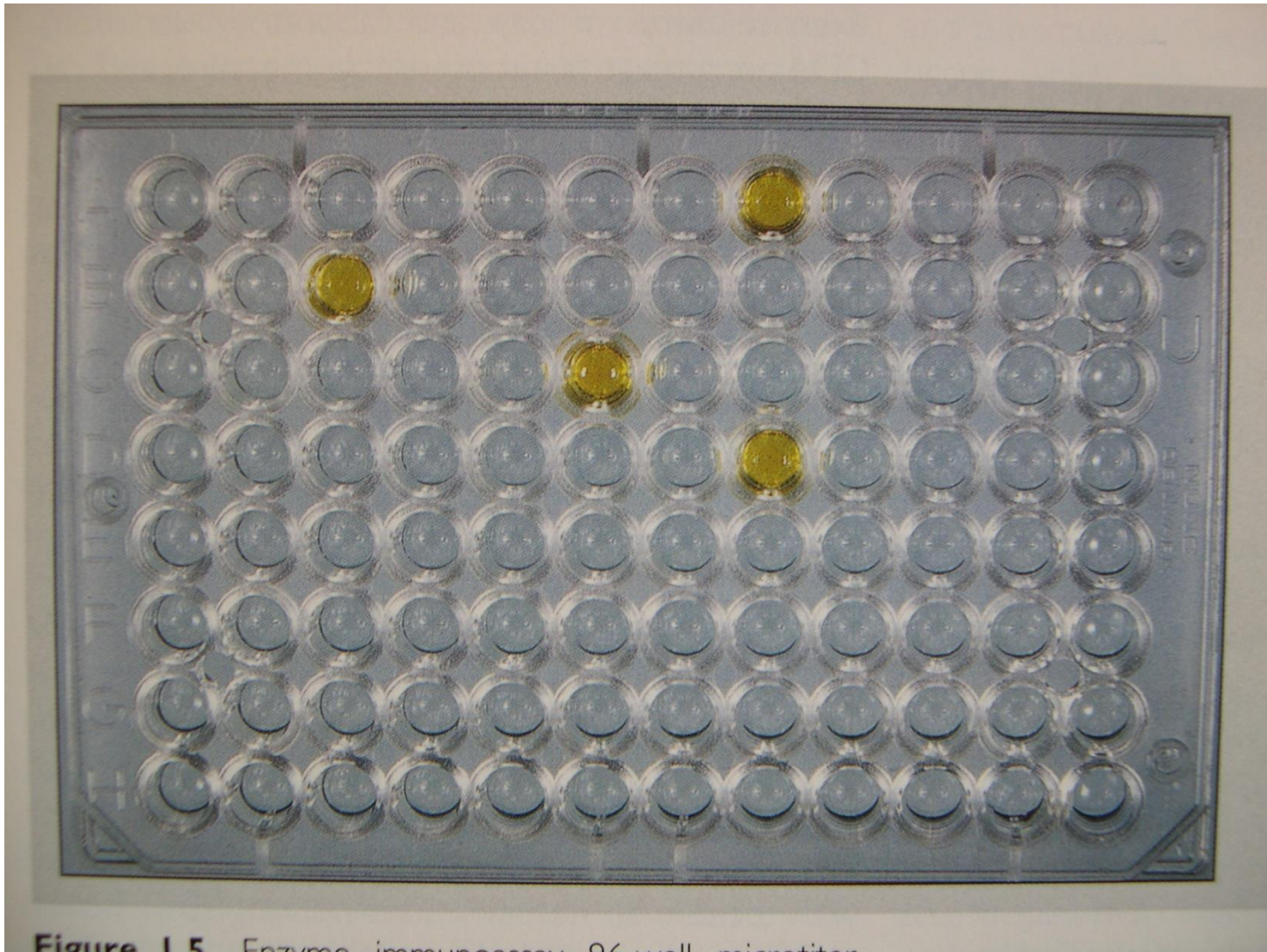


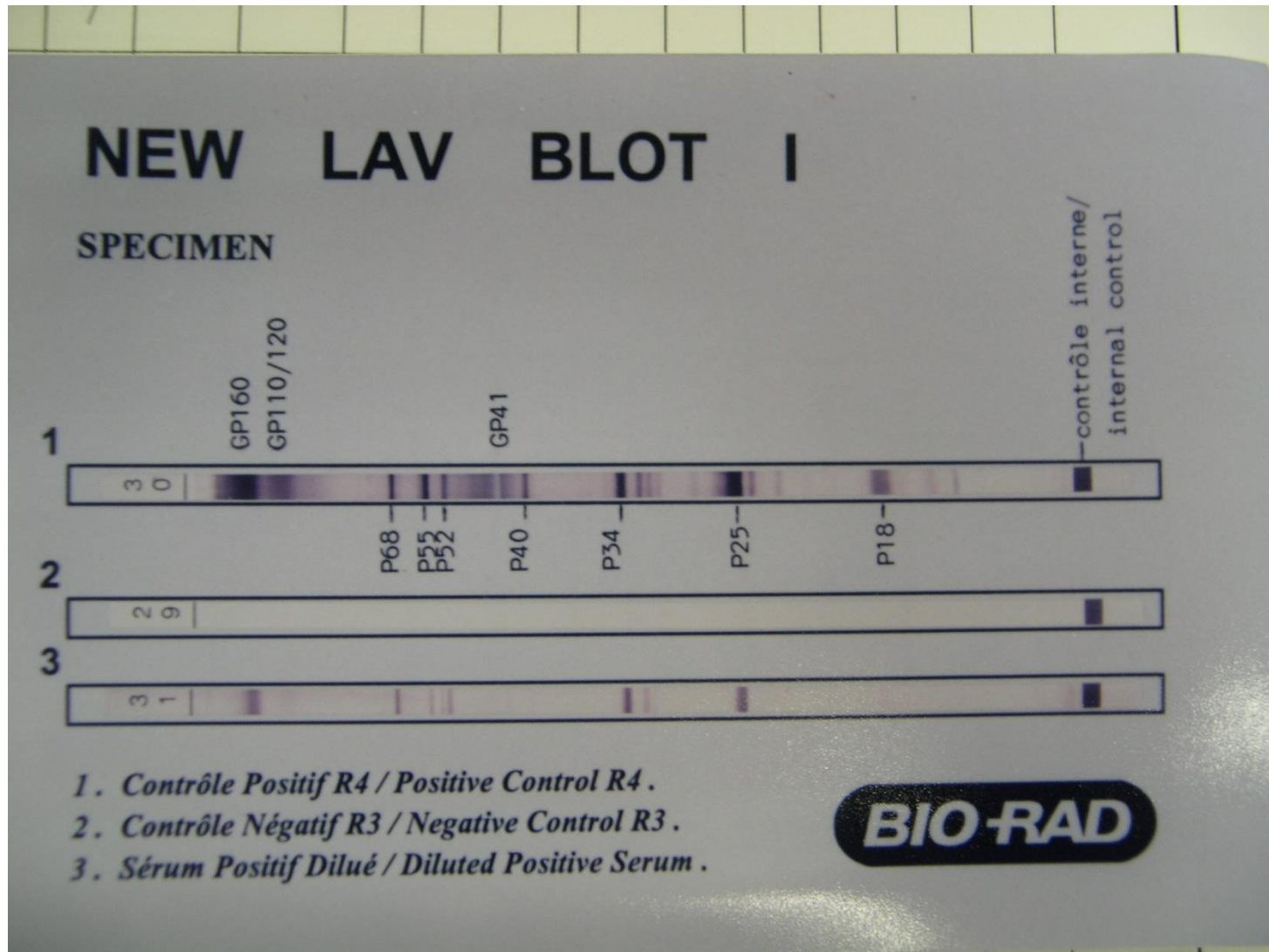
Figure 1.5 Enzyme immunoassay 96 well microtiter

HIV western blot test

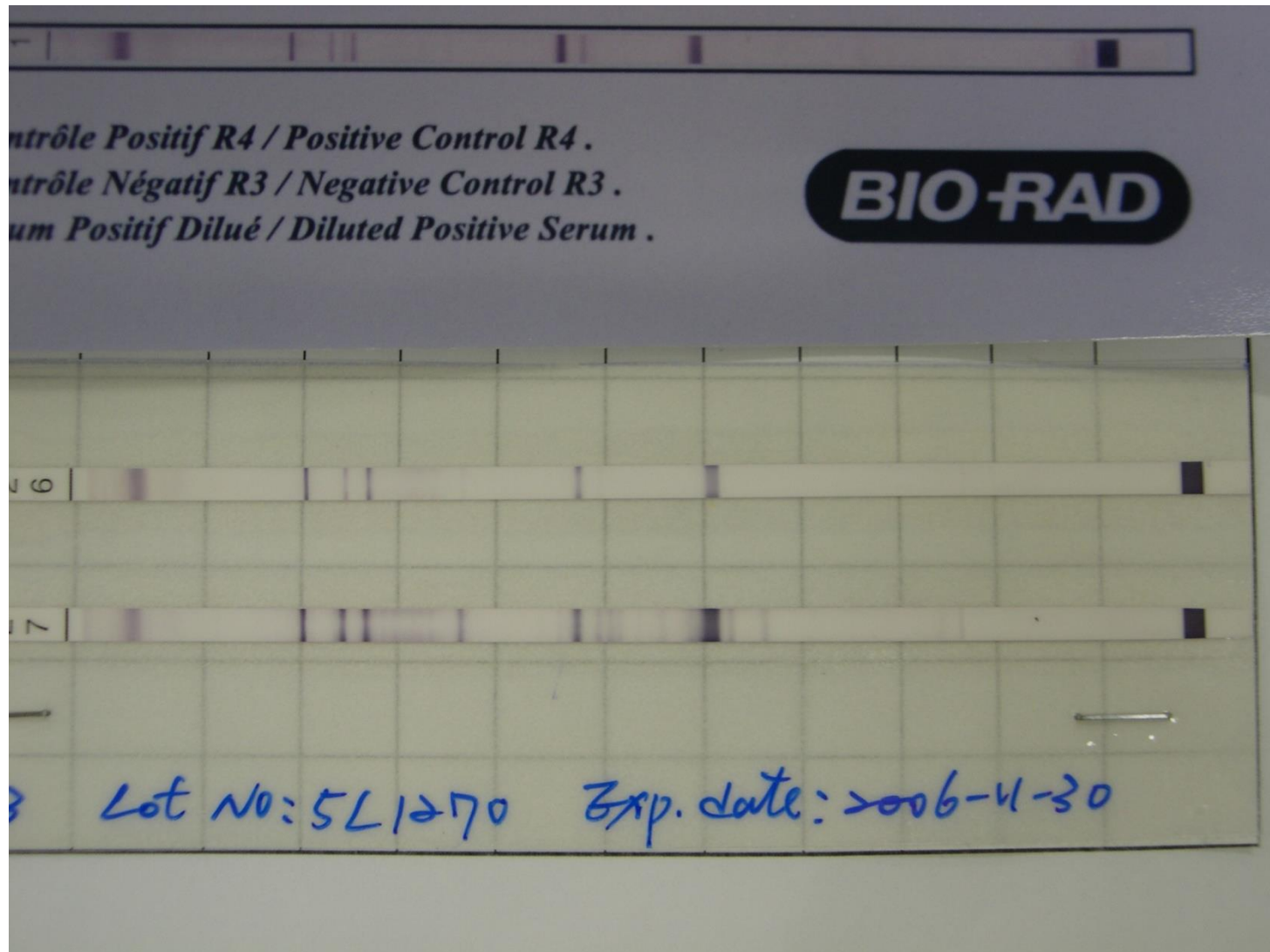
HIV western blot test report forms

- Positive:
 - GP160/120, GP41, P24 **any 2** bands presents (USA CDC criteria)
- Indeterminate: any positive band presents
- Negative: no band

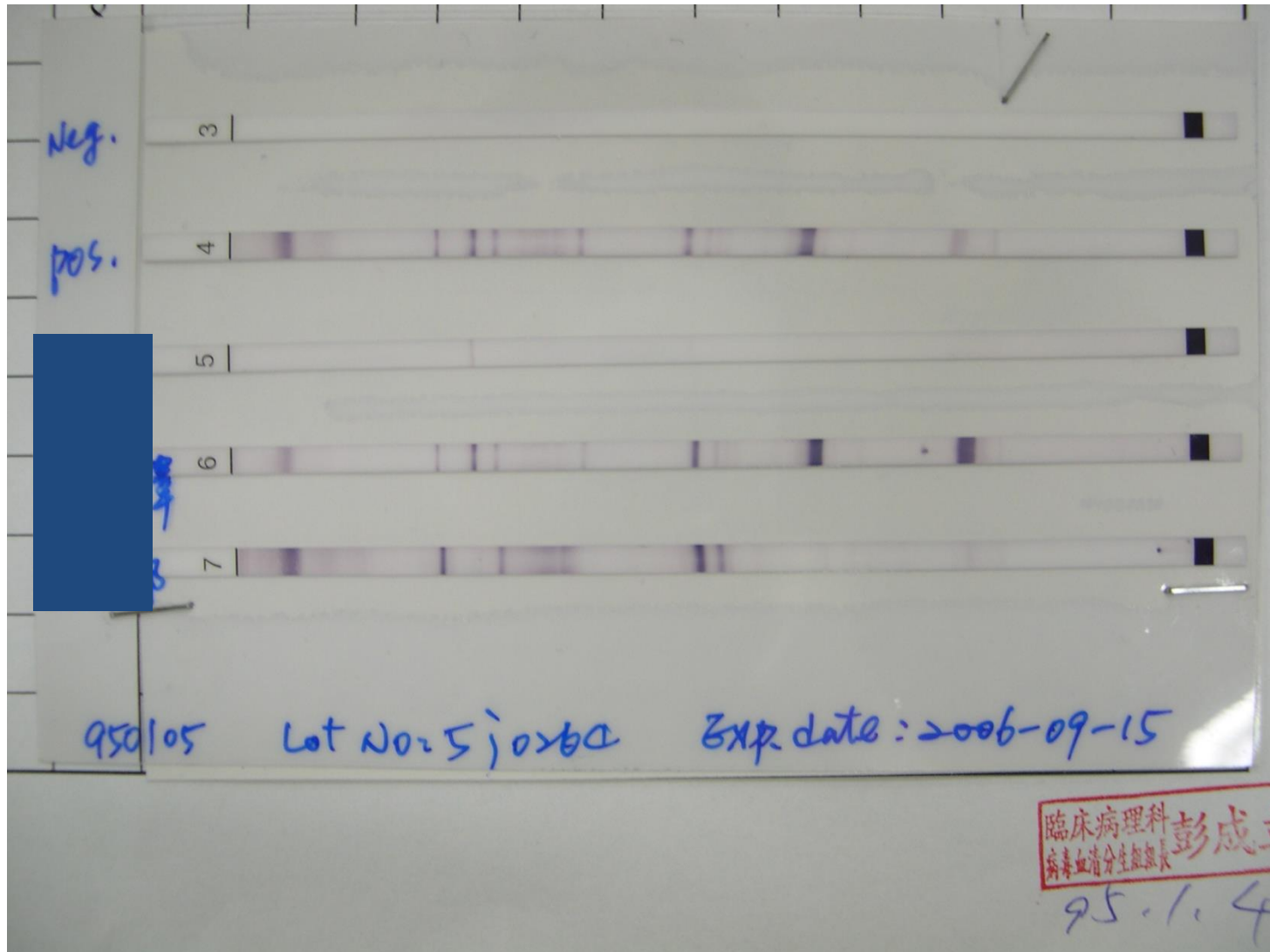
Western blot test (1)



Western blot test (2)



Western blot test (3)



Assessment of HIV-positive persons at initial and subsequent visits

- History
 - medical; psychological; sexual and reproductive health
- HIV disease
 - Virology: PVL; genotypic resistance test (R5 tropism)
 - Immunology: annual CD4 if stable on ART and CD4 > 350 cells/mm³
- Co-infections
 - Syphilis and other STIs; viral hepatitis; others
 - Vaccine-preventable infections

Bacterial infections in adults

- Respiratory tract
 - *Streptococcus pneumoniae*
 - *Nocardia* spp.
 - *Rhodococcus equi*
 - *Haemophilus influenzae*
- GI tract
 - Nontyphoid *Salmonella* spp.
 - *Campylobacter* spp.
 - *Shigella* spp.
- Skin and soft tissue; bone and musculoskeletal; cardiovascular
 - *Staphylococcus aureus*
- GU
 - *E. coli*
 - *Treponema pallidum*
 - *Chlamydia trachomatis*
 - *Neisseria gonorrhoeae*

Fungal infections

- Candidiasis
- *Pneumocystis jirovecii* pneumonia
- Cryptococcosis
- Endemic fungal infections
 - *Penicillium marneffe*i infection
 - Coccidioidomycosis
 - Histoplasmosis

Oral Candidiasis



Candida esophagitis

ID No. :
Name :

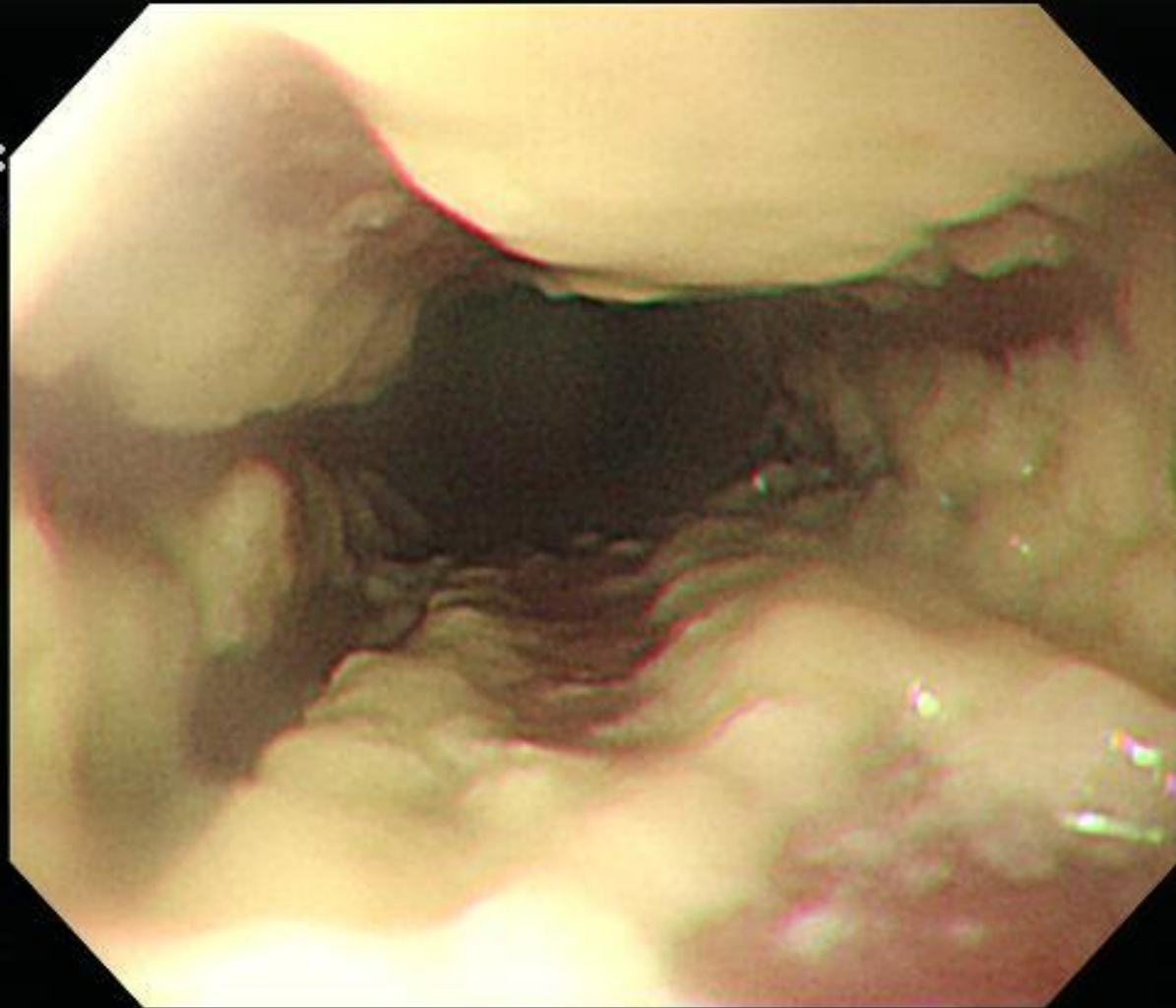
Sex : Age :
D.O.Birth :

10/27/2009
15:02:09

SCV:87

Ct: N Eh: A5
Ce: O Z: 1.0

Physician :
Comment :



Candida esophagitis

ID No. :

Name :

Sex : Age :

D.O.Birth :

10/27/2009

15:09:56

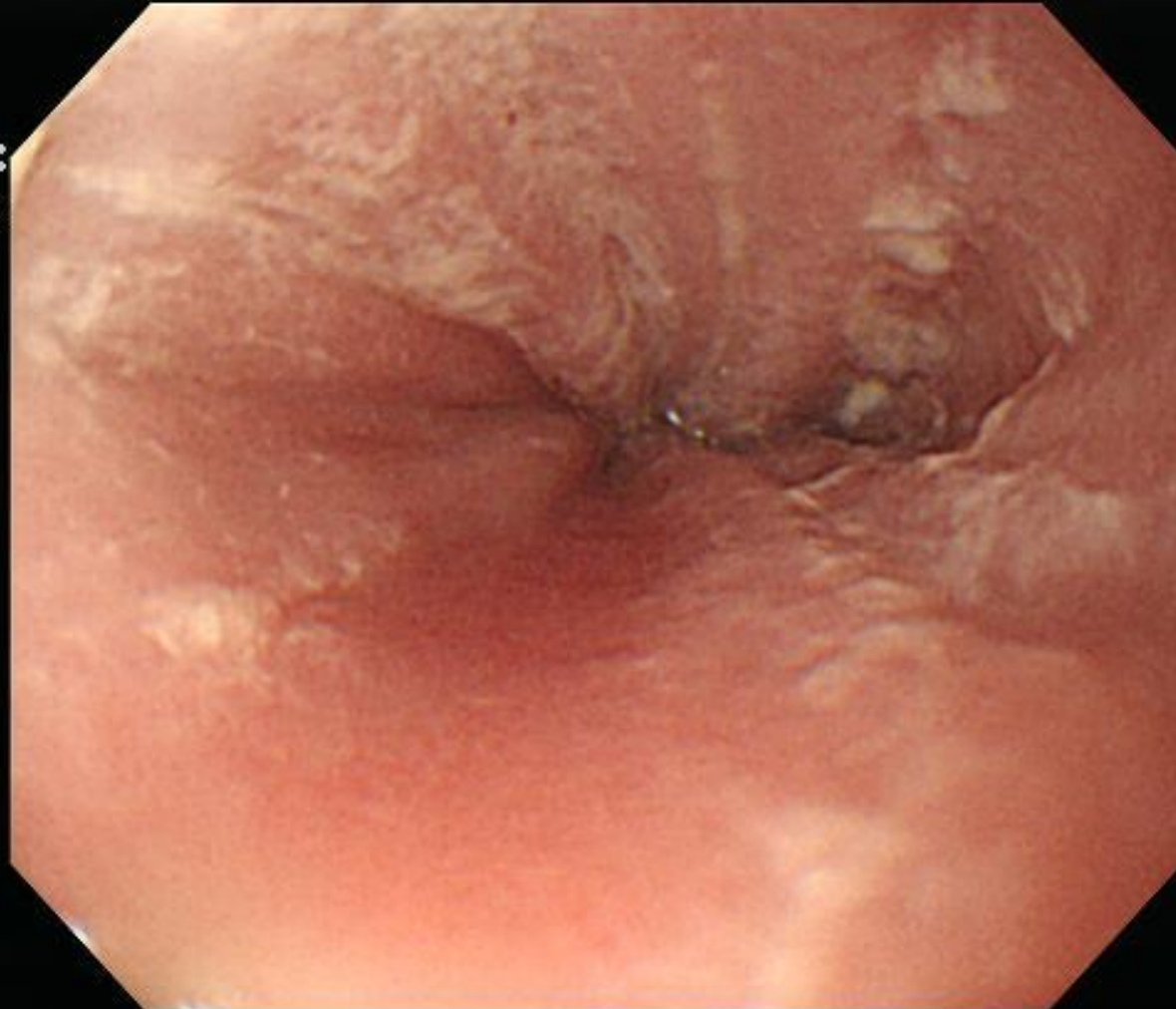
SCV:5

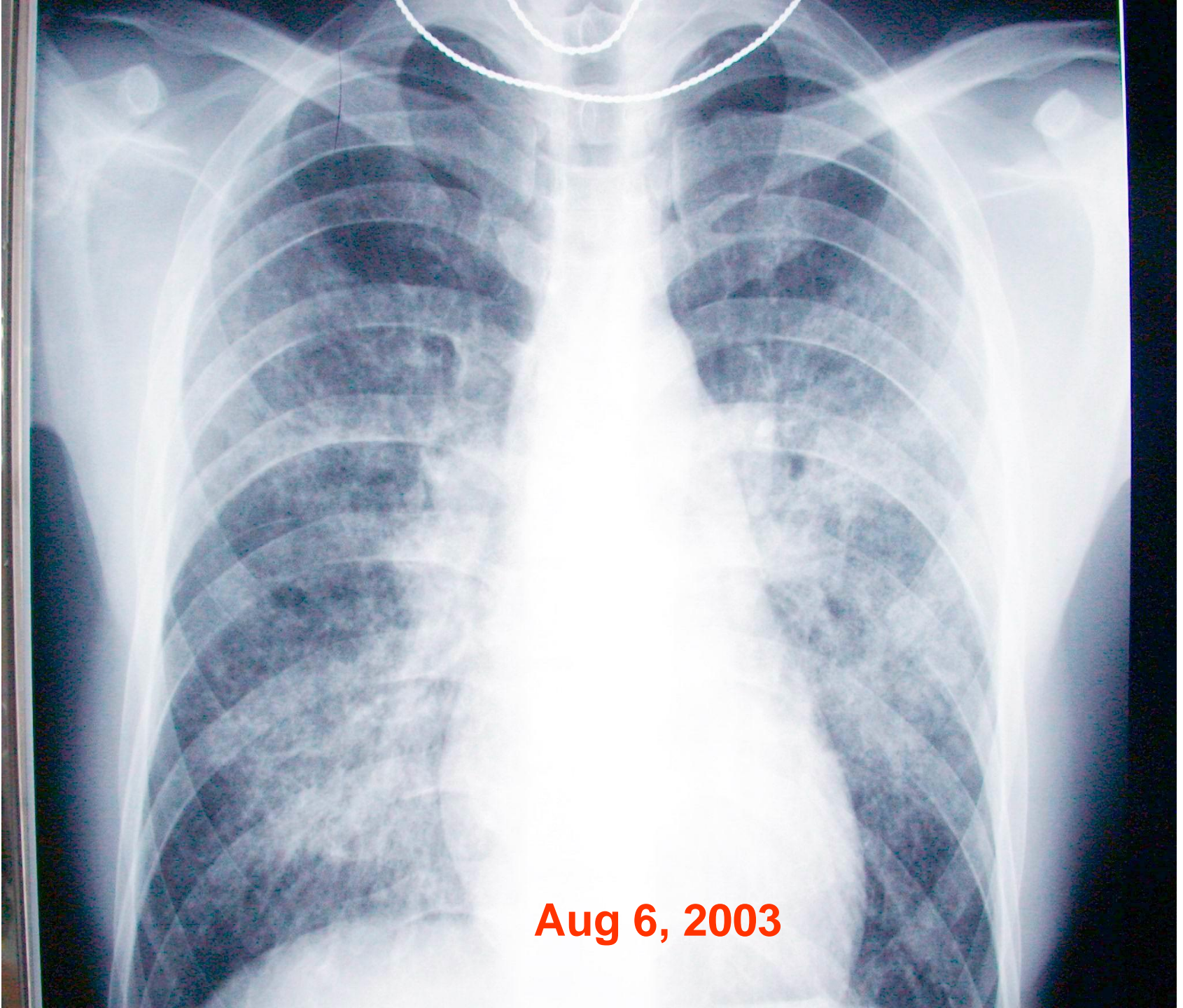
Ct: N Eh: A5

Ce: 0 Z: 1.0

Physician :

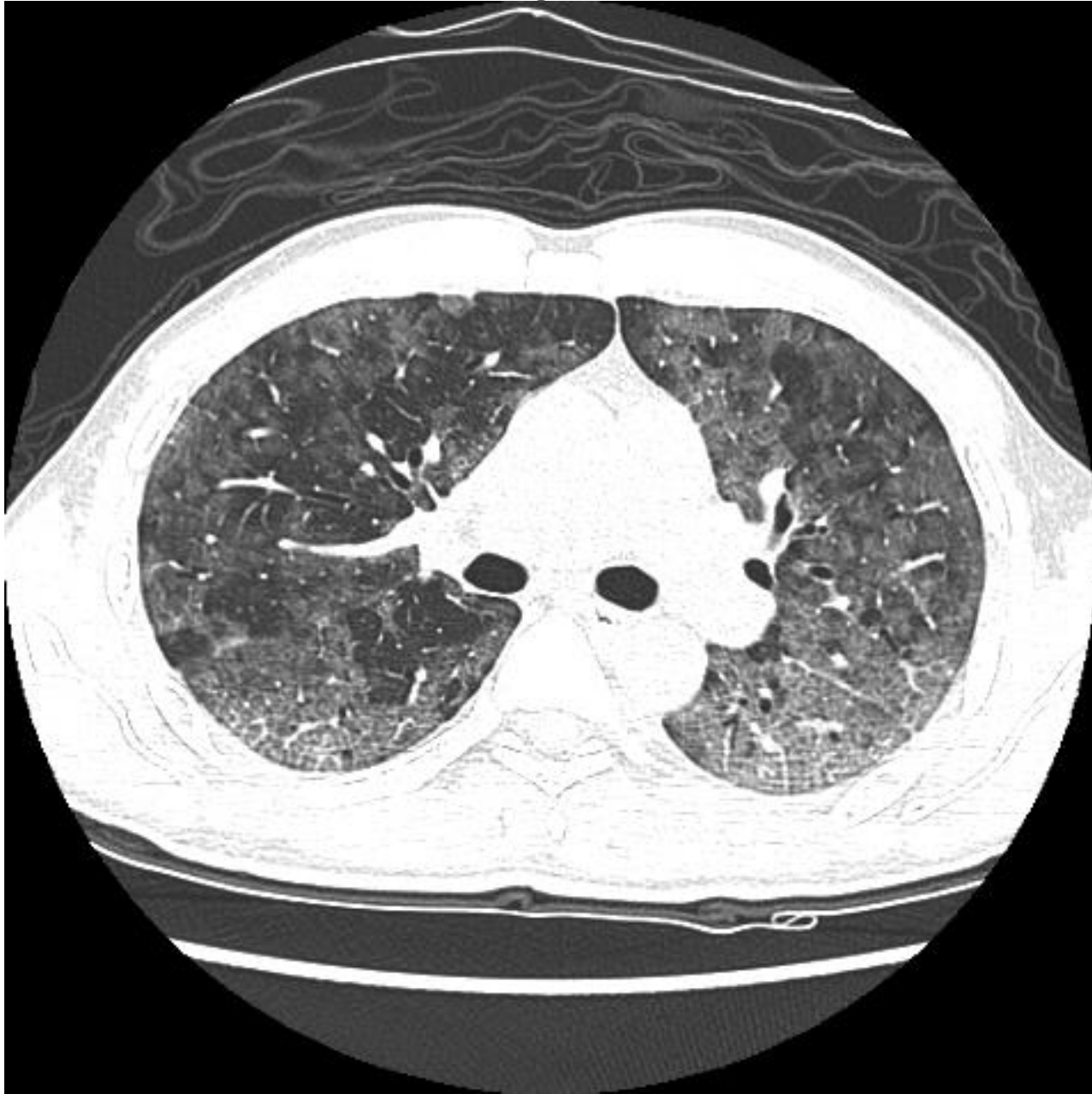
Comment :

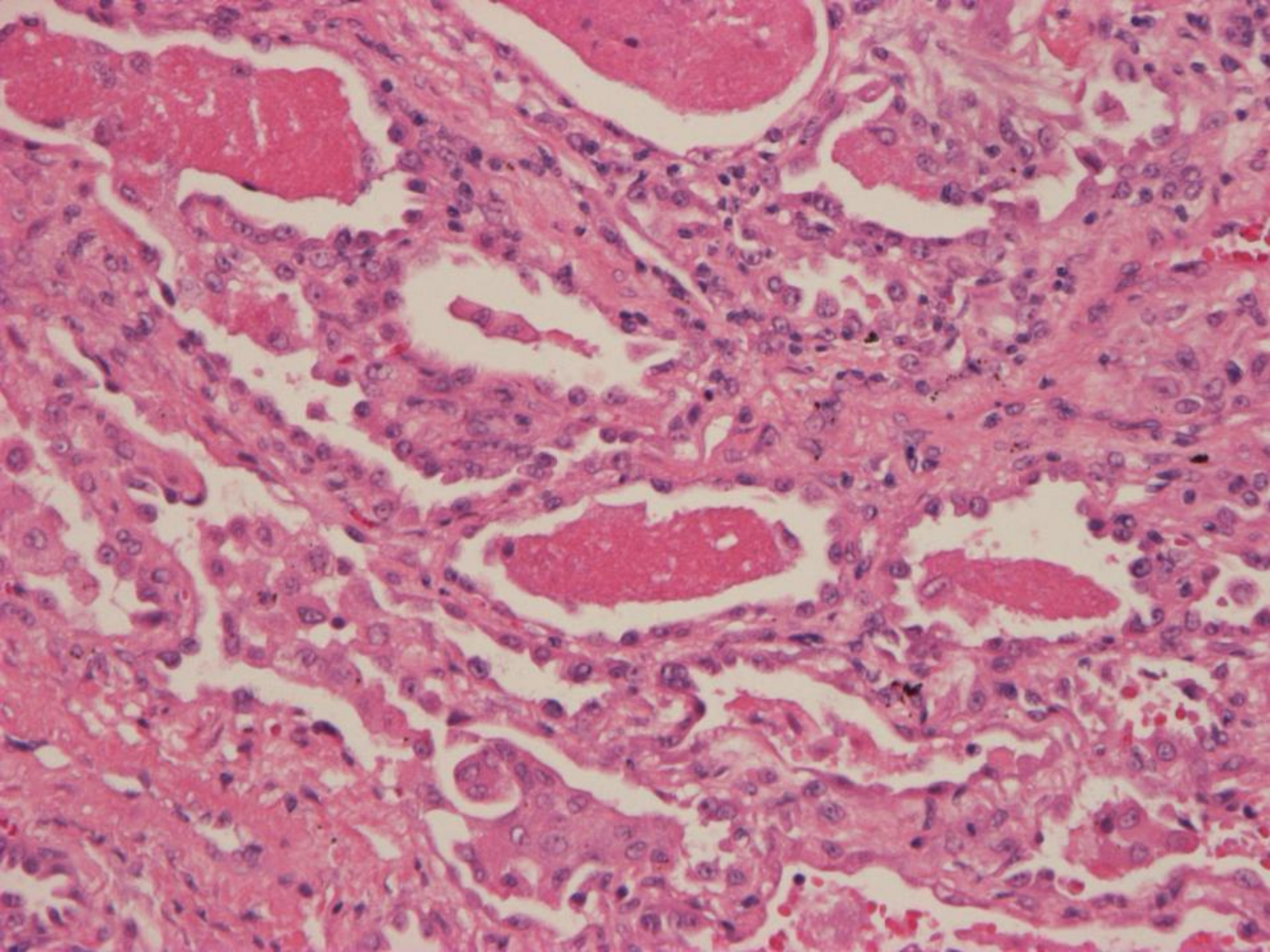


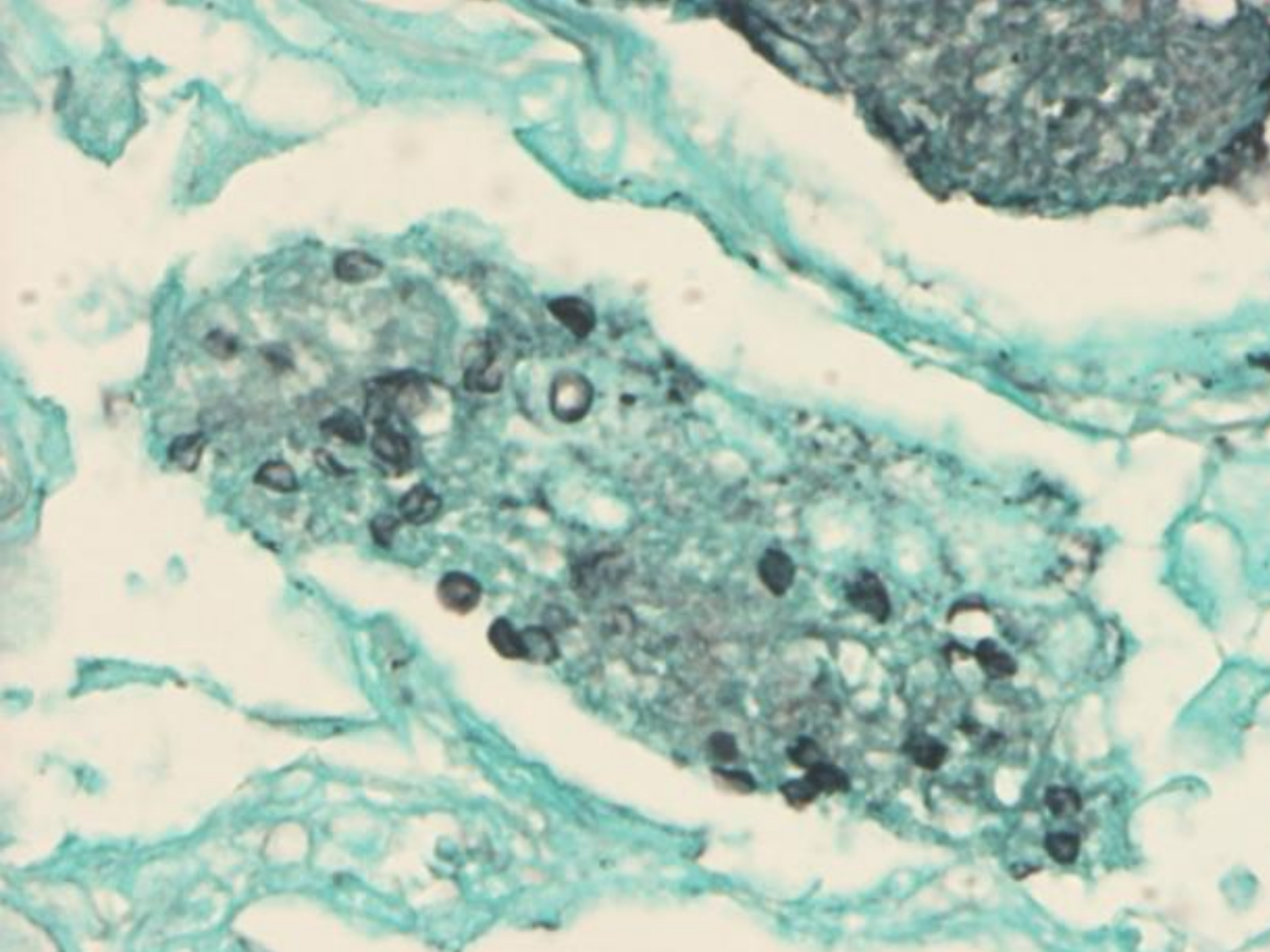


Aug 6, 2003

Interstitial pneumonitis





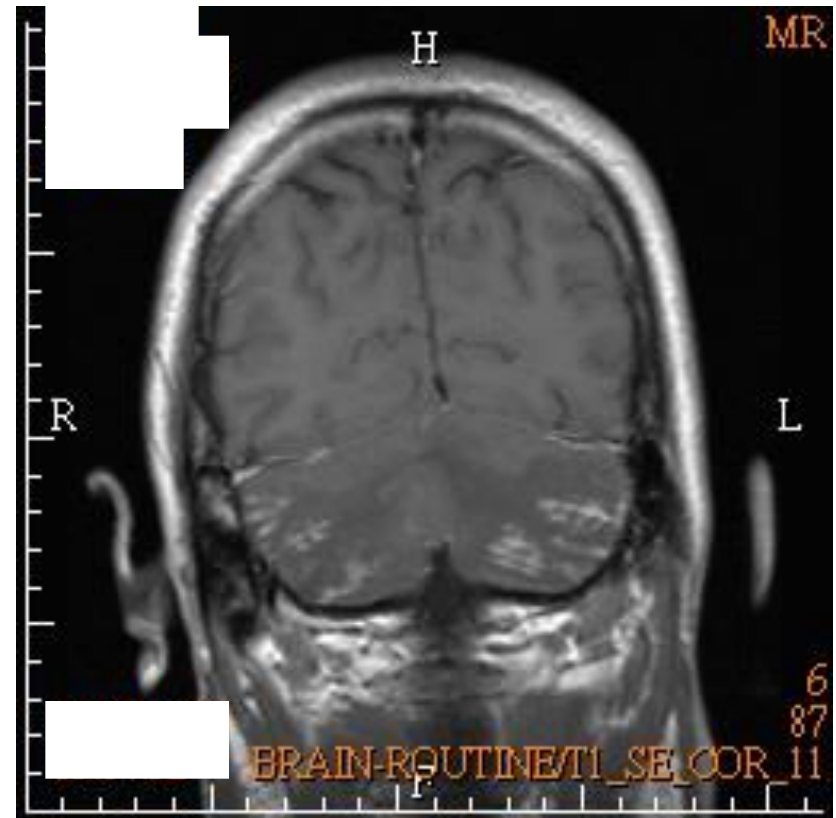
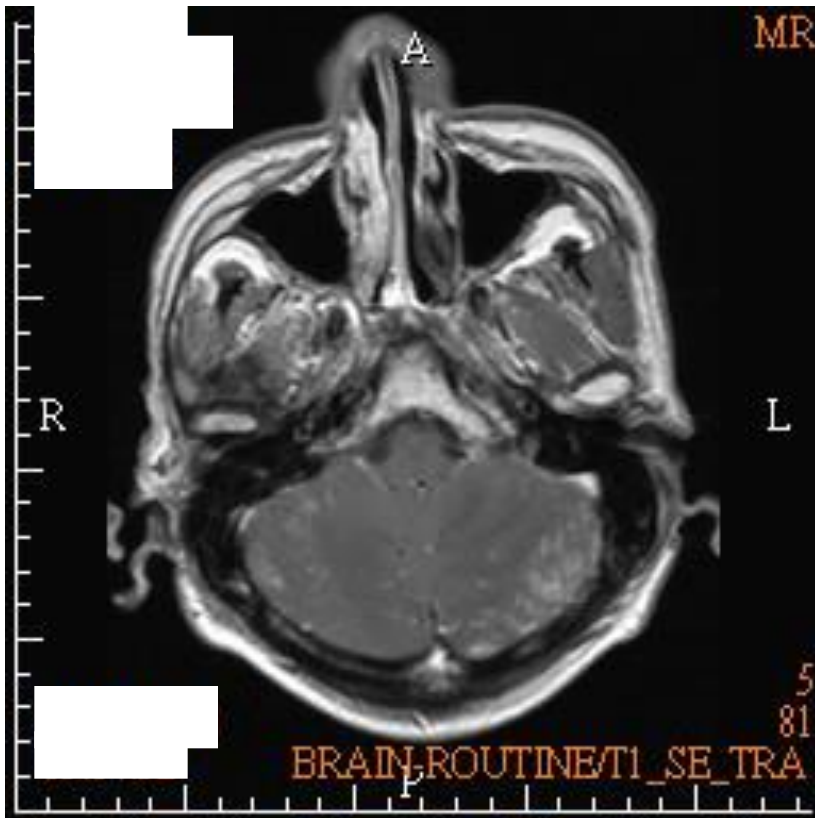


Management of *P. jirovecii* pneumonia

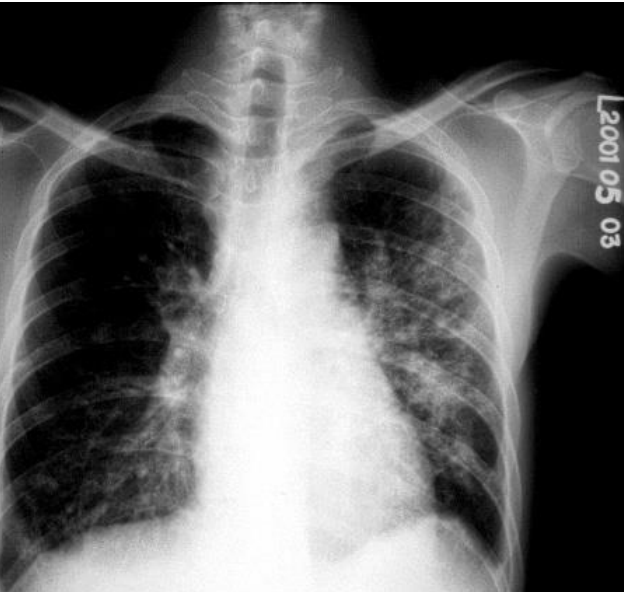
- Trimethoprim-sulfamethoxazole
 - Dosage
 - Adverse effects
- Alternative therapy
- Adjunctive steroid therapy
 - Indications
- Differential diagnosis of interstitial pneumonitis
- Primary and secondary prophylaxis

Cryptococcal Meningitis

A 46 years old man had fever, conscious change for 4 days. He had unstable gait for one month and western blot test+. CD4:22 cell/ul, crypto Ag Blood 1:1024, CSF:>1:2048. Opening pressure: 360 mm H2O.



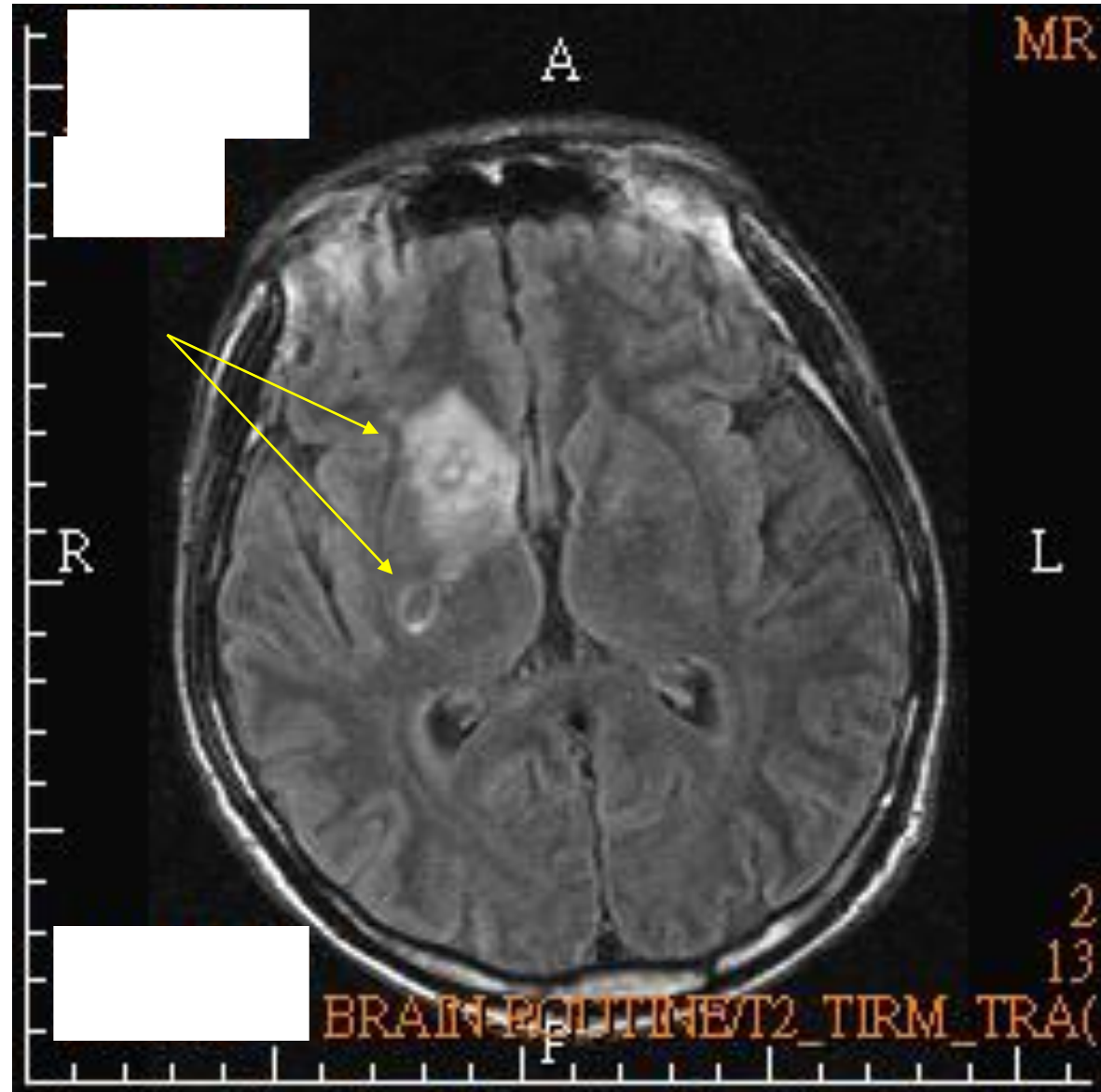
Cryptococcosis



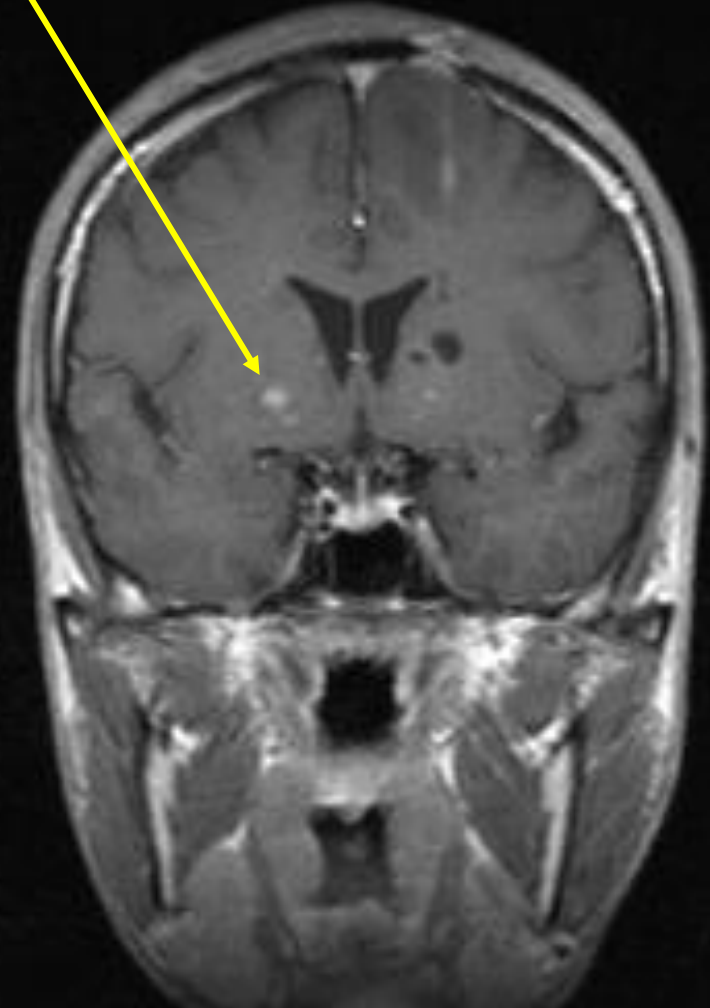
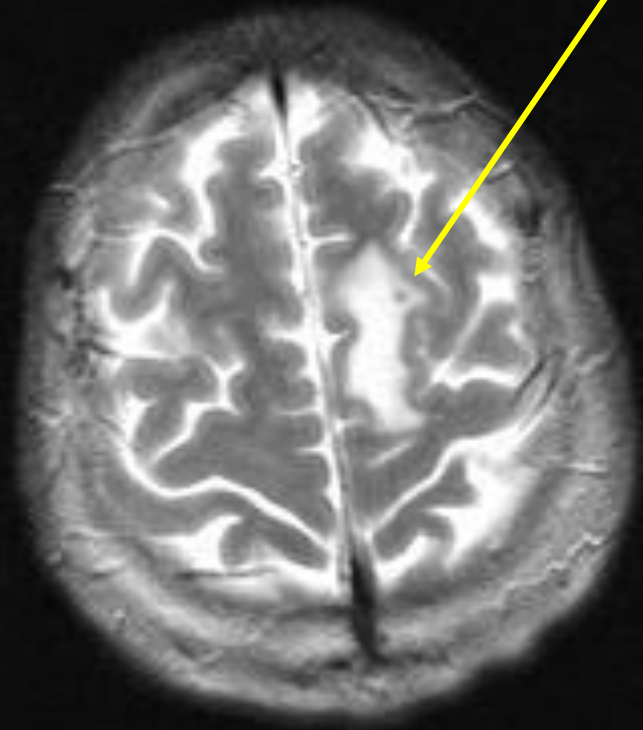
- Diagnosis
 - Cryptococcal antigen of the serum and CSF
 - India ink smears of clinical specimens
 - Cultures of blood and CSF specimens
- Amphotericin B plus flucytosine; followed by fluconazole
 - Adverse effects of ampho-B:
 - anemia; hypokalemia; nephrotoxicity
 - Adverse effects of 5-FC
 - Bone marrow suppression
- Management of increased intracranial pressure (IICP)
 - Repeat lumbar punctures

Cryptococcoma in HIV

- A 30 years old man had headache, fever and consciousness change for 1 week.
- Oral thrush+. MSM for 10 years.
- Blood crypto Ag > 1:1024, CSF crypto Ag >1:1024,
- Western blot test +, CD4:12 cell/ul, HIV viral load >1,000,000 RNA copies/ml

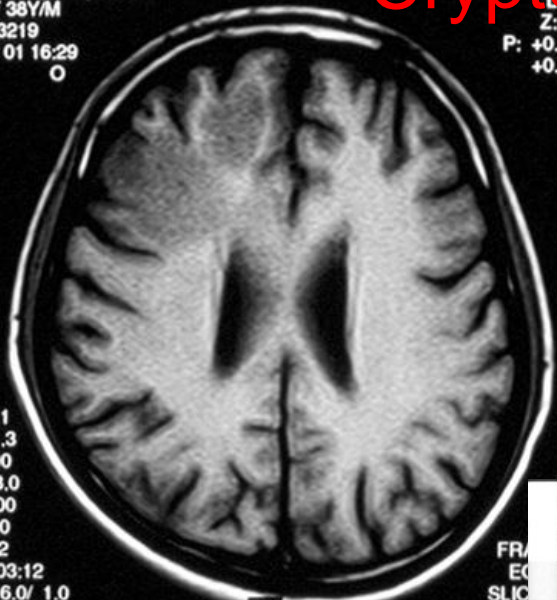


Cryptococcoma in HIV



Cryptococcal meningoencephalitis

Marconi Medical Systems, Inc. Eclipse 1.5T
En Chu Kong Hospital MRI
LIN U.F 38Y/M
ID: 2833219
24 SEP 01 16:29
4250 O



R

SE:
TE: 12.1
BW: 31.3
TR: 500
FOV: 23.0
PS: 1.000
FLIP: 90
NSA: 2
SCAN: 03:12
THICK: 6.0/ 1.0
RES: 192x256

PH

W: 99.0
L: 546
Z: 1.20
P: +0.0 cm
+0.0 cm

Marconi Medical Systems, Inc. Eclipse 1.5T
En Chu Kong Hospital MRI
LIN U.F 38Y/M
ID: 2833219
24 SEP 01 16:49
4250 R



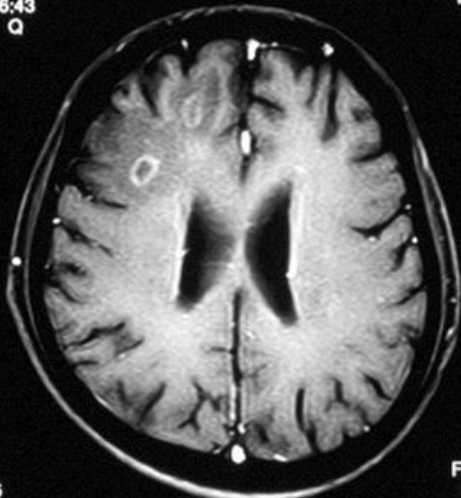
R

SE:
TE: 13.8
BW: 15.6
TR: 684

W:1114
L: 546
Z: 1.20
P: +0.0 cm
+0.0 cm

3.1 R
13.0 P
43.1 H
FRAME: 1/1
ECHO: 1/1
SLICE: 9/19
CONTRAST: +GD
HEAD

Marconi Medical Systems, Inc. Eclipse 1.5T
En Chu Kong Hospital MRI
LIN U.F 38Y/M
ID: 2833219
24 SEP 01 16:43
4250 Q



R

SE:
TE: 14.0
BW: 15.6
TR: 684
FOV: 23.0
PS: 1.000
FLIP: 90
NSA: 2
SCAN: 04:06
THICK: 6.0/ 1.0
RES: 180x256
FATSAT.

PH

W: 99.0
L: 546
Z: 1.20
P: +0.0 cm
+0.0 cm



SE:
TR: 963
TE: 16
EC: 1/1 16Hz
HEAD
FOV: 22x22
5.0thP/1.5sp
17:03:21
256x192/1 NEX
S: 1IF

I110

Sigma 1.5T SVS#MR31000
NATIONAL TAIWAN UNIVERSITY HOSP.
LIAU Y-G
55 M 3959145
06/05/01
10:35
FCS
333
0/ 1.0
x256

Marconi Medical Systems, Inc. Eclipse 1.5T
En Chu Kong Hospital MRI
LIN U.F 38Y/M
ID: 2833219
24 SEP 01 16:19
4250 F



PH

TE: 96.0
BW: 20.8
TR: 6404
FOV: 23.0
PS: 0.914
FLIP: 90
NSA: 1
SCAN: 04:41
THICK: 5.5/ 1.0
RES: 192x256

W:1266
L: 518
Z: 1.00
P: +0.0 cm
+0.0 cm

4.9 R
10.7 P
70.9 H
FRAME: 1/1
ECHO: 1/1
SLICE: 14/20
HEAD

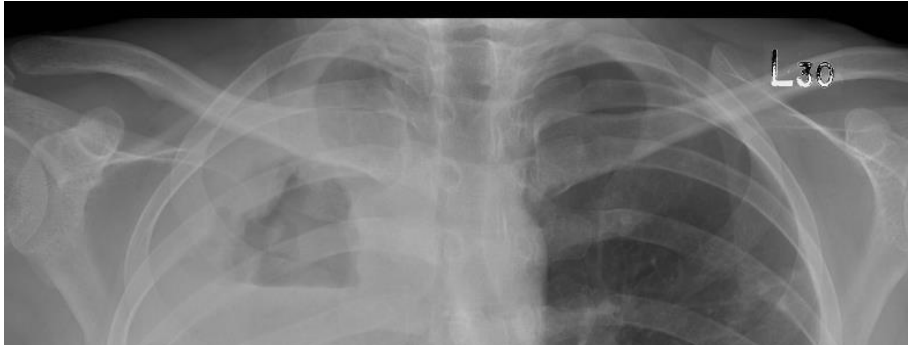
4.9 R
10.5 P
76.2 H
FRAME: 1/1
ECHO: 1/1
SLICE: 14/19
CONTRAST: +GD
HEAD



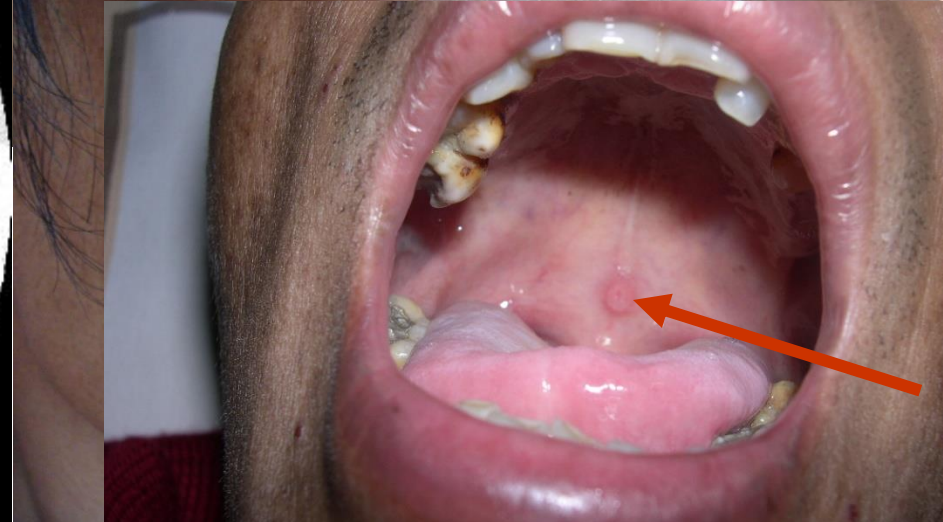
Penicilliosis in AIDS:
this is early skin lesions
caused by *Penecillium
marneffe* infections



Presentation of case



Penicillium marneffei
infection



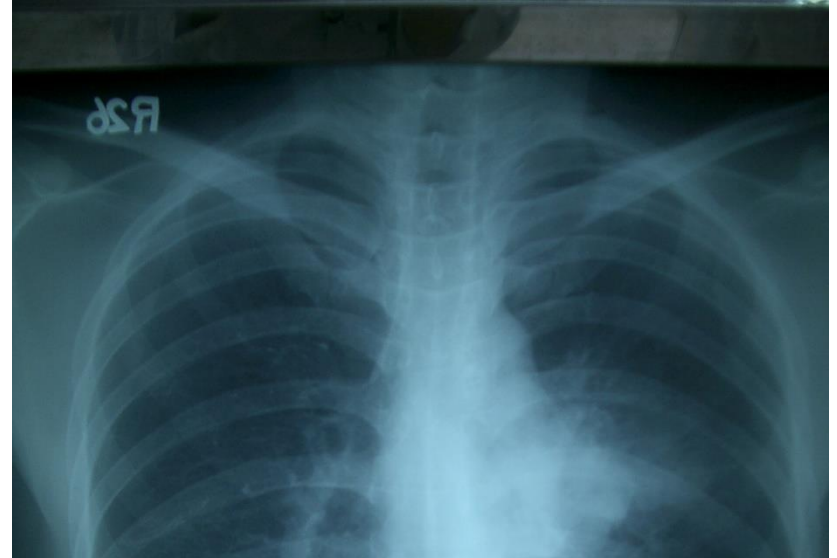
Mycobacteriosis

- Tuberculosis
- Non-tuberculous mycobacterial infections
 - *Mycobacterium avium* complex (MAC) infection
 - *M. kansasii* infection
 - Others

Presentation of case

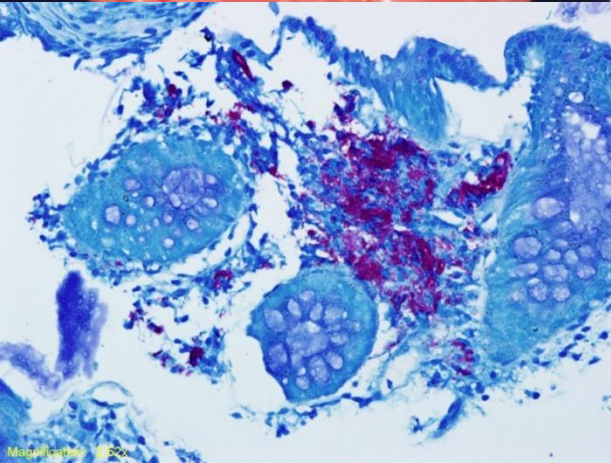
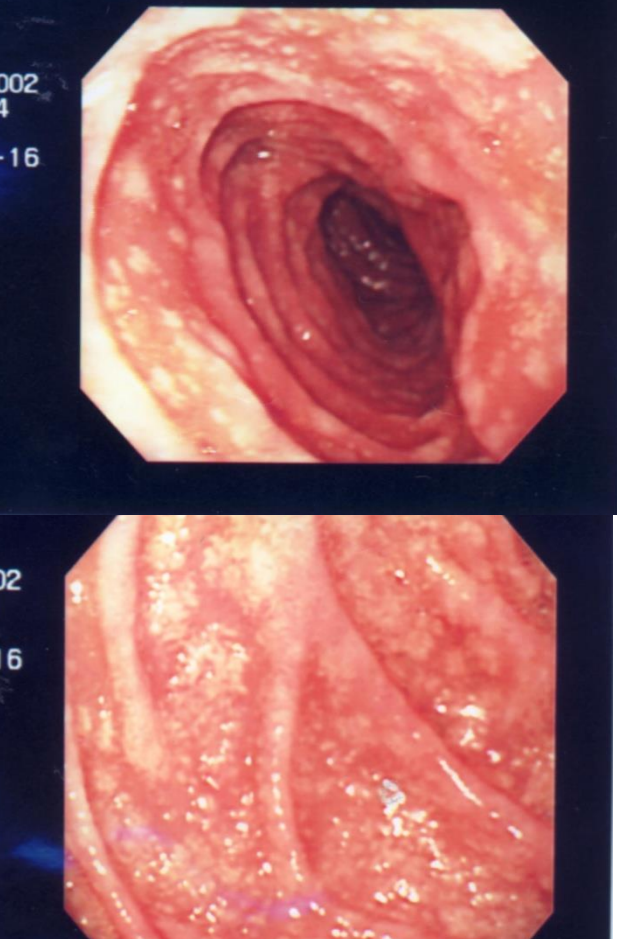
- 33-year-old homosexual
- Productive cough, night sweats, and prolonged fever
- taking HAART for 1 mo
- CD4 increased from 4 to 37 cells/ μ l

M. avium complex
pneumonia



MAC colitis

- Often associated with prolonged fever, elevated ALP, chronic diarrhea
 - disseminated MAC infection
- Ant-MAC therapy:
 - clarithromycin, rifabutin, ethambutol
- Start antiretroviral therapy



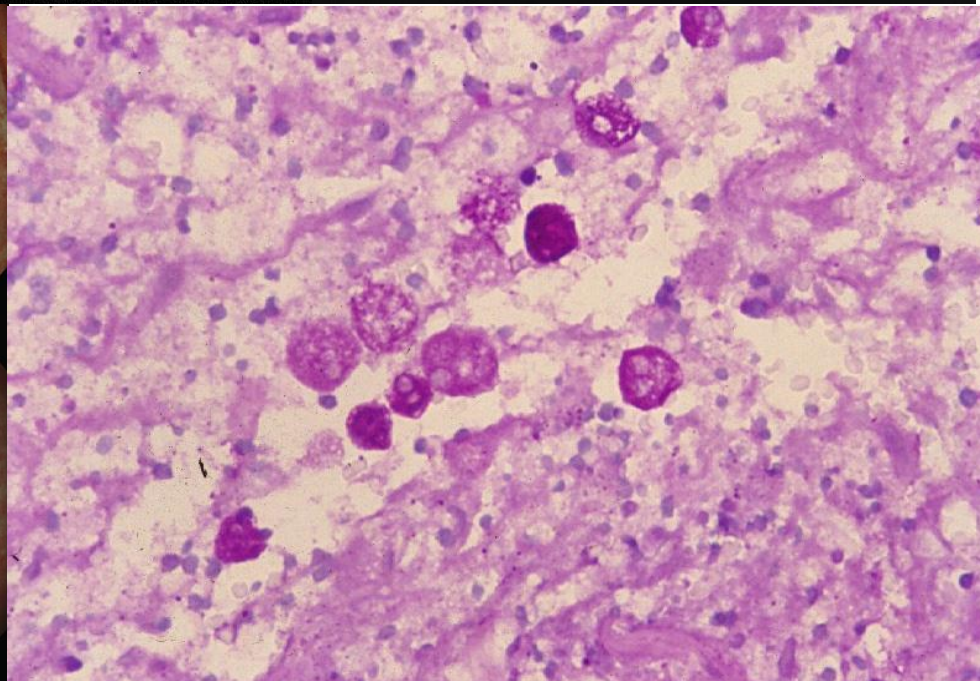
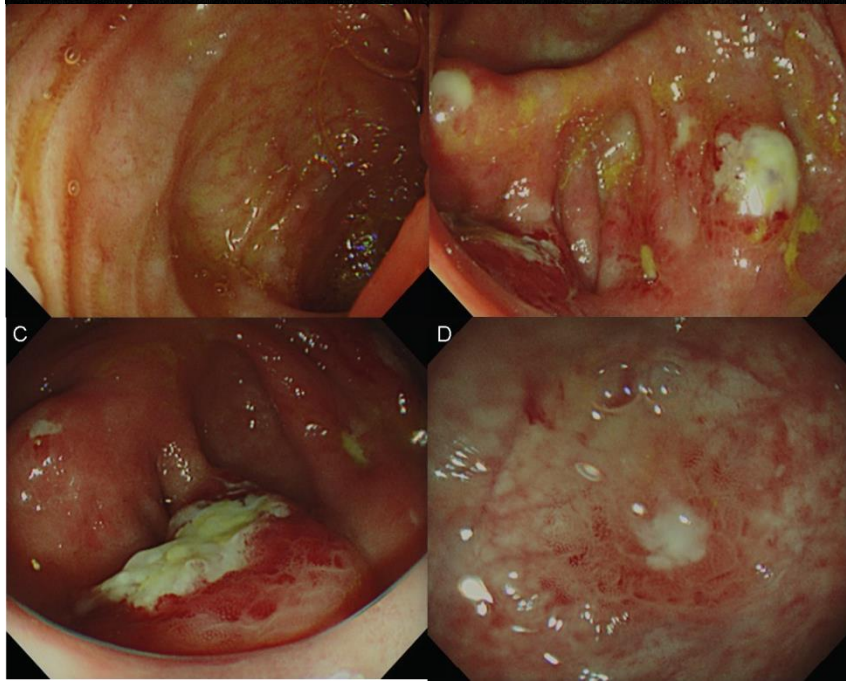
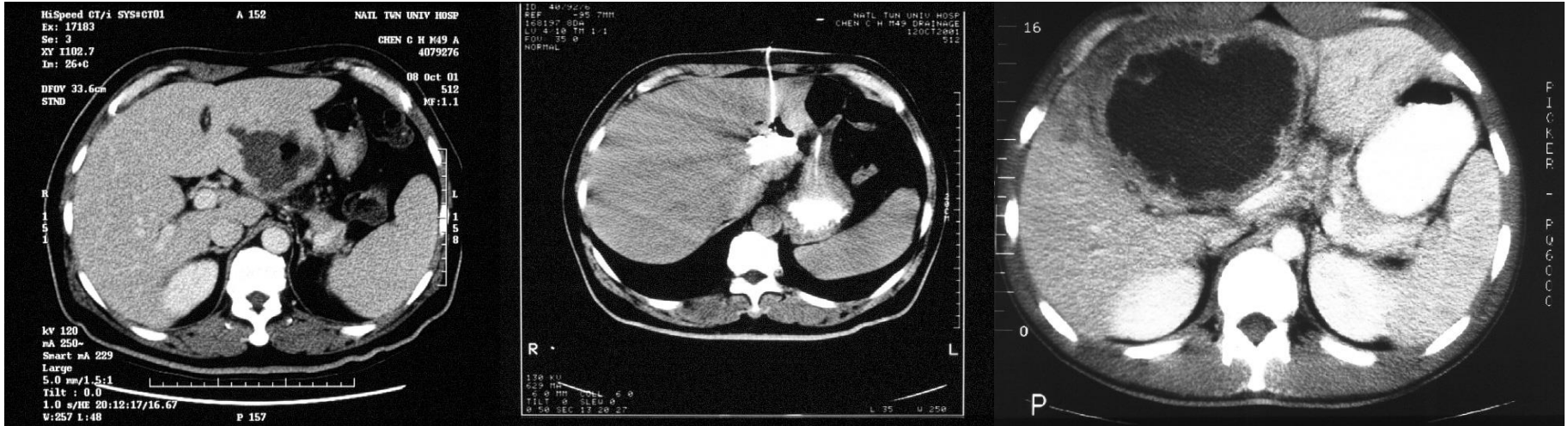
Parasitic infections

- *Entamoeba histolytica*
- *Toxoplasma gondii*
- *Giardia lamblia*
- *Cryptosporidium parvum*
- *Isospora belli*
- Scabies

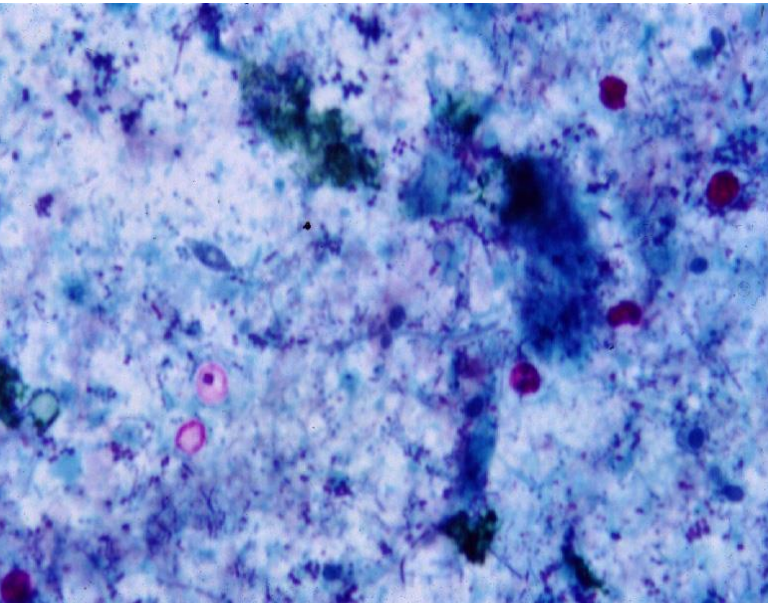
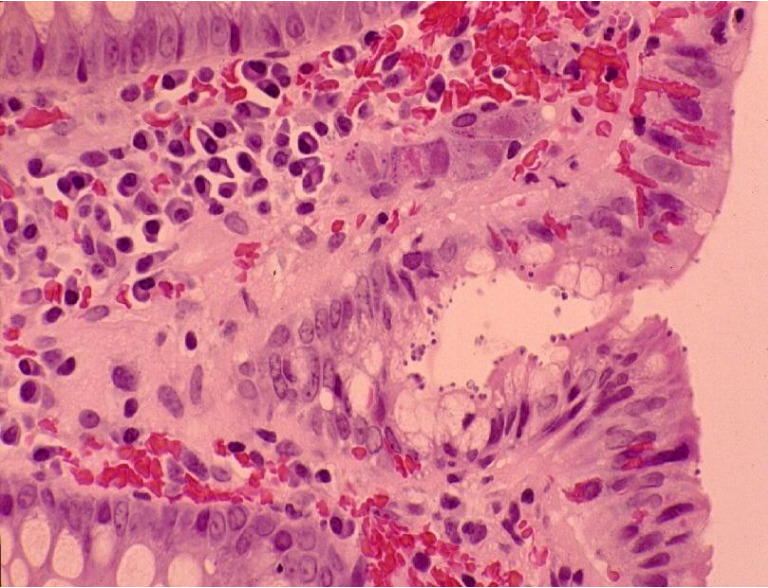
Amoebiasis and men who have sex with men

Hung CC, et al. *PLoS NTD* 2008

Hung CC, et al. *Lancet Infect Dis* 2012



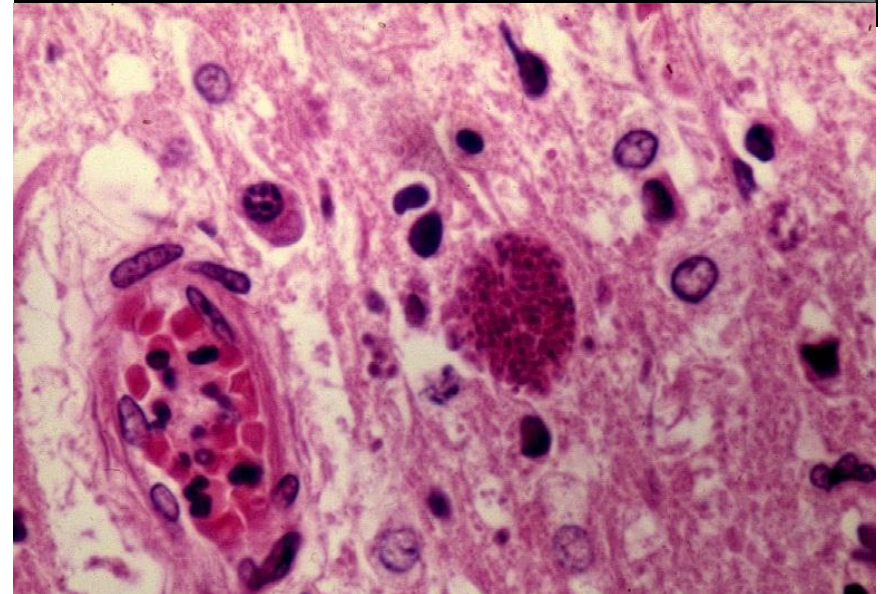
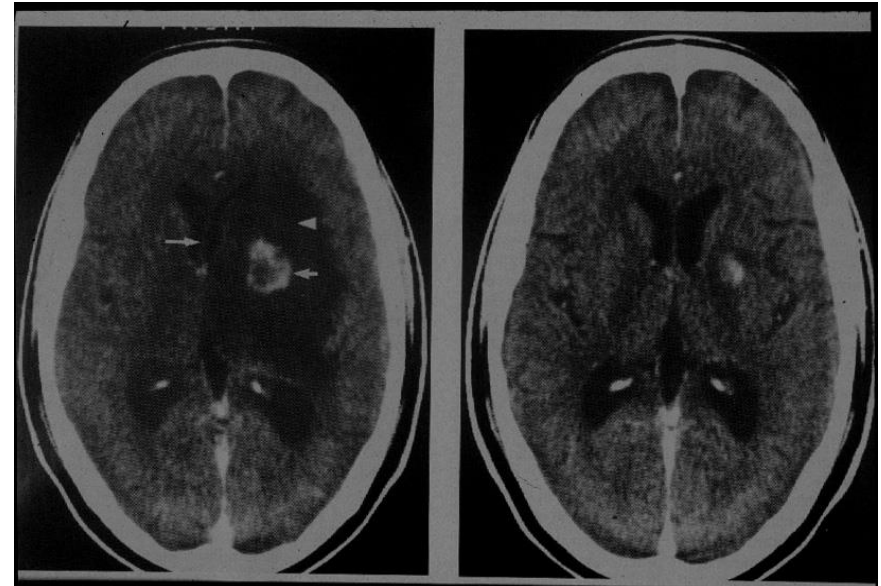
Cryptosporidiosis



- Chronic diarrhea, with wasting
 - Usually afebrile
 - Usually OB (-); rarely pus cells
- Diagnosis
 - Modified acid-fast stains
 - Endoscopy with biopsy
- Treatment
 - Supportive
 - Start antiretroviral therapy

Toxoplasma encephalitis

- Lower seroprevalence in Taiwan
- Presentations:
 - Focal motor deficits developing over days to weeks; encephalitis
- Radiography
 - Multiple, ring-enhanced tumors with perifocal edema
 - Basal ganglia
- Primary prophylaxis
 - TMP-SMX
- Treatment
 - Clindamycin/pyrimethamine
 - Clindamycin/TMP-SMX



Diagnostic approach to intracranial tumors or abscesses

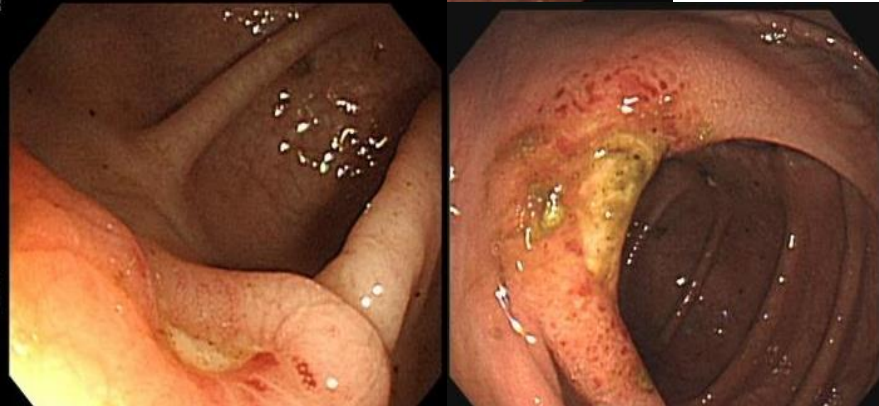
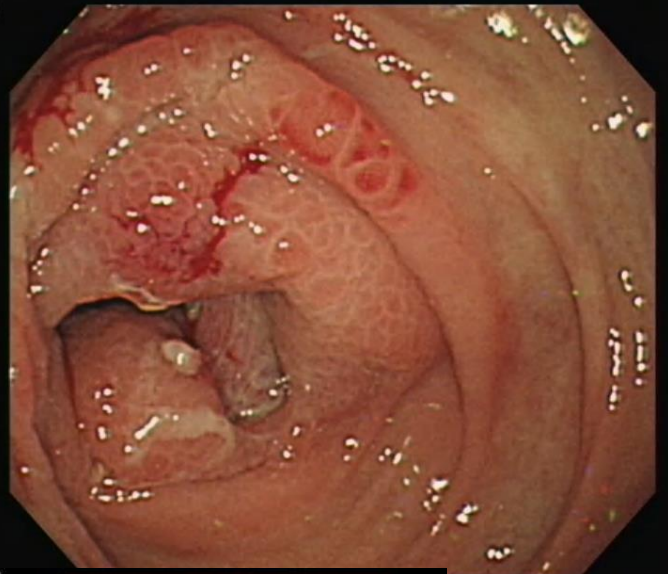
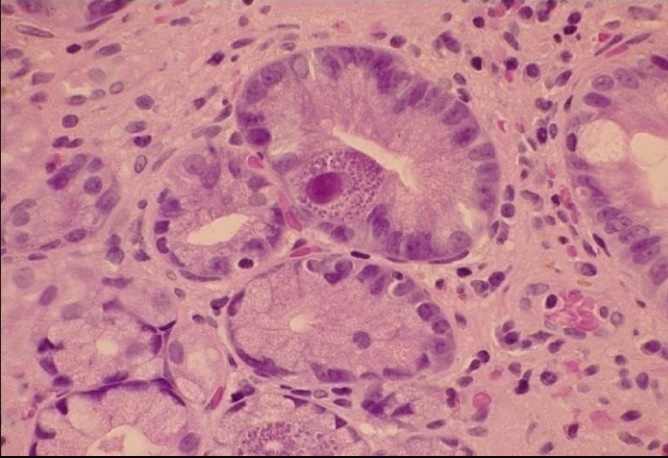
- Serology for *Toxoplasma gondii*
- CSF for cultures (bacteria, *C. neoformans*, *M. tuberculosis*), cytology, *T. gondii* (PCR), EBV viral load, and cryptococcal antigen assays
- Other sites of involvement
- Treatment with clindamycin plus pyrimethamine
- Follow-up of brain imaging 7-10 days later
- Brain biopsy, if no improvement is detected

Viral infections

- Herpes simplex infection
- Herpes zoster
- Cytomegalovirus infection
- Epstein-Barr infection
- Human herpes virus type 8 (HHV-8) infection

CMV colitis

- Chronic diarrhea; often containing blood
- May be associated with fever
- Treatment
 - Ganciclovir
 - Watch for bone marrow suppression
 - Foscarnet
 - Watch for nephrotoxicity; electrolyte imbalance

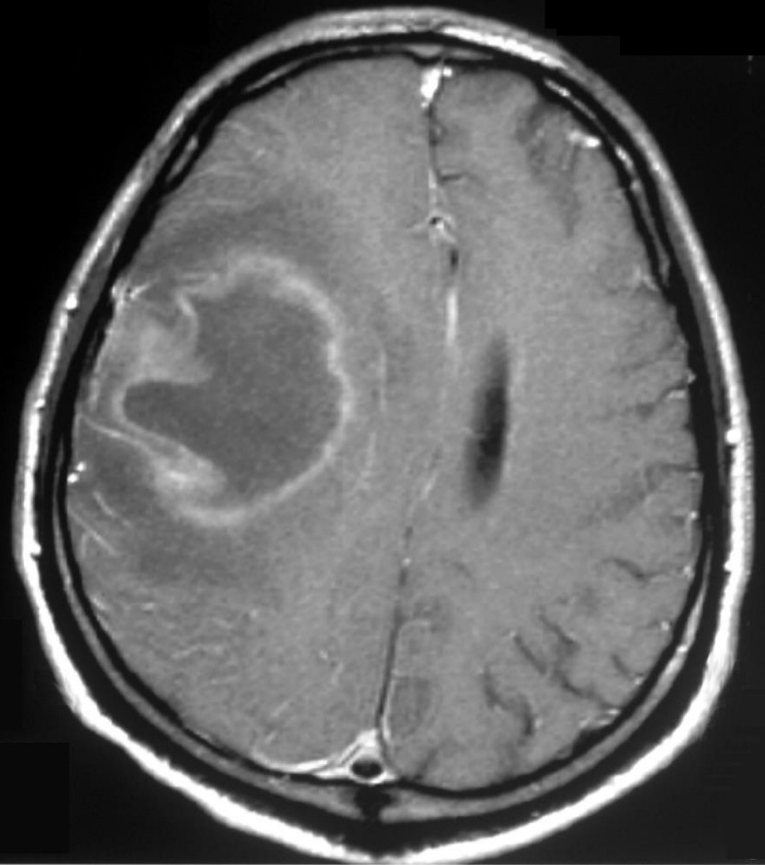
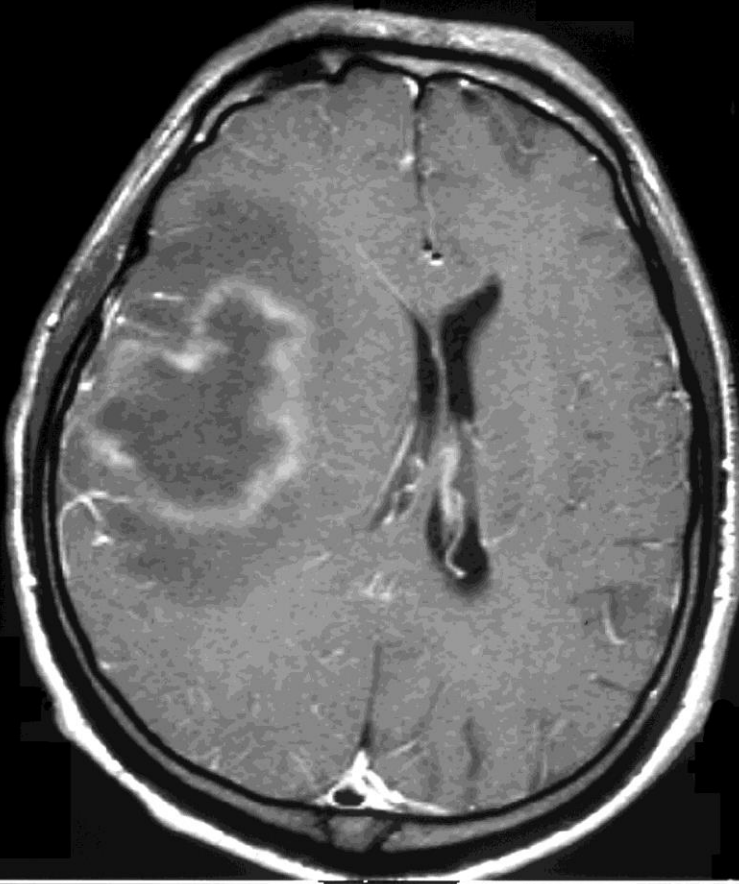


Cytomegalovirus (CMV) Diseases in HIV-infected patients

- Mostly CD4+<50/mm³
- Spectrum of CMV diseases
 - Retinitis
 - Colitis
 - Neuropathy or encephalitis
 - Pneumonitis
 - Adrenalitis
 - Hepatitis
 - Cholangiopathy
- Treatment
 - Ganciclovir 5 mg/kg bid
 - Valganciclovir 900 mg bid
 - Foscarnet 90 mg/kg q12h

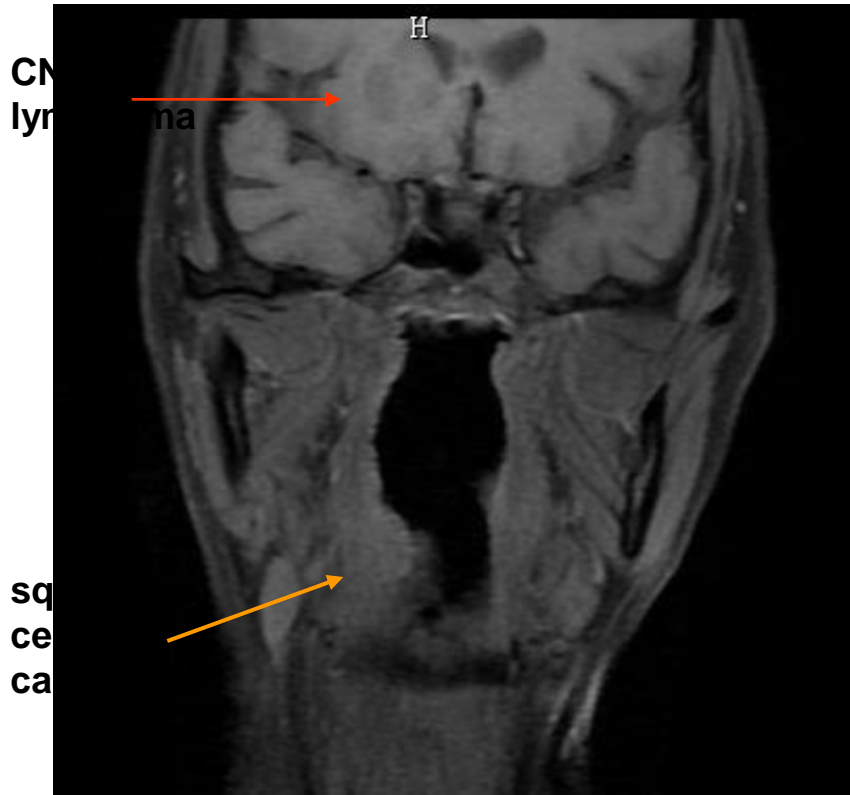


Primary CNS Non-Hodgkin's Lymphoma

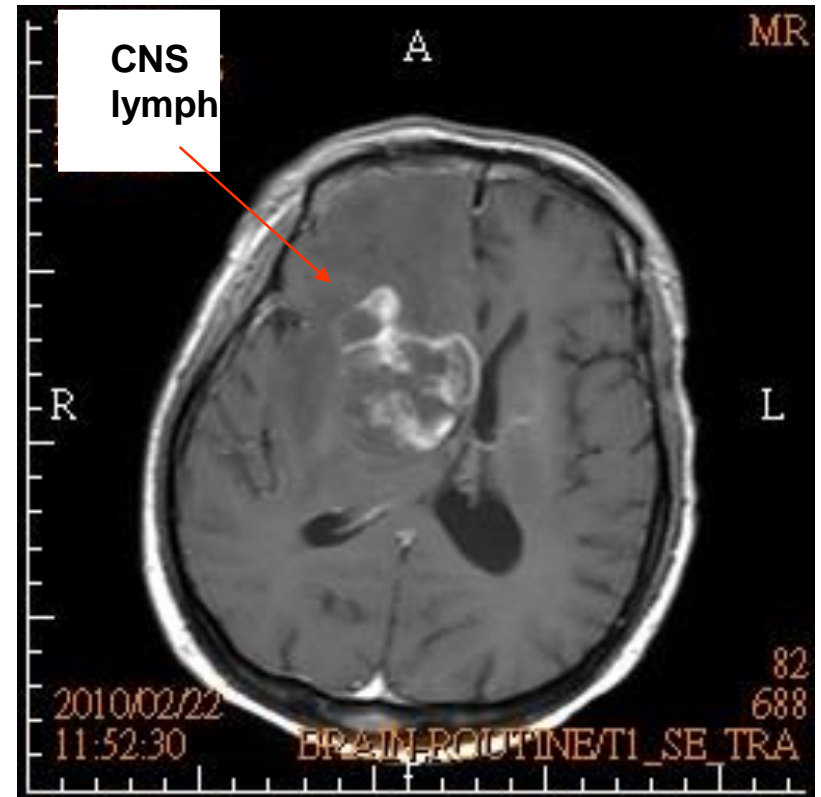


Primary Central Nervous System Lymphoma

2009-11-2 Neck MRI

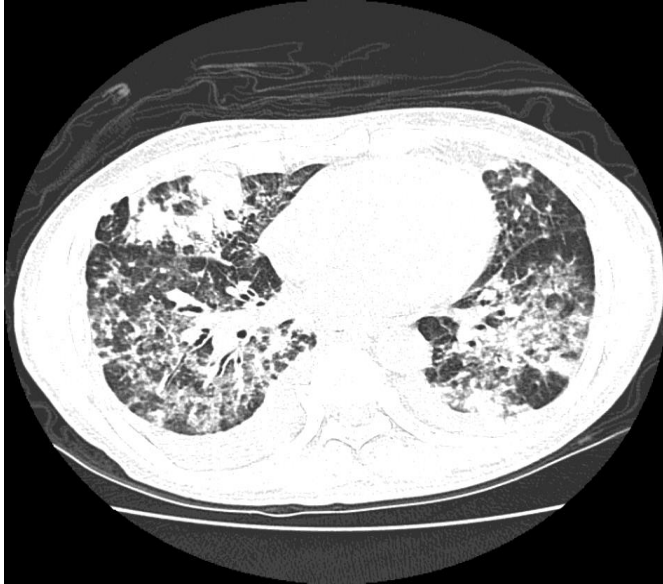


2010-2-22 Brain MRI

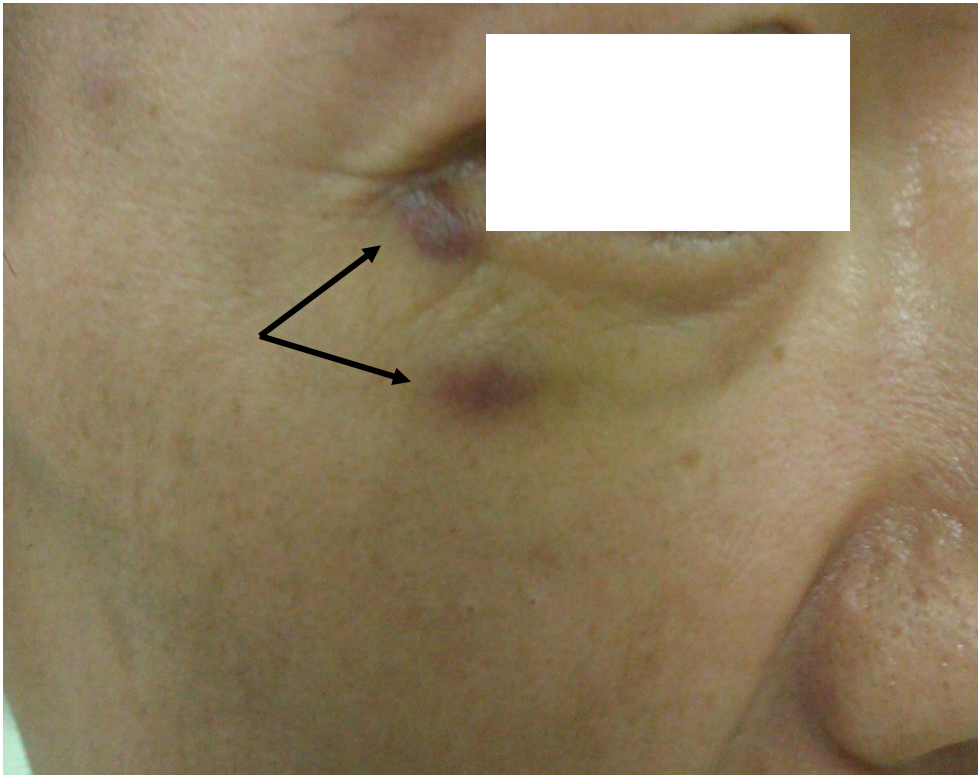
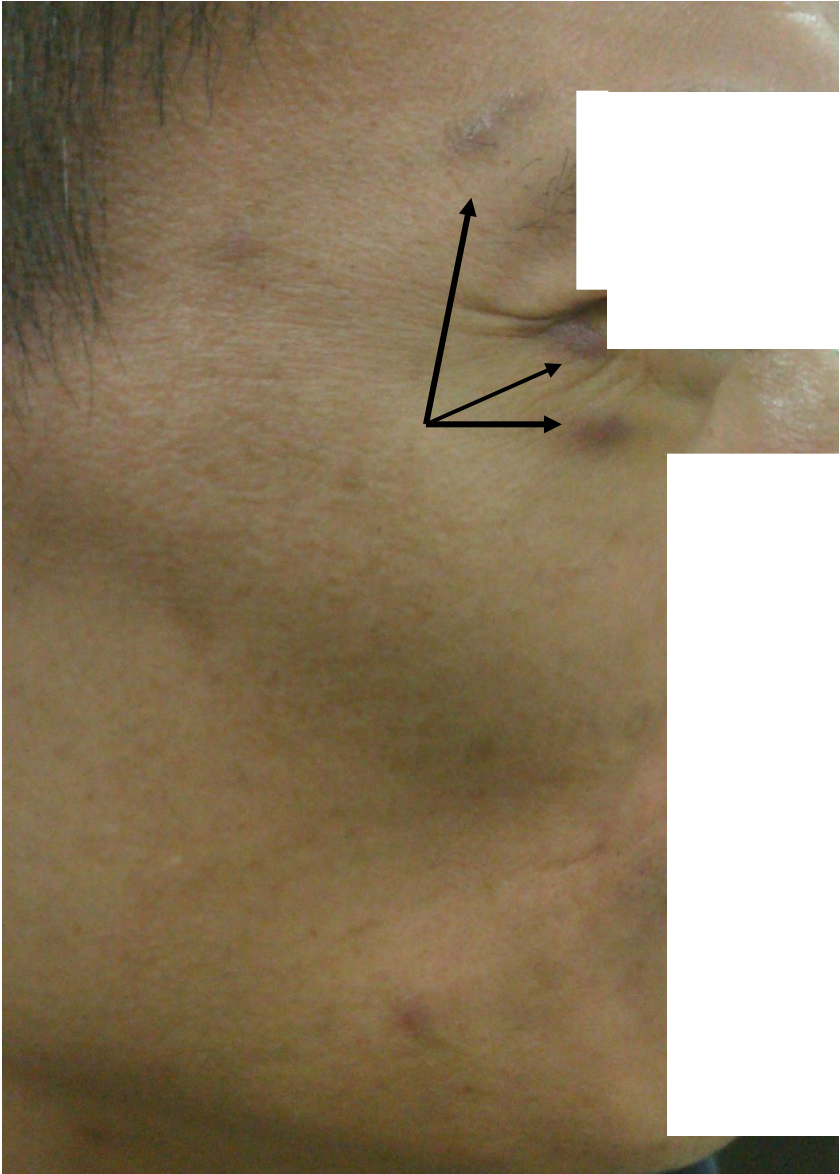


A 37 years old man visited ENT for throat discomfort for 3 weeks, MRI of neck showed mass over hypopharynx, proved squamous cell carcinoma. Oral thrush +, HIV-EIA: + western blot test +, CD4: 36 cell/ul. Received ABC/3TC + lopinavir/ritonavir. He received R/T + C/T for Cancer, regular follow at OPD. Falling down accident on 2010-2-22, brain MRI showed mass over basal ganglion R't, L't hemiparesis +. Brain biopsy proved B cell lymphoma.

Kaposi's sarcoma



Kaposi's sarcoma (arrows)



Coinfections

- Sexually transmitted infections
 - Syphilis: diagnosis; staging; treatment
 - Gonorrhea: antibiotic resistance to quinolones
 - *Chlamydia trachomatis*
- Hepatitis virus infections
 - Epidemiology of hepatitis virus A, B, C, D
 - Treatment of HBV infection
 - Treatment of HCV using directly acting antivirals (DAAs)

Primary syphilis skin manifestation in HIV (1)

A 34 years old man visited our OPD for skin rash over whole body for 4 weeks. He has MSM for 12 years. RPR: 1:64,TPHA>1:1280, HIV-EIA+, western blot test+.



Primary syphilis skin manifestation in HIV (2)



A 29 years old man has HIV for 5 years with regular Antiretroviral therapy (ART), maculopapular skin rash over whole body.

RPR(VDRL)
1:512, TPHA>
1:1280.

Primary syphilis



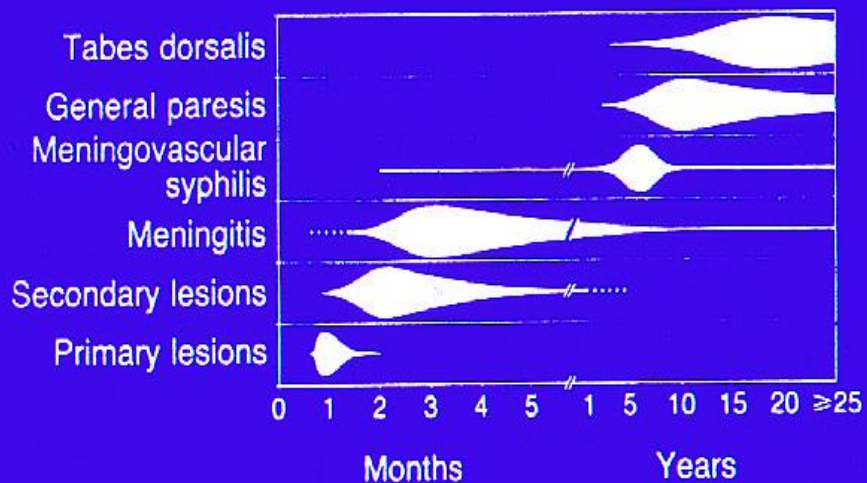


Figure 2. Approximate Time Course of the Clinical Manifestations of Early Syphilis and Neurosyphilis.



Secondary syphilis: condyloma latum



Secondary syphilis skin manifestation in HIV (3)

Patient A forearm



Patient B, hands



Patient B feet

Diagnosis?



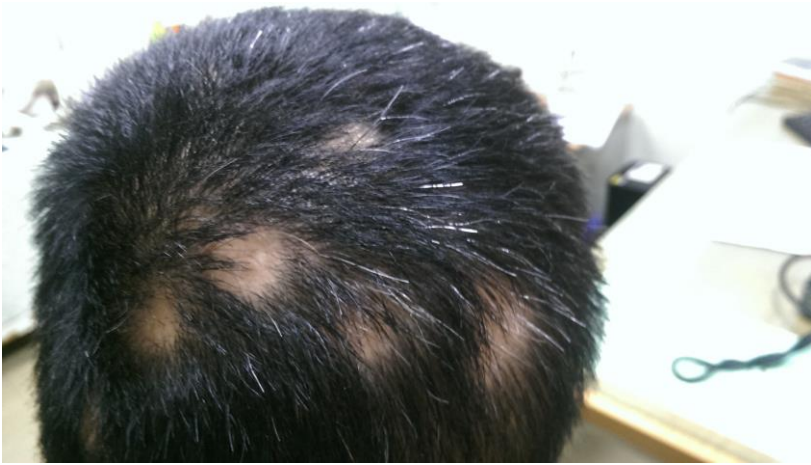
Syphilis

Diagnosis?



Syphilis

Alopecia areata due to syphilis



- RPR=128



Primary infection, latency and recurrence of varicella zoster virus

Disease

3. Varicella (chickenpox)

Encephalitis (rare)

Rash

Pneumonitis

(particularly adults)

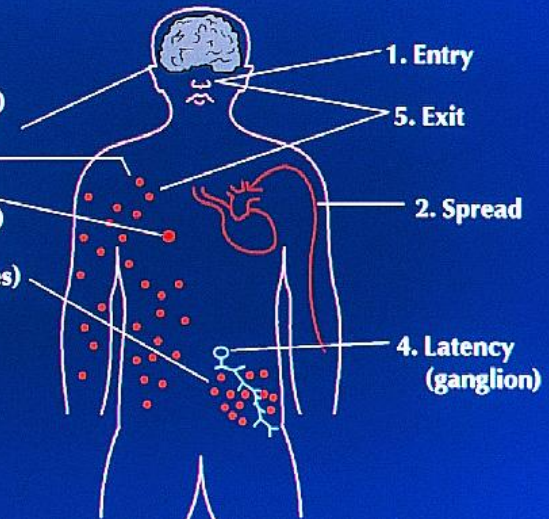
5. Herpes zoster (shingles)

1. Entry

5. Exit

2. Spread

4. Latency (ganglion)

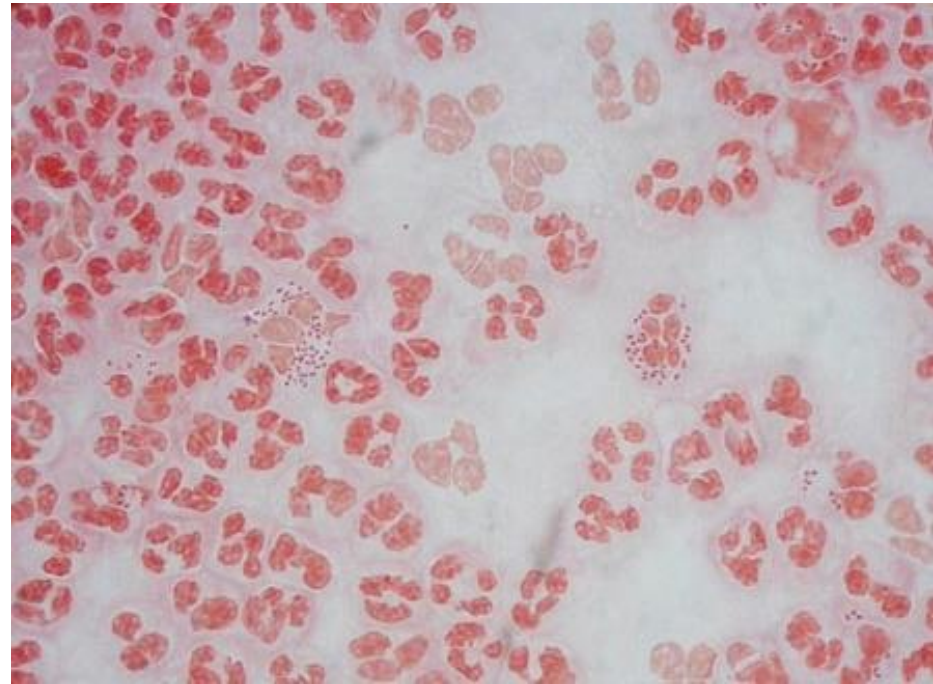


Perianal HSV type 1 infection





Gonorrhoea



Why ceftriaxone 250 mg?

- Increasing numbers of isolates demonstrating decreased susceptibility to cephalosporins in vitro
- Reports of ceftriaxone (125 mg) treatment failures
- Improved efficacy of ceftriaxone 250 mg in pharyngeal infection (which is often unrecognized)

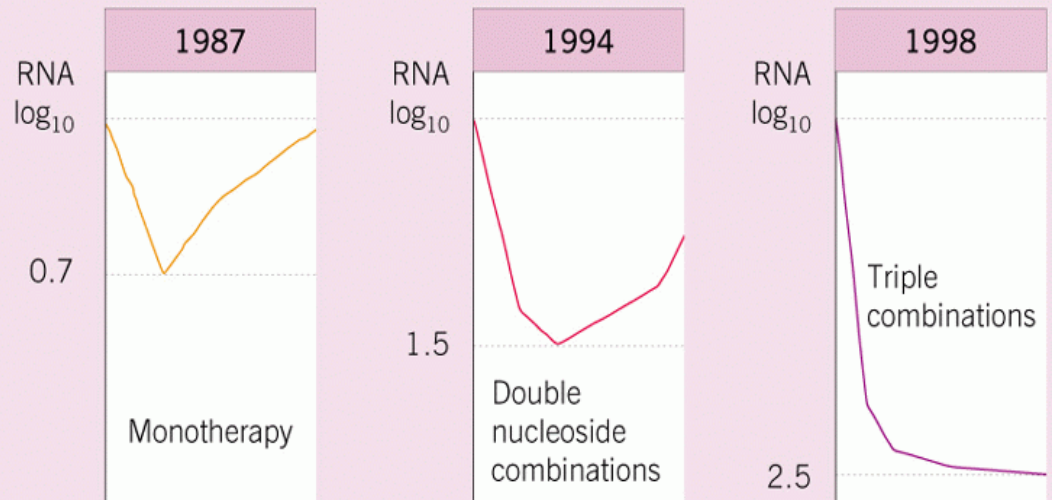
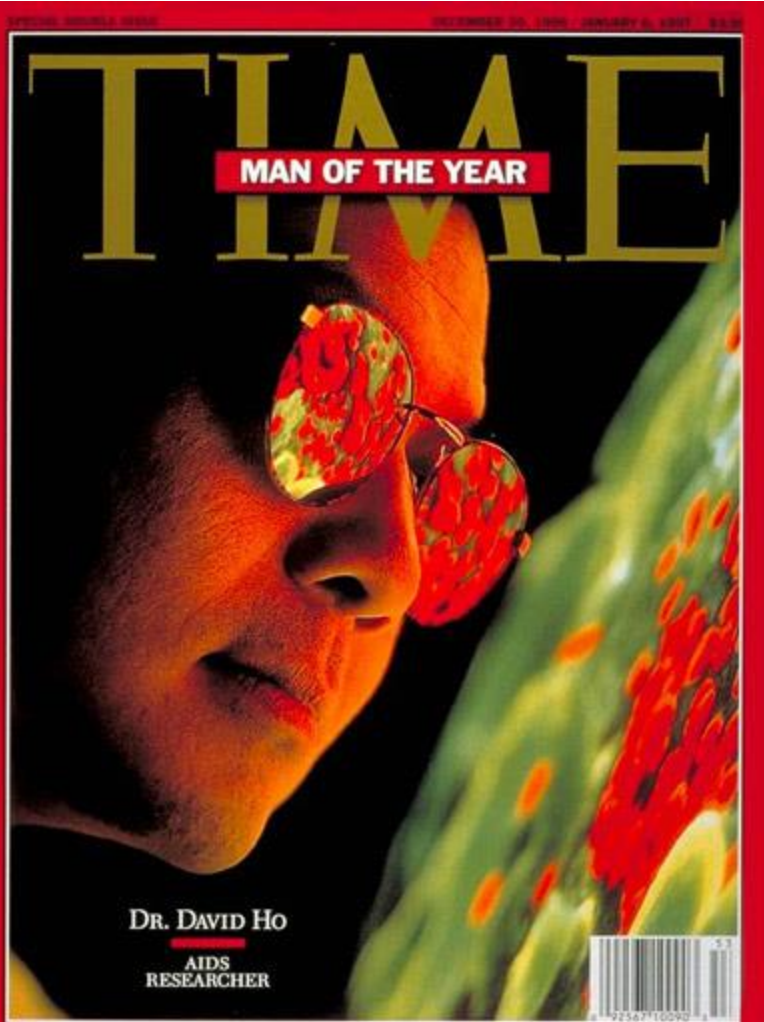


雞尾酒式合併療法

Highly Active Antiretroviral Therapy (HAART)

“Time to Hit, Early and Hard”

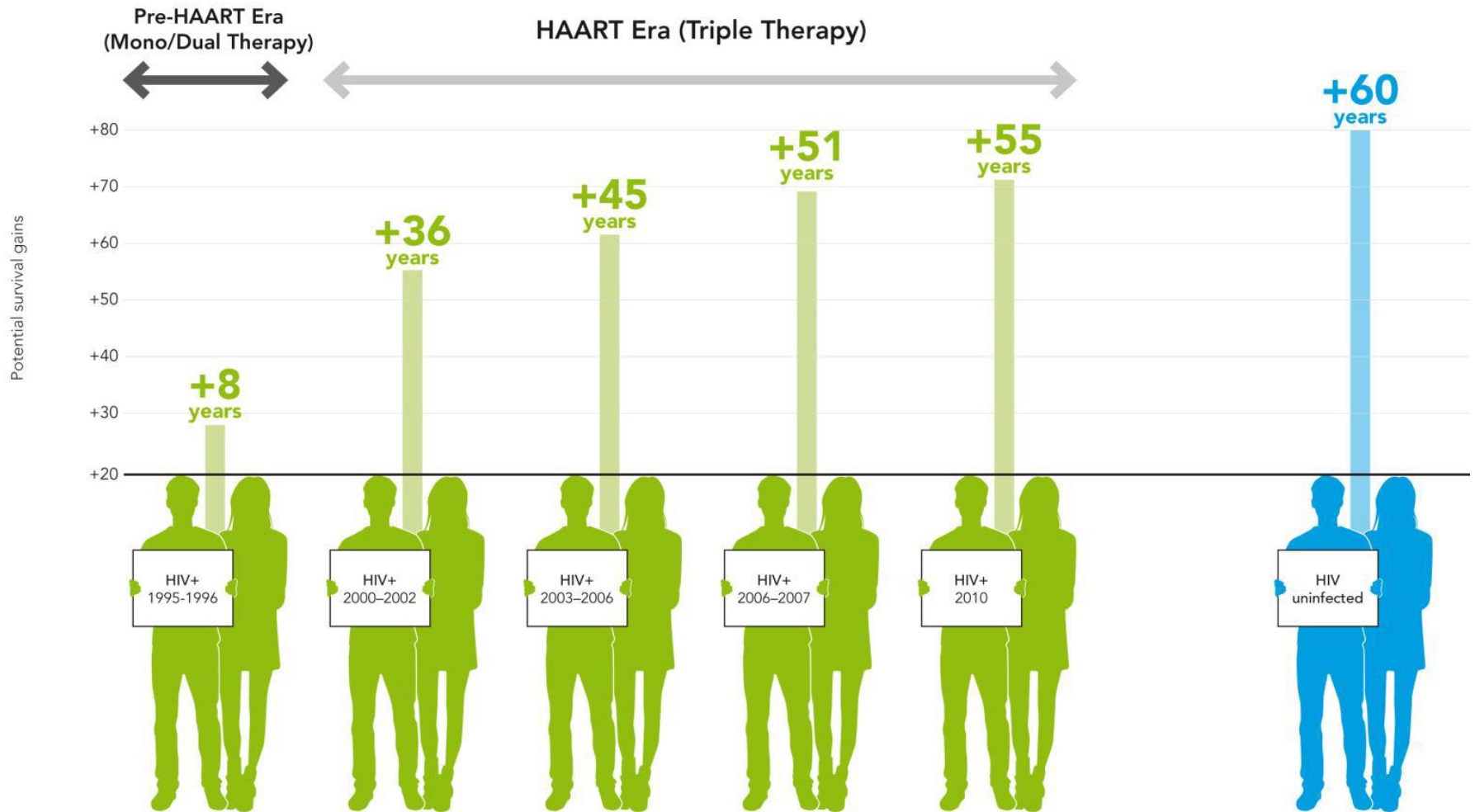
Ho D. *N Engl J Med* 1995; 333: 450-1.



Selecting ARVs for initial therapy

- Primary treatment goals
 - Maximally and durably suppress plasma HIV viral load
 - Restore and preserve immunologic function
 - Reduce HIV-associated morbidity and prolong survival
 - Improve quality of life
 - Prevent HIV transmission

組合式的抗愛滋病毒藥物大幅降低死亡率和延長生存



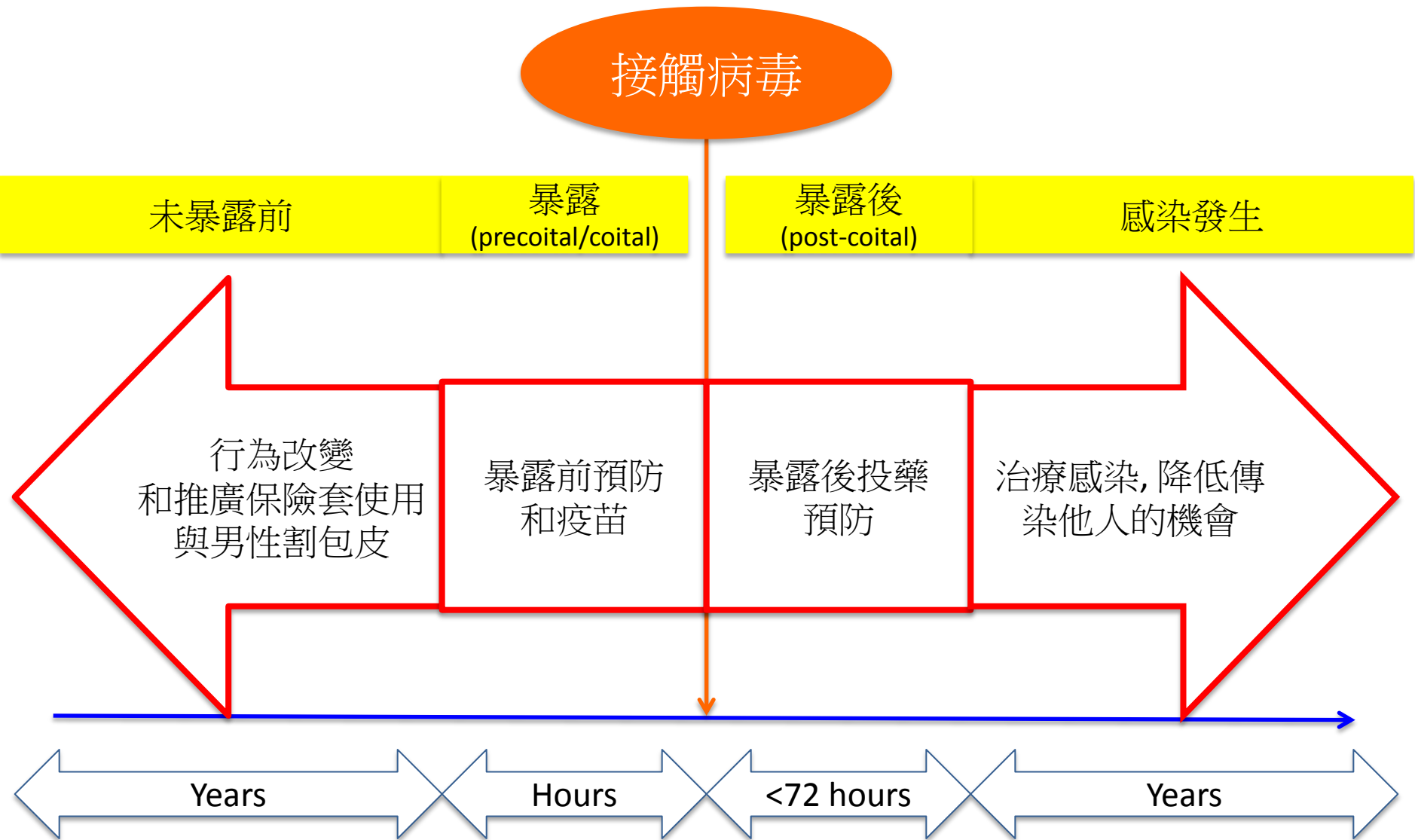
Expected impact of HIV treatment in survival of a 20-year-old person living with HIV in a high income setting (different periods)

When to start cART of HIV-positive persons

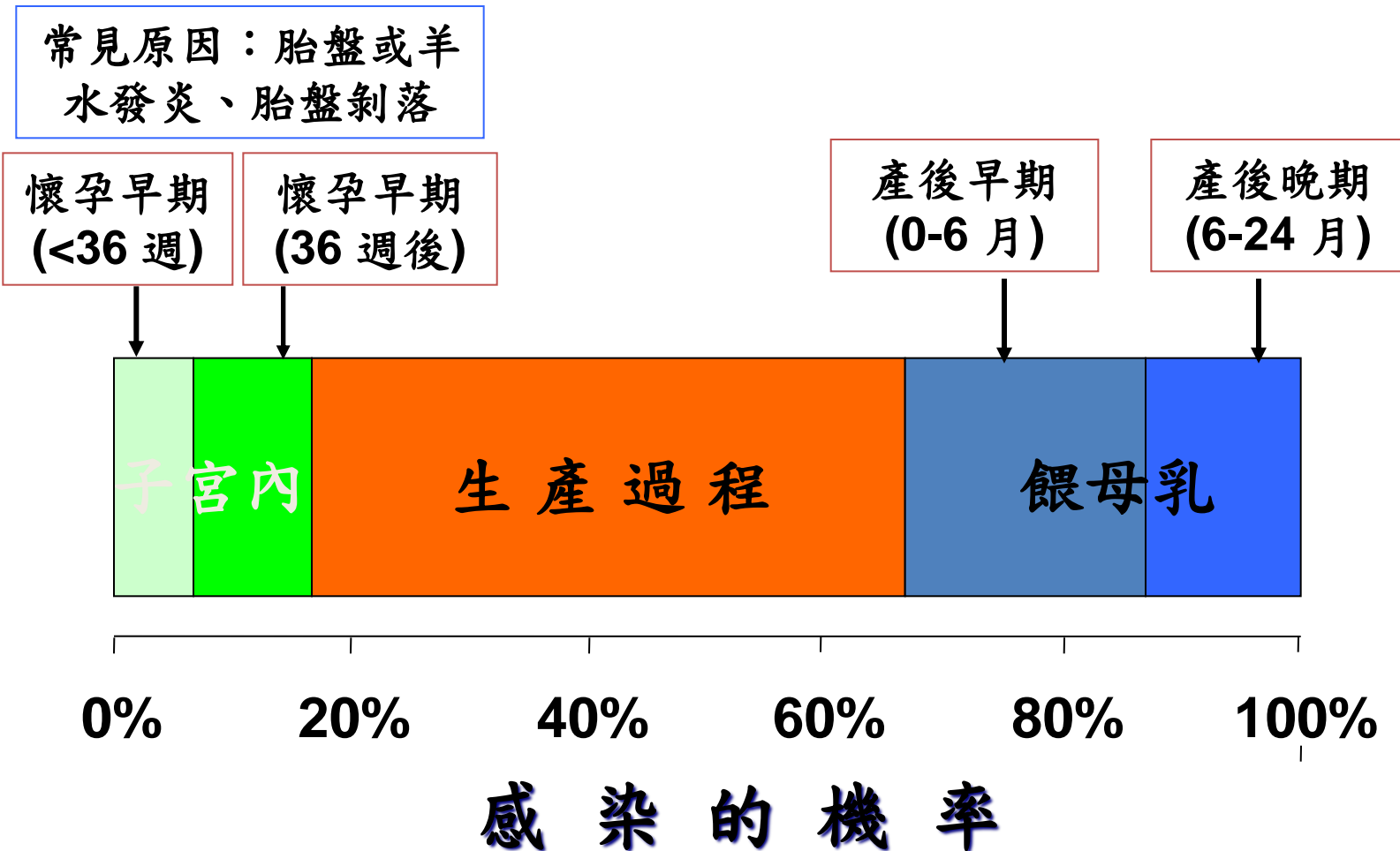
- Assessing HIV(+) persons' readiness to start and maintain ART
- When to start?

Symptomatic HIV disease (CDC B or C conditions)	Asymptomatic HIV infection
Any CD4 count	Current CD4 count
	Any CD4 count
Strong recommended	Strongly recommended

阻止愛滋病毒傳播的時機



愛滋病母子垂直感染發生的時機



醫療環境中暴露愛滋病毒汙染體液後的風險

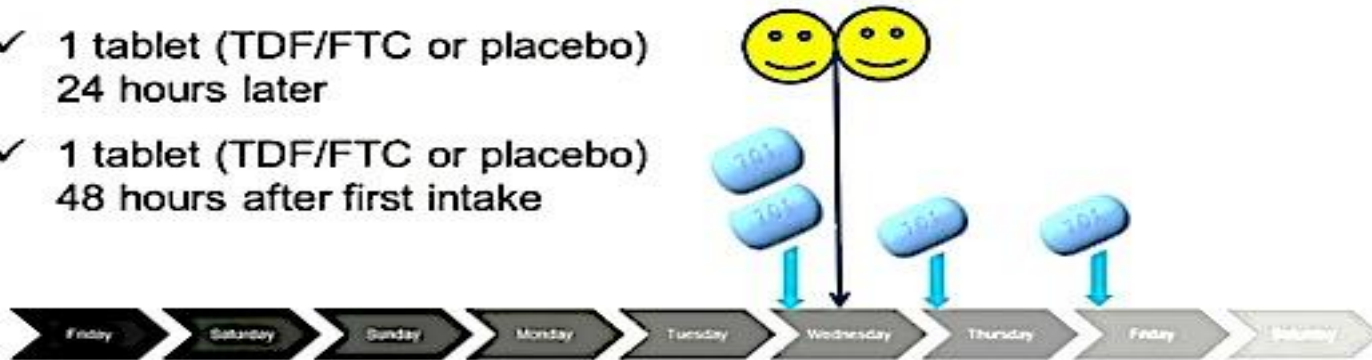
- 由美國疾管局，於33個遭確定有HIV污染的針頭扎到的受感染的醫護人員及665位雖遭針扎但未受感染的對照醫護人員所做的研究, 發現如下:

Risk Factor	Odds Ratio*	95% CI
Deep injury	15	6.0 – 41
Visibly bloody device	6.2	2.2 – 21
Device in artery/vein	4.3	1.7 – 12
Terminally ill SP	5.6	2.0 – 16
AZT PEP	0.19	0.06 – 0.52

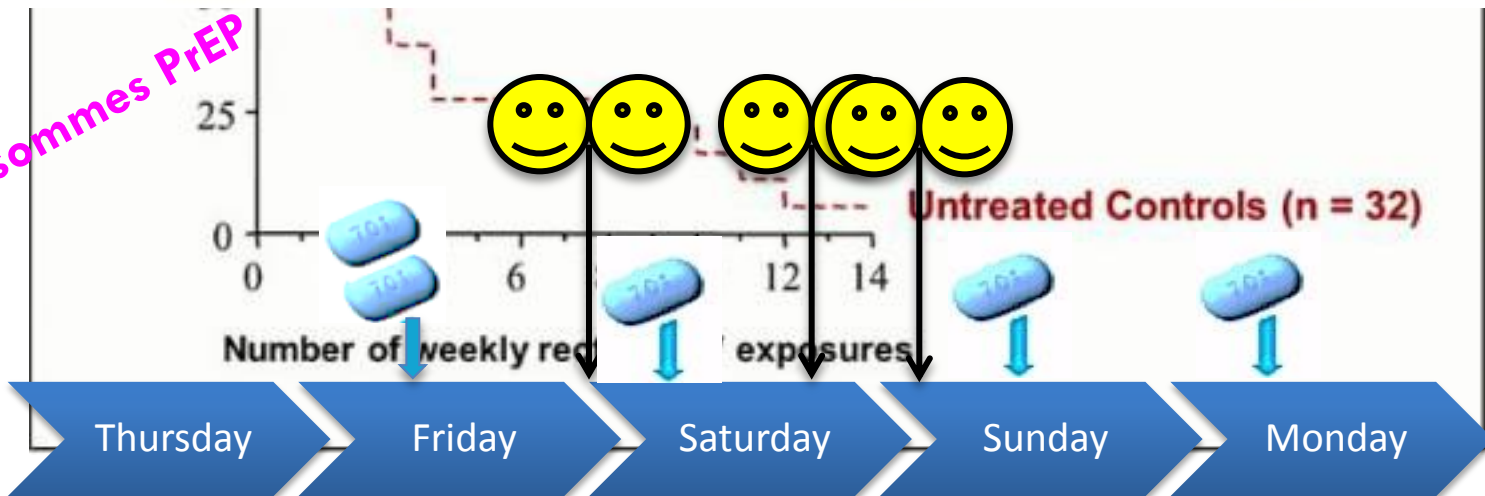
What Does the Future Hold?

Effect of a Double Dose of

- ✓ 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake



Nous sommes PrEP



Thanks for your attention