



**Live and let live**

# Human immunodeficiency virus (HIV) disease

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Edited by : Leen Farouq ☁



# Outline

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- Epidemiology
- Virology
- Transmission
- Basics of Pathogenesis
- Diagnosis
- Acute HIV infection
- Principles of management



Dec 10, 1981 : Gottlieb  
“*Pneumocystis carinii*  
pneumonia and Mucosal  
Candidiasis in Previously  
Healthy Homosexual Men”

4 patients: PCP,  
candidiasis, prolonged  
fever, CMV, Kaposi's  
sarcoma, lymphopenic,  
homosexuals, absent CD4

# Discovery of the HIV (1983)

## WHO DISCOVERED THE AIDS VIRUS?



LUC MONTAGNIER

**O**n a spring day in 1984, Dr. Robert Gallo stood before a press conference at the National Cancer Institute to announce that he had discovered the virus that causes AIDS. What he neglected to mention was that Dr. Luc Montagnier of the Pasteur Institute in Paris had also identified what turned out to be the same virus. The two institutes had previously shared samples; they agreed to publish together and even make a joint announcement. But when the press got wind of the news, the NCI felt compelled to proceed without the French. "If I could relive those days, I wish they had been at the press conference," says Gallo today. "I was a little swept away." It took three years—and the intercession of the French and U.S. Presidents—to smooth the ruffled scientific feathers and work out a settlement in which both researchers call themselves co-discoverers. "It could have happened differently," says Montagnier. "But everybody has their personality."

—By Alice Park



ROBERT GALLO



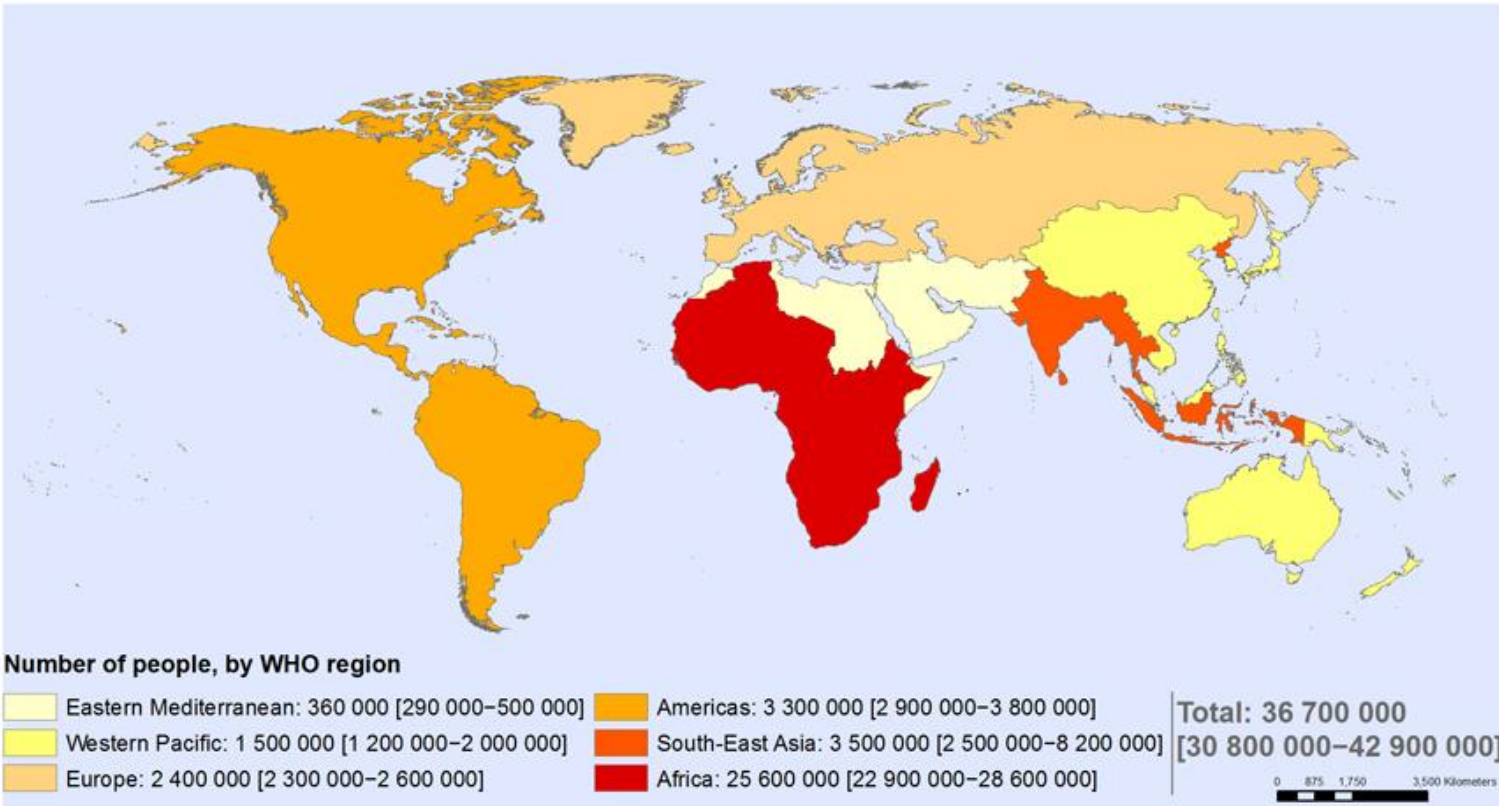
# Epidemiology

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- What is the distribution of HIV?
- What is the trend of mortality?
- What is the trend of incidence?
- Effects of treatment on incidence
- How many people get infected each year?
- Africa and AIDS
- HIV in Jordan

# Africa , South East Asia and India

## Estimated number of people living with HIV, 2016 By WHO region



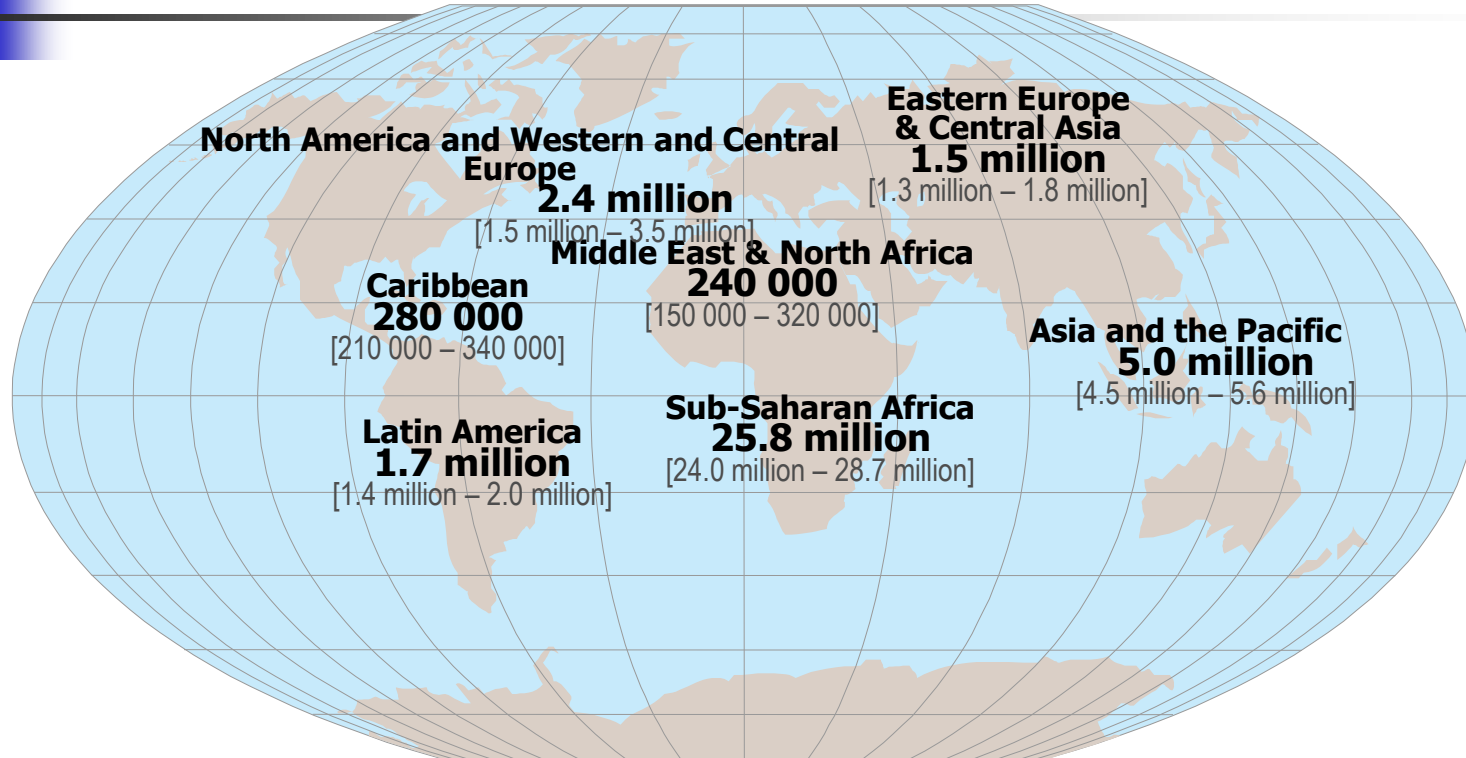
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization  
Map Production: Information Evidence and Research (IER)  
World Health Organization



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# Adults and children estimated to be living with HIV | 2014



**Total: 36.9 million** [34.3 million – 41.4 million]

# Global HIV epidemic – people living with HIV

2017  
Globally  
**36.9 million**  
People living with HIV



**+14%**  
Relative to 2010



# People living with HIV by WHO region (2017)

**36.9** million  
people living  
with HIV globally

 **African**  
**25.7 million**

 **Americas**  
**3.4 million**

 **South-East Asia**  
**3.5 million**

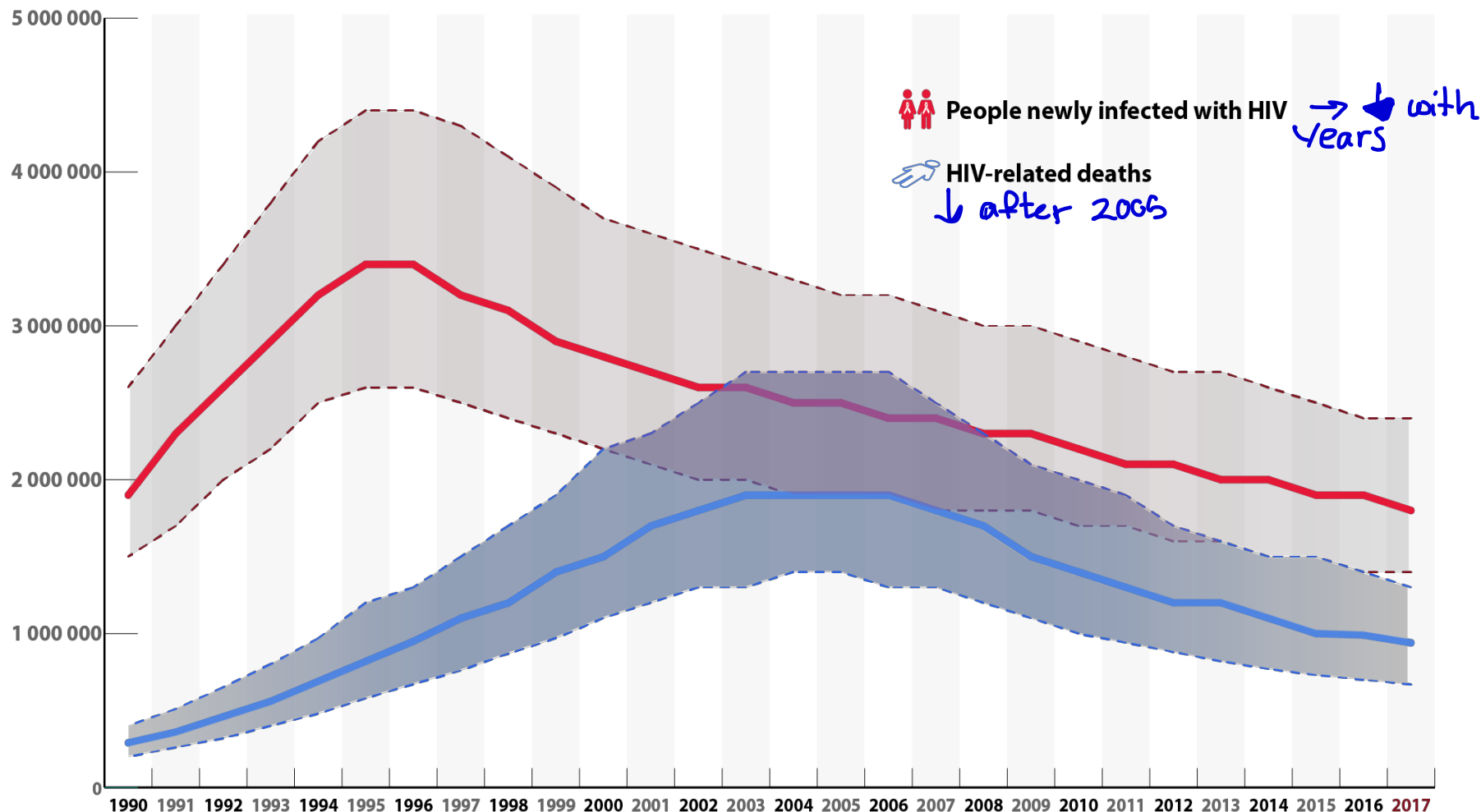
 **Europe**  
**2.3 million**

 **Eastern Mediterranean**  
**350 000**

 **Western Pacific**  
**1.5 million**

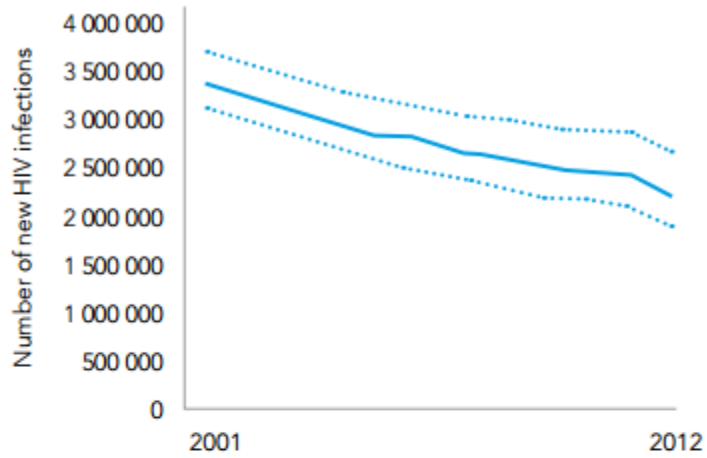
Source: UNAIDS/WHO estimates

# Decline in HIV incidence and mortality over time

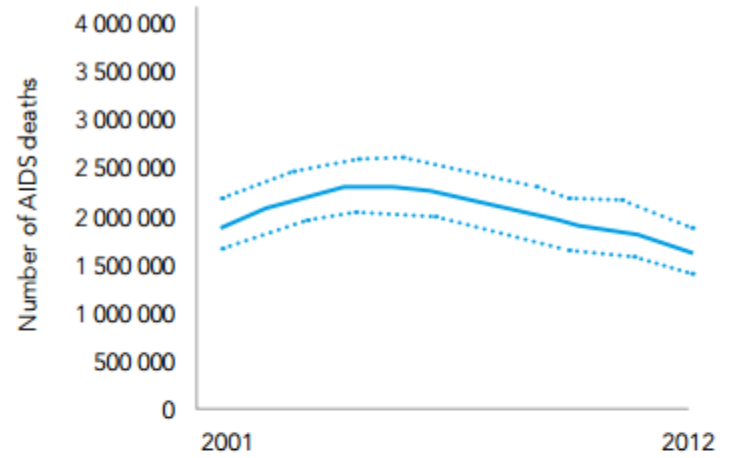


Source: UNAIDS/WHO estimates

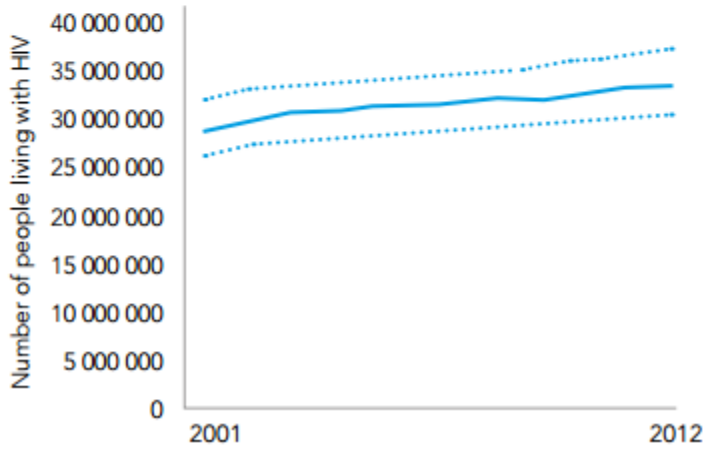
### NEW HIV infection Globally 2001-2012



### IDS Deaths Globally 2001-2012

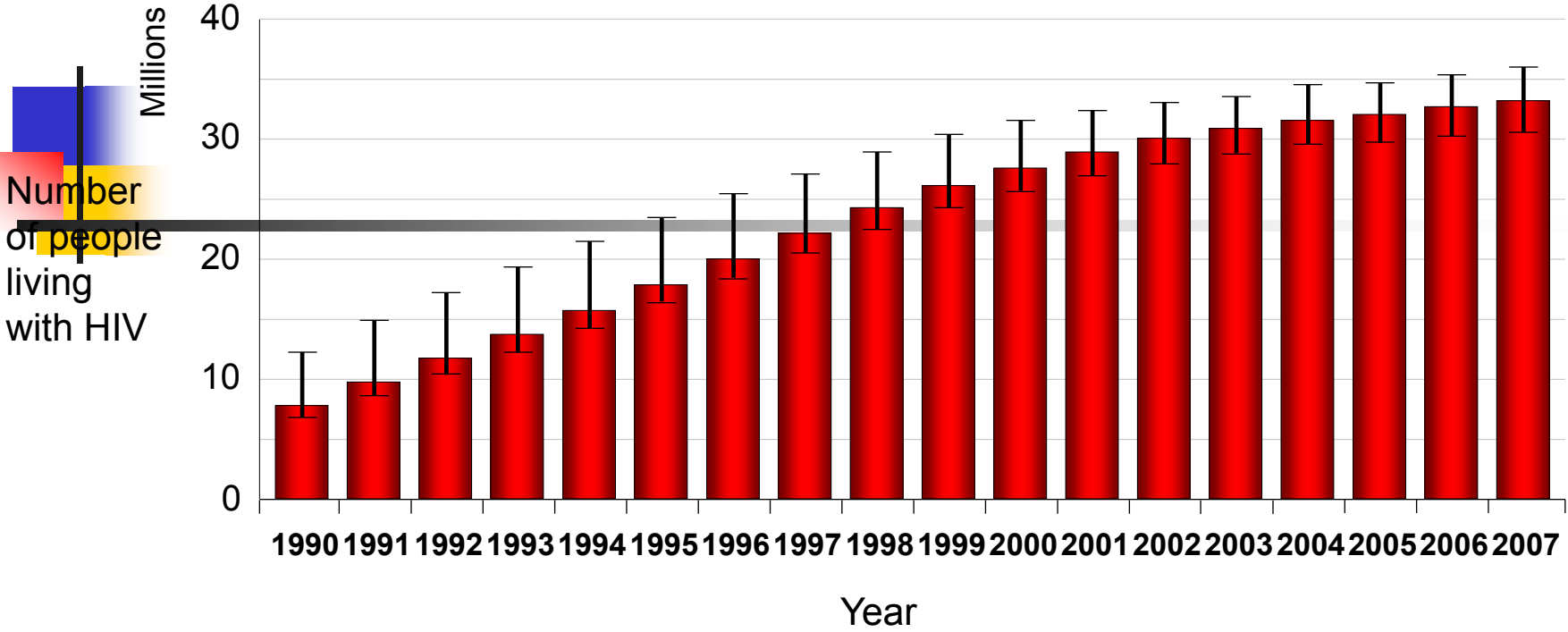


### People living with HIV Globally 2001-2012



- High estimate
- Estimate
- Low estimate

# Estimated number of people living with HIV globally, 1990–2007



 *This bar indicates the range*

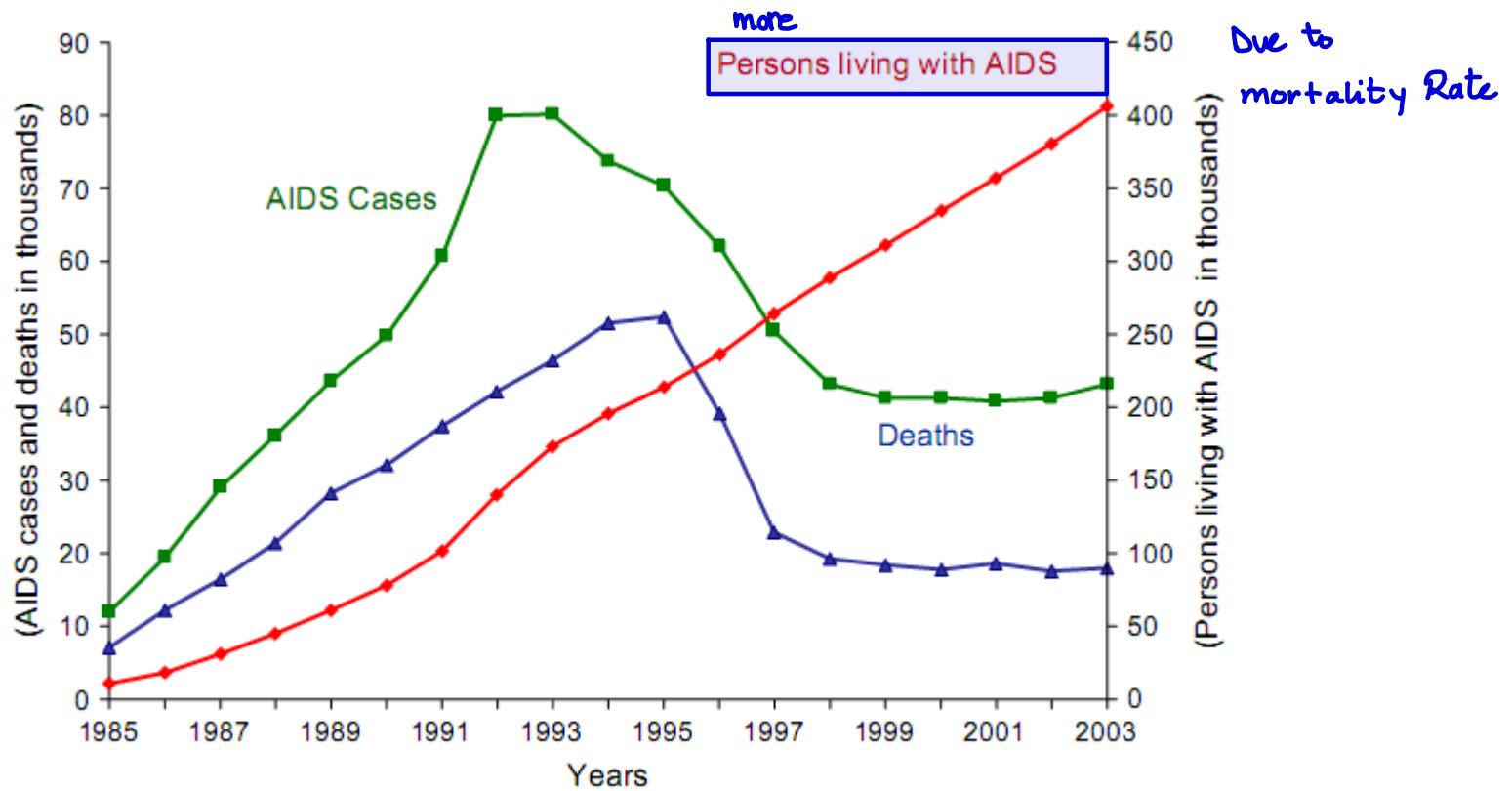
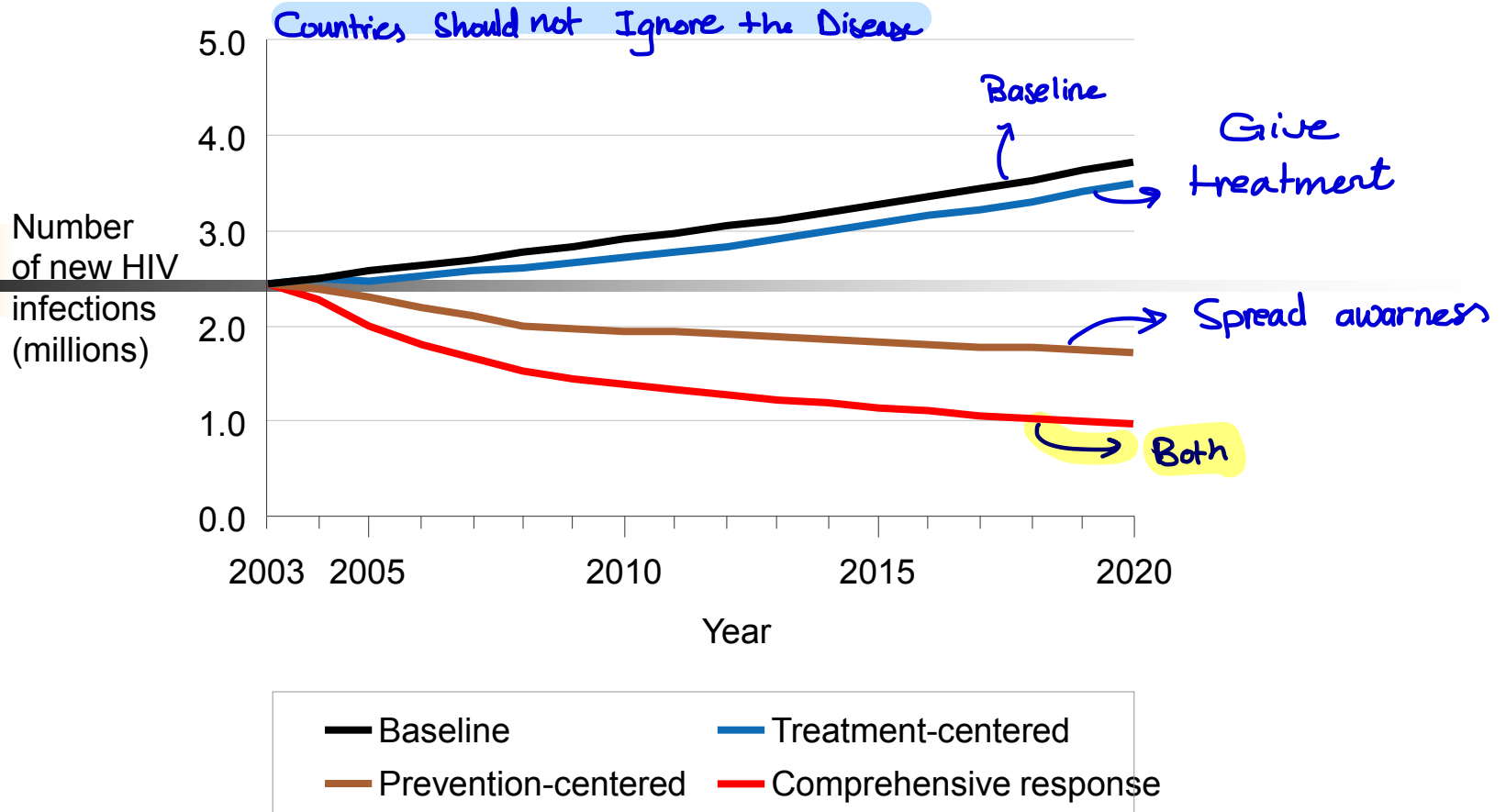


Fig. 3. AIDS cases, deaths, and persons living with AIDS in the United States, 1985–2003.

# Impact of three scenarios on HIV infection in sub-Saharan Africa, 2003–2020





# Huge burden...

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- 5 million new cases / year
  - 5600 new HIV infections/day in 2014
    - 600 in children
    - 5,000 in adults
    - 50% were women
    - 30% were 15-24 years High Risk group
    - 95 % in developing countries
    - 66% in subsaharan Africa
  - 16 million children were orphaned
  - 14 million orphaned in Africa
- these Women will get Pregnant and transmit the Infection to her children*

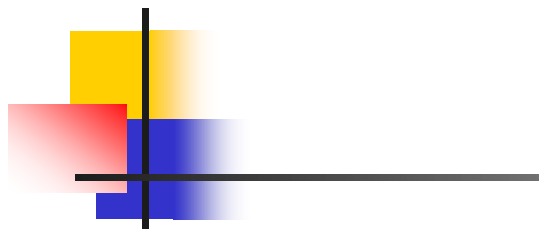
# Africa, the burning continent

- 8% of adults < 45
- > 80% of prostitutes
- In 2013: **70% of the global total**
- **Life expectancy < 40 years**

1. multiple sexual partner
2. STDs:
3. Prostitution
4. mother to child transmission

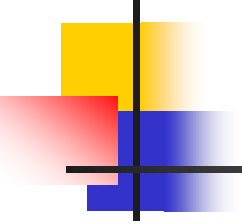






A 15 year old boy in Botswana has 90% chance of dying of AIDS

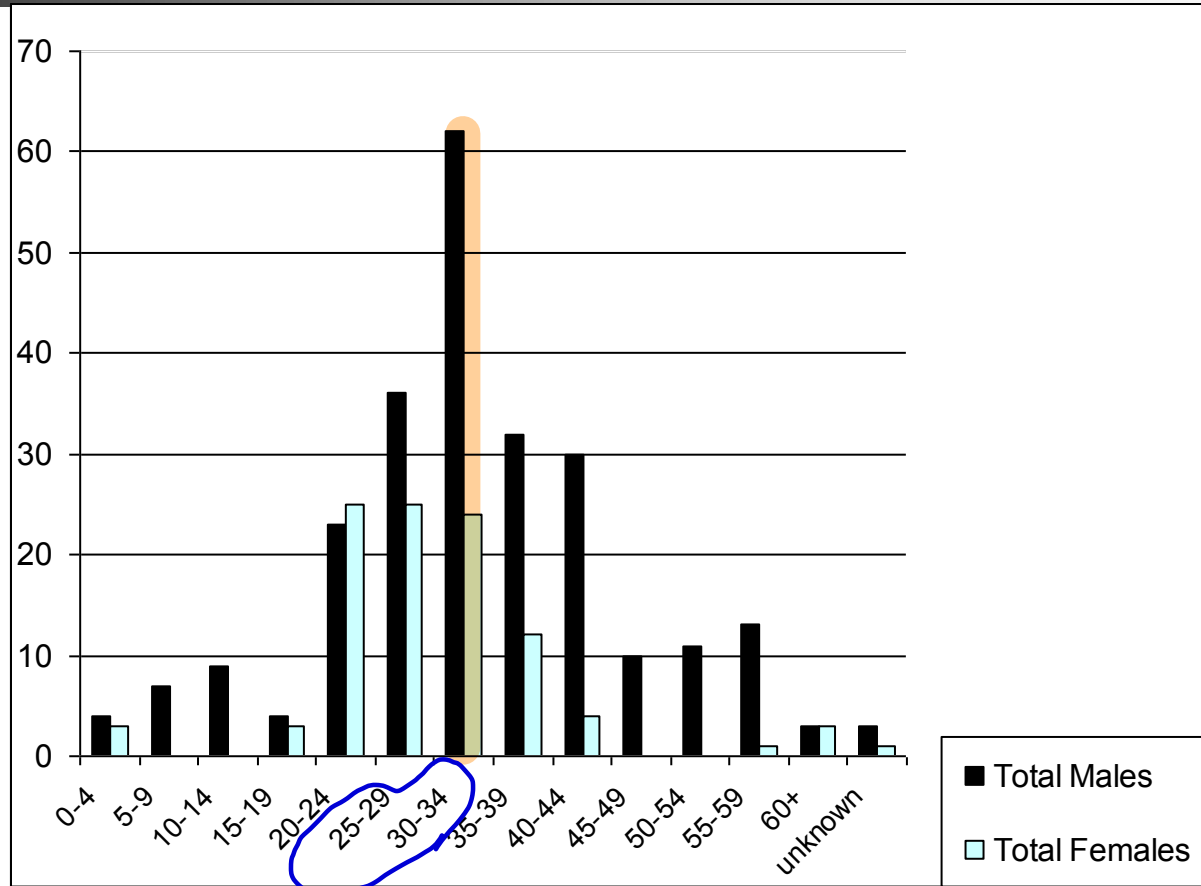


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- 
- “...The AIDS epidemic continues to explode in India, China, Russia, and eastern Europe and may be more destabilizing than international terrorism”

M. Scheld

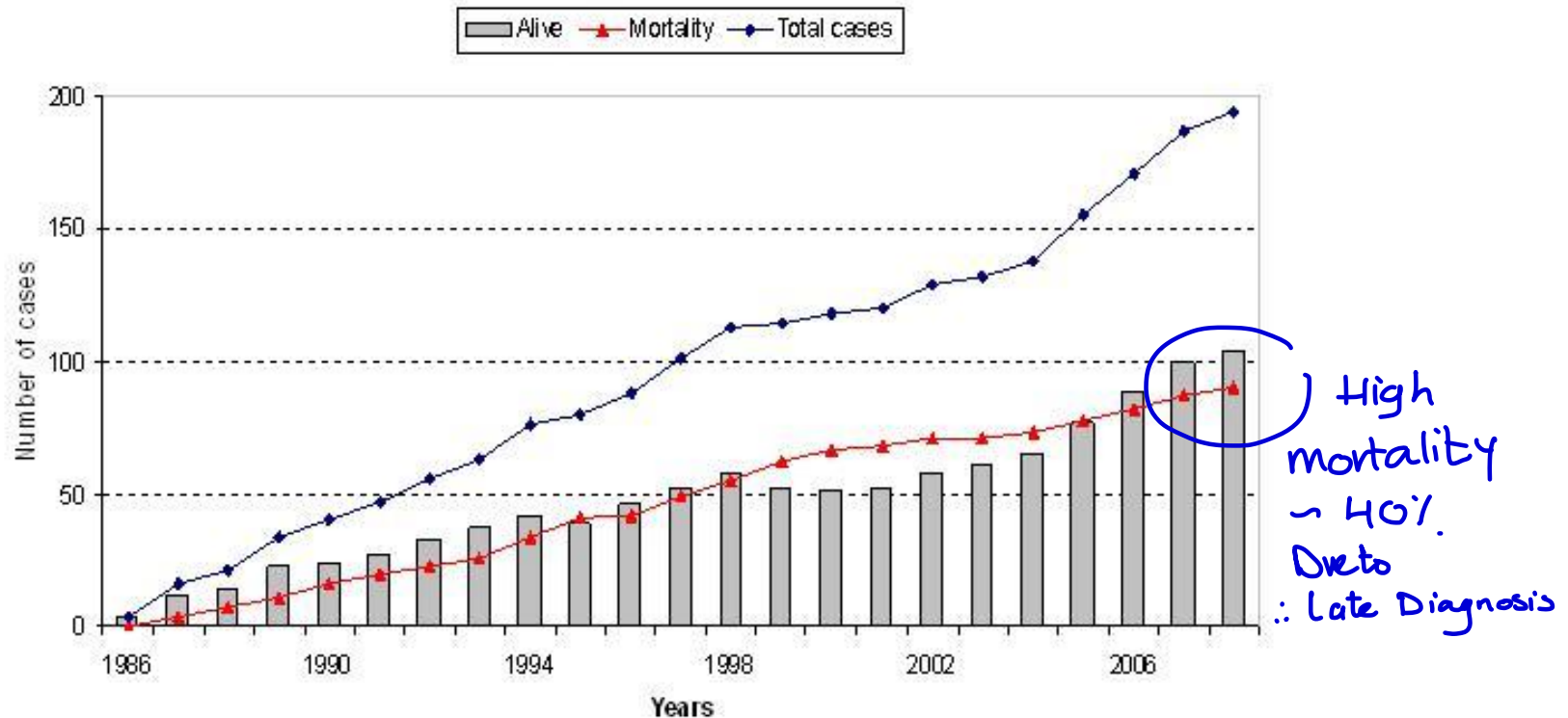
- male > female
- Extreme of Age (Elderly and Children) are Infected

# HIV in Jordan (2010)



High Risk Group (25-35)

# HIV – Jordan: mortality (2010)



# Transmission

- Sexual intercourse
- Mother → child
  - \* during Delivery
  - So, → Cesarean section is Preferred
- IV drug use
  - \* Breast Feeding
- Blood transfusion
- Needlestick injury 0.3%

\* If Blood get over intact skin <15 min → no Infection

\* Damaged skin (Burn, Blisters, psoriasis) → there is Risk of Infection



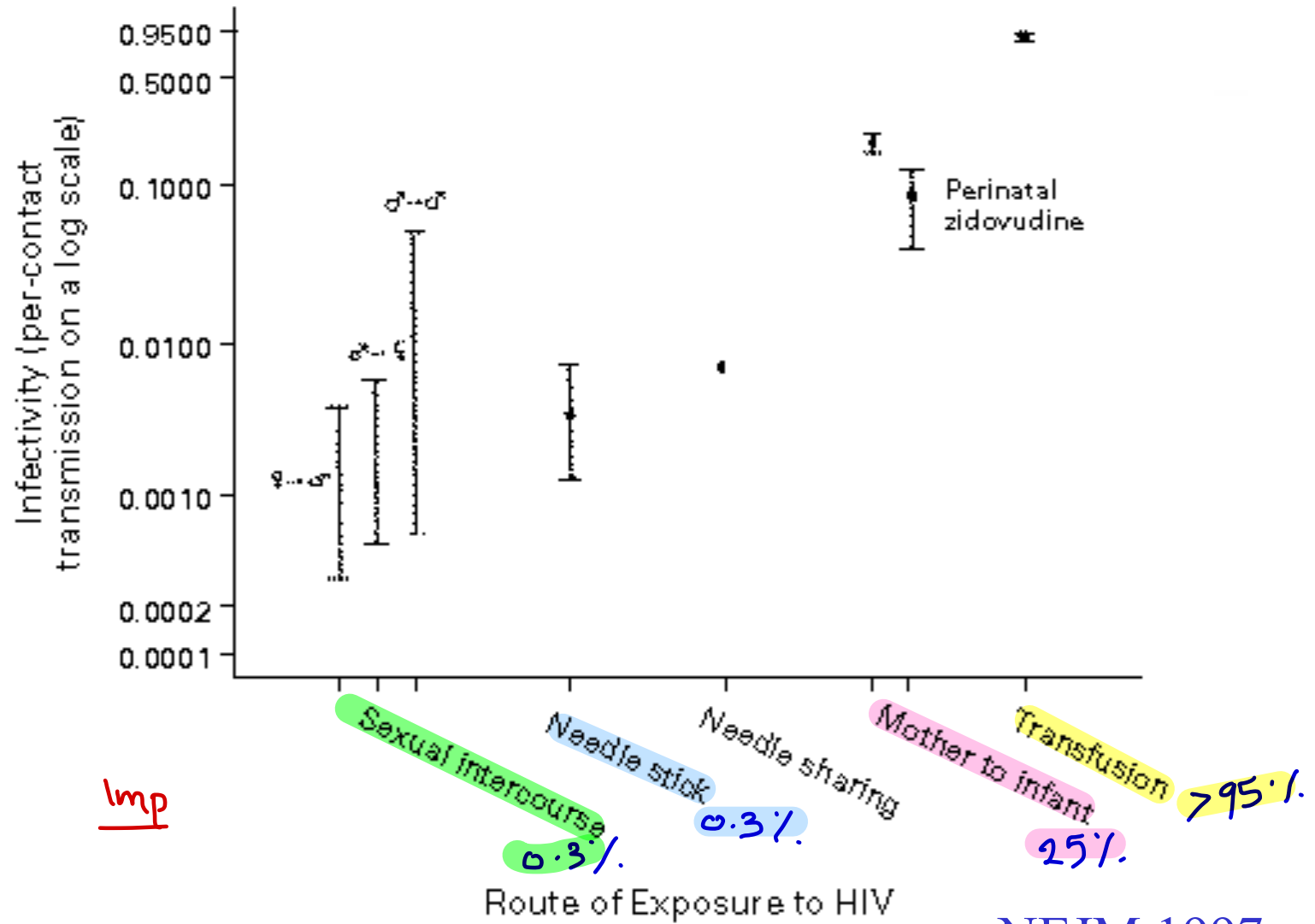


# All body fluids...

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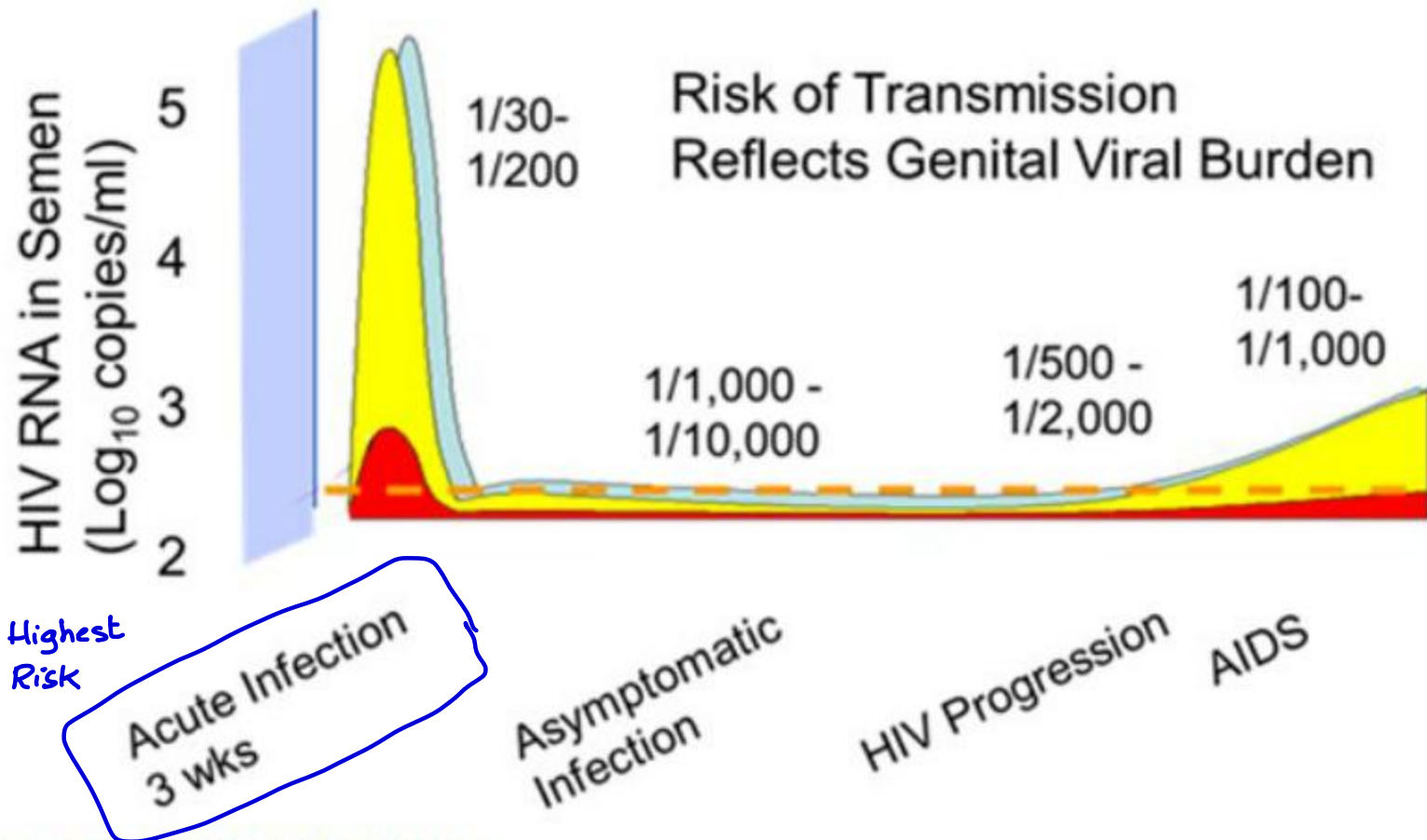
- Blood: PRBCs, FFP, cryo., clotting factors, platelets, IVIG *Good Blood Banking very important*
- Semen
- Vaginal secretion
- Saliva → *the least Common but there some Reported Cases*
- Tears
- Breast milk
- CSF
- BAL fluid
- Amniotic fluid
- Transplanted organs (liver, kidney, heart, bone)

# Transmission risk estimates



NEJM 1997

# Risk of Sexual Transmission of HIV







# Healthcare workers

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- Low risk
- 0.3%
- Universal precautions \*\*\*\*\*
  - Hand washing
  - Gloves, gowns, masks
  - Sharps → Sharp Containers
  - Open lesions...

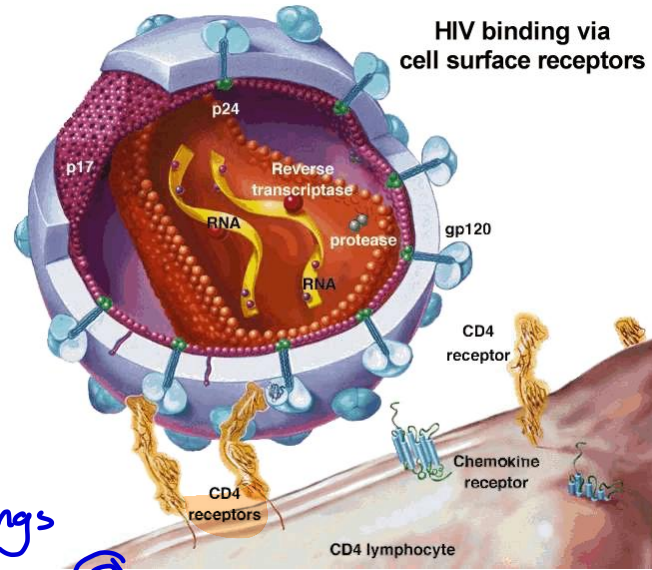
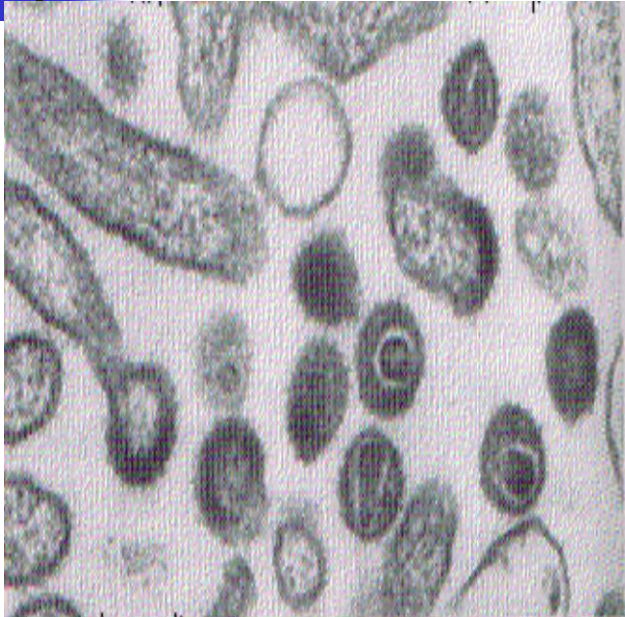
# One hand technique

# No recapping



Recapping .  
Should Be  
By one hand

# HIV Structure *RNA Virus - 2 Separate Strands*



*2 things*

①

②

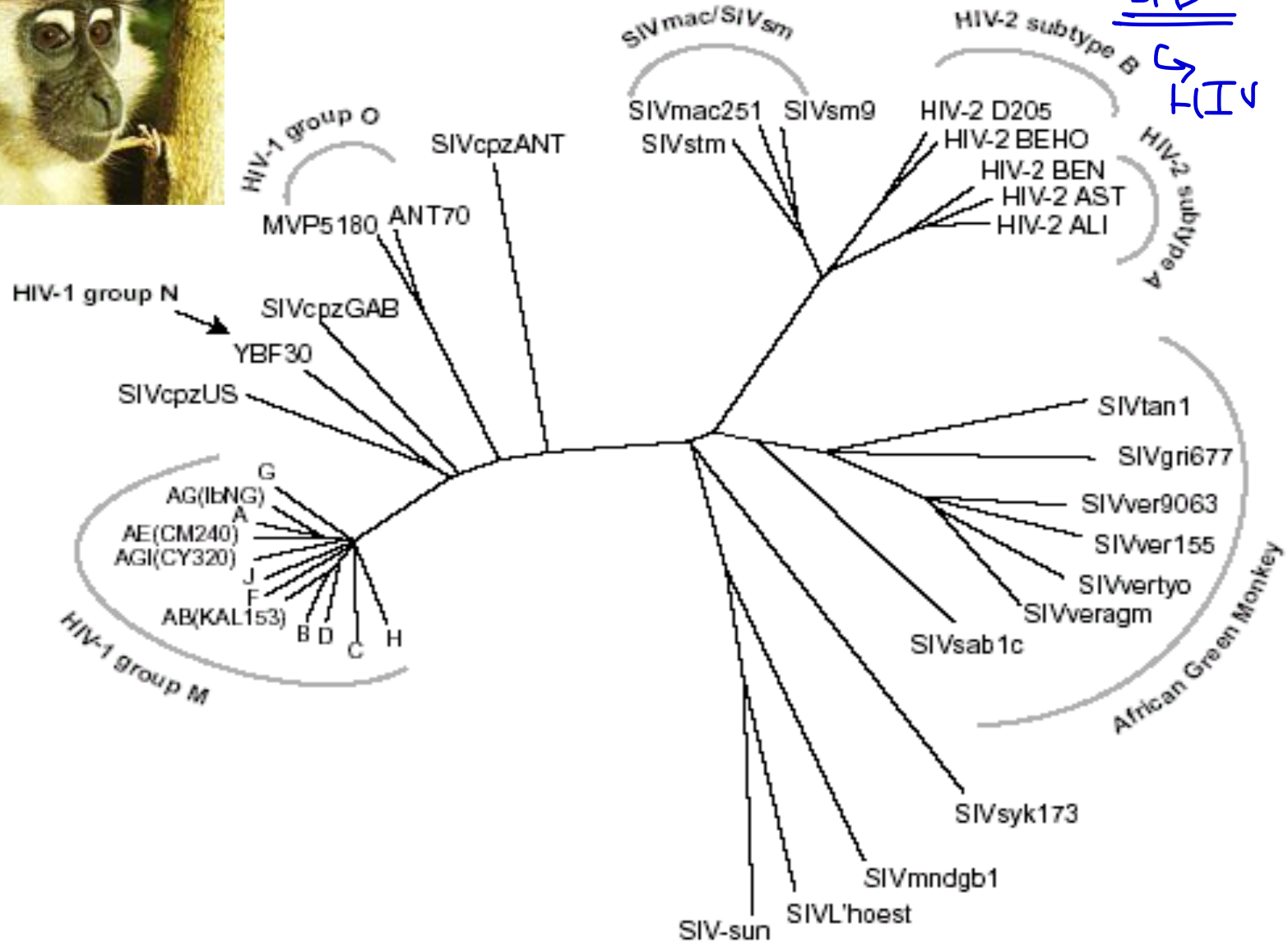
HIV binding via **CD4** & **chemokine receptor**



# Phylogenetic tree

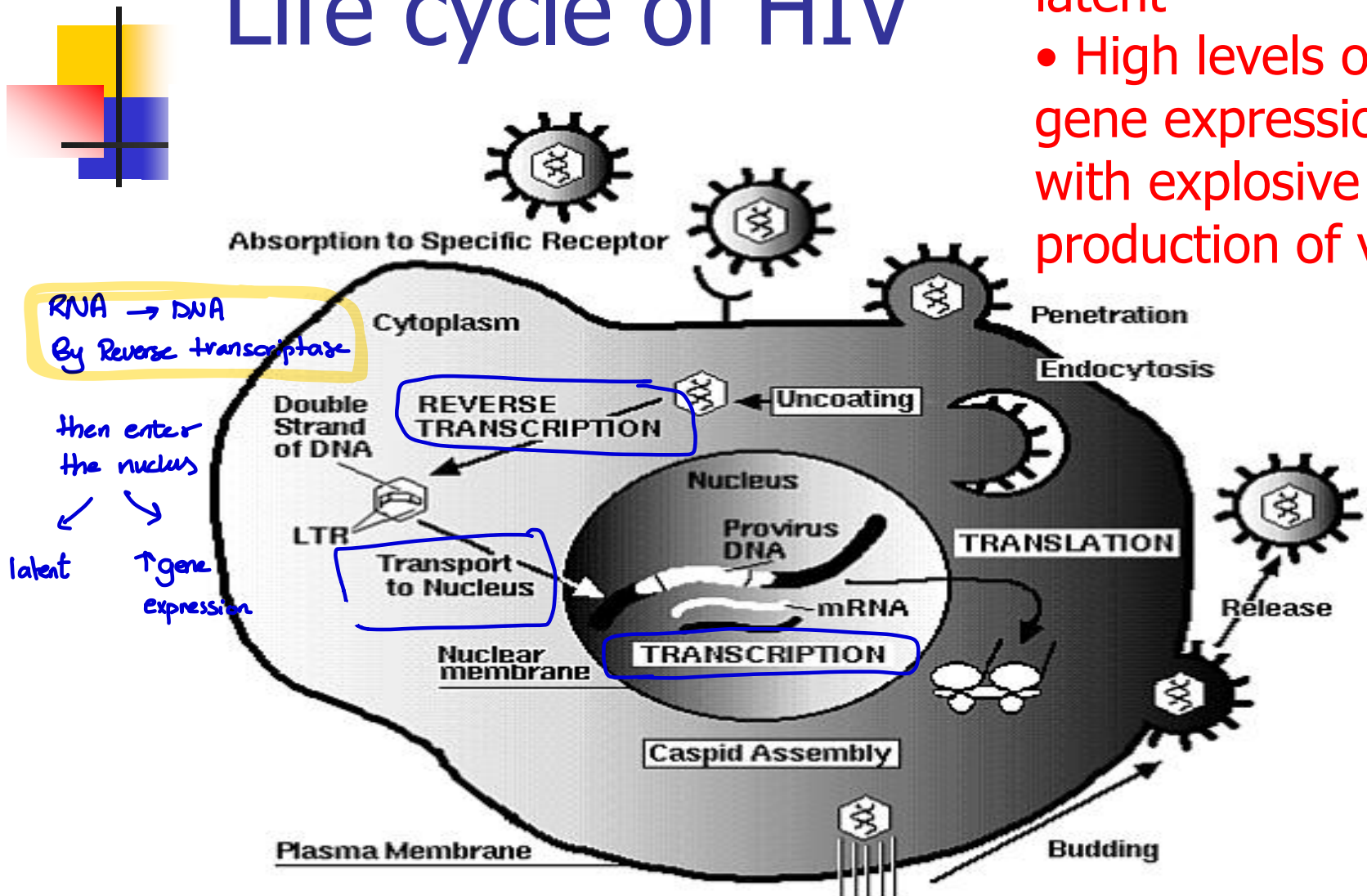
1920

SIV  
↳ HIV



# Life cycle of HIV

- Transcriptionally latent
- High levels of gene expression with explosive production of virus

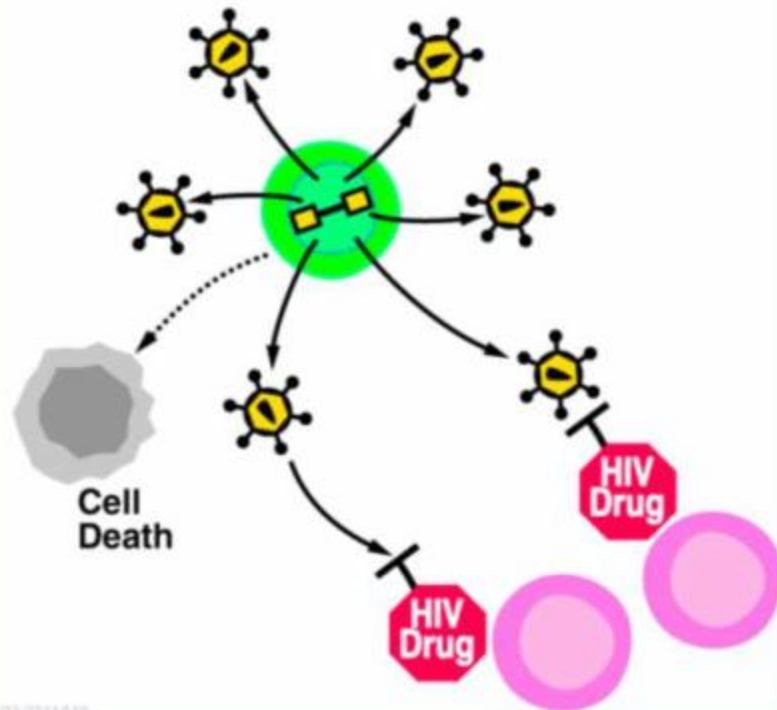


RNA → DNA  
By Reverse transcriptase

then enter  
the nucleus

latent  
↑ gene  
expression

## Productively Infected Cells

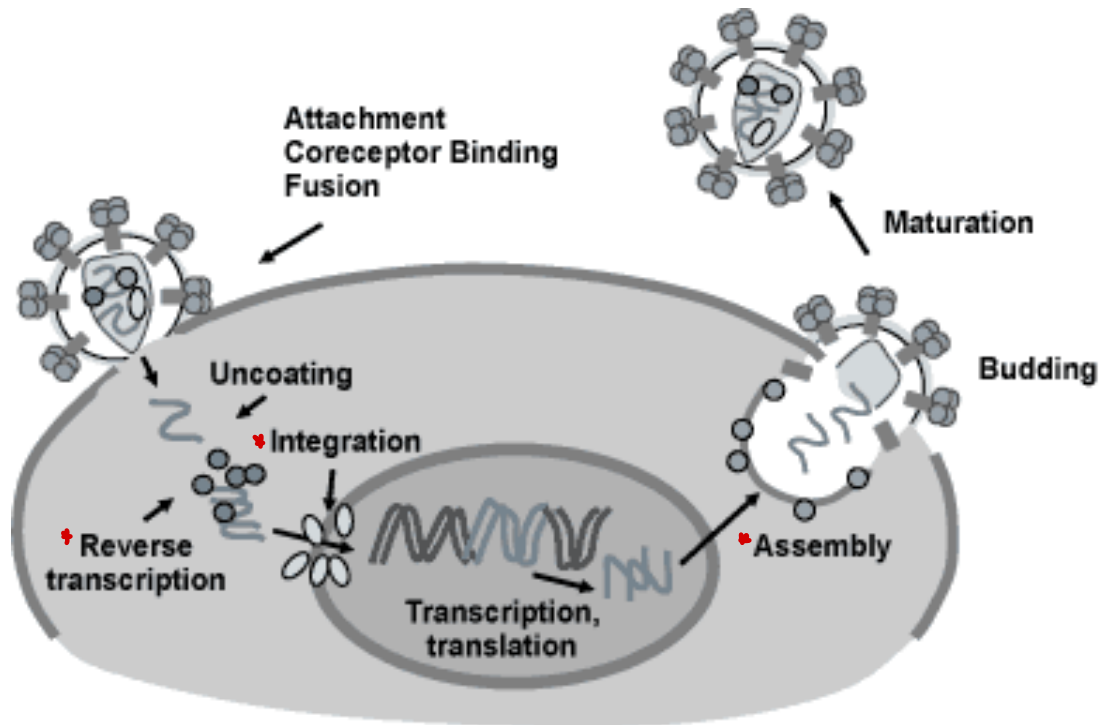


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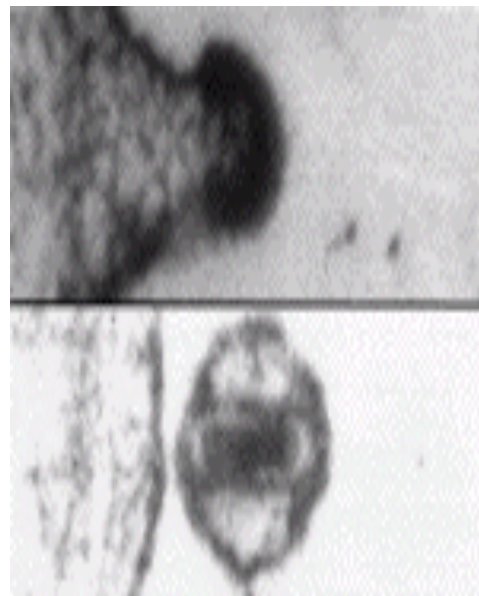
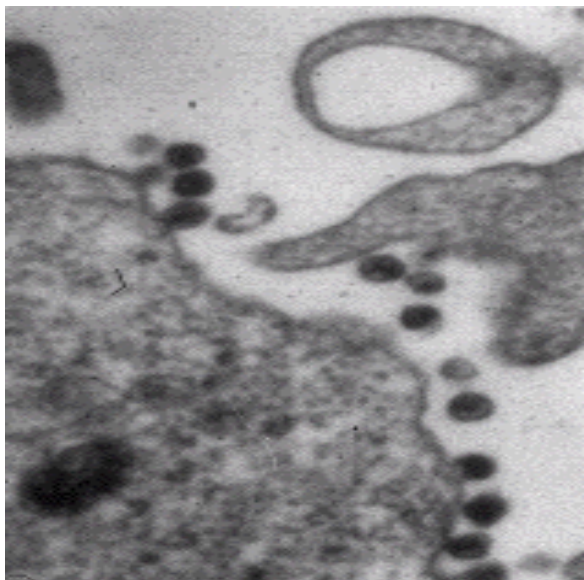
## Latently Infected Cells



1. Attachment
2. Coreceptor binding
3. Fusion
4. Uncoating
5. Reverse transcription
6. Integration *First line treatment*
7. Transcription
8. Translation
9. Assembly
10. Budding
11. Maturation

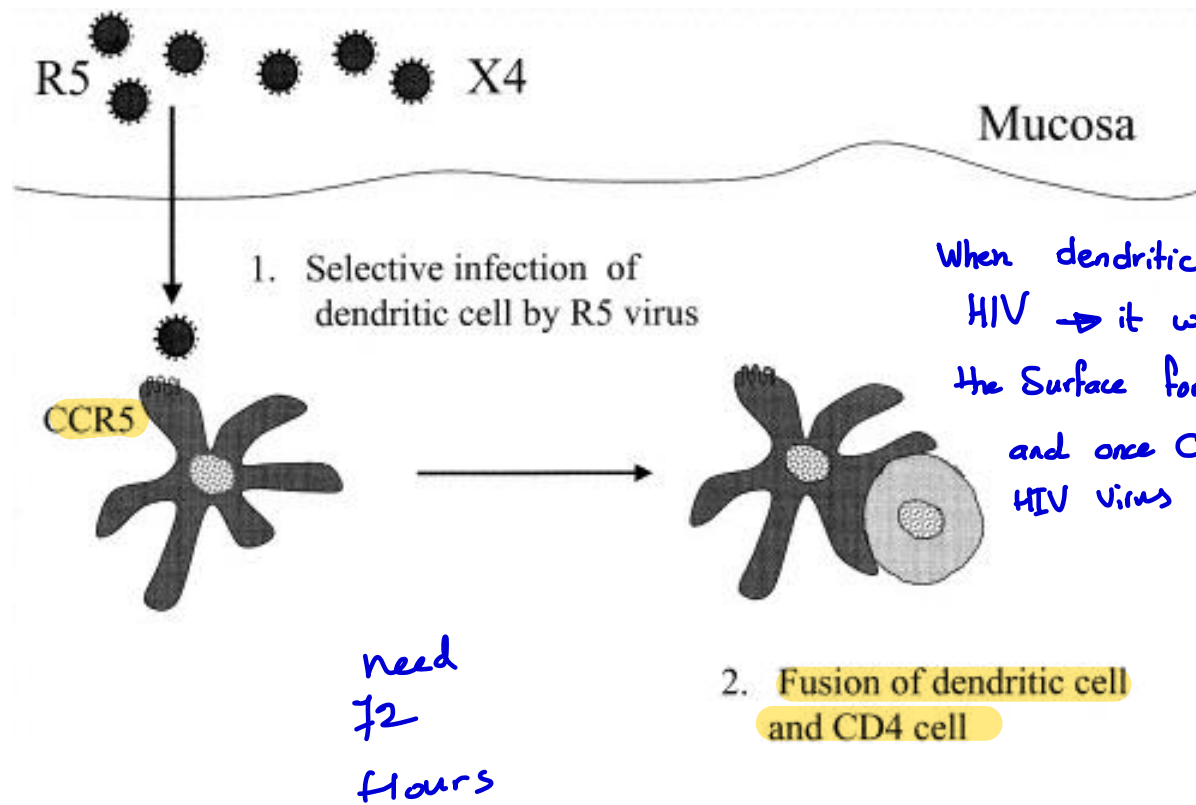


# HIV budding



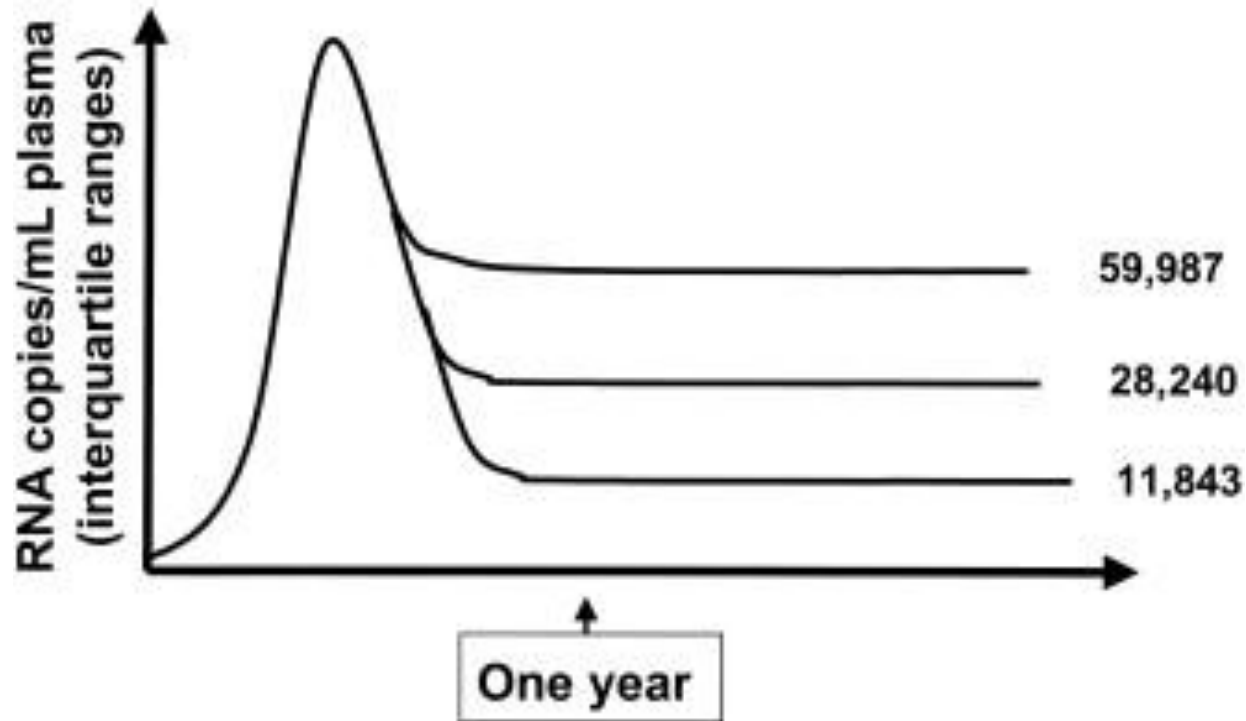


# Transmission



# Viral steady state

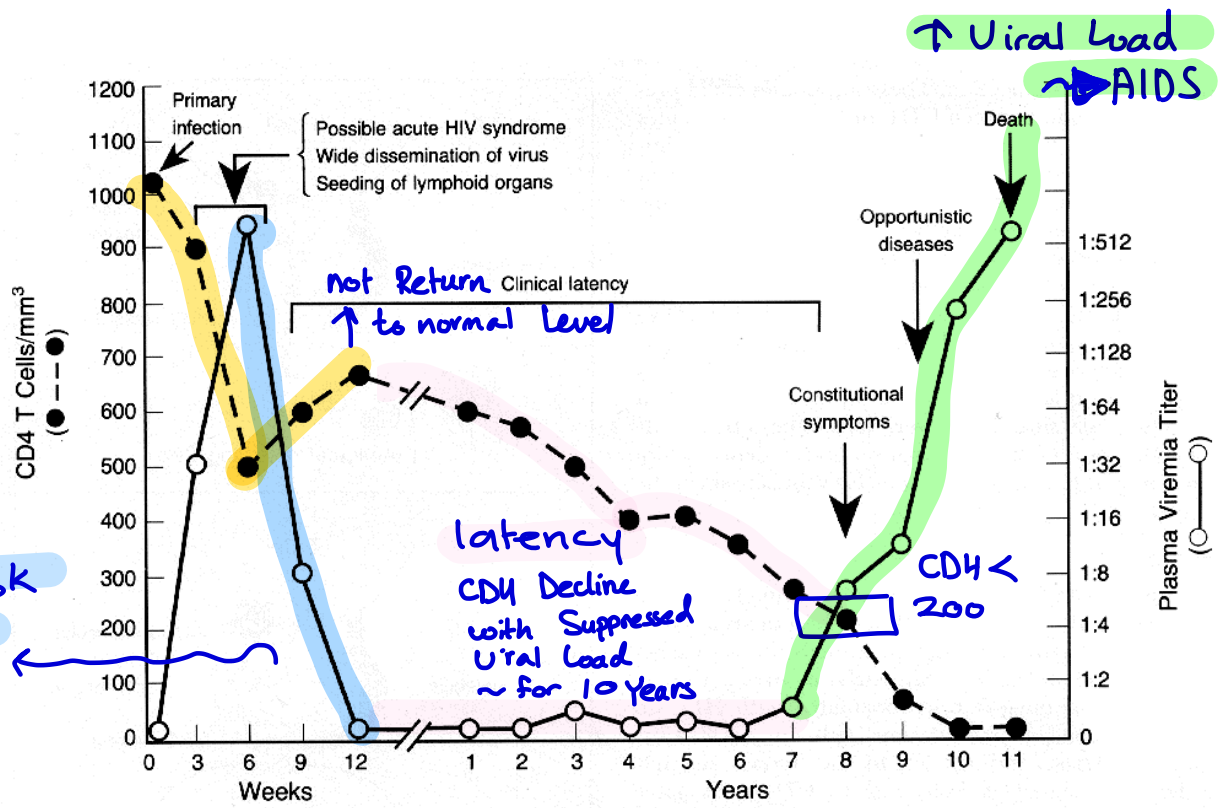
↓ → Better for Patient



Very Important

# Course of HIV infection

The Highest Risk of Infection at this Stage



# Viral load & CD4 as predictors for progression

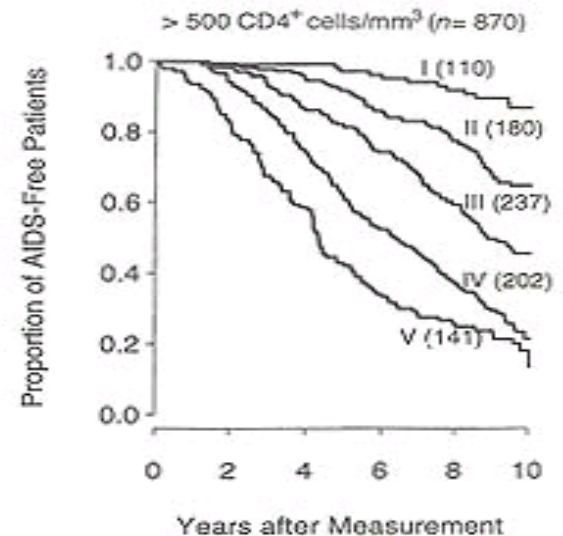
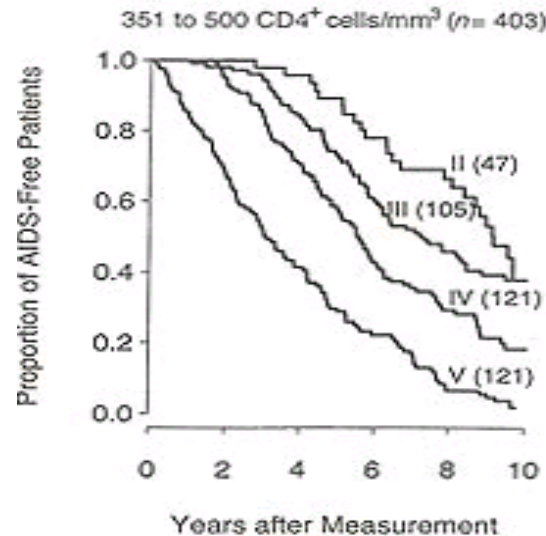
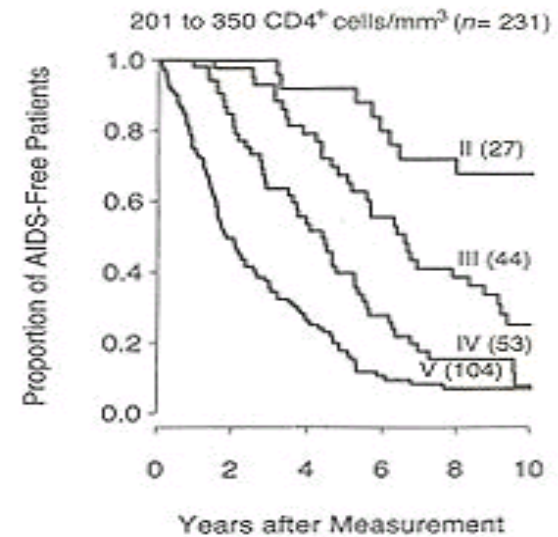
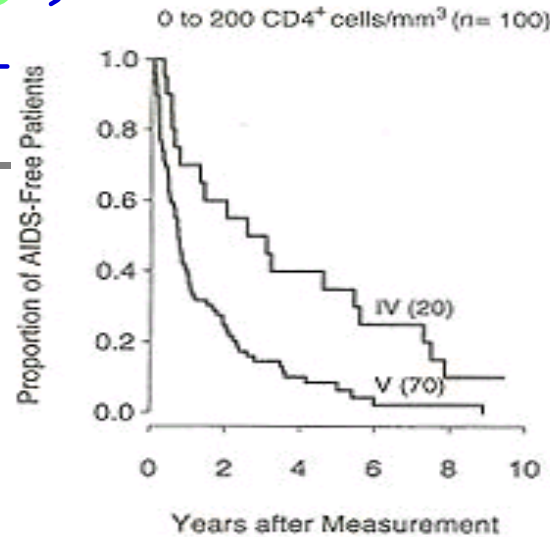
↳ ↑viral load + ↓CD4 → **WORST ONE**

**AIDS within 3 years**

↳ ↓viral load + ↑CD4 →

**AIDS within 10 years**

**Best ONE**



I, 500 copies/mL or less

II, 501 to 3000 copies/mL

III, 3001 to 10,000 copies/mL

IV, 10,001 to 30,000 copies/mL

V, more than 30,000 copies/mL

AIM, 1997



# Acute HIV infection

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- Mononucleosis like picture
  - remember secondary syphilis, EBV
- > 70 % of pts present with symptoms,
  - 2 weeks after acquiring HIV but can present as early as 5 days or as late as 3 months after initial infection
- High viremia  $\approx 10^8$  copies/ml
- Highly infectious
- Dx by PCR followed by serology
  - 4<sup>th</sup> generation Ag/Ab test (10-14 days) Imp



# Signs and Symptoms of Acute HIV occur: 2 weeks – 3 months

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- Fever
- Fatigue/Malaise
- Pharyngitis
- Lymphadenopathy
- Myalgia
- Joint Pain
- Rash *maculopapular Rash On Upper trunk*
- Diarrhea
- Weight Loss
- Headache
- Vomiting
- Oral or genital ulcer

- **Rare presentation**

*Dramatic Presentation*

- Guillain-Barré Syndrome
- aseptic meningitis
- hepatitis

- completely asymptomatic



# RNA test and DX of acute HIV

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- Although acute HIV infection with HIV RNA <10,000 copies/mL has been described, such results could also represent false positive tests
  - further lab tests should be performed (eg, additional antibody testing or repeat HIV RNA or both) to confirm cases in which HIV RNA levels lower than 10,000 copies/mL are noted

# Window Period and HIV Infection

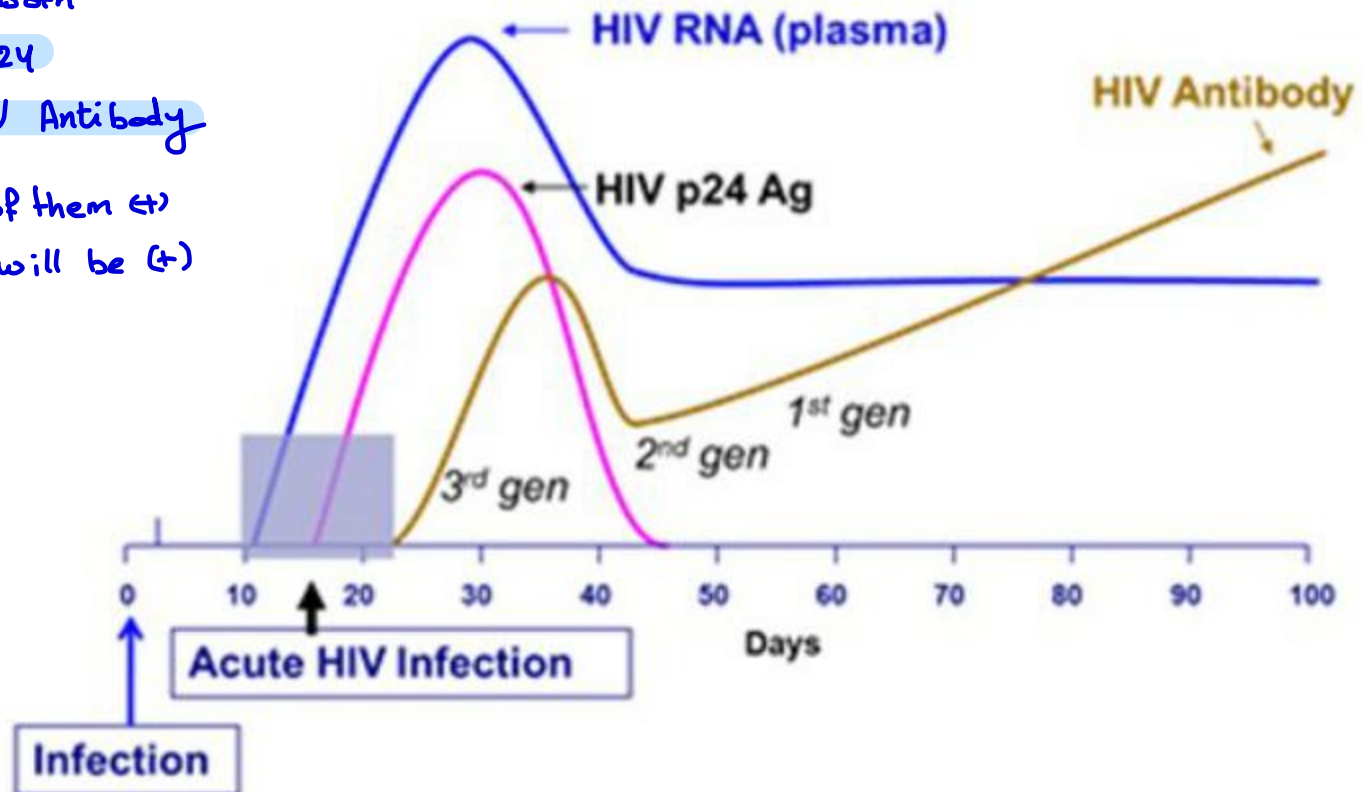
4th generation Ag / Ab

looks for Both

→ Ag P24

→ HIV Antibody

if one of them (+)  
the test will be (+)



Busch MP, et al. *Am J Med* 1997; 102(5B):117-124. Modified diagram based on first iteration in stated source and updated using several publications since 1997.



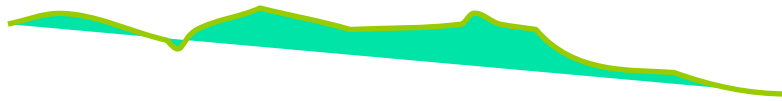


# Persons recommended for evaluation of acute HIV infection with available appropriate tests

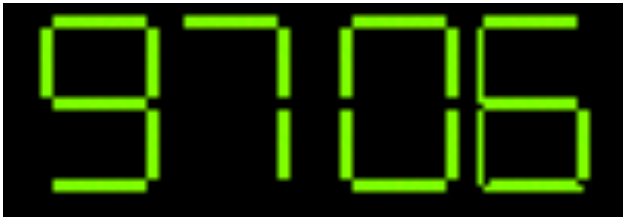
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- All of the following risk groups, ESPECIALLY with **history of an illness with clinical features compatible with acute HIV ("mono" or "flu-like" illness, regardless of severity)**:
- recent sexual or needle-sharing exposure with a known HIV-infected partner or a partner of unknown serostatus in the past **2-6** weeks
- Men who report unsafe sexual practices with other men
- A newly diagnosed STD
- Aseptic meningitis
- Requesting HIV testing *even if the history is negative*
- Pregnant and breastfeeding women

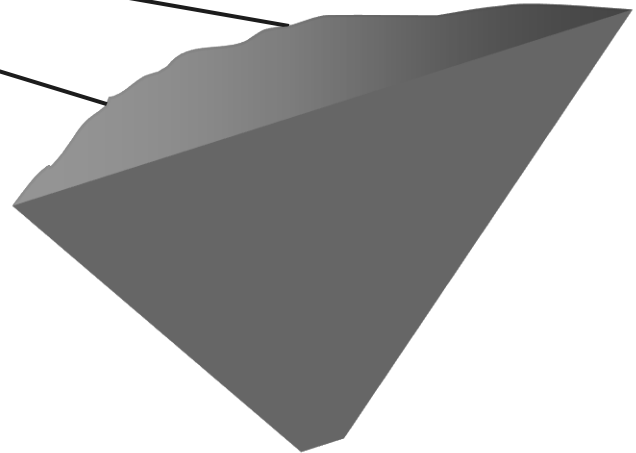
# Viral Load (V.L) & CD4 count



**CD4**

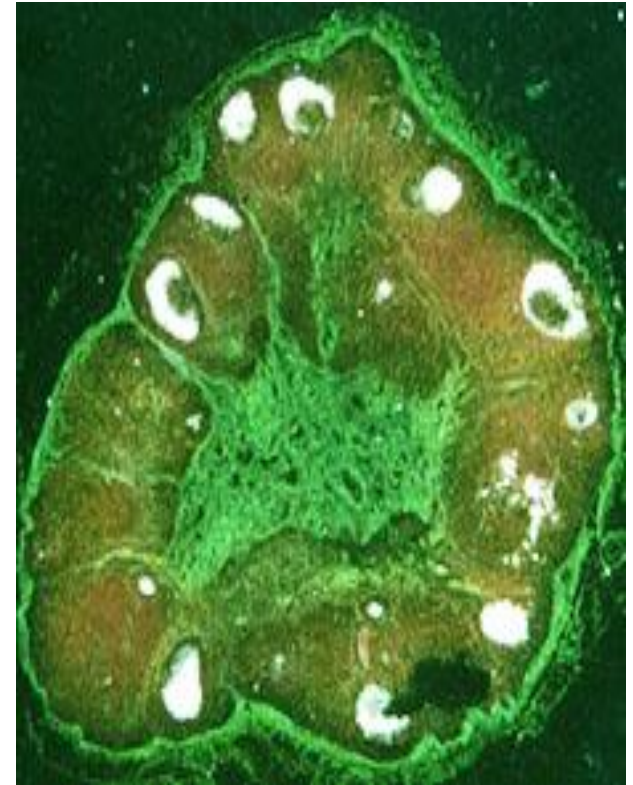


**Viral load**



# HIV = destruction of immunity

- Destruction of CD4 cells
- Evasion of immune response
- Lymph node pathology  
*at the Beg → active then it become atrophied*
- Exhaustion of immunity



2 tests done  
for diagnosis

# HIV Diagnosis

- Viral load (PCR)
  - as early as 7-10 days
- Fourth generation
- ELISA
- Western blot

then

or

+

Should be documented By

10-14  
Days

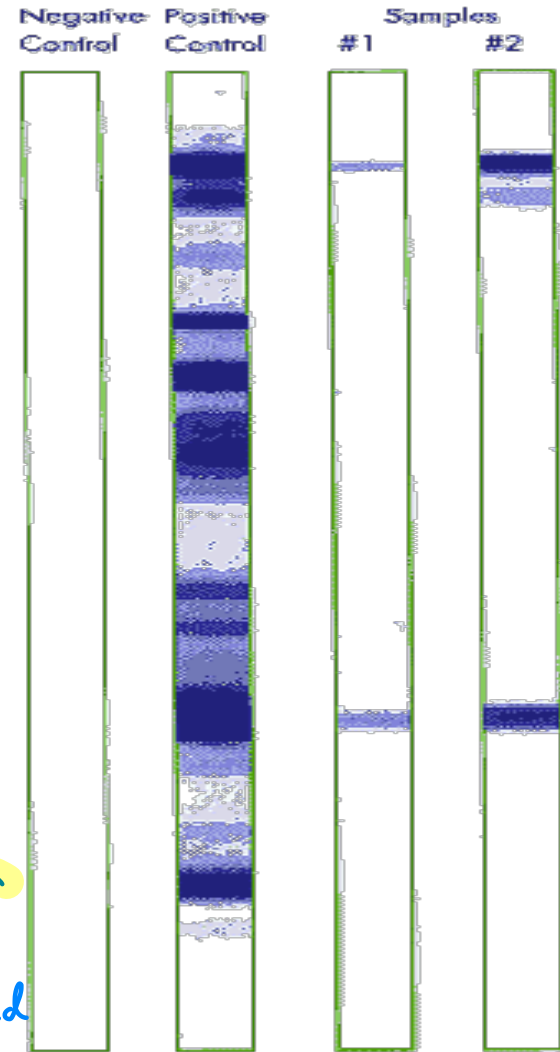
2 theorys

ELISA or  
4th Gen  
then  
W. Blot  
if (+)

ELISA  
then  
Viral Load  
if (+)

if Immunocompromised  
Pt. and ELISA is (+)  
you can do Viral load.

## WESTERN BLOT TESTS



Sample #1 is indeterminate.

Sample #2 is positive.

# CDC Classification (1993)

	A	B	C
CD4	Asymptomatic, acute or PGL	Symptomatic, not A or C	AIDS indicator
≥500	A1	B1	C1
200-499	A2	B2	C2
<200	A3	B3	C3

AIDS  $\left\{ \begin{array}{l} \text{or} \\ \text{AIDS Indicator Symptoms} \\ \text{CD4} < 200 \end{array} \right.$

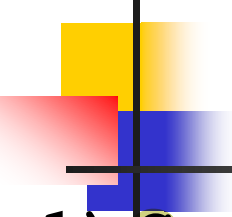
Symptoms Can Happen due to  
Any other diseases

# CDC classification

Bacillary Angiomatosis  
Oral thrush  
Persistent vulvovaginitis  
Fever or diarrhea > 1 month  
Hairy leukoplakia  
VZV  
ITP  
PID  
Peripheral neuropathy

B Symptomatic, not A or C
B1
B2
B3

# CDC AIDS defining diseases (CD4 < 200 cells/ml)

- 
- 1) **Candidiasis** *esophageal (not Oral)*
  - 2) **Cervical cancer**
  - 3) **Coccidioidomycosis**
  - 4) **Cryptococcosis**
  - 5) **CMV** *Invasive Peritonitis*
  - 6) **Encephalopathy**
  - 7) **HSV**
  - 8) **Histoplasmosis**
  - 9) **TB**  $\xrightarrow{\text{CD4} > 200}$
  - 10) **Cryptosporidiosis**
  - 11) **Lymphoma**
  - 12) **PCP** *pneumocystis pneumonia*
  - 13) **Recurrent pneumonia**
  - 14) **MAC**
  - 15) **PML**
  - 16) **Salmonellosis**
  - 17) **Brain Toxoplasmosis**
  - 18) **Wasting**
  - 19) **Kaposi's sarcoma**
  - 20) **Isosporiasis**

**Table 1. Antiretroviral Agents Approved by the FDA and in Phase III Clinical Trials**

Approved Agents					
NRTIs	PIs	NNRTIs	Fusion Inhibitors	Entry Inhibitors	Integrase Inhibitors
Zidovudine	Saquinavir	Nevirapine	Enfuvirtide	Maraviroc	Raltegravir
Didanosine	Ritonavir	Delavirdine			Elvitegravir*
Stavudine	Indinavir	Efavirenz			
Lamivudine	Nelfinavir	Etravirine			
Abacavir	Lopinavir/ritonavir	Rilpivirine			
Tenofovir	Atazanavir				
Emtricitabine	Fosamprenavir				
	Tipranavir				
	Darunavir				
Investigational Agents in Phase III Trials					
					Dolutegravir(S/GSK1349572)

\*Currently approved only as part of the fixed-dose combination of cobicistat/elvitegravir/emtricitabine/tenofovir.



# Highly Active Anti-Retroviral Therapy (HAART) “Cocktail”

C-ART Combined anti retroviral  
Therapy

Usually: 2 NRTI + PI  
Protease ↓

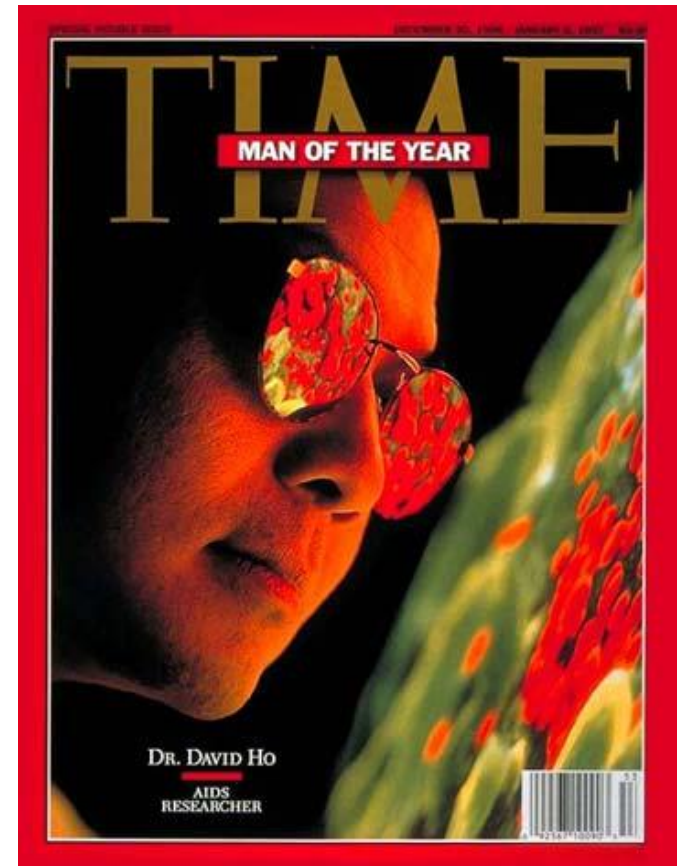
## □ Aim:

- Suppress viral load
- Increase CD4

*Very Good treatment*

## □ Disadvantages:

- Toxicity
- Cost
- Resistance*



# Indication to start HAART

All patients with HIV should be offered treatment

Whatever CD4, Viral Load

as early as possible

## Antiretroviral agents

- NRTI *First ONE*
  - Ziduvudine (AZT)
  - Didanosine (DDI)
  - Stavudine (D4T)
  - Lamivudine (3TC)
- PI
  - Saquinavir
  - Indinavir
  - Ritonavir
  - Nelfinavir
  - Abacavir
- NNRTI
  - Nevirapine
  - Efavirenz



# Conclusions

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- Large & serious epidemic
- Transmission modes
- Basic pathogenesis
- AIDS related illnesses
- The importance of CD4 & VL
- HAART
- Viral resistance (as usual)
- When to start therapy