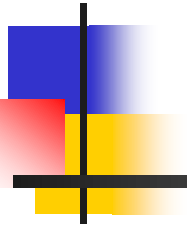




**Live and let live**

# Human immunodeficiency virus (HIV) disease

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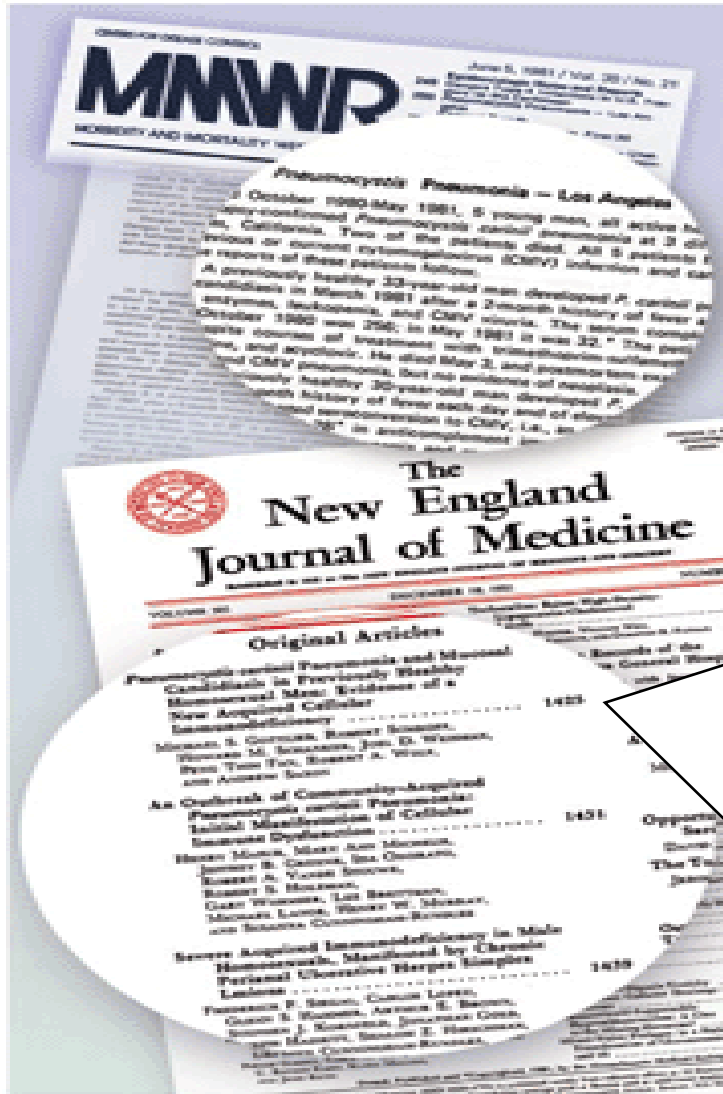




# Outline

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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)

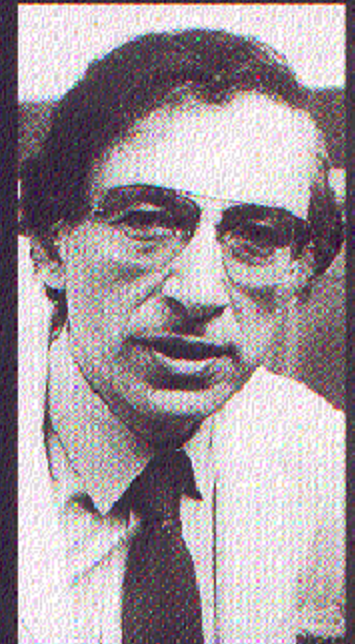
## WHO DISCOVERED THE AIDS VIRUS?



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



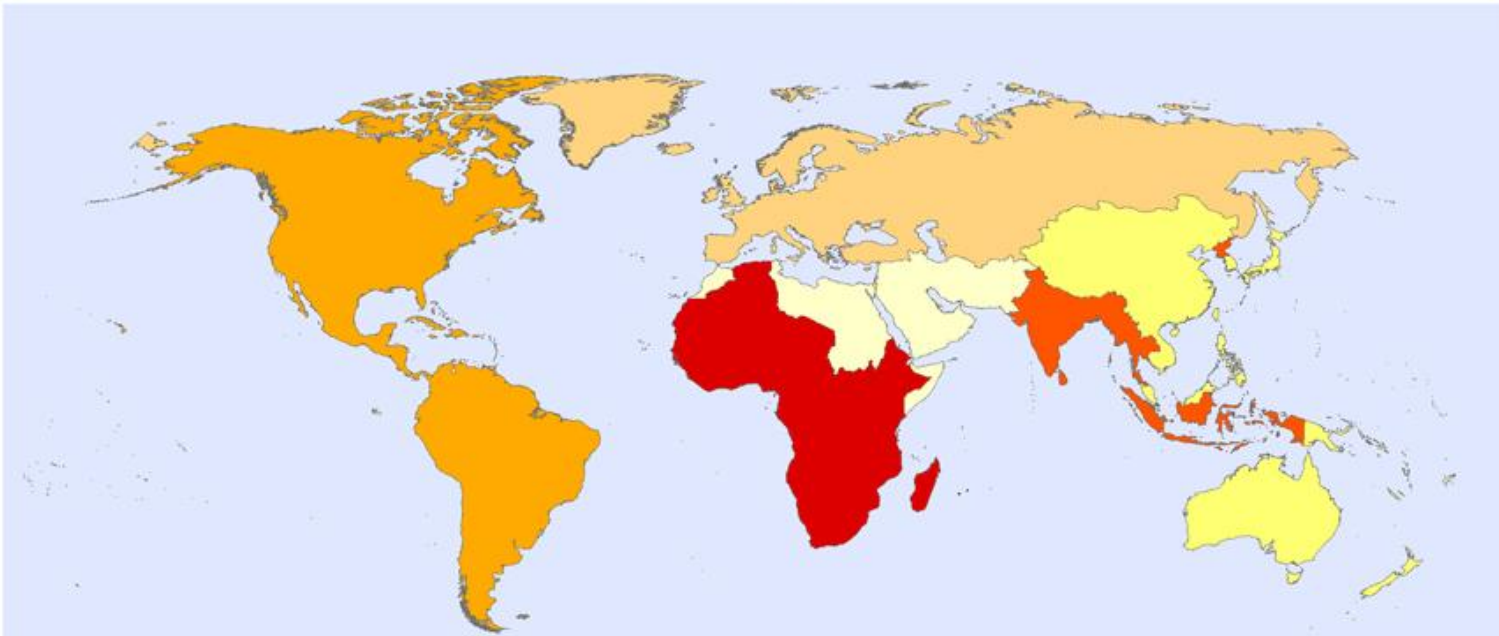
# Epidemiology

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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



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



### Number of people, by WHO region

Eastern Mediterranean: 360 000 [290 000–500 000]	Americas: 3 300 000 [2 900 000–3 800 000]	<b>Total: 36 700 000</b> <b>[30 800 000–42 900 000]</b>
Western Pacific: 1 500 000 [1 200 000–2 000 000]	South-East Asia: 3 500 000 [2 500 000–8 200 000]	
Europe: 2 400 000 [2 300 000–2 600 000]	Africa: 25 600 000 [22 900 000–28 600 000]	

0 875 1,750 3,500 Kilometers

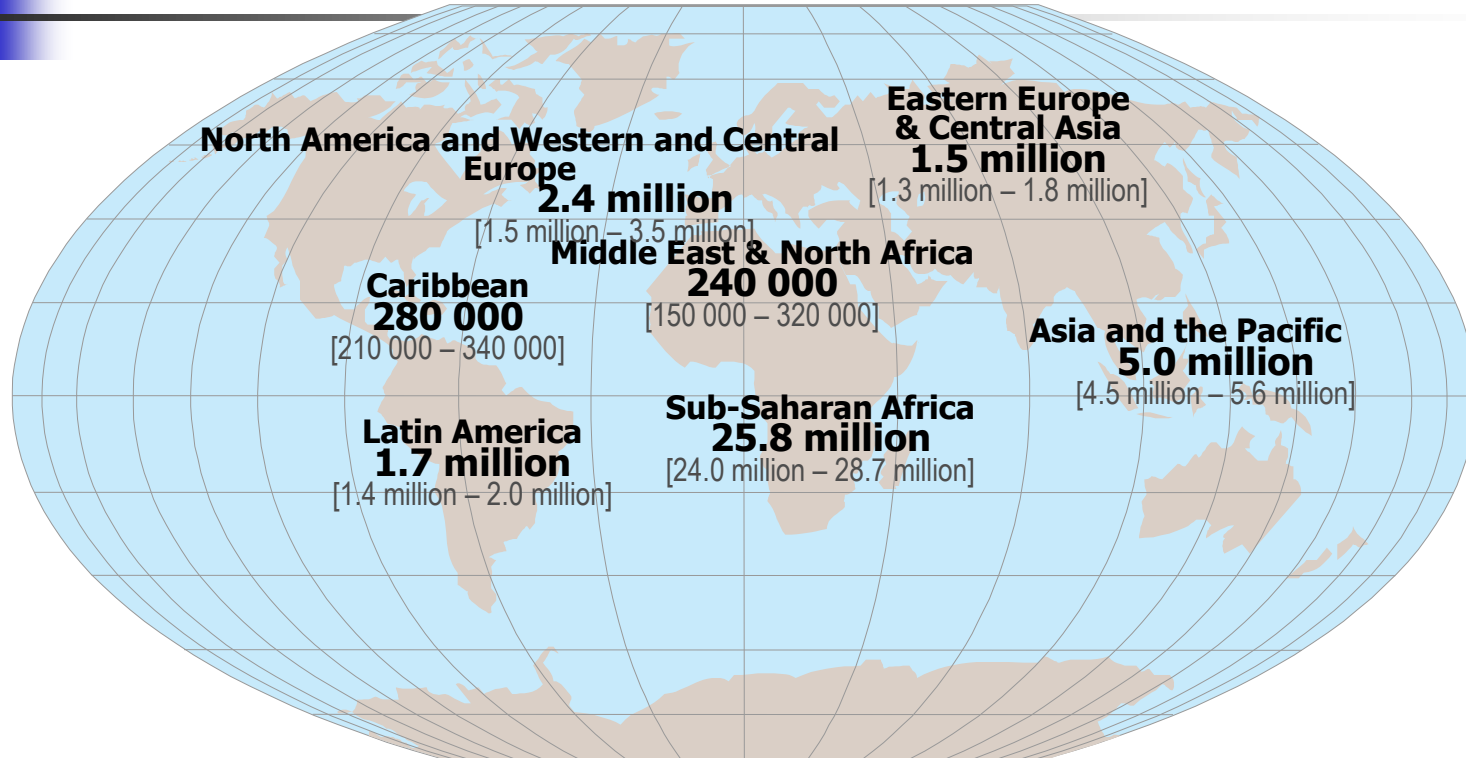
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers 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

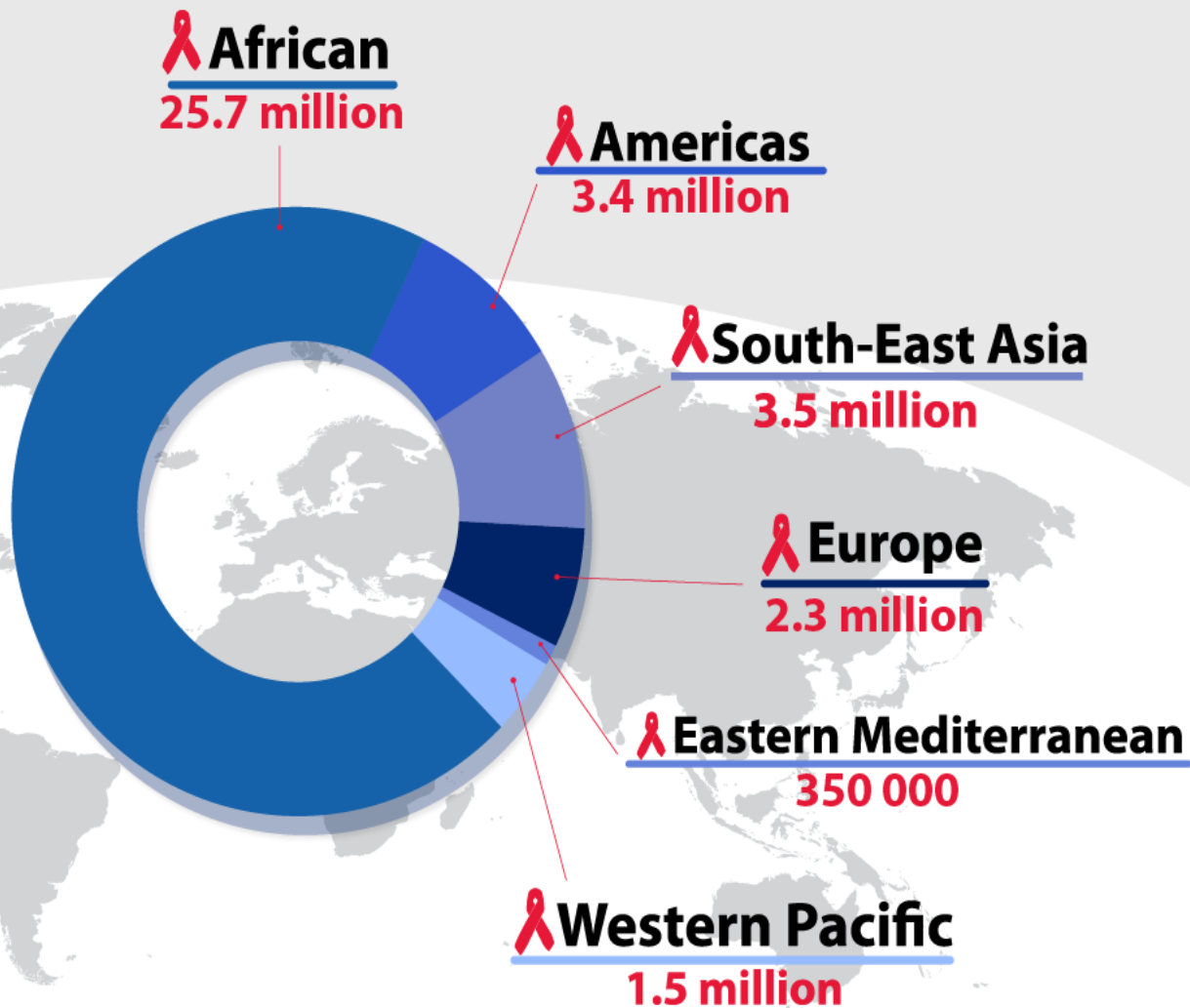


**+14%**  
Relative to 2010



# People living with HIV by WHO region (2017)

**36.9** million  
people living  
with HIV globally

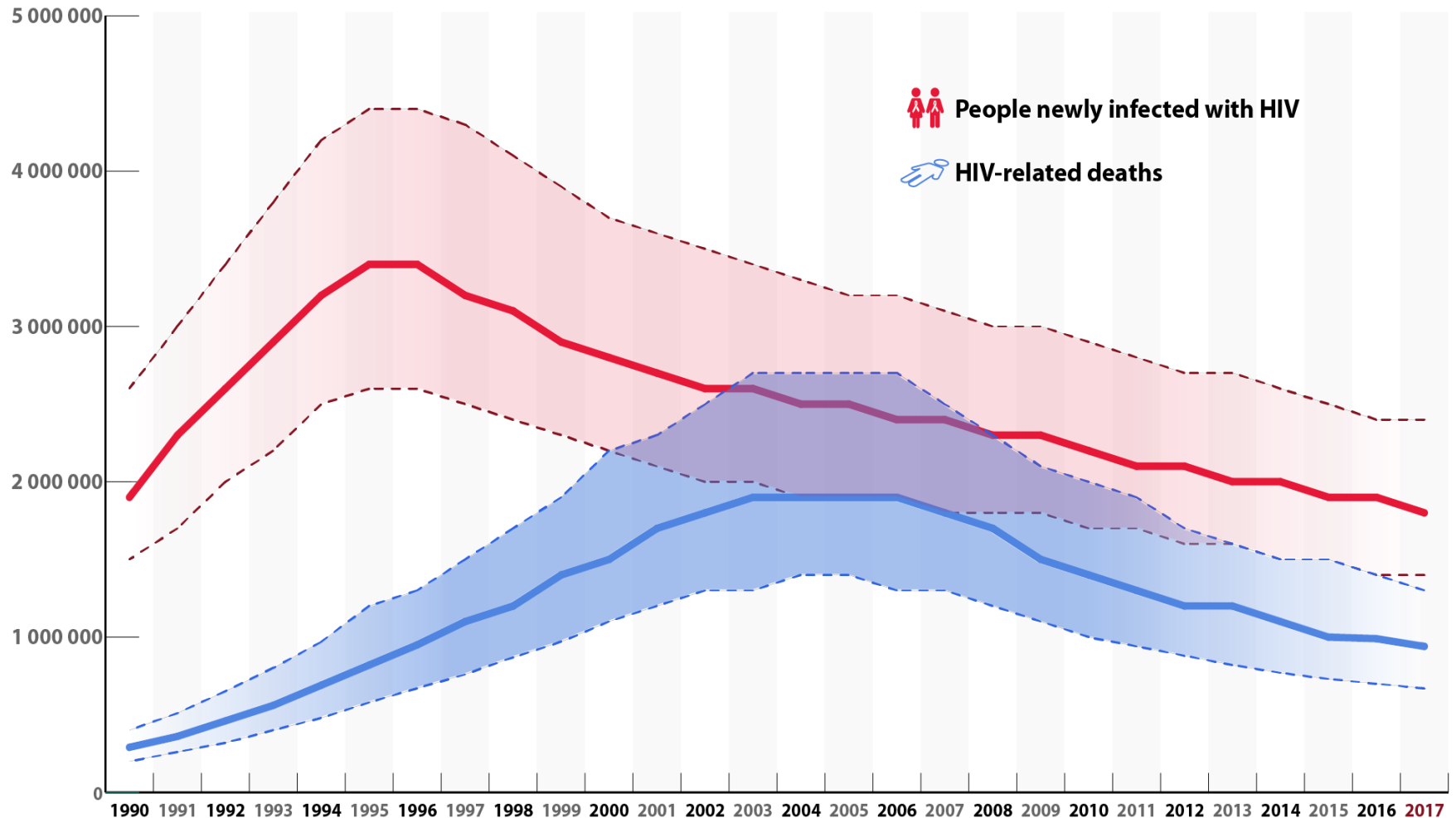


Source: UNAIDS/WHO estimates



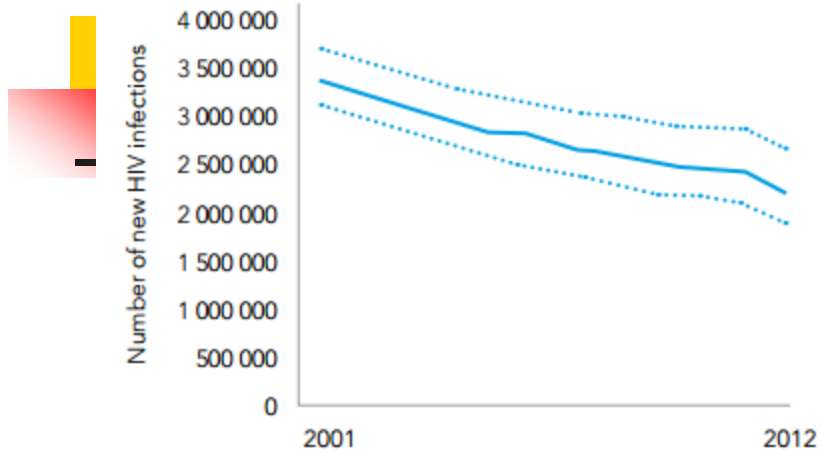
World Health  
Organization

# Decline in HIV incidence and mortality over time

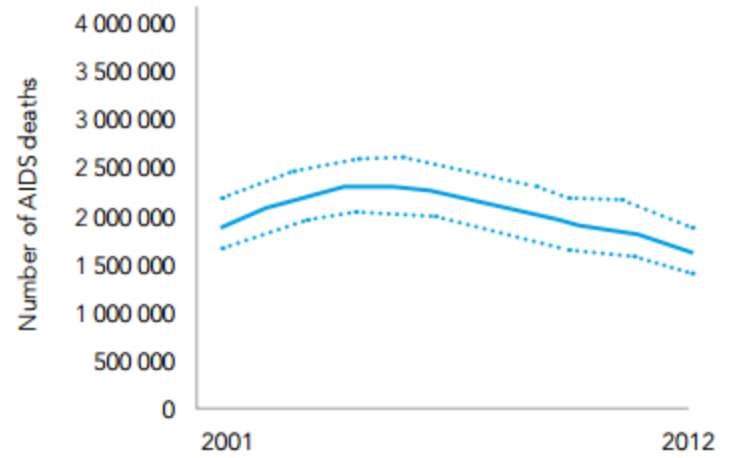


Source: UNAIDS/WHO estimates

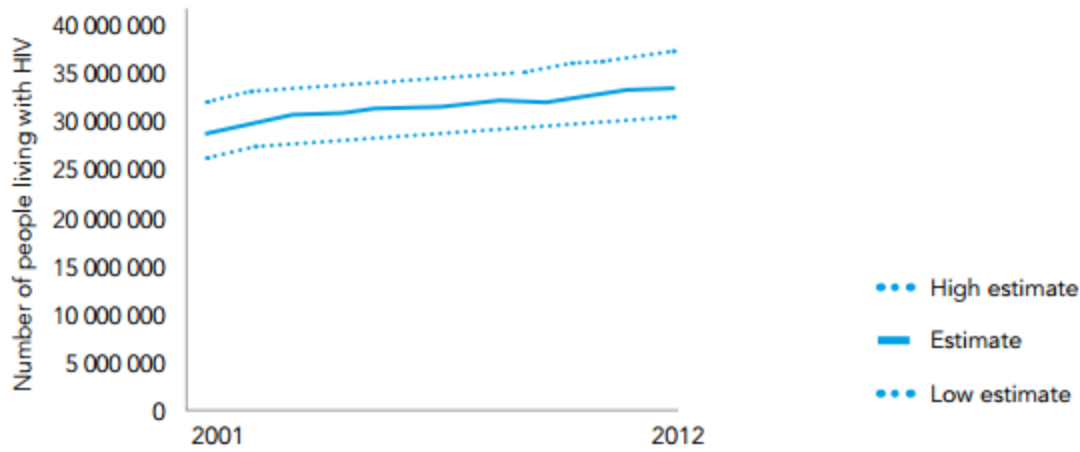
### NEW HIV infection Globally 2001-2012



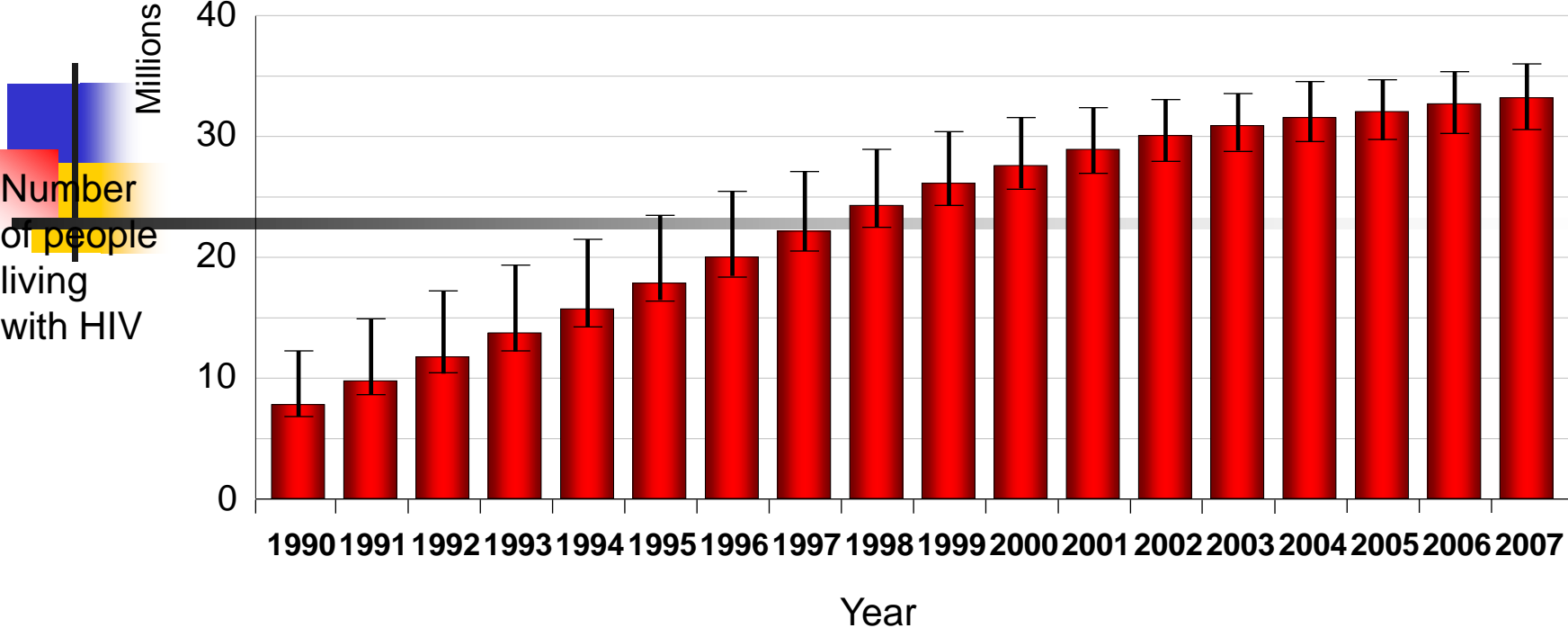
### IDS Deaths Globally 2001-2012



### People living with HIV Globally 2001-2012



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



 *This bar indicates the range*

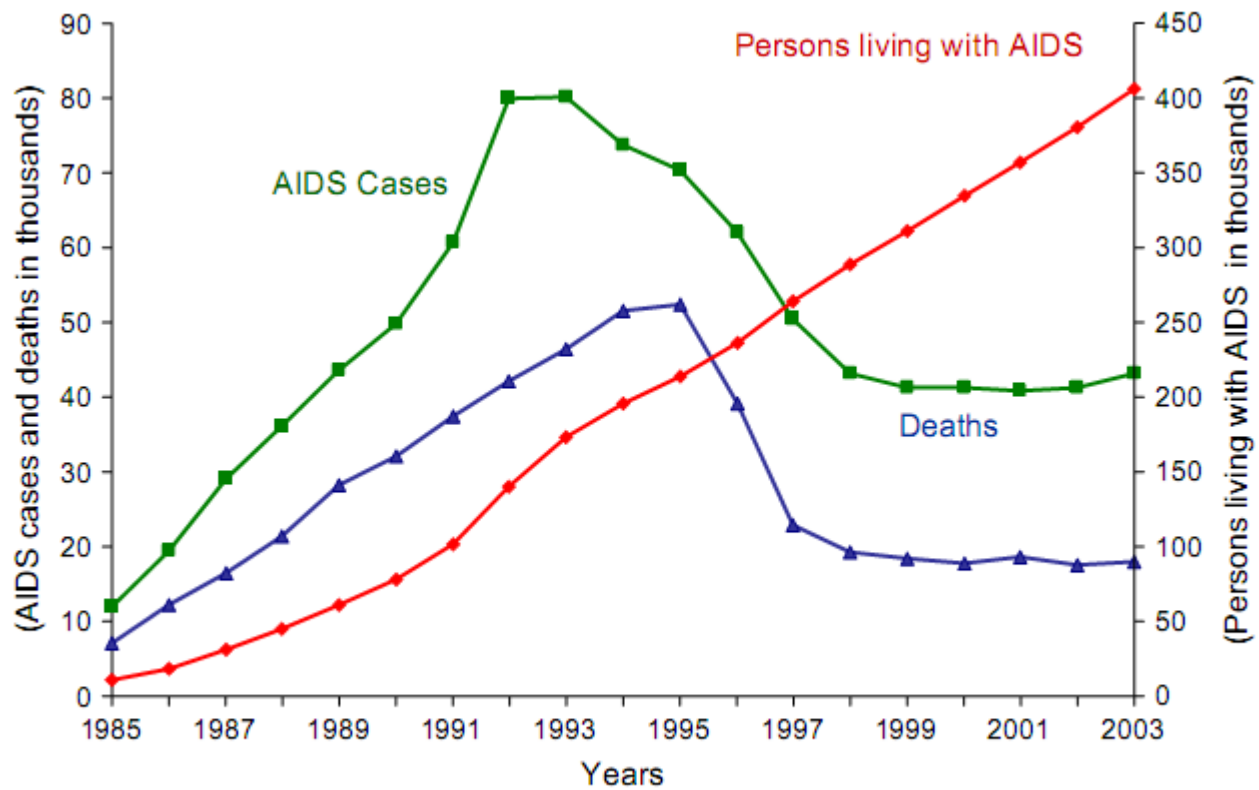
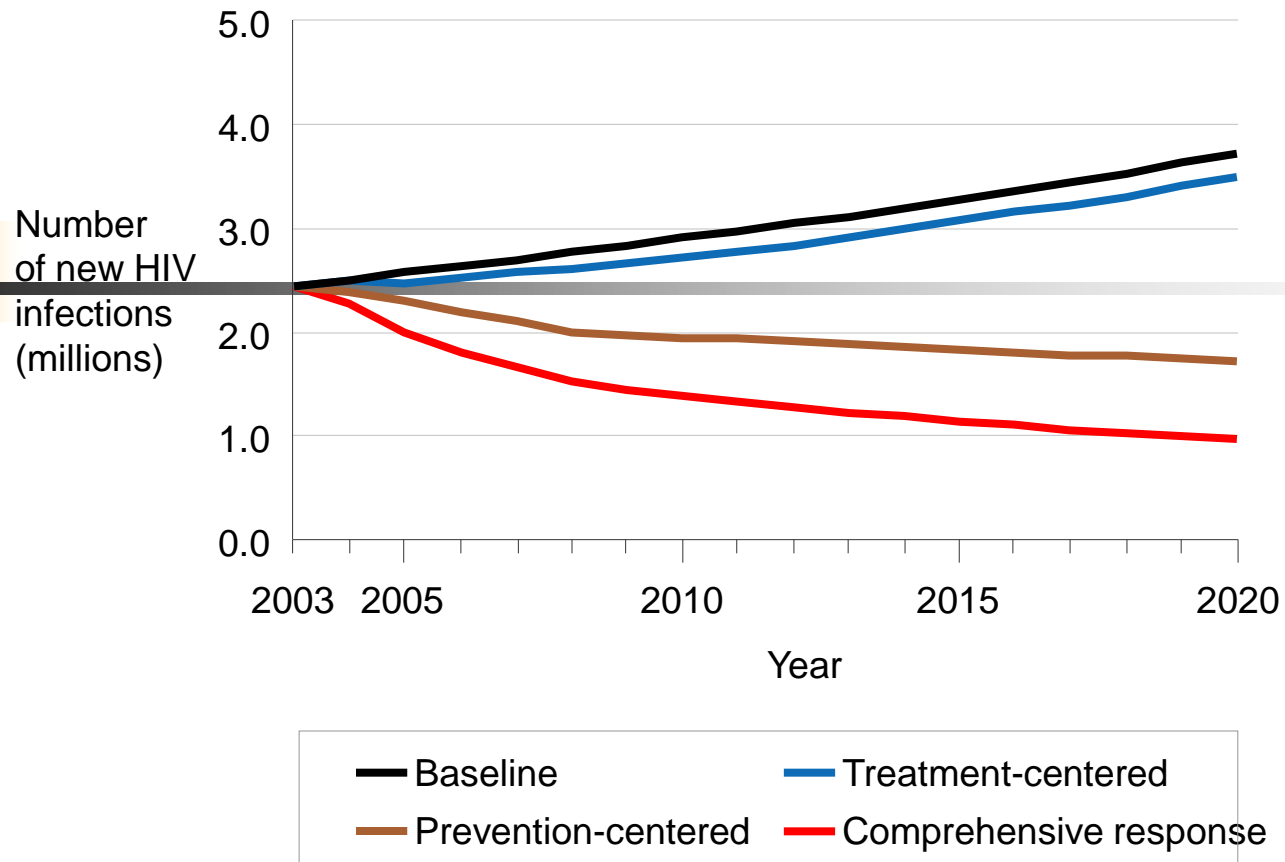


Fig. 3. AIDS cases, deaths, and persons living with AIDS in the United States, 1985–2003.

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



Source: Salomon JA et al. (2005). Integrating HIV prevention and treatment: from slogans to impact





# Huge burden...

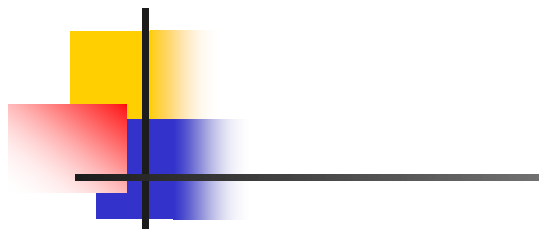
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- 5 million new cases / year
- 5600 new HIV infections/day in 2014
  - 600 in children
  - 5,000 in adults
  - 50% were women
  - 30% were 15-24 years
  - 95 % in developing countries
  - 66% in subsaharan Africa
- 16 million children were orphaned
- 14 million orphaned in Africa

# Africa, the burning continent

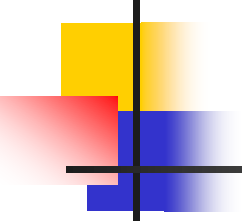
- 8% of adults < 45
- > 80% of prostitutes
- In 2013: **70% of the global total**
- **Life expectancy < 40 years**





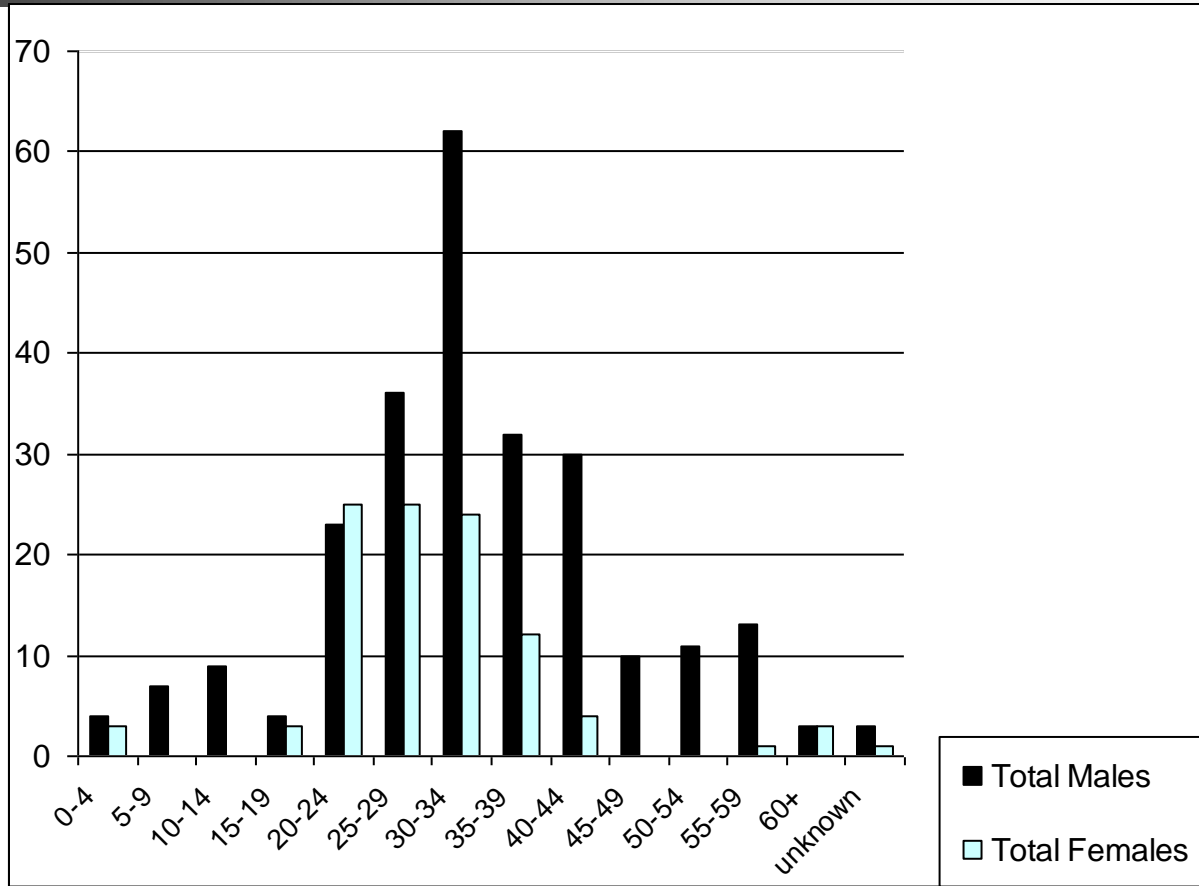
A 15 year old boy in Botswana has 90% chance of dying of AIDS



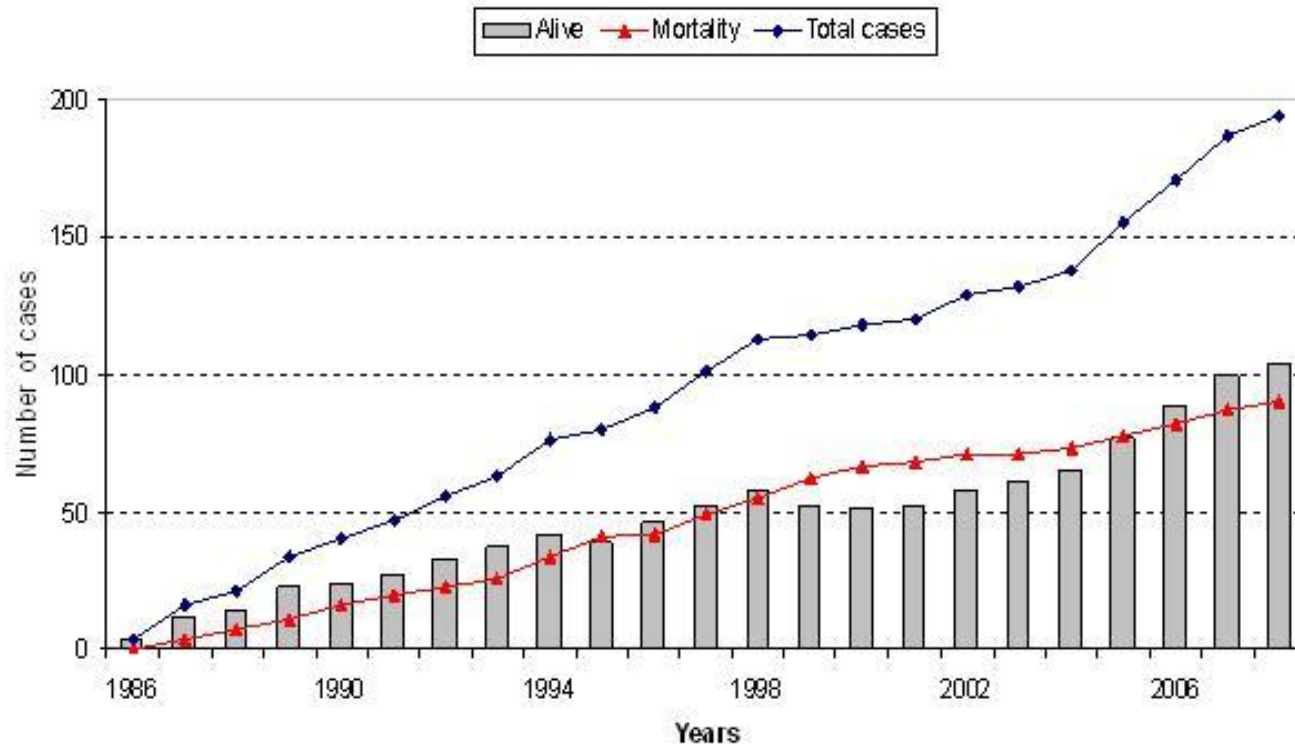
- 
- 
- “...The AIDS epidemic continues to explode in **India, China, Russia, and eastern Europe** and may be more destabilizing than international terrorism”

M. Scheld

# HIV in Jordan (2010)



# HIV – Jordan: mortality (2010)





# Transmission

- Sexual intercourse
- Mother → child
- IV drug use
- Blood transfusion
- Needlestick injury



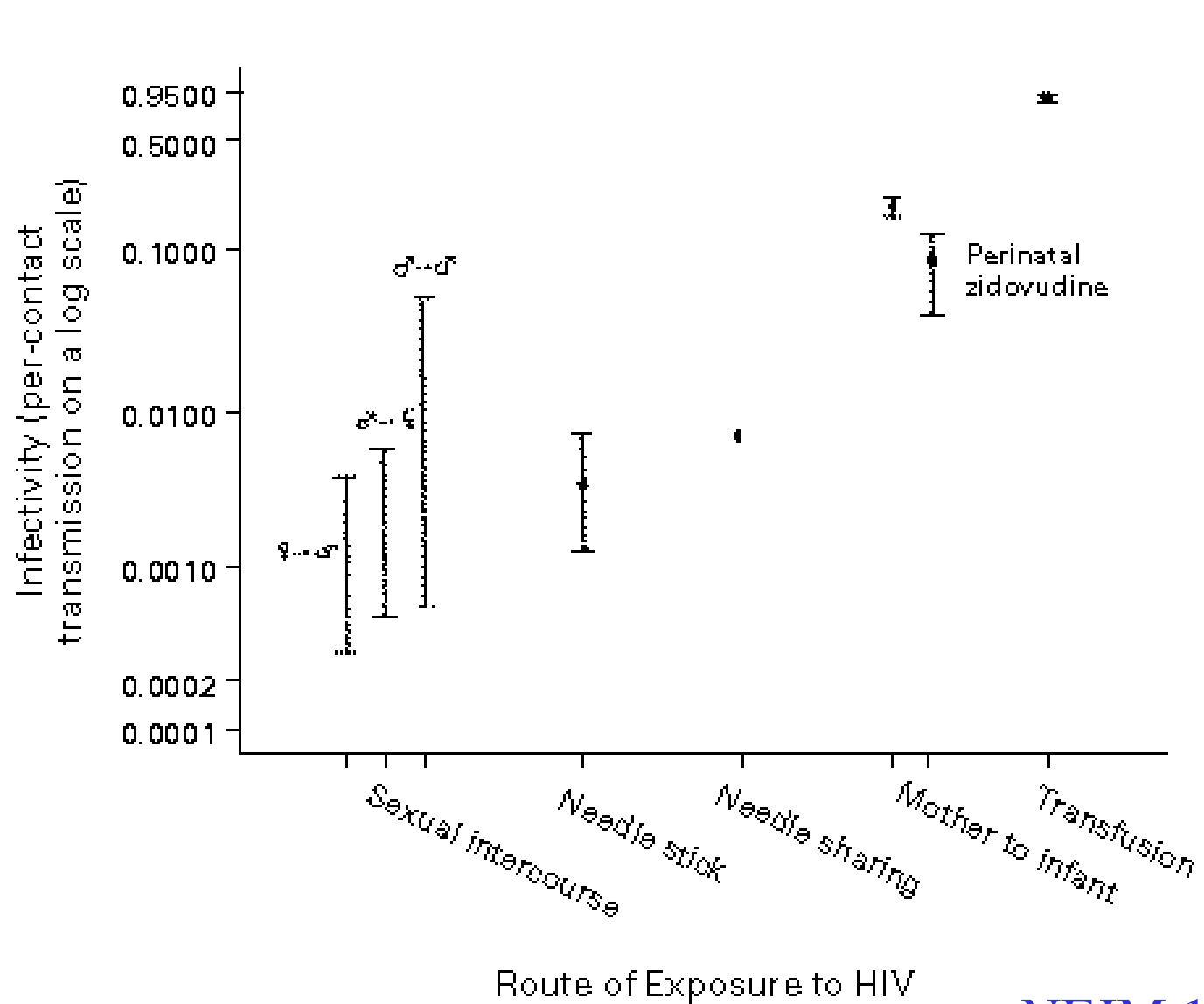


# All body fluids...

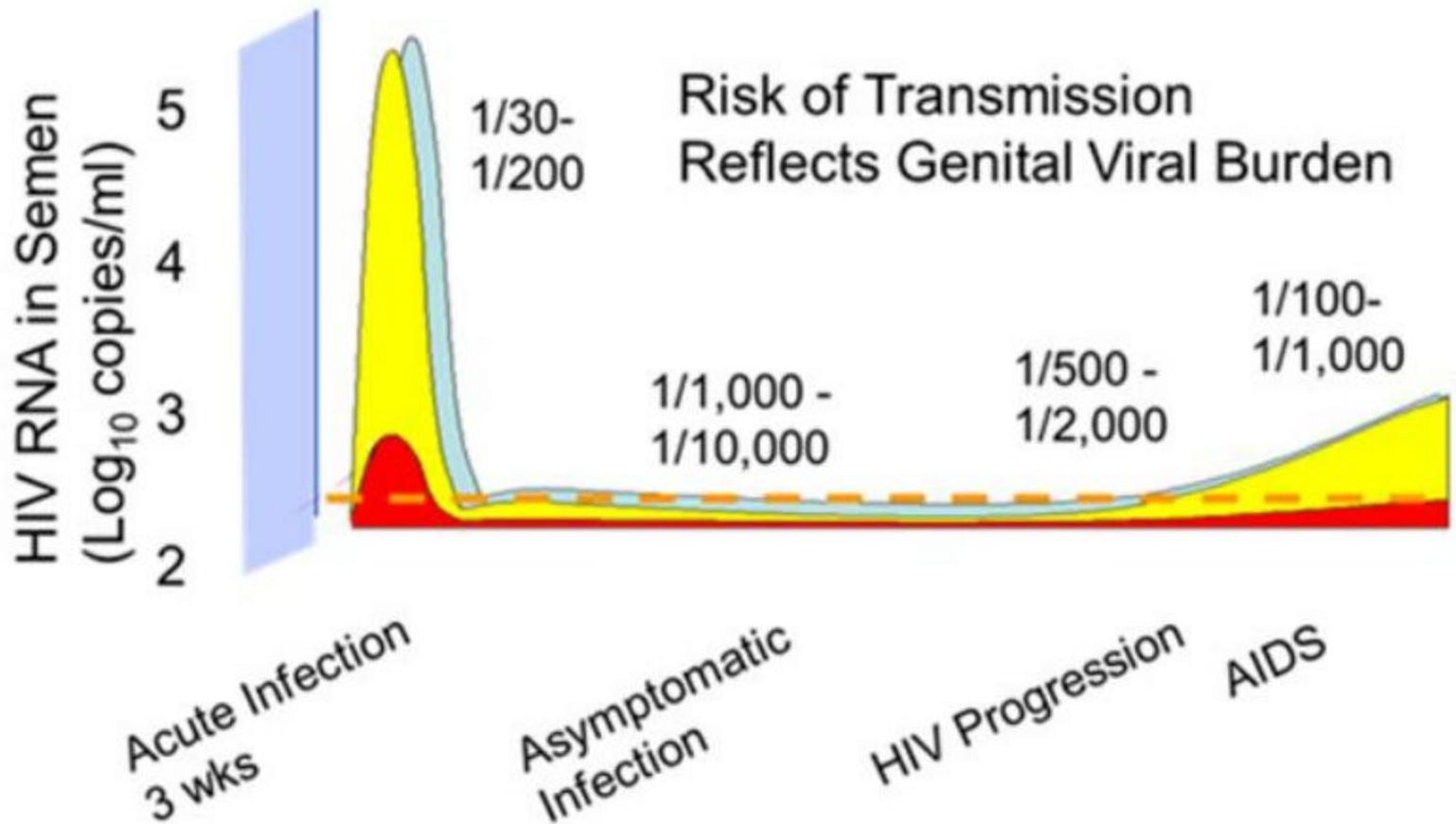
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- Blood: PRBCs, FFP, cryo., clotting factors, platelets, IVIG
- Semen
- Vaginal secretion
- Saliva
- Tears
- Breast milk
- CSF
- BAL fluid
- Amniotic fluid
- Transplanted organs (liver, kidney, heart, bone)

# Transmission risk estimates



# Risk of Sexual Transmission of HIV





# Healthcare workers

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

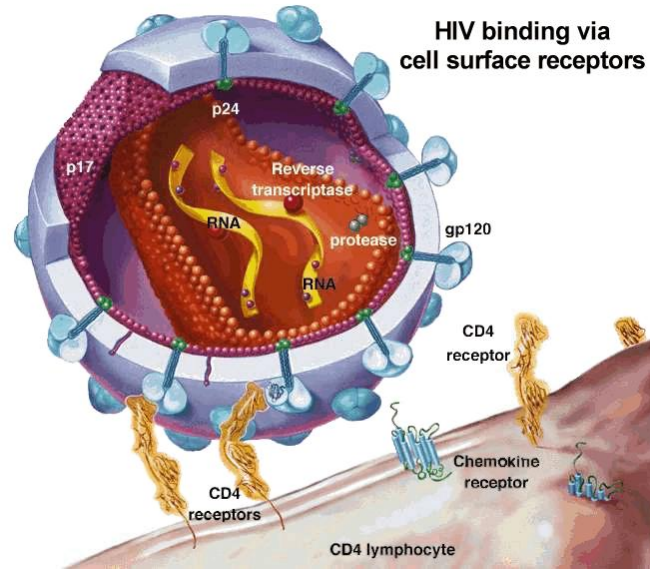
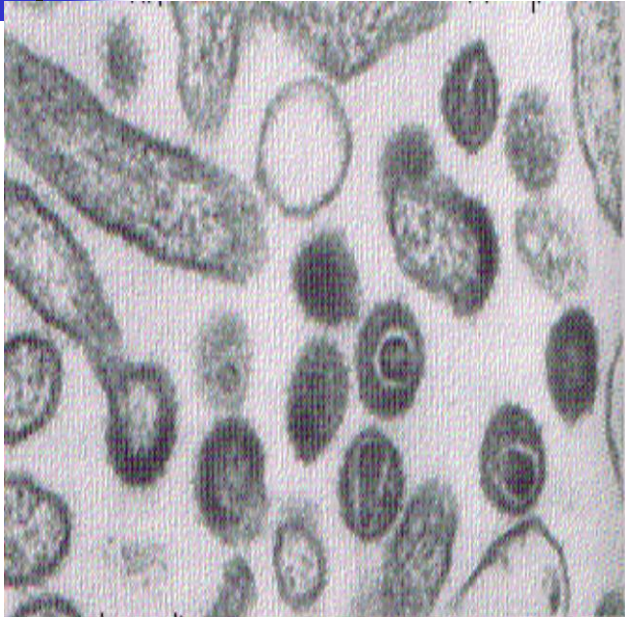
# One hand technique

# No recapping





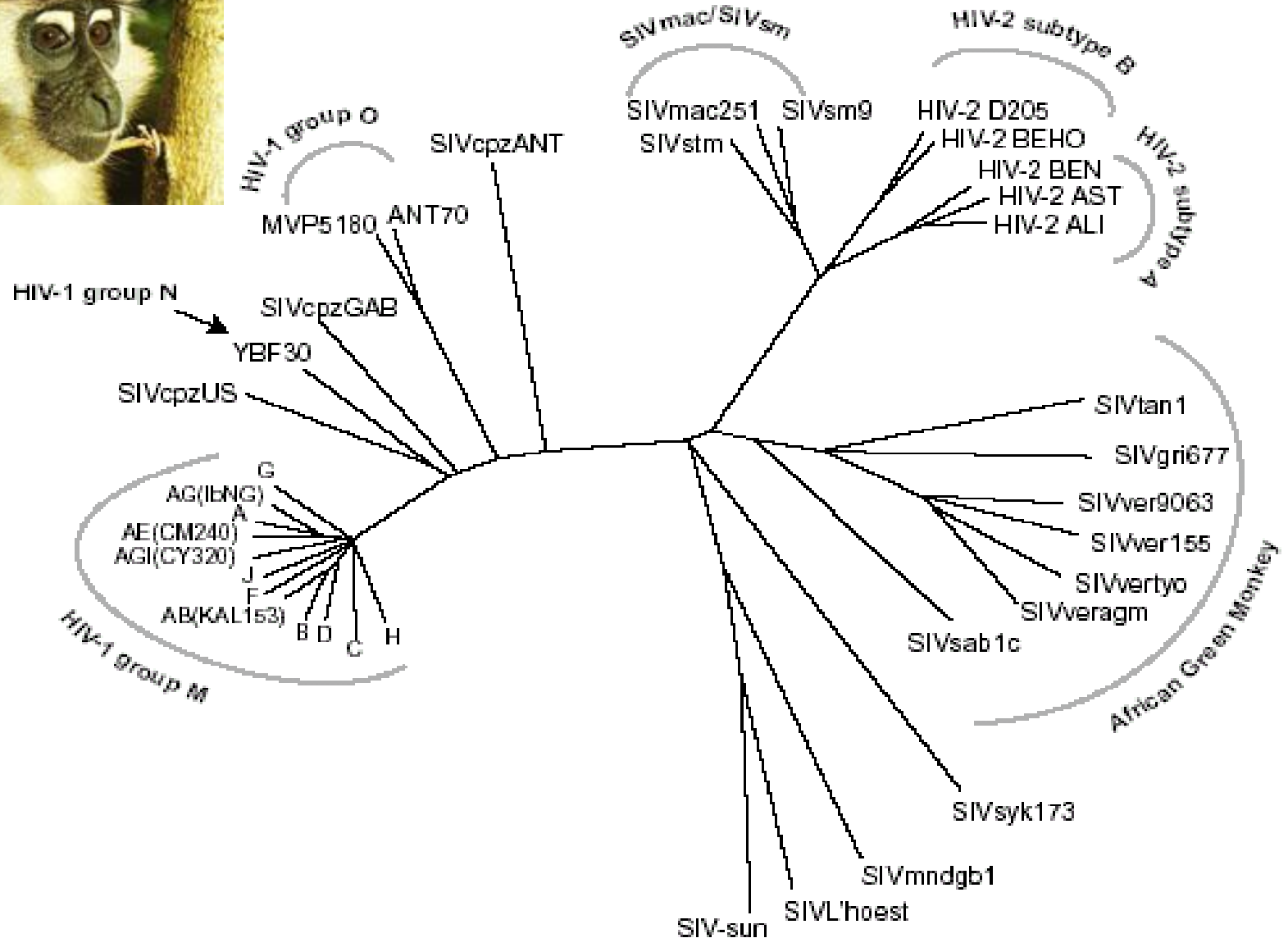
# HIV Structure



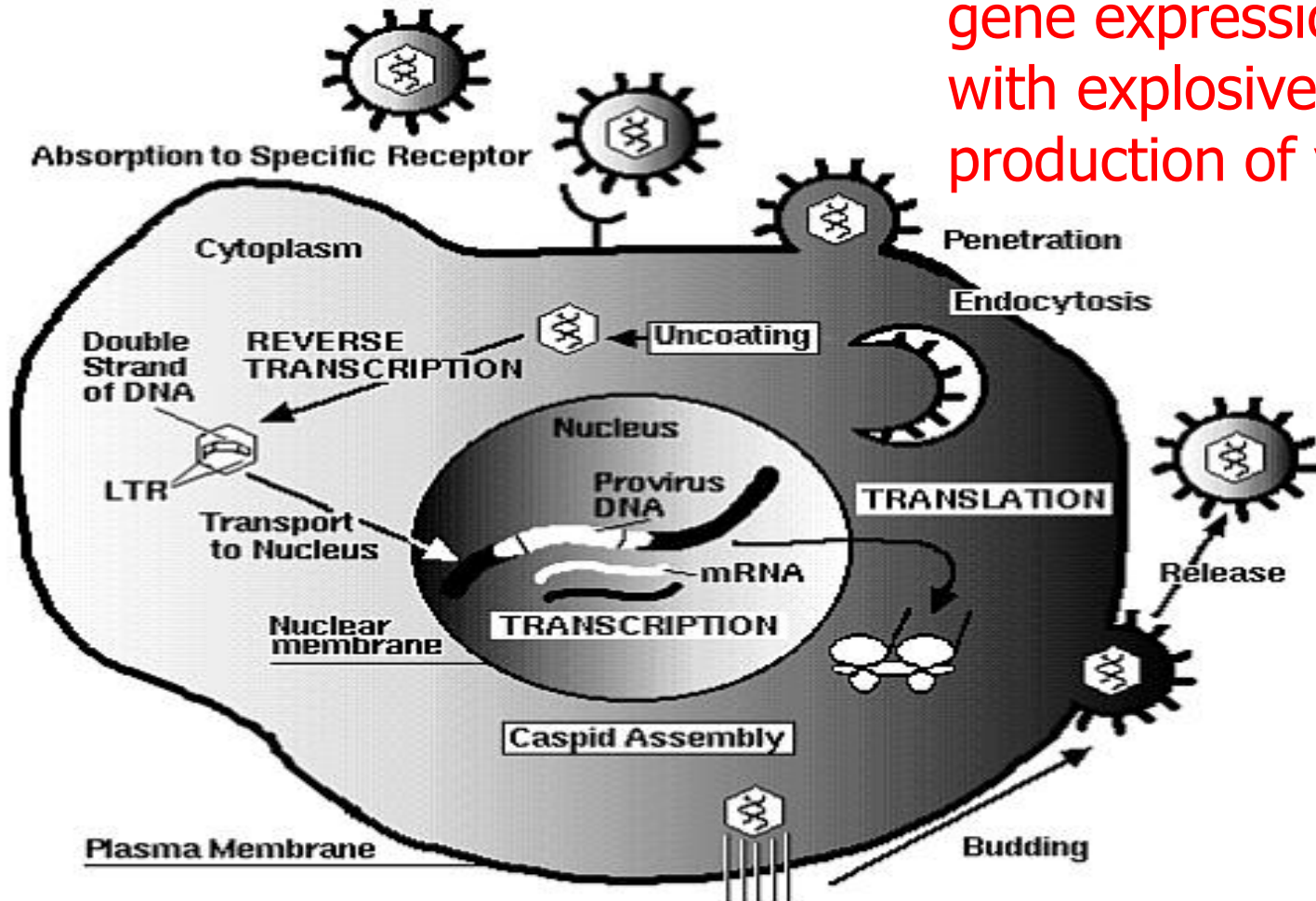
**HIV binding via CD4 & chemokine receptor**



# Phylogenetic tree

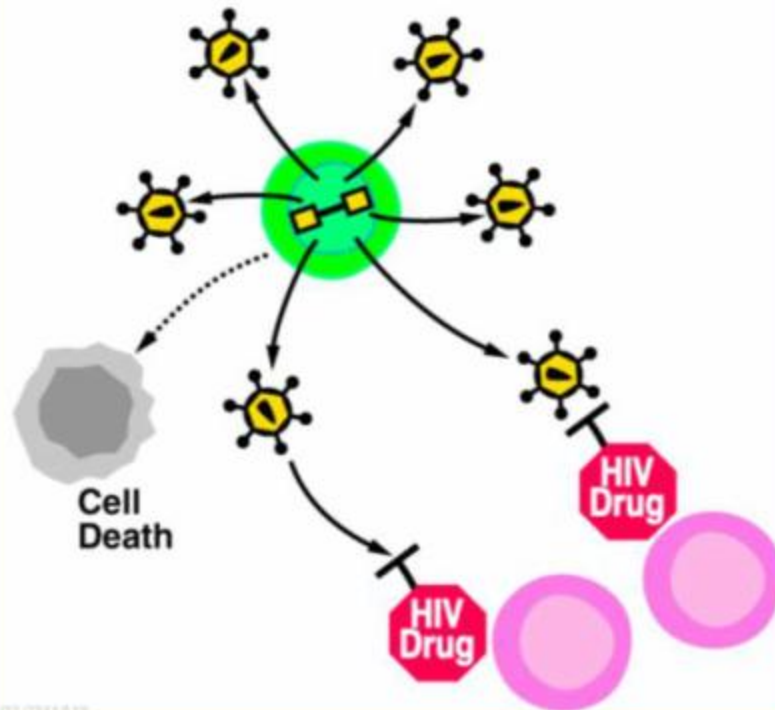


# Life cycle of HIV



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

## Productively Infected Cells

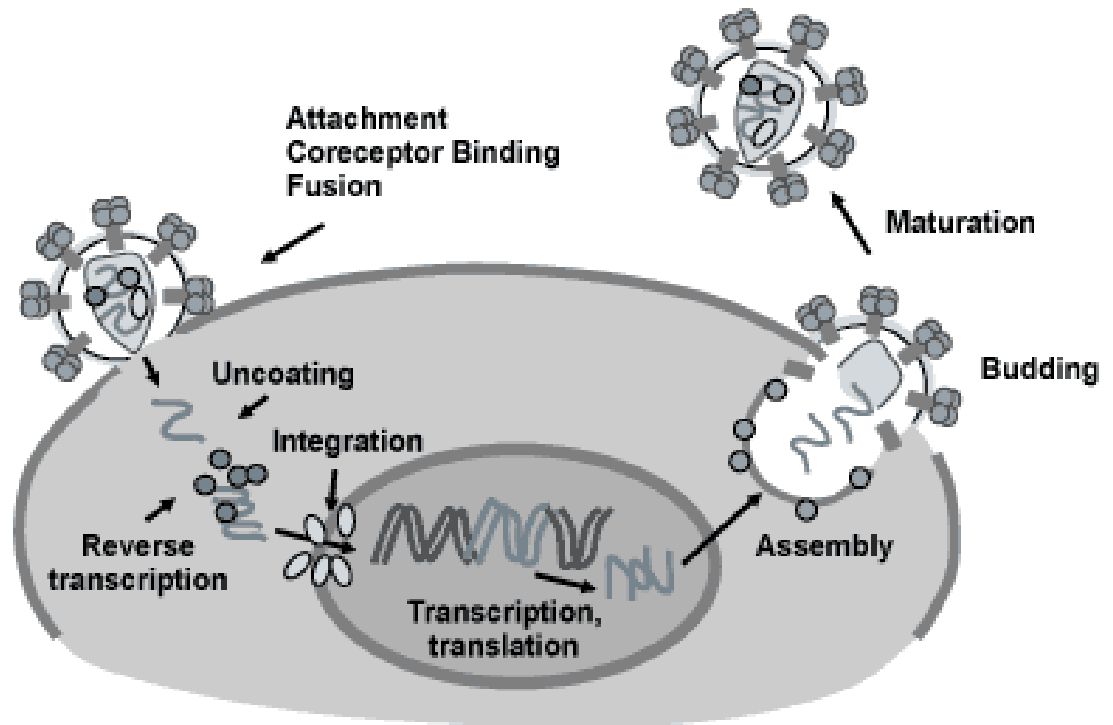


02/03/14 13:13

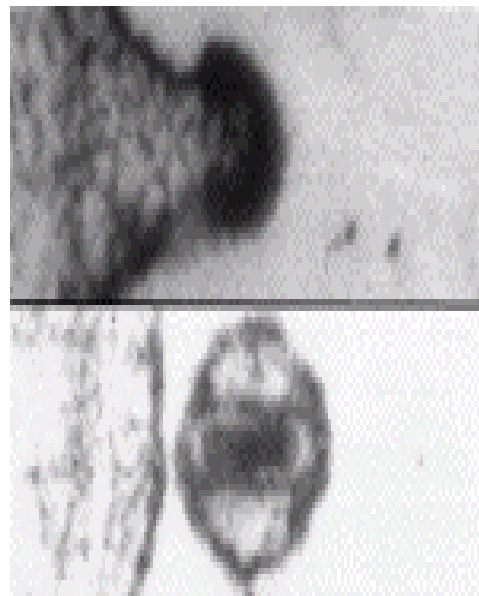
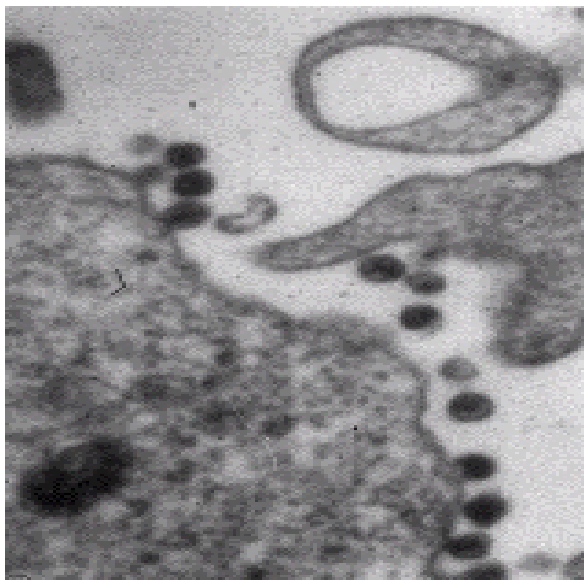
## Latently Infected Cells



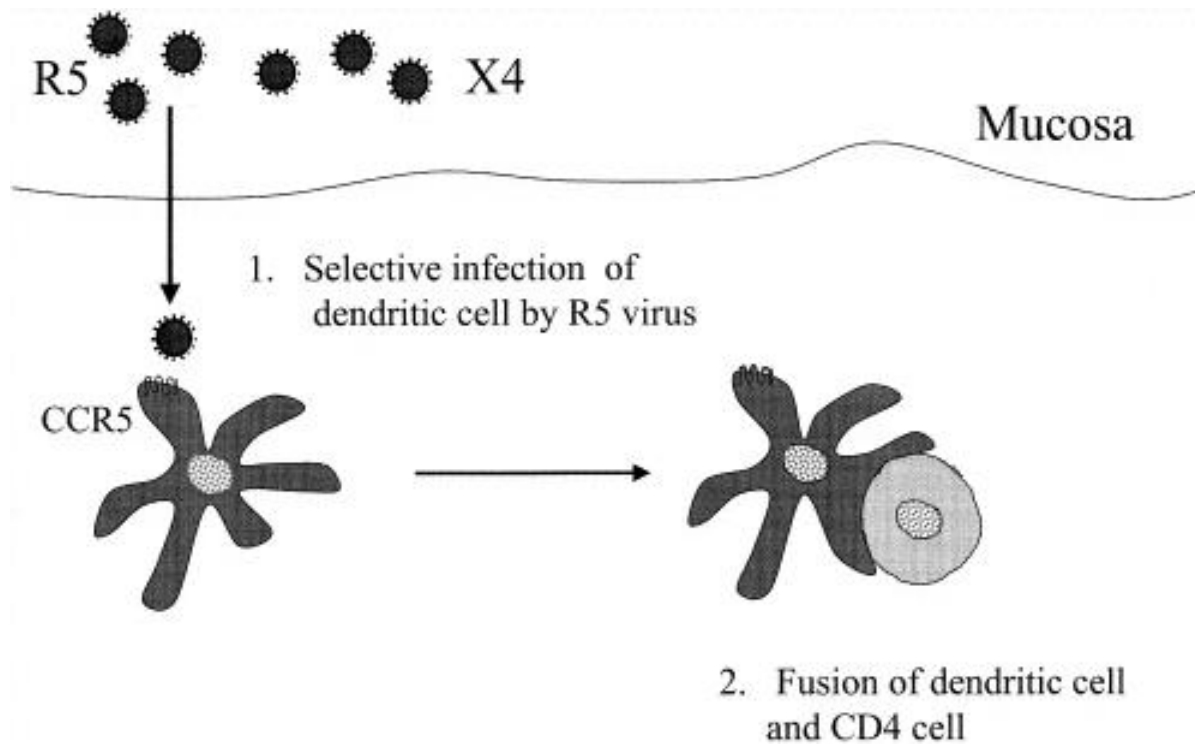
1. Attachment
2. Coreceptor binding
3. Fusion
4. Uncoating
5. Reverse transcription
6. Integration
7. Transcription
8. Translation
9. Assembly
10. Budding
11. Maturation



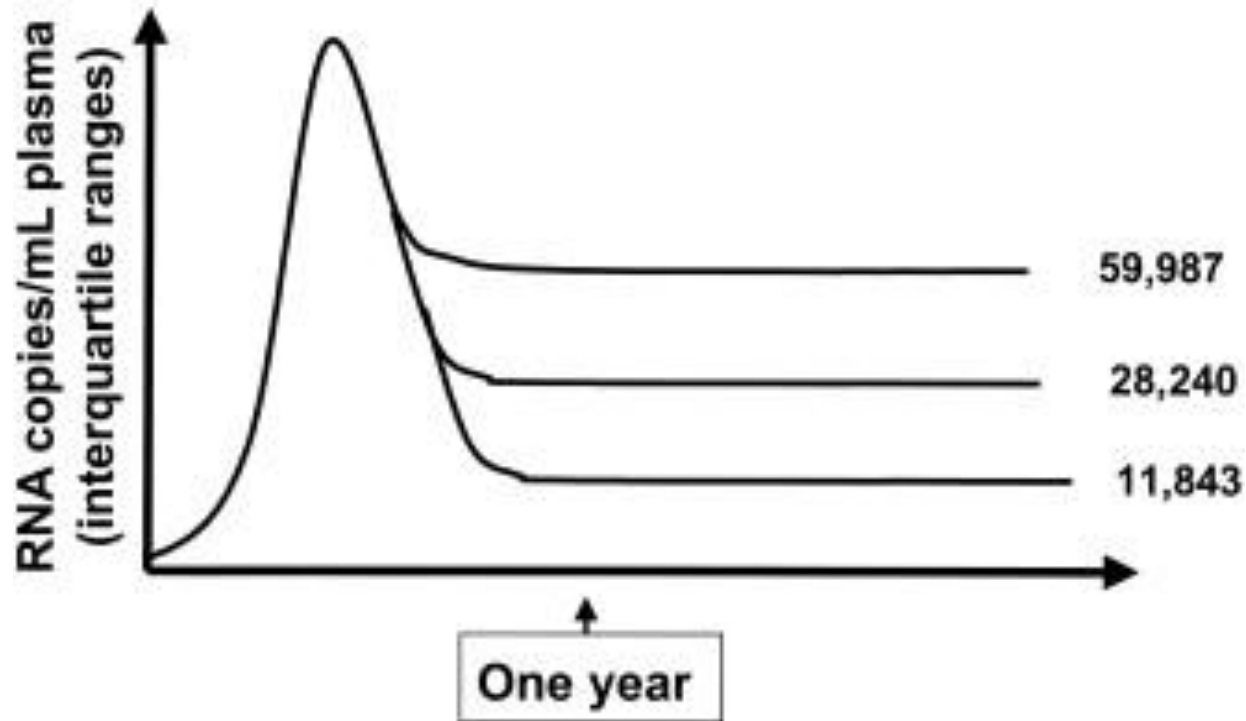
# HIV budding



# Transmission

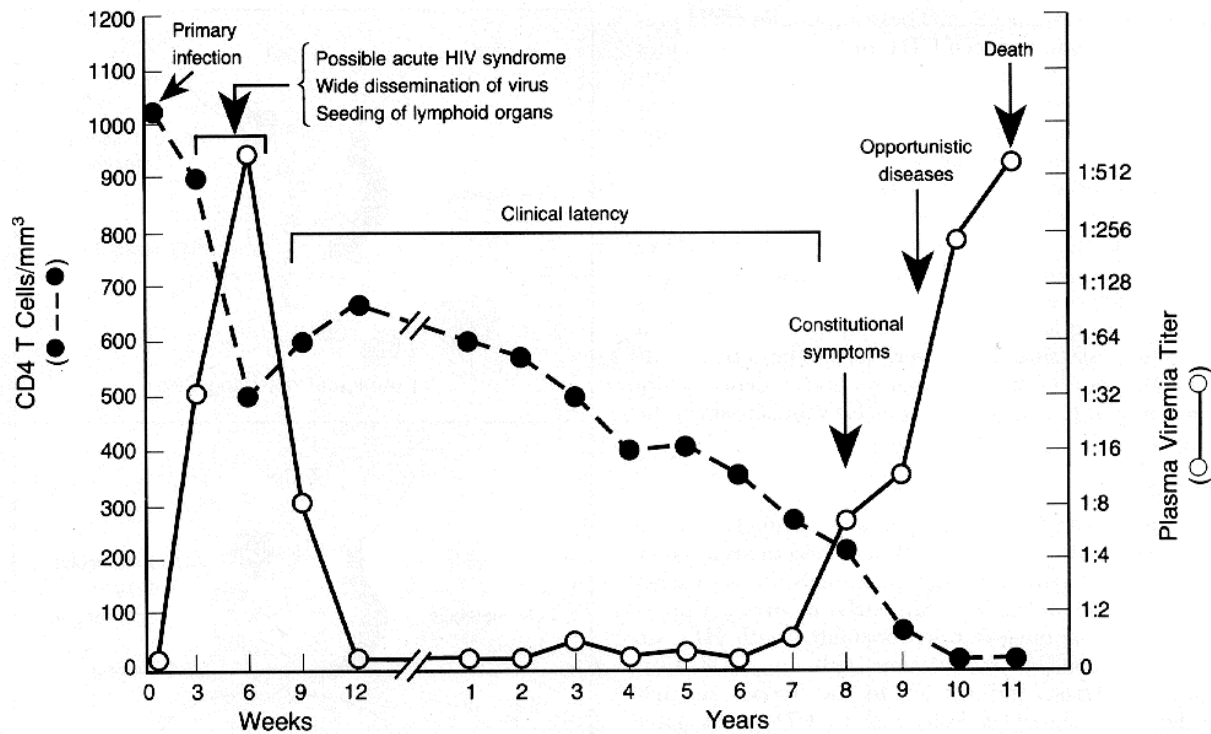


# Viral steady state

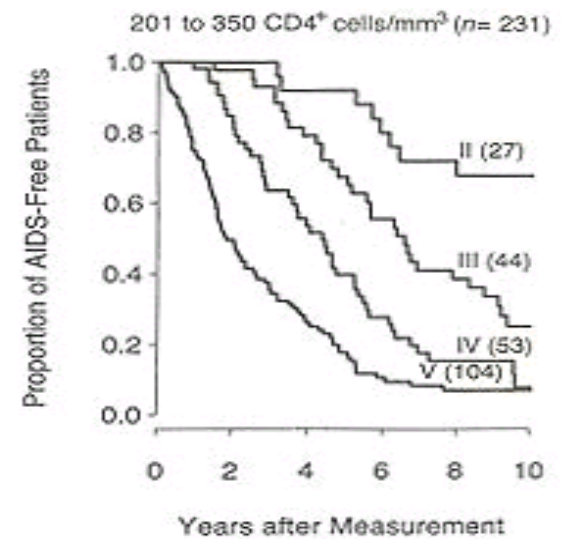
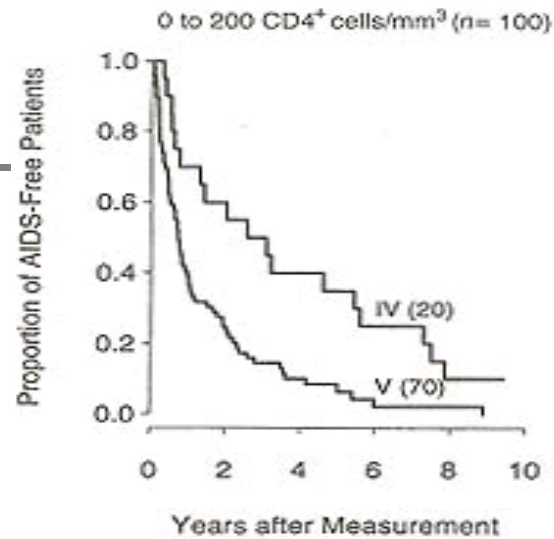
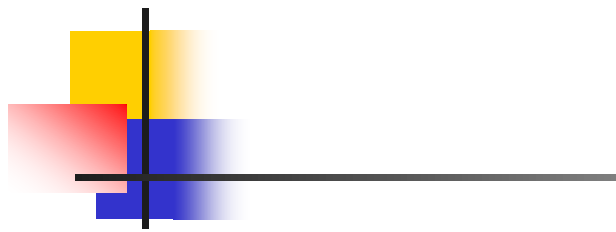




# Course of HIV infection



# Viral load & CD4 as predictors for progression



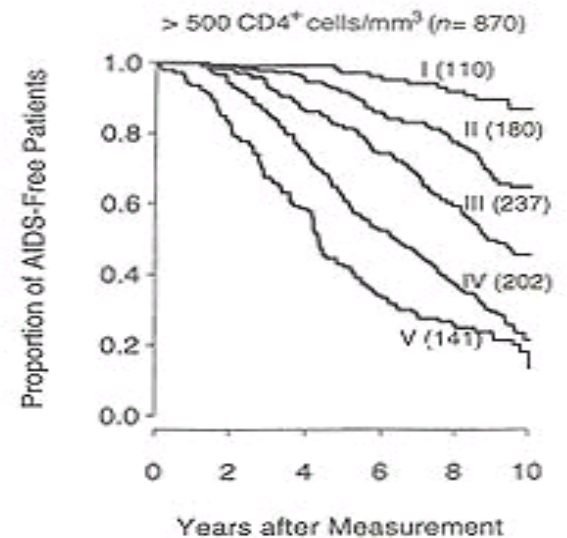
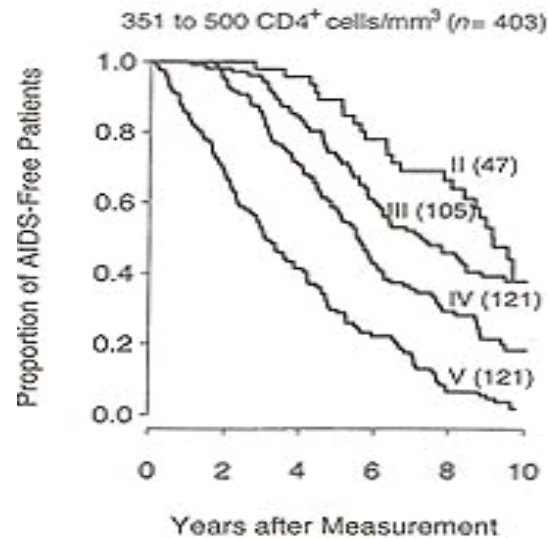
I, 500 copies/mL or less

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

---

- 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)



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

---

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

- **Rare presentation**

- Guillain-Barré Syndrome
- aseptic meningitis
- hepatitis

- completely asymptomatic

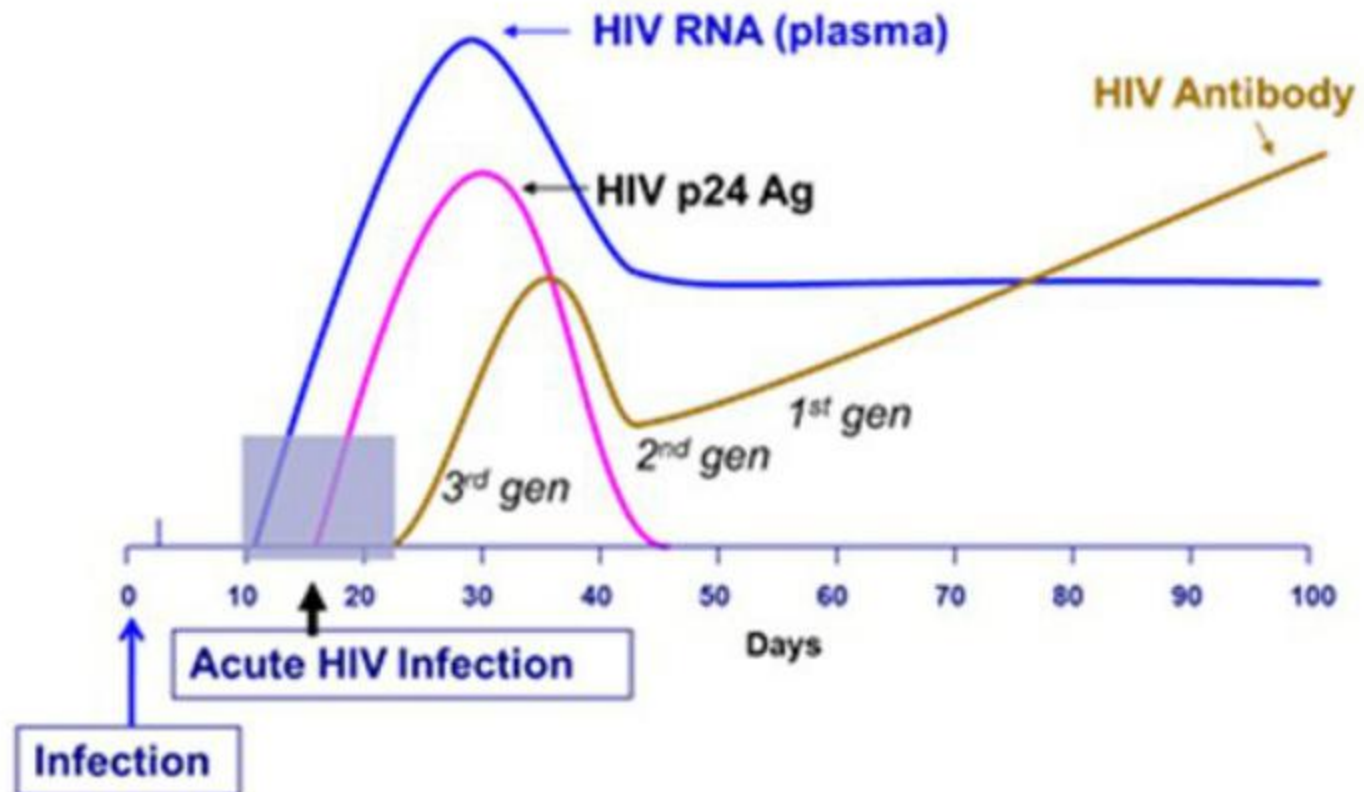


# RNA test and DX of acute HIV

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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



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.

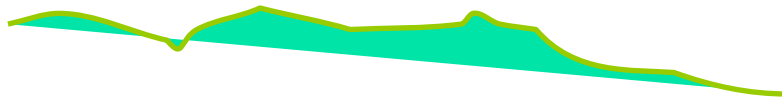
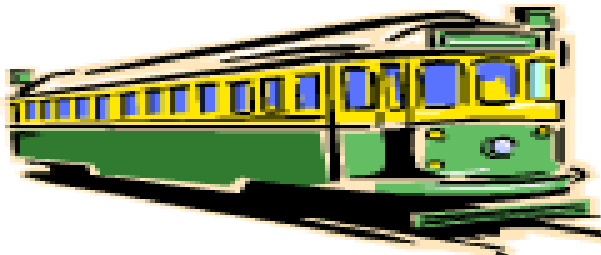


# Persons recommended for evaluation of acute HIV infection with available appropriate tests

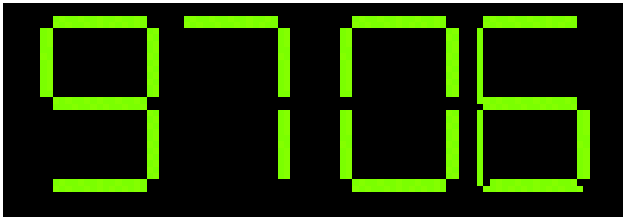
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- All of the following risk groups, ESPECIALLY with **history of an illness with clinical features compatible with acute HIV ("mono" or "flu-like" illness, regardless of severity)**:
- recent sexual or needle-sharing exposure with a known HIV-infected 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
- Pregnant and breastfeeding women

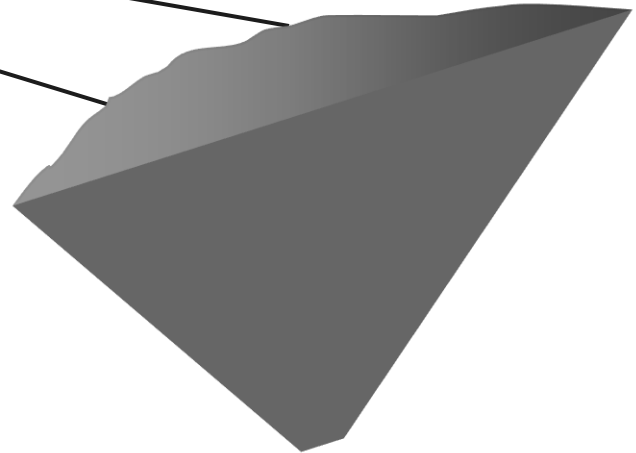
# Viral Load (V.L) & CD4 count



**CD4**



**Viral load**





# HIV = destruction of immunity

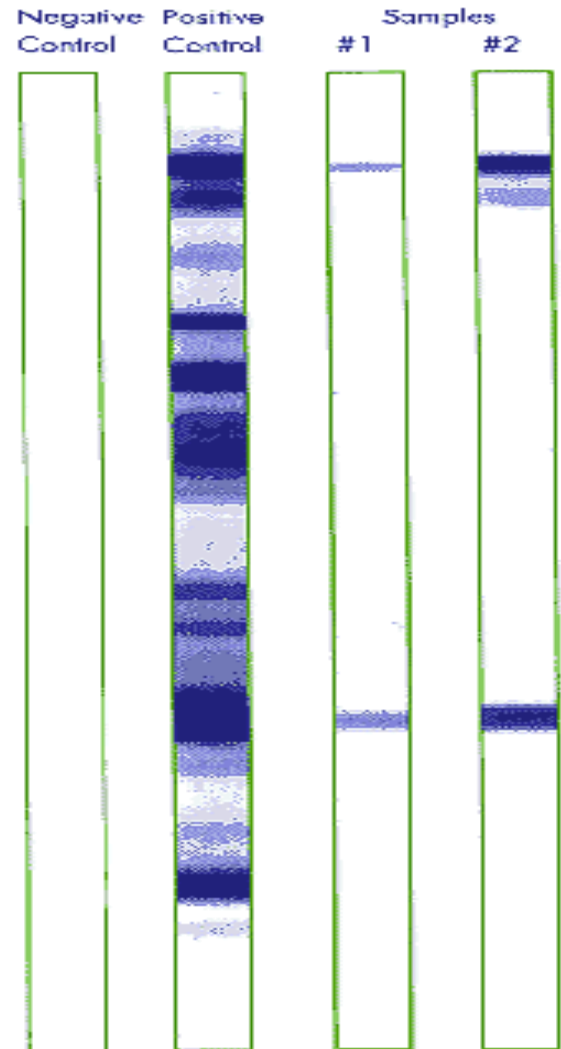
- Destruction of CD4 cells
- Evasion of immune response
- Lymph node pathology
- Exhaustion of immunity



# HIV Diagnosis

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

## 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



# 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)

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- 1) Candidiasis
- 2) Cervical cancer
- 3) Coccidioidomycosis
- 4) Cryptococcosis
- 5) CMV
- 6) Encephalopathy
- 7) HSV
- 8) Histoplasmosis
- 9) TB
- 10) Cryptosporidiosis
- 11) Lymphoma
- 12) PCP
- 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”

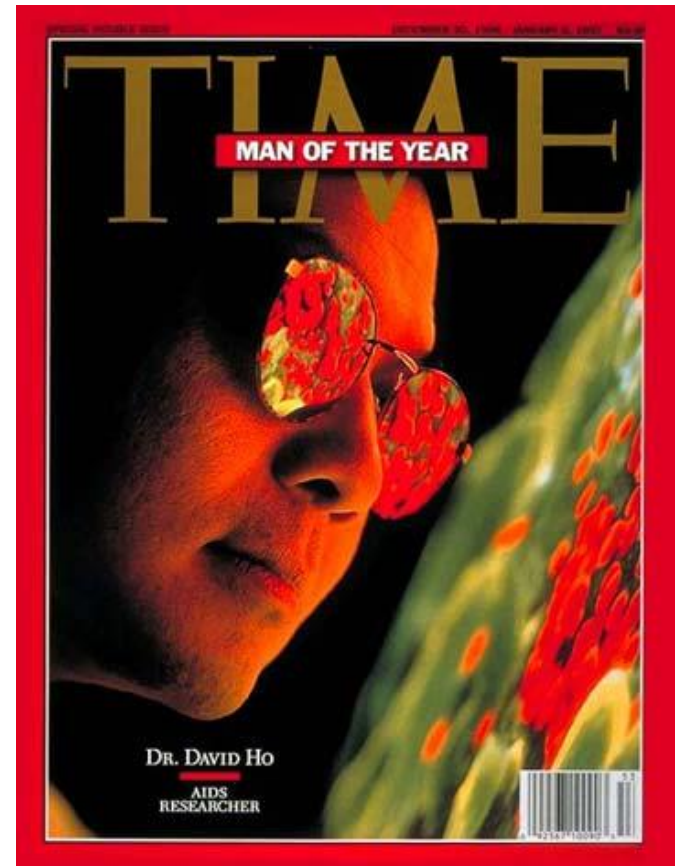
Usually: 2 NRTI + PI

□ Aim:

- Suppress viral load
- Increase CD4

□ Disadvantages:

- Toxicity
- Cost





# Indication to start HAART

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All patients with HIV should be offered treatment





# 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