



# Human immunodeficiency virus (HIV)

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Dr Faris Bakri

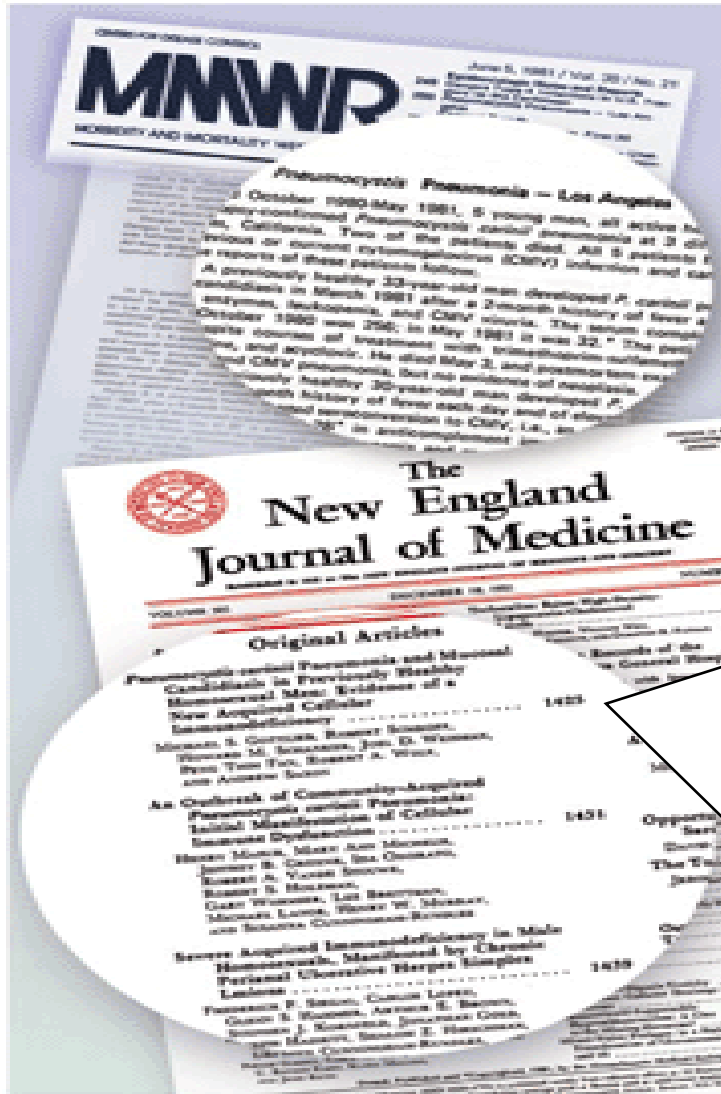
Jordan University Hospital



# Major points

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- Epidemiology
- Biology
- 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)

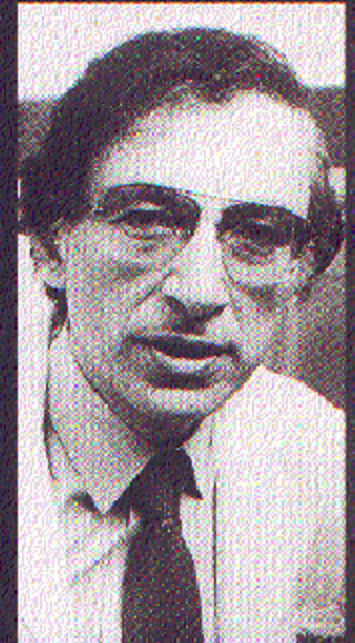
## WHO DISCOVERED THE AIDS VIRUS?



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

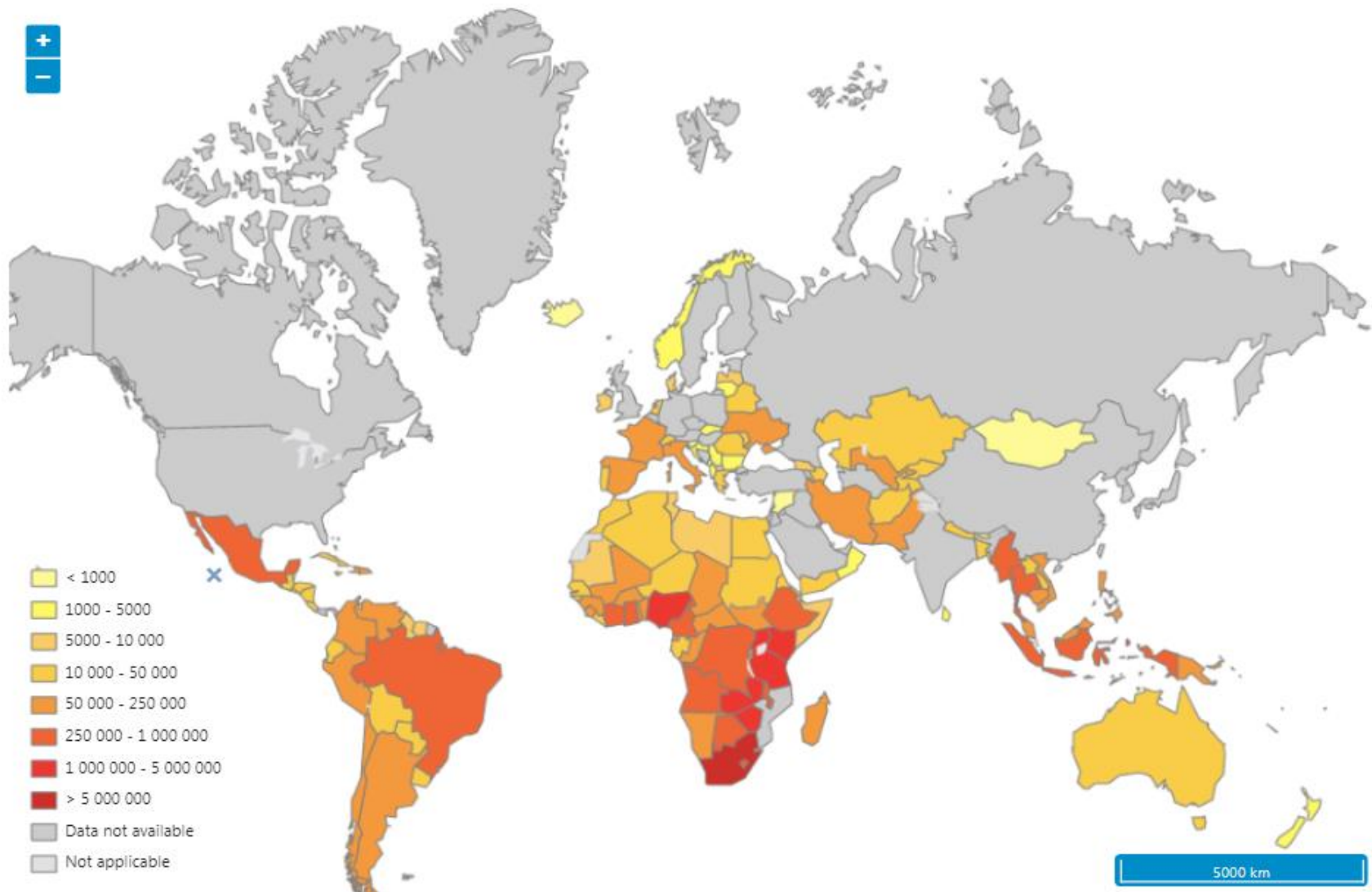


# Epidemiology

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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

# HIV: people living with HIV in 2021





# Huge burden...

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- **84.2 million** [64.0–113.0] since start of epidemic.
- **38.4 million** [33.9–43.8] **alive in 2021.**
- **40.1 million** [33.6–48.6] **died** since start of epidemic

<https://www.unaids.org/en/resources/fact-sheet>

**FIGURE 0.1** New HIV infections, by region, 2015–2021

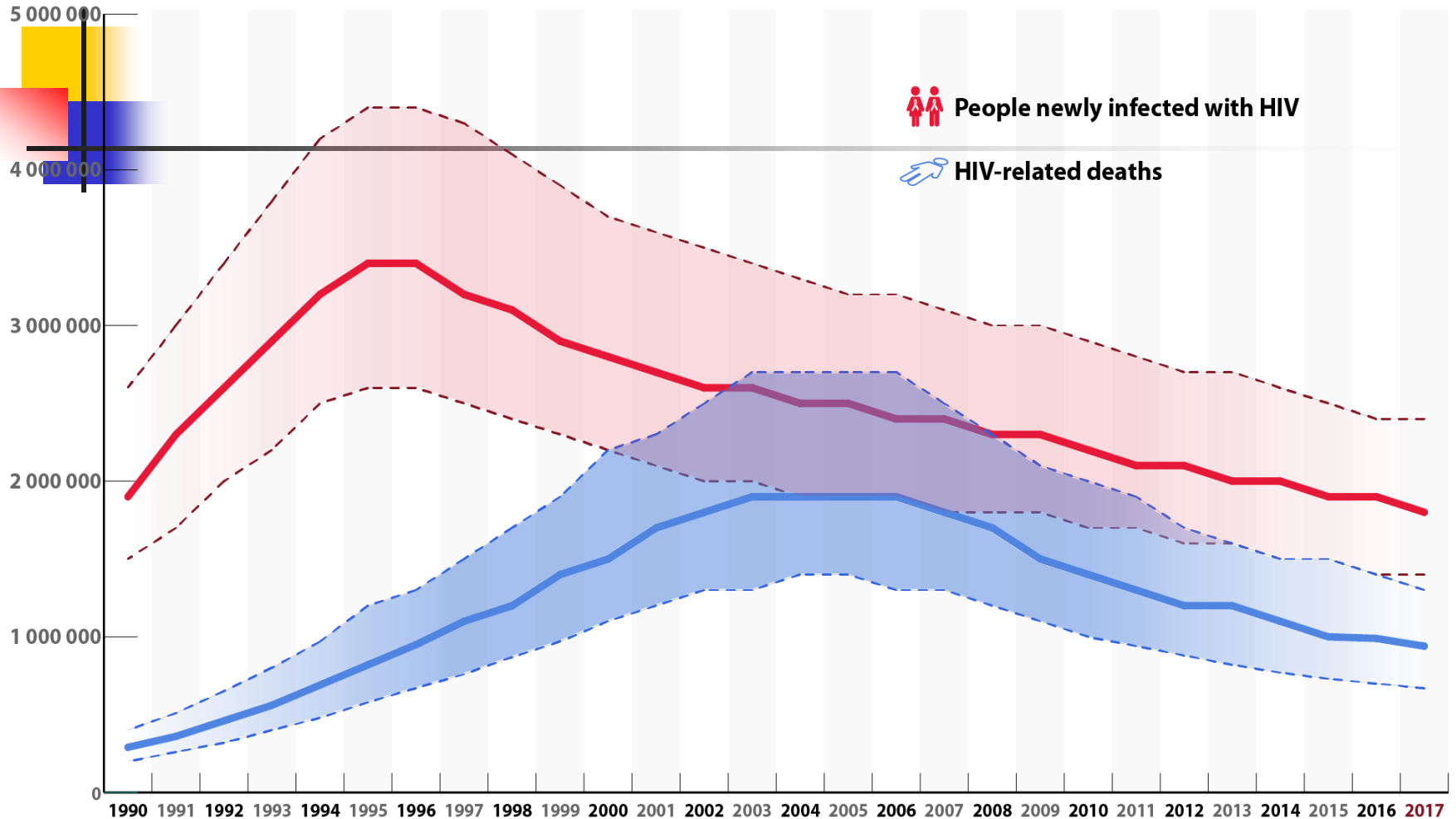


Source: UNAIDS epidemiological estimates, 2022 (<https://aidsinfo.unaids.org/>).

Incidence ↑

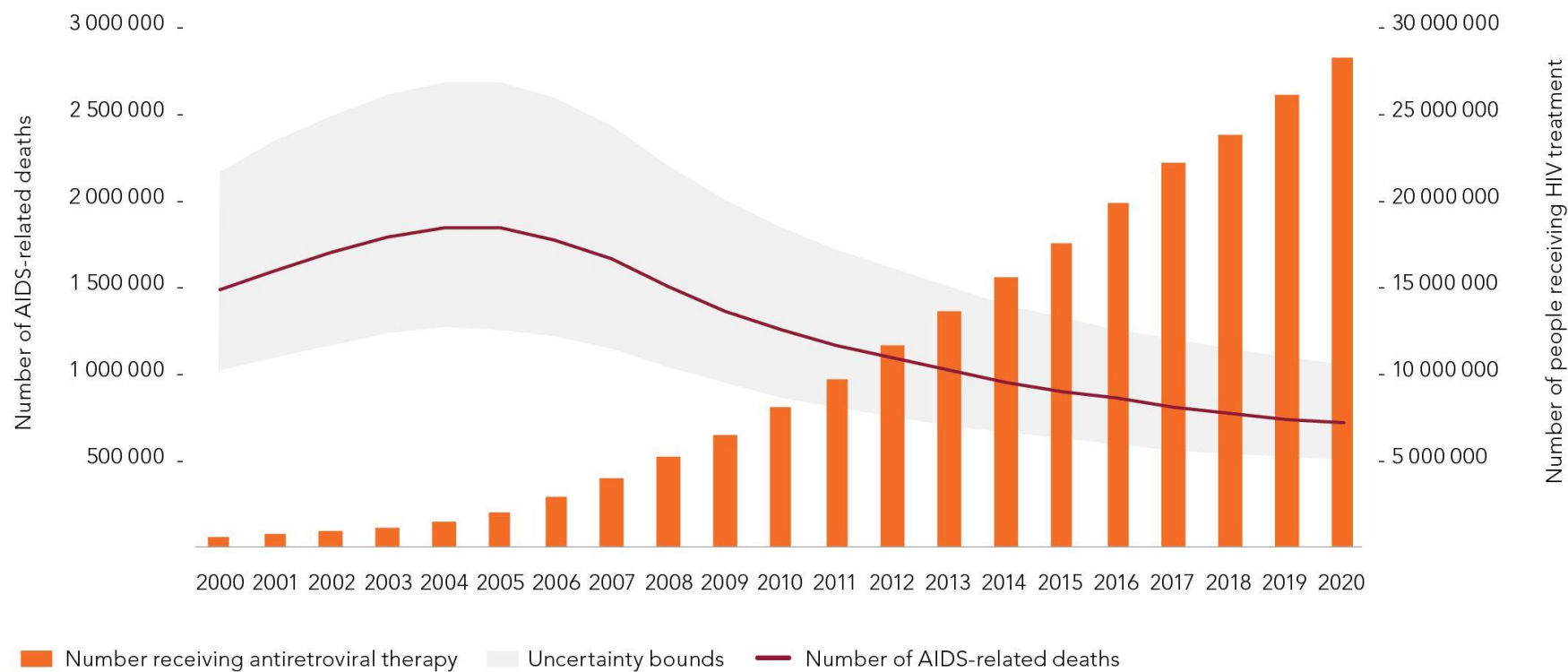


# Decline in HIV incidence and mortality over time



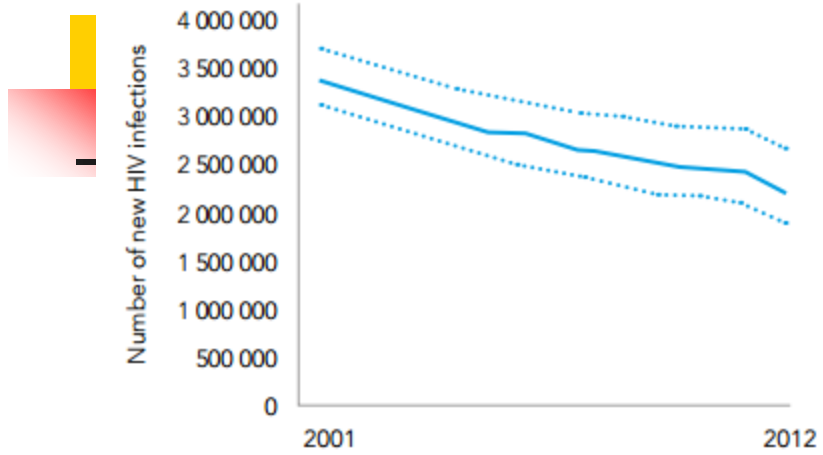
Source: UNAIDS/WHO estimates

## Numbers of AIDS-related deaths and people receiving HIV treatment, global, 2000–2020

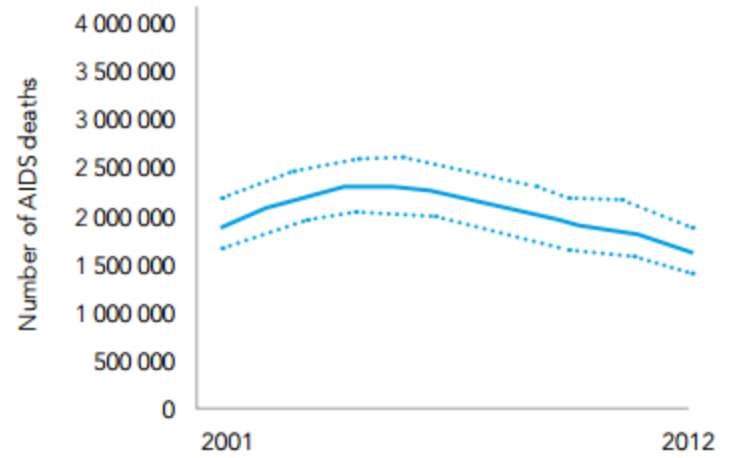


Source: UNAIDS epidemiological estimates, 2021.

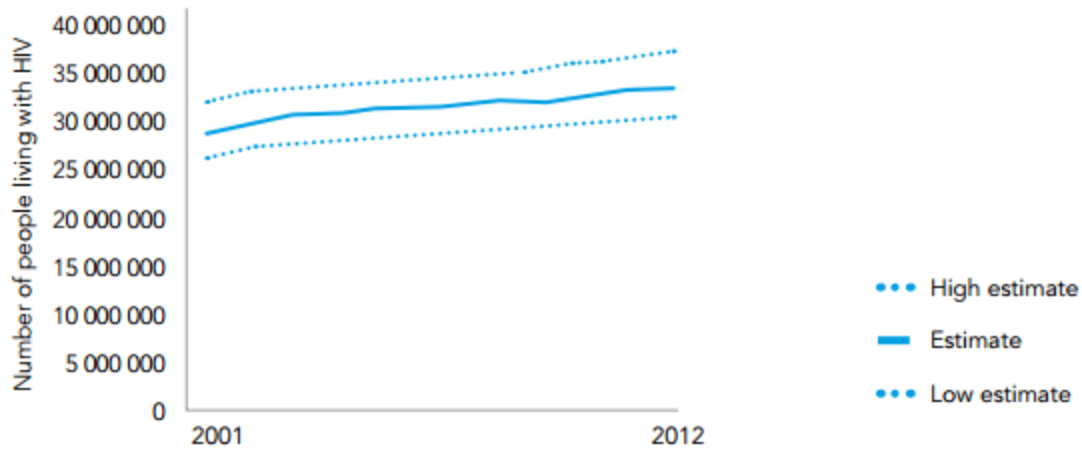
### NEW HIV infection Globally 2001-2012



### IDS Deaths Globally 2001-2012



### People living with HIV Globally 2001-2012



- High estimate
- Estimate
- Low estimate

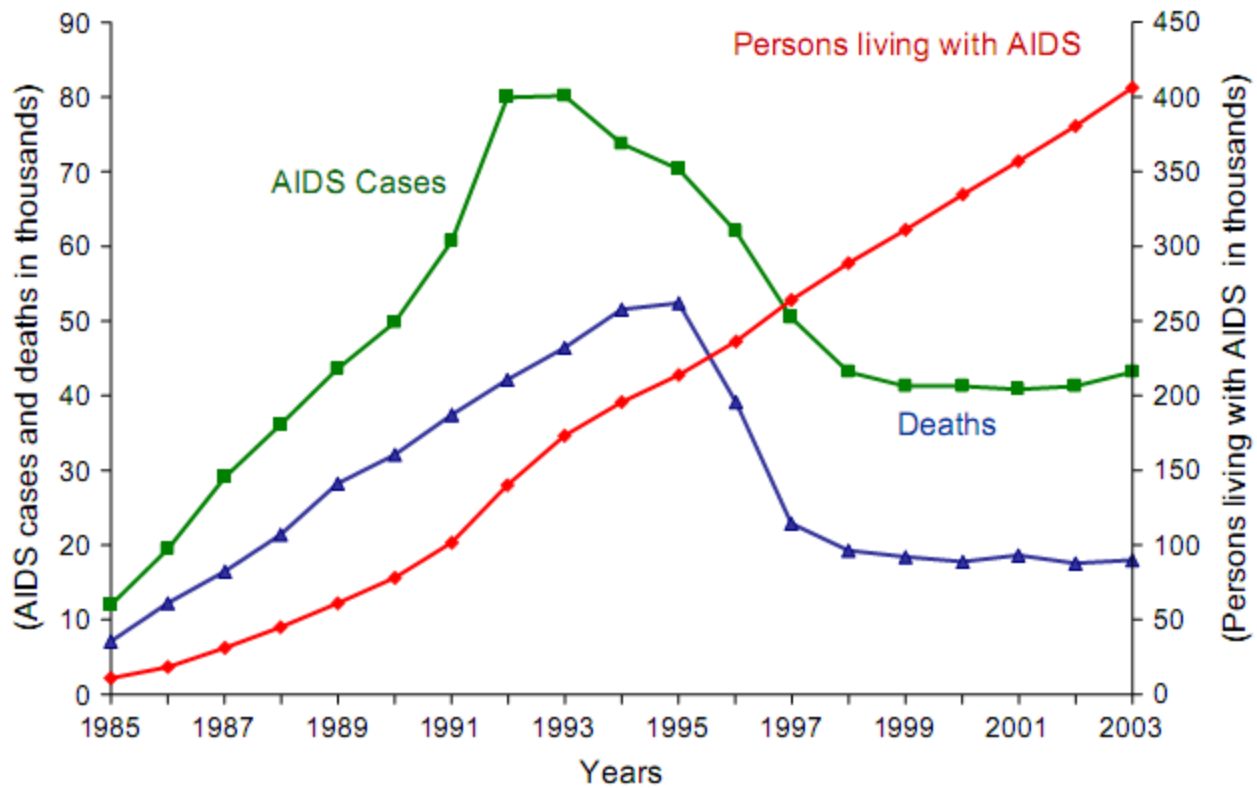
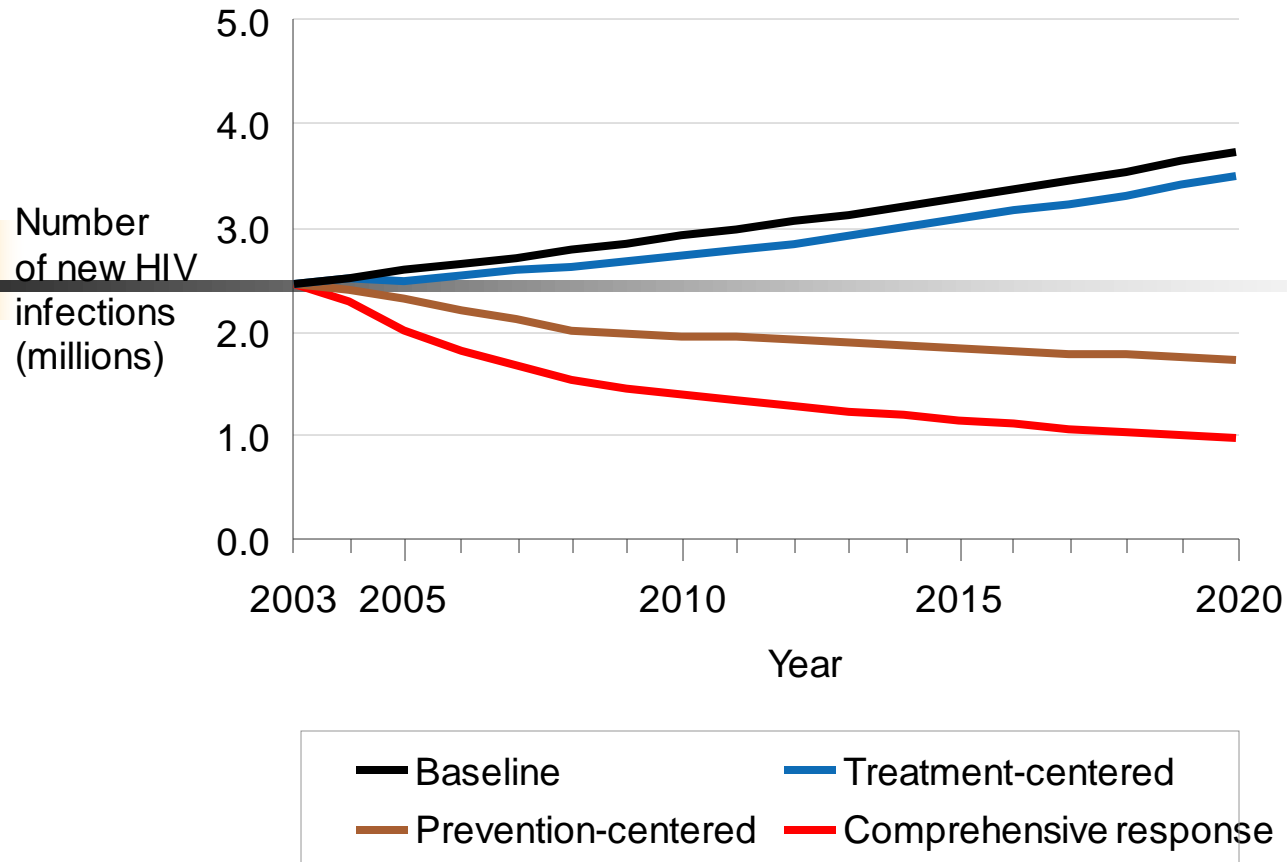
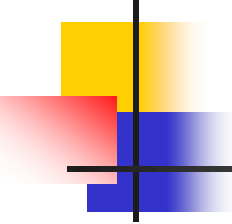


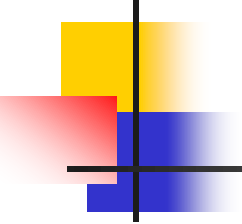
Fig. 3. AIDS cases, deaths, and persons living with AIDS in the United States, 1985–2003.

# 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

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- 38.4 million [33.9–43.8] are alive in 2021
  - 36.7 million [32.3–41.9] adults (15 years or older).
  - 1.7 million [1.3–2.1] children (0–14 years).
  - 54% of all people living with HIV were women and girls.

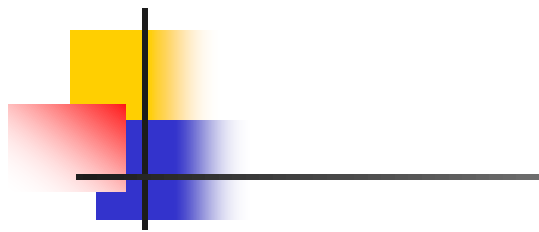
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- 1.5 million new cases / in 2021
  - 1.3 million in adults
  - 0.64 million in women (ie. 50% of infected were women)
  - 0.16 were children
  - 95 % in developing countries
  - 66% in subsaharan Africa
  - 16 million children were orphaned
  - 14 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**
- Causes:
  - Multiple sex partners
  - Prostitution
  - STD's
  - Mother to child transmission

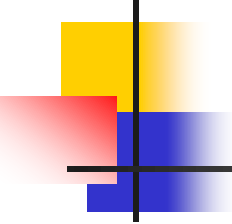






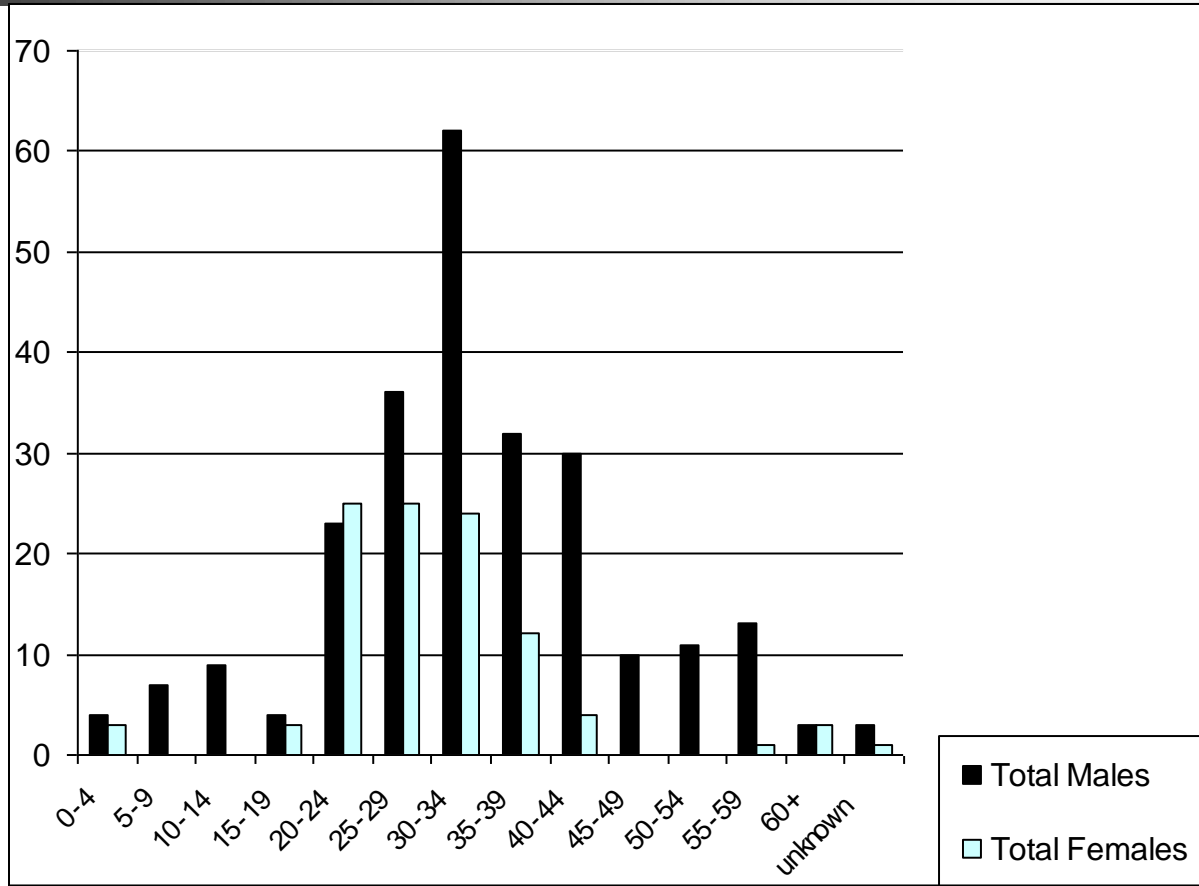
A 15 year old boy in Botswana has 90% chance of dying of AIDS



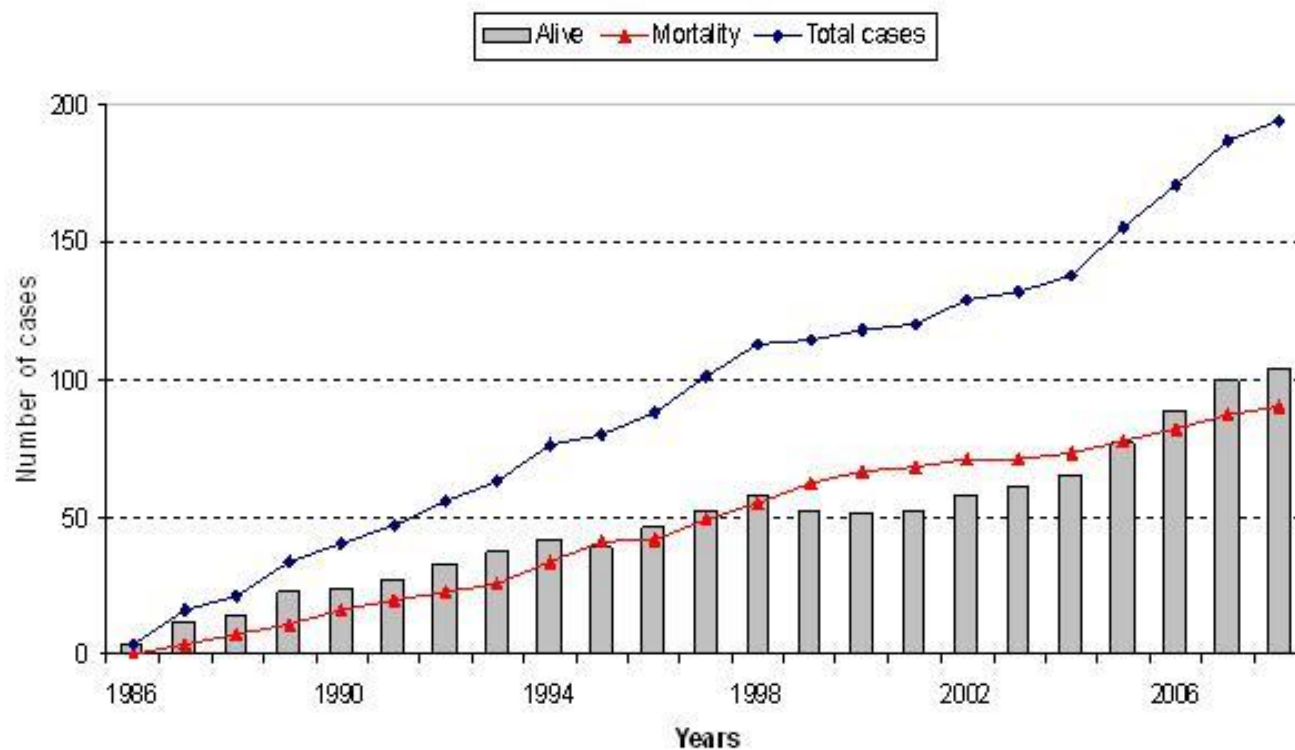
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- “...The AIDS epidemic continues to explode in **India, China, Russia, and eastern Europe** and may be more destabilizing than international terrorism”

M. Scheld

# HIV in Jordan



# HIV – Jordan: mortality



# Transmission

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



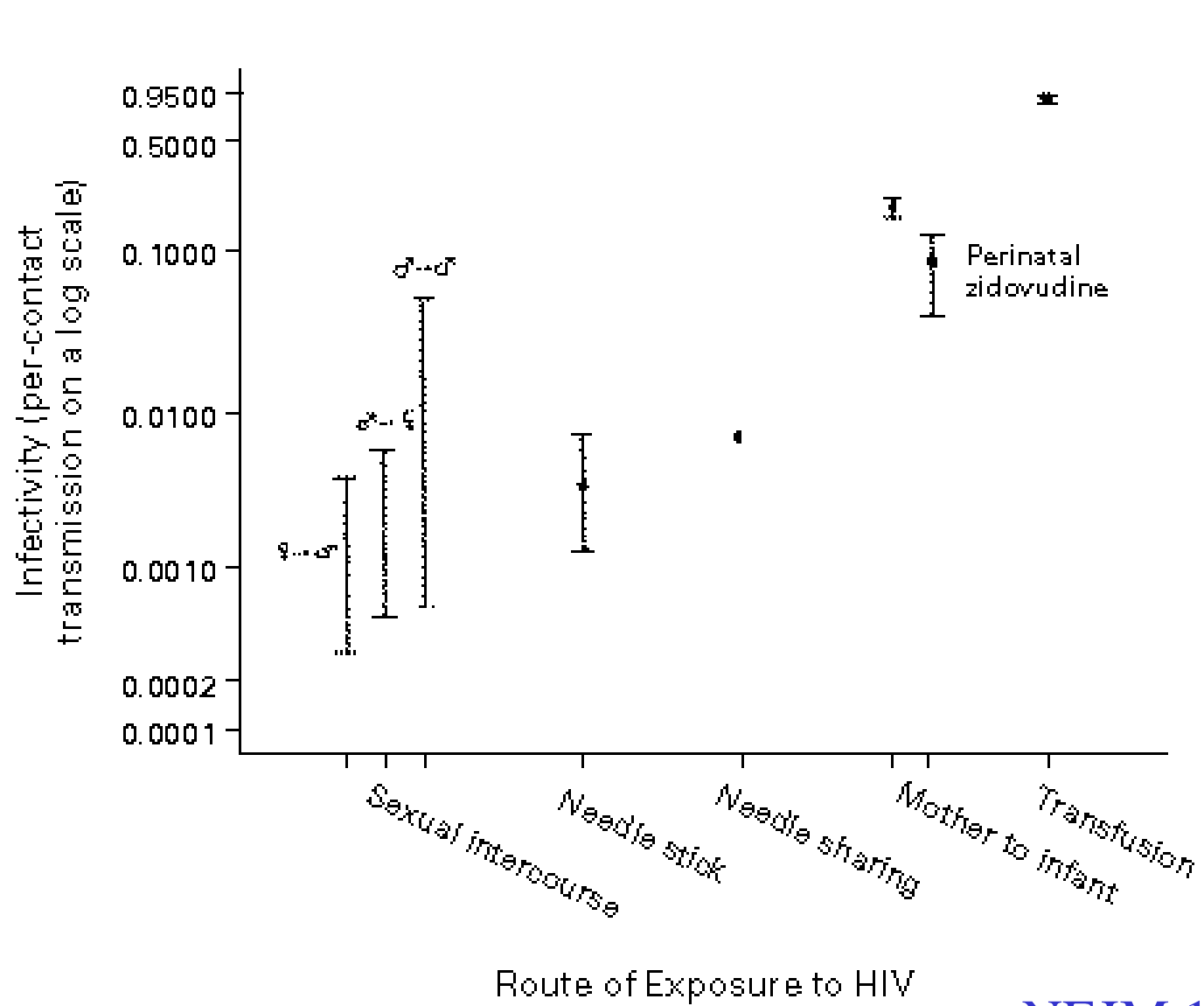


# All body fluids...

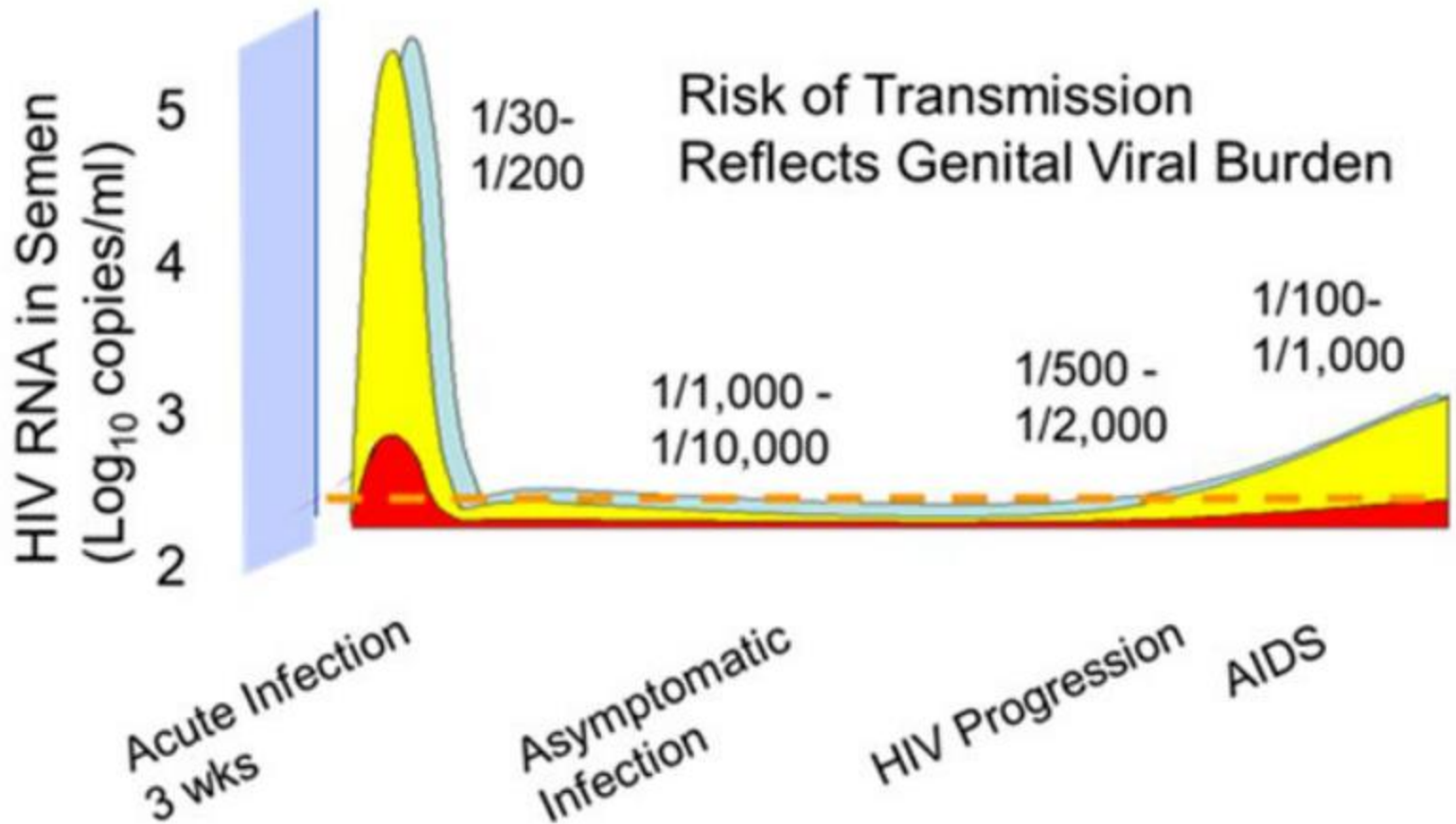
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- Blood: PRBCs, FFP, cryo., clotting factors, platelets, IVIG
- Semen
- Vaginal secretion
- Saliva
- Tears
- Breast milk
- CSF
- BAL fluid
- Amniotic fluid
- Transplanted organs (liver, kidney, heart, bone)

# Transmission risk estimates



# Risk of Sexual Transmission of HIV







# Healthcare workers

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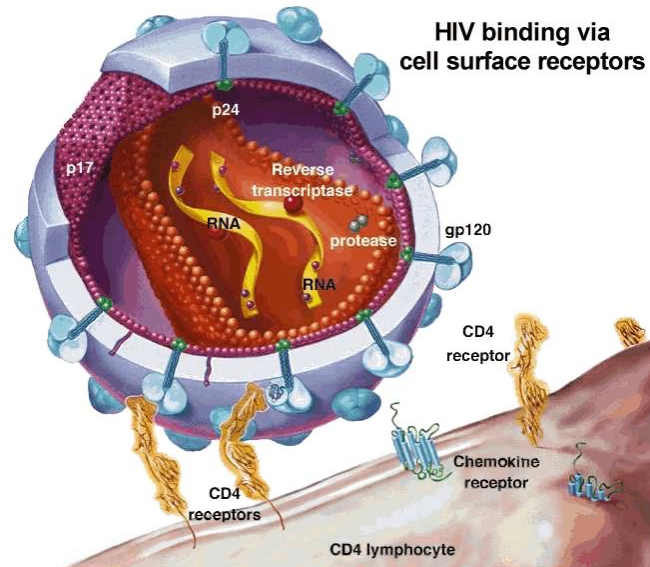
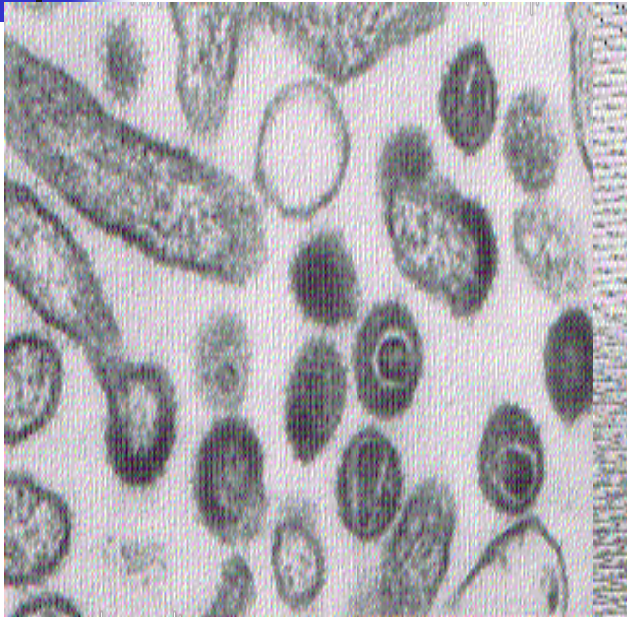
- Low risk
- 0.3%
- Universal precautions \*\*\*\*\*
  - Hand washing
  - Gloves, gowns, masks
  - Sharps
  - Open lesions...

# One hand technique

# No recapping



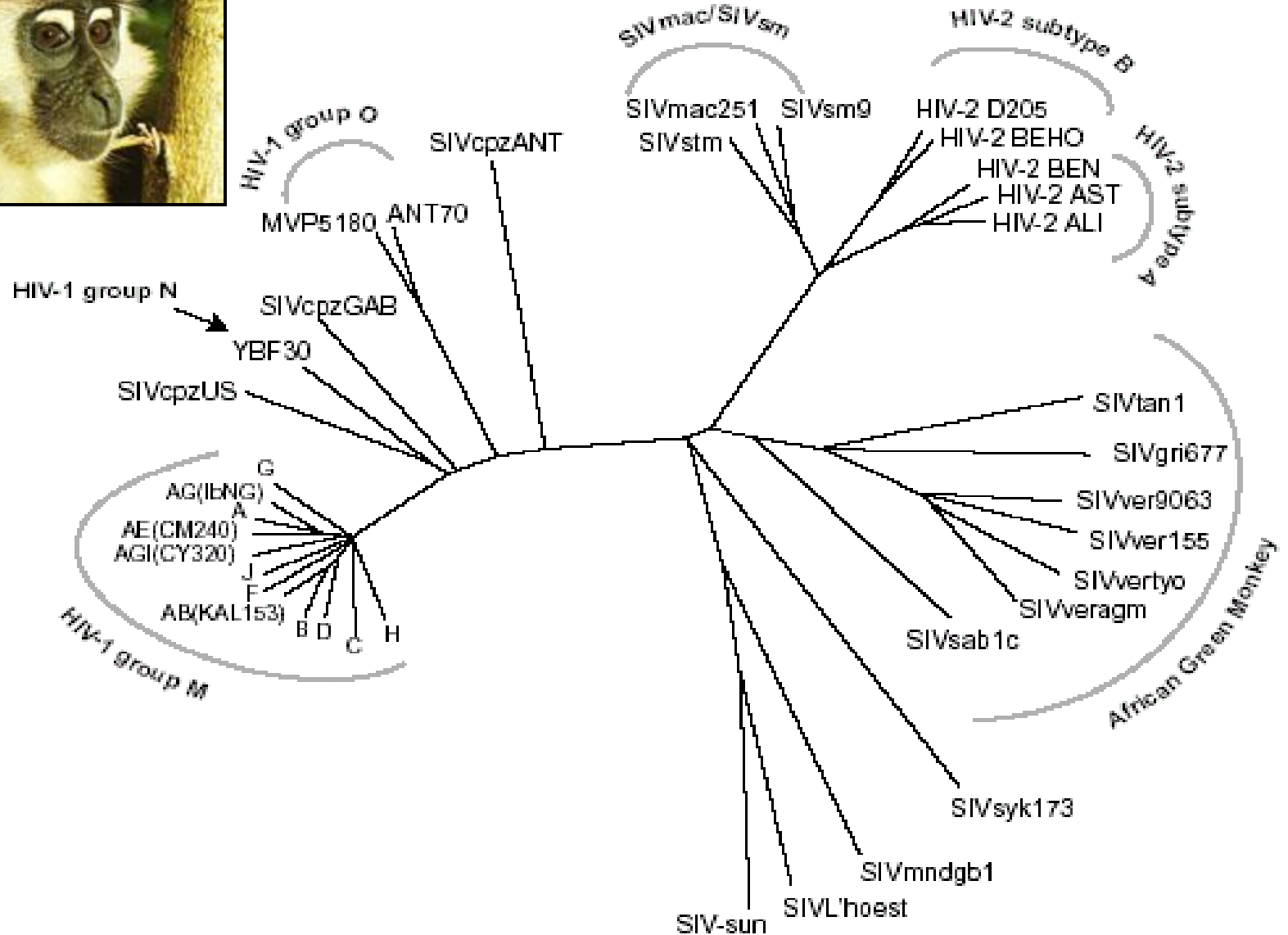
# HIV Structure



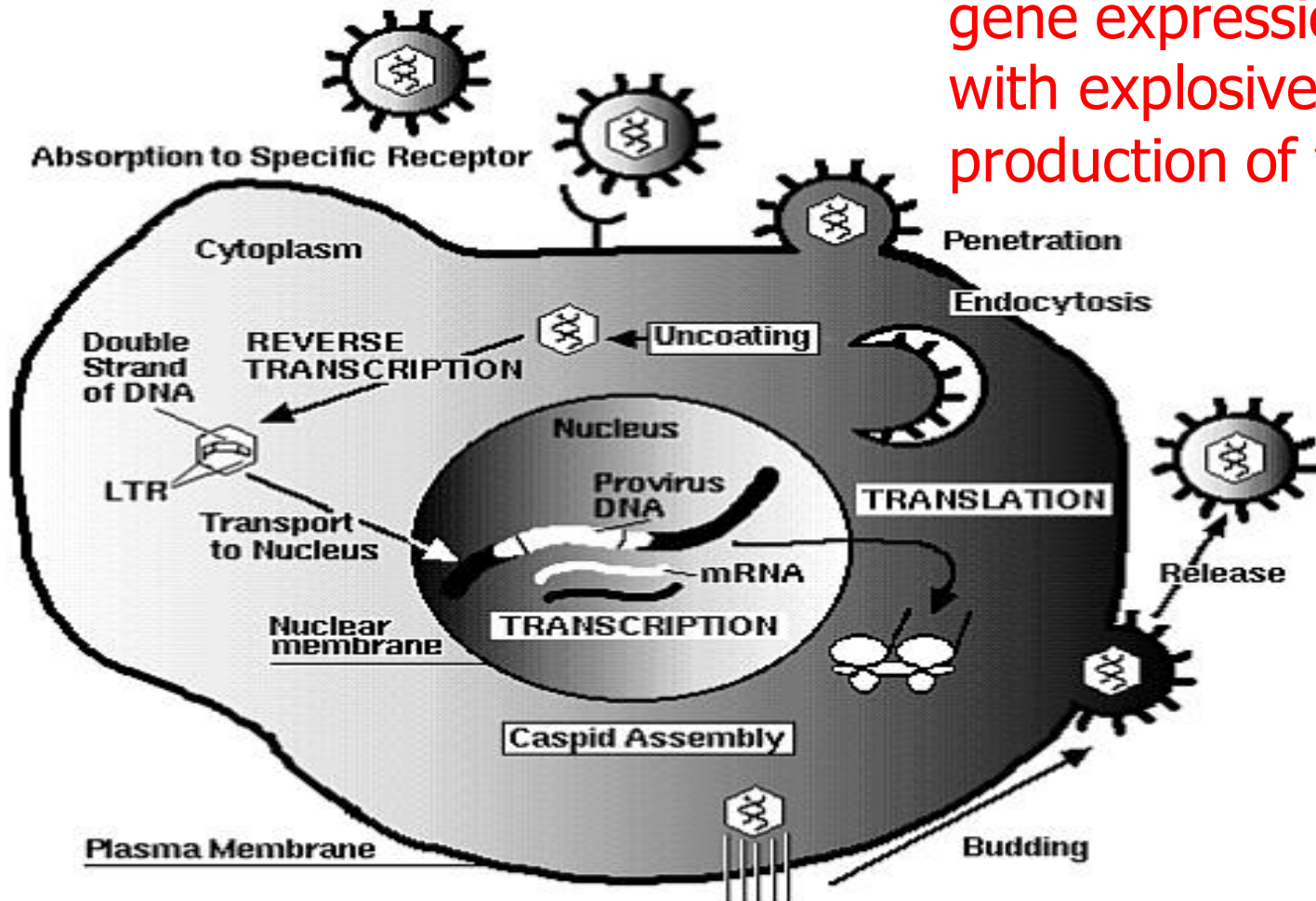
**HIV binding via CD4 & chemokine receptor**



# Phylogenetic tree

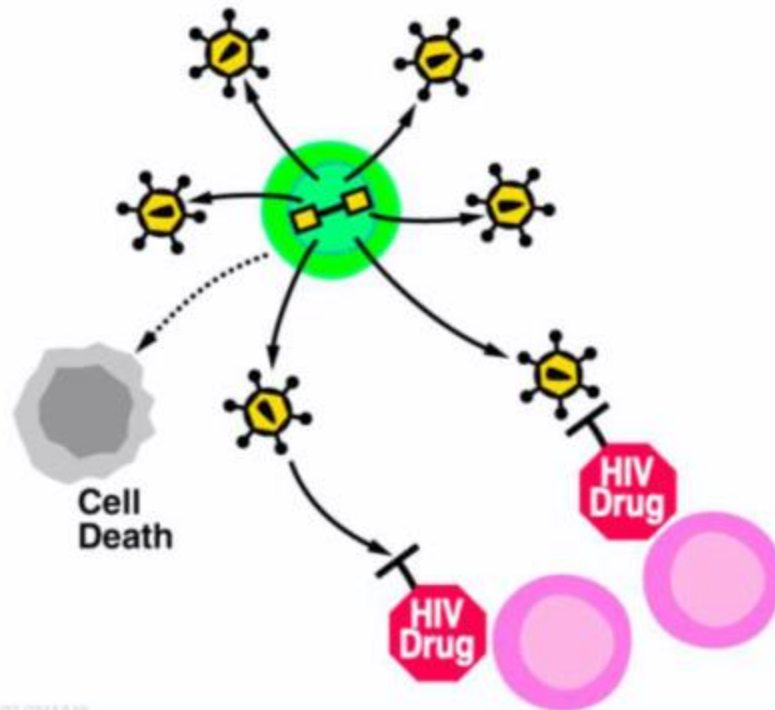


# Life cycle of HIV



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

## Productively Infected Cells

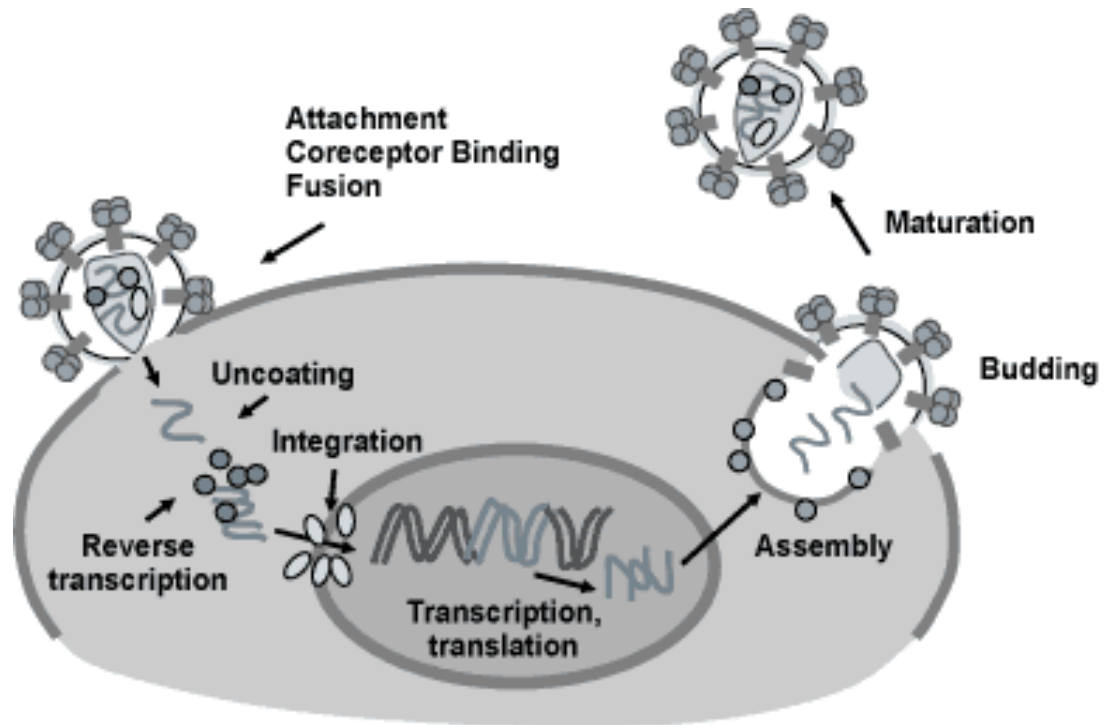


02/03/14 19

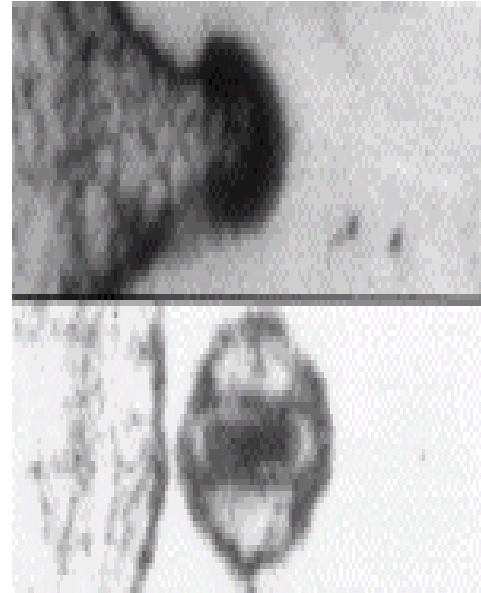
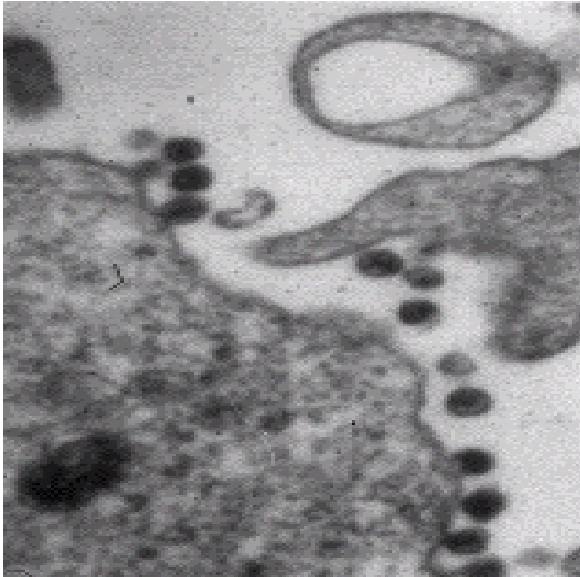
## Latently Infected Cells



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

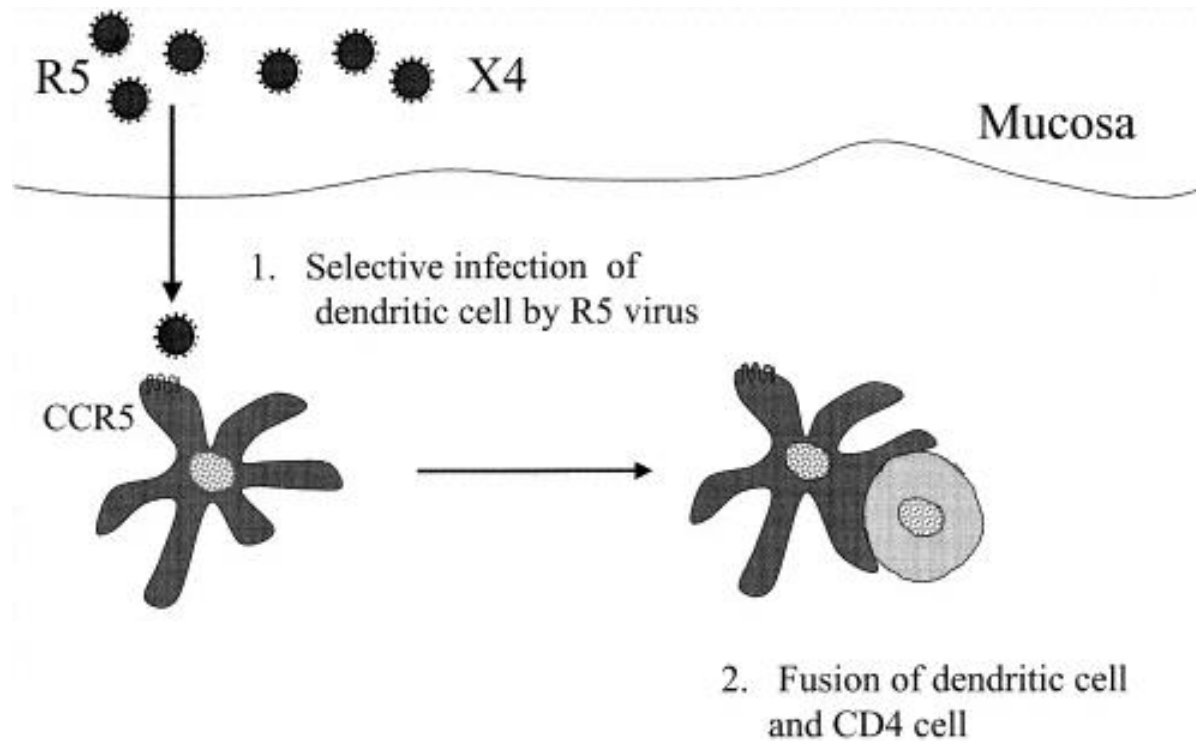


# HIV budding

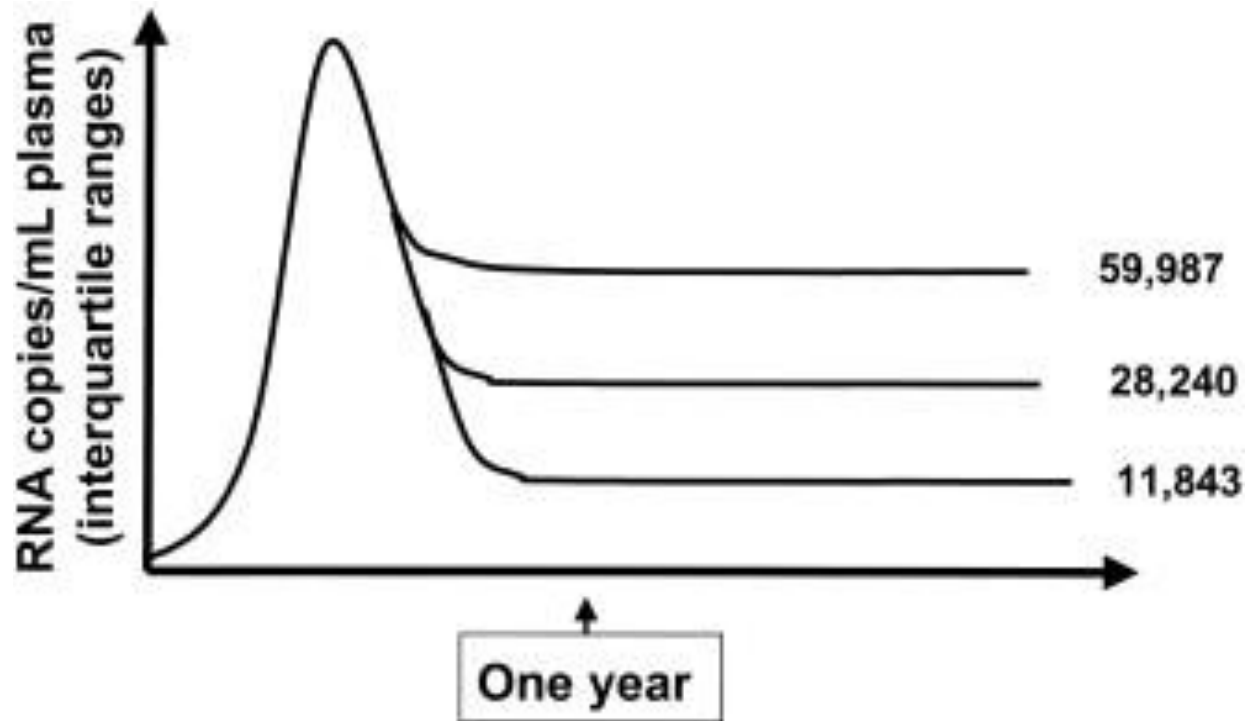




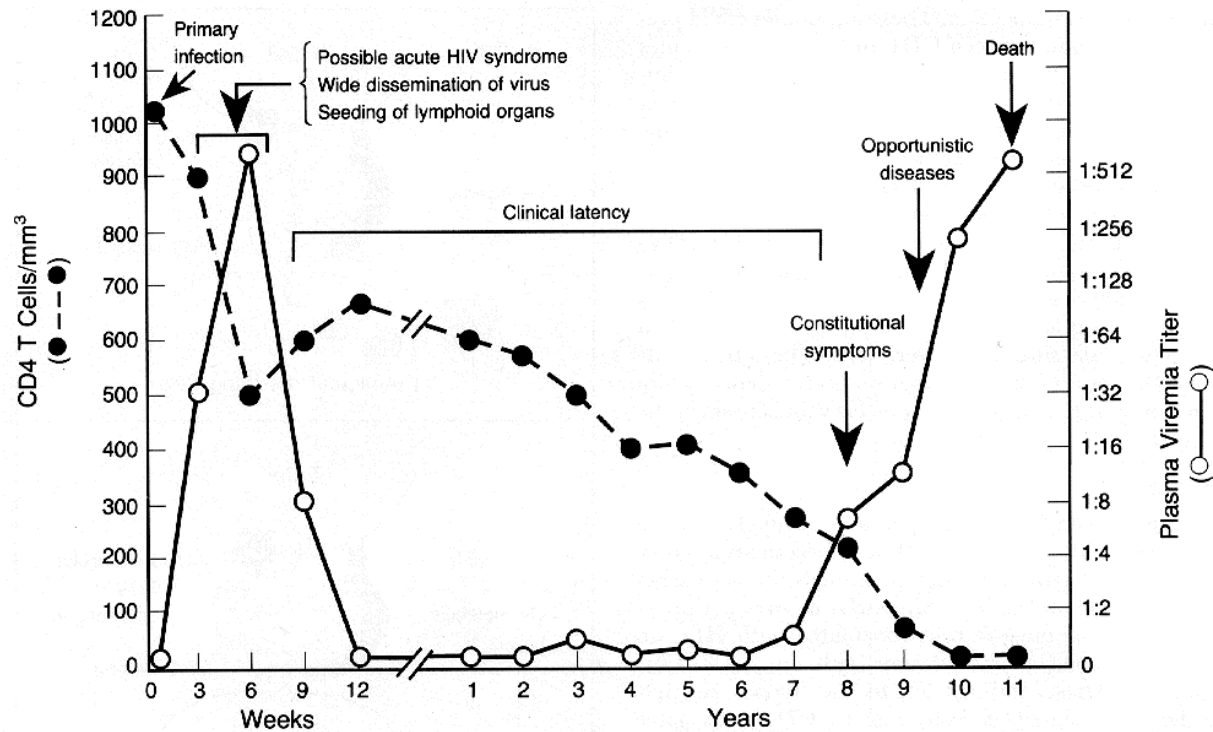
# Transmission



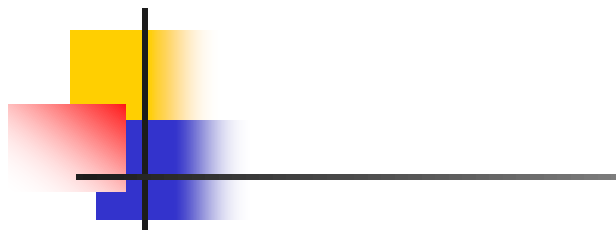
# Viral steady state



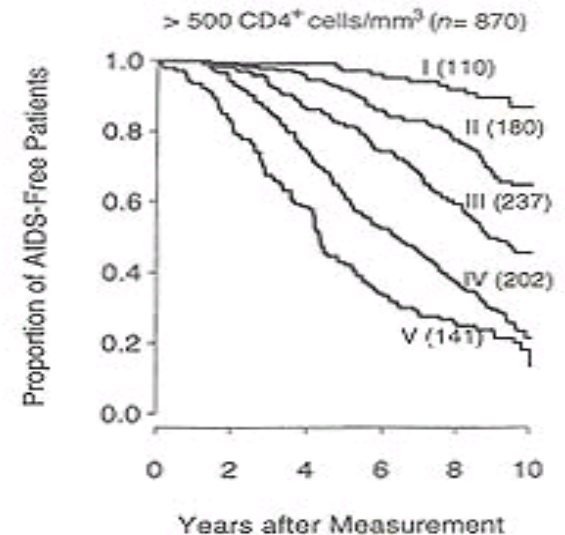
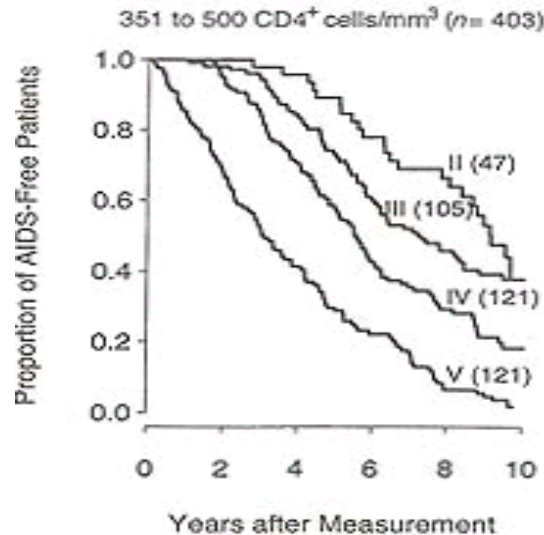
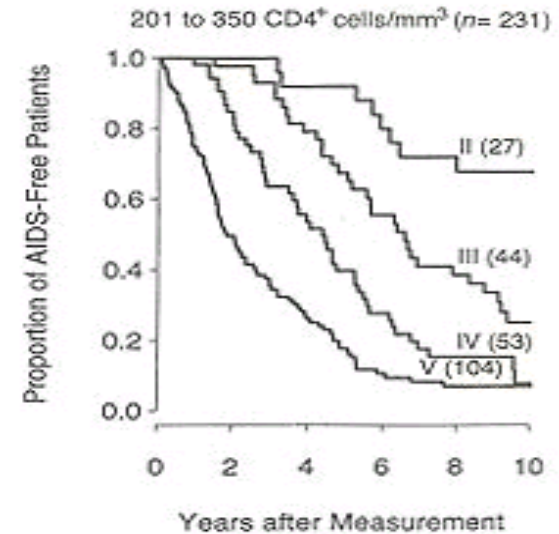
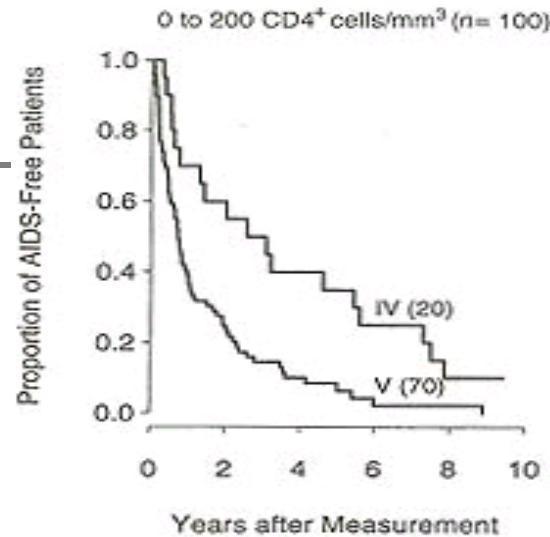
# Course of HIV infection



# 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

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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)



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

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- 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

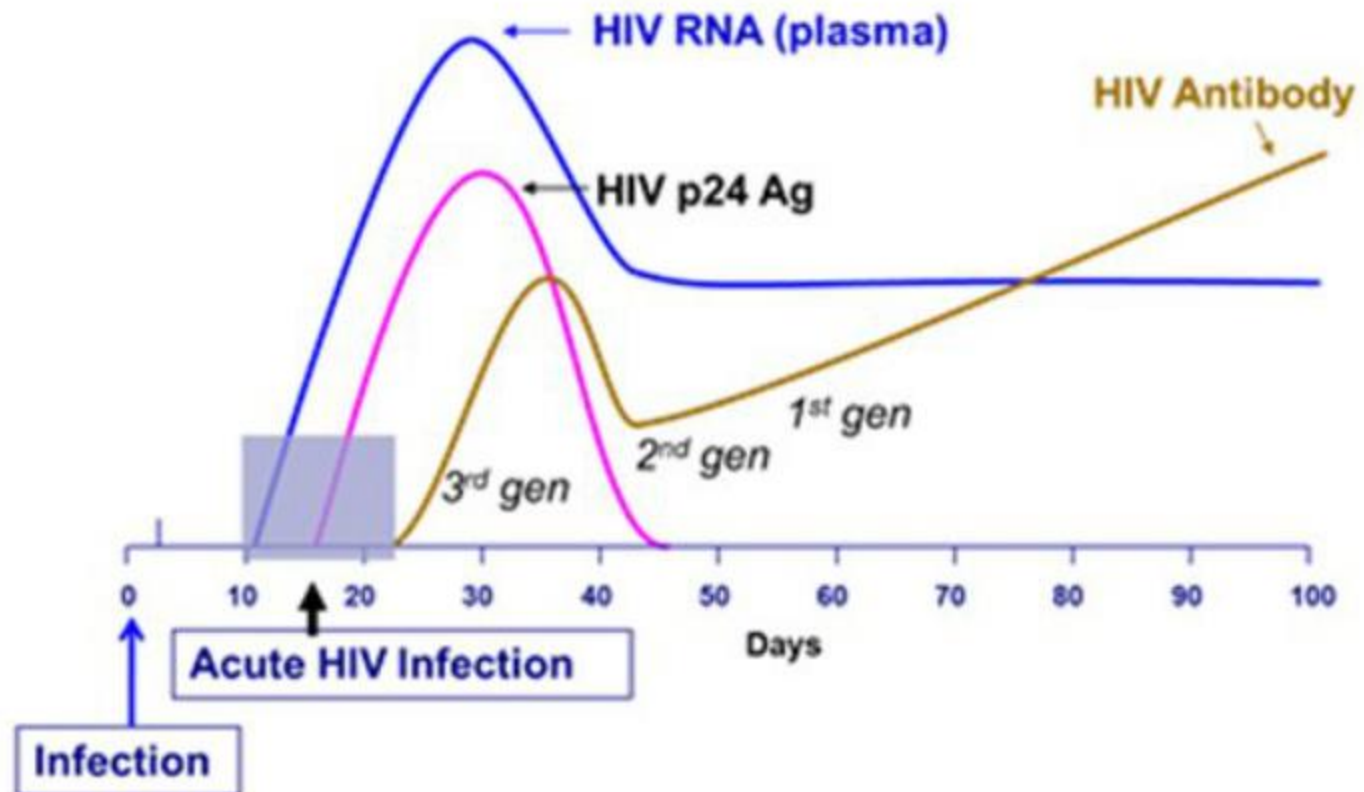


# RNA test and DX of acute HIV

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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.



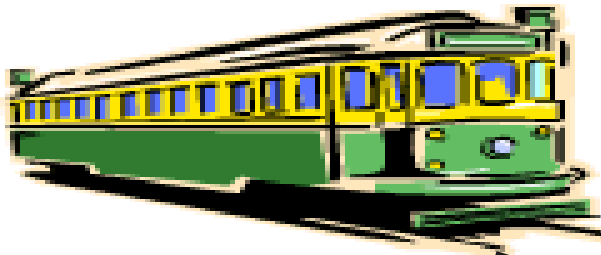


# Persons recommended for evaluation of acute HIV infection with available appropriate tests

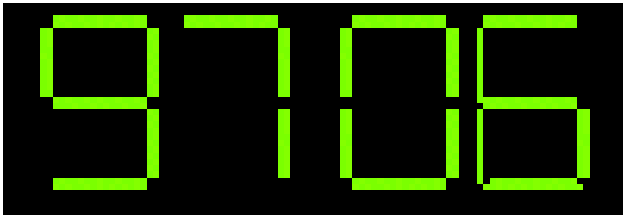
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- All of the following risk groups, ESPECIALLY with **history of an illness with clinical features compatible with acute HIV ("mono" or "flu-like" illness, regardless of severity)**:
- recent sexual or needle-sharing exposure with a known HIV-infected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

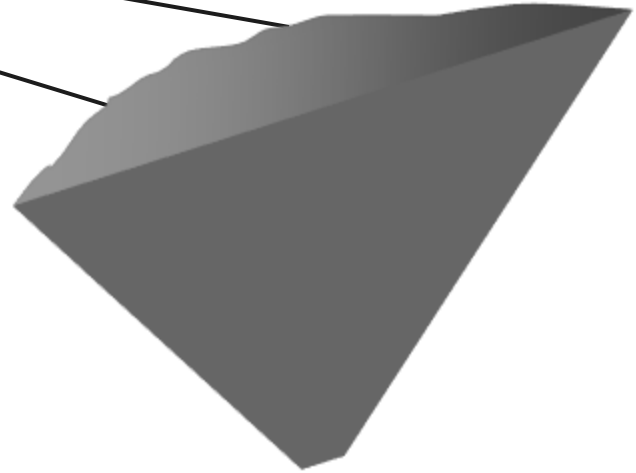
# Viral Load (V.L) & CD4 count



**CD4**

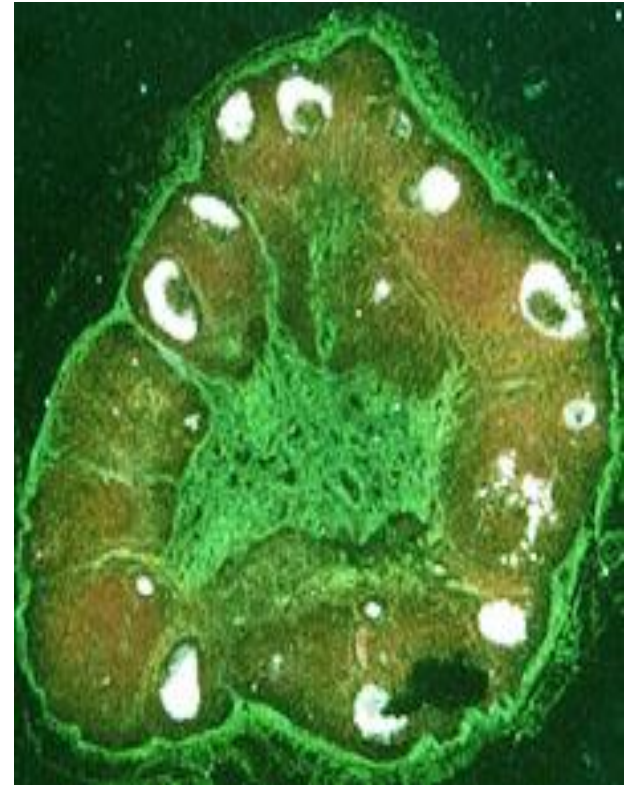


**Viral load**



# HIV = destruction of immunity

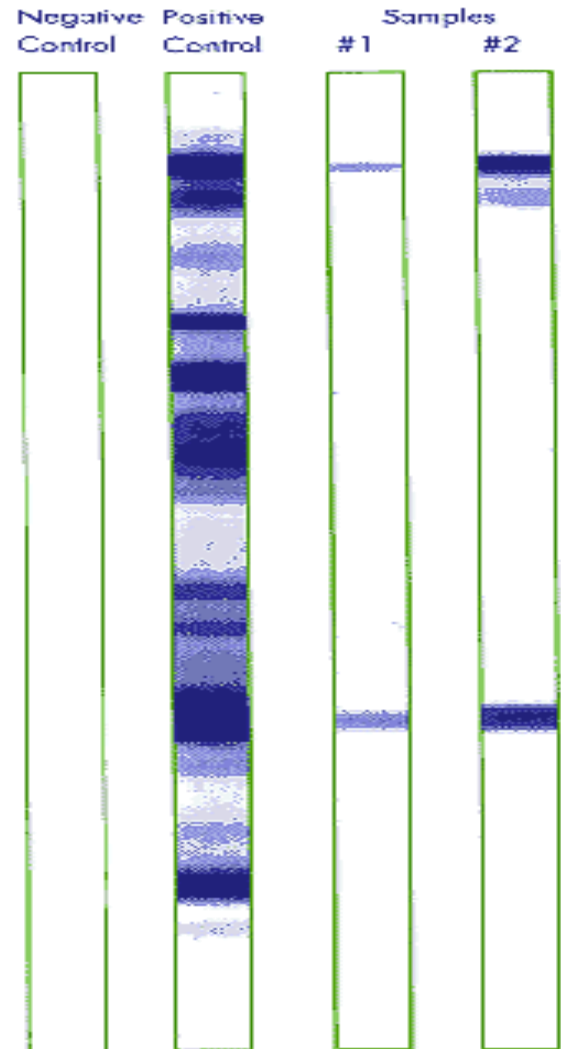
- Destruction of CD4 cells
- Evasion of immune response
- Lymph node pathology
- Exhaustion of immunity



# HIV Diagnosis

- Viral load (PCR)
  - as early as 7-10 days
- 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

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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



# Antiretroviral agents

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## ■ NRTI

- Ziduvudine (AZT)
- Didanosine (DDI)
- Stavudine (D4T)
- Lamivudine (3TC)

## ■ PI

- Saquinavir
- Indinavir
- Ritonavir
- Nelfinavir
- Abacavir

## ■ NNRTI

- Nevirapine
- Efavirenz



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

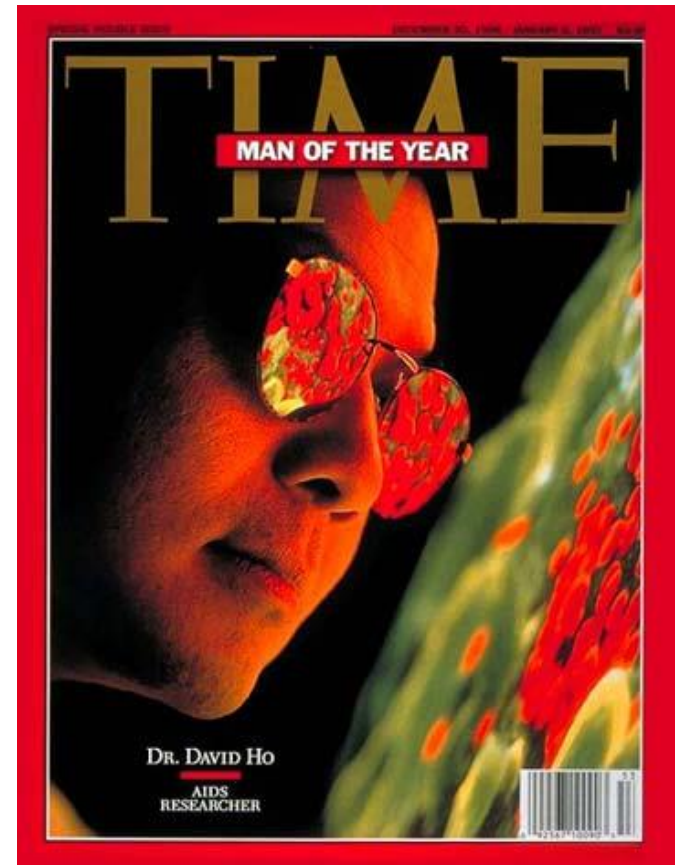
2 NRTI + PI

□ Aim:

- Suppress viral load
- Increase CD4

□ Disadvantages:

- Toxicity
- Cost



**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.

# HIV Medication Chart

## Combination Antiretrovirals

### Single-Tablet Regimens

<b>Atripla</b> <sup>†</sup> (EFV/TDF/FTC) 	<b>Biktarvy</b> (BIC/TAF/FTC) 	<b>Complera</b> (RPV/TDF/FTC) 	<b>Delstrigo</b> (DOR/TDF/3TC) 	<b>Dovato</b> (DTG/3TC) 	<b>Genvoya</b> (EVG/COBI/TAF/FTC) 
<b>Juluca</b> (DTG/RPV) 	<b>Odefsey</b> (RPV/TAF/FTC) 	<b>Stribild</b> (EVG/COBI/TDF/FTC) 	<b>Symtuza</b> (DRV/COBI/TAF/FTC) 	<b>Triumeq</b> (DTG/ABC/3TC) 	

### Long-Acting Injectable Regimens

**Cabenuva**  
(CAB/RPV)  



### Regimens Used in Combination with Other HIV Medications

<b>Combivir</b> <sup>†</sup> (ZDV/3TC) 	<b>Descovy</b> (TAF/FTC) 
<b>Epzicom</b> <sup>†</sup> (ABC/3TC) 	<b>Truvada</b> <sup>†</sup> (TDF/FTC) 


## Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

<b>Emtriva</b> <sup>††</sup> (emtricitabine, FTC) 	<b>Epivir</b> <sup>††</sup> (lamivudine, 3TC) 	<b>Viread</b> <sup>††</sup> (tenofovir DF, TDF) 	<b>Ziagen</b> <sup>††</sup> (abacavir, ABC) 	<b>Vemlidy</b> (tenofovir alafenamide, TAF) FDA approved for <u>HBV only</u> 
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## Entry Inhibitors

**Rukobia**  
(fostemsavir, FTR)  
gp120 Attachment Inhibitor  


**Selzentry**<sup>\*</sup>  
(maraviroc, MVC)  
CCR5 Antagonist  


**Trogarzo**  
(ibalizumab, IBA)  
Post-Attachment Inhibitor  


## Integrase Inhibitors (INSTI)

**Isentress**<sup>\*▲</sup>  
(raltegravir, RAL)  


**Isentress HD**  
(raltegravir, RAL)  


**Tivicay**<sup>\*</sup>  
(dolutegravir, DTG)  


**Vocabria**  
(cabotegravir, CAB)  


## Protease Inhibitors (PI)

<b>Evotaz</b> (ATV/COBI) 	<b>Kaletra</b> <sup>*</sup> (lopinavir/ritonavir, LPV/RTV) 	<b>Prezcobix</b> (DRV/COBI) 	<b>Prezista</b> <sup>*</sup> (darunavir, DRV) 	<b>Reyataz</b> <sup>††</sup> (atazanavir, ATV) 
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## Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

<b>Edurant</b> (rilpivirine, RPV) 	<b>Intelence</b> <sup>†</sup> (etravirine, ETR) 	<b>Pifeltro</b> (doravirine, DOR) 	<b>Sustiva</b> <sup>†</sup> (efavirenz, EFV) 	<b>Viramune</b> <sup>††</sup> (nevirapine, NVP) 
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## Boosting Agents

<b>Norvir</b> <sup>†</sup> (ritonavir, RTV) 	<b>Tybost</b> (cobicistat, COBI) 
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All pills shown in relative size/scale. Medication brand names appear in bold. Generic names and commonly used abbreviations appear in parentheses.

\* Also available in liquid or powder form. † Generic formulation available. ▲ Chewable form available.



# Where to find out more...

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- [www.cdc.gov/mmwr](http://www.cdc.gov/mmwr): STD guidelines



# 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