

# Overview of HIV

## WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

**WRAIR**

Walter Reed Army  
Institute of Research

Soldier Health • World Health



# Historical Perspective

HIV-1 identified officially 05 JUN 1981 (US) CDC

MMWR report of 5 unusual

*Pneumocystis jirovecii* pneumonia cases

Origin: Non-human primates W Africa, ~1900

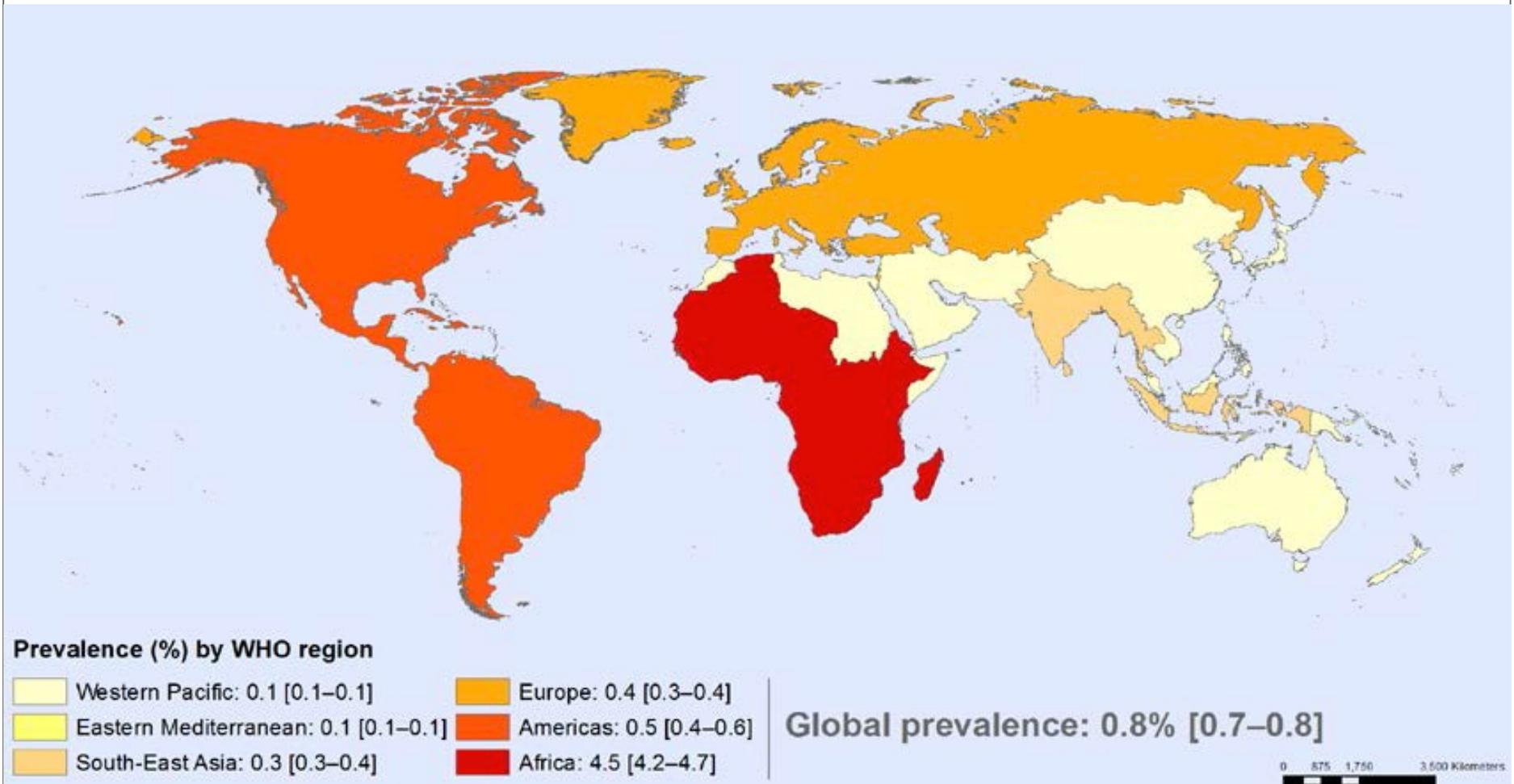
HIV-1: S Cameroon; evolution of Simian Immunodeficiency Virus HIV-2 :

S Senegal – W Cote d'Ivoire, SIV

Early expectations – vaccine in 2 years

(M. Heckler- DHHS, 1984)

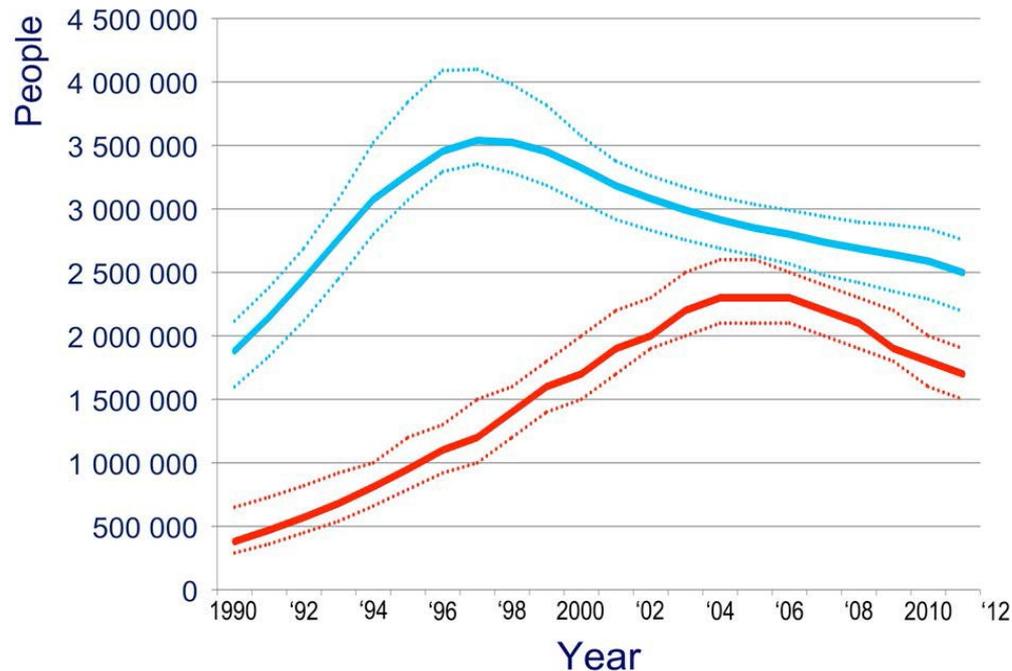
Search for cure and implementation of prevention  
strategies continues...2013



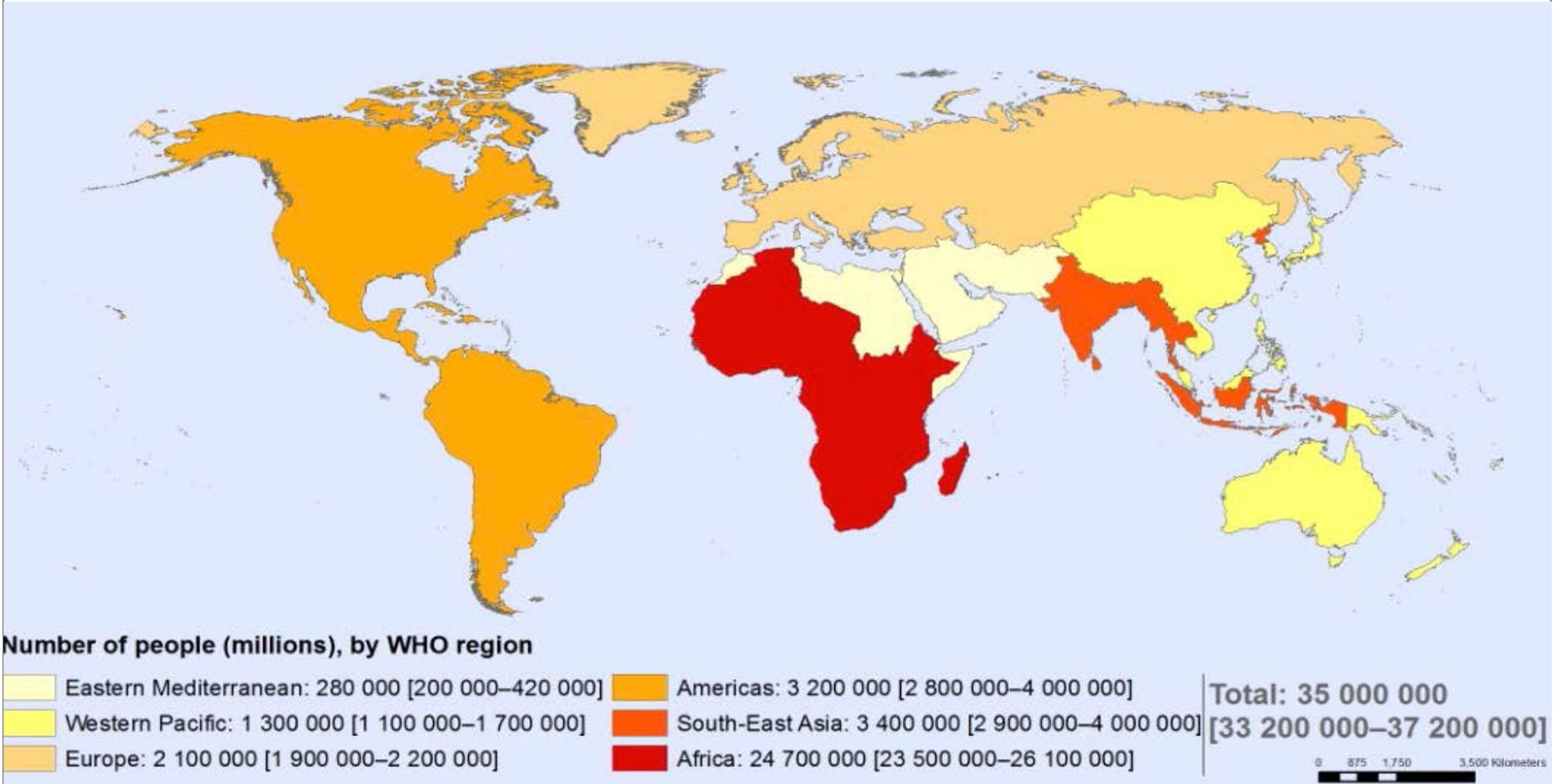
# Knowledge Check

How many new HIV infections occurred in 2012 worldwide?

— New HIV infections      Globally new HIV infections peaked in 1997  
— AIDS-related deaths



# Adults & children living with HIV | 2013



# Over 6,300 New HIV Infections a Day in 2012

~ 95% are in low / middle income countries

~ 700 are in children < 15 years of age

~ 5,500 are in adults  $\geq 15$  years:

47% are among women

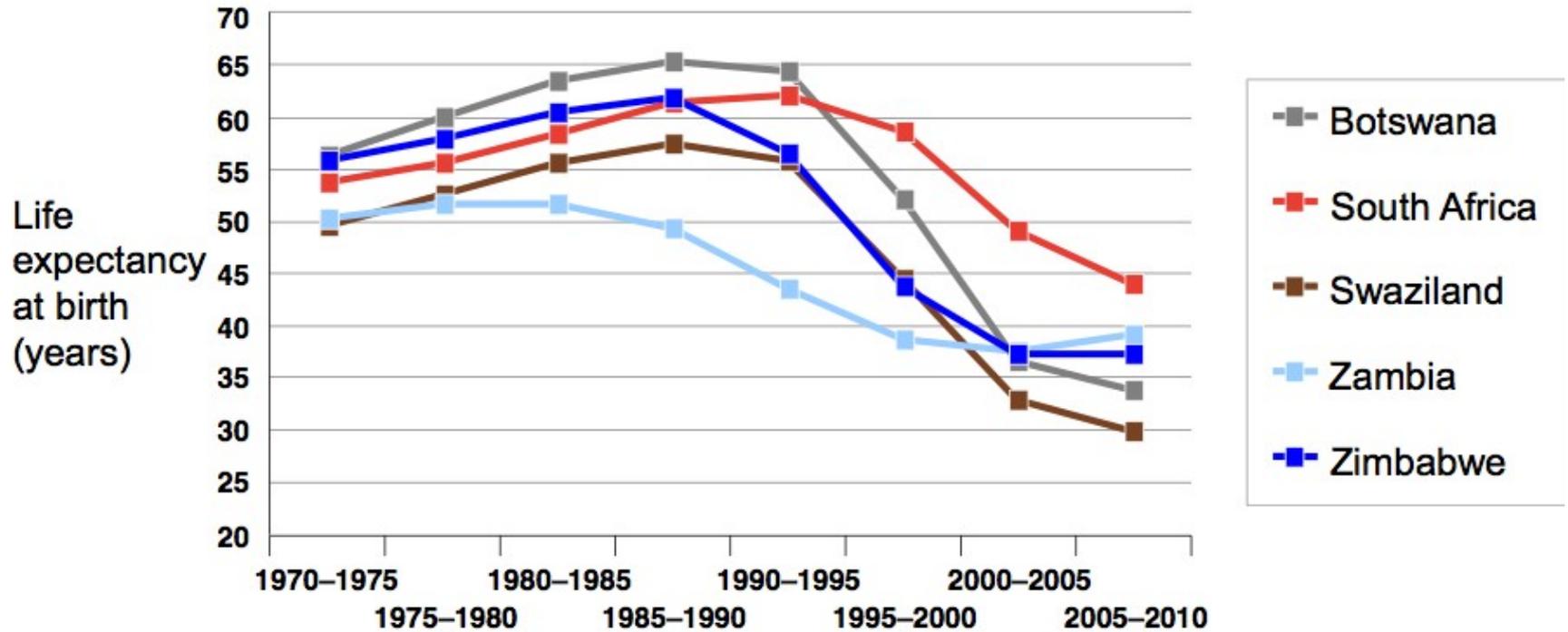
41% are among young people (15-24)

Epi center of epidemic: Sub-Saharan

Africa (70%)



# Impact of AIDS on life expectancy, 1970-2010



Source: United Nations Population Division (2011).

# HIV – A Worldwide Threat

Force readiness and protection

- U.S. and Allied Forces

Stability and security of many nation-states

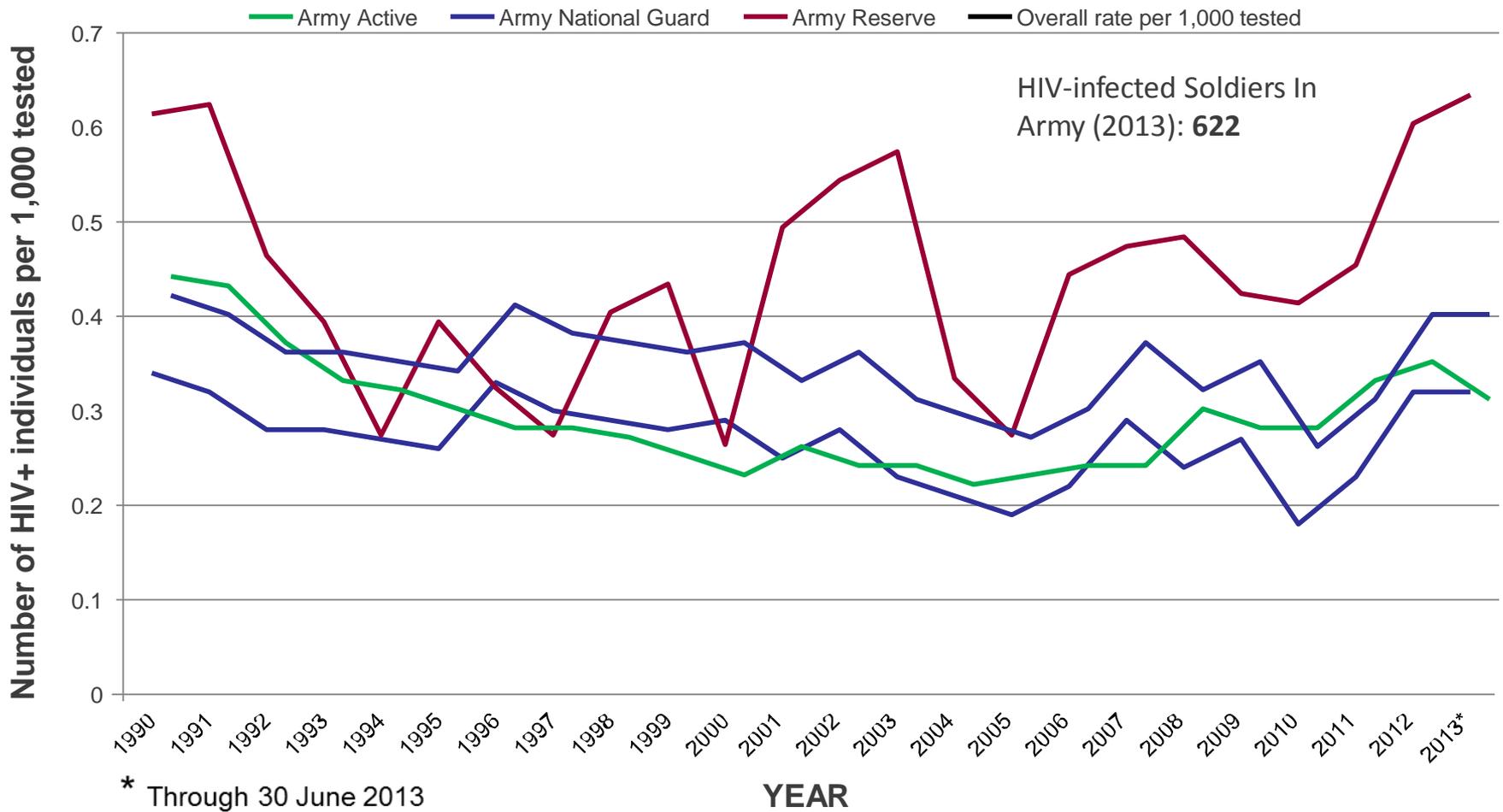
- Epidemic in the least developed, most unreliable regions of the world

National Security Strategy:

- Defuse regional conflicts
- Prevent enemies from using WMD
- Support global economic growth
- **Reduce the toll of HIV/AIDS and other infectious diseases**



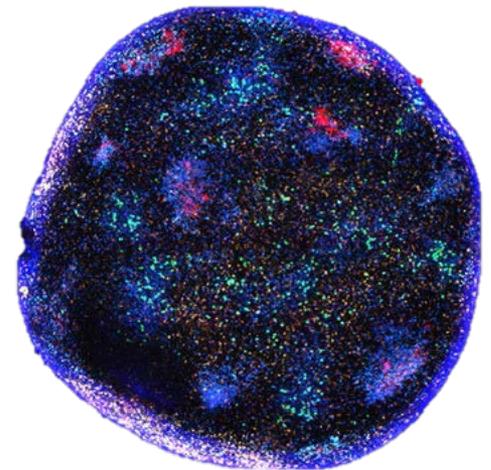
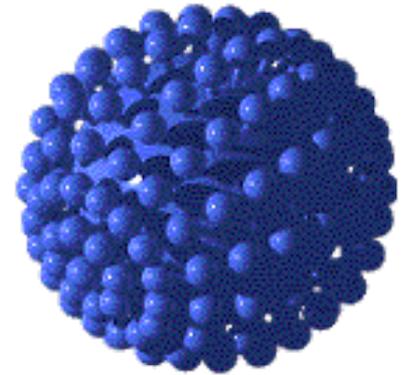
# HIV is an Enduring Problem in the Army



# **HIV Virology, Pathogenesis and Transmission**

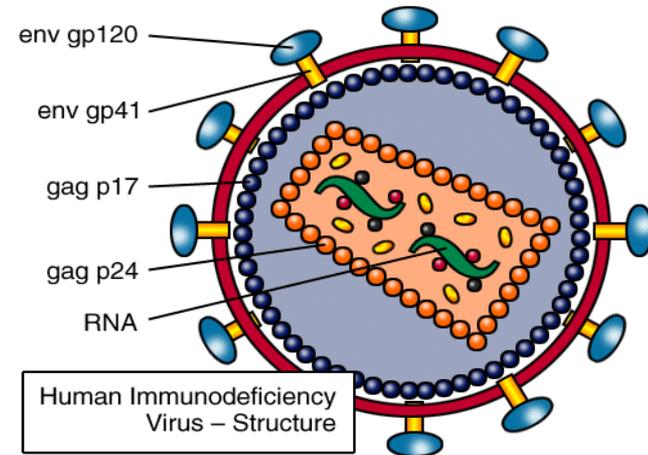
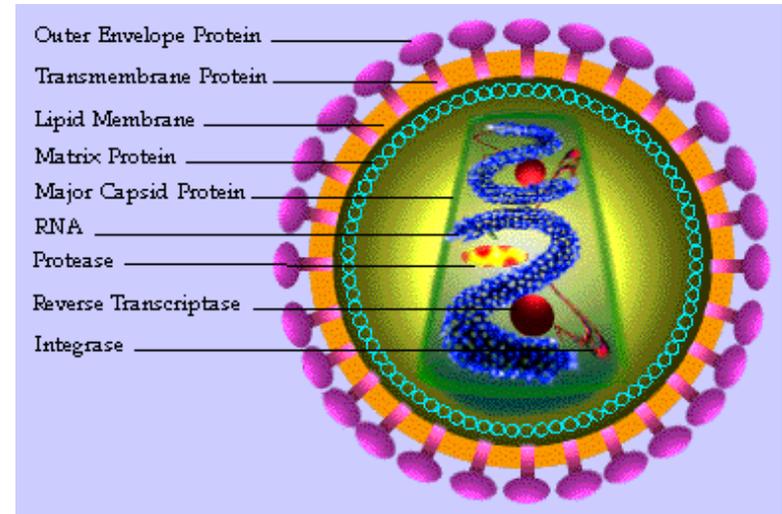
# HIV vs. AIDS

- **What is HIV?**
  - HIV
    - Human
  - Immunodeficiency
    - Virus
  
- **AIDS**
  - Acquired
- Immunodeficiency
  - Syndrome

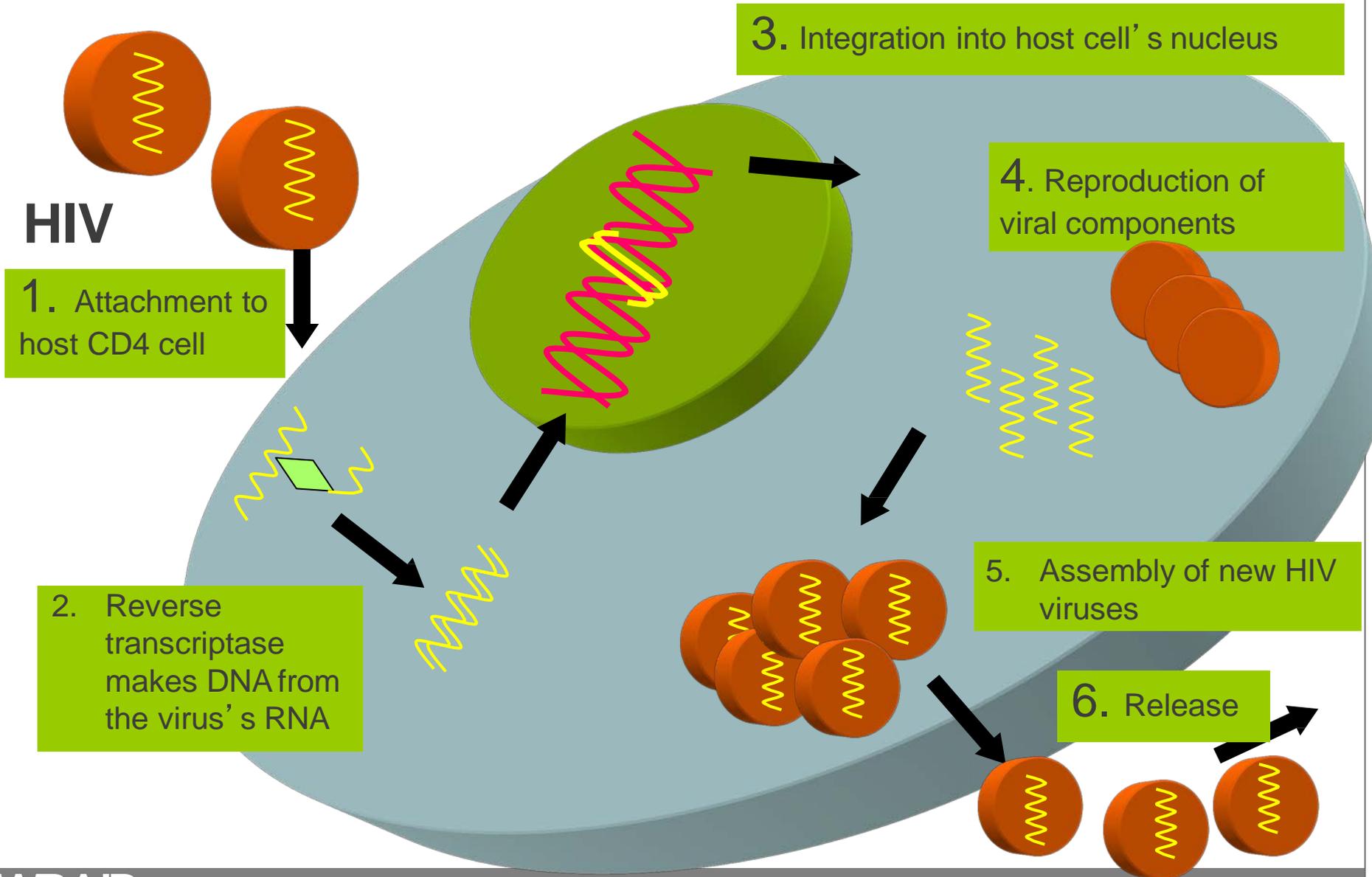


# HIV: Human Immunodeficiency Virus

- HIV is a **retrovirus** and its genetic material, RNA, must be converted into DNA during replication
- HIV must enter other cells in order to replicate
- HIV primarily uses CD4 + T cells for reproduction
  - CD4 receptors on T- helper lymphocytes

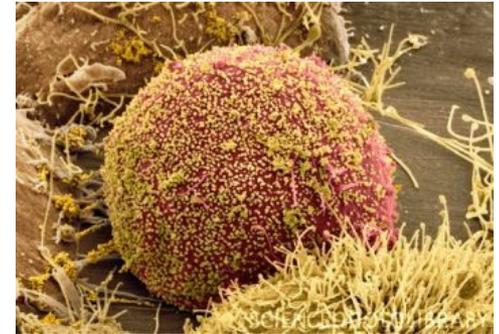


# How HIV Works

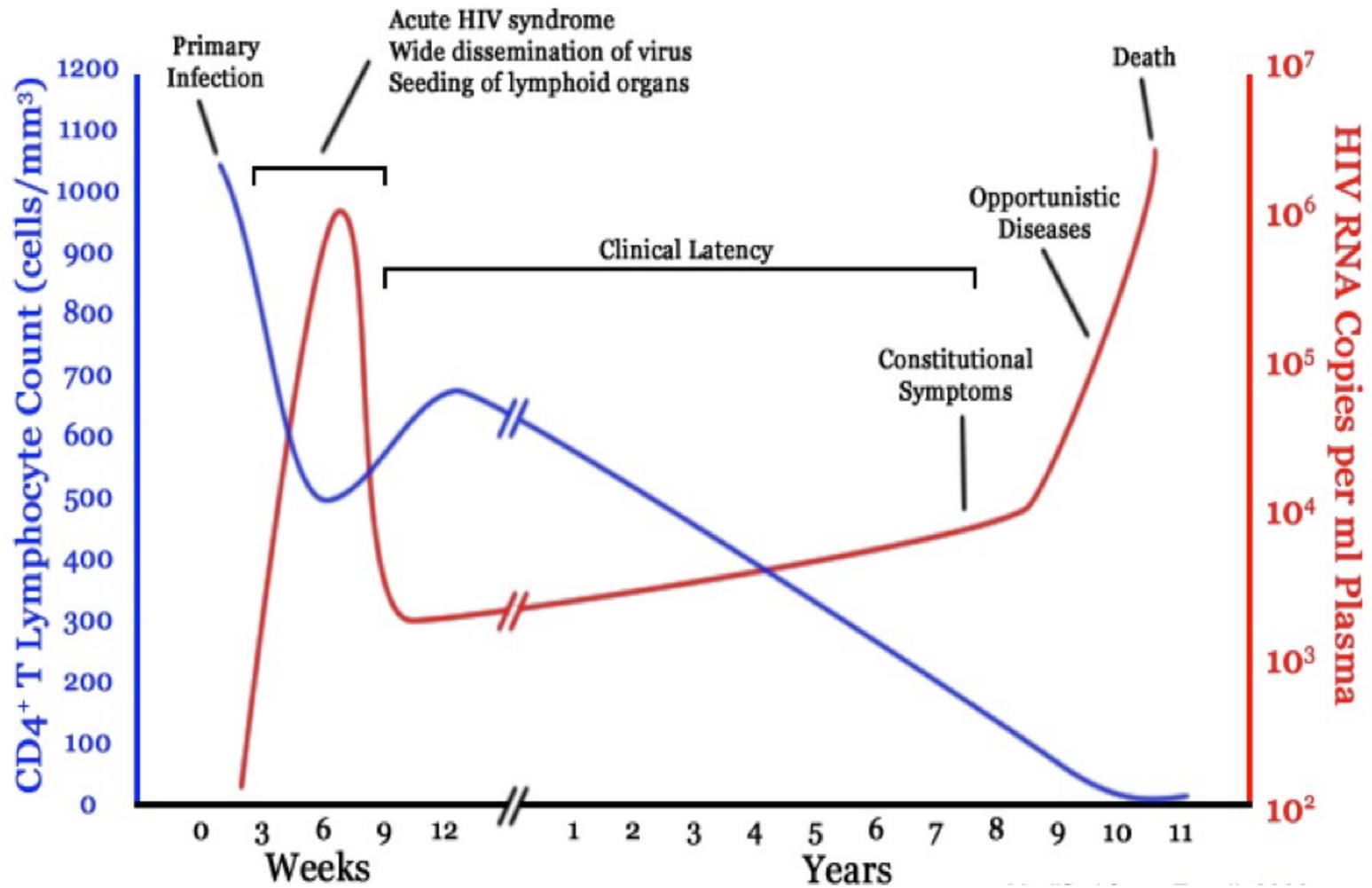


# CD4 + T cell

- Stage disease and guide clinical management
- CD4+ T Helper cells = CD4 T cells = CD4 count
  - CD = Cluster of Differentiation
  - Measured by Flow Cytometry
  - Normal range 500 – 1400 cells/mm<sup>3</sup>
  - A product of
    - white blood cell count
    - the percentage of lymphocytes,
    - percentage of lymphocytes that bears the CD4 receptor
- As HIV infects more CD4+ cells, CD4 count decreases
  - Effectively weaken the immune system
- CD4 percent
  - How many of your total lymphocytes (white blood cells) are CD4+
  - More stable than CD4 count



# Natural History of HIV Infection



Modified from Fauci, 2000

# Viral Load

Human immunodeficiency virus type 1 (HIV-1) RNA quantification = viral load measurement (VL)

Used in management of persons infected with HIV-1

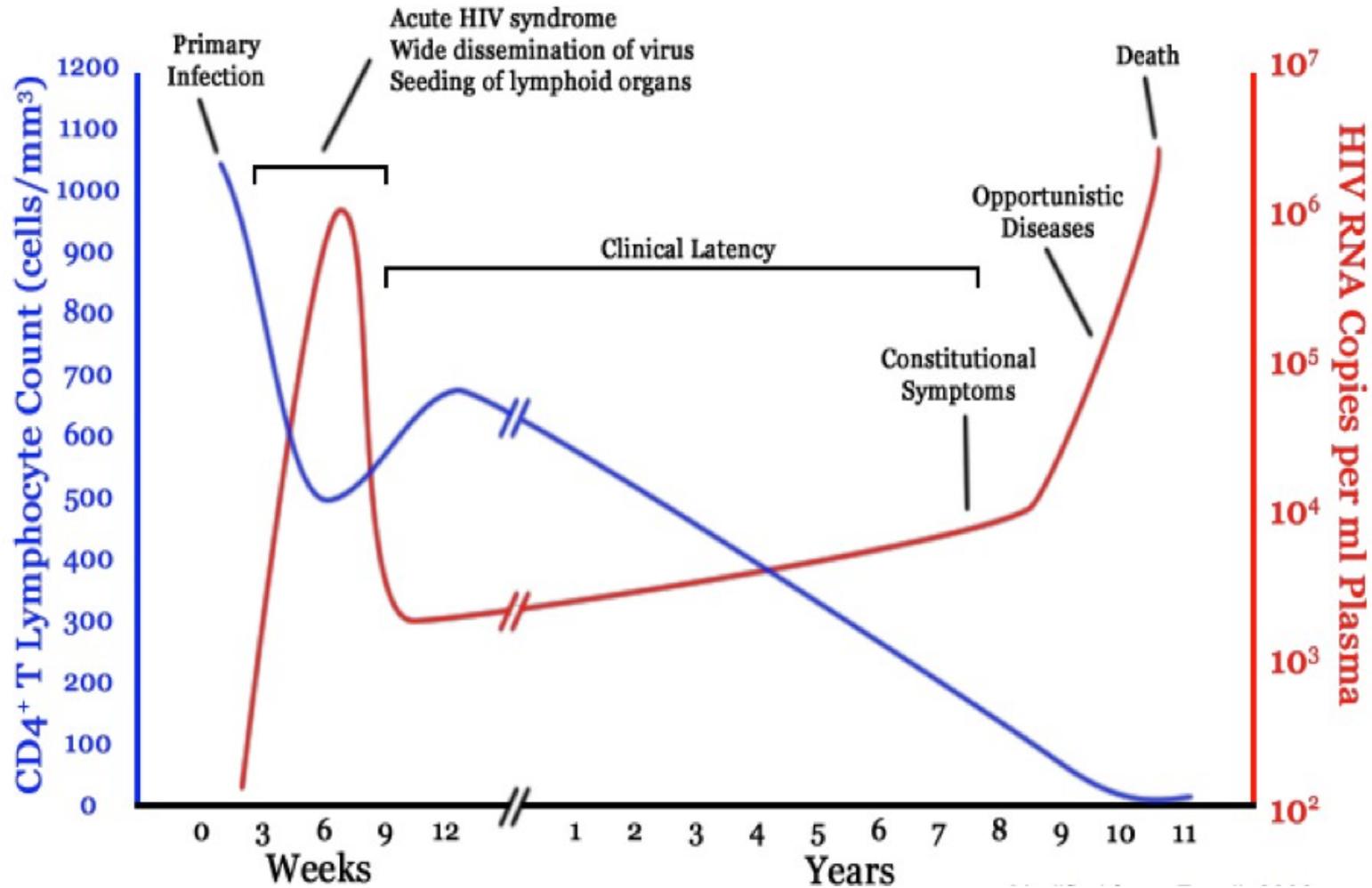
VL is predictor of the time to progression to AIDS and death – independent of CD4 T cell counts

ART – Antiretroviral therapy

VL used in determining when to initiate ART

Monitoring the response to ART

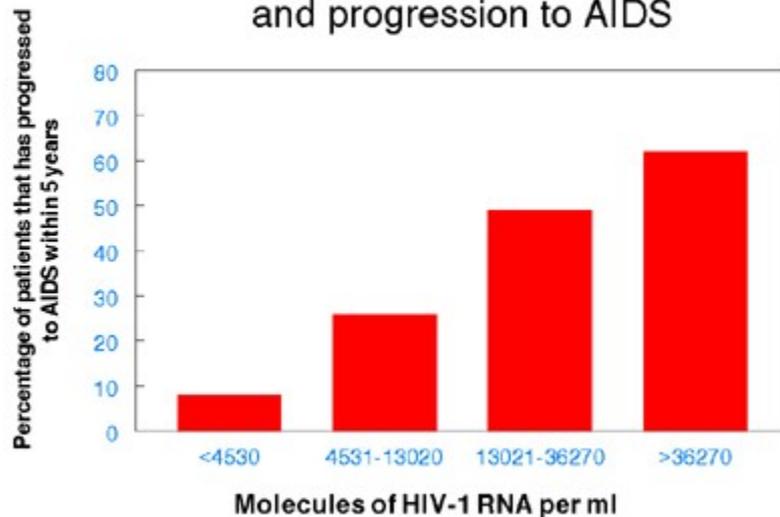
# Natural History of HIV Infection



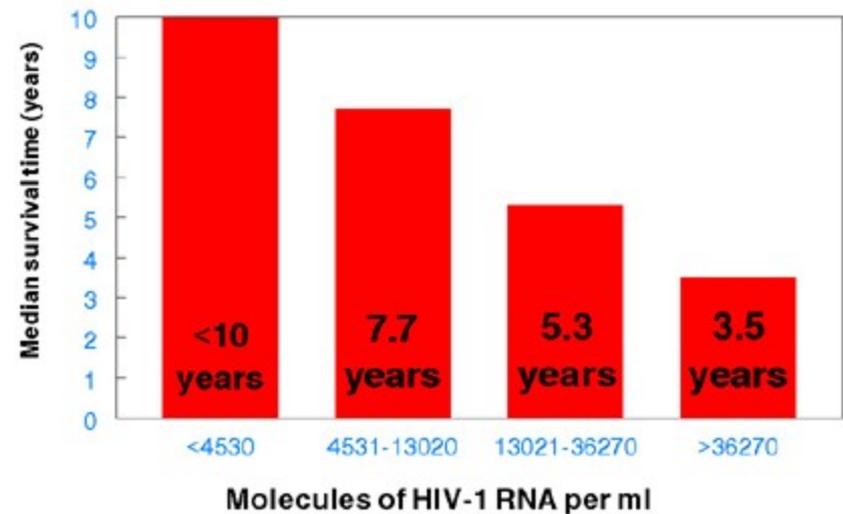
Modified from Fauci, 2000

# Viral Setpoint and Prognosis

Relation between baseline viral load and progression to AIDS



Relation between baseline viral load and median survival time



HIV RNA levels 1 year after untreated infection are relatively stable and predict subsequent disease progression. (Data are from the Multicenter AIDS Cohort Study (MACS), Mellors *et al. Science* 272: 1167-1170)

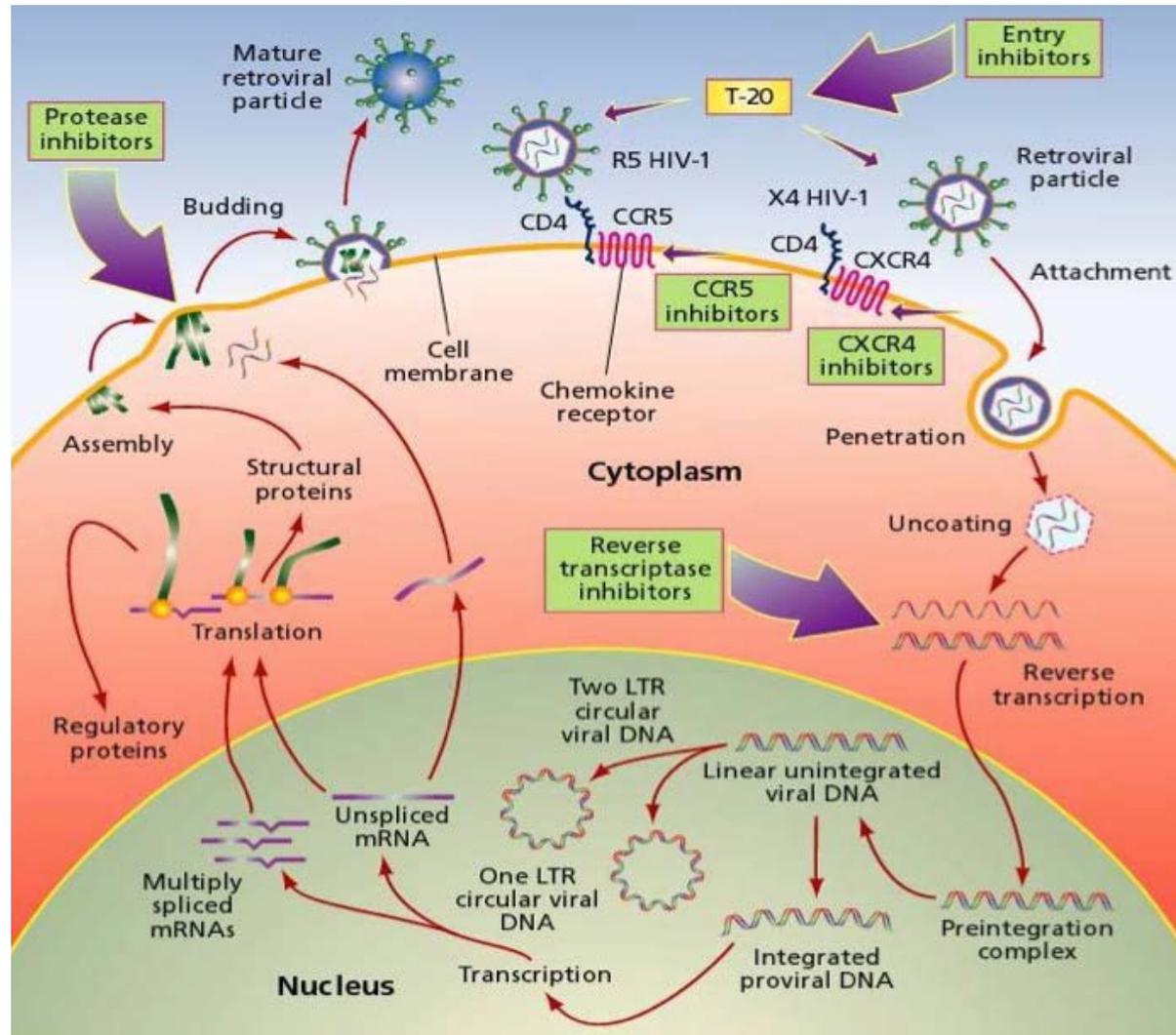
# Treatment

Antiretroviral therapy = ART Antiretroviral  
Medications = ARVs

HAART = Highly active antiretroviral therapy  
Combination therapy

Use medicines from TWO different drug classes Block  
replication at different stages of life cycle Effective in  
reducing viral load

# HIV life cycle and mechanisms of anti-virals



# Antiretroviral Medications (ARVs)

Nucleoside- and Nucleotide-analog Reverse  
Transcriptase Inhibitors (NRTIs)

Non-nucleoside analog Reverse Transcriptase  
Inhibitors (NNRTIs)

Protease Inhibitors (PIs)

Integrase inhibitors

Entry Inhibitors (including fusion inhibitors)

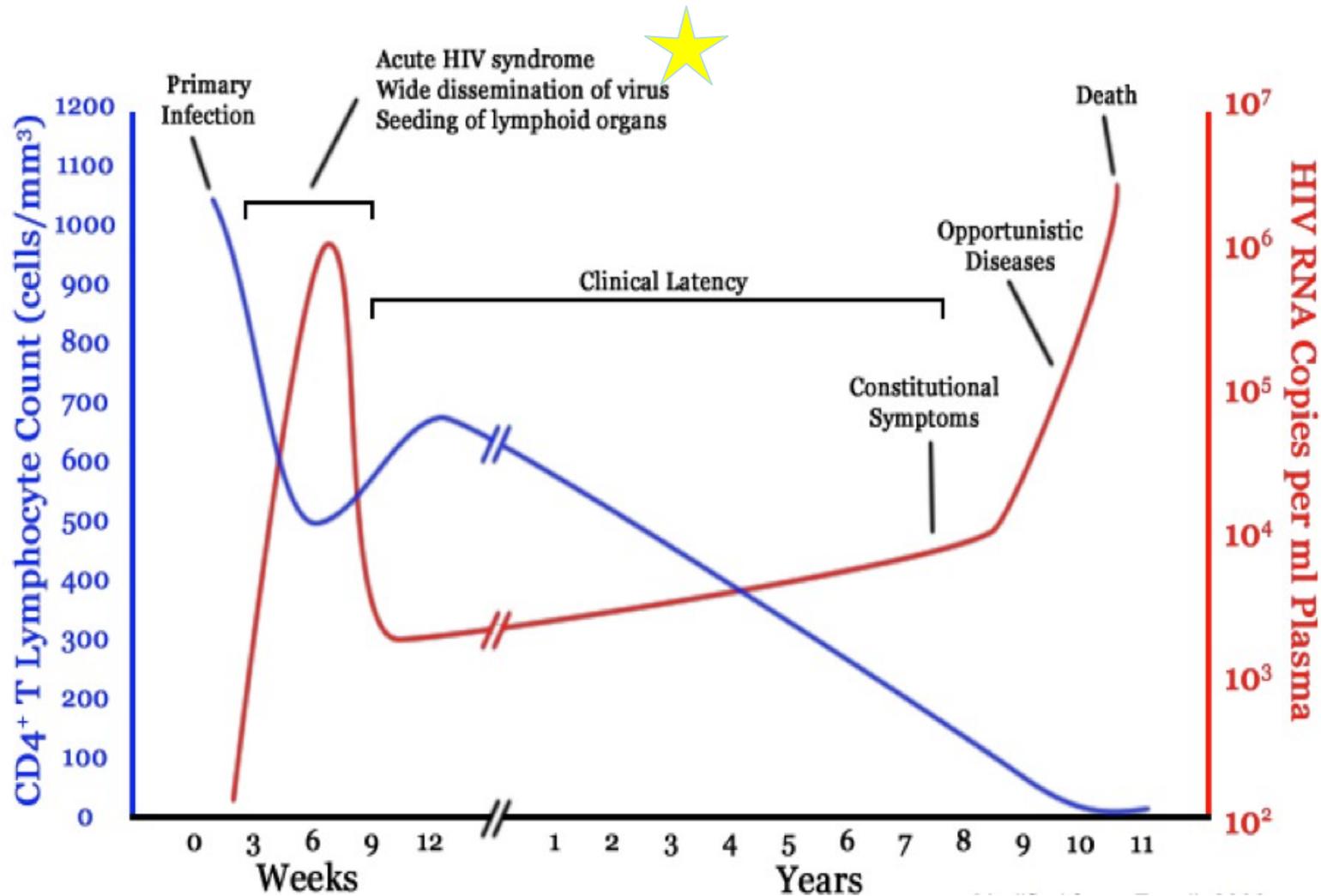
Pharmacokinetic Enhancers

# Case Study

**Which of the following is the most likely diagnosis?**

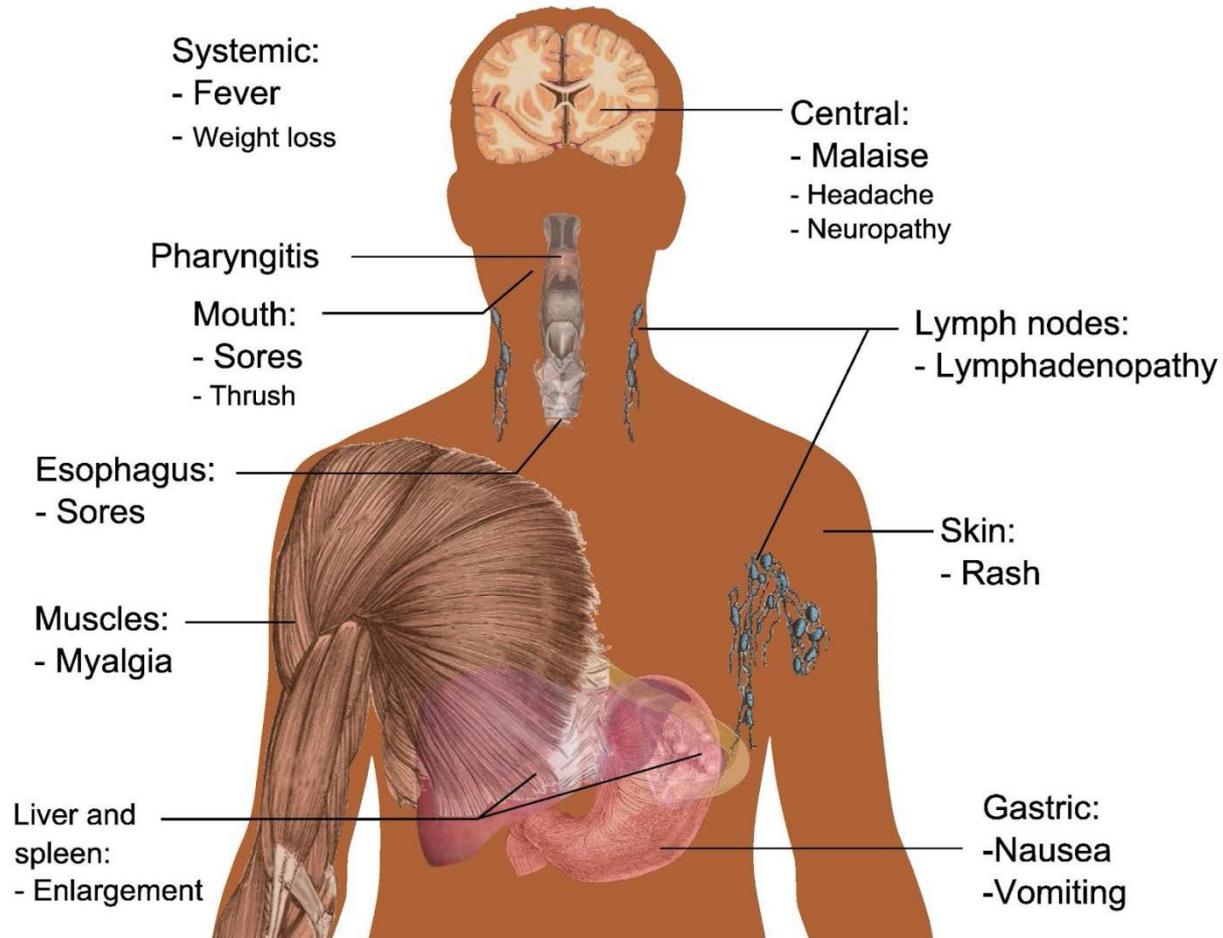
Acute HIV infection  
Infectious mononucleosis  
Streptococcal pharyngitis  
Influenza

# Acute HIV Infection



Modified from Fauci, 2000

# Symptoms of Acute HIV Infection



# Frequency Symptoms in Acute HIV-1 Infection

<b>Fever</b>	<b>&gt;80-90%</b>
<b>Fatigue</b>	<b>&gt;70-90</b>
<b>Rash</b>	<b>&gt;40-80</b>
<b>Headache</b>	<b>32-70</b>
<b>Lymphadenopathy</b>	<b>40-70*</b>
<b>Pharyngitis</b>	<b>50-70*</b>
<b>Myalgia/arthralgia</b>	<b>50-70</b>

Kahn and Walker. NEJM 1998. 339(1):33-9.

\*higher in younger patients, Vanhems. JAIDS 2002;31:318-321.



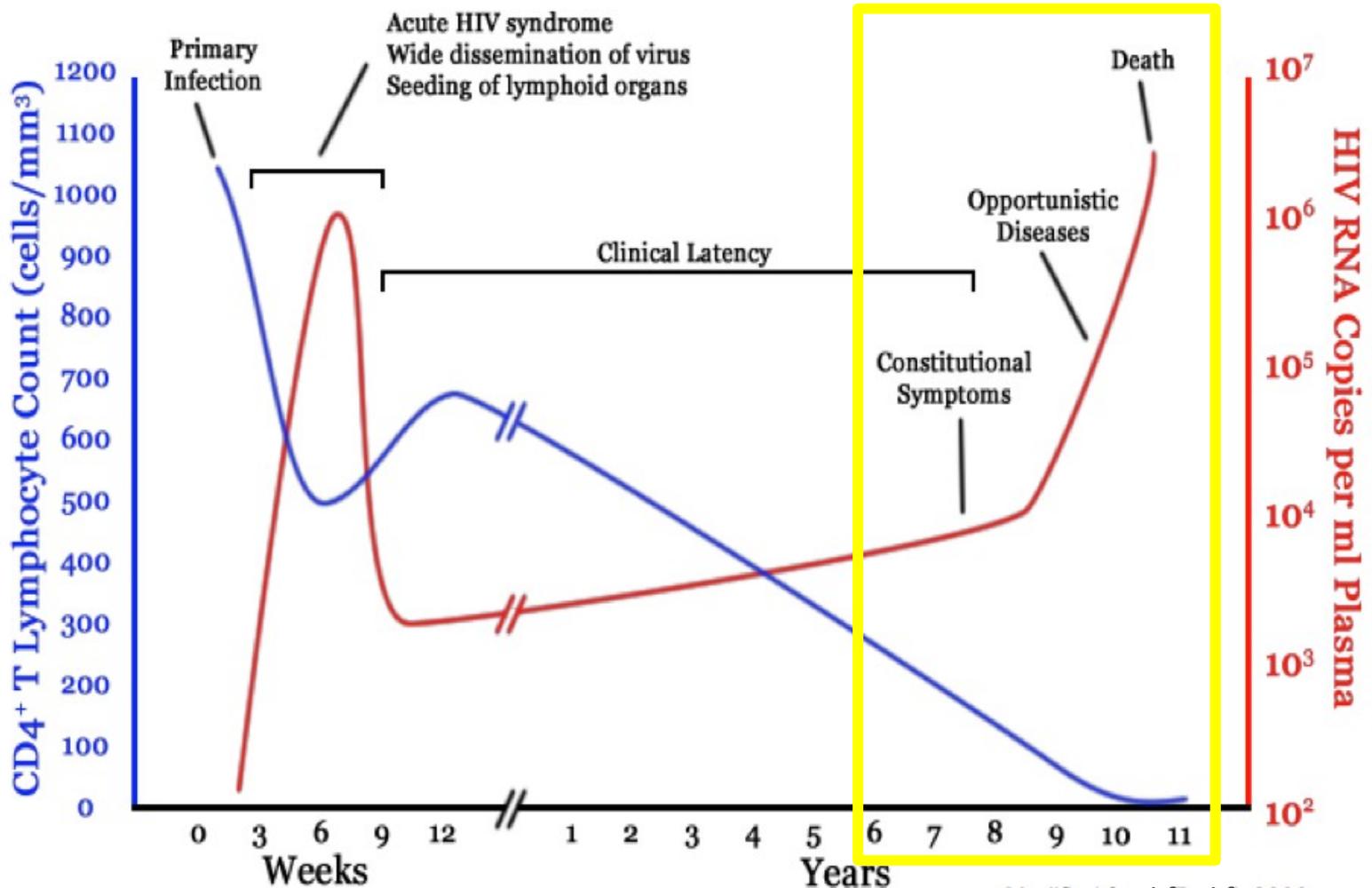
DOIA

(c) University Erlangen,  
Department of Dermatology  
Phone: (+49) 9131 - 85 - 2727





# Advanced Stages & Opportunistic Infections



Modified from Fauci, 2000

# Advanced Stages of HIV / AIDS

CD4 < 200 mm<sup>3</sup>

Opportunistic infections

Immunocompromised = Increased risk In US:

Pneumocystis pneumonia, Kaposi's  
sarcoma

In Sub-Saharan Africa: diarrhea, tuberculosis Prophylaxis for OIs

becomes important What one receives for prophylaxis depends on:

Patient's medical history Patient's environment CD4  
count

Review guidelines as needed – consult expert

Know that under 200, patients at risk

# AIDS

## AIDS

CD4 cell count below 200/mm<sup>3</sup> regardless of the presence or absence of symptoms

## WHO stages

Clinical staging guideline

Still used in field where CD4 & VL results may be limited

## AIDS defining conditions

Serious conditions in people with HIV that define stage

*P. jirovecii* pneumonia

Esophageal candidiasis

Kaposi's sarcoma Tuberculosis

# Transmission Routes

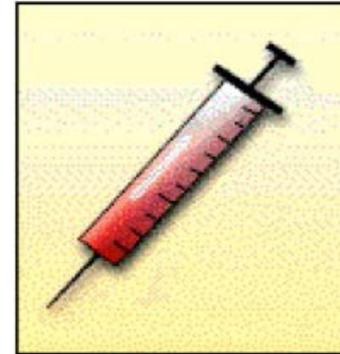


**Unprotected  
sexual intercourse  
with an infected partner**



**Vertical  
transmission**  
(from mother  
to child)

- in utero
- during delivery
- breastmilk



**Injection drug use**  
(rare: infected  
blood/blood products)



**HIV INFECTION**

# Risk of Specific Exposures

**Table 1. Estimated per-act probability of acquiring HIV from an infected source, by exposure route.**

Exposure route	Risk per 10 000 exposures to an infected source	95% Confidence interval
Parenteral exposure		
Blood transfusion	9250	(8900–9610)
Needle-sharing injection drug use	63 <sup>b</sup>	(41–92)
Percutaneous needle stick	23	(0–46)
Sexual exposure <sup>a</sup>		
Receptive anal intercourse	138 <sup>c</sup>	(102–186)
Insertive anal intercourse	11 <sup>d</sup>	(4–28)
Receptive penile–vaginal intercourse	8 <sup>e</sup>	(6–11)
Insertive penile–vaginal intercourse	4 <sup>e</sup>	(1–14)
Receptive oral sex	Low <sup>f</sup>	(0–4)
Insertive oral sex	Low <sup>f</sup>	(0–4)
Vertical transmission		
Mother-to-child transmission	2260 <sup>g</sup>	(1700–2900)

Patel et al., 2014

# HIV Diagnostics: Serology vs. RDT

## Serology

Detection of serum IgG antibody against HIV-1 antigens  
Positive tests confirmed with repeat tests or corroborating laboratory data (e.g. western blot) False negative - rare but can be seen in acute infection

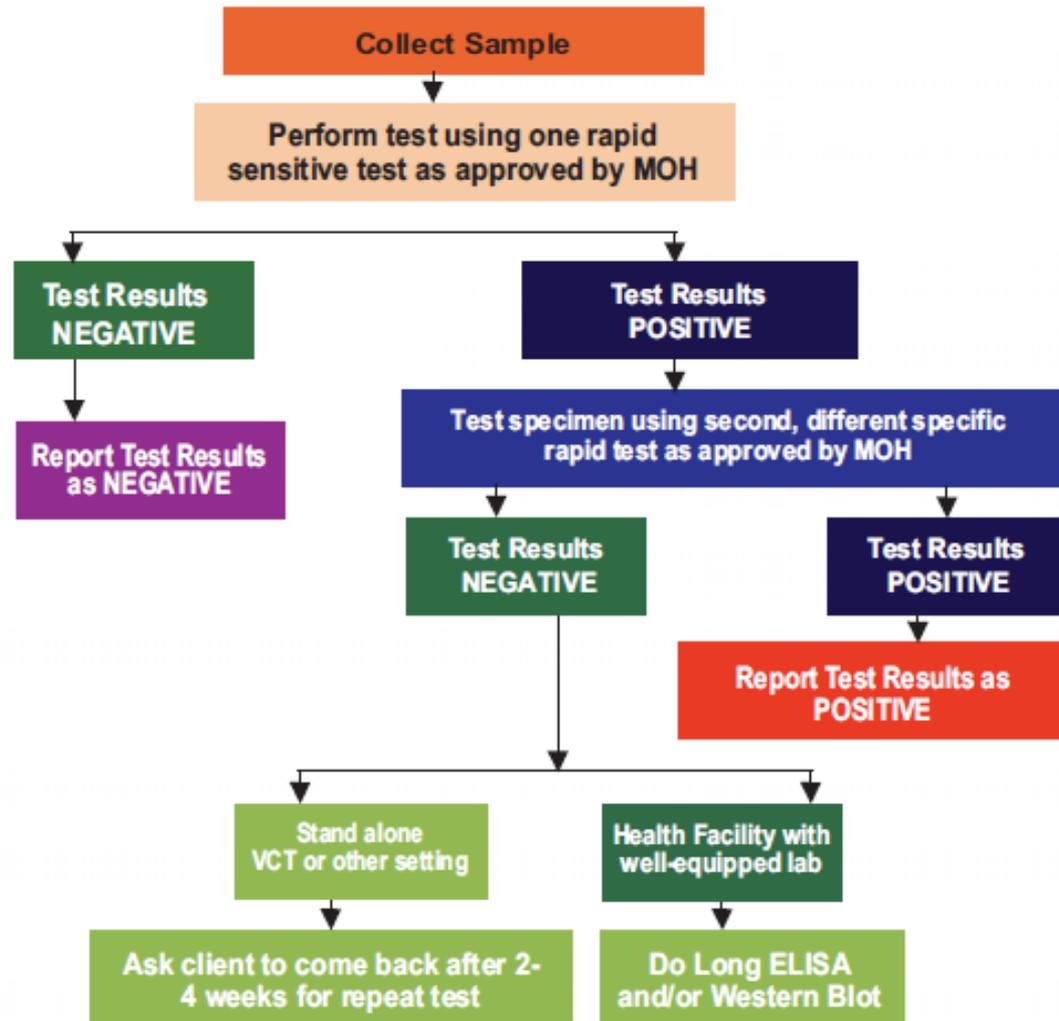
## RDT = Rapid Diagnostic Test

Low cost and available in minutes Preferred now in US for point of care (and in field)

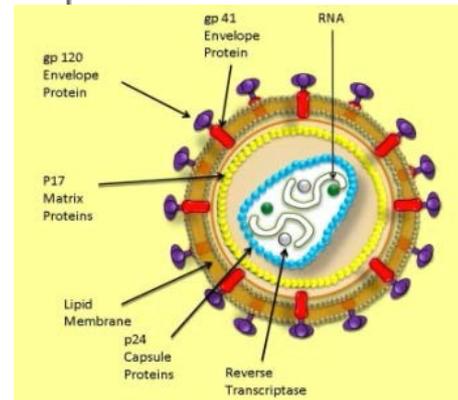
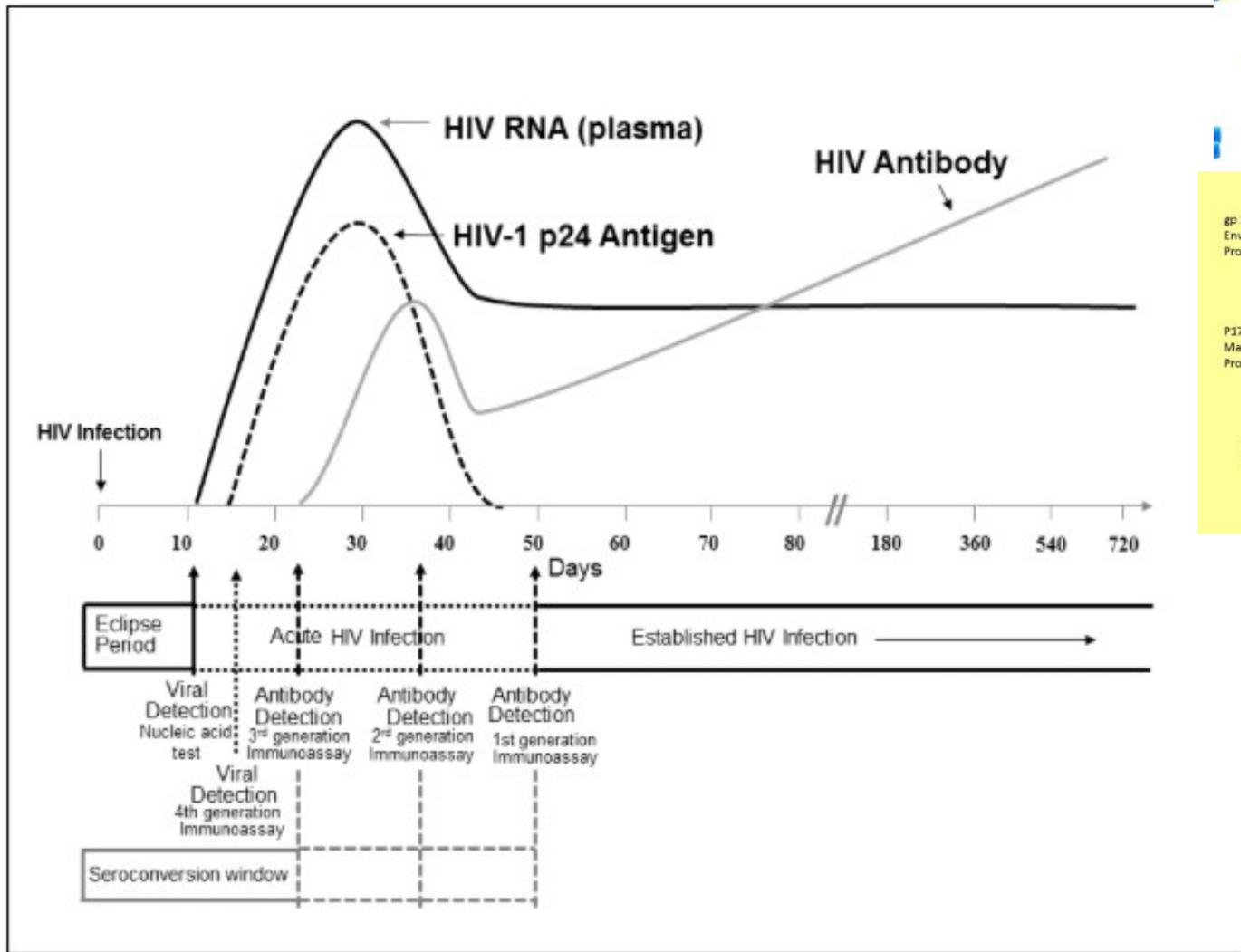
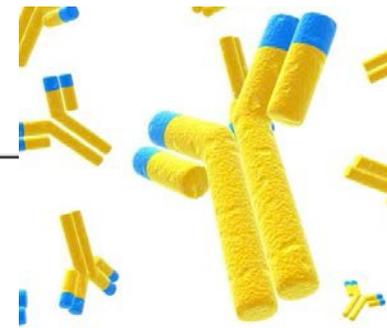
Blood, plasma, serum, saliva



# HIV Testing: Serial Algorithm



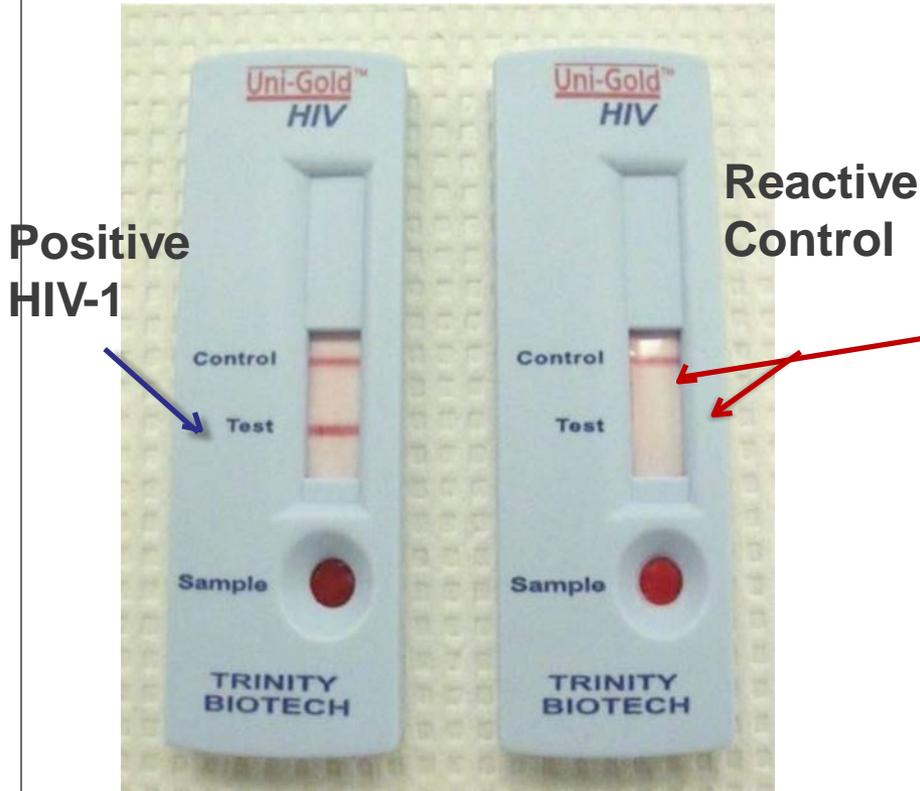
# HIV Diagnosis



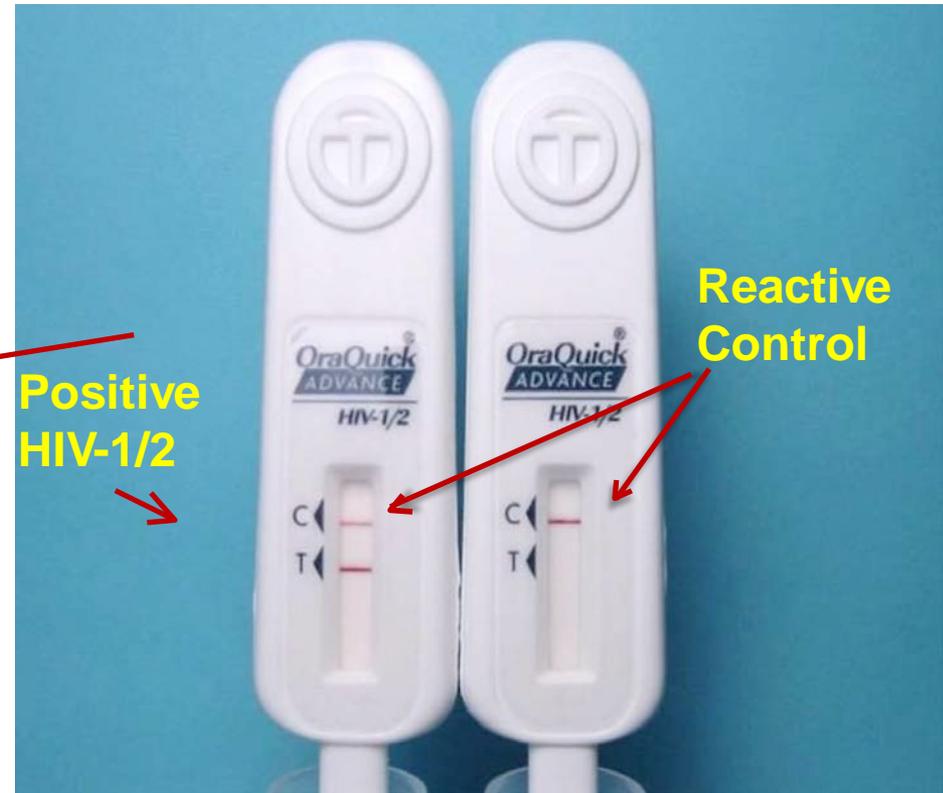
<http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf>

# Rapid Immunoassay - RIA

Uni-Gold Recombigen and OraQuick Advance  
HIV-1/2



Results in 10-12 minutes



Results in 20 minutes

# Military HIV Screening Process

DoDI 6485.01 requires biannual screening for Soldiers

Positive screens are sent to WRAIR for confirmatory testing

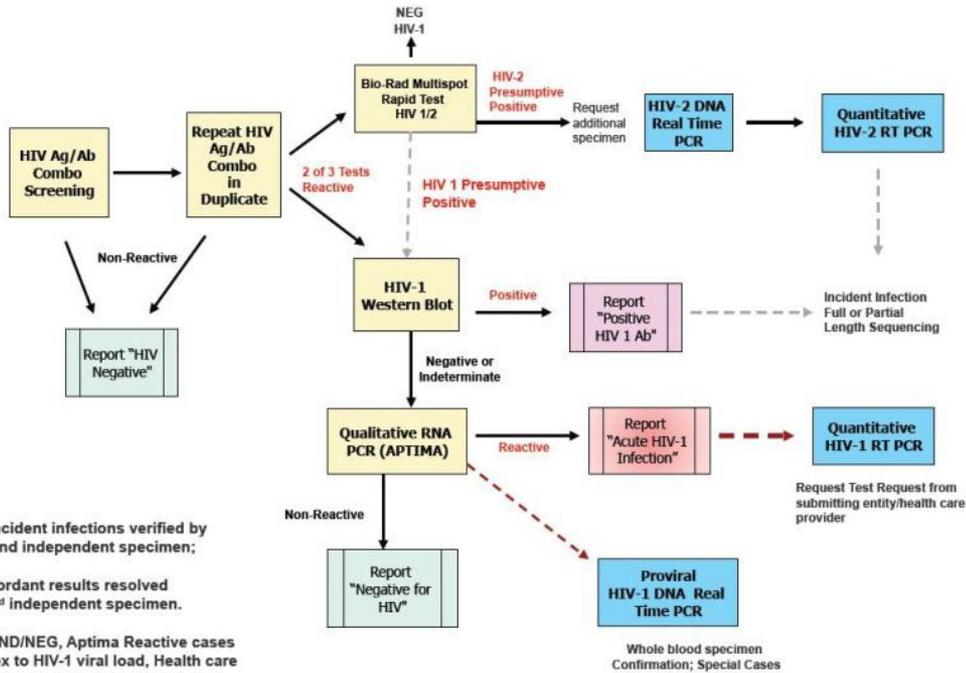
Have to be confirmed within 30 days per AR600- 110

Additional samples tested if positive Results sent to reporting/notification POCs, PHC

New positives/mo: ~30

Incl. dependents, DA civilians Army has highest incidence in DoD Still less than general population

# HIV Diagnostics and Reference Laboratory



All incident infections verified by second independent specimen;

Discordant results resolved by 3<sup>rd</sup> independent specimen.

WB IND/NEG, Aptima Reactive cases Reflex to HIV-1 viral load, Health care Provider contacted for test request

HIV DIAGNOSTICS AND REFERENCE LABORATORY  
9100 Brookville Road, BLDG. 508, Silver Spring, MD 20910  
Serology Clinical Test Request Form

TEST REQUESTED	SPECIMEN REQUIREMENT	DRAW TUBE
<input type="checkbox"/> HIV Algorithm <sup>1</sup>	4 ml serum or plasma (cold pack/frozen)	SST/EDTA
<input type="checkbox"/> Acute HIV Algorithm	4 ml serum or plasma (cold pack/frozen)	SST/EDTA

SHIP FROZEN IF SAMPLE WILL NOT BE RECEIVED AT HDRL WITHIN 72 HOURS.

PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient Stamp <b>must include:</b> Full Name <sup>®</sup> , FMP <sup>®</sup> /SSN <sup>®</sup> , DOB <sup>®</sup>	POC* _____
	Physician Name* _____
	Clinic / Center* _____
	Center Address* _____
	_____
	Telephone Number _____
	Fax Number _____
Specimen Draw Date / Time*: _____	(Commercial # only; please include area/country code)
Ship Date: _____	Alternate POC Name _____
Sample Storage (circle): Frozen / Refrig / Ambient	Alternate POC Phone _____
Sample Shipping (circle): Dry Ice / Cold Pack / Ambient	

\*Required

# Common Problems

Wrong test requested or out of order  
Viral load test ordered first due to clinical presentation

Needs to be a screen test or it won't trigger algorithm or be reported to PCM,  
PHC Genotypes ordered unnecessarily

Viral load needs to be  $> 1000$  cp/mL

Test request forms, sample tubes not filled out completely

Confirmation kits not processed correctly  
Confirmed HIV+ individuals exempt  
from biannual testing requirement

# Health Care Personnel - Exposure to HIV

## What is Exposure?

Contact with potentially infectious blood, tissue, or body fluids in a manner that allows for possible transmission of HIV

A percutaneous injury (*e.g.* a needlestick or cut with a sharp object)

Contact of mucous membrane or non-intact skin (*e.g.* exposed skin that is chapped, abraded, or afflicted with dermatitis)

## Body Fluids of Concern

Concern: blood, semen, vaginal secretions, other body fluids contaminated with visible blood

**Not** considered infectious unless they contain blood: feces, nasal secretions, saliva, gastric secretions, sputum, urine, and vomitus

Intact skin is an effective barrier against HIV infection

# Management of Health Care Personnel Exposed to HIV

Risk of transmission varies depending type of exposure

High if source has high HIV viral load, large volume, deep exposure

Risk after exposure to body fluids is low

After a needle-stick injury is about 3 per 1000 with no prophylaxis

Once exposed  What next?

Determine HIV status of source patient If

Positive or Unknown,

RDT – test patient (if result within 2 hours)

Post Exposure Prophylaxis (PEP)

# Management of Health Care Personnel Exposed to HIV

**PEP = POST EXPOSURE PROPHYLAXIS**

**START AS SOON AS POSSIBLE – HOURS VS. DAYS**

**IF UNSURE OF REGIMEN, START BASIC REGIMEN VS. DELAY**

**ADMINISTER FOR 4 WEEKS**

**SIDE EFFECTS COMMON**

**GI – NAUSEA, VOMITING, DIARRHEA**

**HEADACHE, FATIGUE**

**EXPERT CONSULTATION RECOMMENDED**

# Management of Health Care Personnel

## PEP CONTINUED

RE-EVALUATE EXPOSED HCP WITHIN 72 HOURS OF EXPOSURE

ADDITIONAL INFORMATION ABOUT EXPOSURE OR SOURCE PATIENT

IF THE SOURCE IS FOUND TO BE HIV NEGATIVE, PEP SHOULD BE DISCONTINUED

HOW OFTEN TO TEST FOR HIV IN EXPOSED PATIENT?

BASELINE, 6 WEEKS, 3 MONTHS AND 6 MONTHS  
MOST SEROCONVERTERS – WITHIN 3 MONTHS



<http://www.aids-ed.org/>

# Which drugs to use?\*

## Truvada™ 1 PO Once Daily

[**Tenofovir DF** (Viread®; TDF) 300mg + **emtricitabine** (Emtriva™; FTC) 200mg]

**PLUS**

## Raltegravir (Isentress®; RAL) 400mg PO Twice Daily

One drug or drug pair from the left column with one pair of nucleoside/nucleotide reverse transcriptase inhibitors from the right column.

Raltegravir (Isentress® ; RAL)	Tenofovir DF (Viread® ; TDF) + emtricitabine (Emtriva™ ; FTC); available as Truvada™
Darunavir (Prezista® ; DRV) + ritonavir (Norvir® ; RTV)	Tenofovir DF (Viread® ; TDF) + lamivudine (Epivir® ; 3TC)
Etravirine (Intelence® ; ETR)_	Zidovudine (Retrovir™ ; ZDV; AZT) + lamivudine (Epivir® ; 3TC); available as Combivir®
Rilpivirine (Edurant™ ; RPV)	Zidovudine (Retrovir™ ; ZDV ; AZT) + emtricitabine (Emtriva™ ; FTC)
Atazanavir (Reyataz® ; ATV) + ritonavir (Norvir® ; RTV)	
<b>Lopinavir/ritonavir (Kaletra® ; LPV/RTV)</b>	

\*CDC, 2005

# Current ARV Medications

## ● PI

- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

### **NRTI**

Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC)  
Lamivudine (3TC)  
Stavudine (d4T) Tenofovir (TDF) Zidovudine (AZT, ZDV)

### **NNRTI**

Delavirdine (DLV)  
Efavirenz (EFV)  
Etravirine (ETR)  
Nevirapine (NVP)

## ● II

- Raltegravir (RAL)
- Elvitegravir (EVG)
- Dolutegravir (DTG)

## ● Fusion Inhibitor

- Enfuvirtide (ENF,T20)

## ● CCR5 Agonist

- Maraviroc (MVC)

# **HIV Prevention: Turning the Tide**

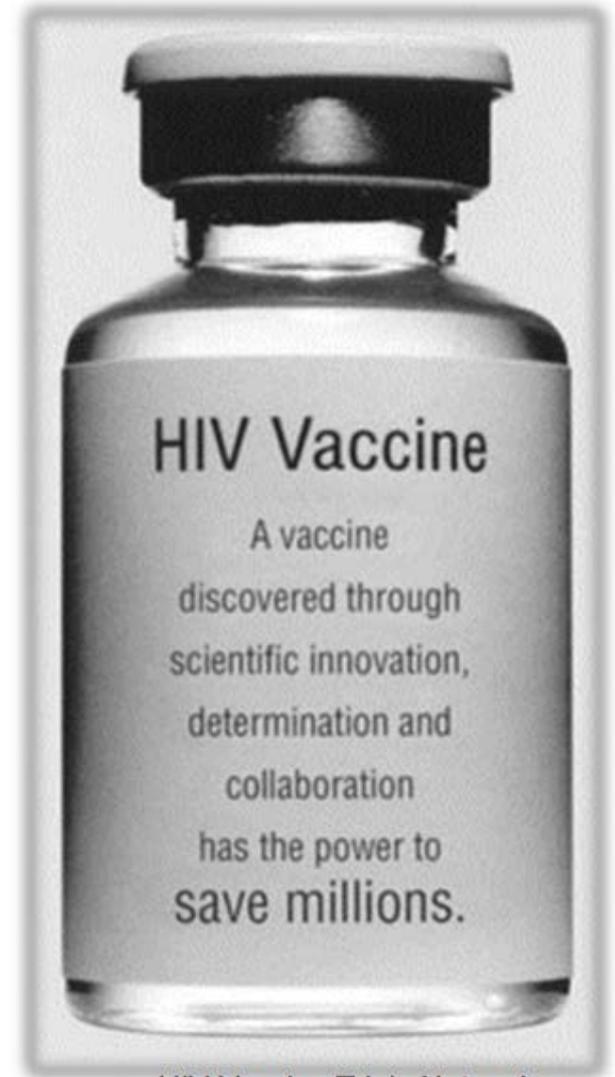
# Leading the Battle Against HIV



The U.S. Military HIV Research Program conducts research to develop an effective preventive HIV vaccine and integrates prevention, treatment, diagnostics and monitoring as part of an international effort to protect U.S. and allied troops and reduce the impact of HIV infection worldwide.

# When will an HIV Vaccine be available?

- a. A vaccine is available now
- b. Next year
- c. 5 years
- d. 10 years
- e. Don't know



HIV Vaccine Trials Network

# RV144

Modest results, but first sign of protection in humans

N=16,000 Thai volunteers at community risk

Canarypox vector x 4 + gp120 x 2

Modified intention to treat efficacy 31.2%  
(95% CI, 1.1 to 52.1; P = 0.04)

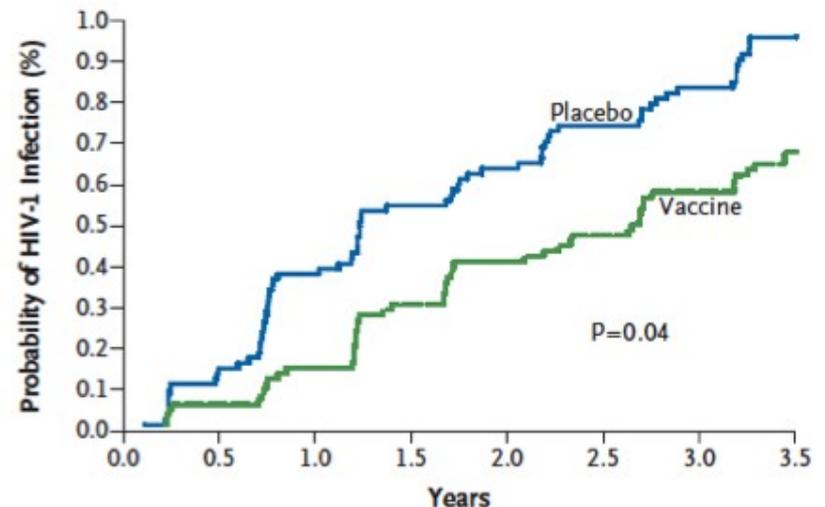
No effect on viral load



## Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pittisutthithum M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Prem Sri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Bix, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kanasol, M.D., and Jerome H. Kim, M.D., for the MOPH-TAVEG Investigators\*

Modified Intention-to-Treat Analysis



# References

UNAIDS REPORT ON THE GLOBAL AIDSEPIDEMIC

[WWW.UNAIDS.ORG/EN/KNOWLEDGECENTRE/HIVDATA/GLOBAL\\_REPORT](http://WWW.UNAIDS.ORG/EN/KNOWLEDGECENTRE/HIVDATA/GLOBAL_REPORT)

DHHS GUIDELINES FOR USE OF ART IN ADULTS AND ADOLESCENTS

[WWW.AIDSINFO.NIH.GOV/GUIDELINES](http://WWW.AIDSINFO.NIH.GOV/GUIDELINES)

MILITARY HIV RESEARCH PROGRAM

([WWW.HIVRESEARCH.ORG](http://WWW.HIVRESEARCH.ORG)) INTERNATIONAL AIDS VACCINE

INITIATIVE ([WWW.IAVI.ORG/PAGES/HOME](http://WWW.IAVI.ORG/PAGES/HOME))

STEP PAPER: BUCHBINDER *ET AL.* *LANCET*, 2008 RV144 THAI TRIAL PAPER:

RE RKS - NGARM *ET AL.* *NEJM*, 2009