

Overview of HIV

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The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.



Outline

- Background and Epidemiology
- HIV Virology, Transmission, and Pathogenesis
- Acute HIV infection
- HIV Diagnostics
- Management of Health Care Personnel Exposed to HIV
 - Post-exposure prophylaxis
- HIV Prevention—turning the tide

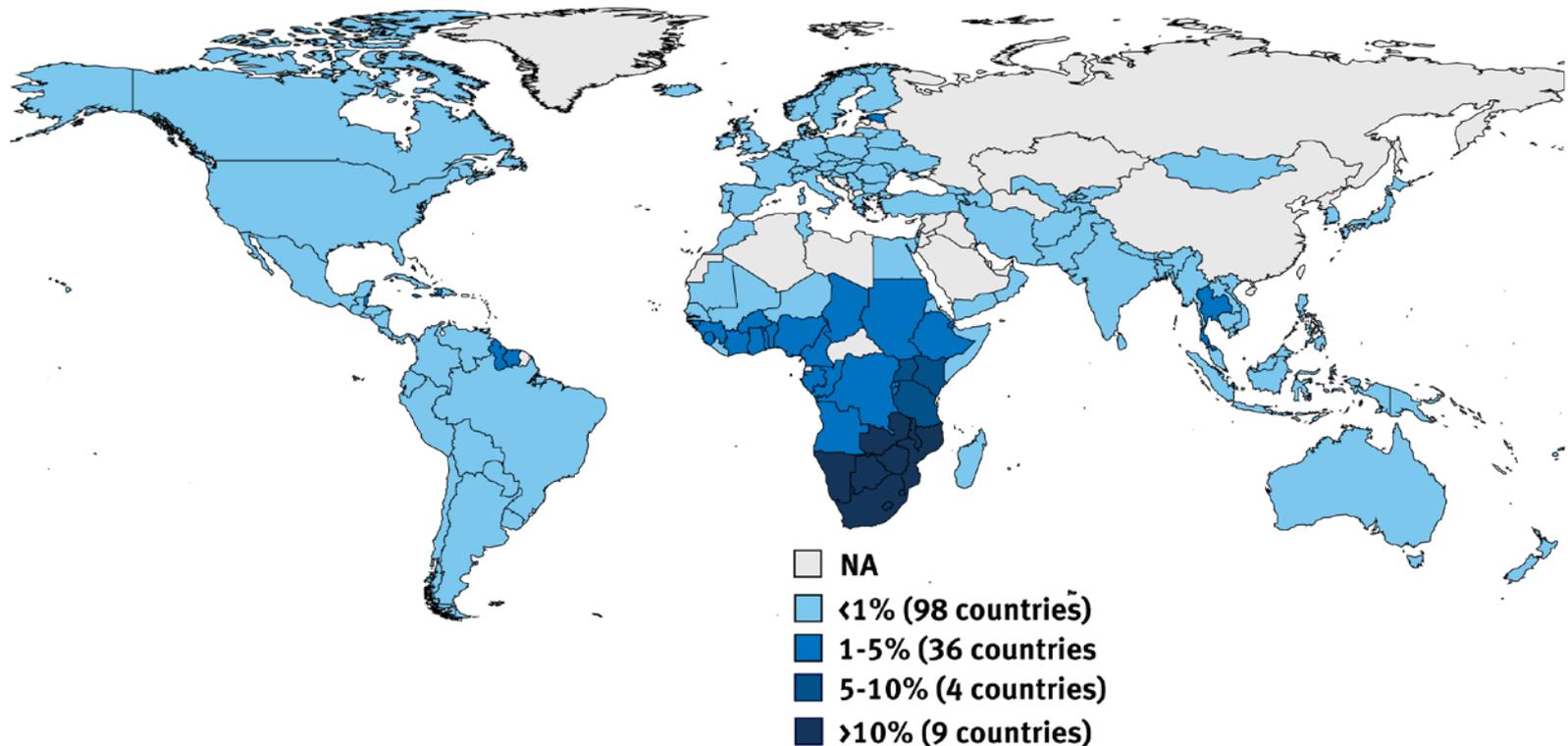
Historical Perspective

- HIV-1 identified officially 05 JUN 1981 (US)
 - CDC MMWR report of 5 unusual Pneumocystis pneumonia cases
- Origin: non-human primates W Africa
 - HIV-1: S Cameroon; evolution of Simian Immunodeficiency Virus (SIV)
 - HIV-2 : S Senegal – W Cote d'Ivoire, SIV
- Early expectations – vaccine in 2 years
(M. Heckler- NIH Director)
- Search for cure and implementation of prevention strategies continues ... 2013

HIV – Adult Prevalence Rate 2012

Adult HIV Prevalence Rate, 2012

Global HIV/AIDS Prevalence Rate = 0.8%



NOTES: Data are estimates. Prevalence rates include adults ages 15-49. The estimate for Sudan represents data for South Sudan. An estimate was not provided for Sudan.

SOURCE: Kaiser Family Foundation, www.GlobalHealthFacts.org, based on UNAIDS, Report on the Global AIDS Epidemic; 2013.

Question

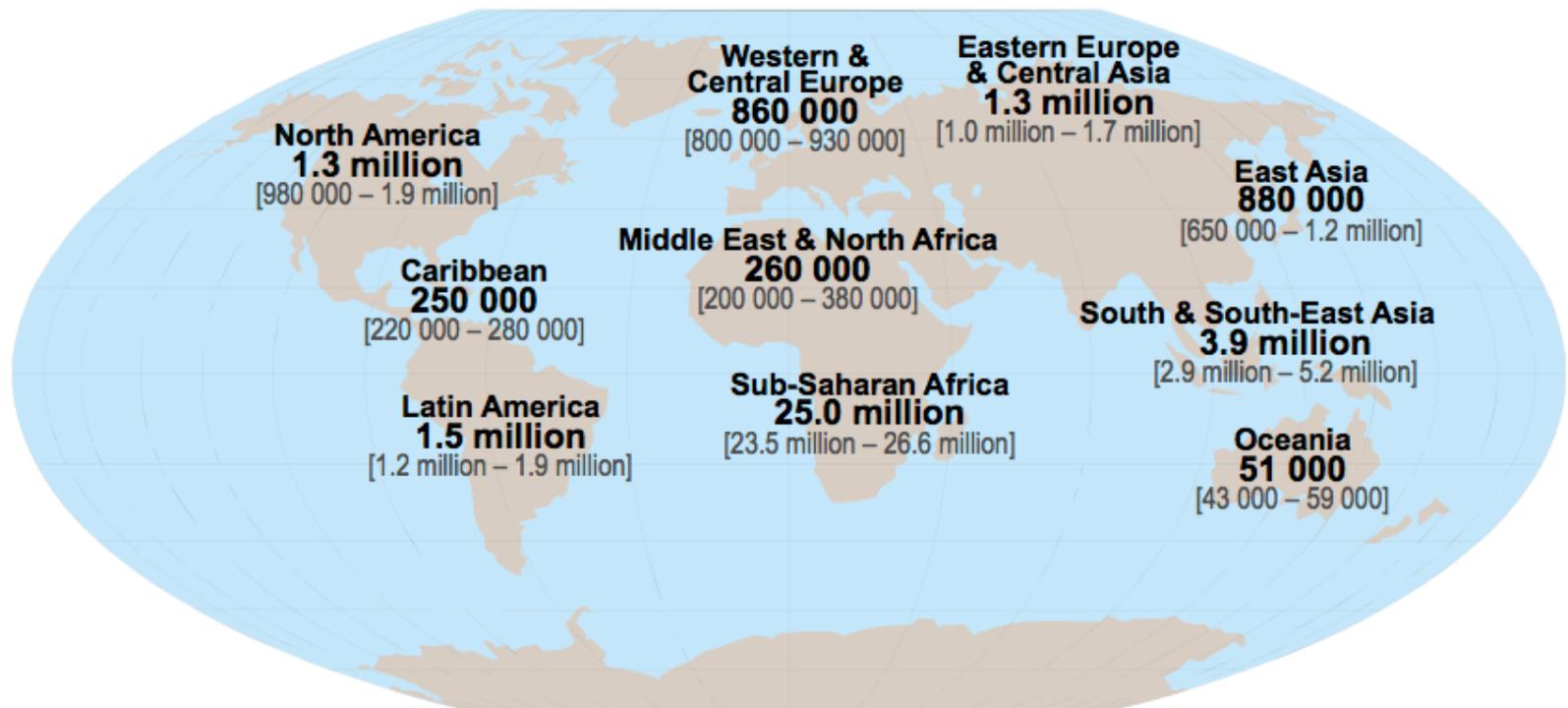
- How many new HIV infections occurred in 2012 worldwide?
 - a) 80,700
 - b) 750,000
 - c) 2,300,000
 - d) 5,100,000



Adults and children estimated to be living with HIV | 2012

New infections: 2,300,000

Estimated Deaths: 1,600,000



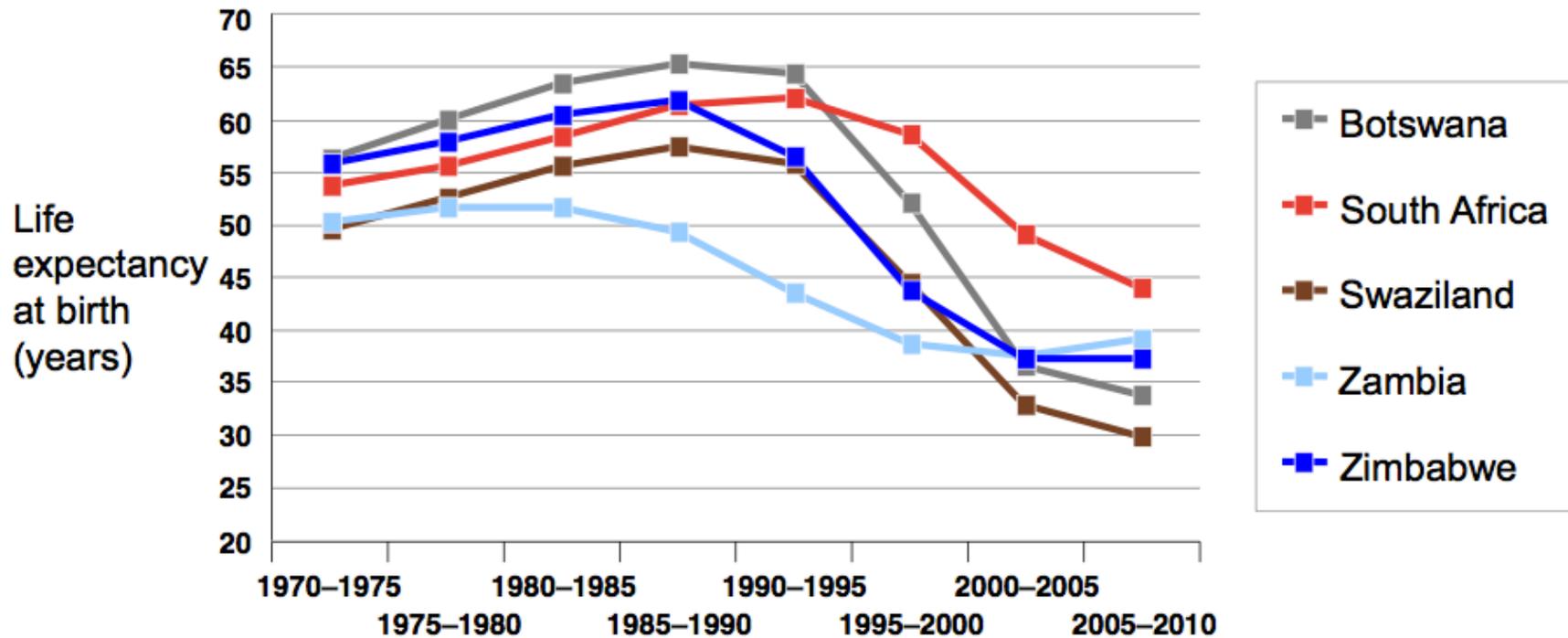
Total: 35.3 million [32.2 million – 38.8 million]

Over 6,300 new HIV Infections a day in 2012

- About 95% are in low/ middle income countries
- ~ 700 are in children under 15 years of age
- ~ 5,500 are in adults aged 15 years and older, of whom:
 - 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 in five African countries, 1970-2010



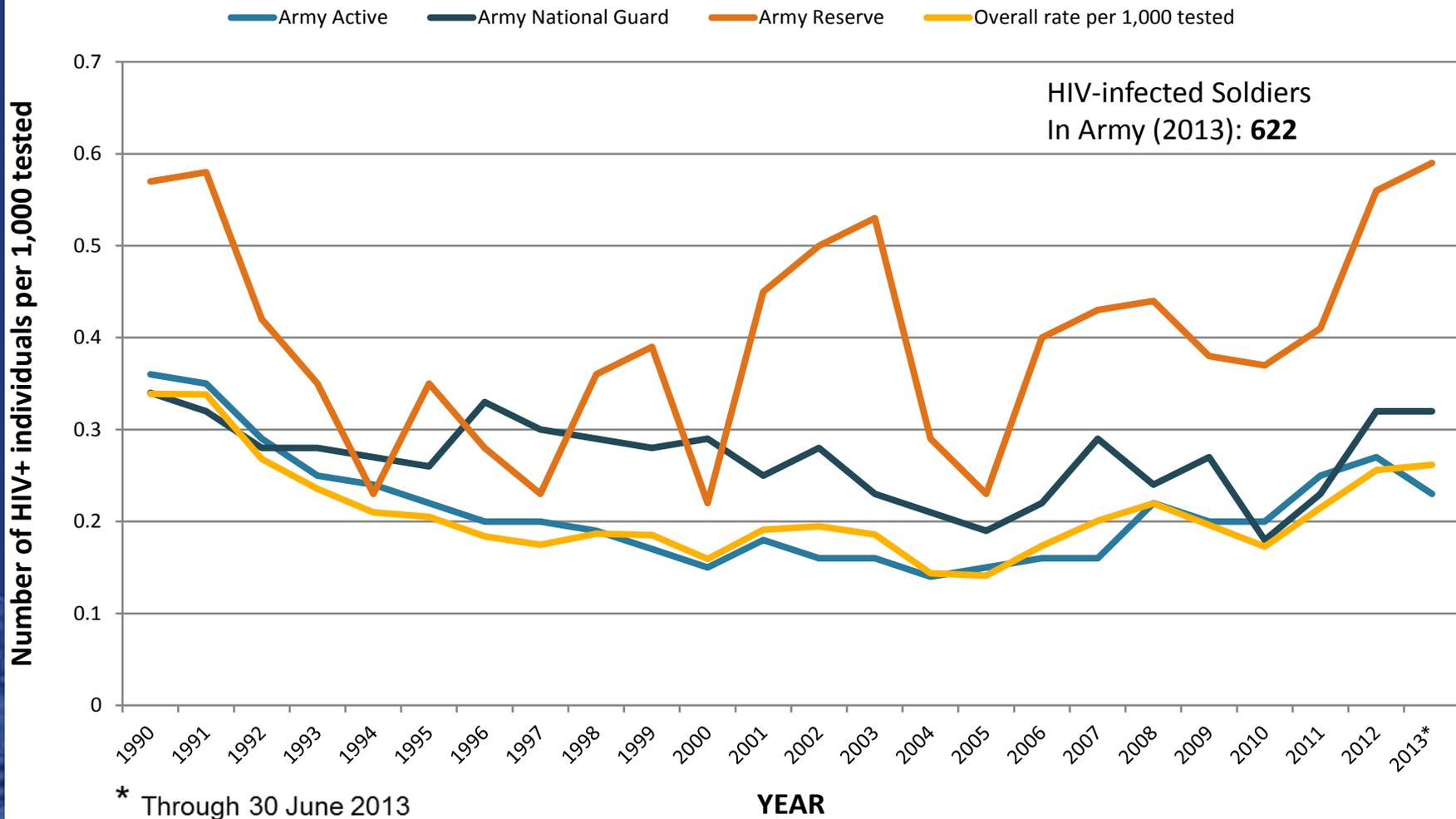
HIV – A Worldwide Threat

- 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
- All affect impact of global epidemic & DoD





HIV is an Enduring Problem in the Army

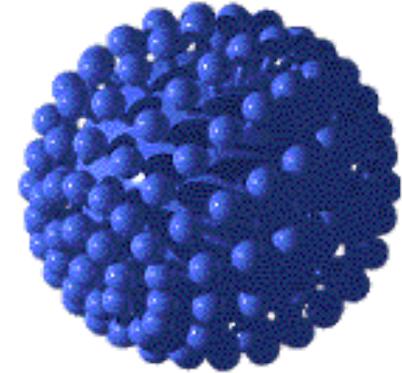


HIV Virology, Pathogenesis and Transmission

HIV vs. AIDS

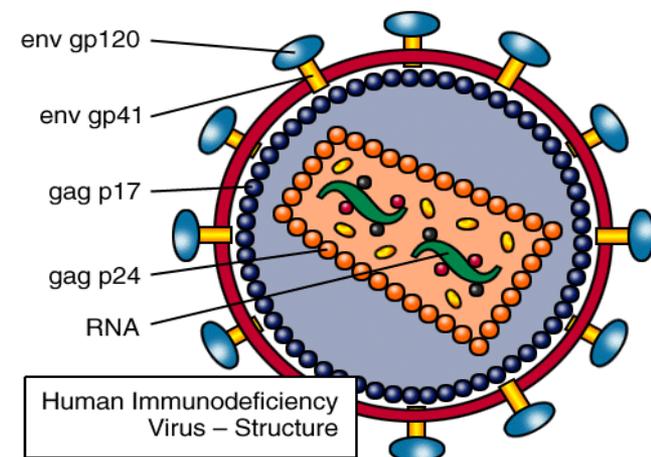
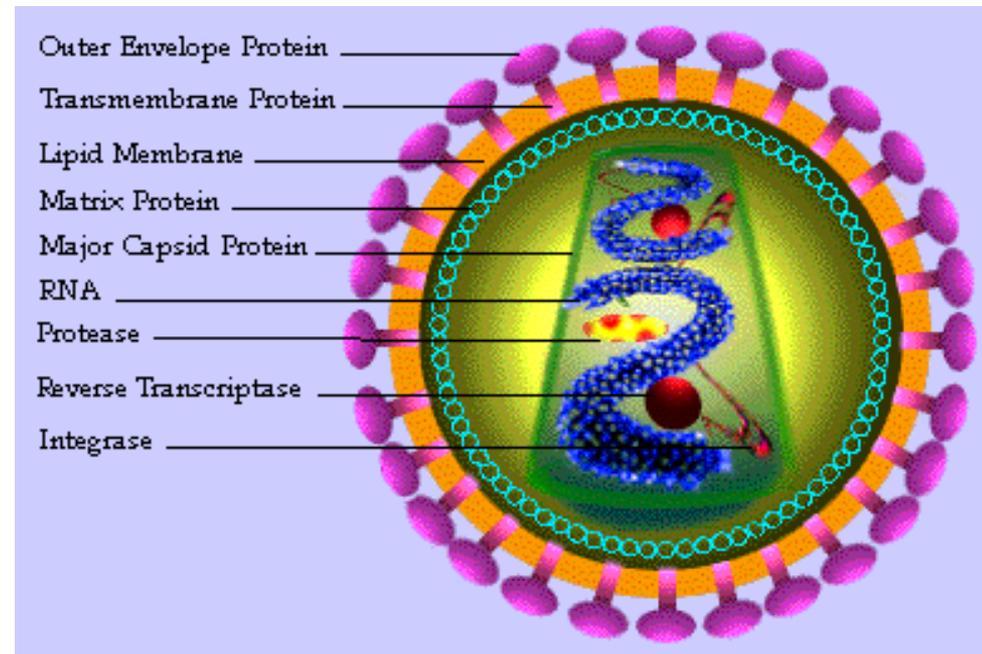
- HIV
 - Human
 - Immunodeficiency
 - Virus

- AIDS
 - Acquired
 - Immunodeficiency
 - Syndrome



HIV: Human Immunodeficiency Virus

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



How HIV Works

MHRP

HIV

1. Attachment to host CD4 cell

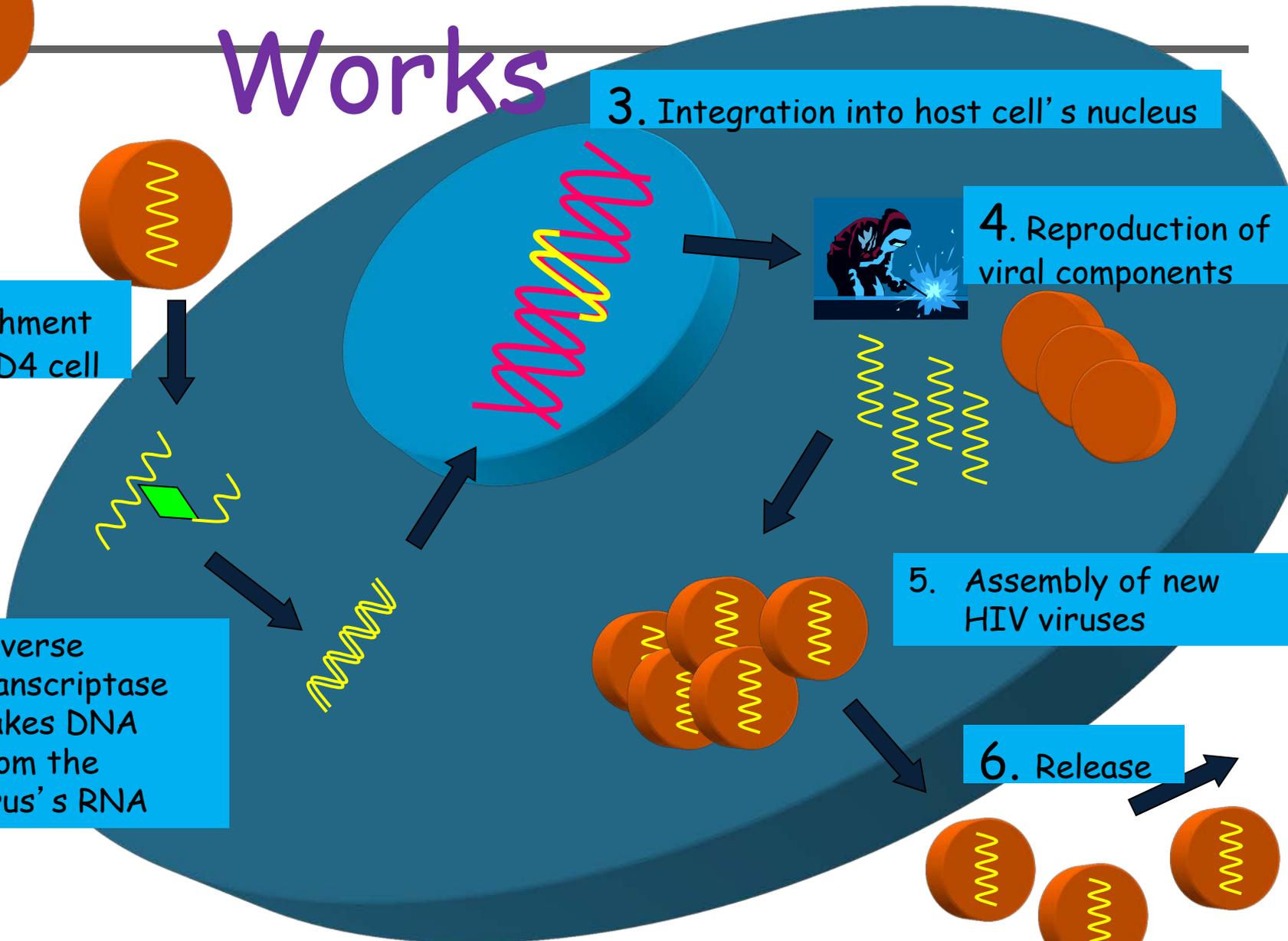
3. Integration into host cell's nucleus

4. Reproduction of viral components

2. Reverse transcriptase makes DNA from the virus's RNA

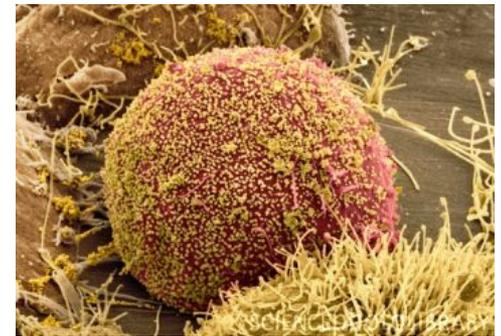
5. Assembly of new HIV viruses

6. Release

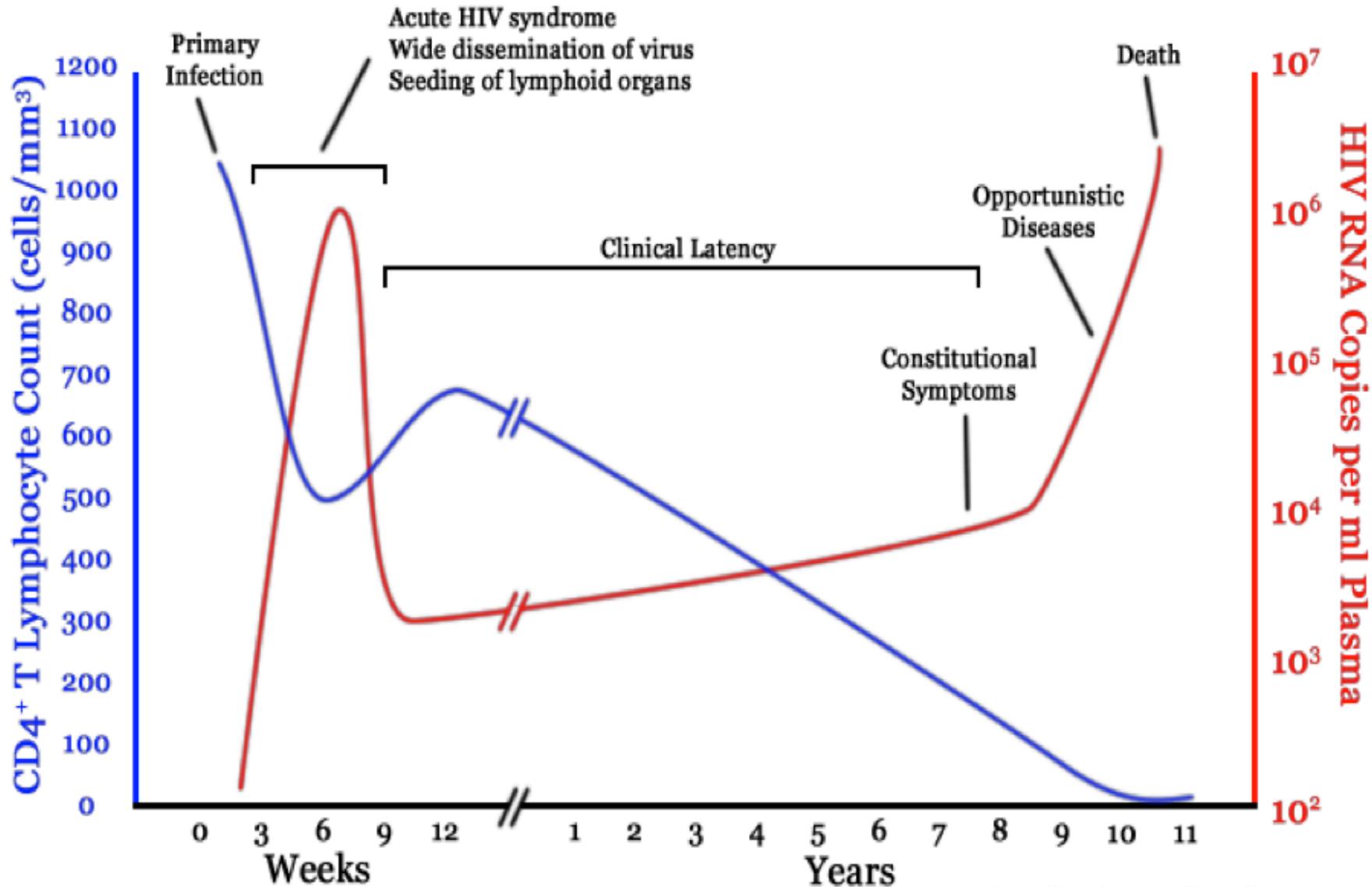


CD4

- Stage disease and guide clinical management
- CD4+ Helper T cells = CD4 T cells = CD4 count
 - CD = Cluster Determinant
 - Measured by Flow Cytometry
 - Normal range 500 – 1400 cells/mm³
 - Broad range because 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



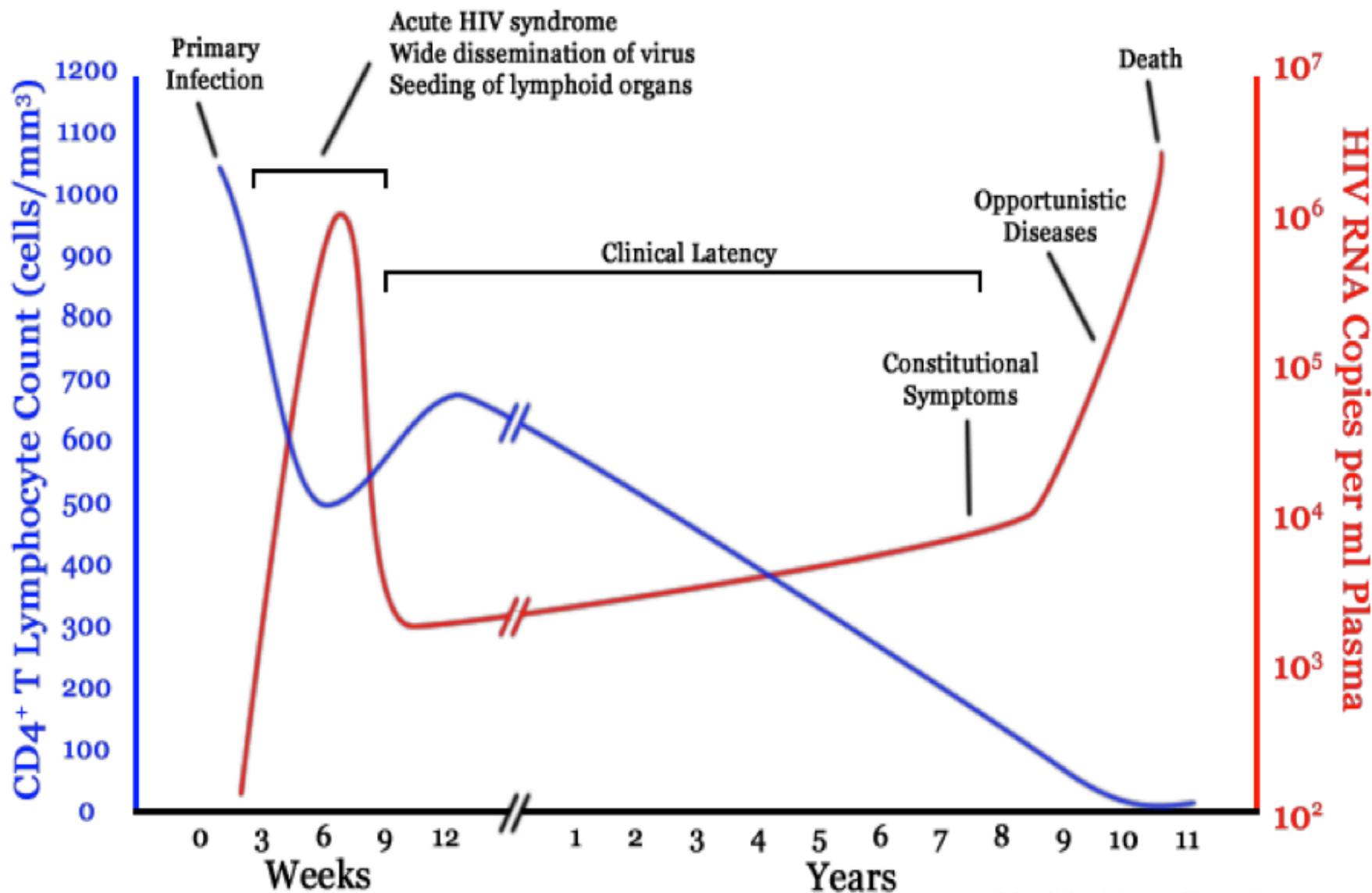
Modified from Fauci, 2000

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 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

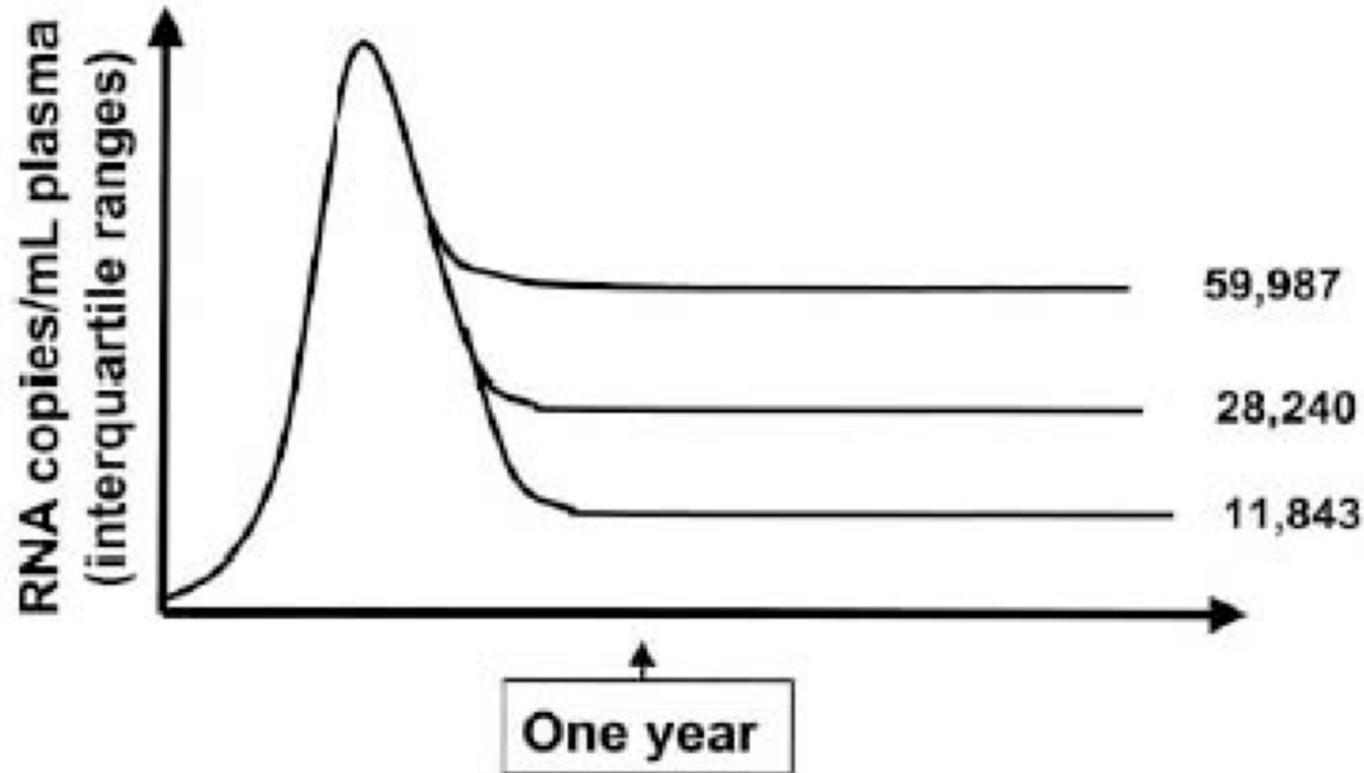
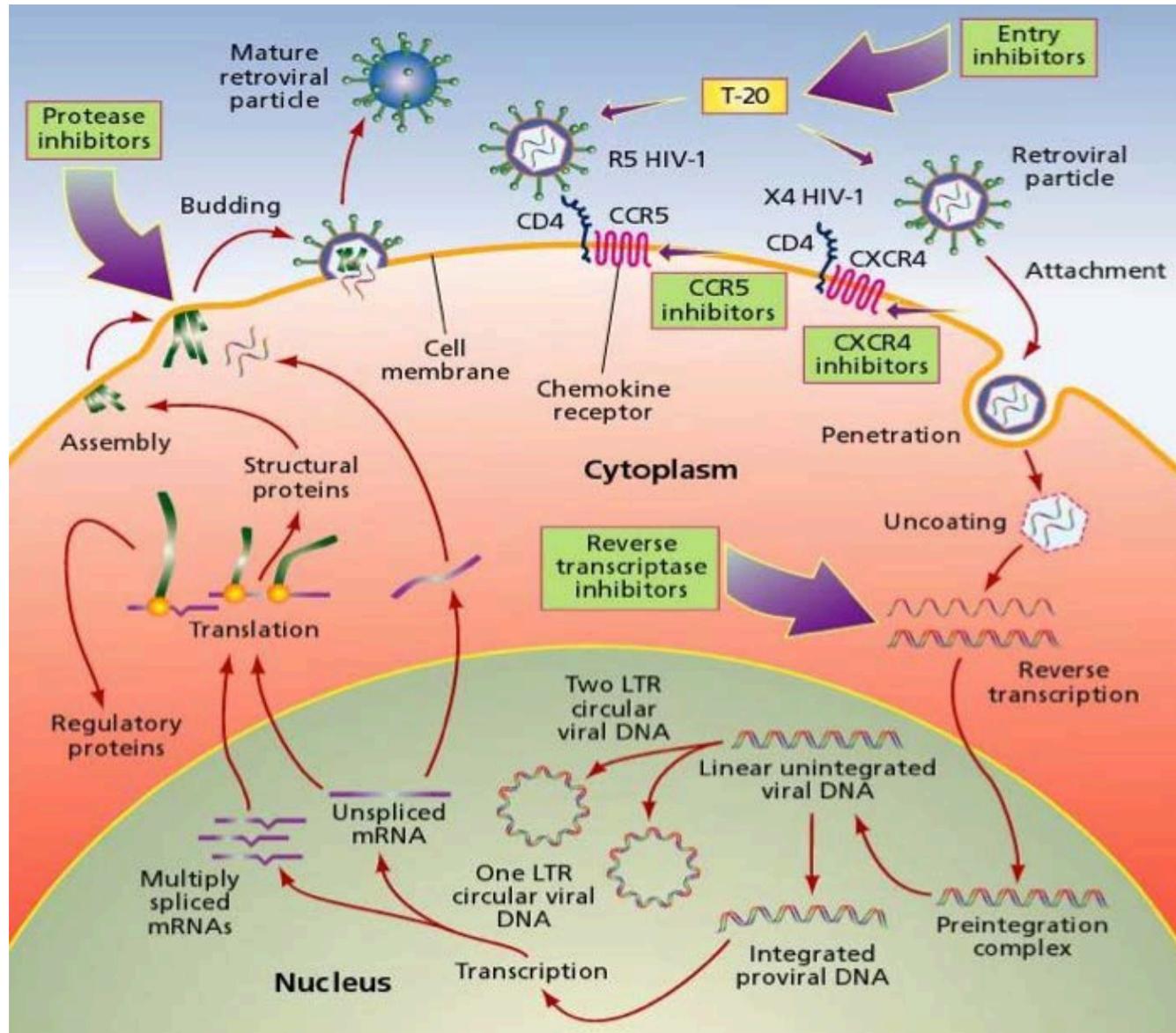


Figure 2. HIV RNA levels 1 year after untreated infection are relatively stable and predict subsequent disease progression. Data are from the Multicenter AIDS Cohort Study.

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

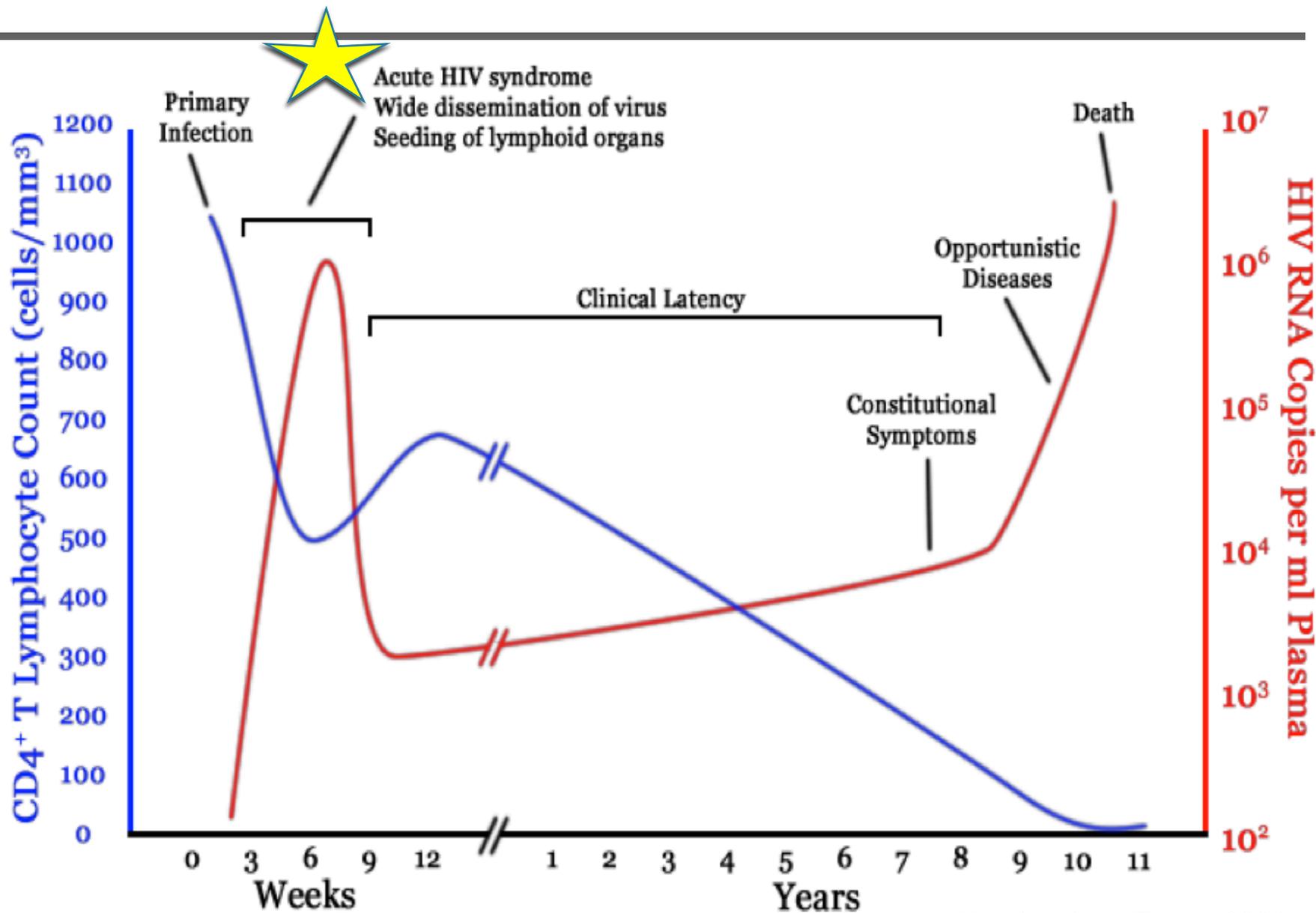
- 25 yo sexually active man presents with a 3-week hx fever, fatigue, head ache, mild sore throat.
- On physical exam, the patient is alert & oriented.
- T 38.2 C. A maculopapular rash is present over trunk & face. A few ulcers are seen on soft palate.
- Cervical lymph nodes are slightly enlarged, and her neck is stiff.
- WBC 3.6, Hct 34%, platelets 90,000. Monospot & serum RPR are negative.

Case continued

Which of the following is the most likely diagnosis?

- Acute HIV infection
- Infectious mononucleosis (“Mono”)
- Strep throat
- Flu

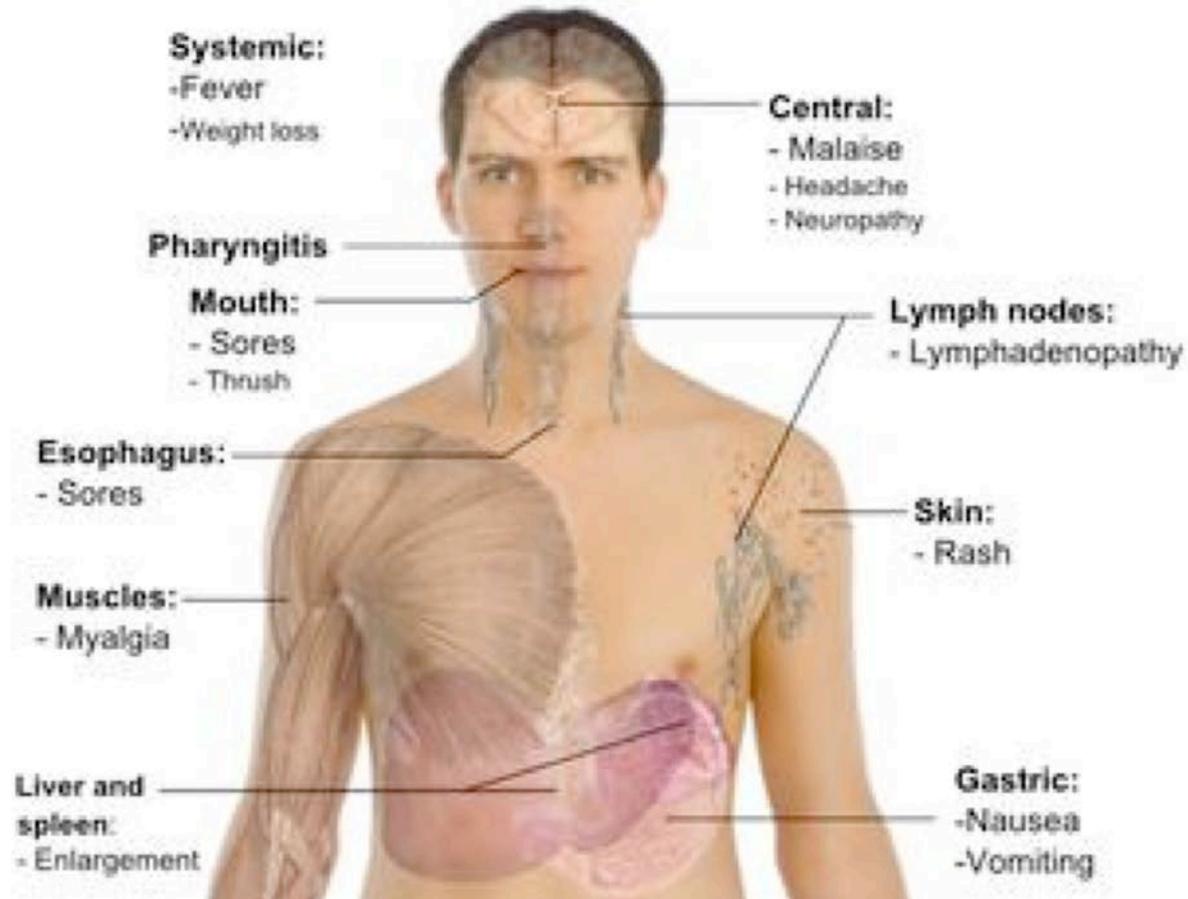
Acute HIV Infection



Modified from Fauci, 2000

Symptoms of Acute HIV Infection

Main symptoms of Acute HIV infection



Frequency Symptoms in Acute HIV-1 Infection

- **Fever** >80-90%
- **Fatigue** >70-90
- **Rash** >40-80
- **Headache** 32-70
- **Lymphadenopathy** 40-70*
- **Pharyngitis** 50-70*
- **Myalgia/arthralgia** 50-70

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

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



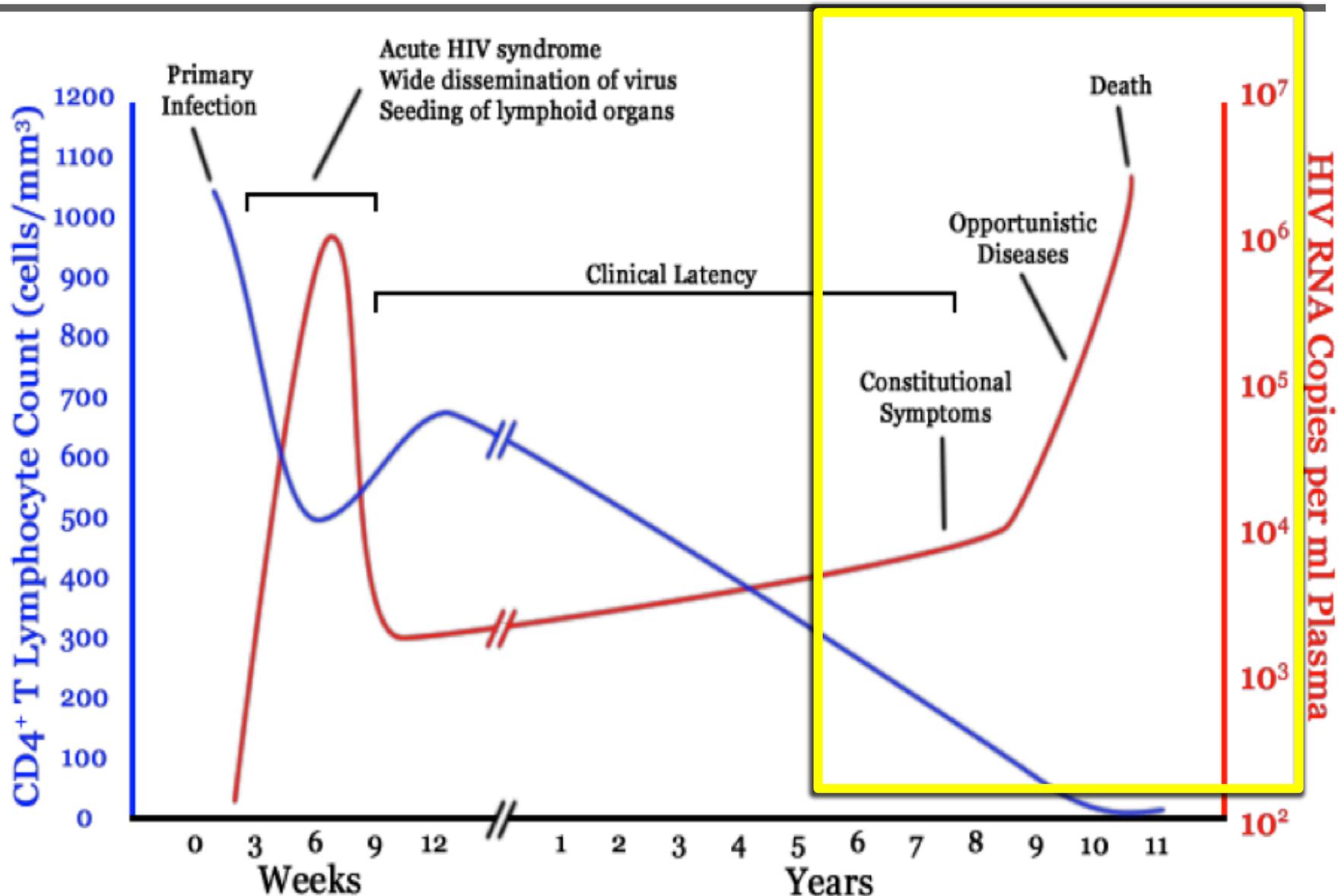
DOIA

(c) University Erlangen,
Department of Dermatology
Phone: (+49) 91 31 - 85 - 2727





Advanced Stages & Opportunistic Infections



Advanced Stages of HIV / AIDS

- CD4 < 200mm³
- Opportunistic infections
 - Immunocompromised = Increased risk
 - In US: Pneumocystis pneumonia, Kaposi's sarcoma
 - In Sub-Saharan Africa: malaria, diarrhea, pneumonia
 - Prophylaxis for OIs becomes important
 - What you are prophylaxed for depends on:
 - Patient's medical history
 - Patient's environment
 - CD4 count
 - Review guidelines as needed – consult expert
- Know that under 200, patients at risk

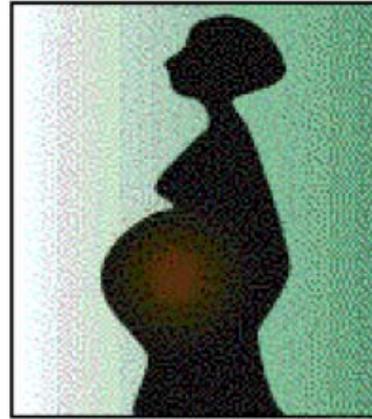
AIDS

- AIDS
 - CD4 cell count below $200/\text{mm}^3$ regardless of the presence or absence of symptoms
 - WHO stages
 - Clinical staging guideline
 - Still used in field where CD4 and VL results may be limited
 - AIDS defining conditions
 - Serious conditions in people with HIV that define stage
 - P. carinii pneumonia
 - Esophageal candidiasis
 - Kaposi's sarcoma
 - Tuberculosis

Transmission Routes

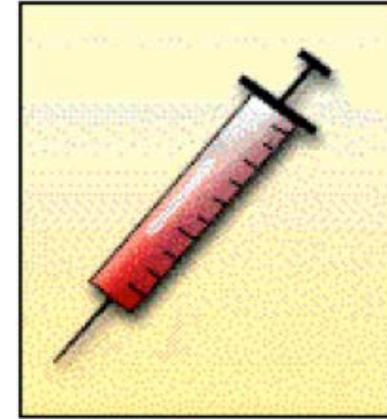


**Unprotected
sexual intercourse
with an infected partner**



**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

Per Contact Transmission Rate

- Transfusion 95%

- Untreated Perinatal Transmission 15-30%

- Occupational Transmission:
 - Needle Stick 0.3%
 - Mucous Membrane 0.01-0.1%

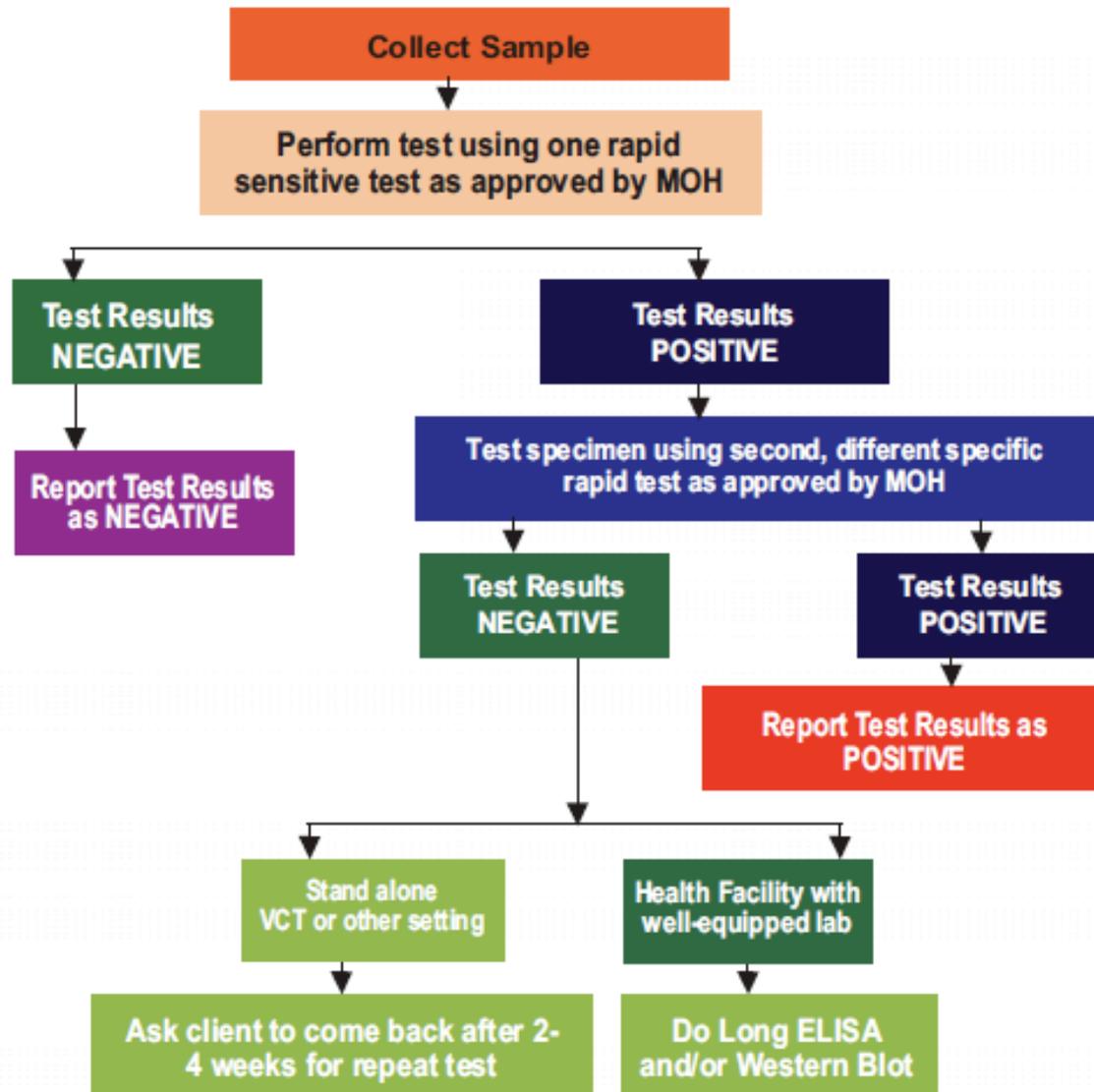
HIV Diagnostics: Serology vs. RDT

- Serology
 - Detection of IgG antibody against HIV-1 antigens in serum
 - Positive tests confirmed with repeat tests or corroborating laboratory data (eg, Western blot assays)
 - 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

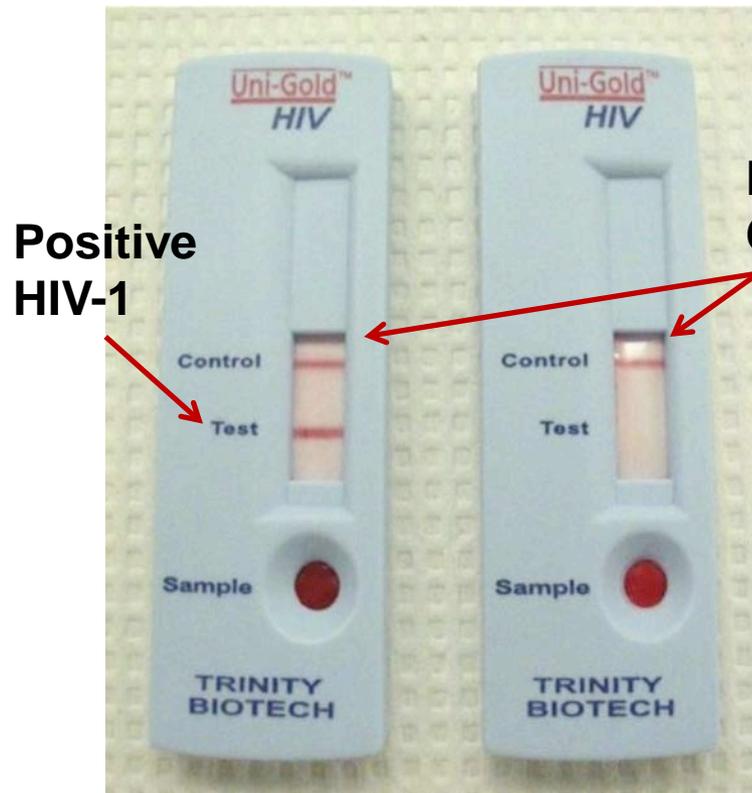


HIV testing: serial algorithm

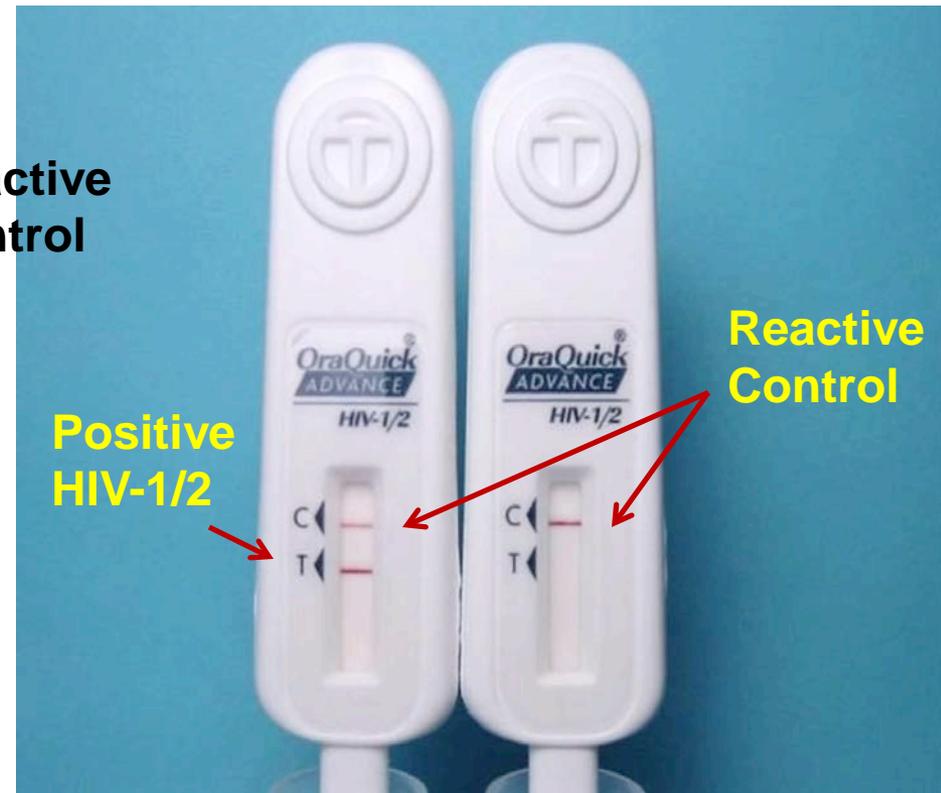


Rapid Immunoassay - RIA

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



Results in 10-12 minutes



Results in 20 minutes

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 (eg, a needlestick or cut with a sharp object)
 - Contact of mucous membrane or nonintact skin (eg, 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 needlestick injury is about 3 per 1000 with no prophylaxis

- Once determined 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 - Complex

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)	
Lopinavir/ritonavir (Kaletra® ; LPV/RTV)	

*CDC
, 2005

Current ARV Medications

- **NRTI**
 - Abacavir (ABC)
 - Didanosine (ddl)
 - Emtricitabine (FTC)
 - Lamivudine (3TC)
 - Stavudine (d4T)
 - Tenofovir (TDF)
 - Zidovudine (AZT, ZDV)
- **PI**
 - Atazanavir (ATV)
 - Darunavir (DRV)
 - Fosamprenavir (FPV)
 - Indinavir (IDV)
 - Lopinavir (LPV)
 - Nelfinavir (NFV)
 - Ritonavir (RTV)
 - Saquinavir (SQV)
 - Tipranavir (TPV)
- **Integrase Inhibitor (II)**
 - Raltegravir (RAL)
- **Fusion Inhibitor**
 - Enfuvirtide (ENF, T-20)
- **CCR5 Antagonist**
 - Maraviroc (MVC)
- **NNRTI**
 - Delavirdine (DLV)
 - Efavirenz (EFV)
 - Etravirine (ETR)
 - Nevirapine (NVP)

HIV Prevention: Turning the Tide

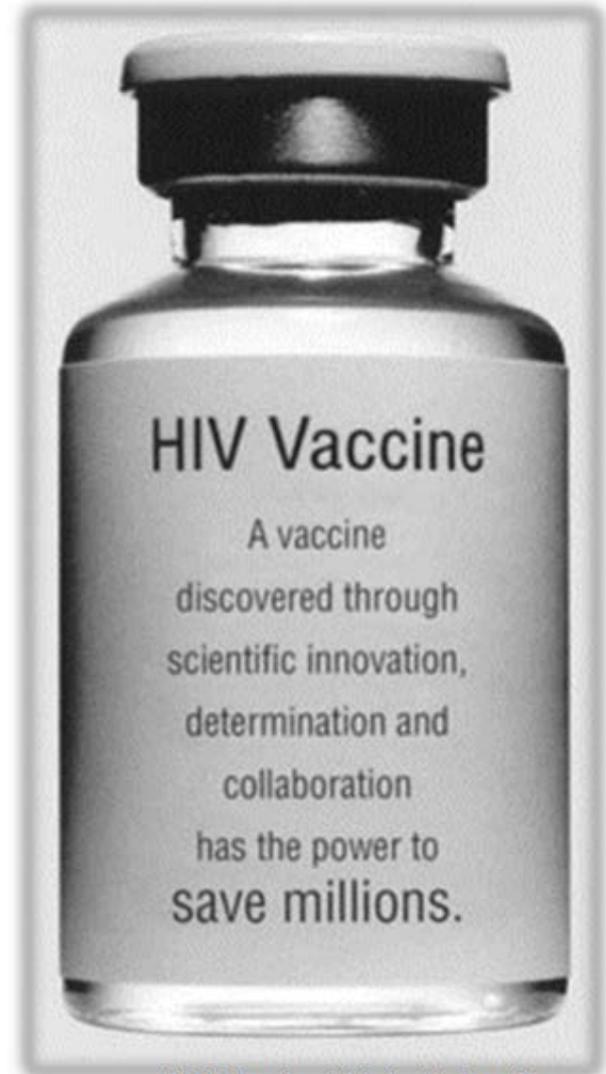
Leading the battle against HIV



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

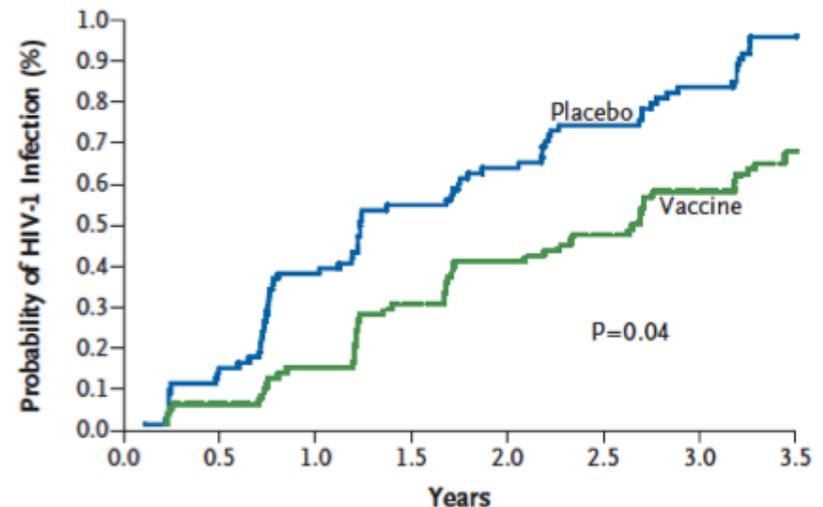
- Modest results, but first sign of protection in humans
 - N=16,000 Thai volunteers at community risk
 - Canarypox vector x 4 + gp120 x 2
 - Modified intention to treat efficacy 31.2% (95% CI, 1.1 to 52.1; P = 0.04)
 - No effect on viral load

The NEW ENGLAND
JOURNAL of MEDICINE

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. Birx, 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 Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH-TAVEG Investigators*

Modified Intention-to-Treat Analysis



QUESTIONS?

Thank you...

Feel free to email/call with other questions:

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+1-301-500-3688

References

- UNAIDS Report on the Global AIDS Epidemic www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/default.asp
- DHHS Guidelines for Use of ART in Adults and Adolescents www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7
- Military HIV Research Program www.hivresearch.org/home.php
- International AIDS Vaccine Initiative www.iavi.org/Pages/home.aspx
- STEP paper: Buchbinder et al. Lancet, 2008
- RV144 Thai Trial Paper: Rerks-Ngarm et al, NEJM, 2009