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Overview of HIV

Christina Polyak, MD, MPH

Research Physician

U.S. Military HIV Research Program,
Walter Reed Army Institute of Research

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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

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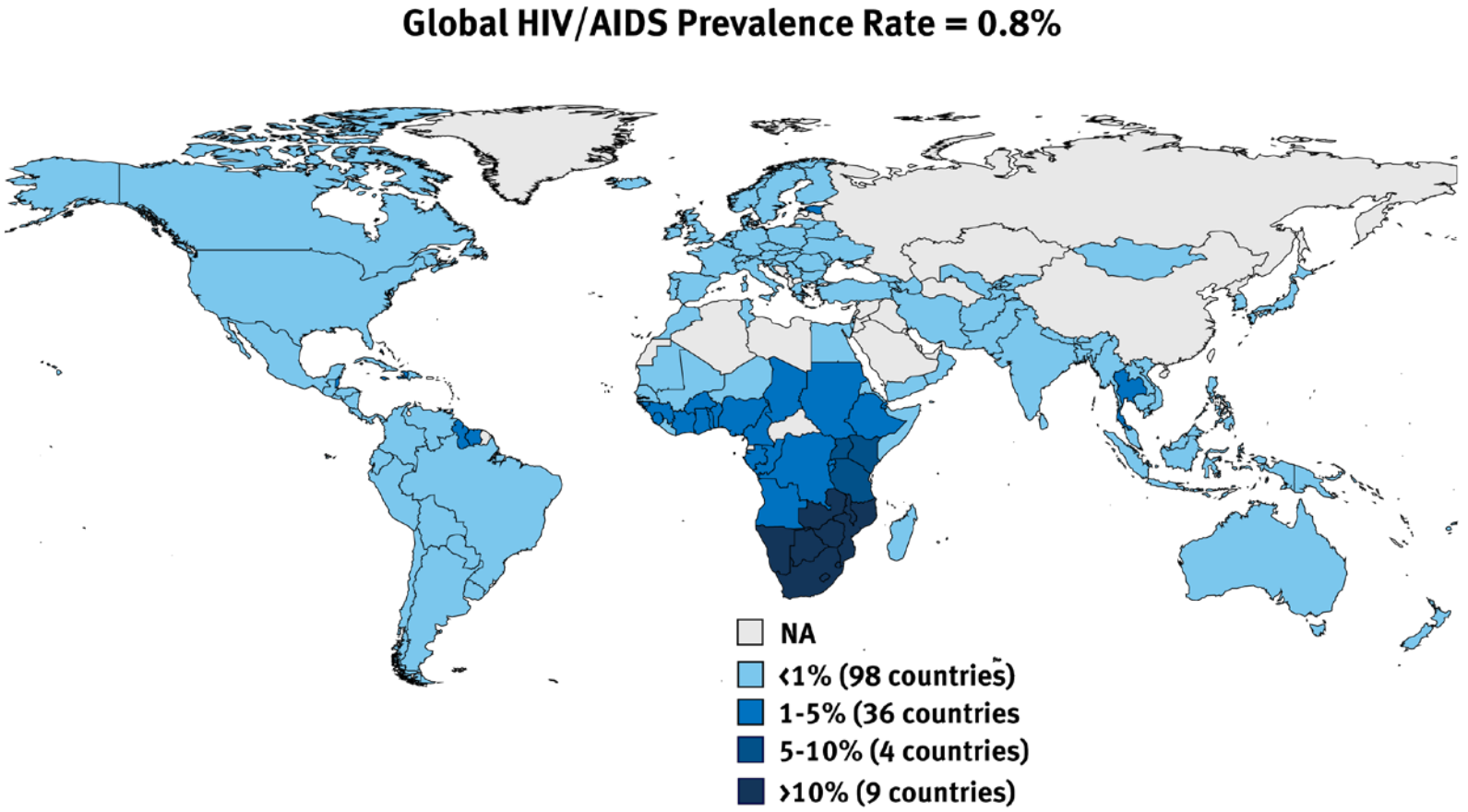
HIV – Adult Prevalence Rate 2012

Adult HIV Prevalence Rate, 2012



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.

THE HENRY J. KAISER FAMILY FOUNDATION

Question

- How many new HIV infections occurred in 2012 worldwide?

a) 80,700

b) 750,000

c) 2,300,000

d) 5,100,000

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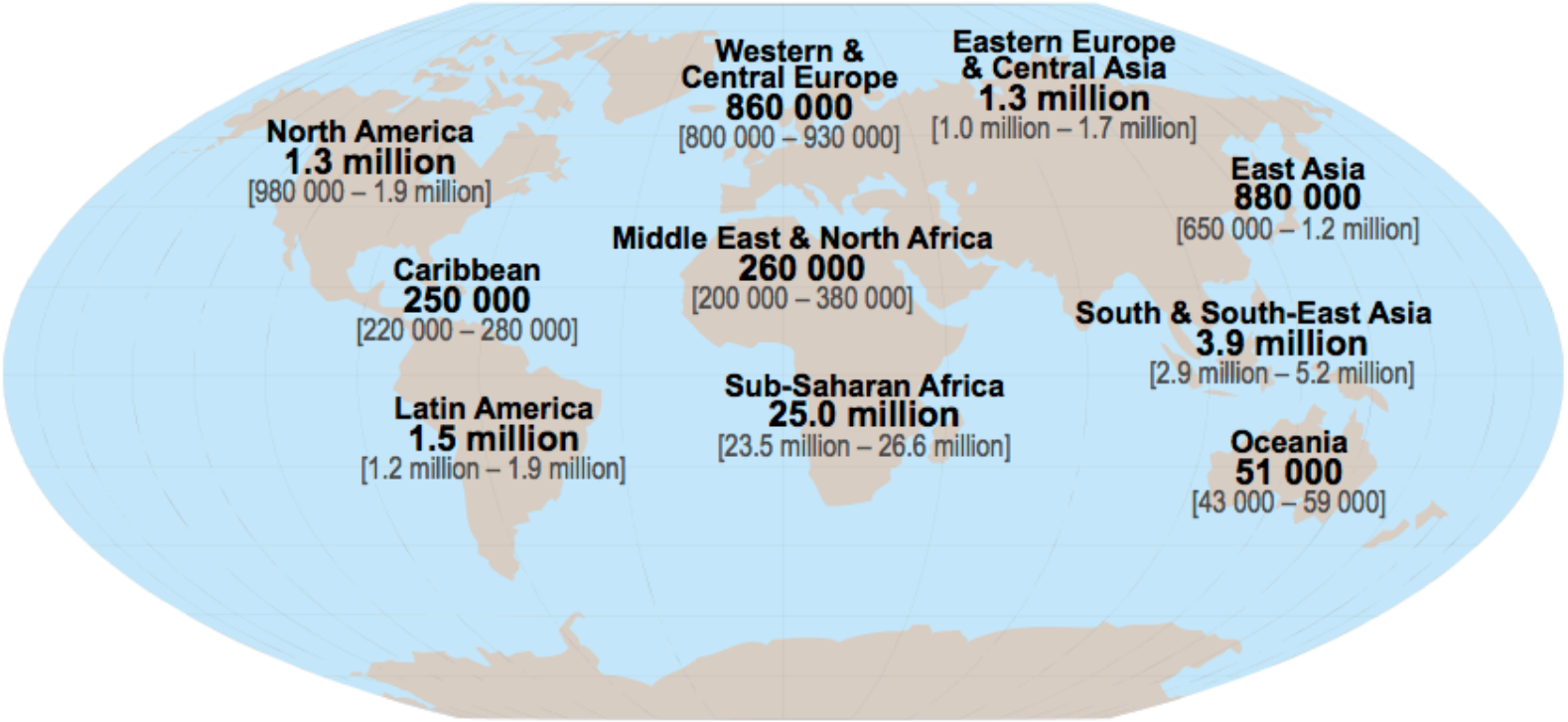
Adults and children estimated to be living with HIV | 2012

New infections: 2,300,000
Estimated Deaths: 1,600,000



Total: 35.3 million [32.2 million – 38.8 million]

Source: UNAIDS, 2013

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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%)

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Impact of global epidemic

- Societal Structure + Global Economics
  - High HIV prevalence among people in the most productive years of their lives → long-term adverse strain on the socio-economic structure
  - Political Instability?

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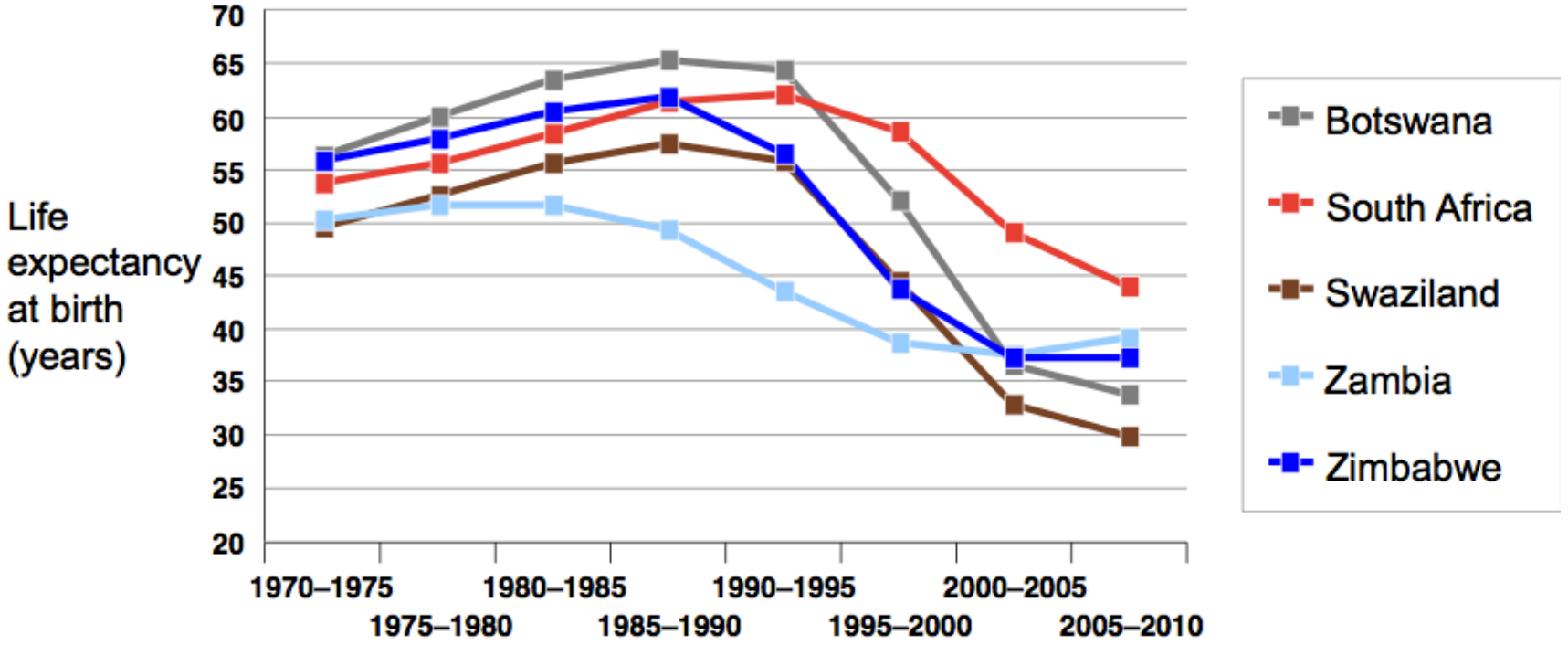
Impact of AIDS on life expectancy in five African countries, 1970-2010



Source: United Nations Population Division (2011).

Impact of global epidemic - DoD

- National Security
  - Destabilization of Countries, Economies
  - Defense Forces loosing soldiers
    - Malawi: HIV/AIDS reduced forces by 40%
    - Uganda: More soldiers died from AIDS than from war in 20 year insurgency
- HIV in US DoD?

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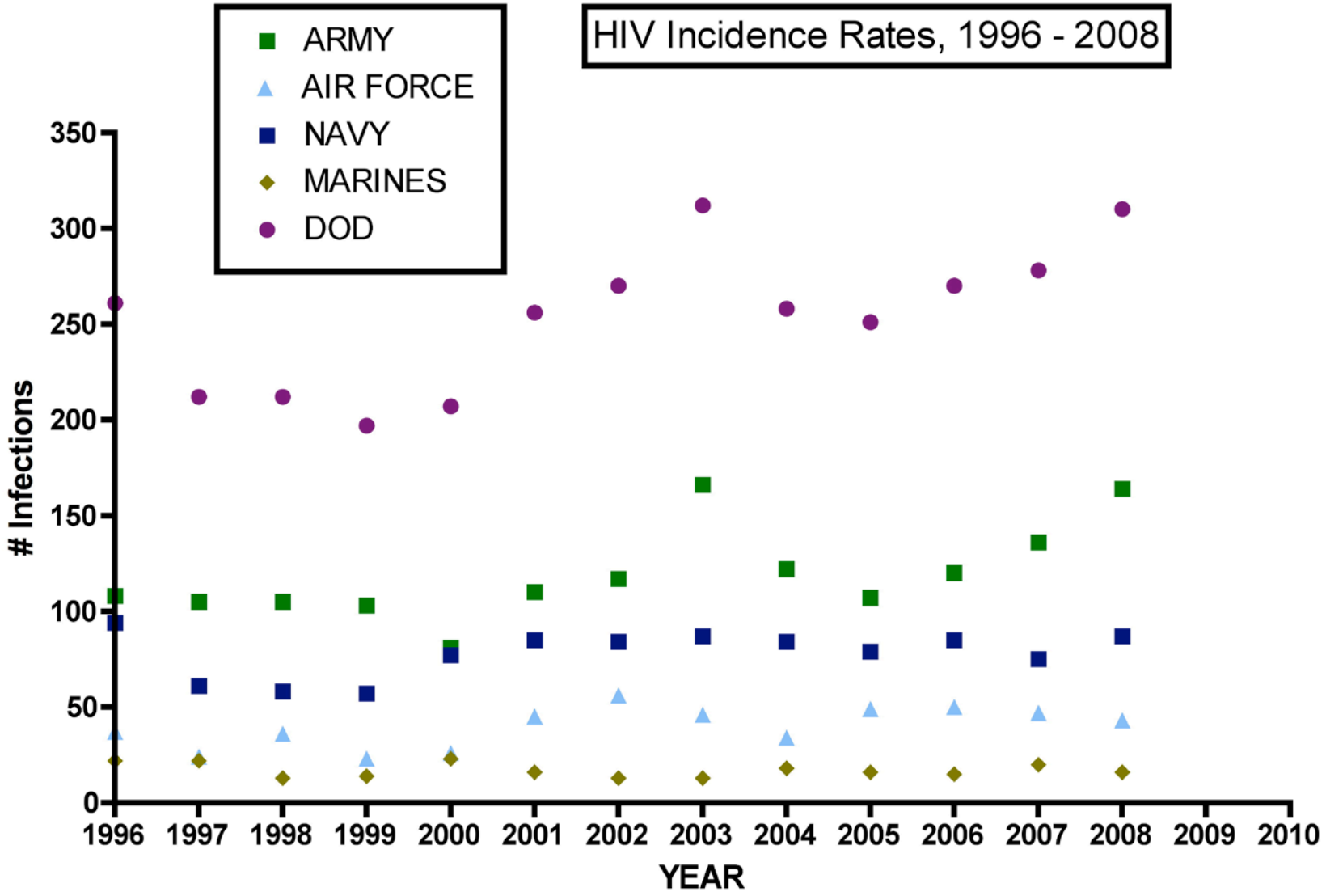
DoD HIV Infection Rates: 1996 - 2008



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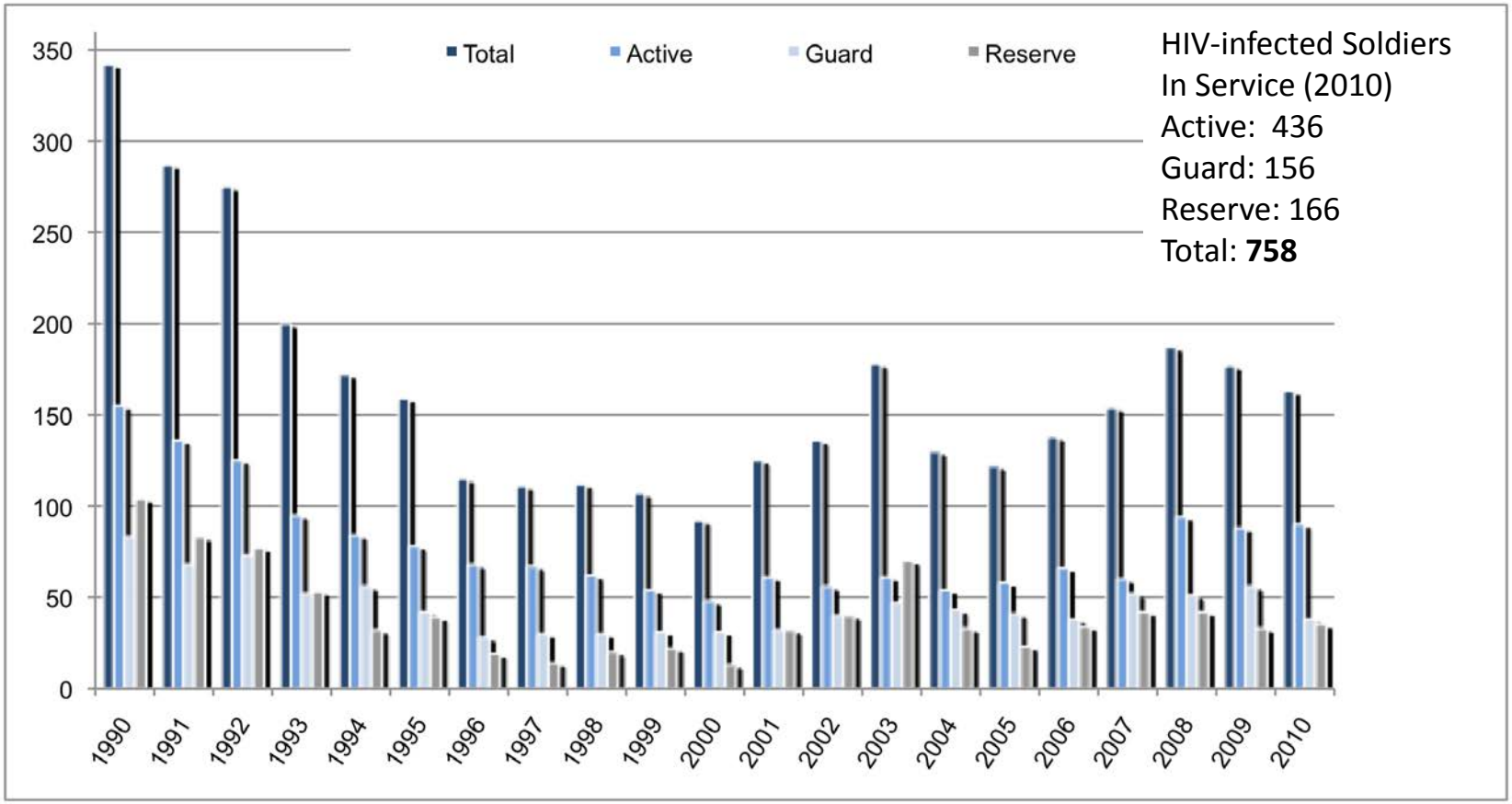
HIV is an Enduring Problem in the Army

Counts of New HIV-1 Infections in U.S. Army



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HIV Virology, Pathogenesis and Transmission

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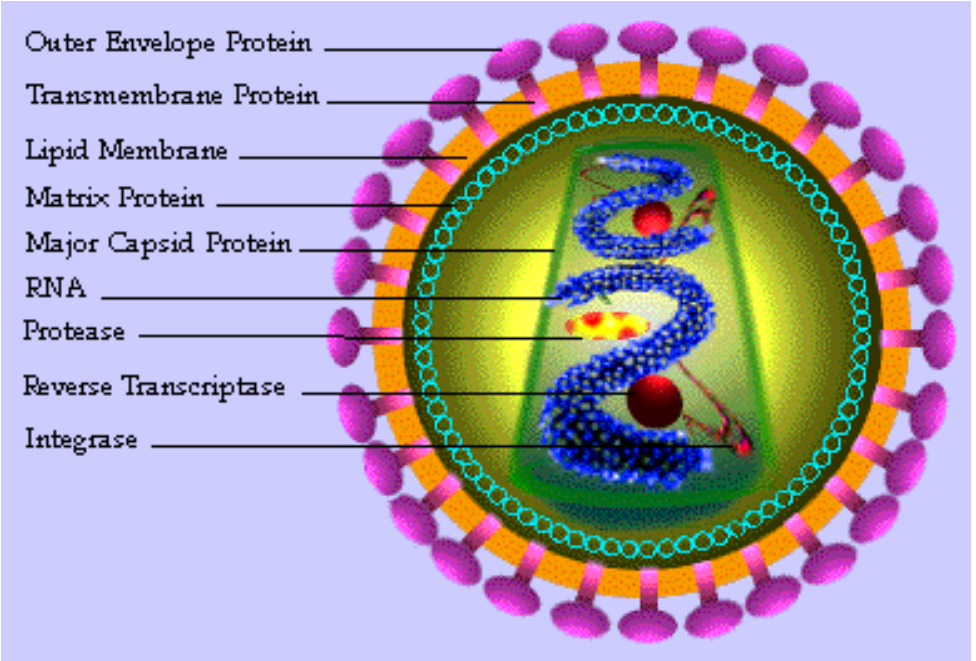
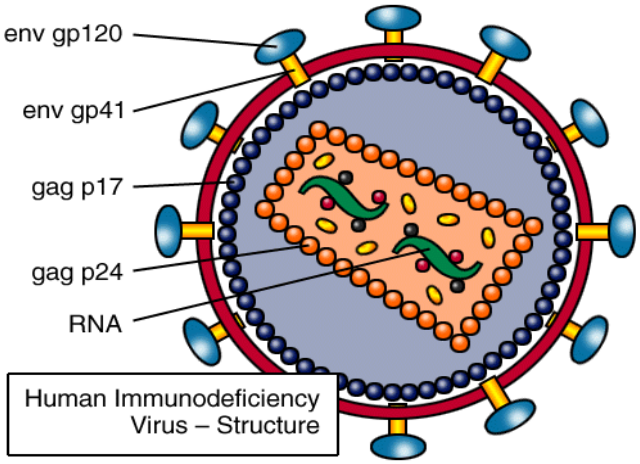
HIV: Human Immunodeficiency Virus

- 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)





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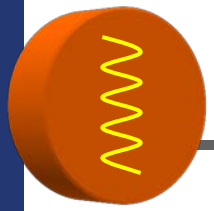
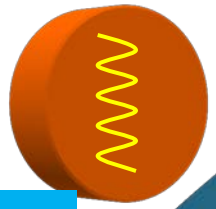
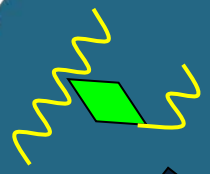
How HIV Works



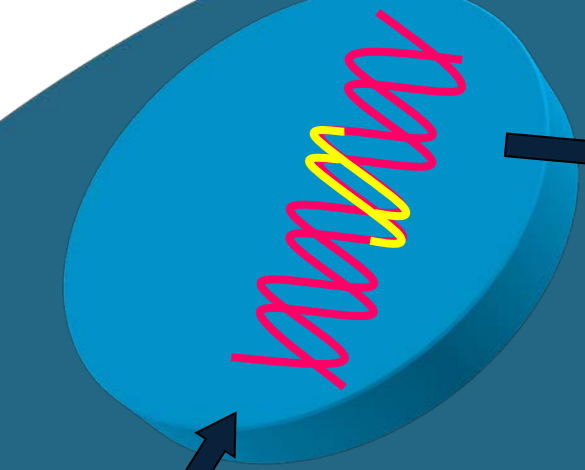
HIV



1. Attachment to host CD4 cell

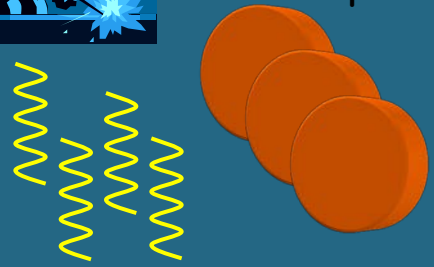


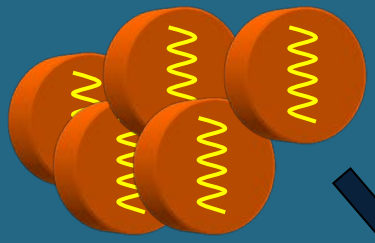
2. Reverse transcriptase makes DNA from the virus's RNA



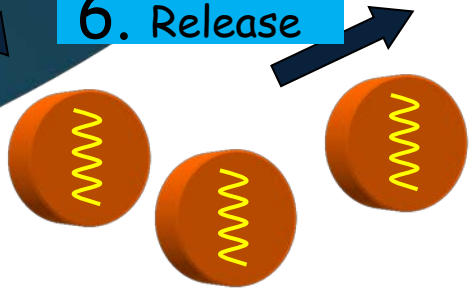
3. Integration into host cell's nucleus

4. Reproduction of viral components





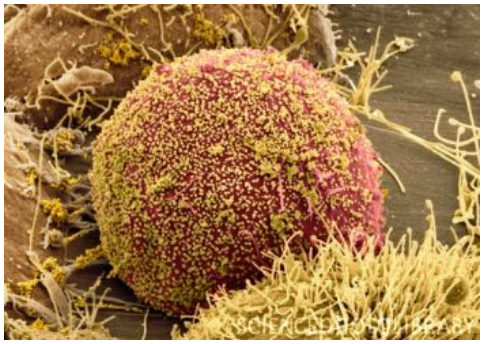
5. Assembly of new HIV viruses



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/mm^3
  - 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
- CD4 percent
  - How many of your total lymphocytes (white blood cells) are CD4+
  - More stable than CD4 count

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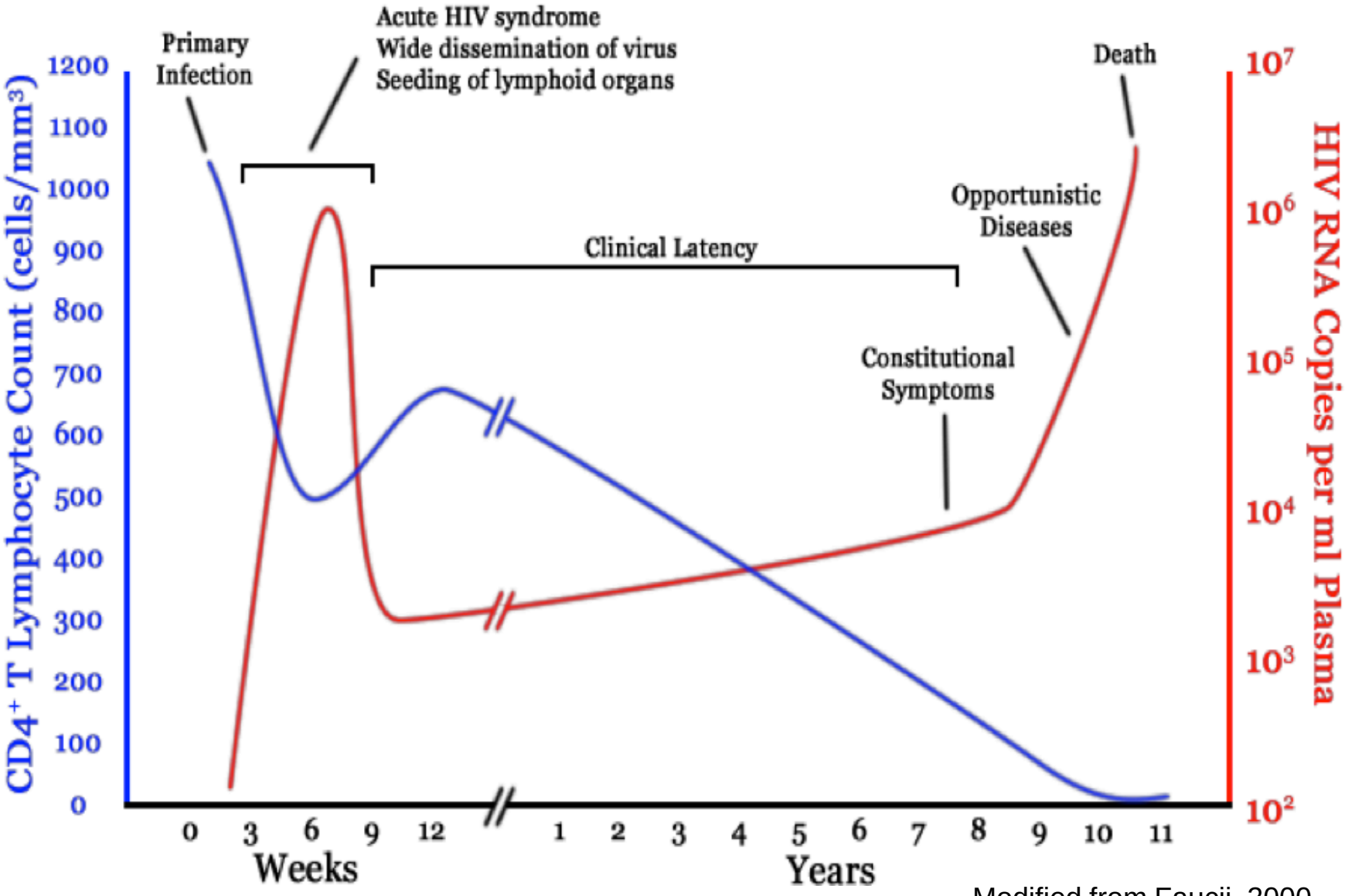
Natural History of HIV Infection



Modified from Faucii, 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

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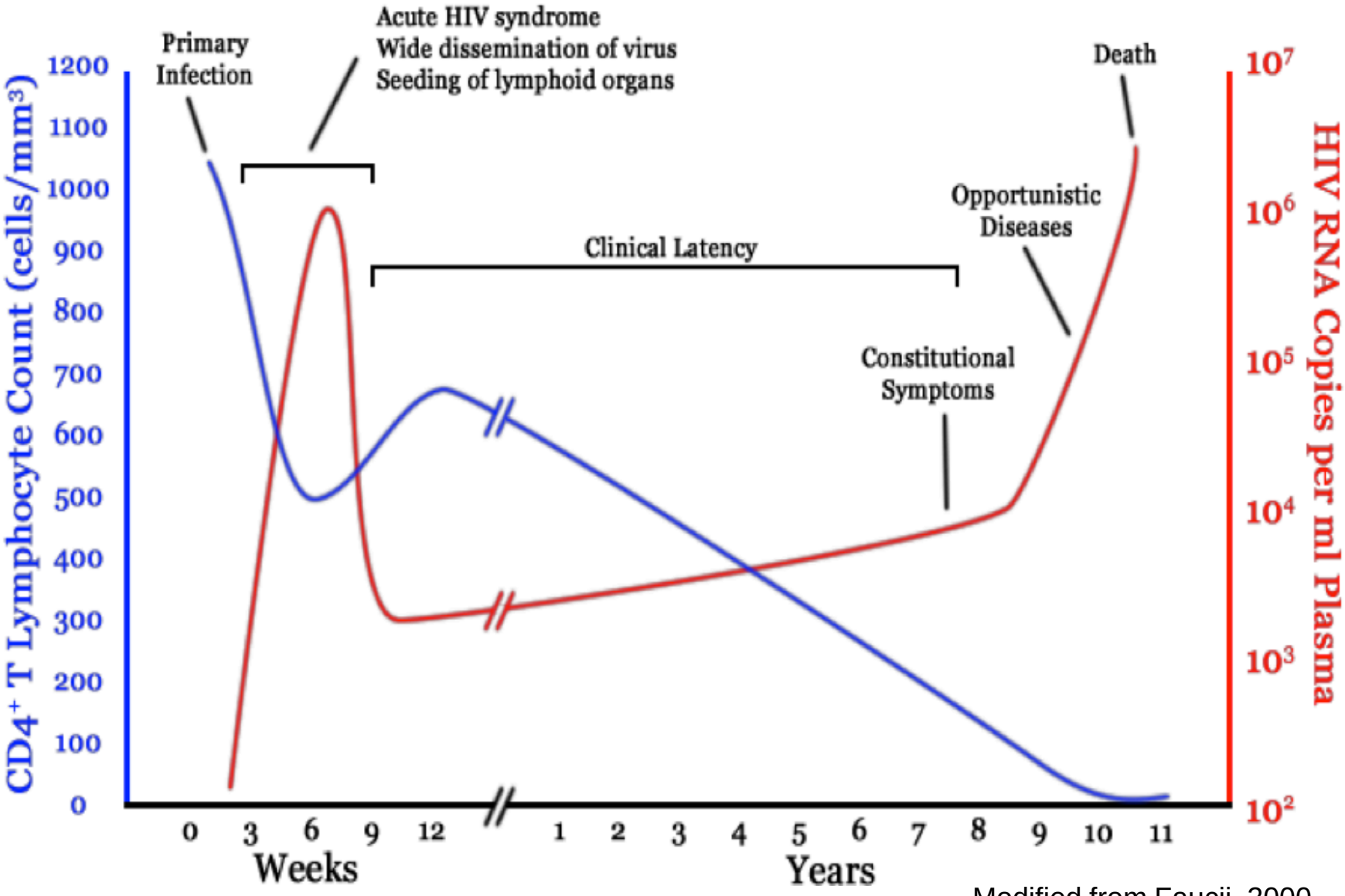
Natural History of HIV Infection



Modified from Faucii, 2000

Viral Setpoint and Prognosis

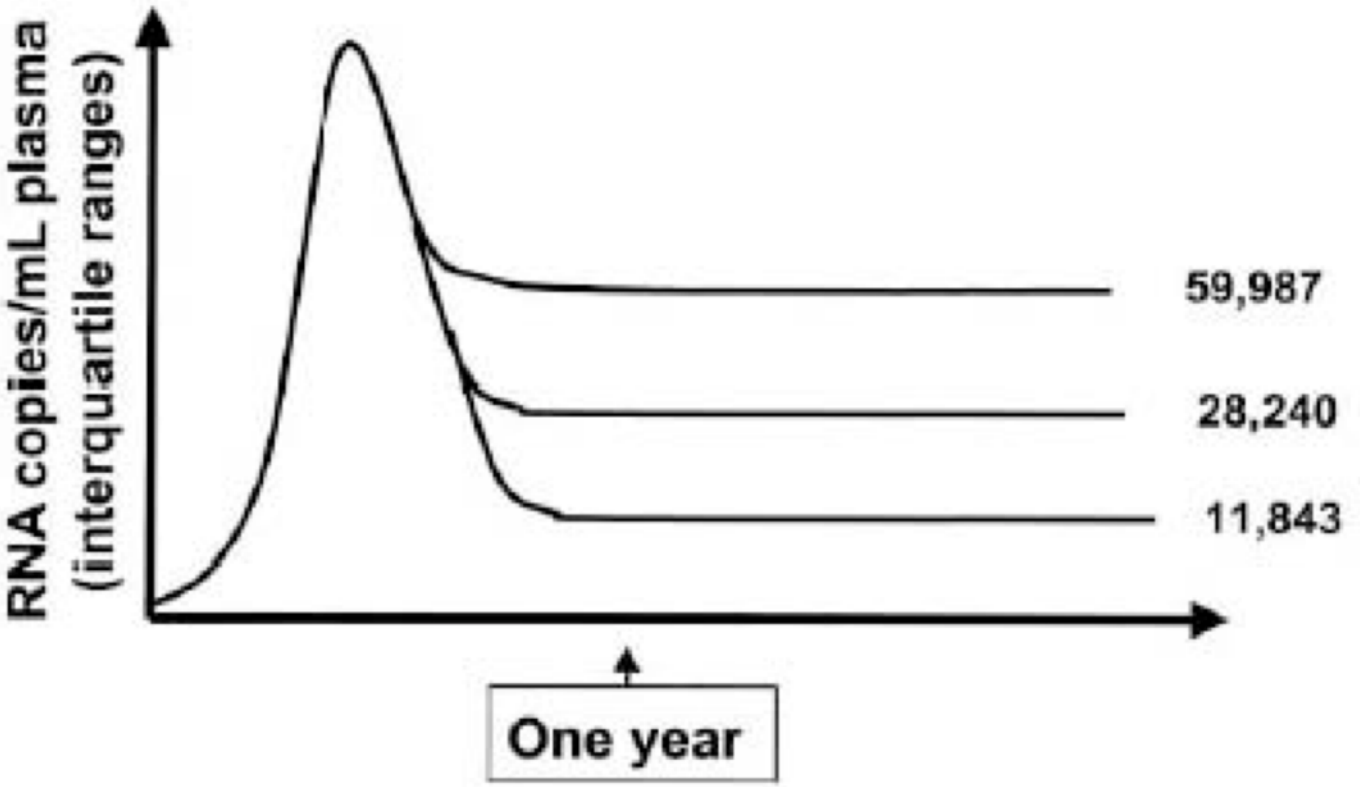


Figure 2. HIV RNA levels 1 year after untreated infection are relatively stable and predict subsequent disease progression. Data are from the Multicenter AIDS Cohort Study.

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Disease Progression

- Over time, CD4 count decreases, VL increases
- Antiretroviral therapy = ART
- Antiretroviral Medications = ARVs
- HAART = Highly active antiretroviral therapy
  - Term falling out of favor
- Combination therapy
  - Use medicines from TWO different drug classes
  - Block replication at different stages of life cycle
  - Effective in reducing viral load

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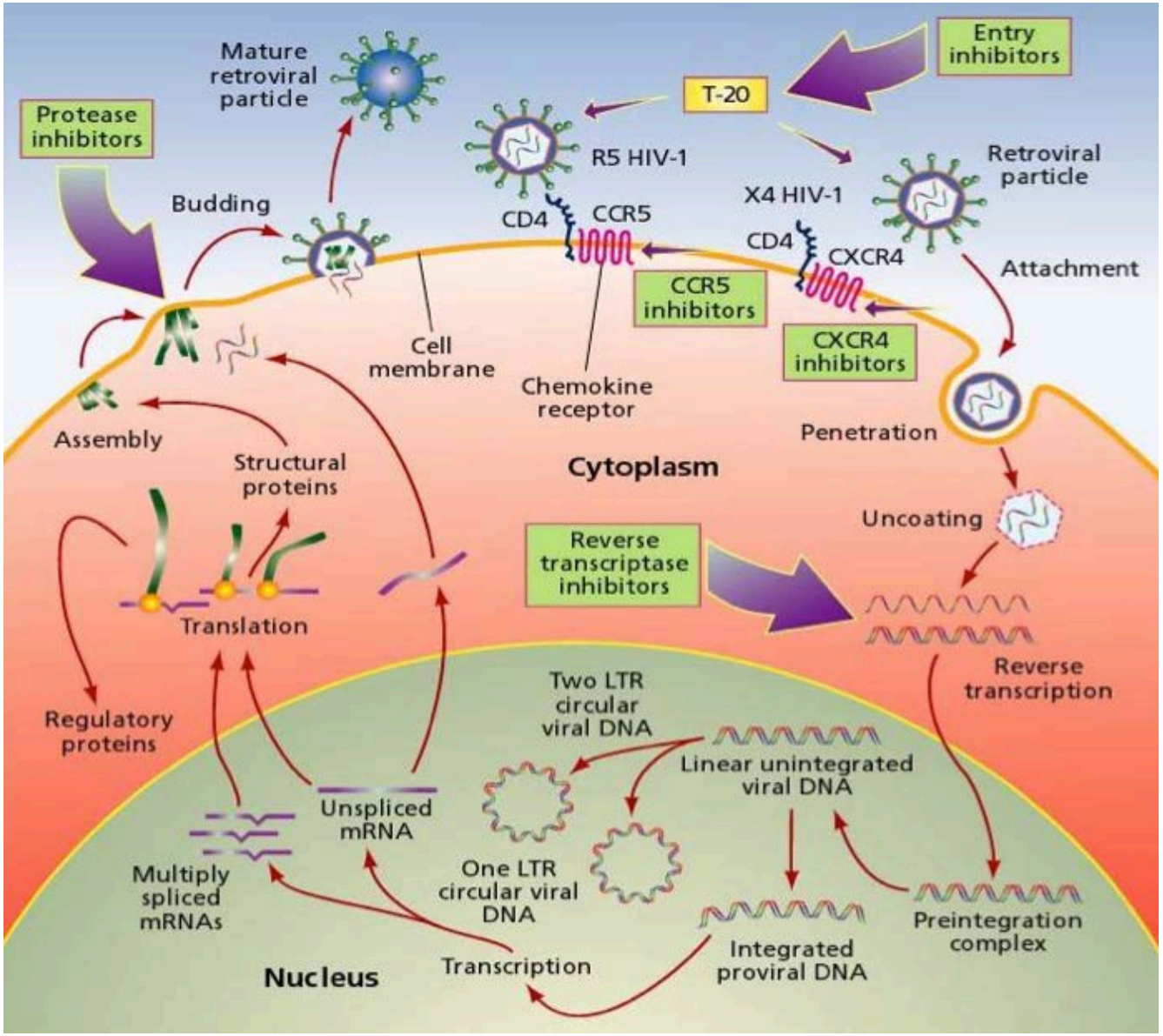
HIV life cycle and mechanisms of anti-virals



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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

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Advanced Stages of HIV / AIDS

- CD4 < 200mm^3
- 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

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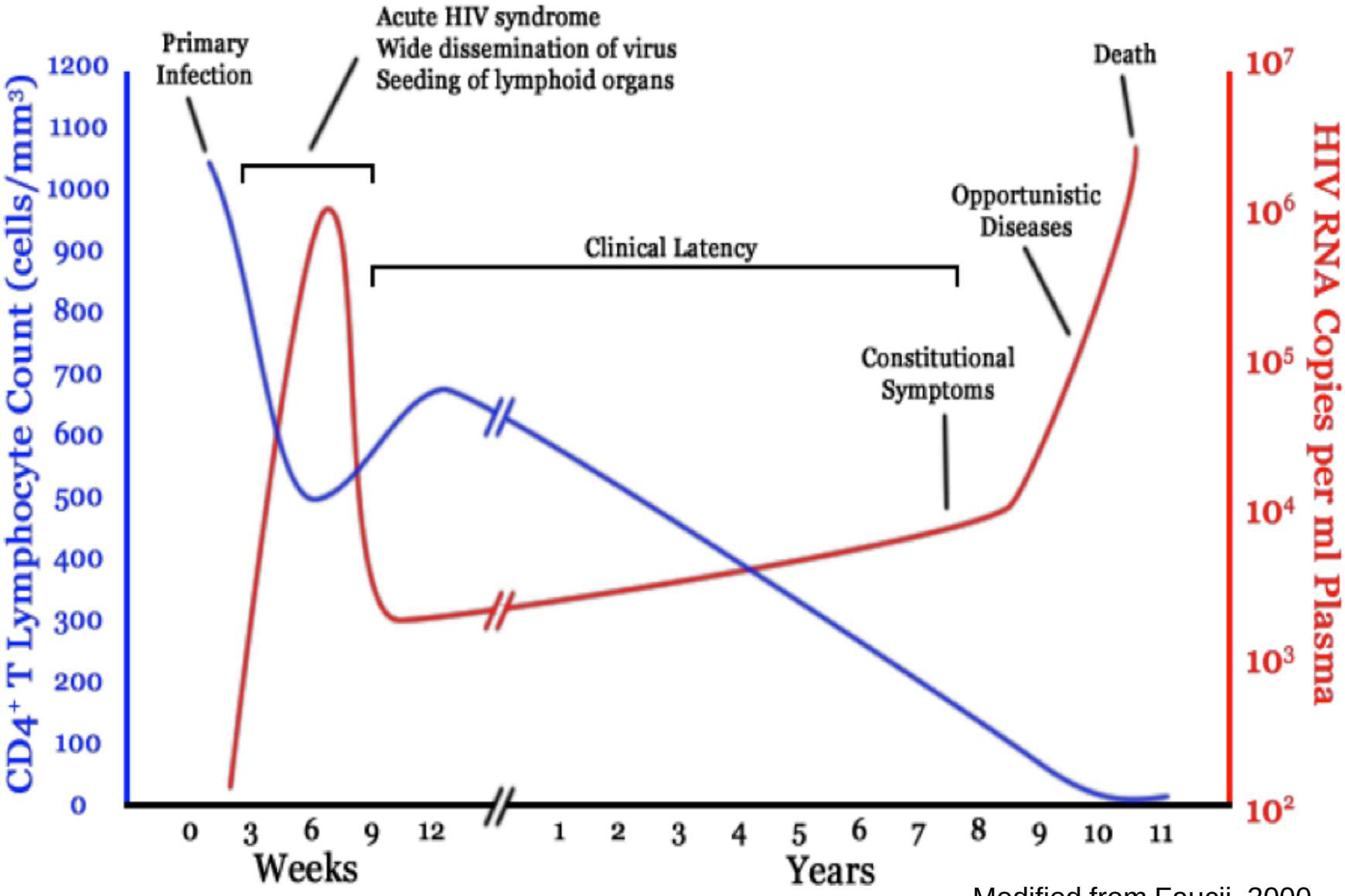
Natural History of HIV Infection



Modified from Faucii, 2000

AIDS

- AIDS
  - CD4 cell count below 200/mm3 regardless of the presence or absence of symptoms
  - WHO stages
  - Conditions that define HIV diagnosis
    - P. carinii pneumonia — 42.6 percent
    - Esophageal candidiasis - 15.0 percent
    - Wasting — 10.7 percent
    - Kaposi's sarcoma — 10.7 percent
    - Disseminated M. avium infection — 4.8 percent
    - Tuberculosis — 4.5 percent

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%

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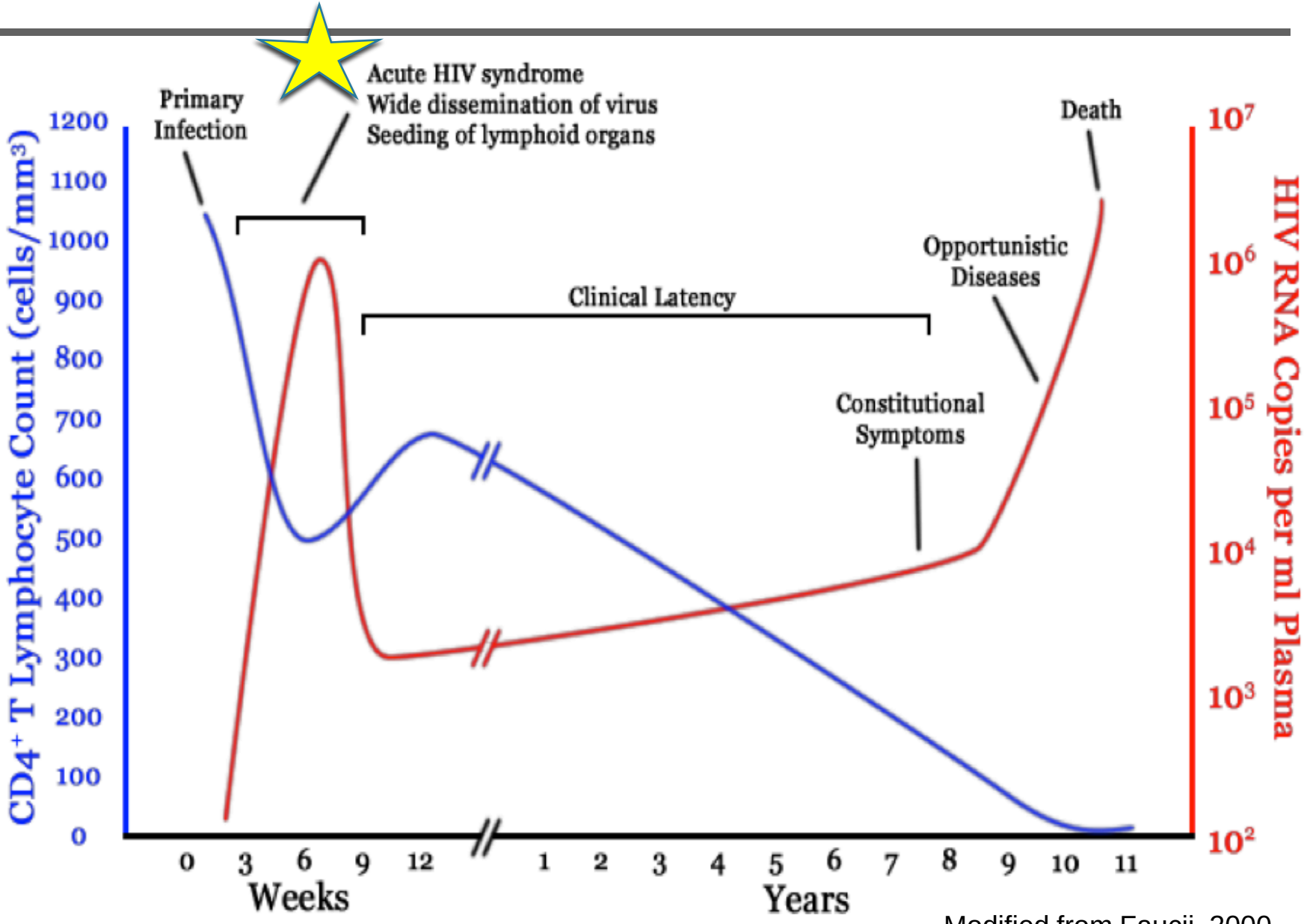
Acute HIV Infection



Modified from Faucii, 2000

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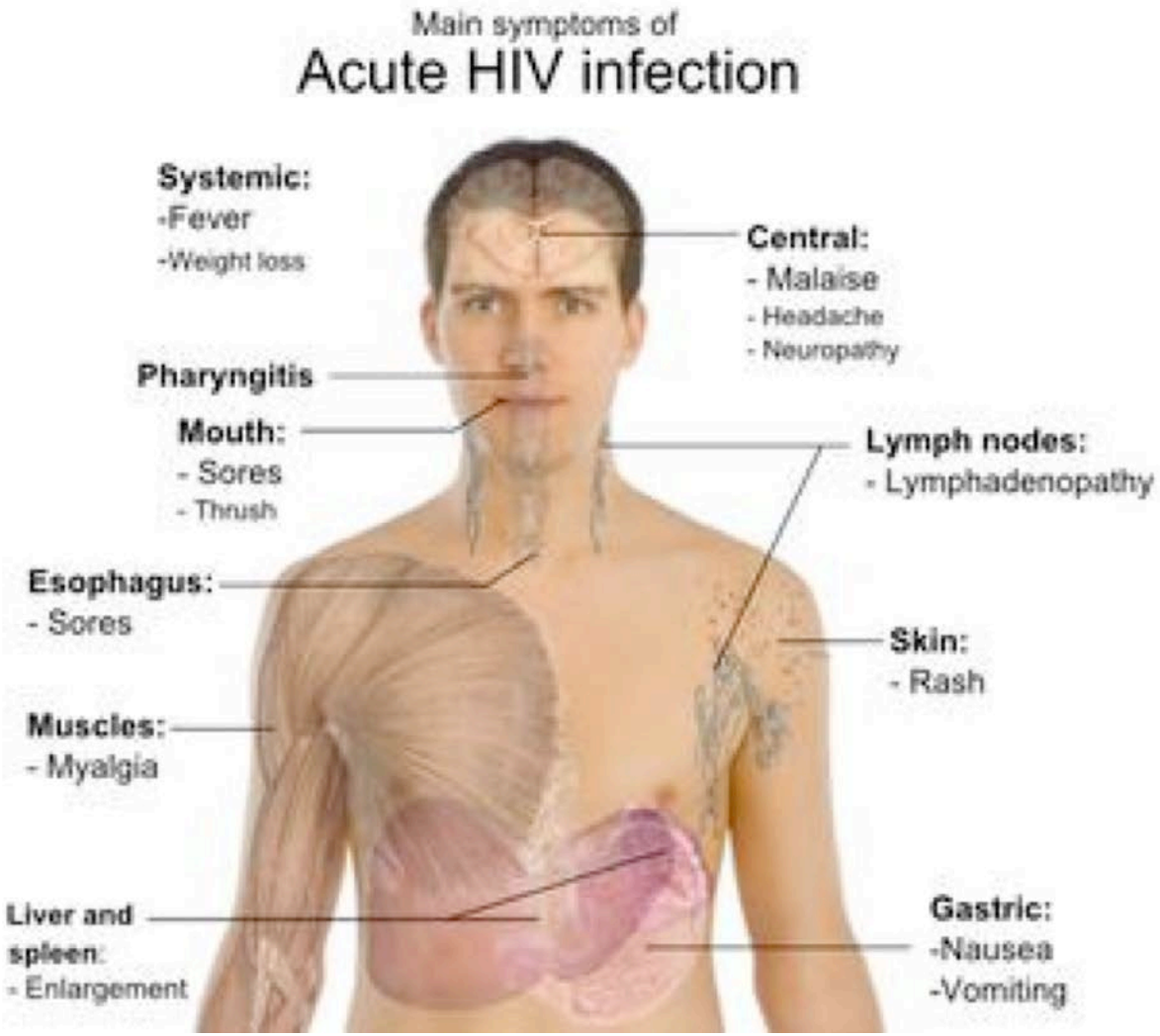
Symptoms of Acute HIV Infection



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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.

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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

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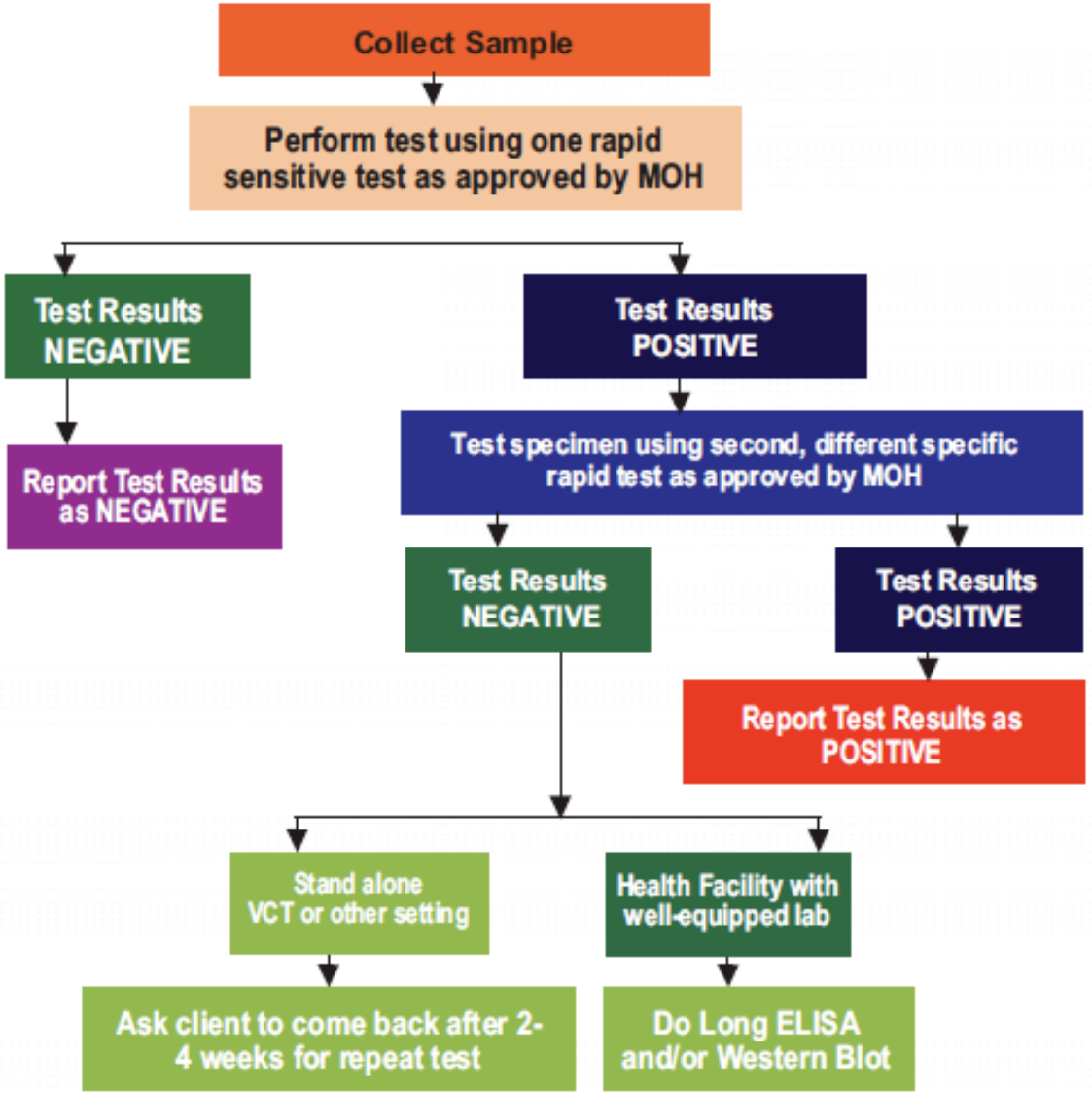
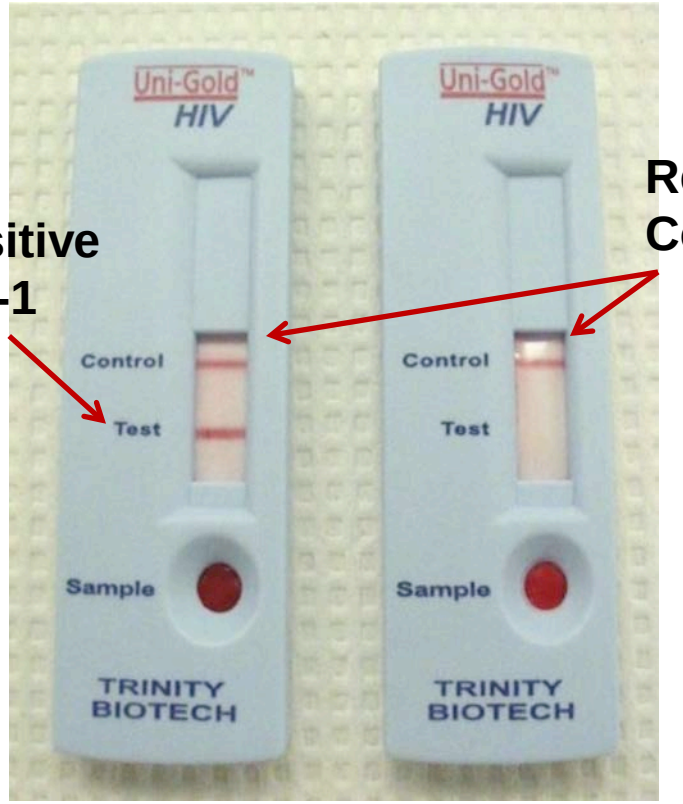
HIV testing: serial algorithm



Rapid Immunoasay - RIA

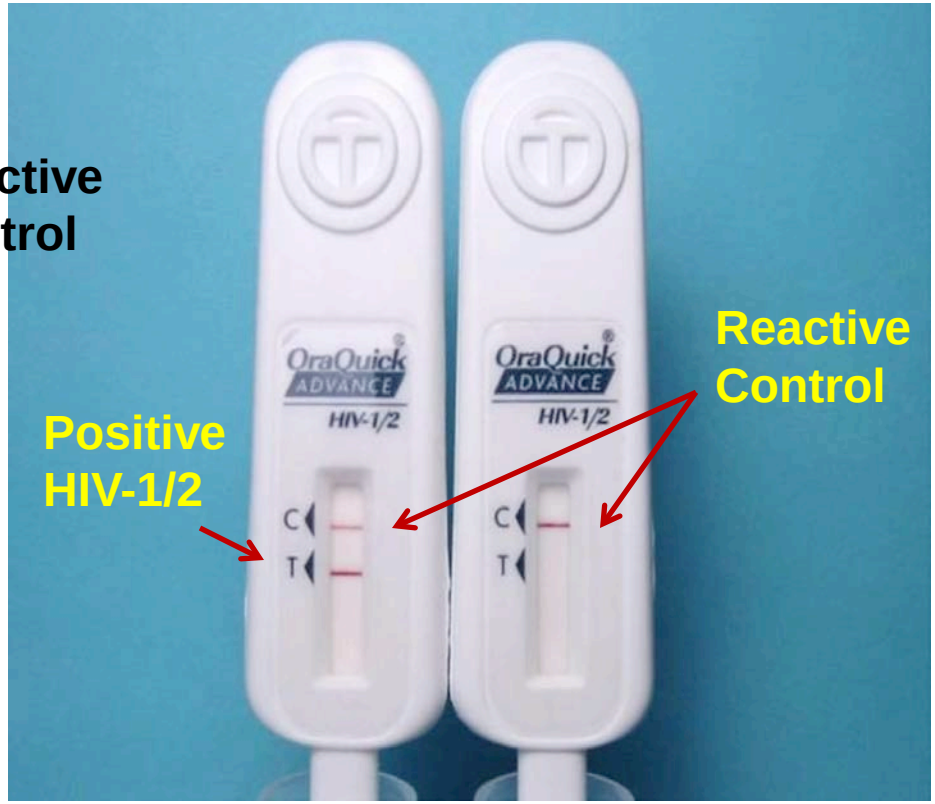
Uni-Gold Recombigen and OraQuick Advance HIV-1/2



Positive HIV-1

Reactive Control

Results in 10-12 minutes



Positive HIV-1/2

Reactive Control

Results in 20 minutes

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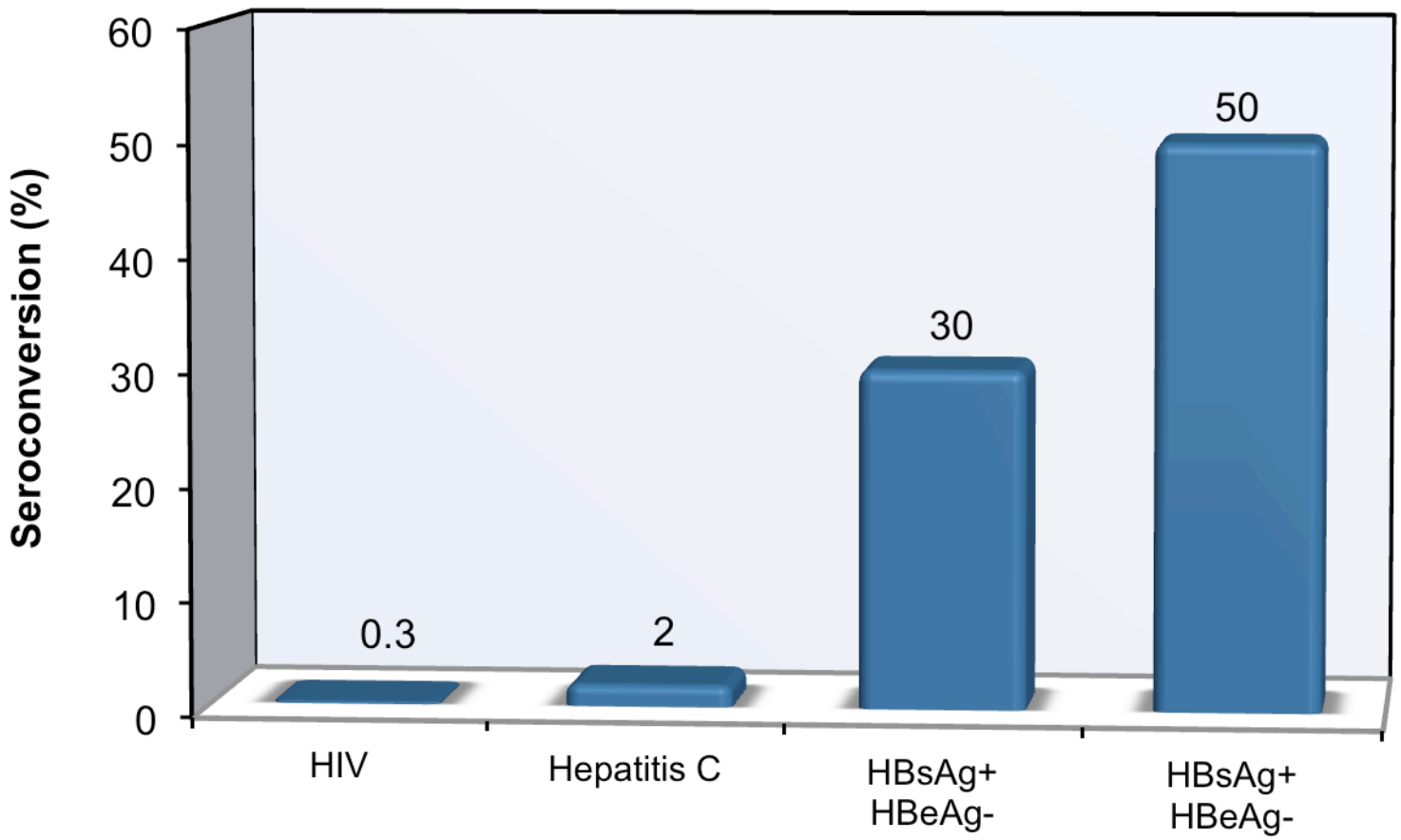
Management of Health Care Personnel Exposed to HIV

- Exposure of body fluids from people infected with HIV
- Occupational – Health Care Worker – exposure
- Risk of transmission varies depending type of exposure
  - High if source has high viral load, large volume, deep exposure
  - Risk after exposure to body fluids is low
    - 20 of 6135 cases (0.33 percent) following percutaneous exposure
    - No cases after 2712 intact skin exposures
- Varies by profession
  - Nurses (48.6%), then physicians in training (7.7%), then non-lab technologists (4.5%)

Estimated Risk of Seroconversion with Percutaneous Injury



Source: CDC and Prevention. MMWR Morb Mortal Weekly Rep. 2001;50(RR-11):1-42.

Postexposure Management

- Critically important in reducing likelihood of transmission
- Legal rights of employee and institution
- ? Exposure = contact with potentially infectious blood, tissue or body fluids
- 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 if tolerated
  - Side effects common
    - GI – nausea, vomiting, diarrhea
    - Headache, fatigue
  - Expert consultation recommended - Complex

Not considered infectious for HIV, unless visibly bloody

- Feces
- Nasal Secretions
- Saliva
- Sputum
- Sweat
- Tears
- Urine
- Vomitus

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

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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) + emtrictabine (Emtriva™ ; FTC)
Atazanavir (Reyataz® ; ATV) + ritonavir (Norvir® ; RTV)	
Lopinavir/ritonavir (Kaletra® ; LPV/RTV)	

*CDC , 2005

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Current ARV Medications

- **NRTI**
  - Abacavir (ABC)
  - Didanosine (ddl)
  - Emtricitabine (FTC)
  - Lamivudine (3TC)
  - Stavudine (d4T)
  - Tenofovir (TDF)
  - Zidovudine (AZT, ZDV)
- **NNRTI**
  - Delavirdine (DLV)
  - Efavirenz (EFV)
  - Etravirine (ETR)
  - Nevirapine (NVP)
- **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)

HIV Prevention: Turning the Tide

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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.

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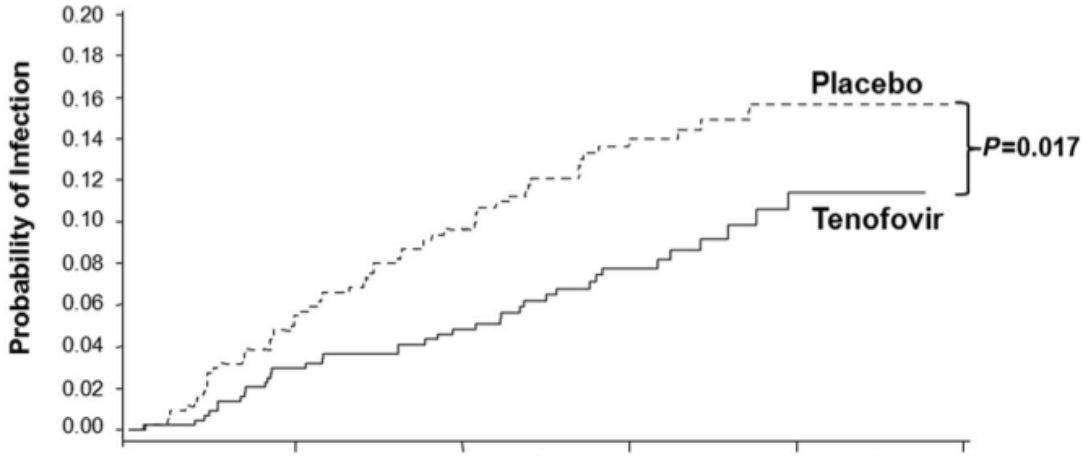
Adult male circumcision

- Reduction in transmission from **HIV+ women to HIV – men by 50-60%**
  - Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta M, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. *PLoS Med 2005;* ***2: 1112–22***
  - Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; **369: 657–66.**
  - Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomisedcontrolled trial. *Lancet 2007;* ***369: 643–56.***
- No effect on transmission from **HIV+ men to HIV- women**

Search for a Microbicide

- CAPRISA 004 (July 2010)
  - Tenofovir intravaginal gel pre and post coitus
  - 39% efficacy (95% CI: 6-60%)
  - Effect on HSV 2



Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 10.2	5.6 vs 9.1
Effectiveness (*P*-value)	**47% (0.064)**	**50% (0.007)**	**47% (0.004)**	**40% (0.013)**	**39% (0.017)**

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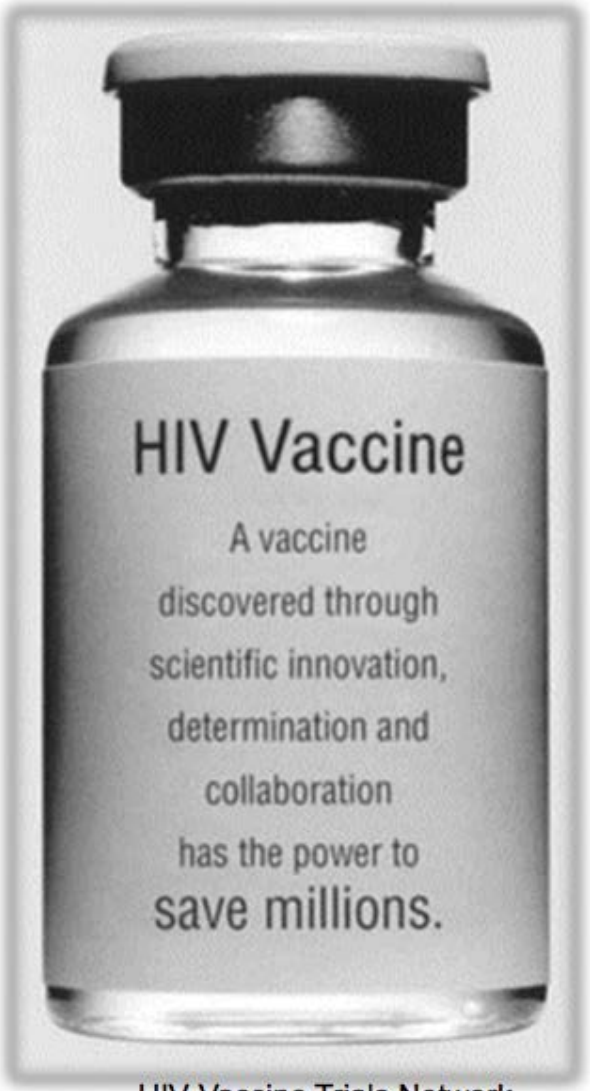
When will an HIV Vaccine be available?

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



HIV Vaccine Trials Network

RV144

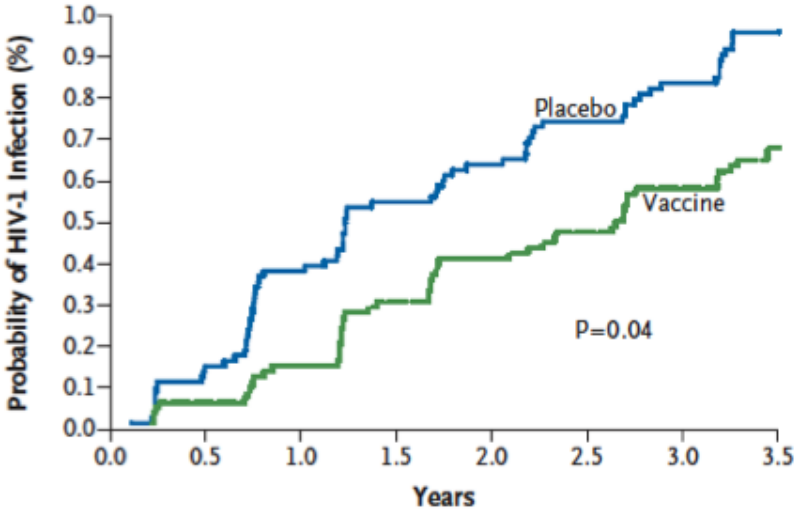
- Modest results, but first sign of protection in humans
  - N=16,000 Thai volunteers at community risk
  - Canarypox vector x 4 + gp120 x 2
  - Modified intention to treat efficacy 31.2% (95% CI, 1.1 to 52.1; P = 0.04)
  - No effect on viral load

The NEW ENGLAND JOURNAL of MEDICINE

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

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum 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 Premsri, 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



MHRP

QUESTIONS?

Thank you…

Feel free to email/call with other questions:

cpolyak@hivresearch.org

+1-301-500-3688

MHRP

References

- UNAIDS Report on the Global AIDS Epidemic www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2 008/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

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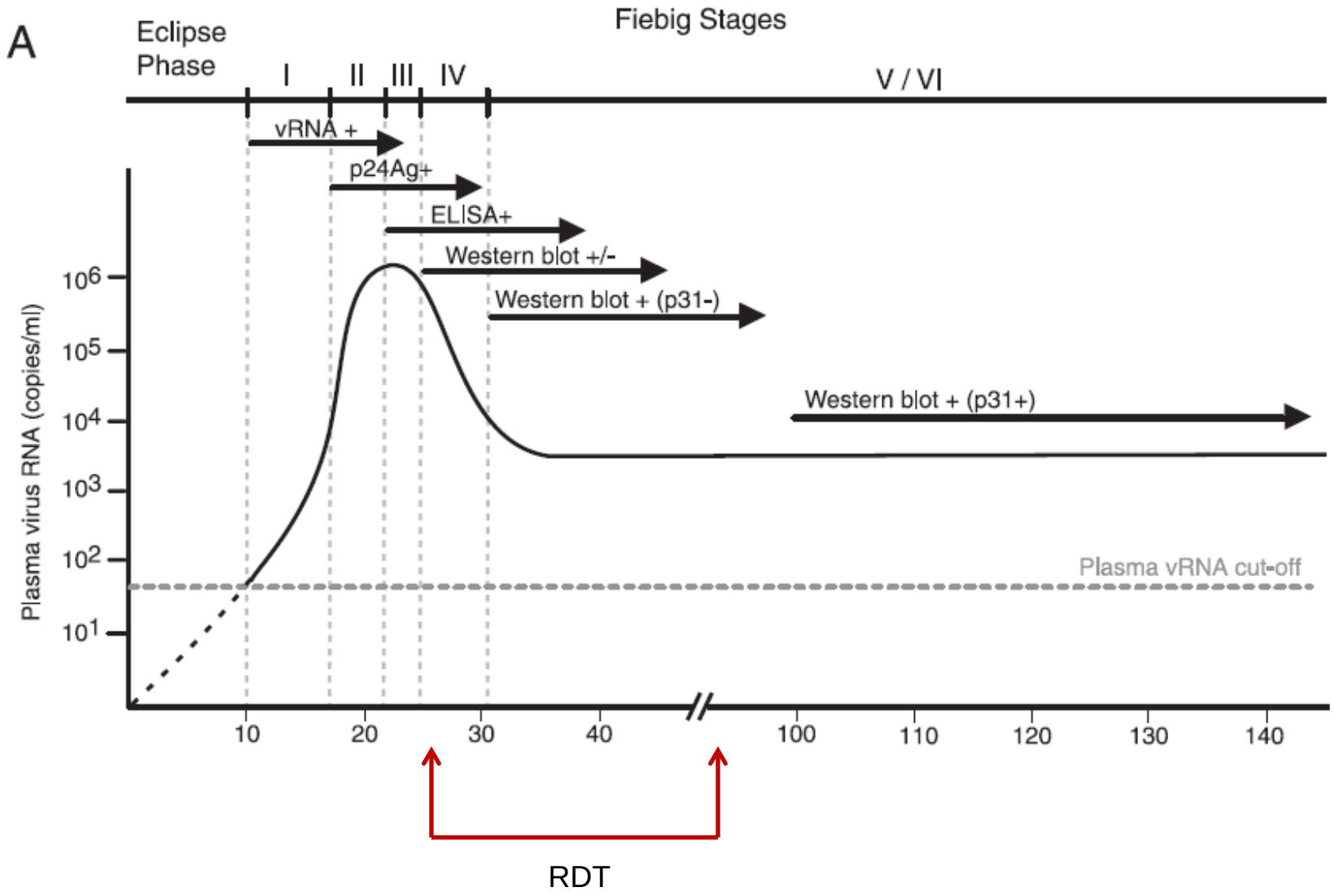
HIV Infection Staging



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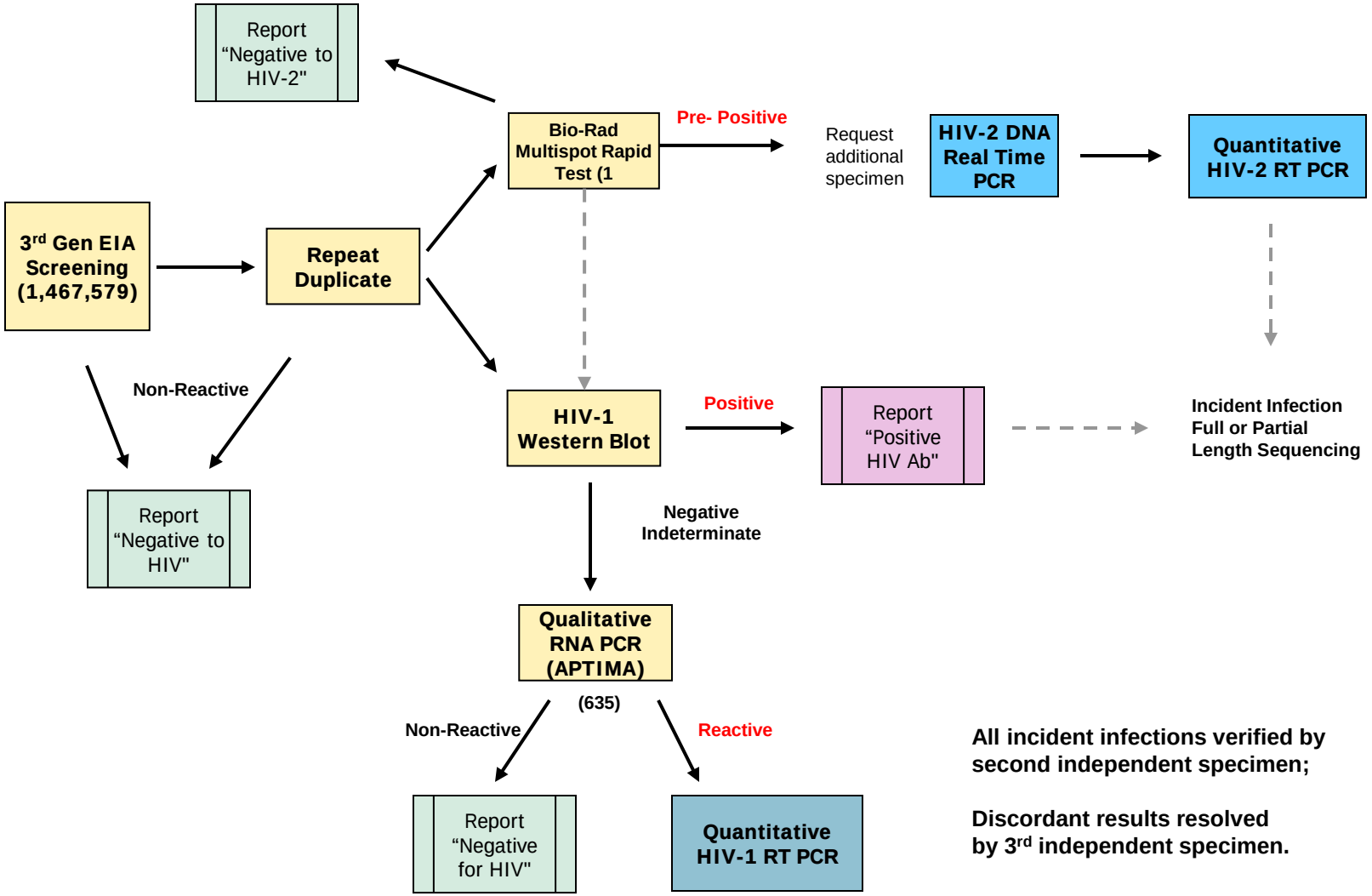
US Army HIV Diagnostic Algorithm



All incident infections verified by second independent specimen;

Discordant results resolved by 3rd independent specimen.

Which Drugs to Use?

- Consultation with an expert is recommended
- Expanded ≥ 3-drug PEP regimens:
  - Preferred:
    - LPV/RTV (Kaletra) + basic 2-drug regimen
  - Alternative:
    - ATV* ± RTV
    - FPV ± RTV
    - IDV** ± RTV
    - SQV + RTV
    - NFV***
    - EFV***

+ basic 2-drug regimen

If ATV is coadministered with TDF, RTV must be included in the PEP regimen.
**Avoid in late pregnancy
***Avoid in pregnancy