HIV Overview

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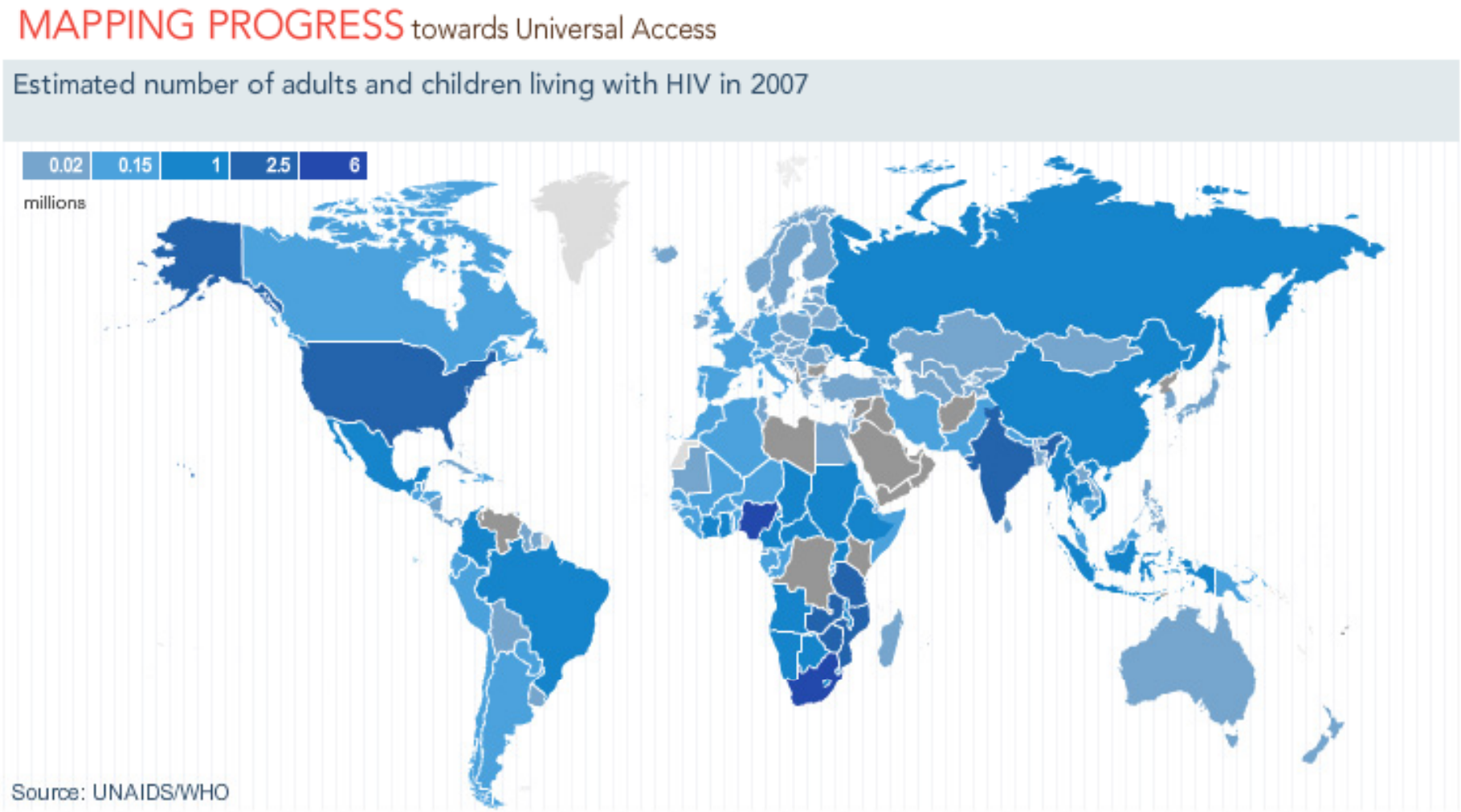
www.hivresearch.org

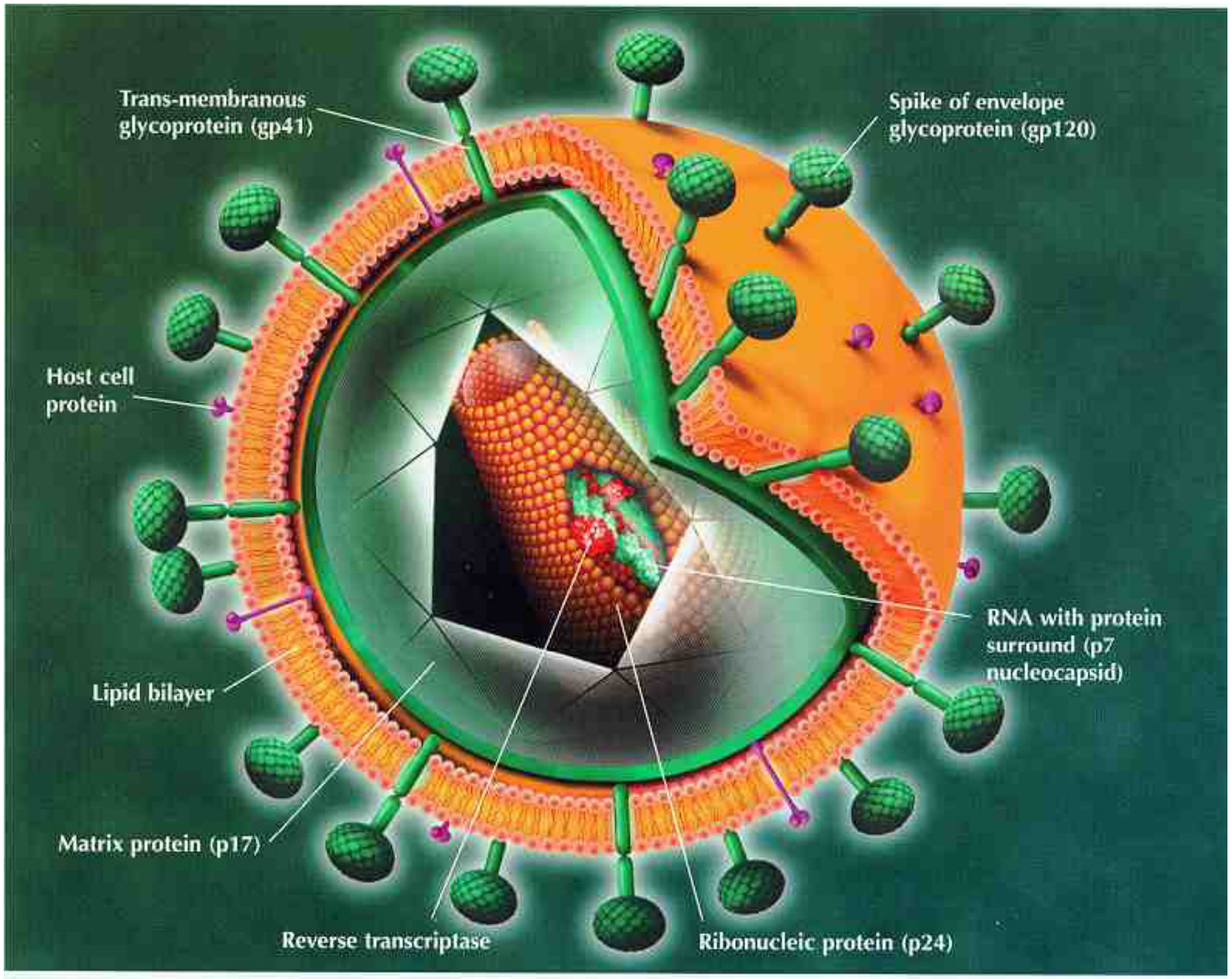
Outline

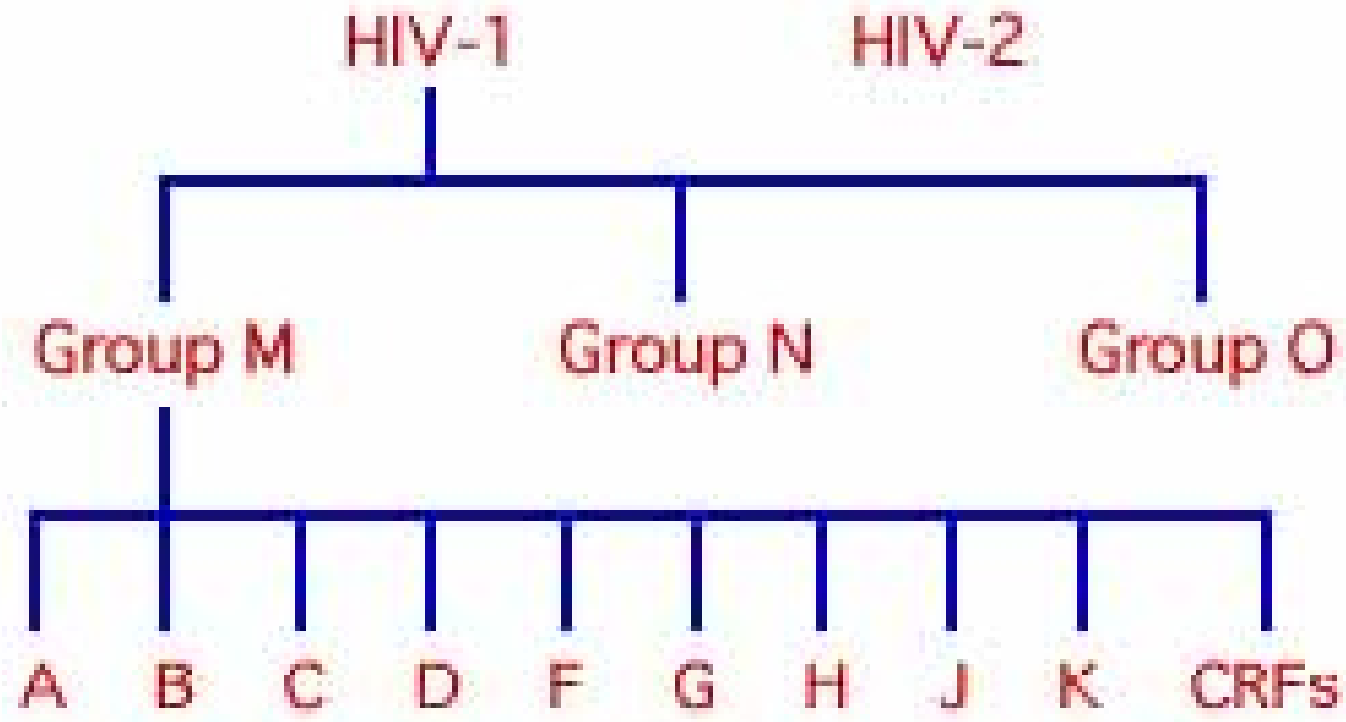
- HIV Virology, Transmission, and Pathogenesis
- Acute HIV infection
- HIV Diagnostics
- Post-exposure prophylaxis
- Treatment
- HIV Prevention—turning the tide

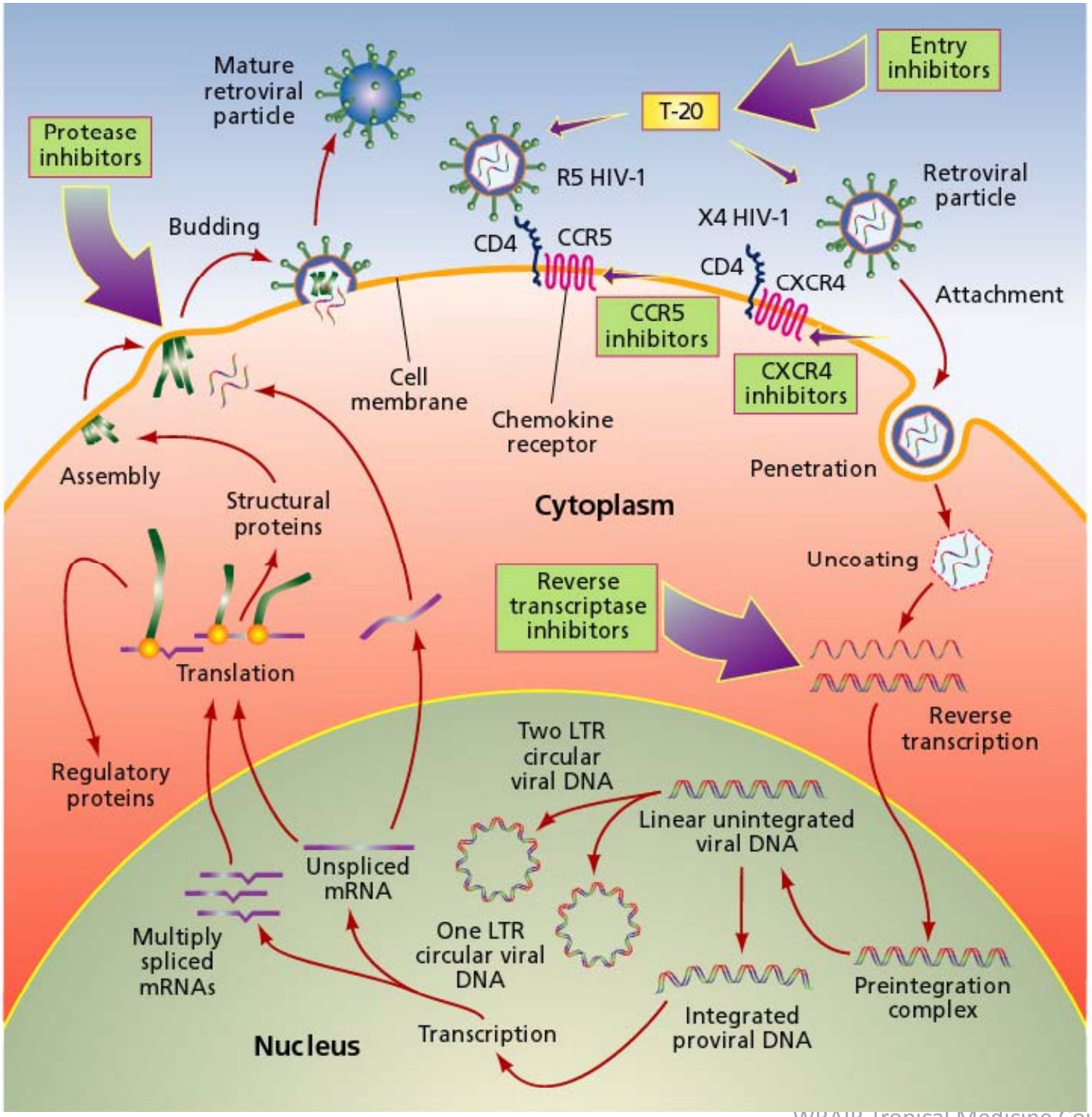
HIV Virology, Transmission, and Pathogenesis

HIV/AIDS Pandemic




Trans-membranous glycoprotein (gp41)
Spike of envelope glycoprotein (gp120)
Host cell protein
RNA with protein surround (p7 nucleocapsid)
Lipid bilayer
Matrix protein (p17)
Reverse transcriptase
Ribonucleic protein (p24)

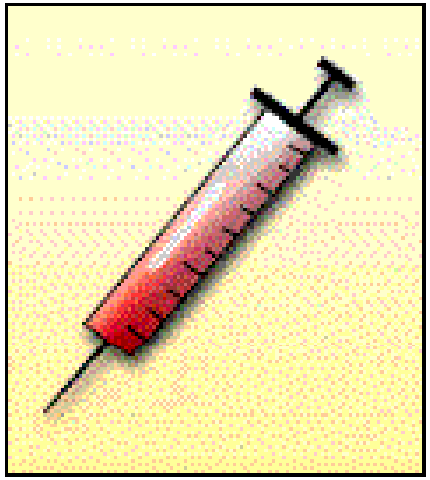

HIV-1
HIV-2
Group M
Group N
Group O
A
B
C
D
F
G
H
J
K
CRFs


Mature retroviral particle
Protease inhibitors
Budding
T-20
Entry inhibitors
R5 HIV-1
CD4
CCR5
X4 HIV-1
CD4
CXCR4
Retroviral particle
Attachment
CCR5 inhibitors
CXCR4 inhibitors
Cell membrane
Chemokine receptor
Assembly
Structural proteins
Cytoplasm
Penetration
Uncoating
Reverse transcriptase inhibitors
Translation
Reverse transcription
Regulatory proteins
Two LTR circular viral DNA
Linear unintegrated viral DNA
Unspliced mRNA
Multiply spliced mRNAs
One LTR circular viral DNA
Integrated proviral DNA
Preintegration complex
Transcription
Nucleus

Unprotected sexual intercourse with an infected partner

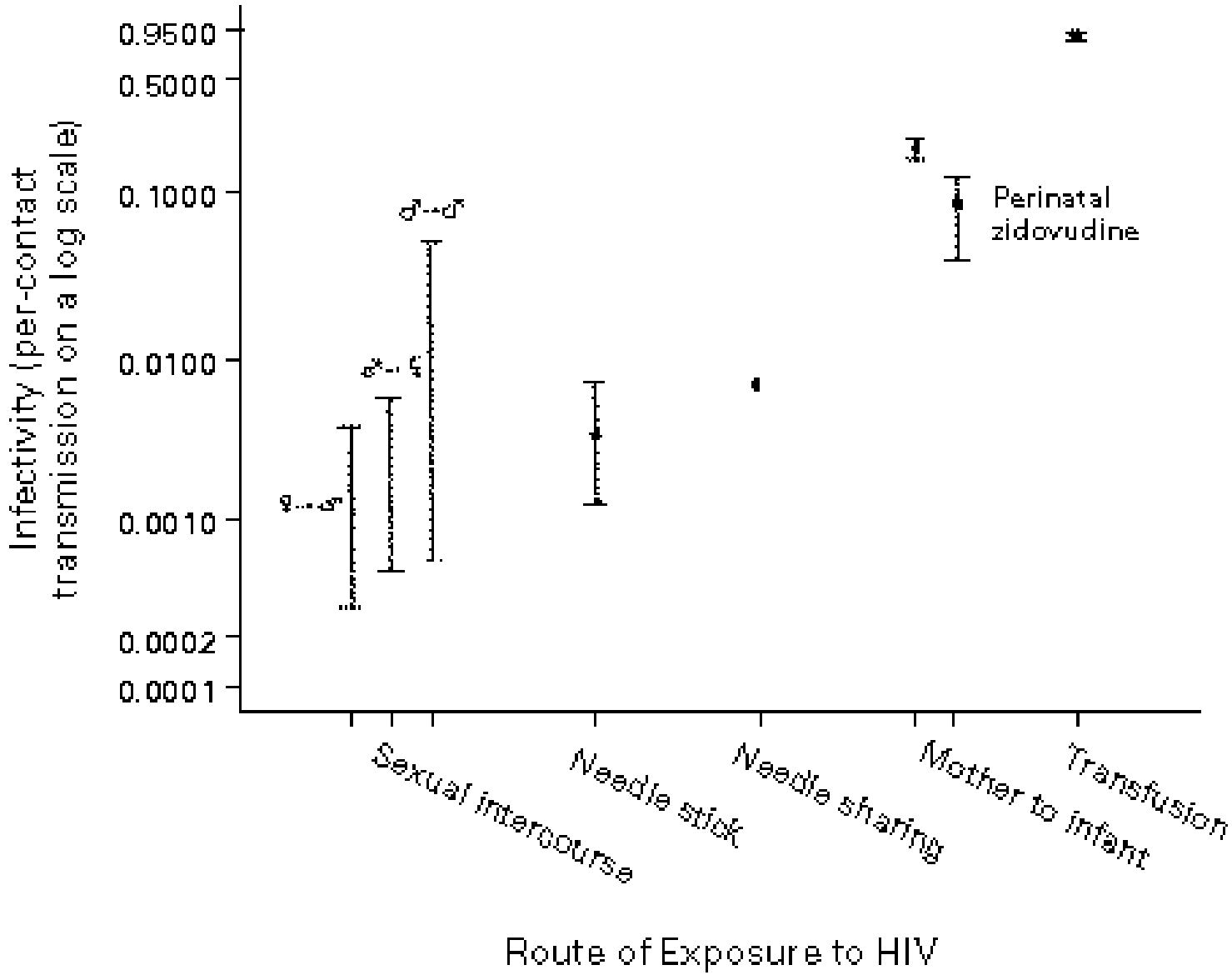
Vertical transmission
(from mother to child)

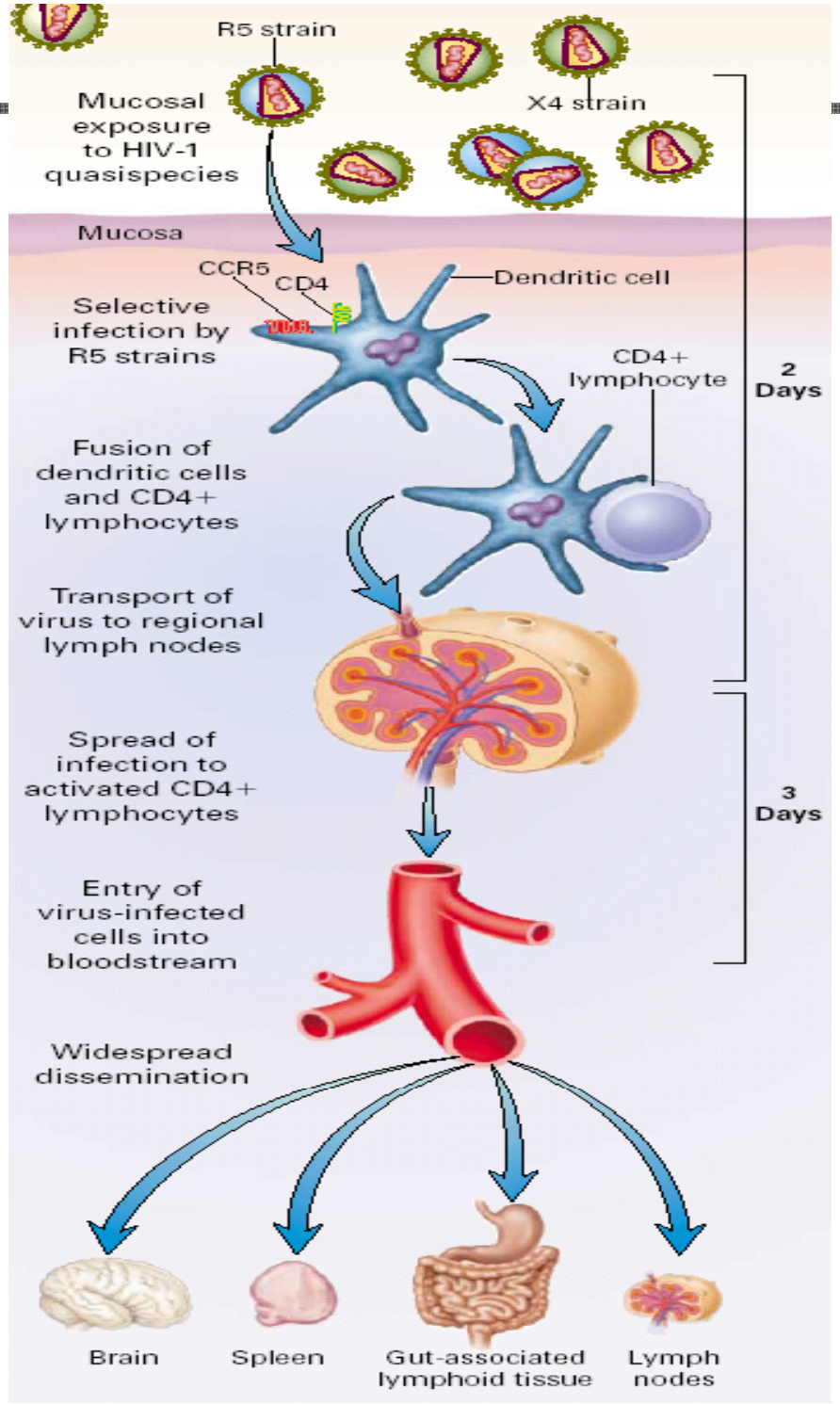
- **in utero**
- **during delivery**
- **breastmilk**



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

HIV INFECTION


0.9500
0.5000
0.1000
0.0100
0.0010
0.0002
0.0001
Infectivity (per-contact transmission on a log scale)
Perinatal zidovudine
Sexual intercourse
Needle stick
Needle sharing
Mother to infant
Transfusion
Route of Exposure to HIV


R5 strain
X4 strain
Mucosal exposure to HIV-1 quasispecies
Mucosa
CCR5
CD4
Dendritic cell
Selective infection by R5 strains
CD4+ lymphocyte
2 Days
Fusion of dendritic cells and CD4+ lymphocytes
Transport of virus to regional lymph nodes
Spread of infection to activated CD4+ lymphocytes
3 Days
Entry of virus-infected cells into bloodstream
Widespread dissemination
Brain
Spleen
Gut-associated lymphoid tissue
Lymph nodes

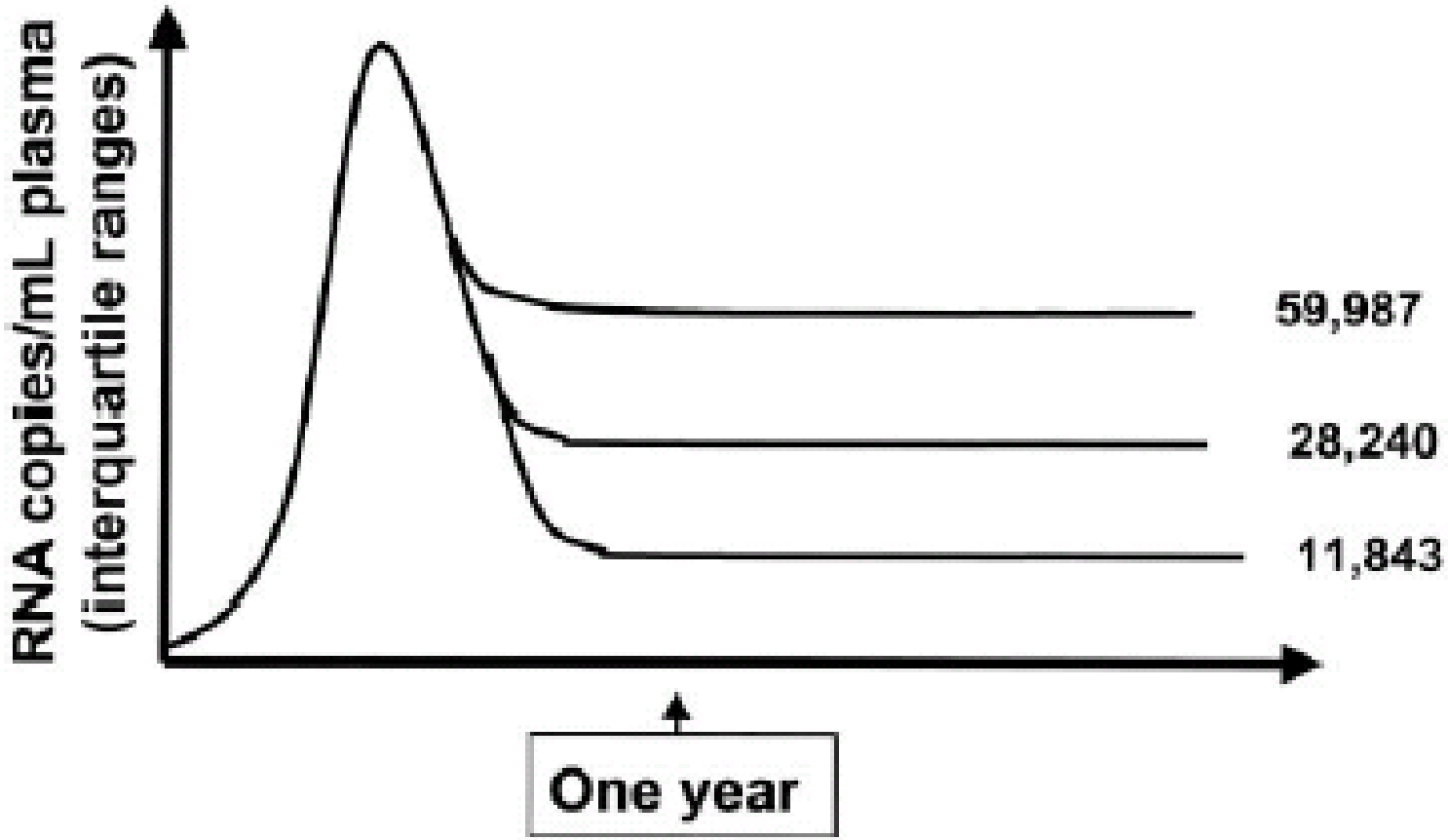


Figure 2. HIV RNA levels 1 year after untreated infection are relatively stable and predict subsequent disease progression. Data are from the Multicenter AIDS Cohort Study [21].

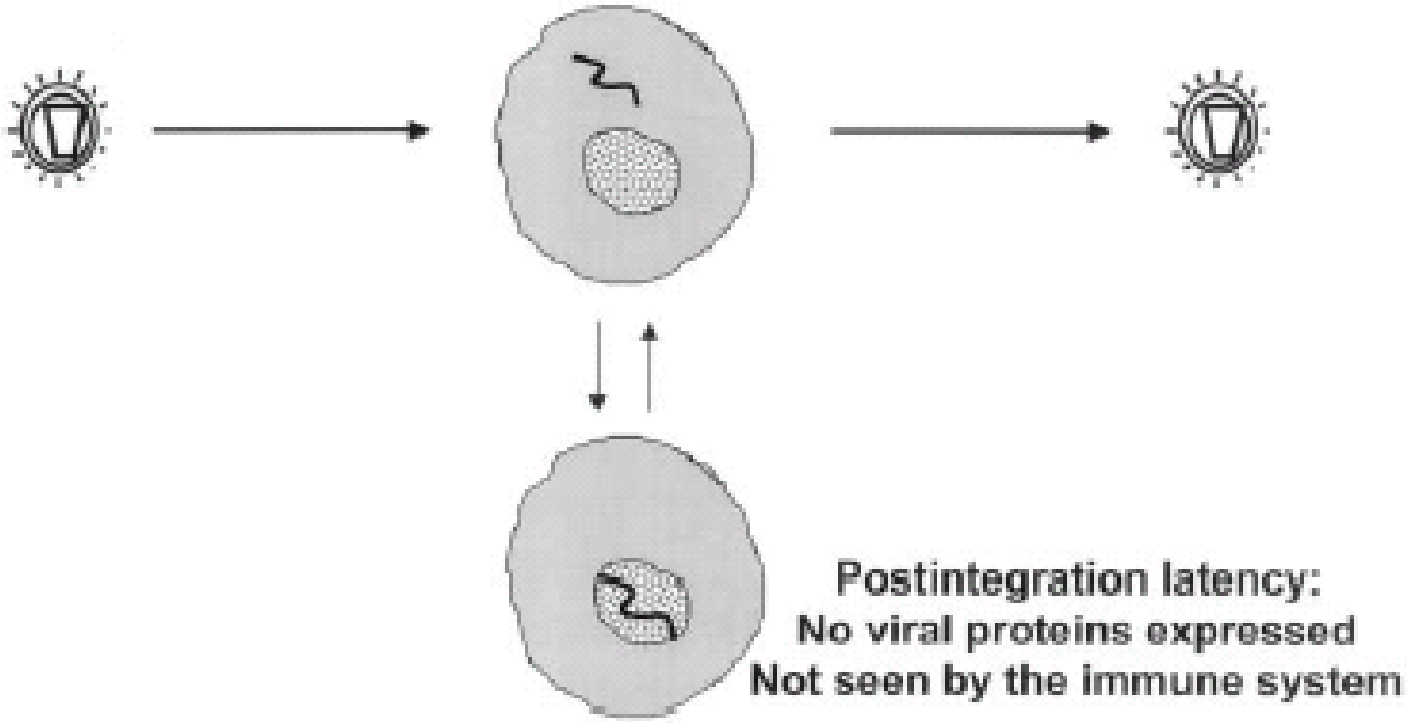
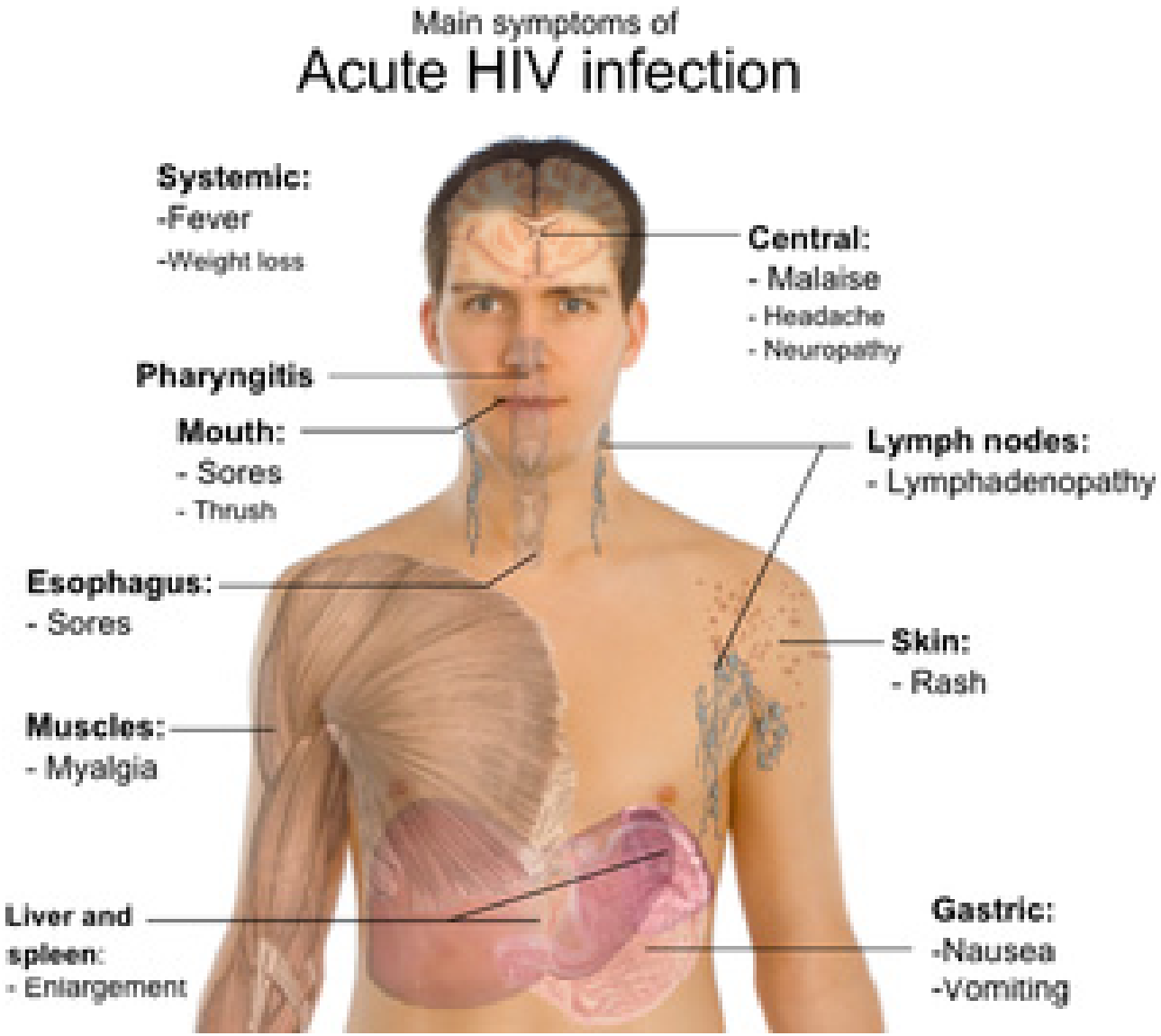


Figure 3. Establishment of the latent reservoir. This reservoir is established within days of initial infection. It consists of integrated proviral DNA that is transcriptionally inactive but replication competent. Because the reservoir is long lasting and not affected by antiretroviral therapy or anti-HIV immunity, the latent reservoir makes prospects for eradication of HIV infection very unlikely.

Acute HIV Infection

Symptoms of Acute HIV Infection



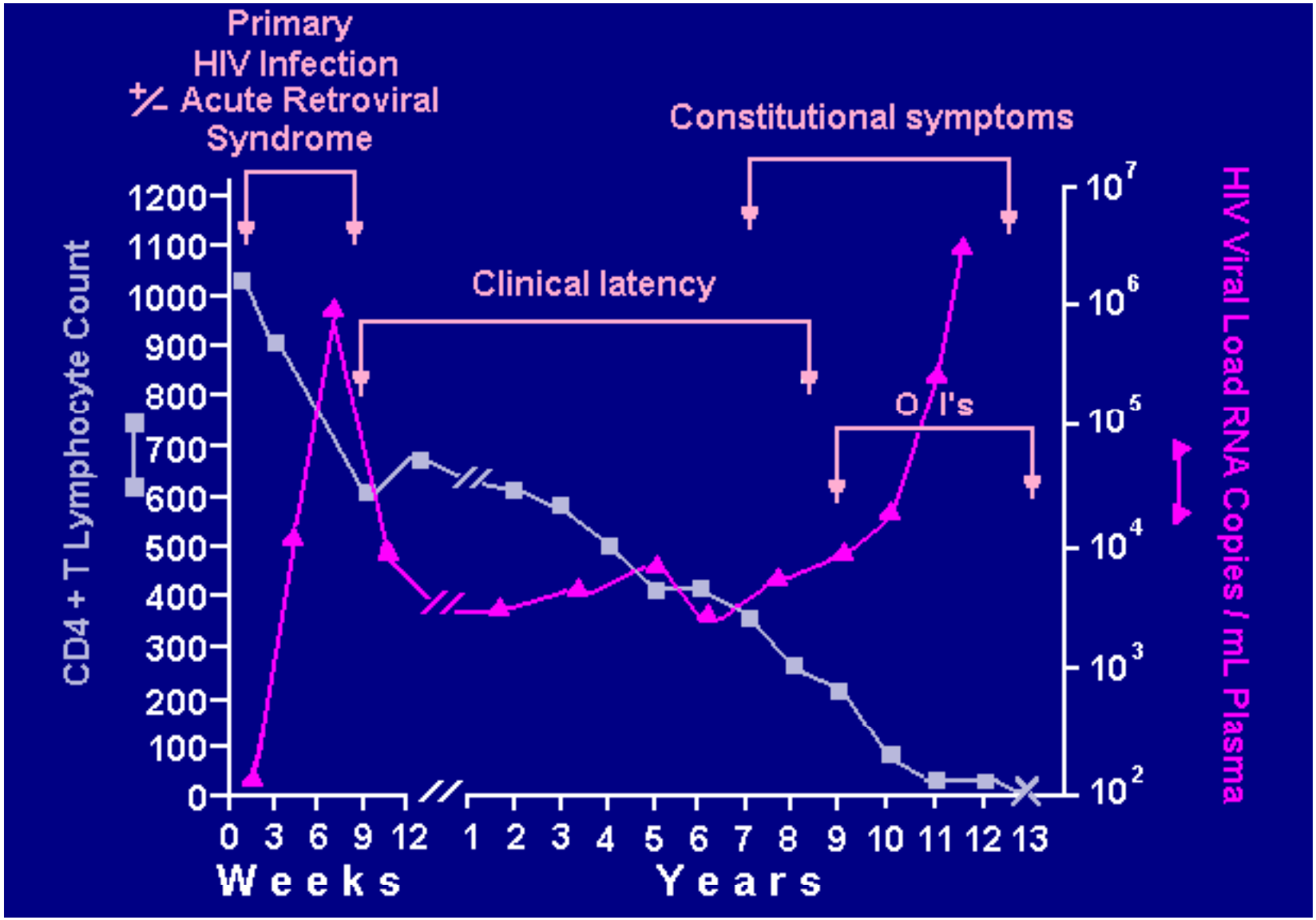
Frequency of Symptoms and Findings in Acute HIV-1 Infection

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.

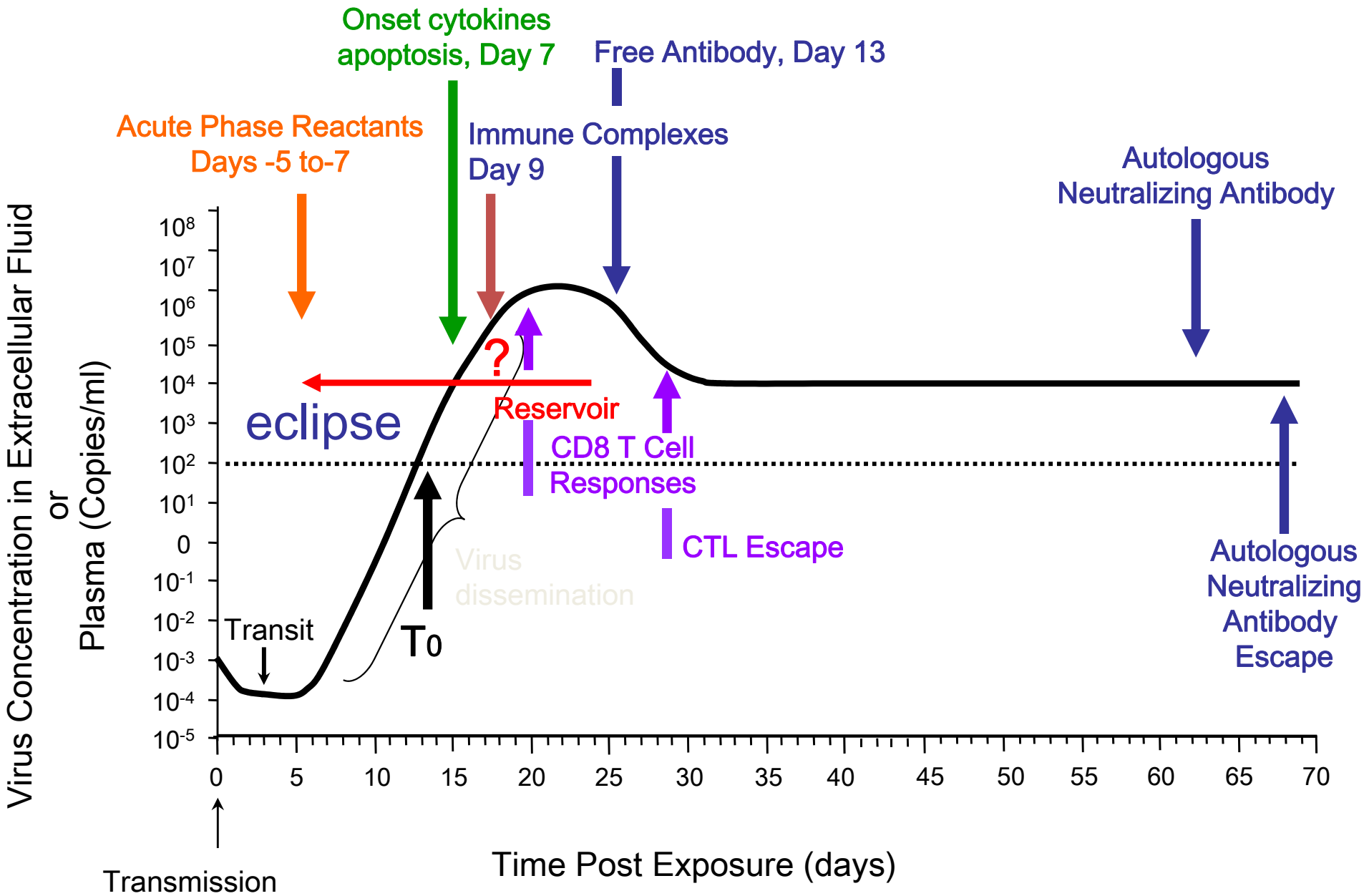
*highest in younger patients, Vanhems. JAIDS 2002;31:318-321.

Natural history of untreated HIV infection



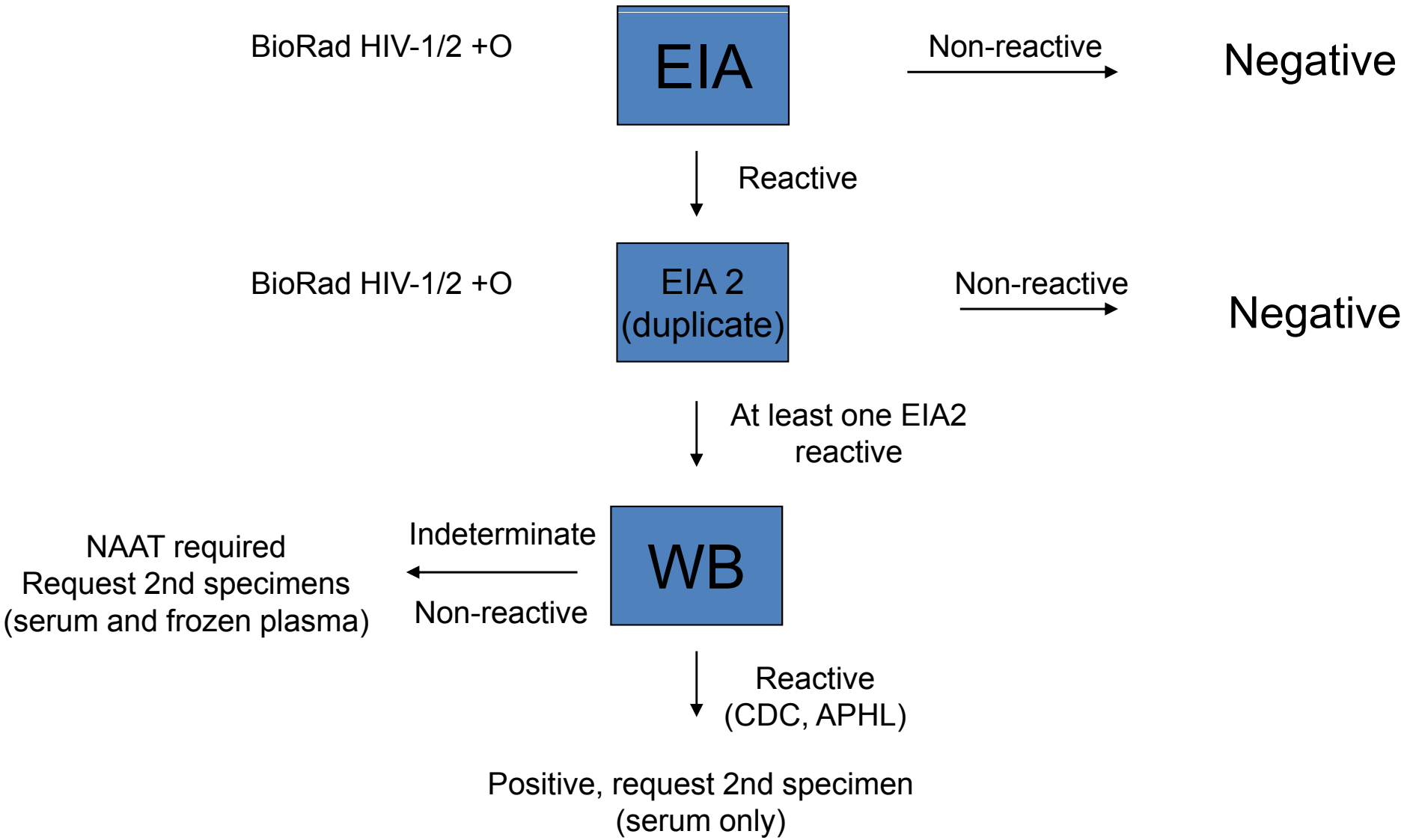
Fauci, 1996; Ann Intern Med 124: 654-663

Acute HIV-1 Infection



HIV Diagnostics

Reference Laboratory HIV Diagnostics

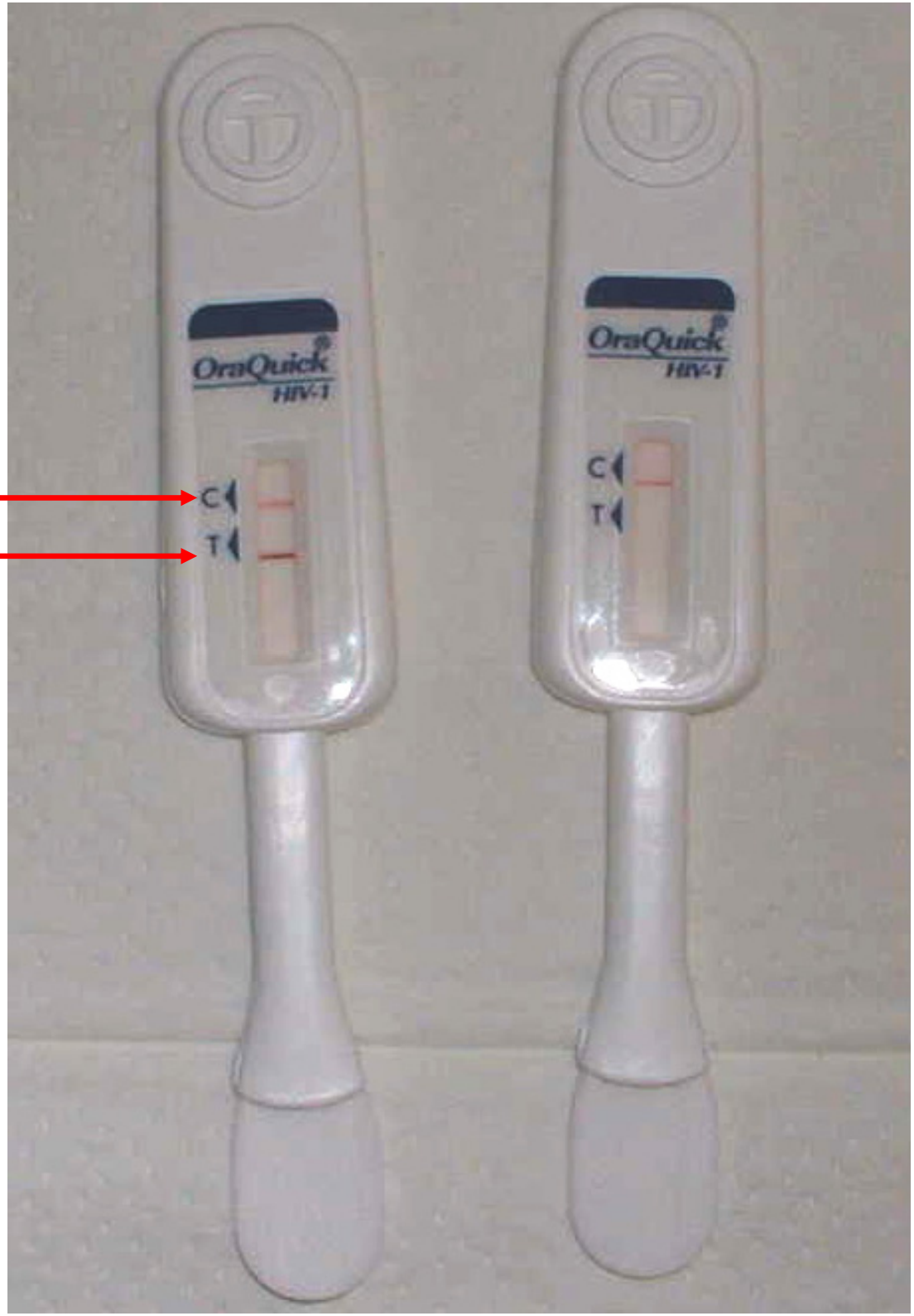


Rapid Point of Care Tests for HIV infection

- OraQuick Advance Rapid HIV-1/2 Antibody Test
  - US FDA approved, CLIA waved
  - 20 min test
  - No cold chain
  - Approved for clinical use (pre-donation screening)
  - Sensitivity/specificity = 99.6%/100% (fs WB)
  - Use for exposures
  - Use for pre-screening of emergent blood donors

OraQuick HIV-1

Control line
HIV line



Post-exposure prophylaxis

Websites to Access the Guidelines

- http://www.aidsetc.org
- http://aidsinfo.nih.gov

Occupational Risk Exposures in Health Care Personnel

- Percutaneous injury (needlestick, cut)

  OR

- Contact of mucous membrane or nonintact skin

- WITH:

  - Blood
  - Tissue
  - Other body fluids that are potentially infectious (cerebrospinal, synovial, pleural, pericardial, peritoneal, or amniotic fluids; semen or vaginal secretions)

NOT Considered Infectious for HIV, unless *Visibly Bloody*

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

Risk of HIV Infection following Occupational Exposure to HIV-Infected Blood

- Approximately 0.3% following percutaneous exposure
- Approximately 0.09% following mucous membrane exposure

Factors Associated with Increased Risk

- Visible contamination of device (such as needle) with patient's blood
- Needle having been placed directly into vein or artery
- Hollow-bore (vs solid) needle
- Deep injury
- Source patient with terminal illness
- High viral load
  (not established in occupational exposure)

Toxicity of PEP Regimens

- PEP should be given for a full 4 weeks
- Side effects of ARV drugs are common, and a major reason for not completing PEP regimens
- Therefore, to the extent possible, regimens that are tolerable for short-term use should be selected

Initiating PEP

- PEP should be started as soon as possible, preferably within hours, rather than days, following exposure
- When uncertain as to which drugs to choose, start the basic regimen rather than delay
- PEP should be administered for 4 weeks, if tolerated

Initiating PEP (2)

- Reevaluate exposed HCP within 72 hours of exposure, especially as additional information about the exposure or source patient becomes available
- If the source is found to be, PEP should be discontinued
- Rapid HIV testing of the source patient can facilitate decisions regarding PEP when the source patient's HIV status is unknown

Selecting the PEP Regimen

- Selection of number (2 or ≥3) of drugs is based on assessment of ***risk*** for HIV infection
- Selection of which agents to use is based largely on potential ***toxicity*** of PEP drugs and on likelihood of ***efficacy*** (especially in the case of resistant virus)
  - Few data on efficacy of individual ARV agents in PEP

How Many Drugs to Use?

- 2-drug PEP regimens improve tolerability and therefore chances of completing full 4 weeks
- ≥3-drug PEP regimens provide potentially greater antiviral activity
- Guidelines recommend more drugs for higher-risk exposures

PEP for Percutaneous Injuries

Exposure Type ***Infection Status of Source***

	HIV+, class 1	HIV+, class 2
Less severe	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP
More severe	Recommend expanded 3-drug PEP	Recommend expanded ≥3-drug PEP

PEP for Percutaneous Injuries (2)

Exposure Type ***Infection Status of Source***

	Unknown HIV status*	**Unknown source**
Less severe	Generally, no PEP warranted; consider basic 2-drug PEP if source has HIV risk factors	Generally, no PEP warranted; consider basic 2-drug PEP if exposure to HIV-infected persons is likely
More severe	As above	As above

*If PEP is given and source is later determined to be HIV negative, PEP should be discontinued.

PEP for Percutaneous Injuries (3)

Exposure Type	***Infection Status of Source***
	HIV negative
Less severe	No PEP
More severe	No PEP

PEP for Mucous Membrane and Nonintact Skin Exposures

Exposure Type ***Infection Status of Source***

	HIV+, class 1	HIV+, class 2
Less severe	Consider basic 2-drug PEP	Recommend basic 2-drug PEP
More severe	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP

PEP for Mucous Membrane and Nonintact Skin Exposures (2)

Exposure Type	*Infection Status of Source*	
	Unknown HIV status*	**Unknown source**
Less severe	Generally, no PEP warranted	Generally, no PEP warranted
More severe	Generally, no PEP warranted; consider basic 2-drug PEP if source has HIV risk factors	Generally, no PEP warranted; consider basic 2-drug PEP if exposure to HIV-infected persons is likely

*If source is determined to be HIV negative after PEP is initiated, discontinue PEP.

PEP for Mucous Membrane and Nonintact Skin Exposures (3)

Exposure Type	***Infection Status of Source***
	HIV negative
Less severe	No PEP
More severe	No PEP

Which Drugs to Use?

- Consultation with an expert is recommended
- Regimens should be chosen to minimize potential drug toxicities and maximize the likelihood of adherence
- Consideration should be given to the history of the source person, including history of and response to ART and disease stage

Which Drugs to Use? (2)

- If the source patient's virus is known or suspected to be resistant to ARVs, the PEP regimen should consist of drugs to which the source's virus is unlikely to be resistant
- If information on possible resistance is not immediately available, PEP (if indicated) should not be delayed; changes can be made later

Which Drugs to Use? (3)

Basic 2-drug regimens:

- Preferred:
  - ZDV + 3TC or FTC
  - TDF + 3TC or FTC
- Alternative:
  - d4T + 3TC or FTC
  - ddI + 3TC or FTC

Which Drugs to Use? (4)

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 coadmnistered with TDF, RTV must be included in the PEP regimen.
** Avoid in late pregnancy.
*** Avoid in pregnancy.

Which Drugs to Use? (5)

ARV agents generally NOT recommended for PEP:

- NVP
- DLV
- ABC
- ddC
- ddI + d4T

ARV agents to be used for PEP only with expert consultation:

- ENF

Treatment

Recommendations for Initiating ART

Clinical Category or CD4 Count	Recommendation
▪History of AIDS-defining illness ▪CD4 count <350 cells/µL ▪CD4 count 350-500 cells/µL ▪Pregnant women ▪HIV-associated nephropathy (HIVAN) ▪Hepatitis B (HBV) coinfection, when HBV treatment is indicated*	Initiate ART

* Treatment with fully suppressive drugs active against both HIV and HBV is recommended.

Recommendations for Initiating ART (2)

Clinical Category or CD4 Count	Recommendation
CD4 count >500 cells/μL, asymptomatic, without conditions listed above	50% of the Panel favors starting ART; 50% views ART as optional

Recommendations for Initiating ART (3)

- "Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence."
- Patients may choose to postpone ART
- Providers may elect to defer ART, based on patients' clinical and/or psychosocial factors

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Consider More Rapid Initiation of ART

- Pregnancy
- AIDS-defining condition
- Acute opportunistic infection
- Lower CD4 count (eg, <200 cells/μL)
- Rapid decline in CD4
- Higher viral load
- HIVAN
- HBV coinfection when HBV treatment is indicated

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Consider Deferral of ART

- Clinical or personal factors may support deferral of ART
  - If CD4 is low, deferral should be considered only in unusual situations, and with close follow-up
- When there are significant barriers to adherence
- If comorbidities complicate or prohibit ART
- “Elite controllers” and long-term nonprogressors

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Current ARV Medications

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)

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)

Initial Treatment: Choosing Regimens

- 3 main categories:
  - 1 NNRTI + 2 NRTIs
  - 1 PI + 2 NRTIs
  - 1 II + 2 NRTIs
- Combination of NNRTI, PI, or II + 2 NRTIs preferred for most patients
- Fusion inhibitor, CCR5 antagonist not recommended in initial ART
- Few clinical end points to guide choices
- Advantages and disadvantages to each type of regimen
- Individualize regimen choice

Initial Treatment: Preferred

NNRTI based	▪EFV/TDF/FTC[1,2]
PI based	▪ATV/r + TDF/FTC[2] ▪DRV/r (QD) + TDF/FTC[2]
II based	▪RAL + TDF/FTC[2]
Pregnant Women	▪LPV/r (BID)[3] + ZDV/3TC

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.

AETC NATIONAL RESOURCE CENTER

HIV Prevention—turning the tide

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 malecircumcision 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

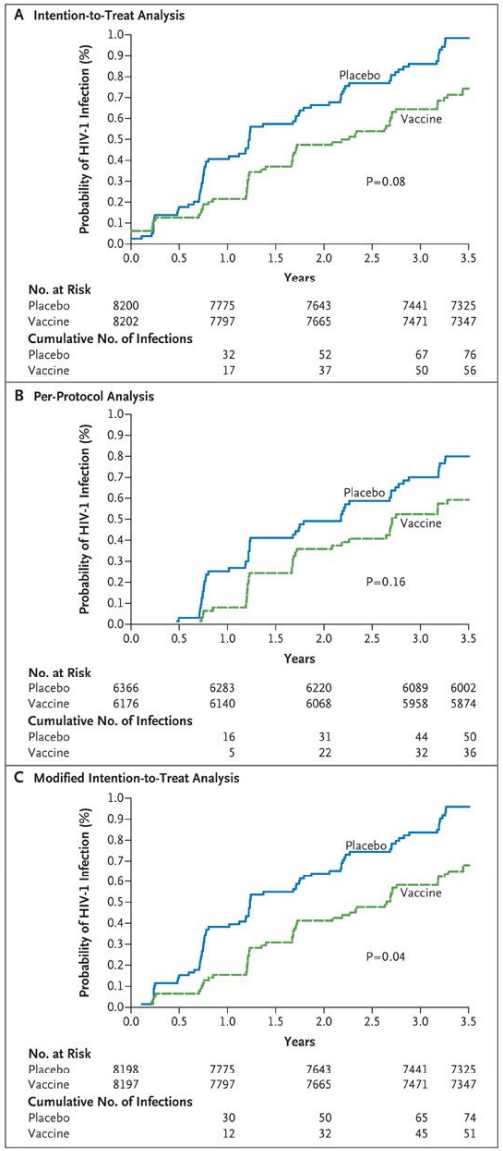
The NEW ENGLAND JOURNAL of MEDICINE

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

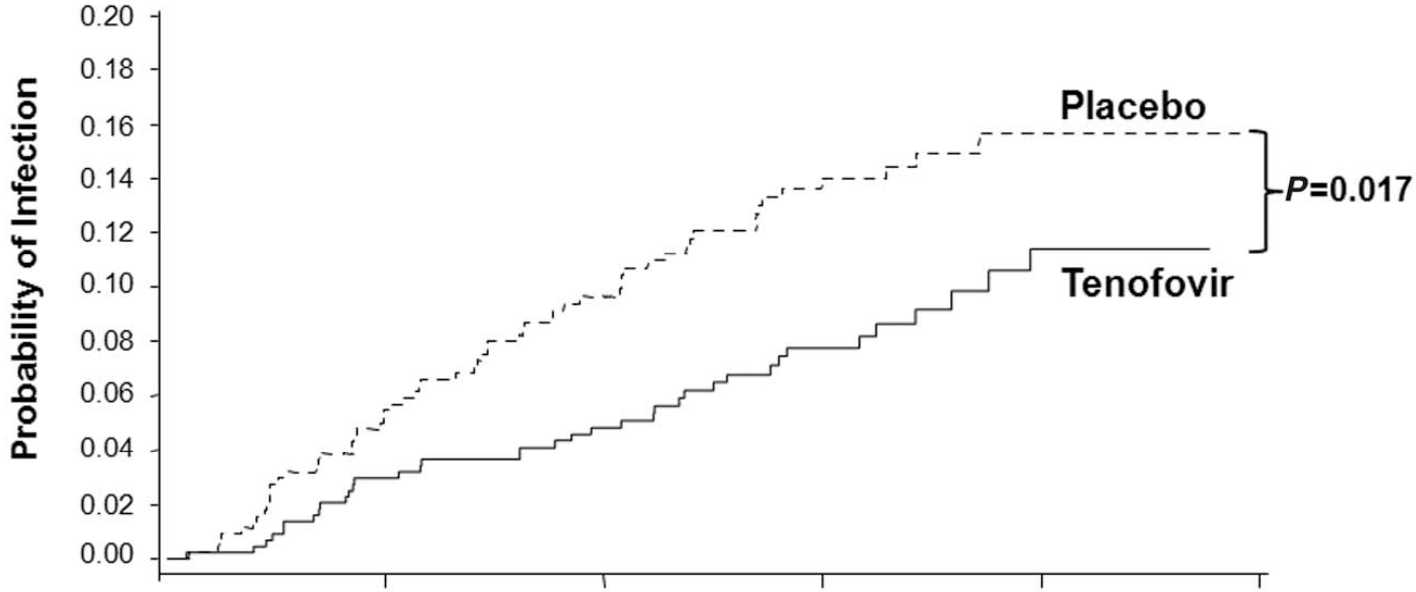
Supachai Rerks-Ngarm, M.D., Punnee Pittisutthithum M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, 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*

NEJM 361:2209 (03 Dec 09)

RV 144 Primary Population Efficacy



Tenofovir gel protects women from male to female infection



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)**

SCIENCE VOL 329, 3 SEPTEMBER 2010 (Caprisa 004)

Coming steps

- Pre-exposure prophylaxis
- Improved antiretroviral microbicides
- Test and treat
- Extend the impact of RV 144
- New generation HIV vaccines