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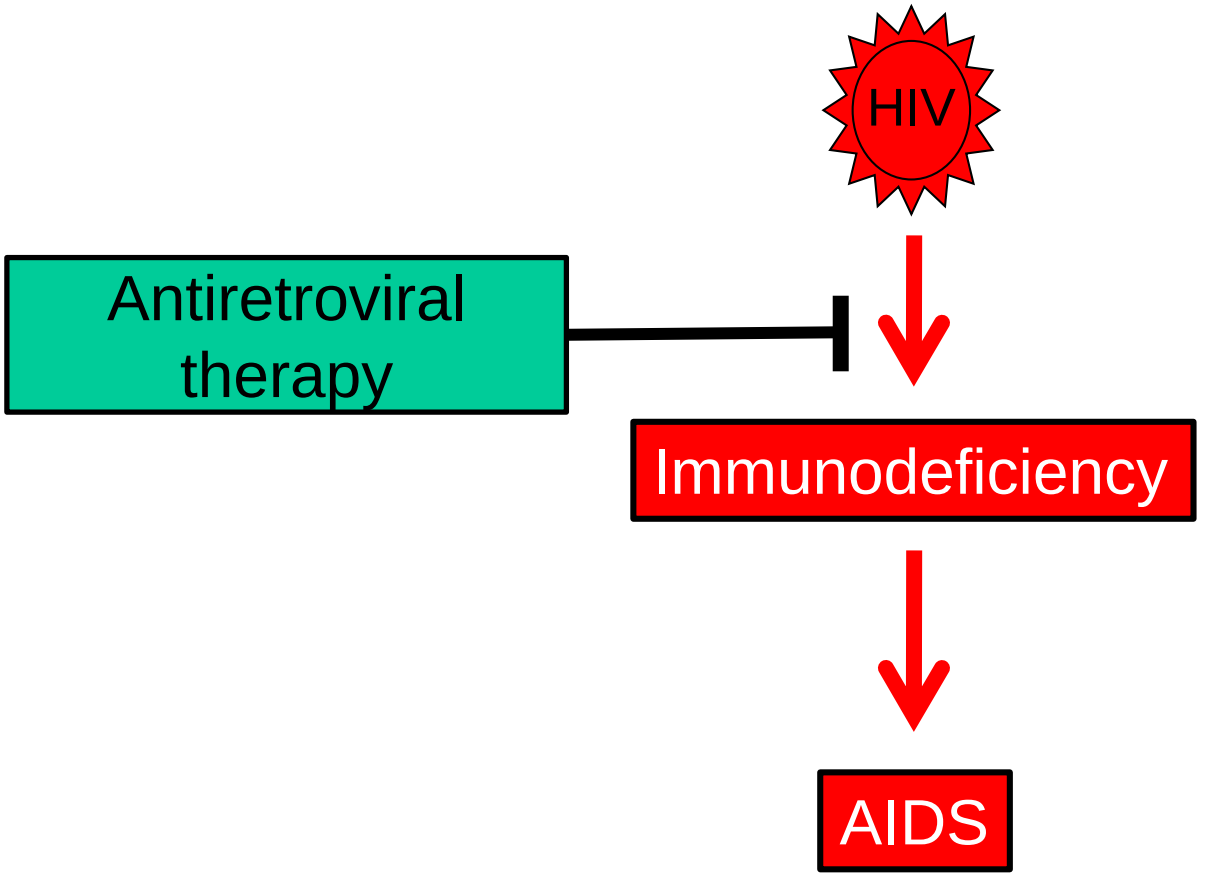
Immunodeficiencies

Part 2: HIV and AIDS

Clinical Immunology Seminars, 16.5.2019

Andri Rauch
Universitätsklinik für Infektiologie
Inselspital PKT2B – 3010 Bern
andri.rauch@insel.ch

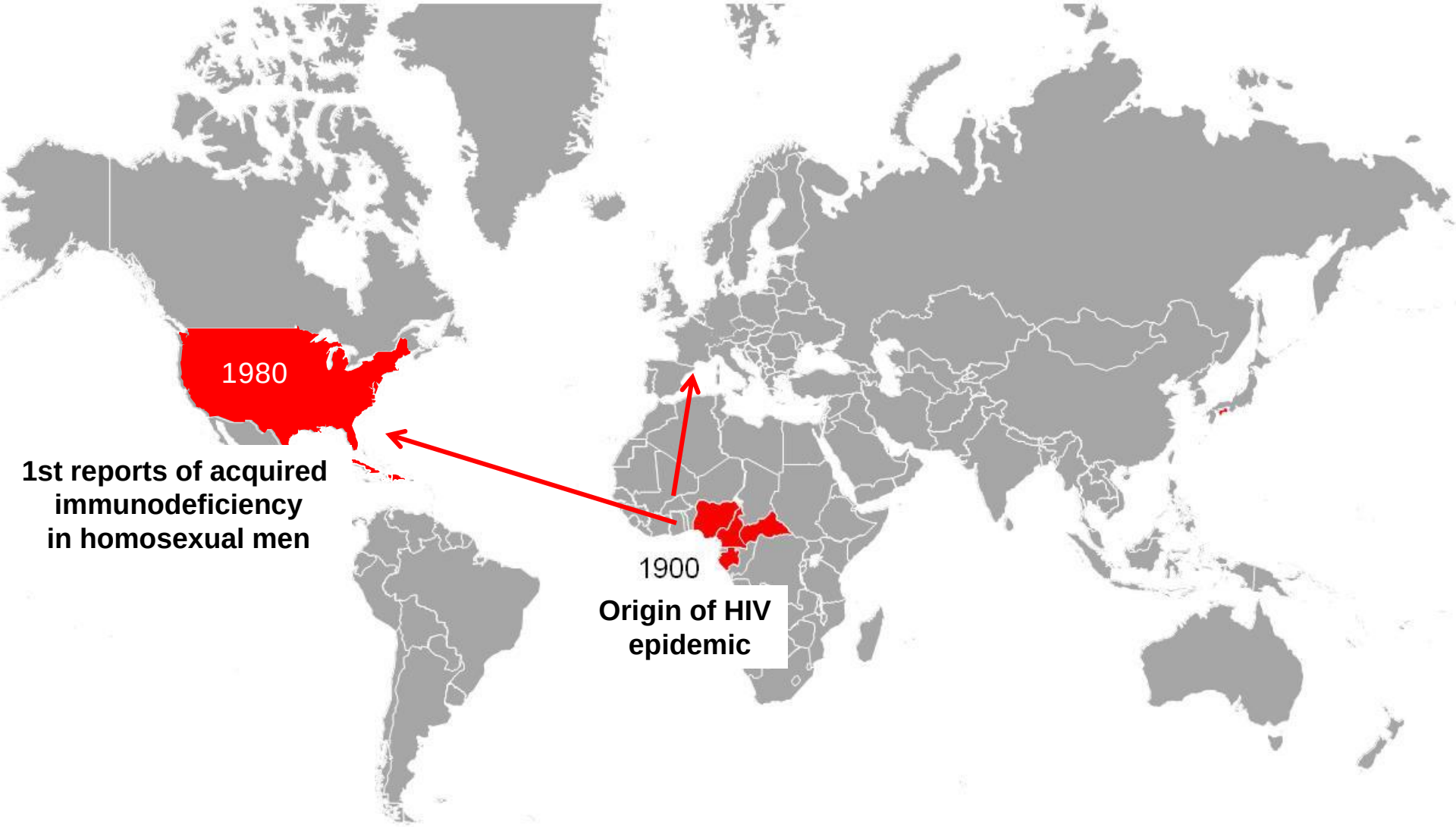
Outline



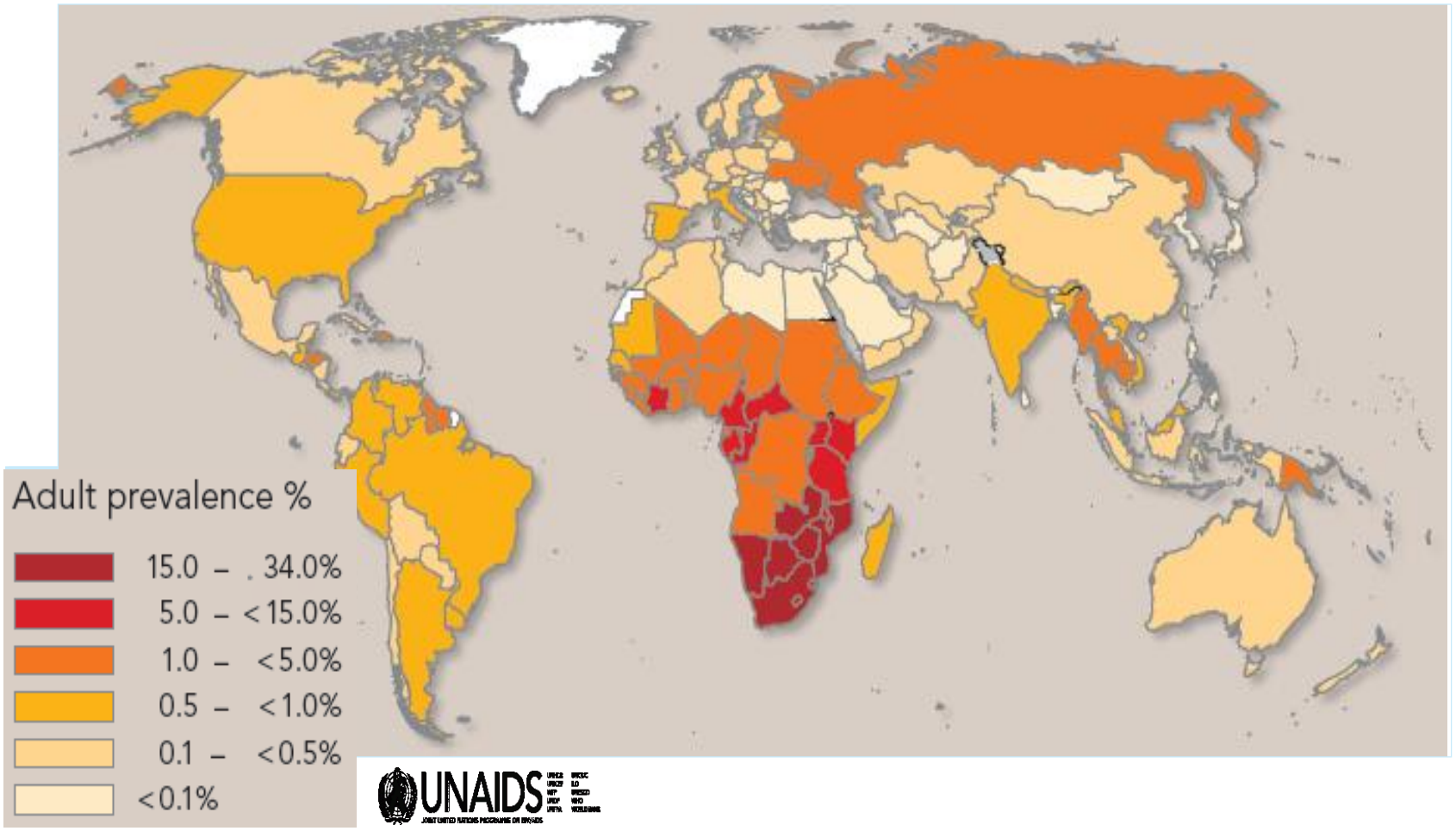
History + life cycle

Causes + consequences

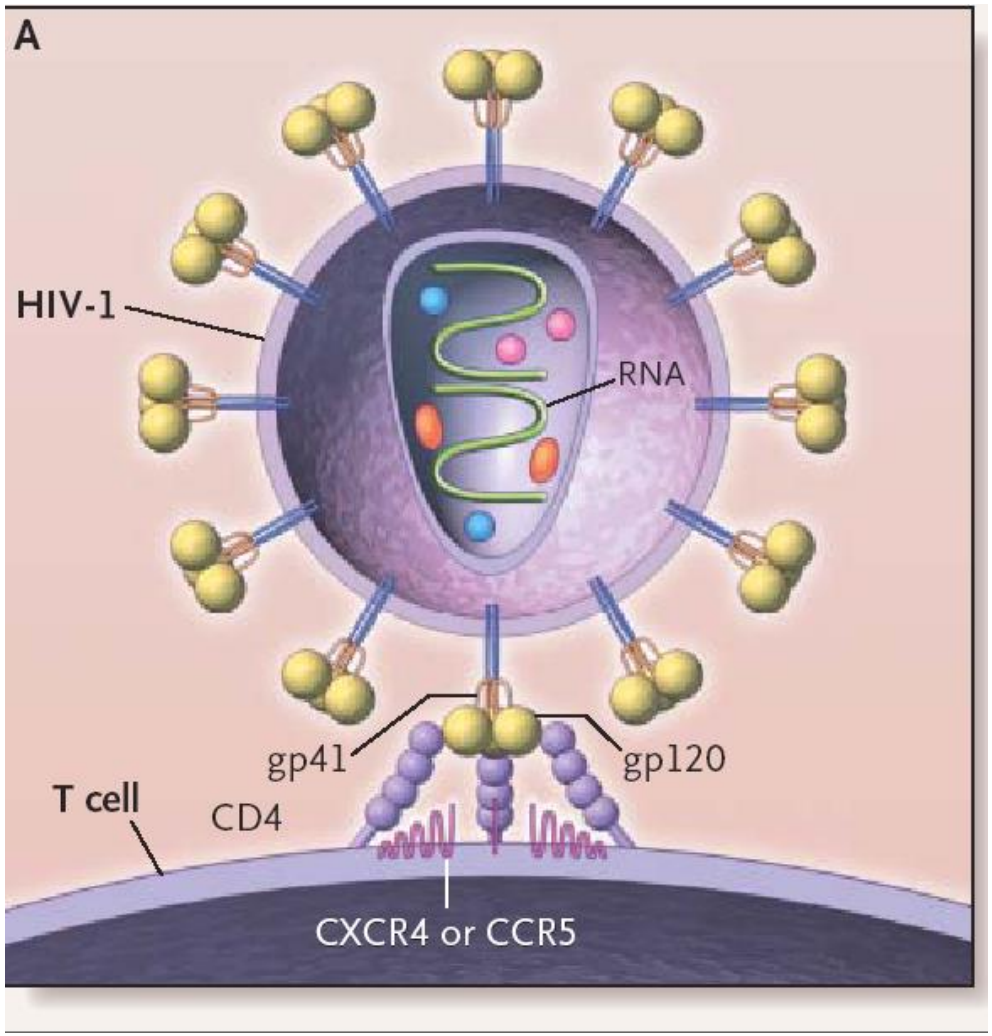
History of HIV



Worldwide spread of HIV



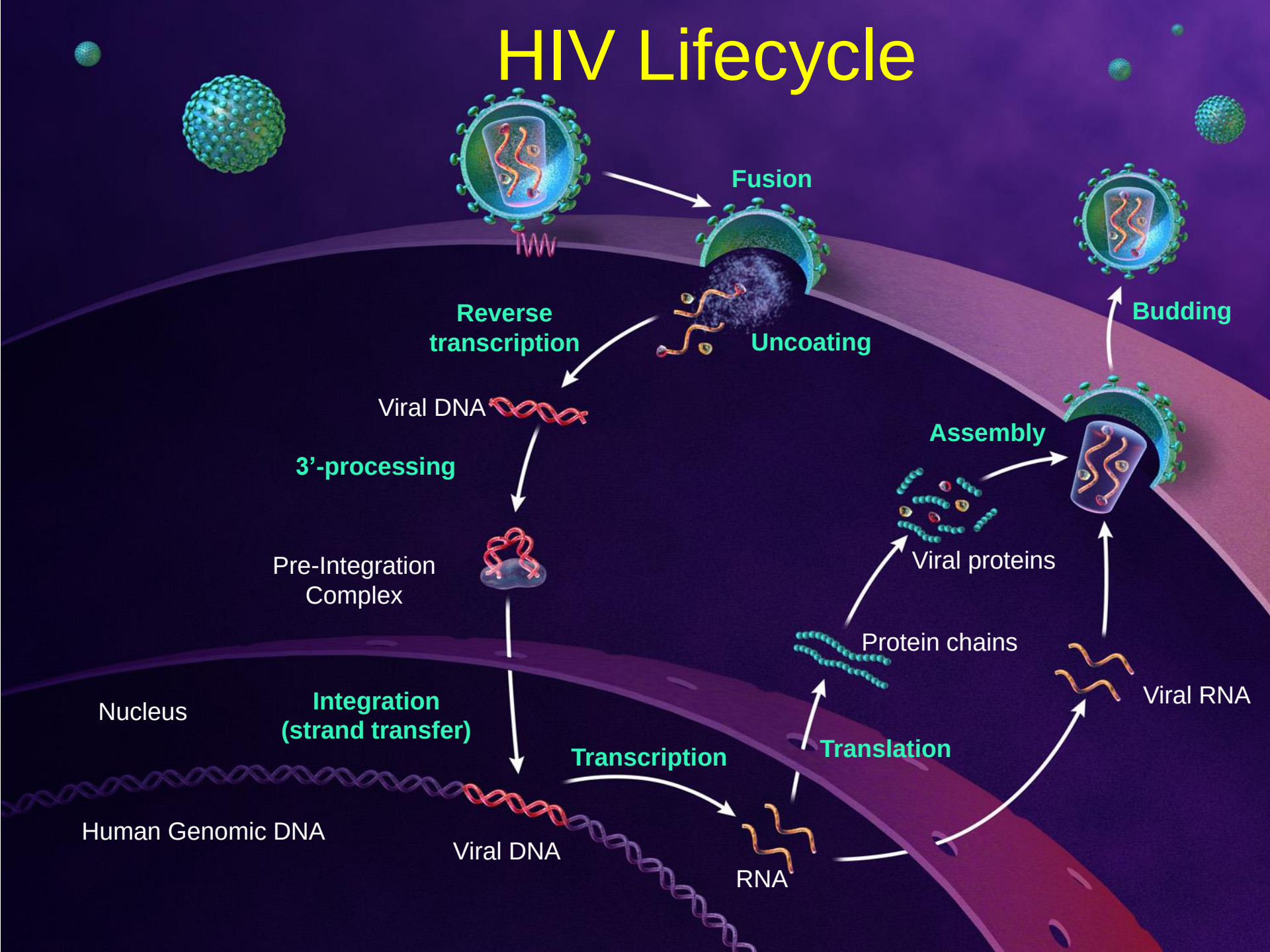
HIV attachment to host cells



Receptor: CD4
Co-receptor: CXCR4 or CCR5

Kilby, J. M. et al. N Engl J Med 2003;348:2228-2238

HIV Lifecycle



Early events in HIV-infection

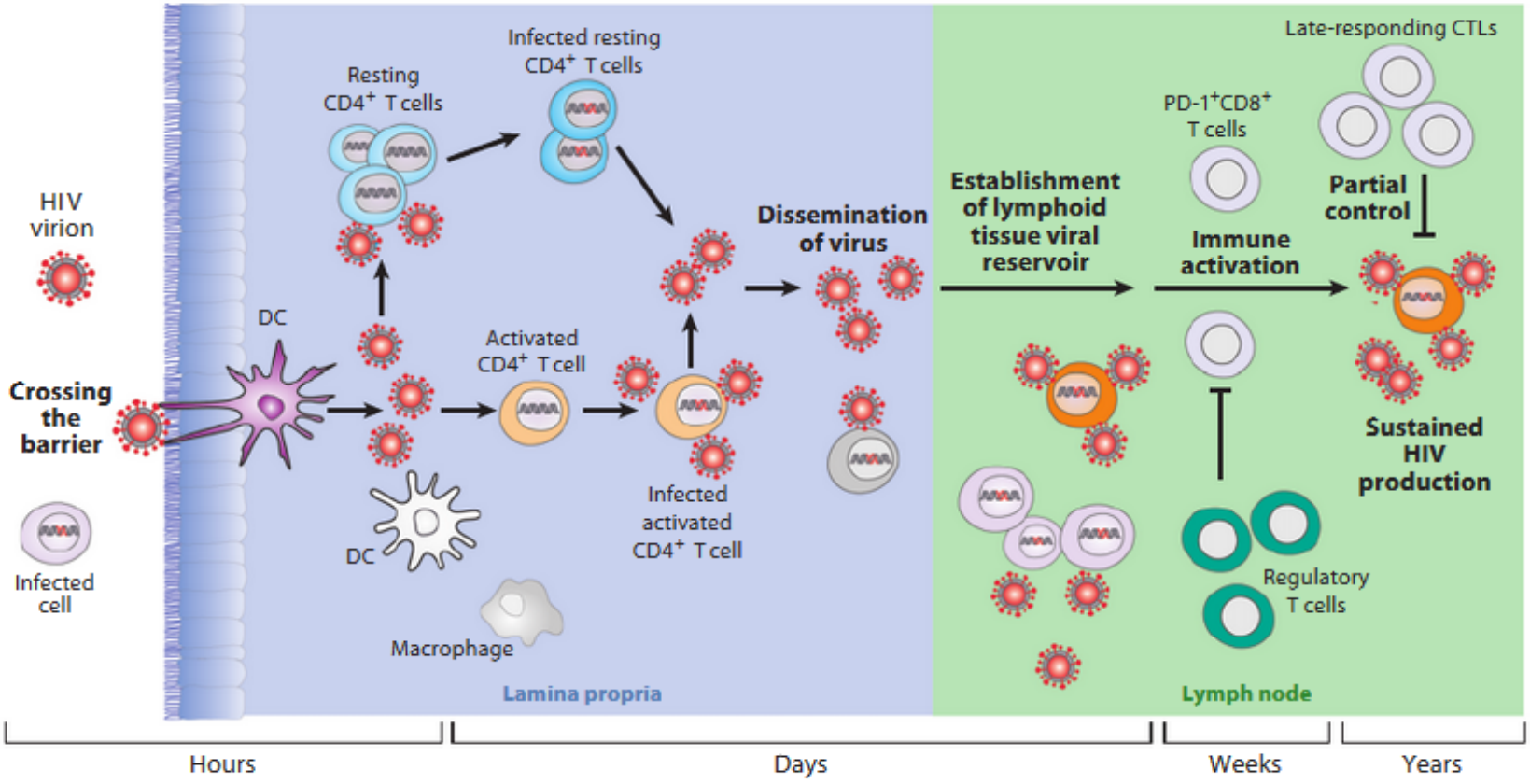
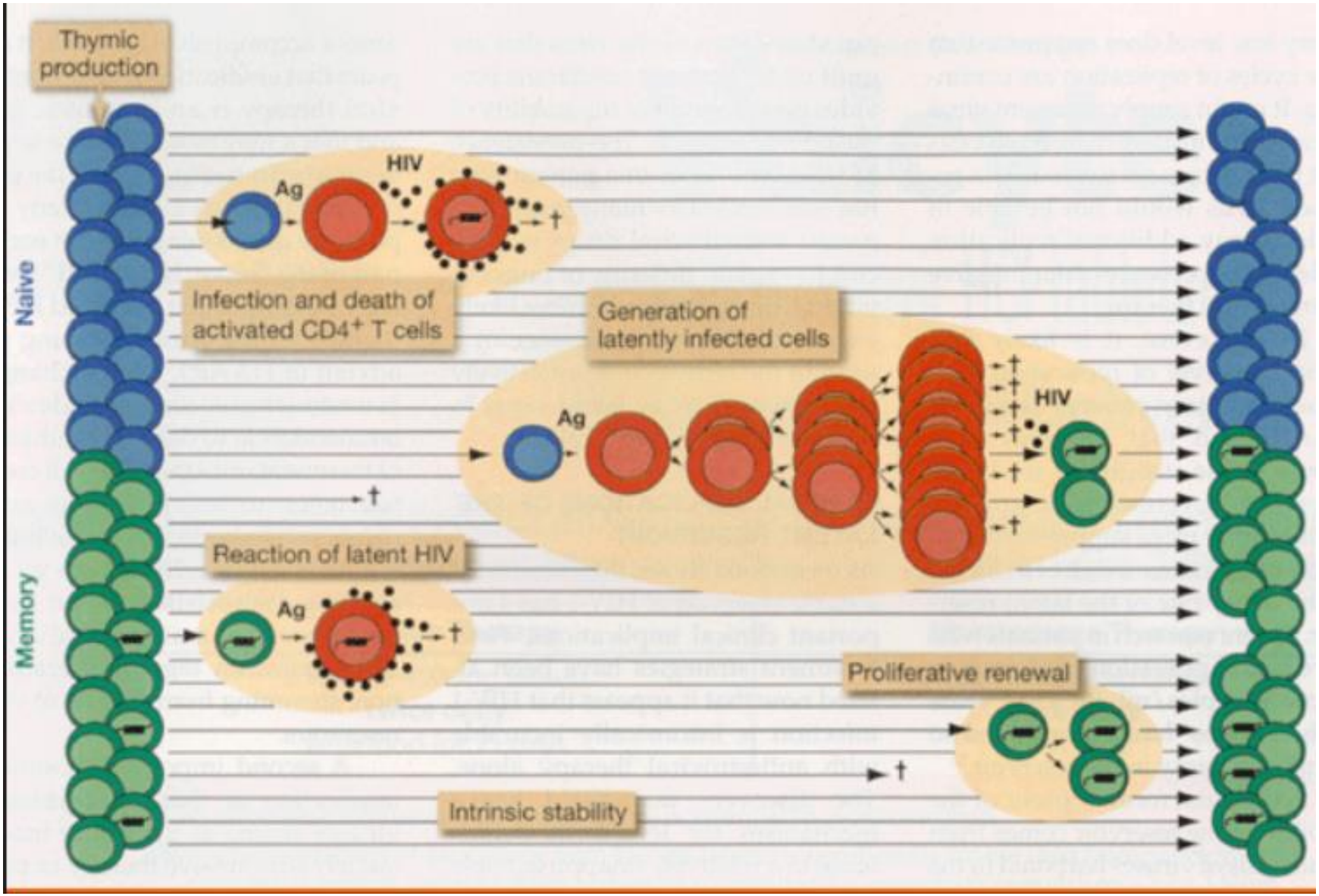


Figure 1

Phases of infection following exposure to human immunodeficiency virus (HIV). Infection begins with transmission across a mucosal barrier, either by a cell-free virus, infected cell, or virion attached to dendritic cells (DCs) or Langerhans cells (LCs). Early low-level propagation probably occurs in partially activated $CD4^+$ T cells, followed by massive propagation in activated $CD4^+$ T cells of the gut-associated lymphoid tissue lamina propria. Dissemination of HIV to other secondary lymphoid tissues and establishment of stable tissue viral reservoirs ensue. Immune response lags behind the burst of viremia and provides only partial control of viral replication. Adapted from Reference 5. Abbreviations: CTL, cytotoxic T lymphocyte; PD-1, programmed death 1.

Moir, Annu. Rev. Pathol. Mech. Dis. 2011. 6:223–48

Establishment of HIV latency

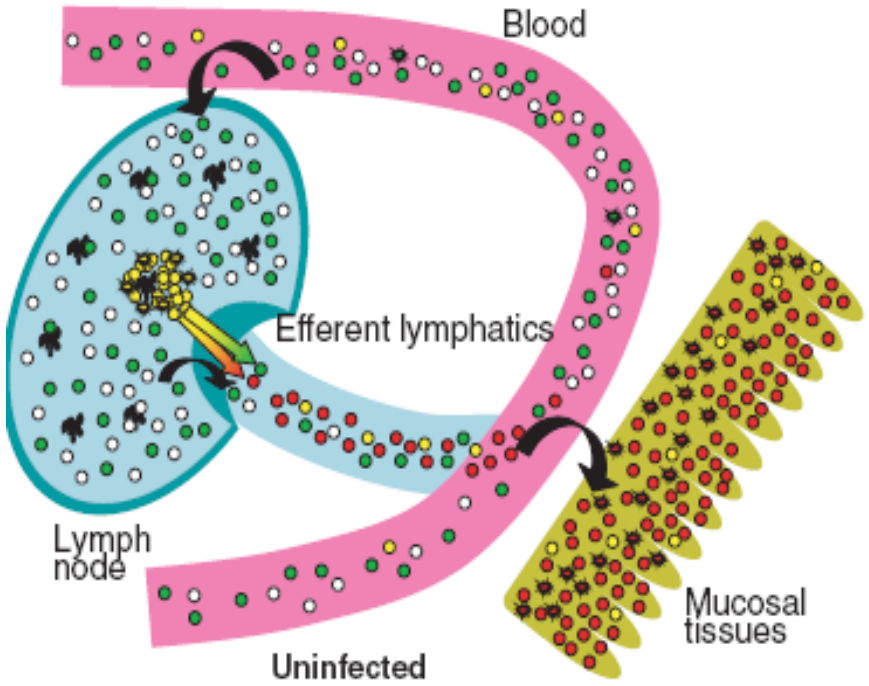


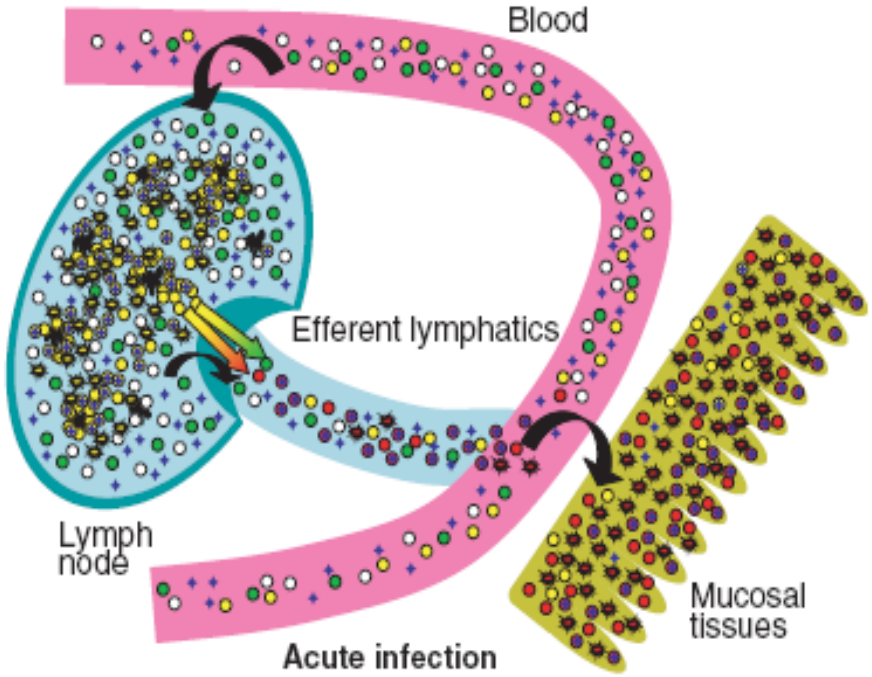
Siliciano et al, 2011

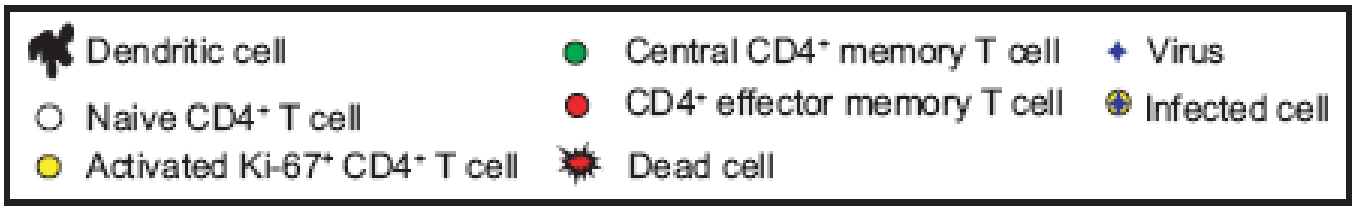
Effect of acute HIV infection on CD4+ T cell subsets

uninfected

Acute HIV infection infects CCR5+ CD4+ T cells (mainly effector memory)





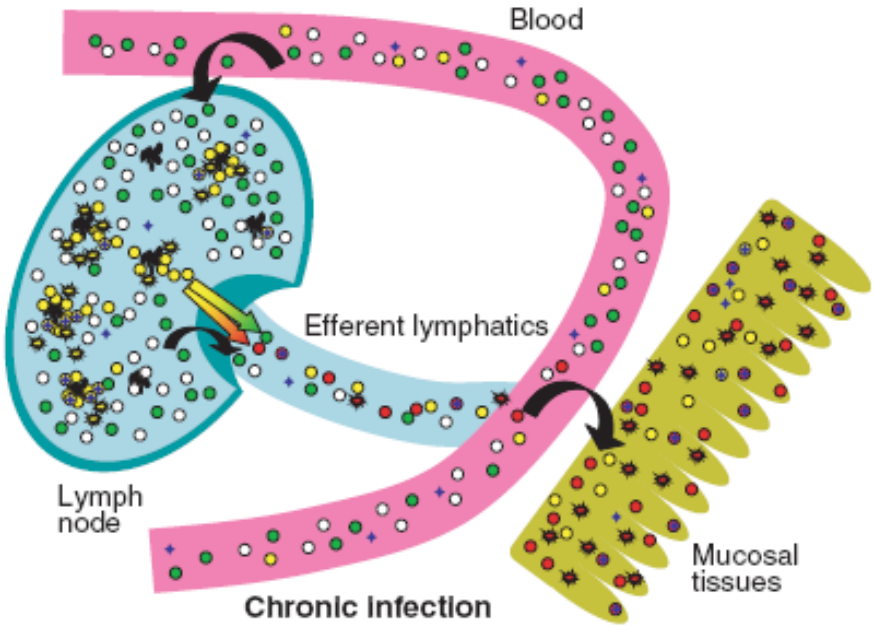


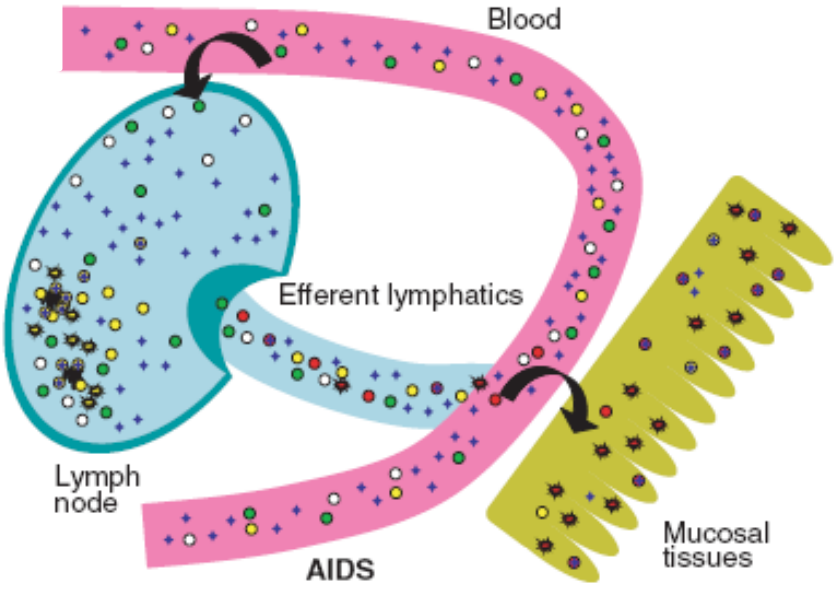
Grossman et al, Nat Med 2006

CD4+ T cell depletion in chronic infection

- Continuous infection in lymph nodes/mucosa
- Generation of new short-lived CD4+em
- Death of CD4+cm
- Destruction of lymph-node architecture

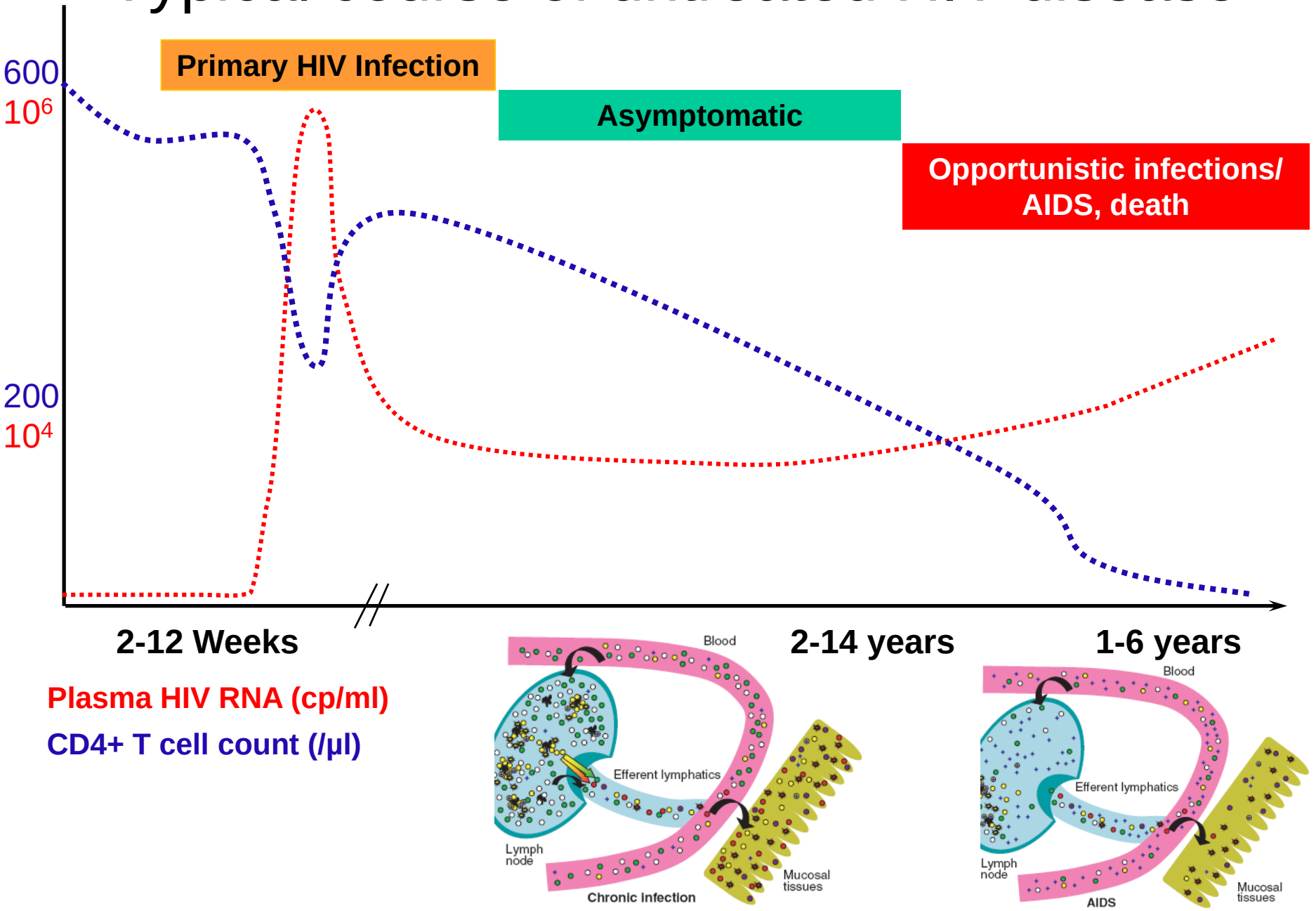
AIDS:
- CXCR4-tropic HIV infects naive and resting memory cells
- Critical loss of CD4+em and CD4+cm



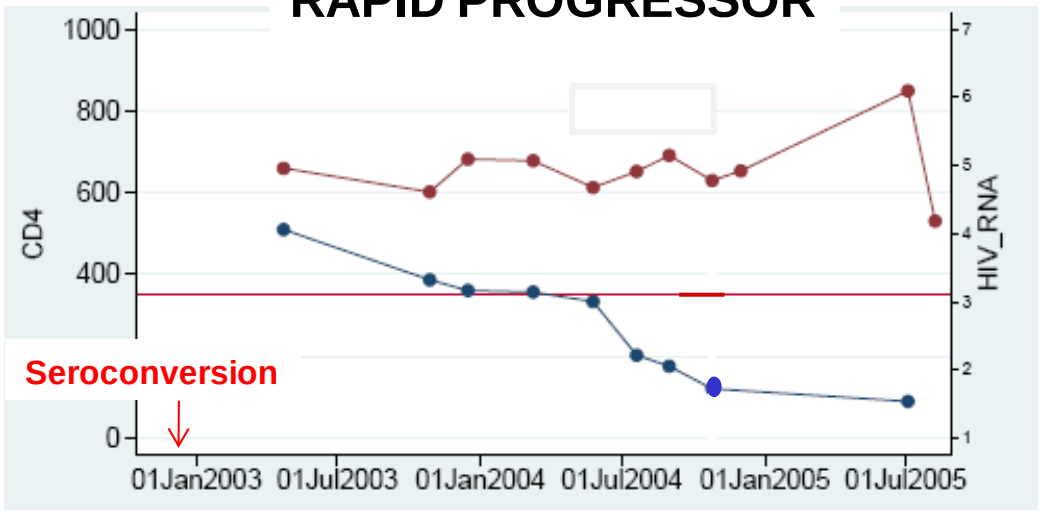


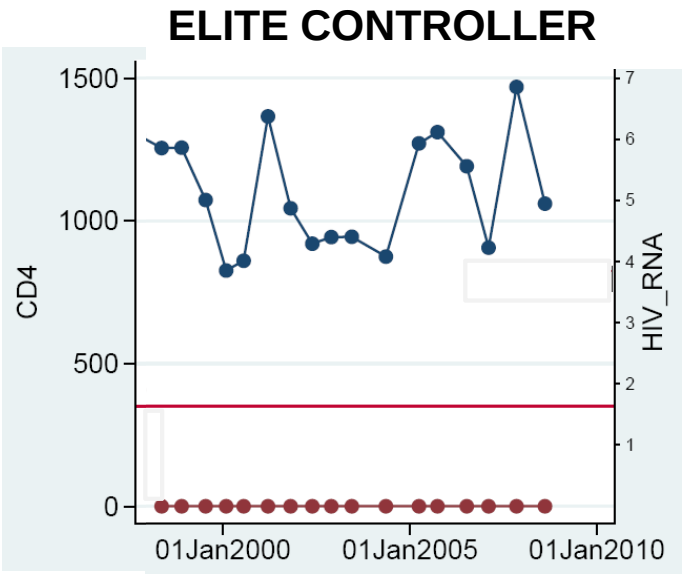
Grossman et al, Nat Med 2006

Typical course of untreated HIV disease



Extreme courses of HIV disease





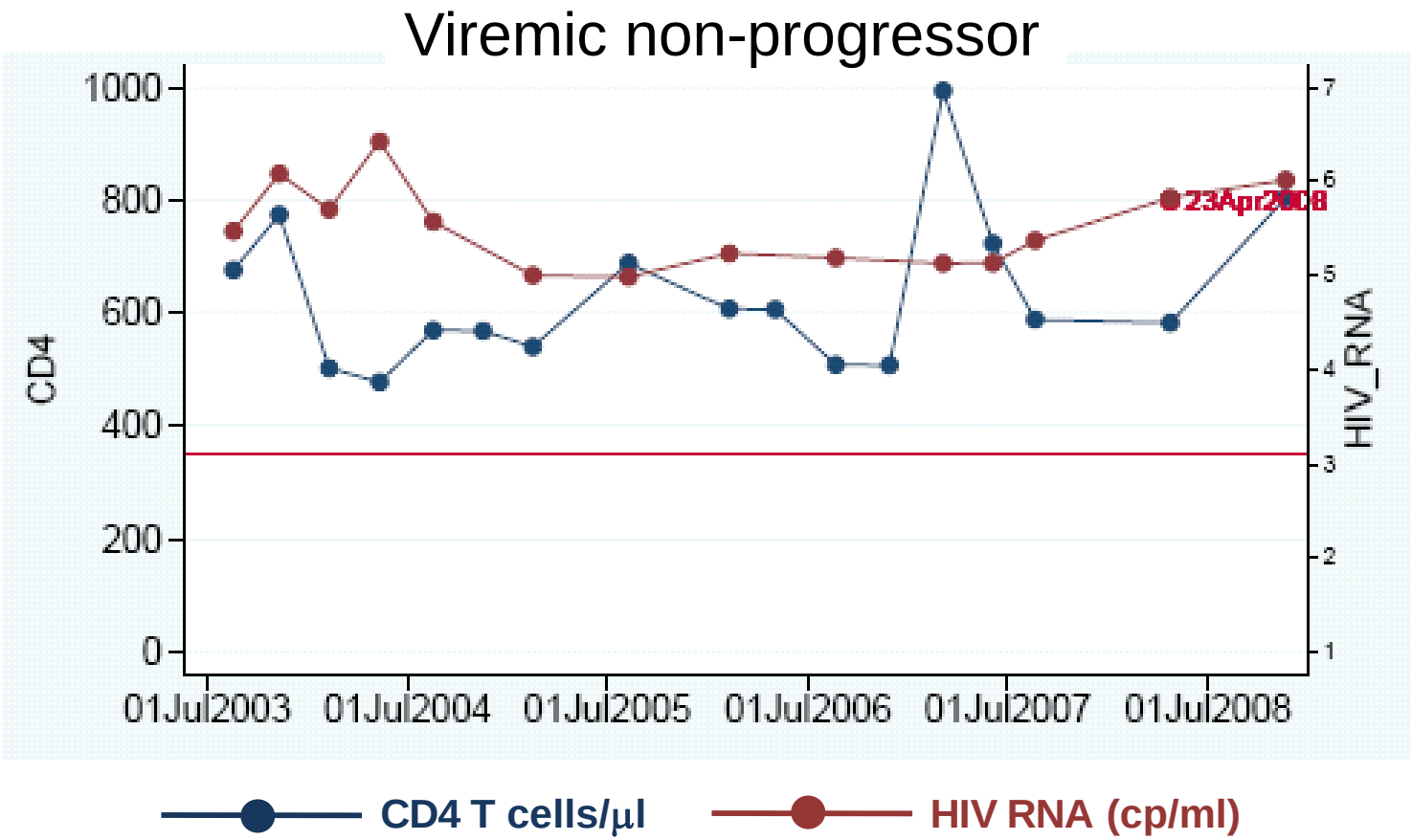
CD4 T cells/µl HIV RNA (cp/ml)

SWISS HIV COHORT STUDY

~5%

~1%

Unusual course of HIV disease: Non-progression despite high viremia

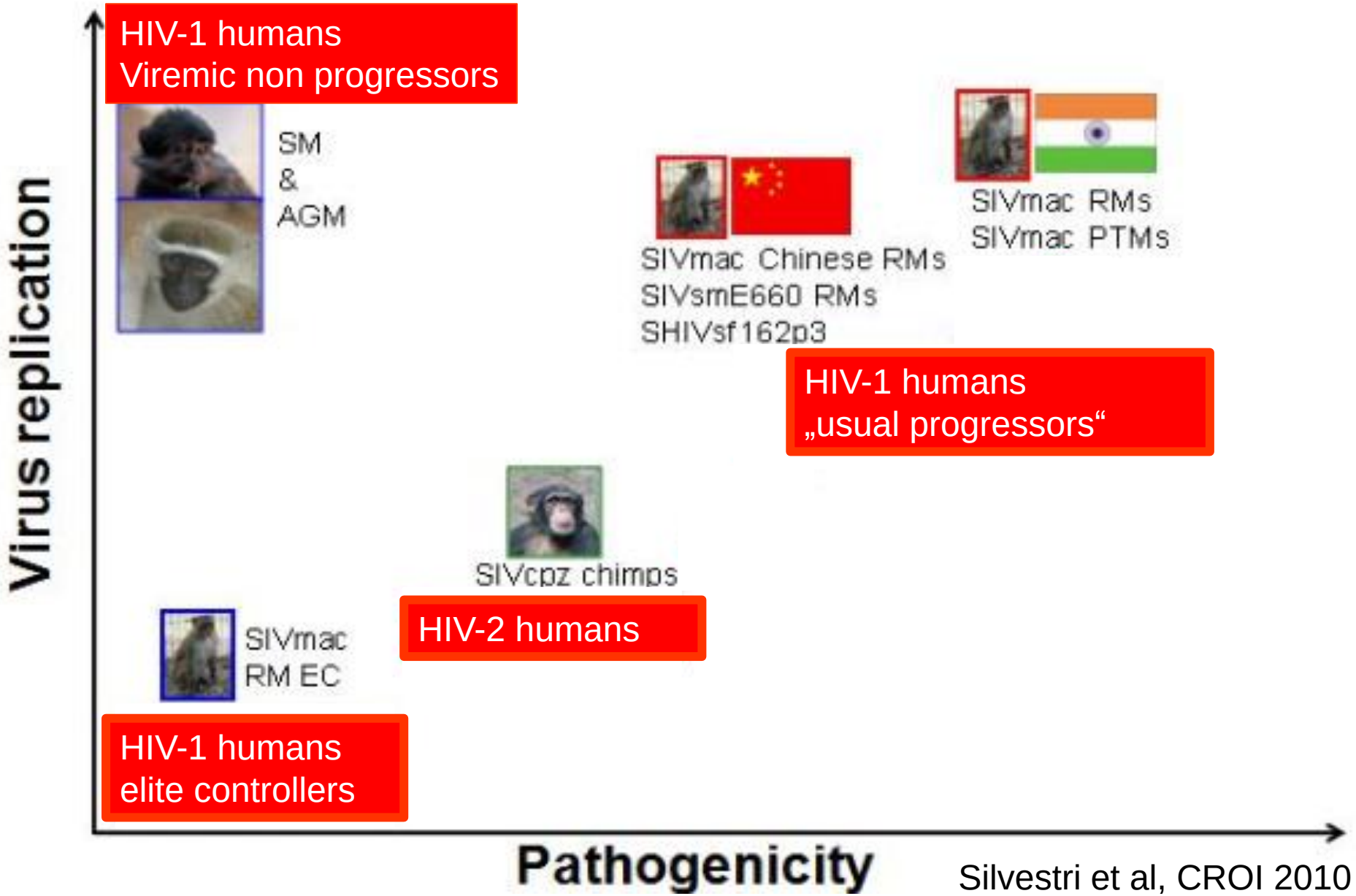


SWISS HIV COHORT STUDY

0.1%

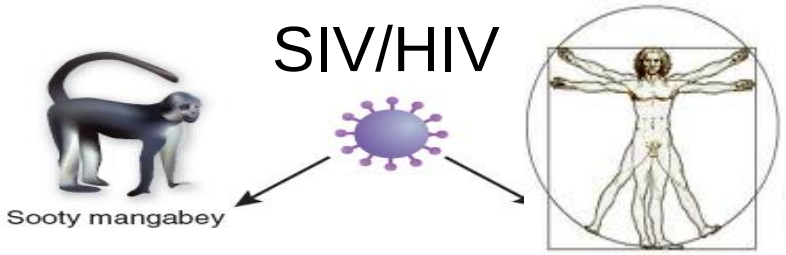
Rotger et al, Journal of Clinical Investigation, in press

Comparative AIDS Research:



Silvestri et al, CROI 2010

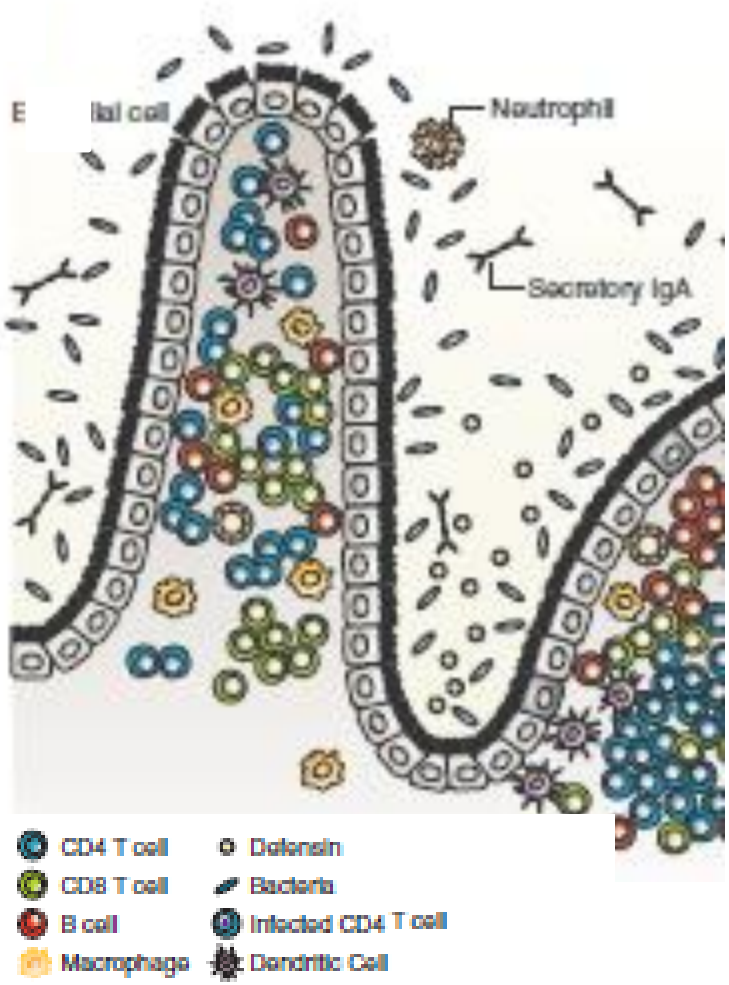
Non-pathogenic vs pathogenic SIV/HIV disease



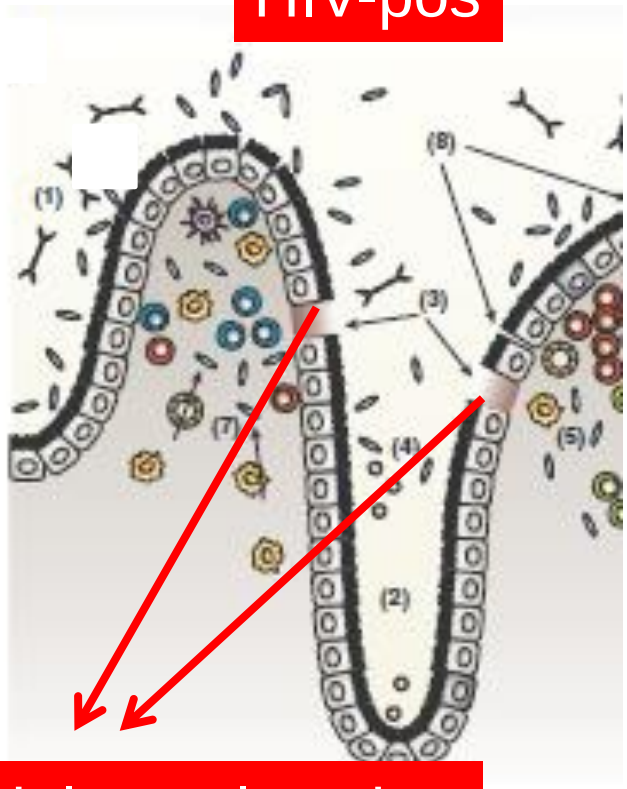
AIDS	**No**	**YES**
CD4 T cell depletion	**No**	**YES**
Viral load	**High**	**High**
CCR5 expression on T cells upon activation	**No**	**Yes**
Microbial translocation	**No**	**Yes**
IMMUNE ACTIVATION	**No**	**Yes**

HIV-associated damage to the GI-tract fuels immune activation

Healthy



HIV-pos



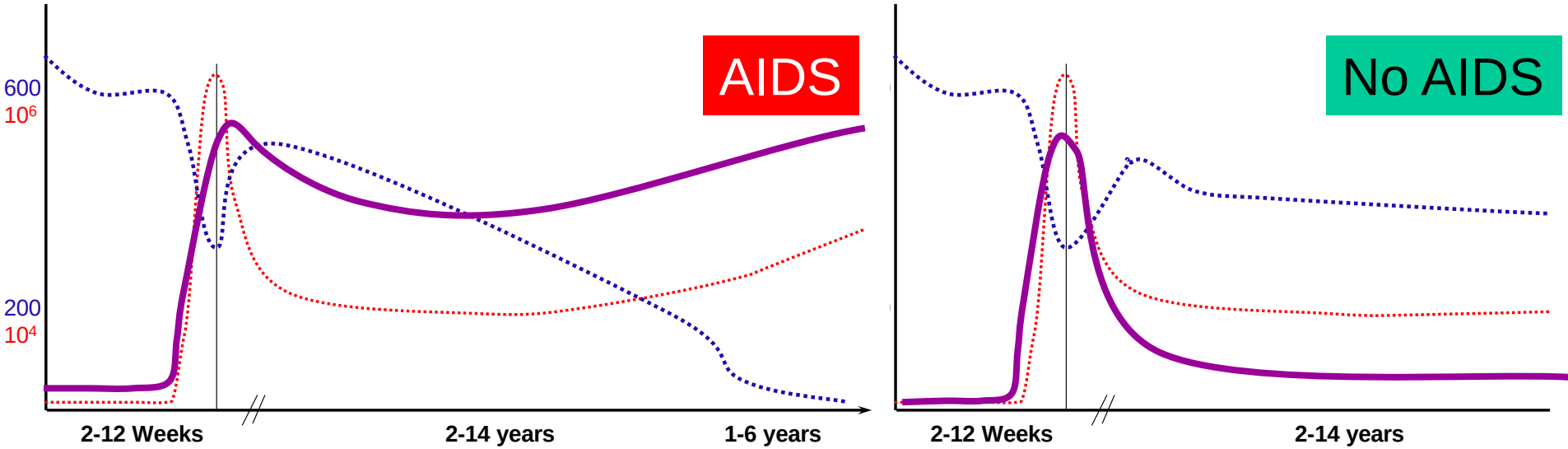
Bacterial translocation

Immune activation

Pathogenic vs non-pathogenic HIV/SIV disease

Pathogenic: (most) humans, macaques

Non-pathogenic: Sooty mangabeys



Plasma HIV RNA (cp/ml)

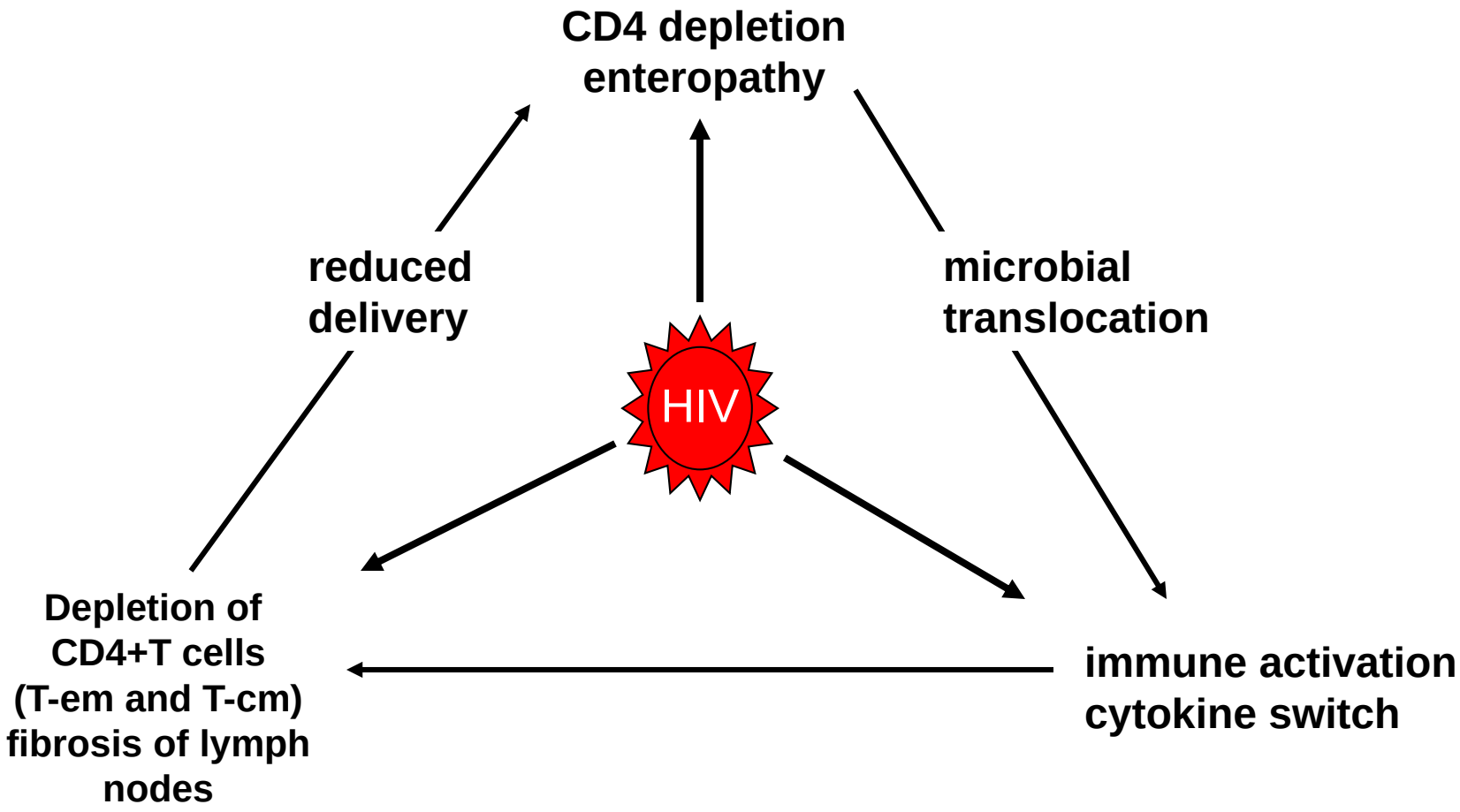
CD4 -cells (/µl)

Immune activation

- increased proliferation and activation of T cells
- increased susceptibility to apotpsis
- high levels of proinflammatory cytokines and chemokines
- high levels of interferon-stimulated genes

Rotger et al, Journal of Clinical Investigation, 2012

Immune activation and HIV



Adapted from
Douek et al
Annu Rev Med 2009

Mechanisms of CD4$^+$ T cell depletion: not only the virus!

Destruction of CD4$^+$ T cells

Direct destruction of infected cells (<1%!!)

- Virus (envelope, Vpr) mediated apoptosis
- Disruption of cell membranes

Indirect induction of death in uninfected cells

- Cytolysis by HIV-specific cytolytic T cells/NK cells
- Triggering of apoptosis upon **immune activation**
- Apoptosis following interaction with antigen-presenting cell

Impaired CD4+ T-cell production

Direct effects of virus

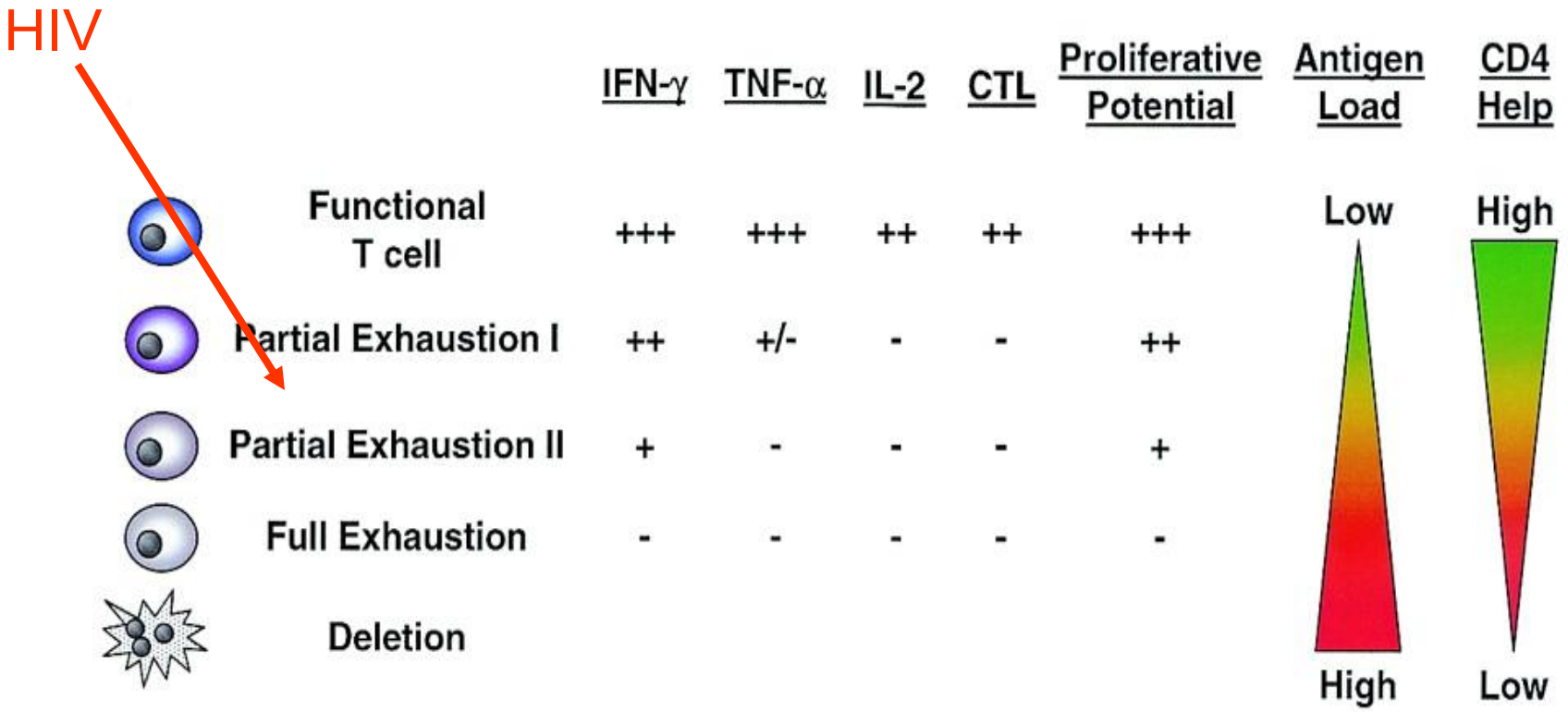
- Infection-mediated death of progenitor cells
- Destruction of stromal network for haematopoiesis

Indirect effects

- Cytokine dysfunction
- Opportunistic infections of bone marrow
- Infiltrating malignancies
- Myelotoxic drugs

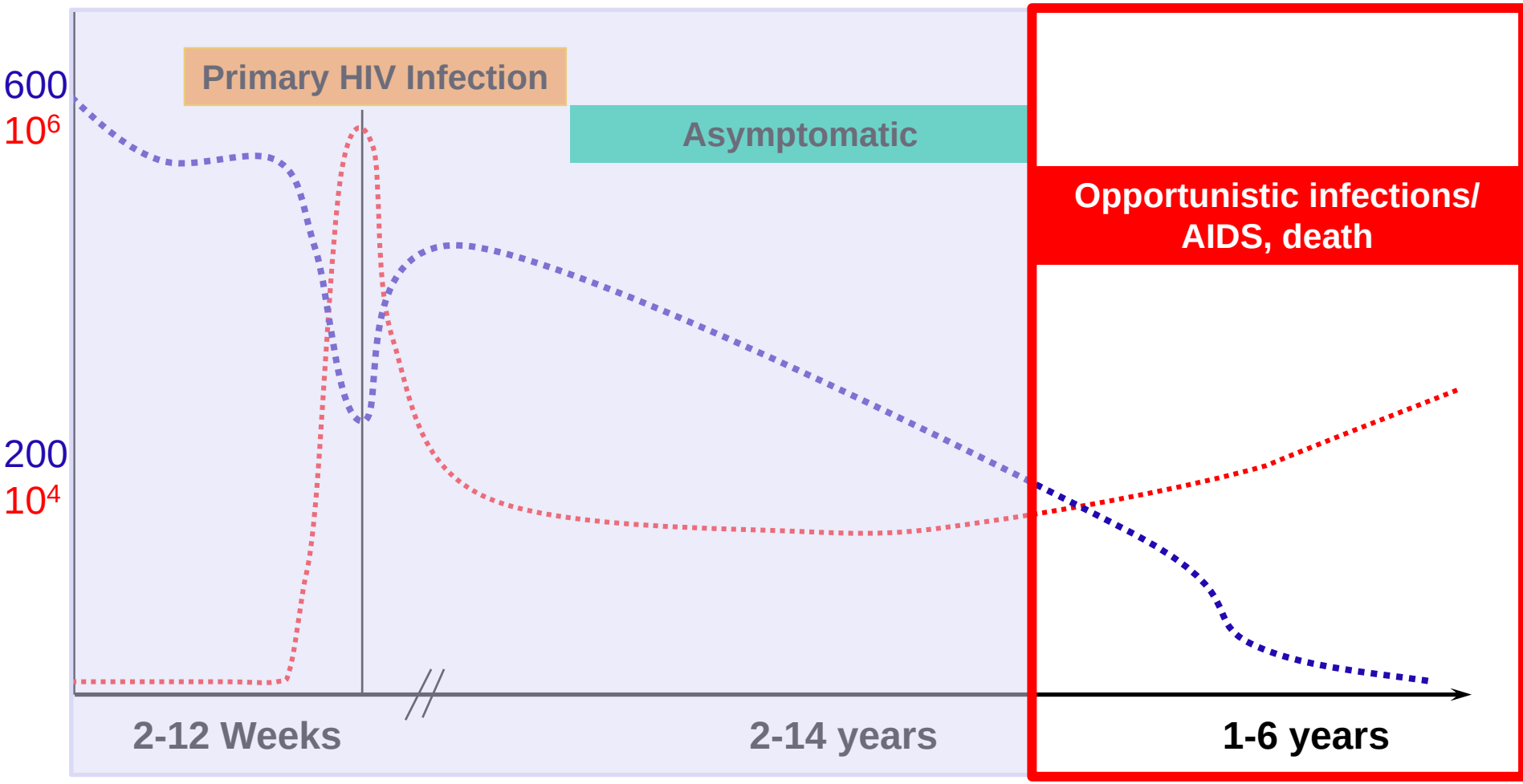
Adapted from McCune, Nature 2001

CD8-T cell exhaustion



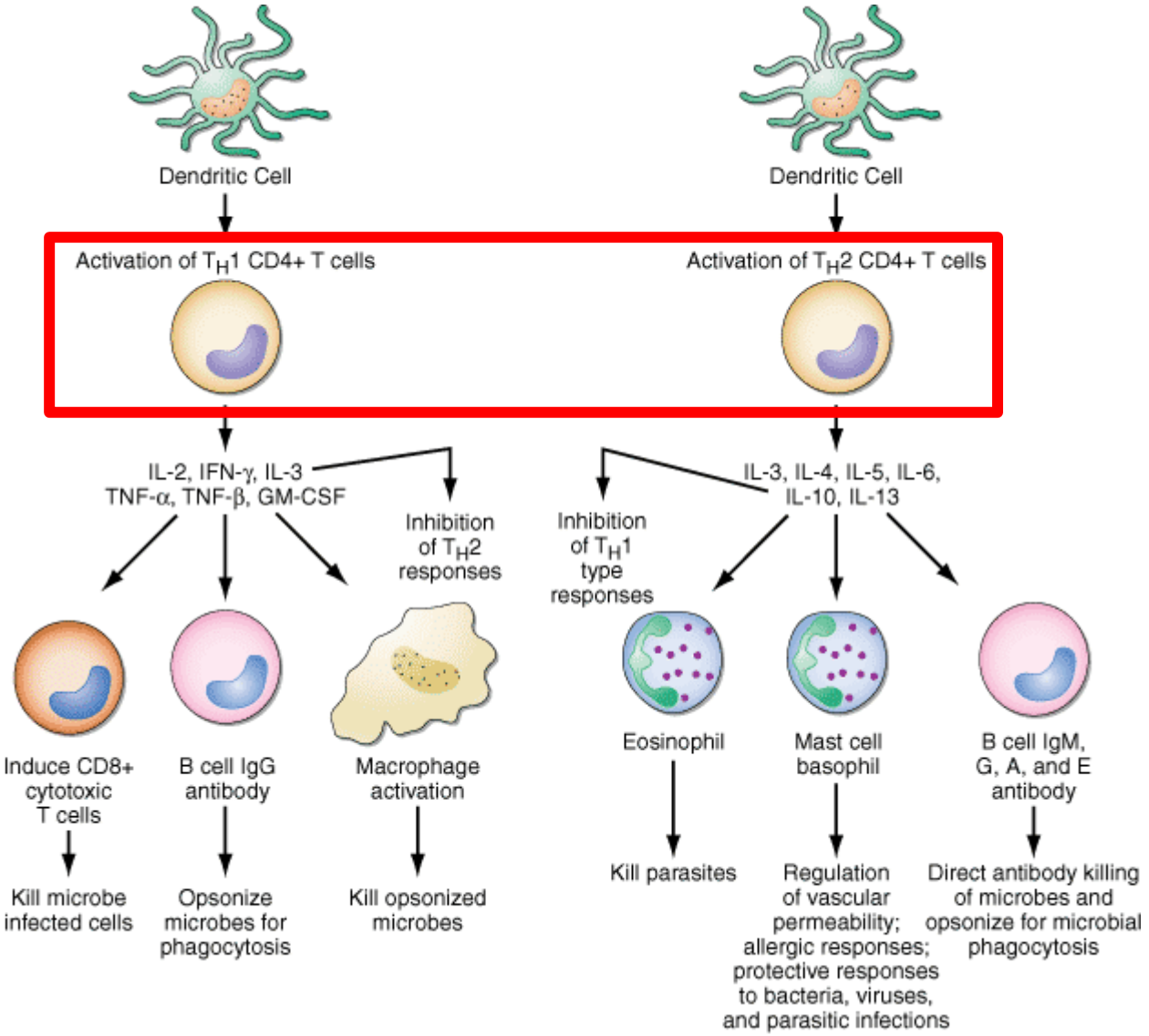
Adapted from Freeman et al, J Exp Med 2006

Consequences of HIV-induced immunodeficiency



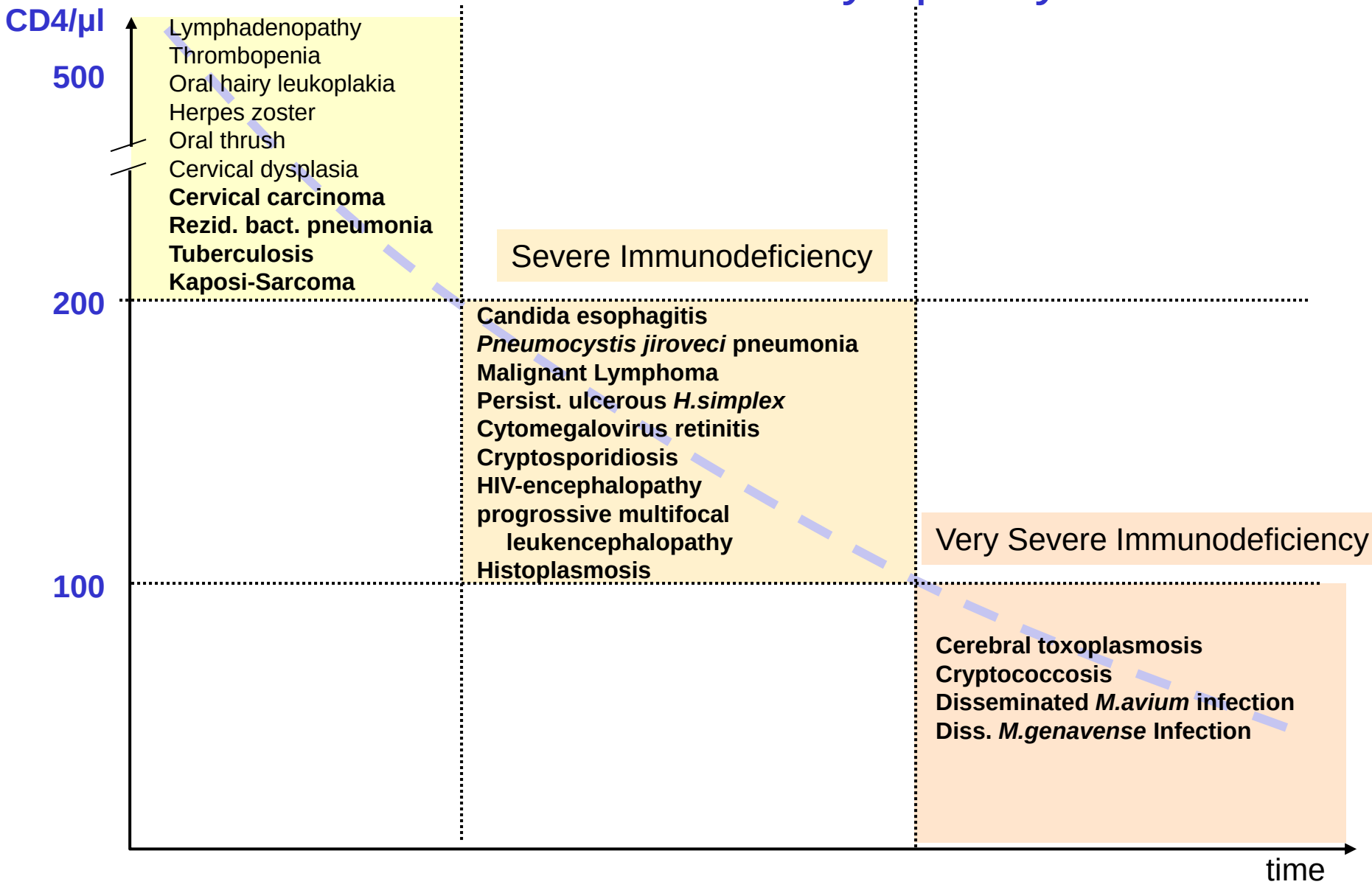
Plasma HIV RNA (cp/ml)
CD4+ T cell count (/µl)

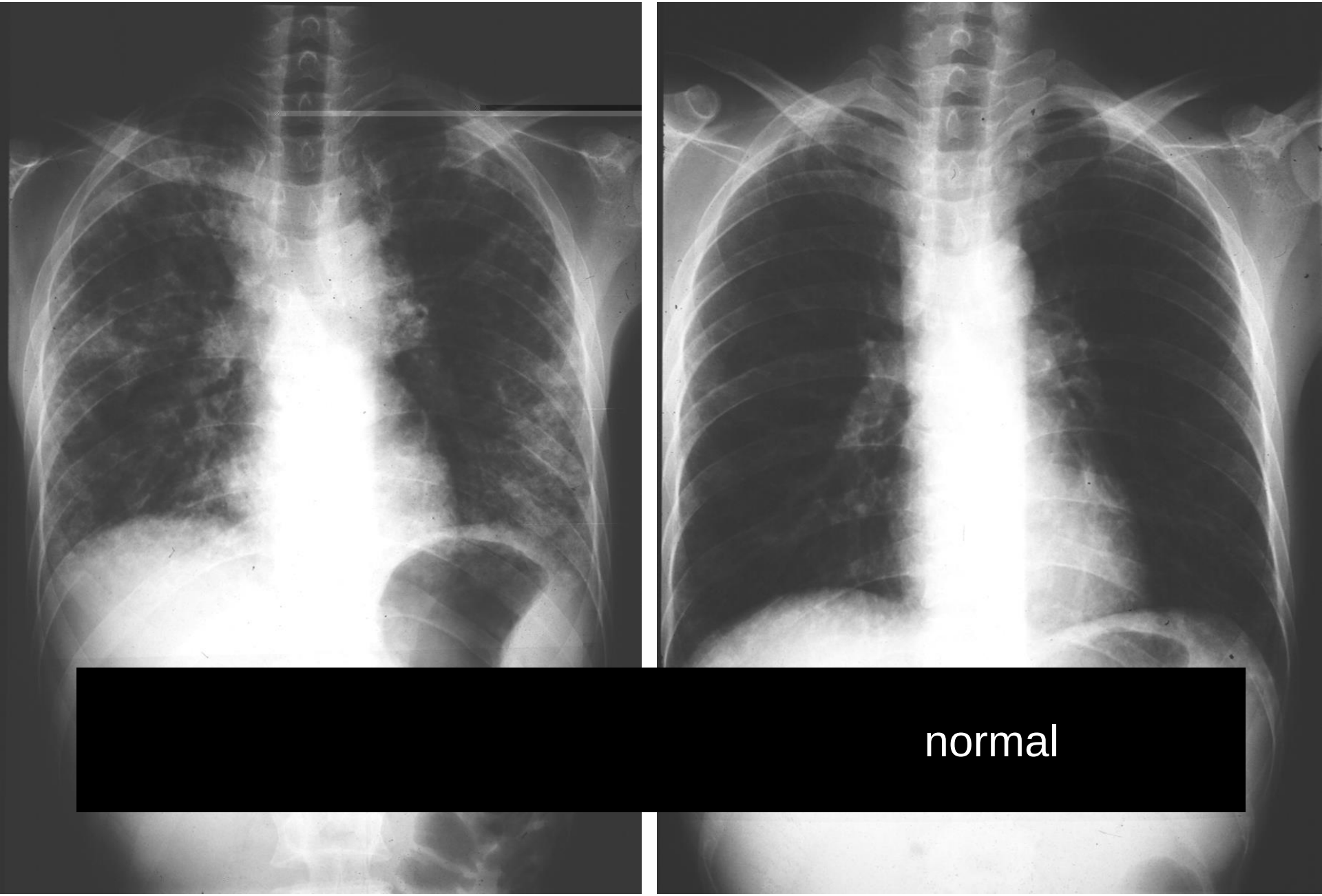
CD4 T + cells: At the center of immune defense

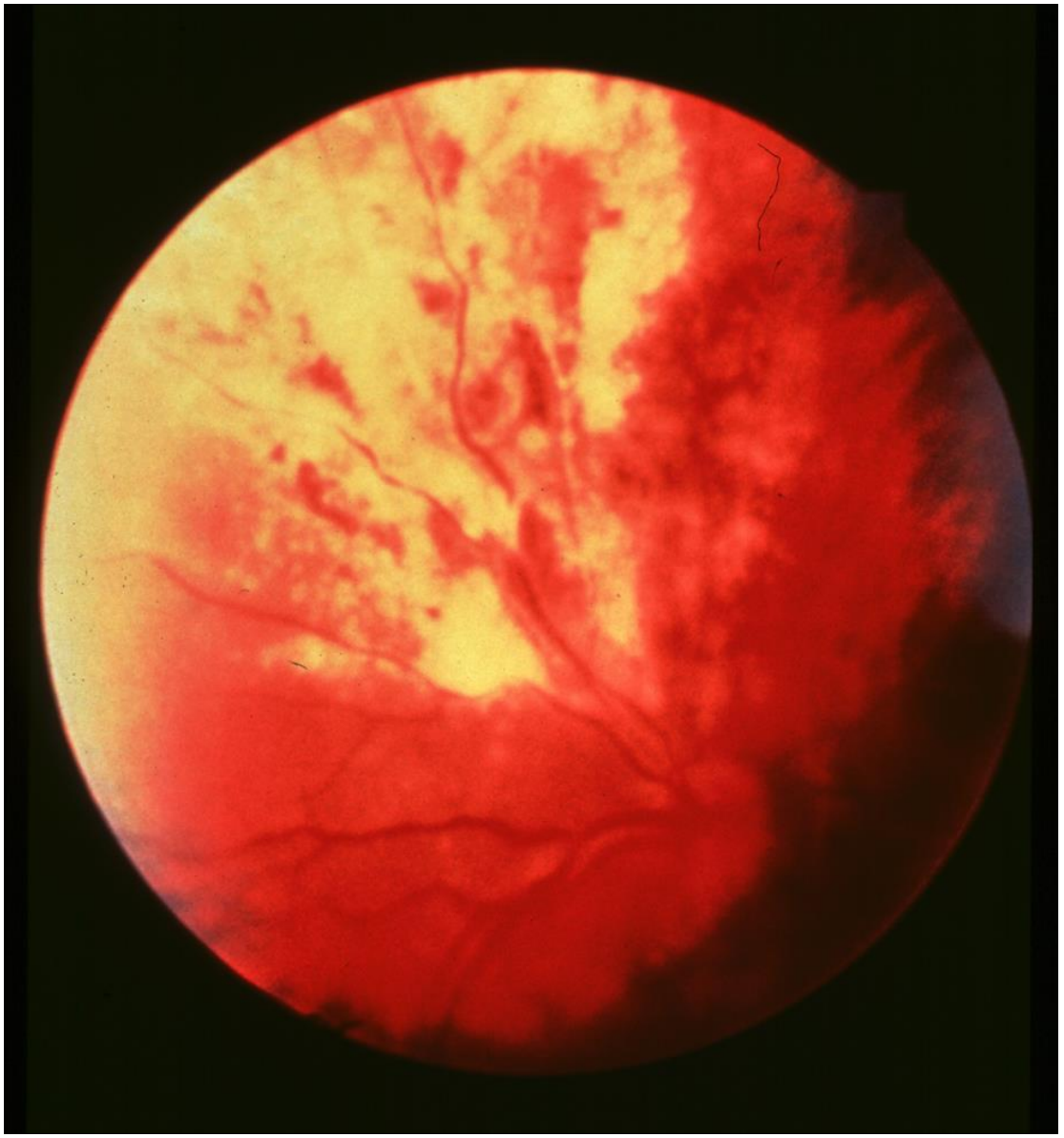


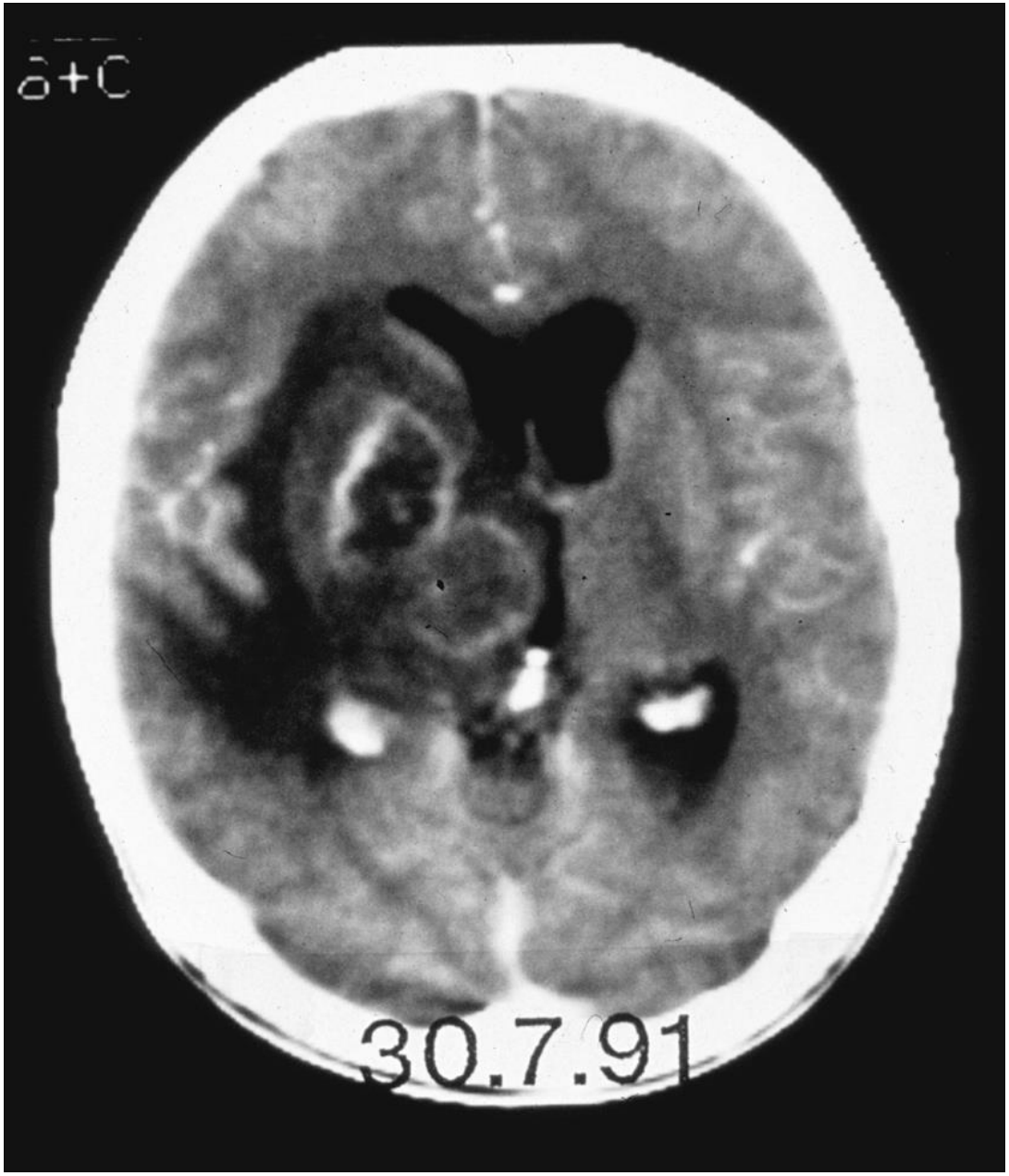
Fauci et al, Harrison's Principles of Internal Medicine, 17th edition

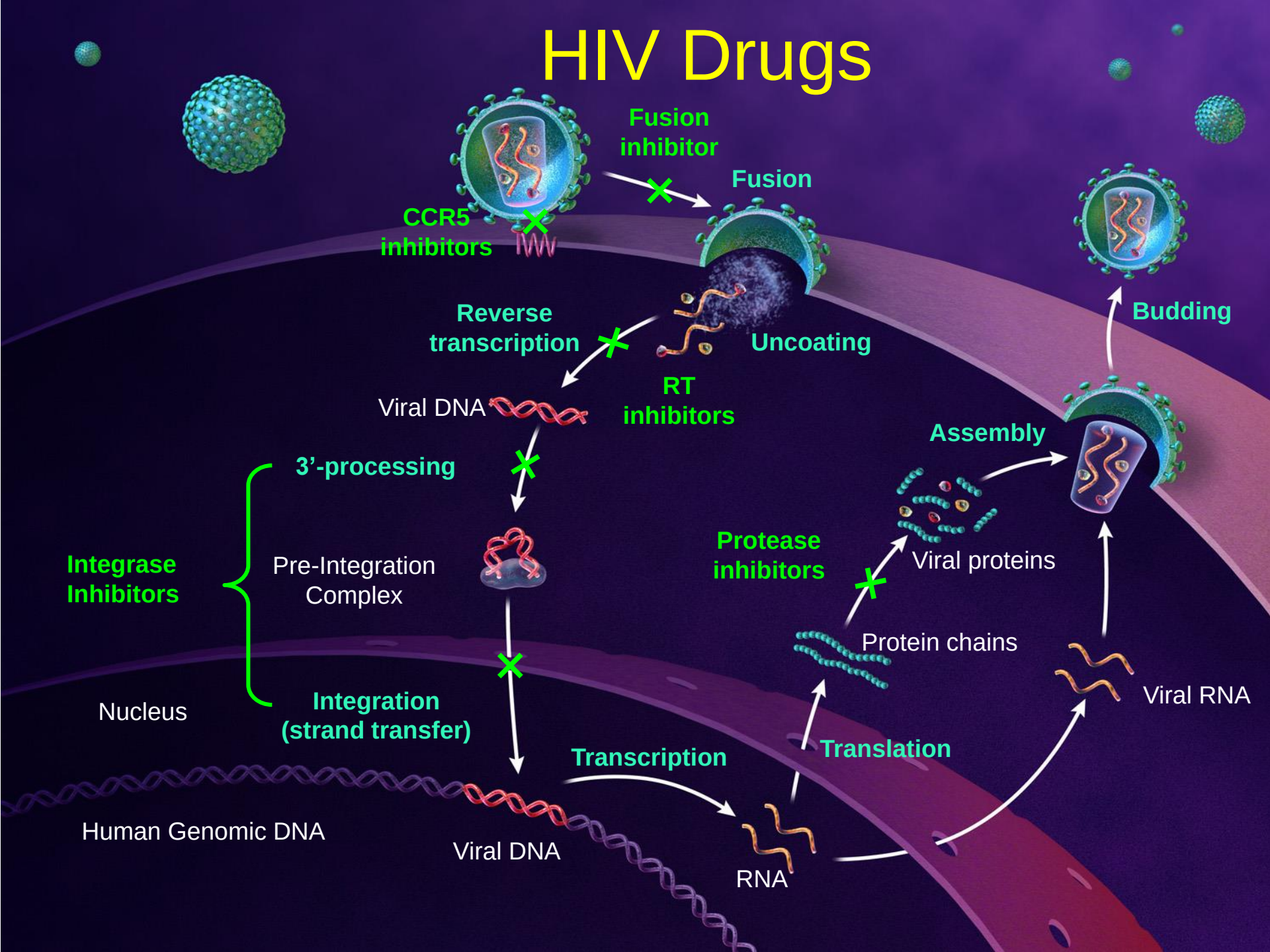
Opportunistic Diseases and CD4 lymphocyte count



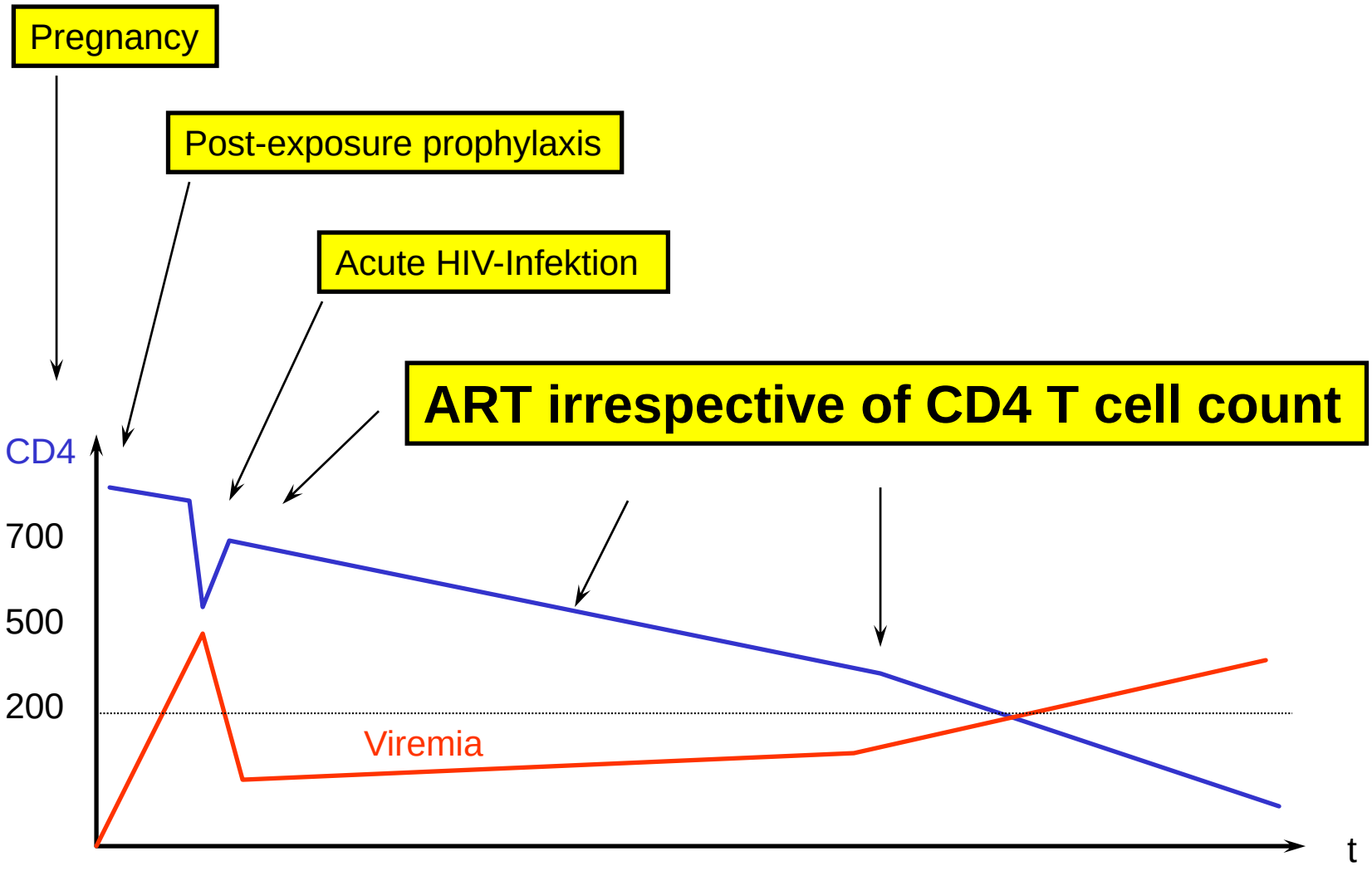

normal



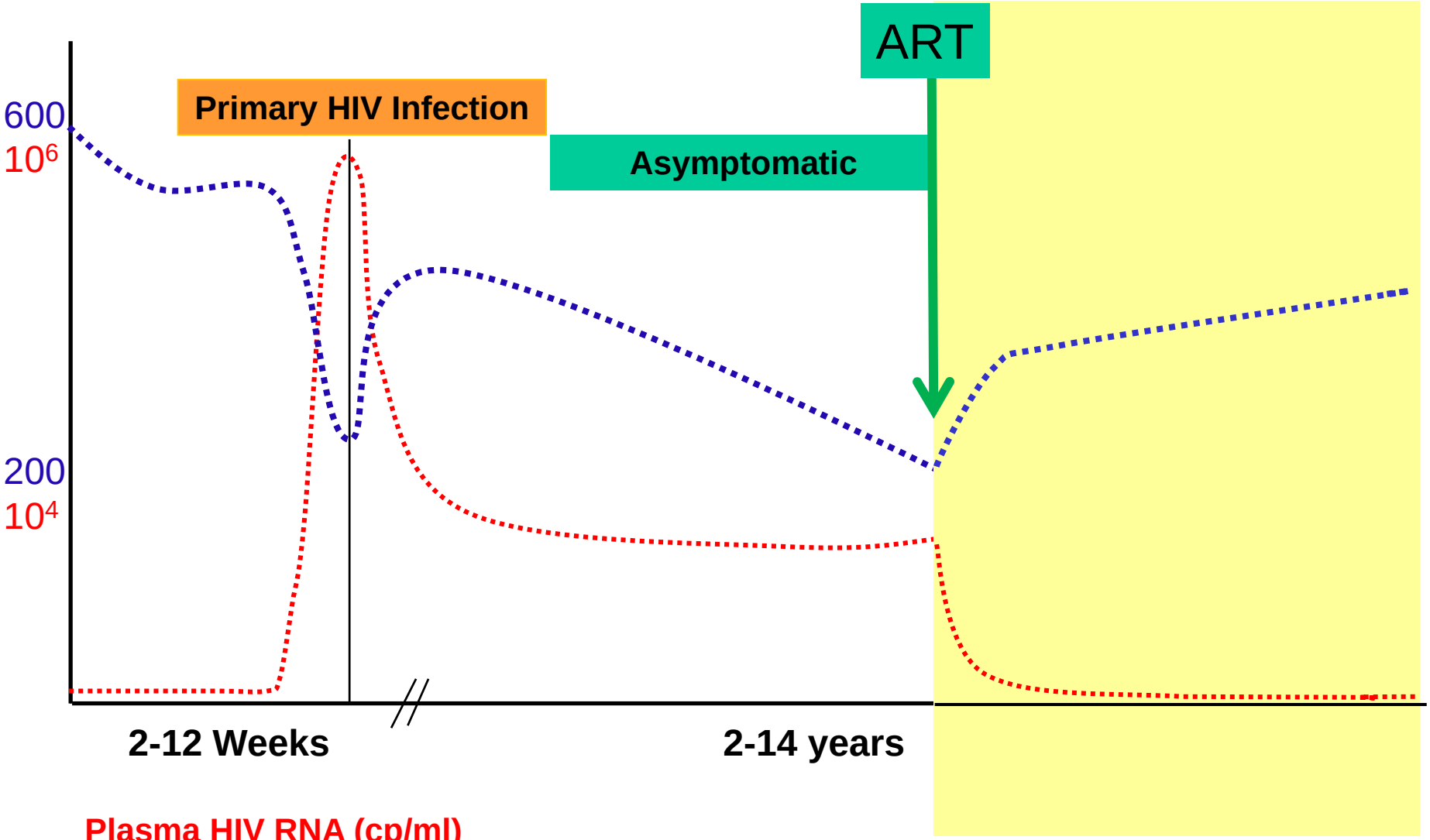

a+c
30.7.91


HIV Drugs
Fusion inhibitor
Fusion
CCR5 inhibitors
Budding
Reverse transcription
Uncoating
RT inhibitors
Viral DNA
Assembly
3'-processing
Integrase Inhibitors
Pre-Integration Complex
Protease inhibitors
Viral proteins
Protein chains
Nucleus
Integration (strand transfer)
Transcription
Translation
Viral RNA
Human Genomic DNA
Viral DNA
RNA

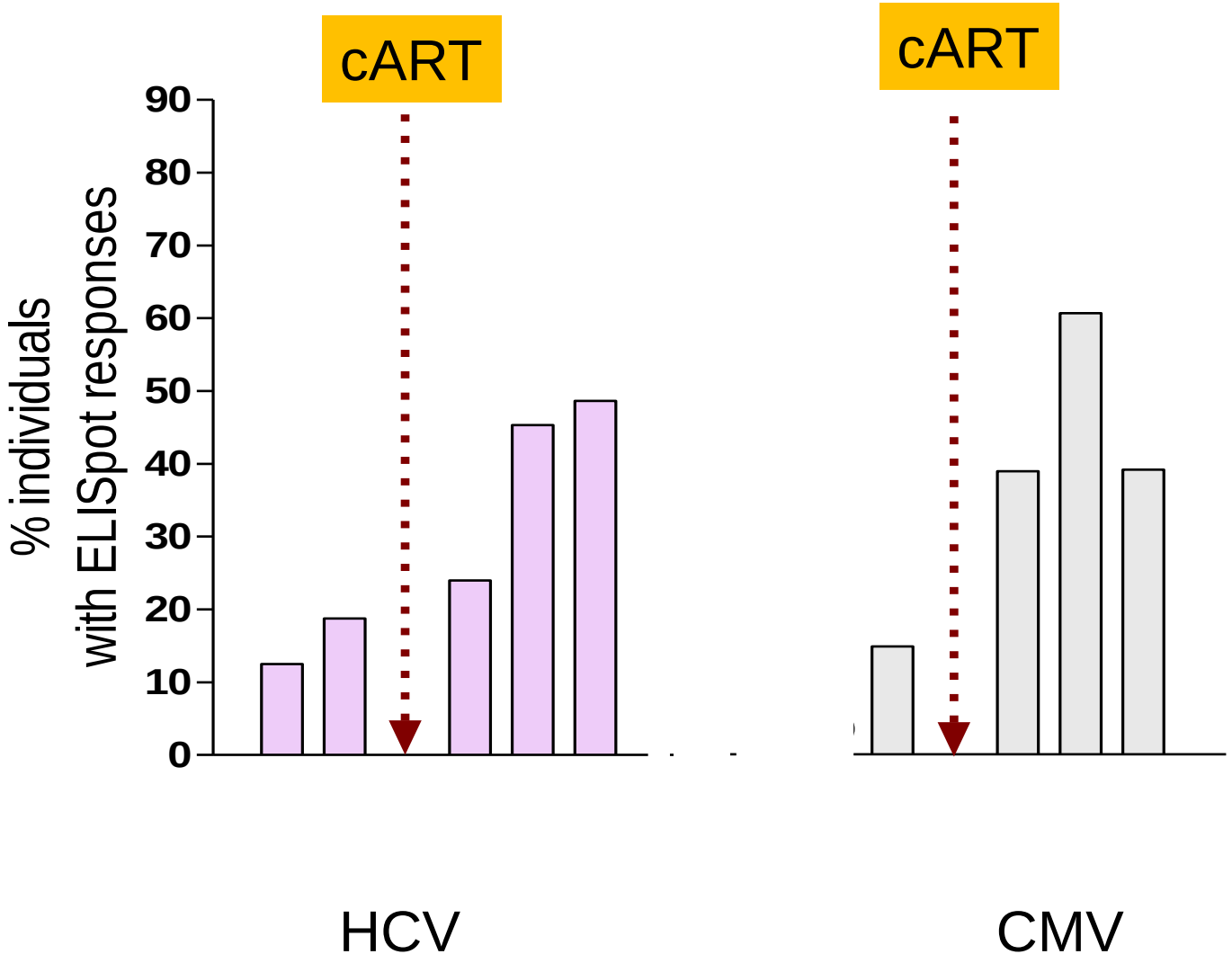
Indications for ART 2019



Effect of antiretroviral therapy

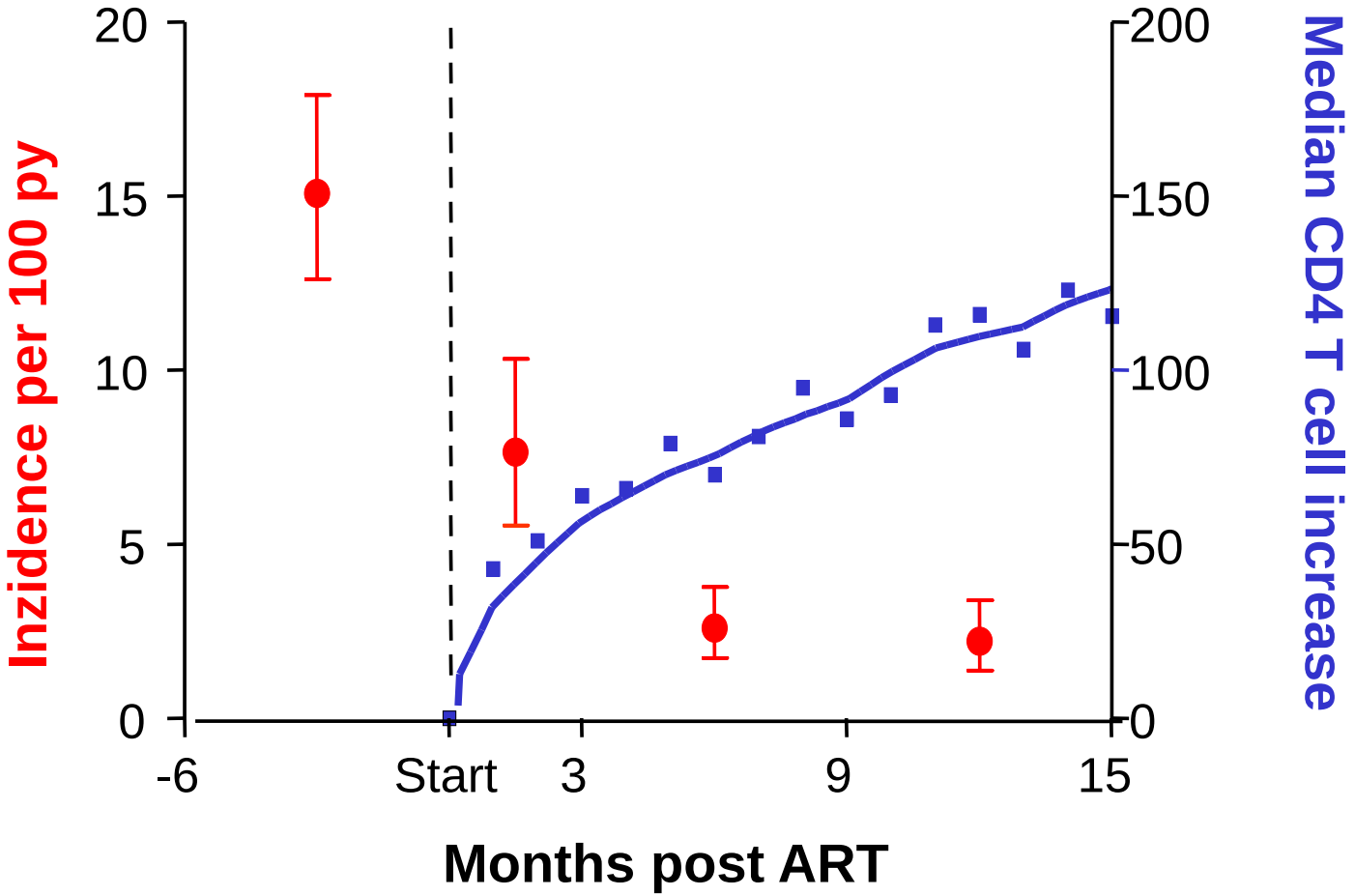


Successful cART is associated with increases in CD4+ T-cell responses to HCV and CMV



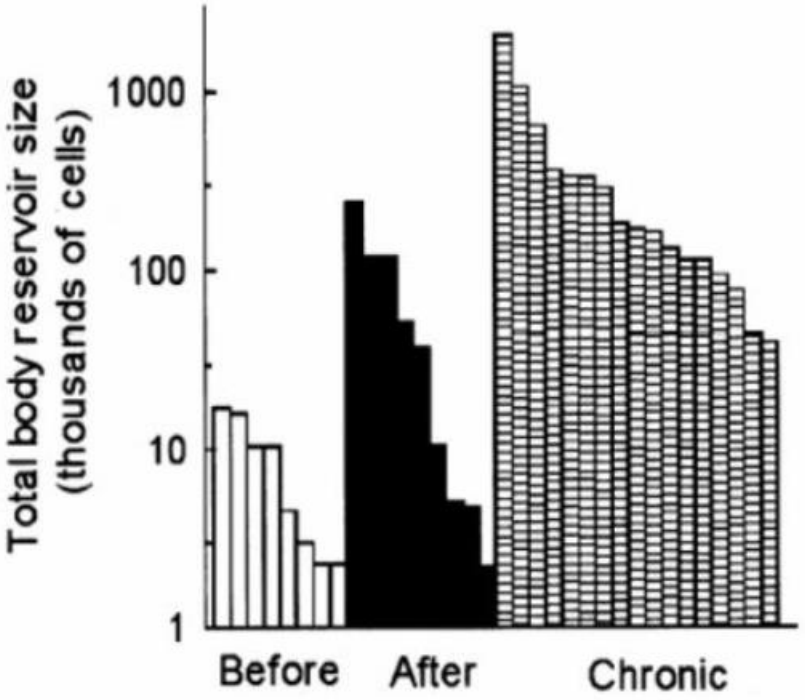
Rohrbach et al, GUT 2011

New opportunistic infections

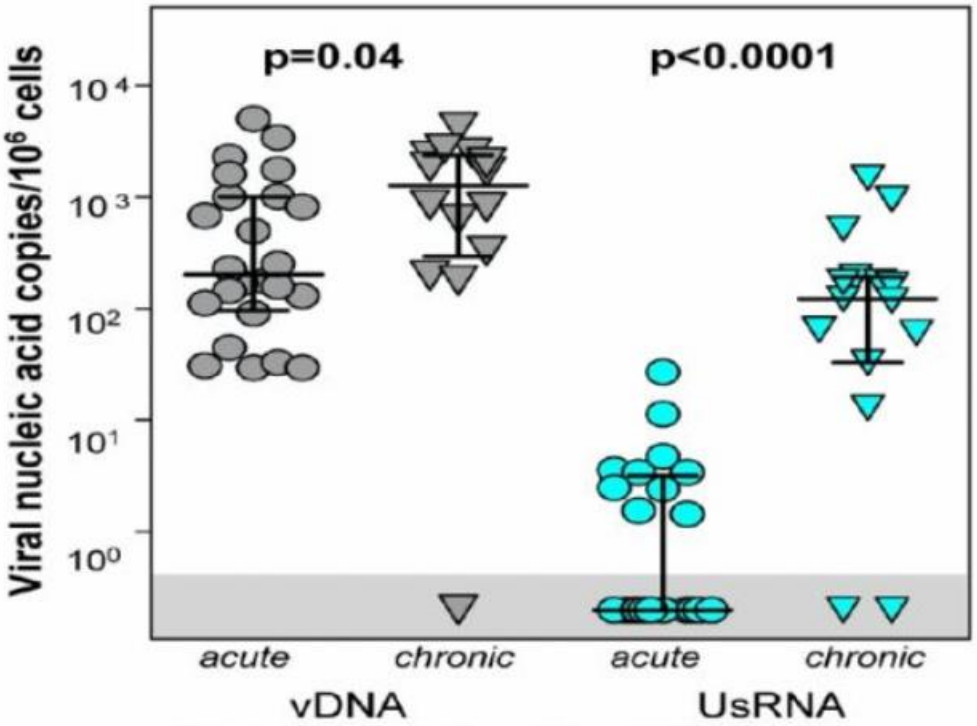


SWISS HIV COHORT STUDY

Early ART reduces viral reservoir



Strain et al, JID, 2005

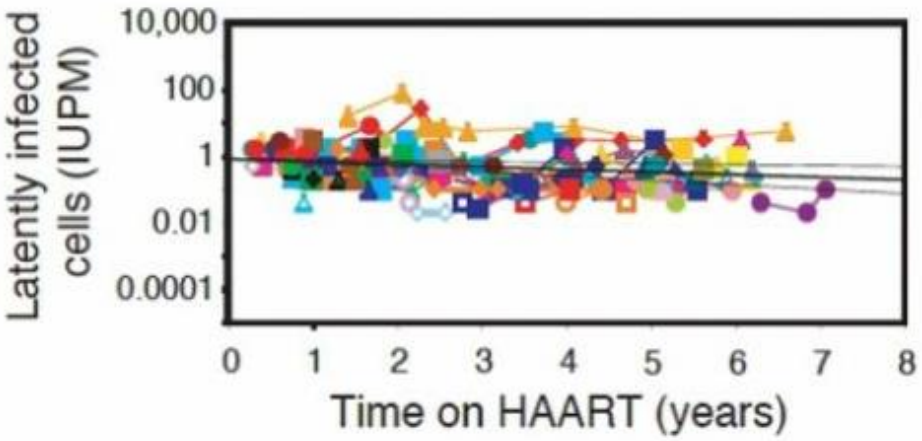


Schmid et al, Plos One, 2010

Archin, PNAS, 2012, Josefsson, PNAS, 2013, Williams, Elife, 2014

…but cure is still not (yet) achievable (with very few exceptions)

Very slow decay of the latent reservoir



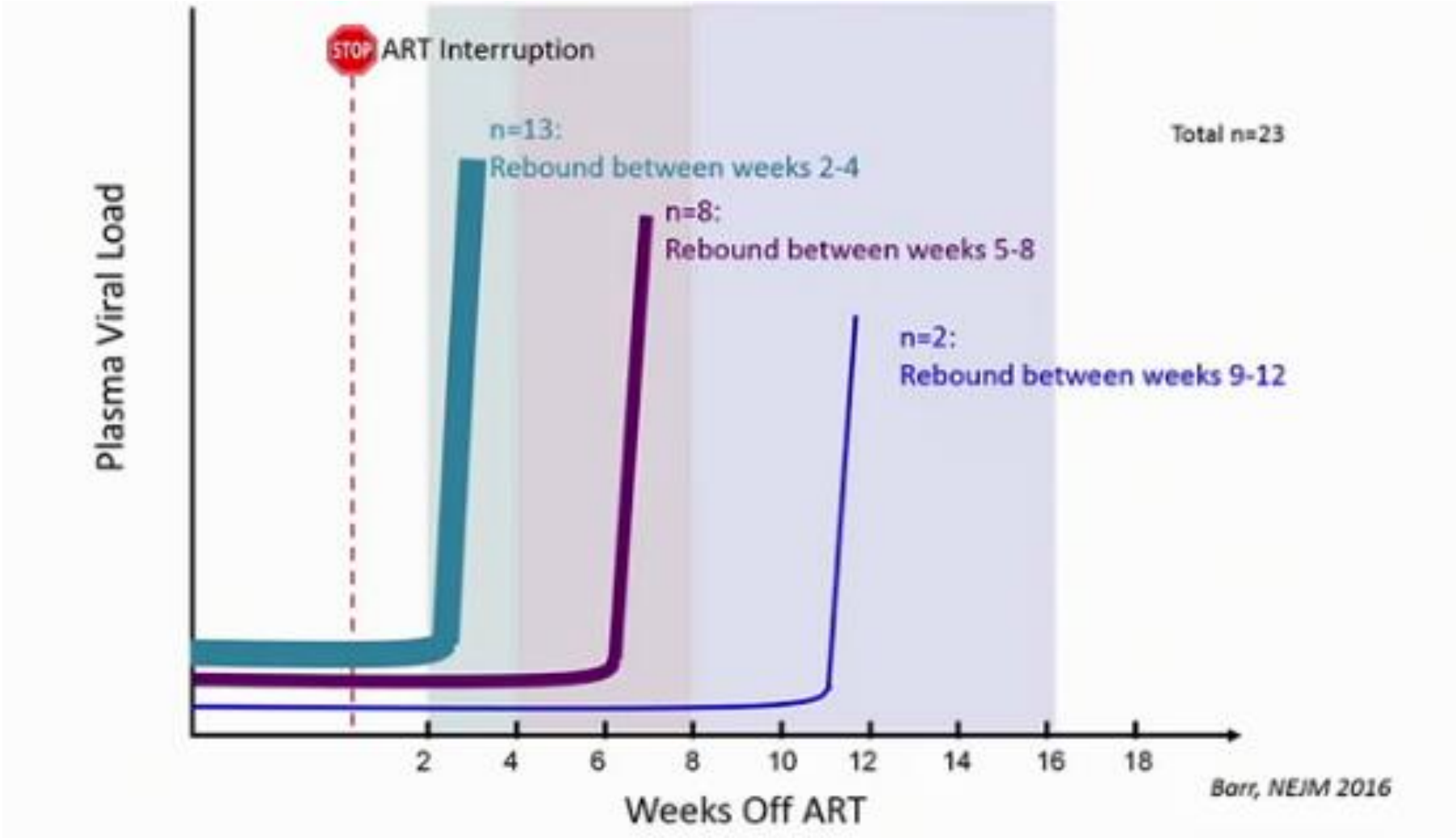
The viral outgrowth assay measures
$t_{1/2}$ = 44 months

- It would take 60 years to eradicate a low reservoir estimate of 10^5cells!

Siliciano et al, Nature Medicine, 2003

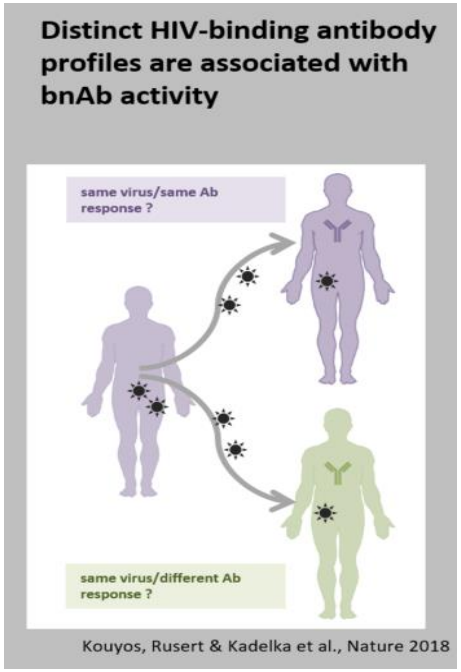
H. Günthard, CROI 2018

Broadly neutralizing antibodies did not prevent viral rebound after ART interruption



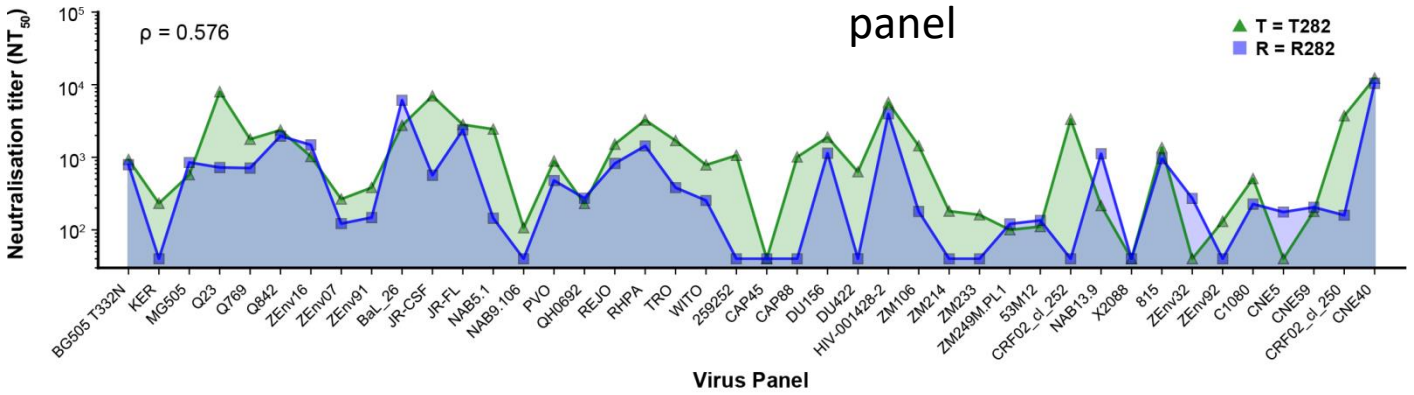
Ananworanich, CROI 2017

The search for the best HIV antibodies



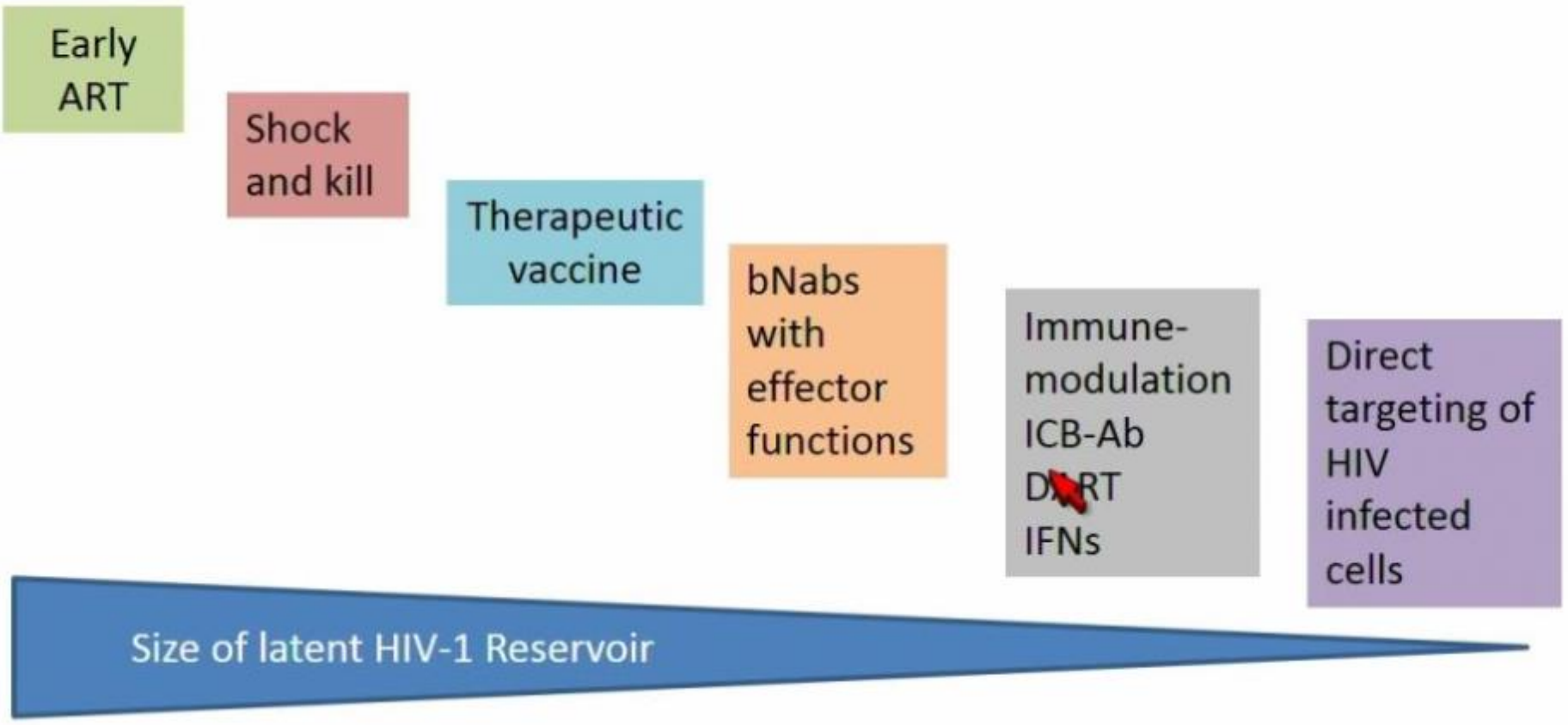
Induction of almost identical bnAbs in two patients with fully different genetic background

40 virus panel



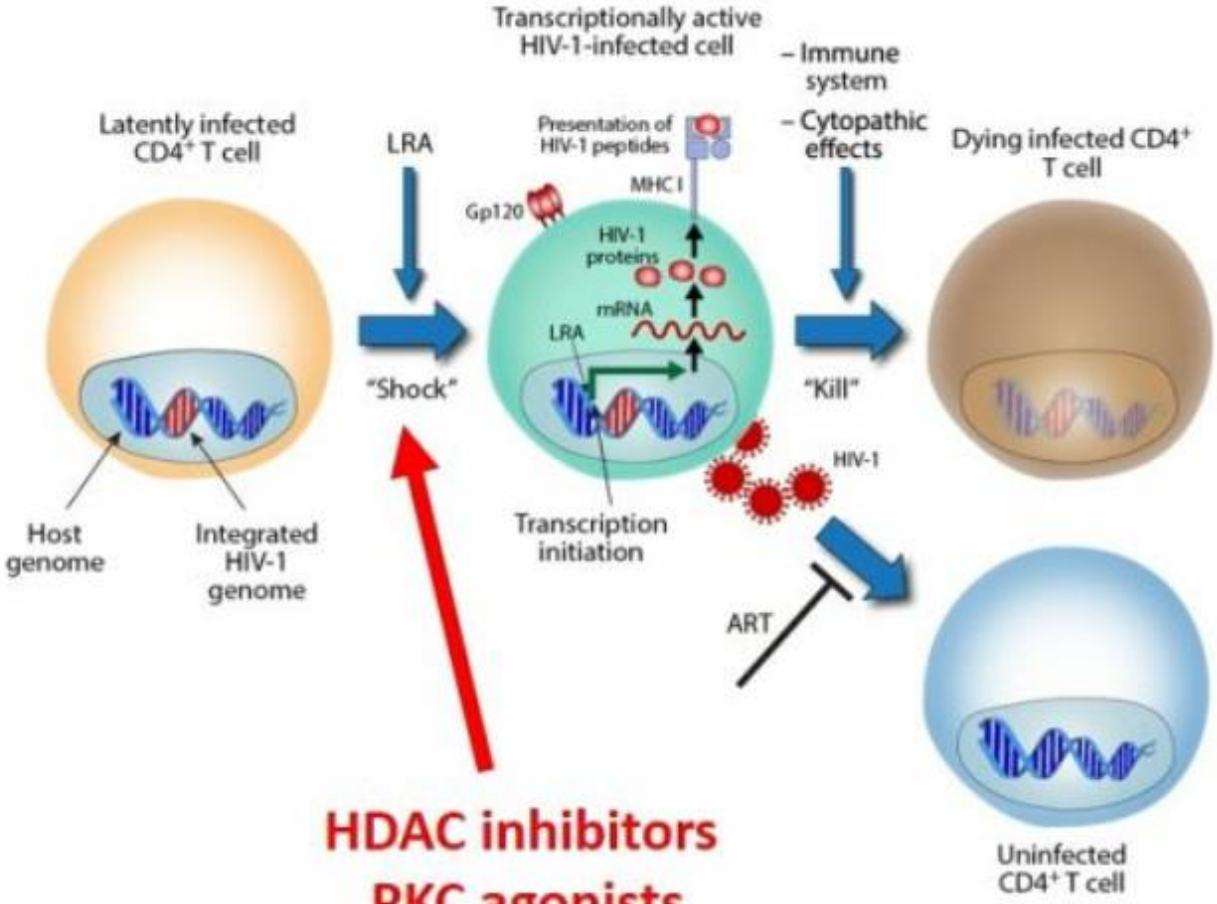
Kouyos, Rusert & Kadelka et al., Nature 2018

Strategies for reducing the latent reservoir



H. Günthard, CROI 2018

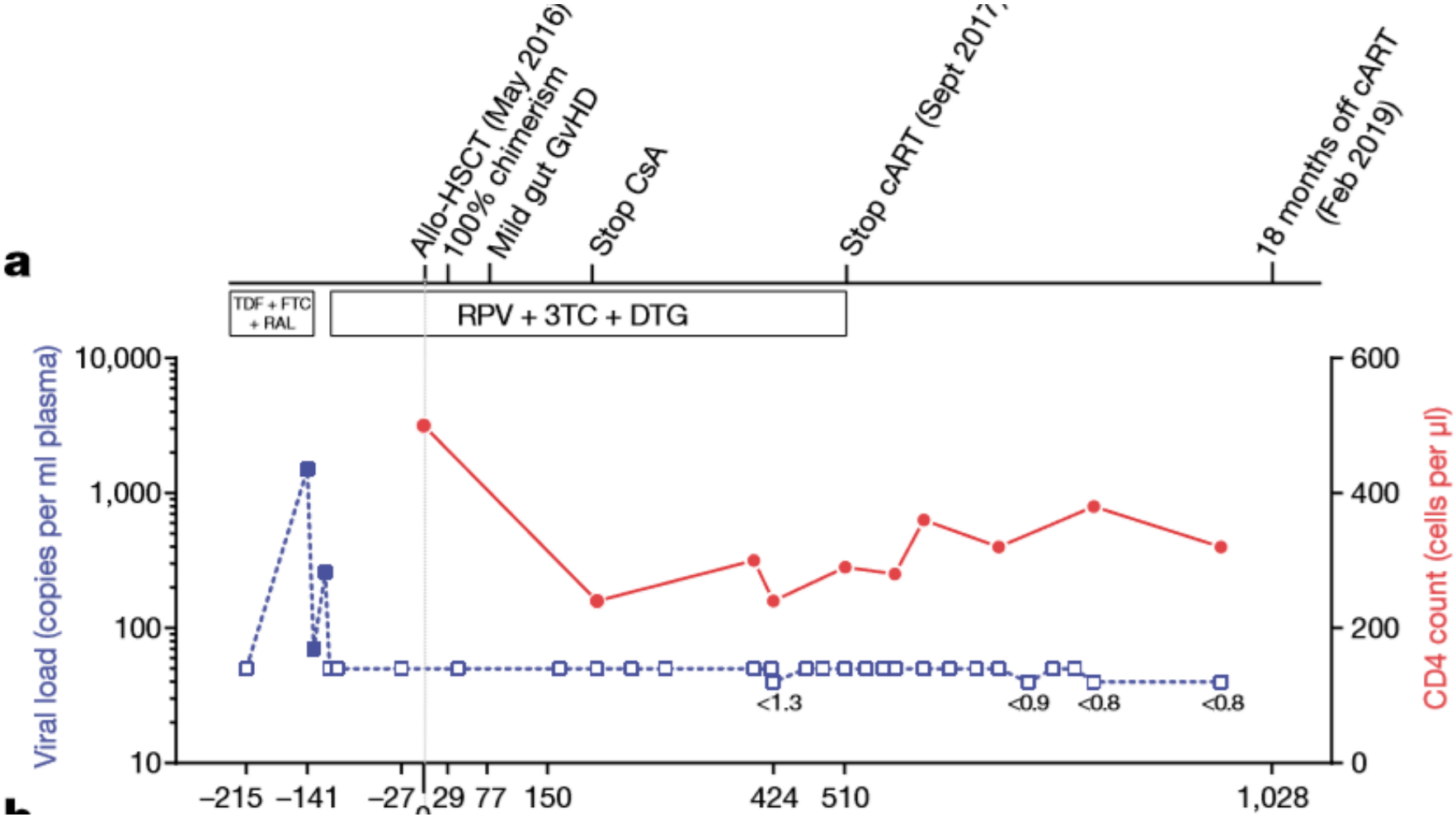
Shock and kill strategy



Perreau et al, Trends Mol Med, 2017

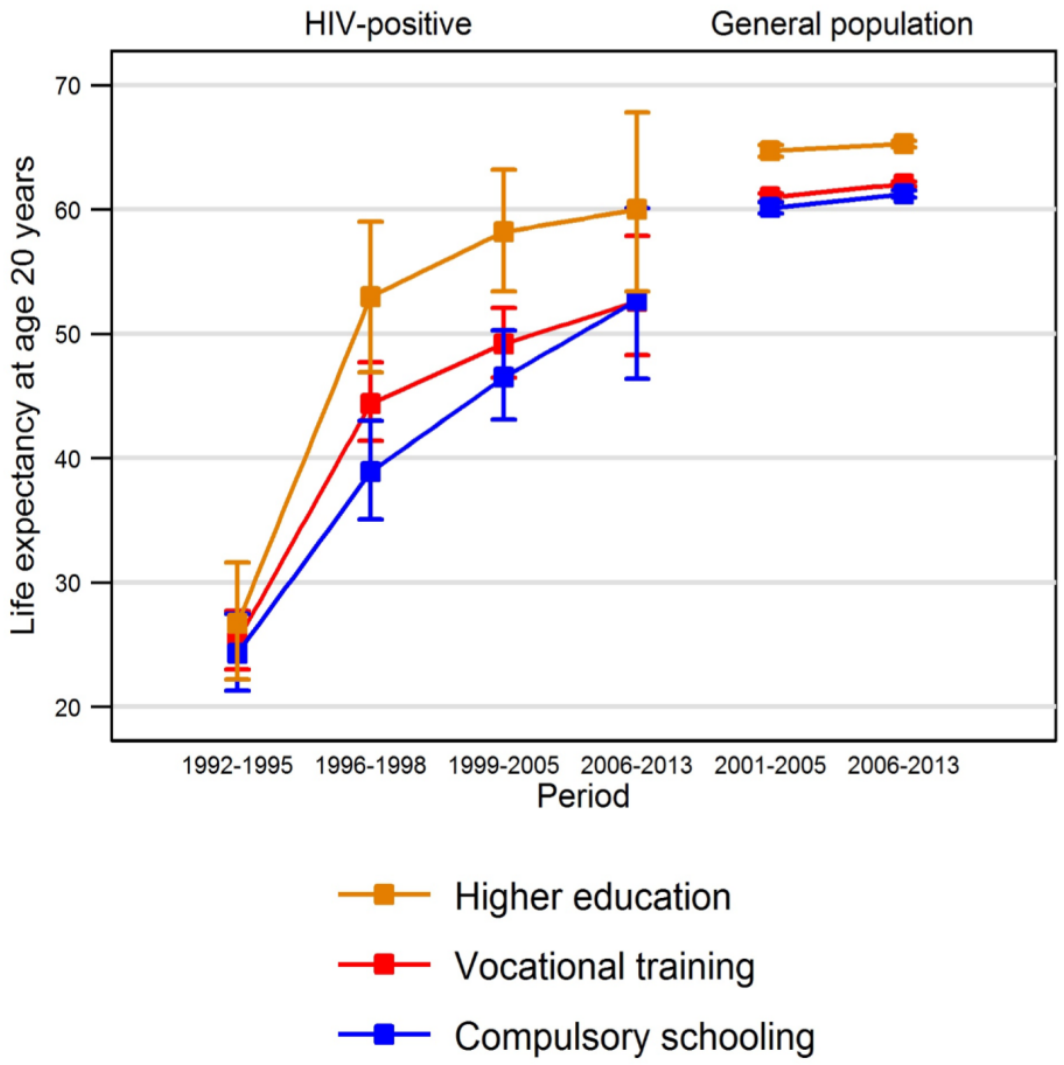
HIV remission (cure?): A very rare event

CCR5d32hom!



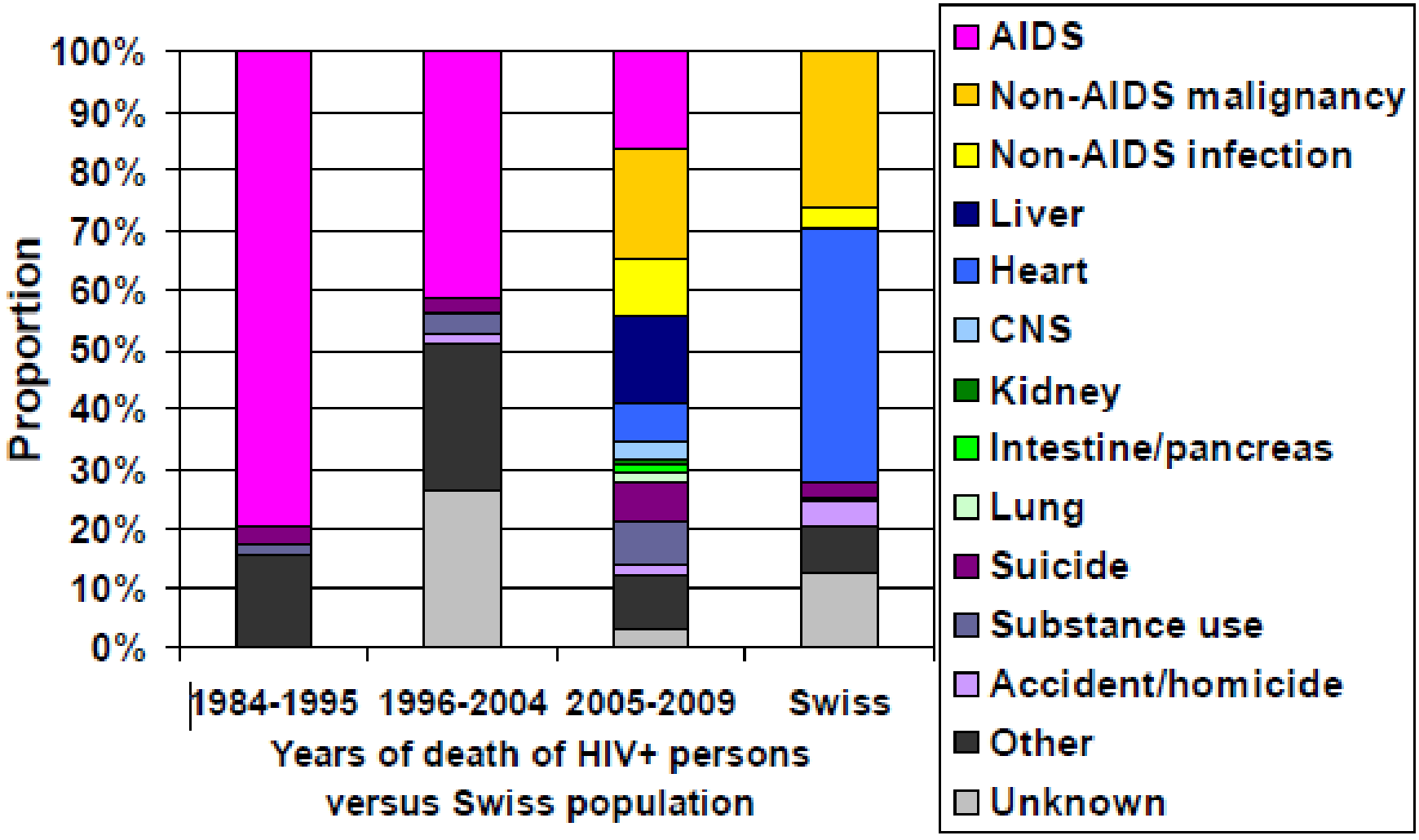
Gupta et al, NATURE 2019

Life expectance in HIV-positive individuals and in the general population in Switzerland



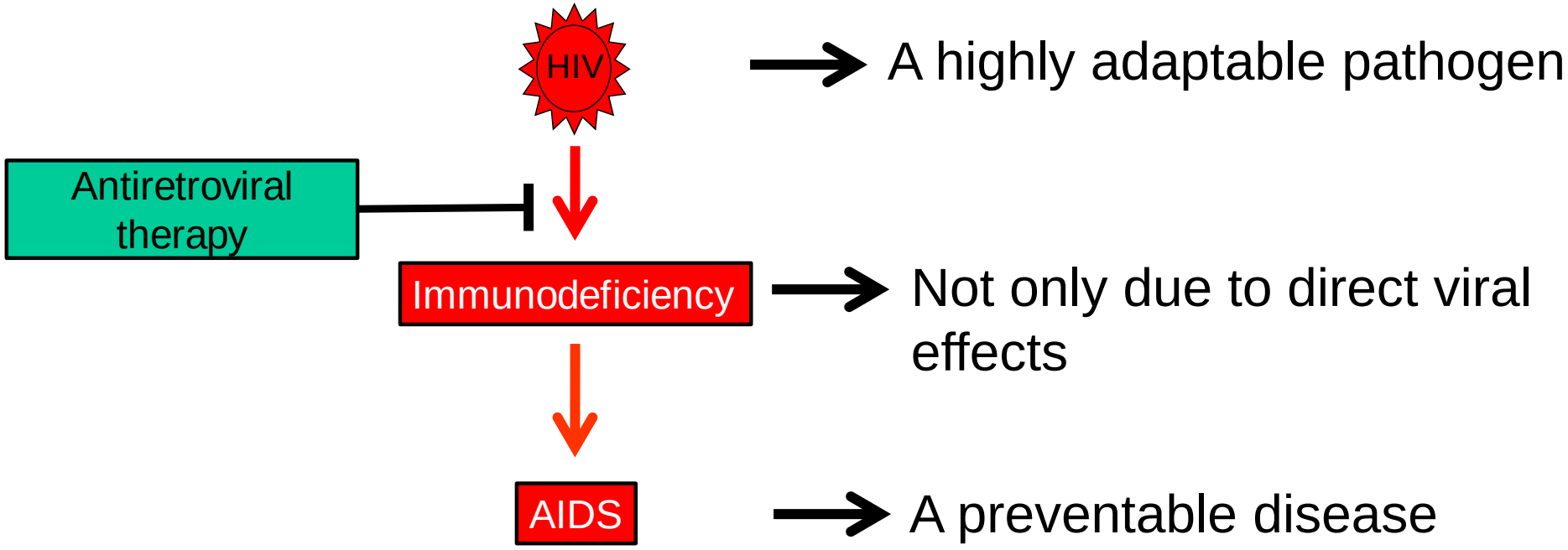
A. Gueler et al, and M. Egger for the Swiss HIV Cohort Study and Swiss National Cohort

Changing causes of death in the SHCS



Ruppik et al, CROI 2011

Summary


HIV
A highly adaptable pathogen
Antiretroviral therapy
Immunodeficiency
Not only due to direct viral effects
AIDS
A preventable disease