Review on Molecular Virology and Pathogenesis of HIV

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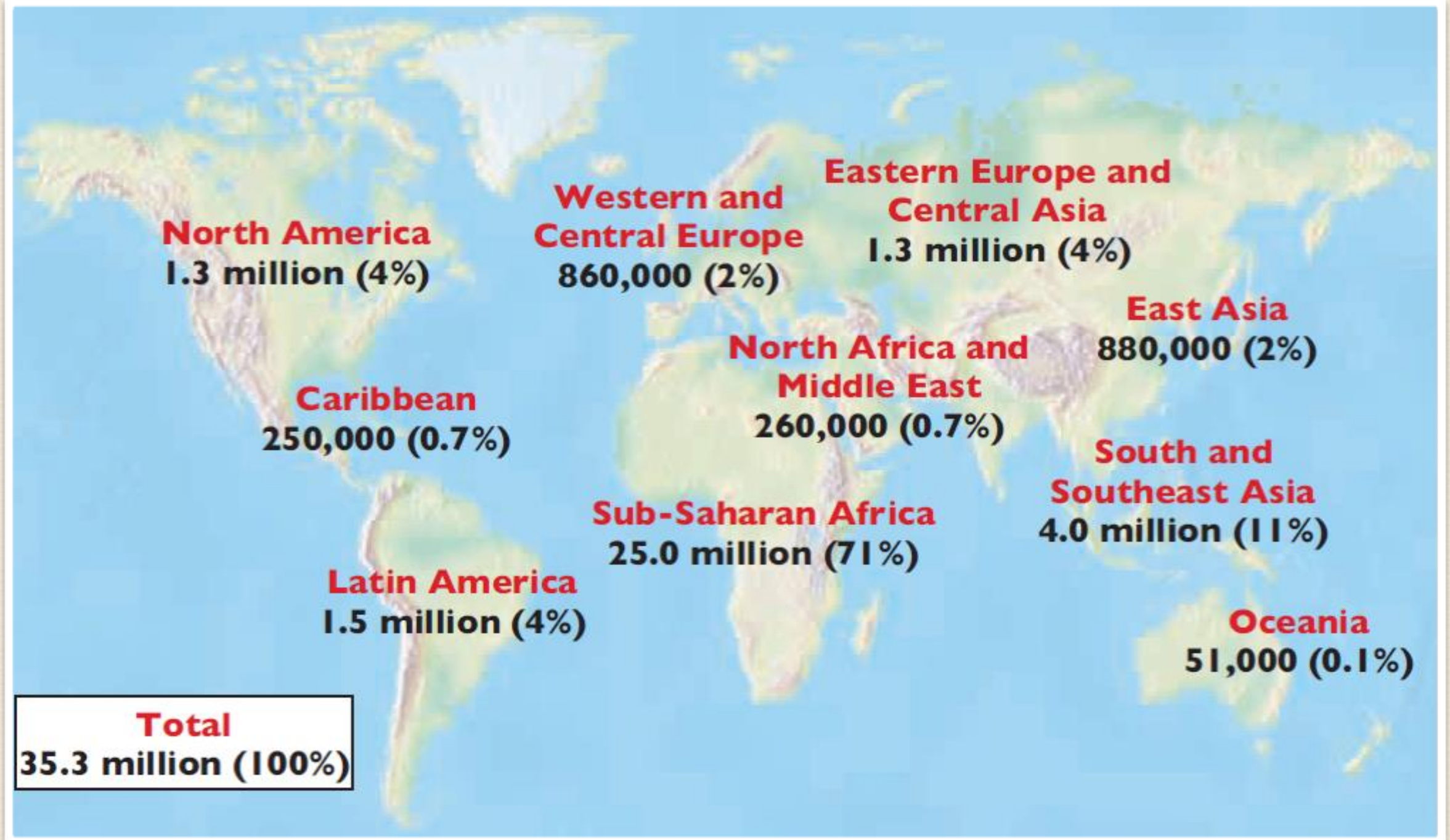
Montagnier & Gallo


North America
1.3 million (4%)
Western and
Central Europe
860,000 (2%)
Eastern Europe and
Central Asia
1.3 million (4%)
East Asia
880,000 (2%)
North Africa and
Middle East
260,000 (0.7%)
Caribbean
250,000 (0.7%)
South and
Southeast Asia
4.0 million (11%)
Sub-Saharan Africa
25.0 million (71%)
Latin America
1.5 million (4%)
Oceania
51,000 (0.1%)
Total
35.3 million (100%)

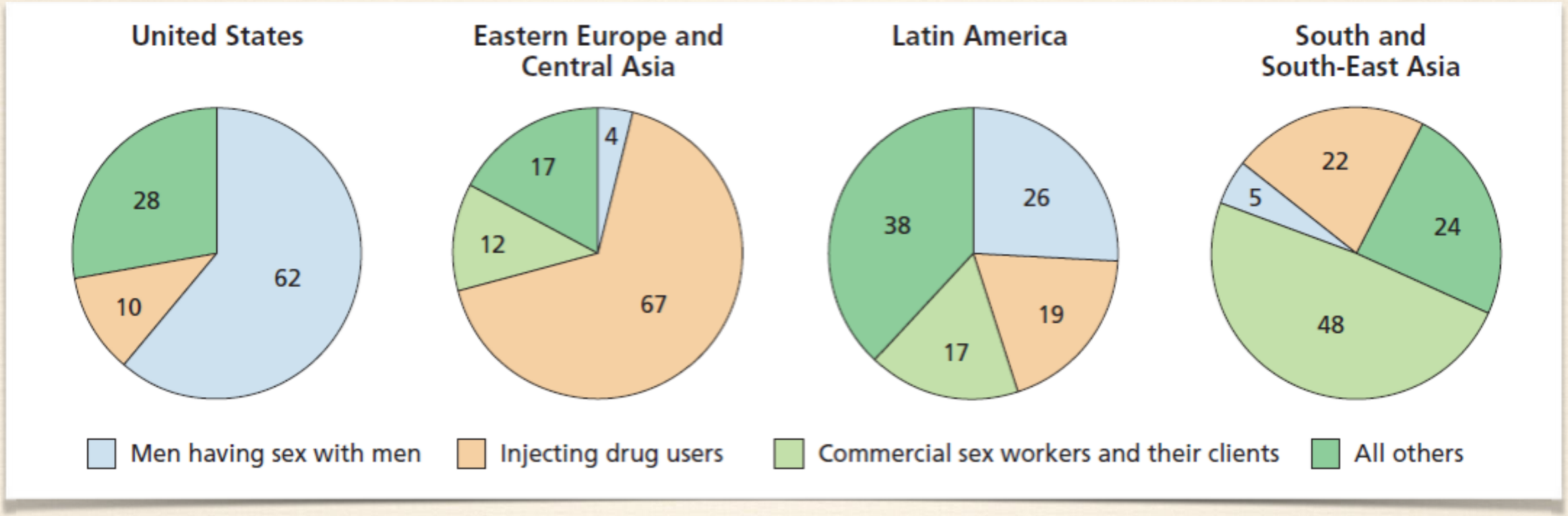

United States
62
10
28
Eastern Europe and Central Asia
4
67
12
17
Latin America
26
19
17
38
South and South-East Asia
5
48
24
22
Men having sex with men
Injecting drug users
Commercial sex workers and their clients
All others

Table 1 | **Risk of HIV acquisition from an HIV-infected source*,‡**

Exposure route	Infections per 10,000 contacts	95% CI
Parenteral exposure		
Blood transfusion	9,250	8,900–9,610
Injection drug use with sharing equipment	63	41–92
Needle stick injury	23	0–46
Sexual exposure without condom use		
Receptive anal sex	138	102–186
Insertive anal sex	11	4–28
Receptive vaginal sex	8	6–11
Insertive vaginal sex	4	1–14
Receptive oral sex	Low	0–4
Insertive oral sex	Low	0–4
Vertical transmission		
At the time of birth	2,260	1,700–2,900

Fluid	Virus isolation[b]	Estimated quantity of virus[c]
Cell-free fluid		
Cerebrospinal fluid	21/40	10–10,000
Ear secretions	1/8	5–10
Feces	0/2	None detected
Milk	1/5	<1
Plasma	33/33	1–5,000[d]
Saliva	3/55	<1
Semen	5/15	10–50
Sweat	0/2	None detected
Tears	2/5	<1
Urine	1/5	<1
Vaginal-cervical	5/16	<1
Infected cells		
Bronchial fluid	3/24	Not determined
PBMC	89/92	0.001–1%[d]
Saliva	4/11	<0.01%
Semen	11/28	0.01–5%
Vaginal-cervical fluid	7/16	Not determined

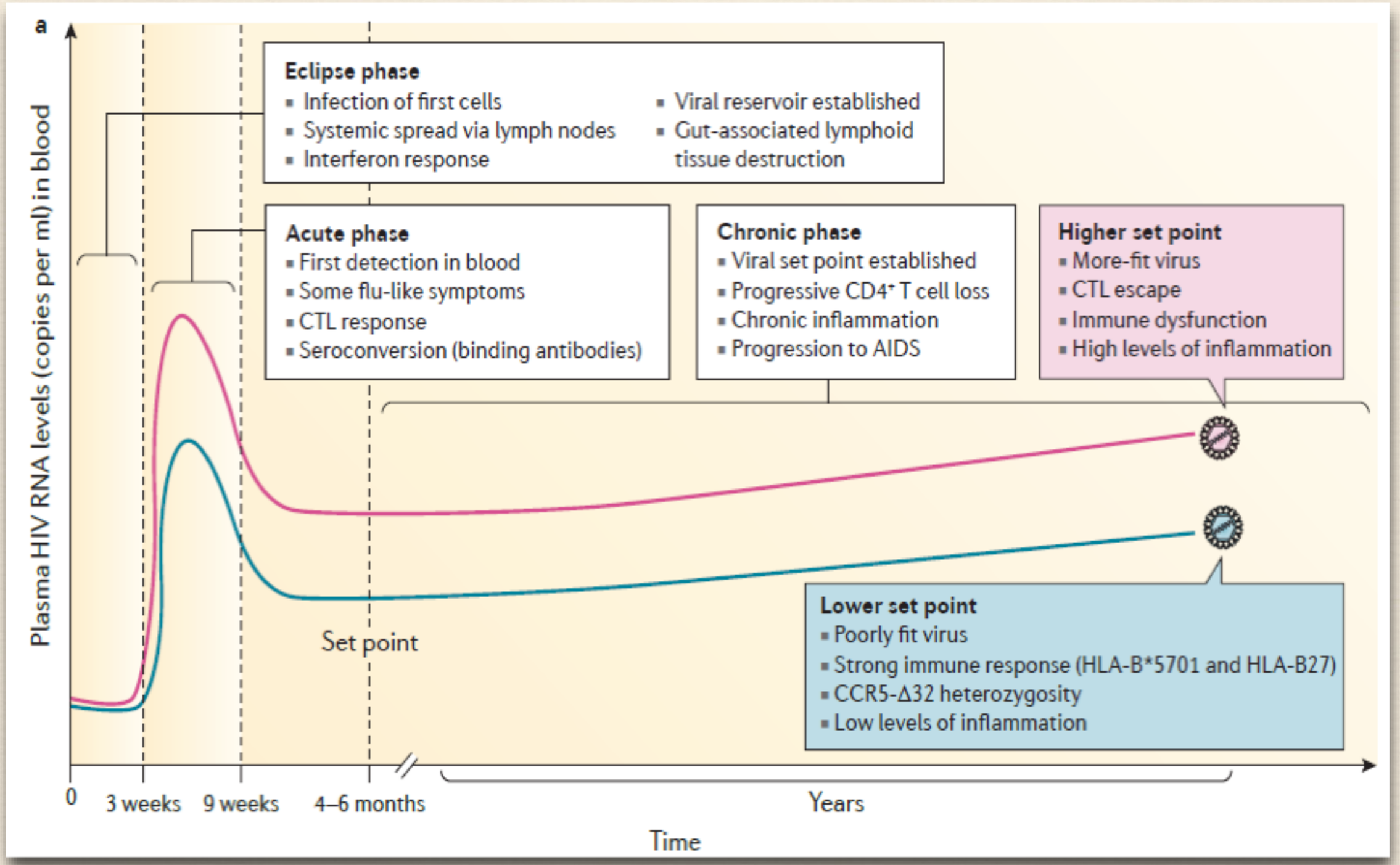
[a]Adapted from Table 2.1 (p. 28) of Levy JA, *HIV and the Pathogenesis of AIDS*, 3rd ed. ASM Press, Washington, DC, 2007.

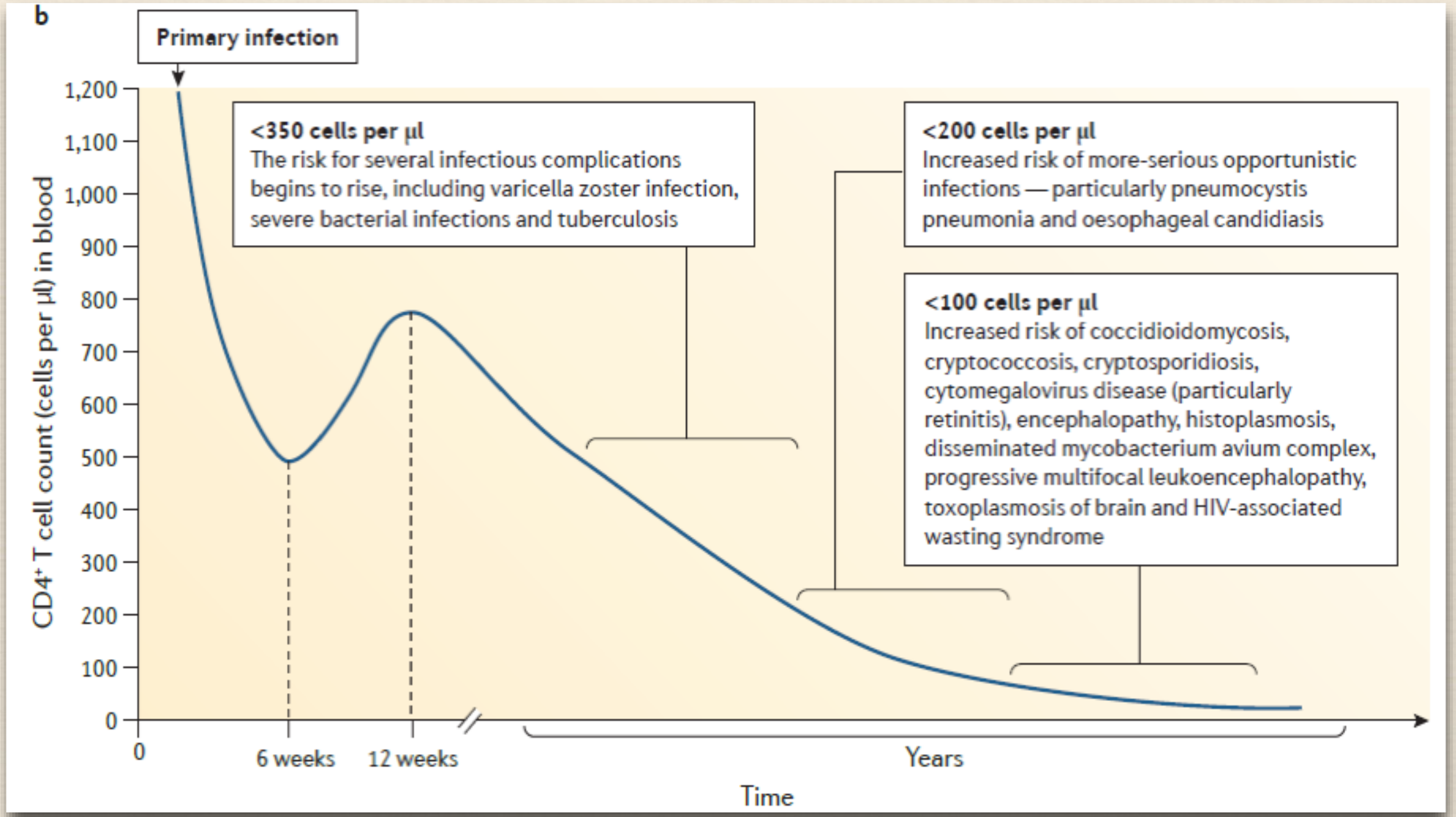
[b]Number of samples positive/number analyzed.

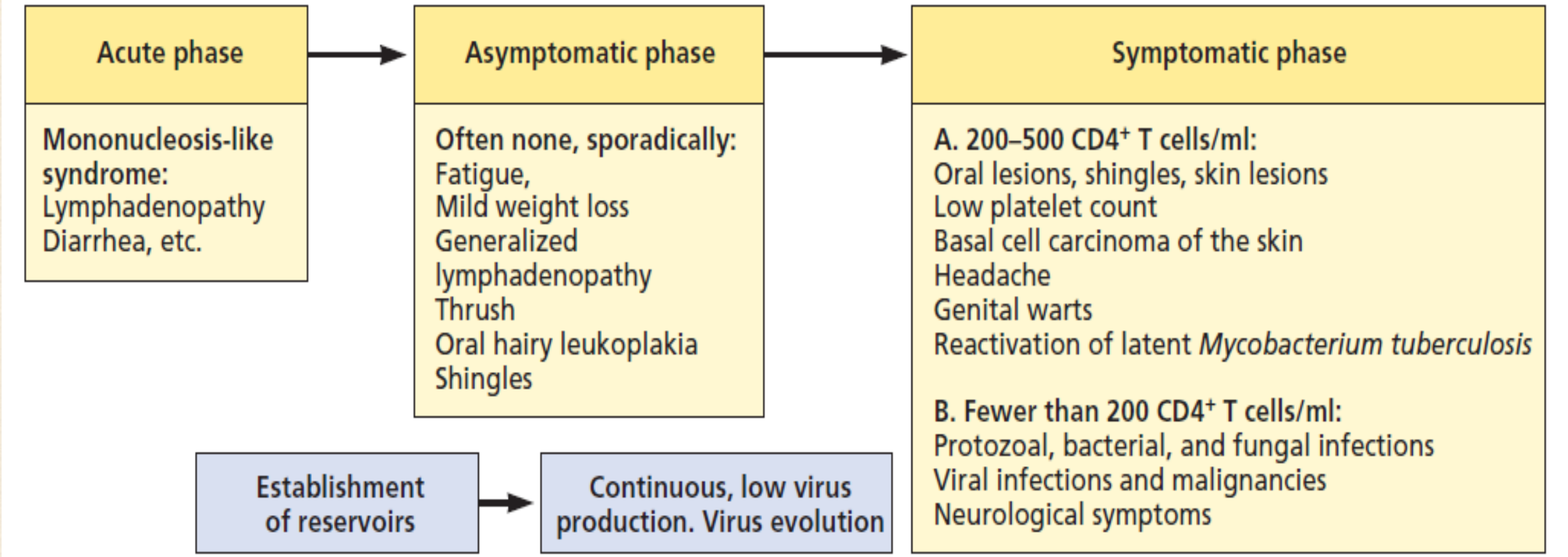
[c]For cell-free fluid, units are infectious particles per milliliter; for infected cells, units are percentages of total cells capable of releasing virus. Results from studies in the laboratory of J. A. Levy are presented.

[d]High levels associated with acute infection and advanced disease ($\sim 5 \times 10^6$ PBMCs/ml of blood).

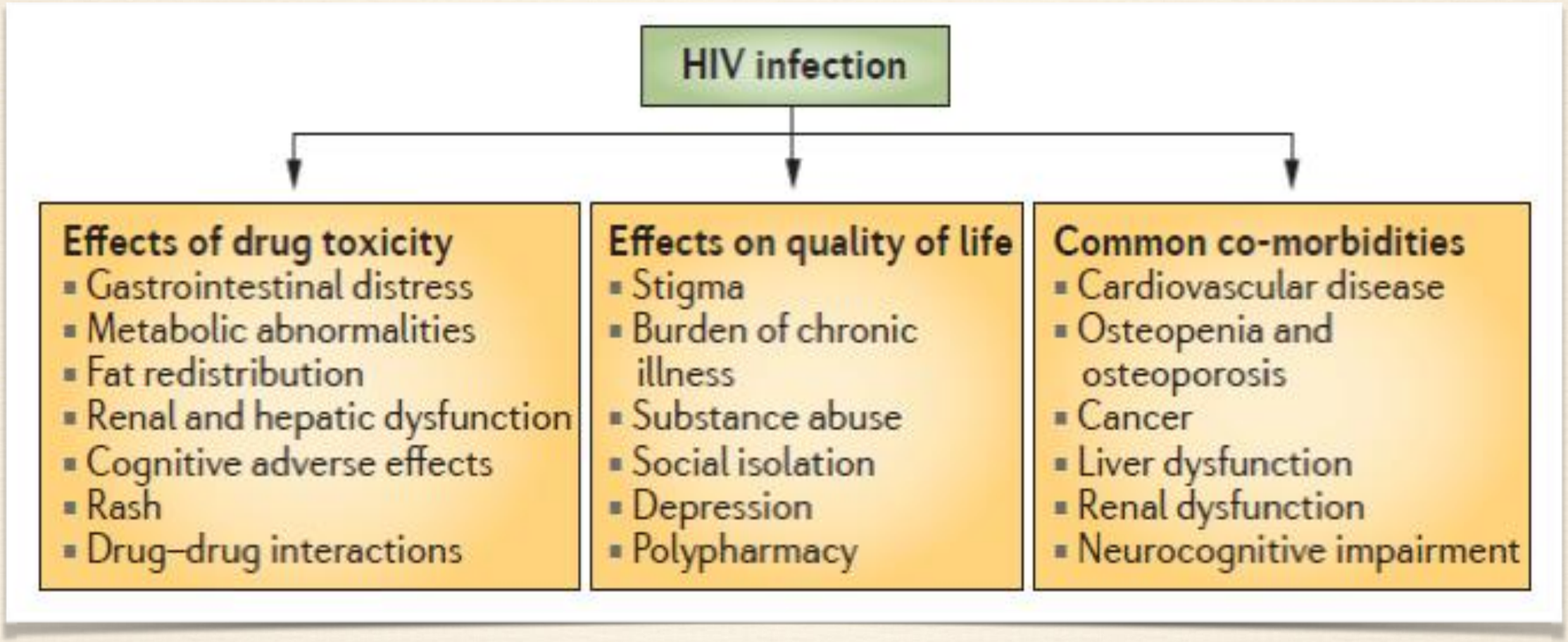
Course of HIV Infection and AIDS



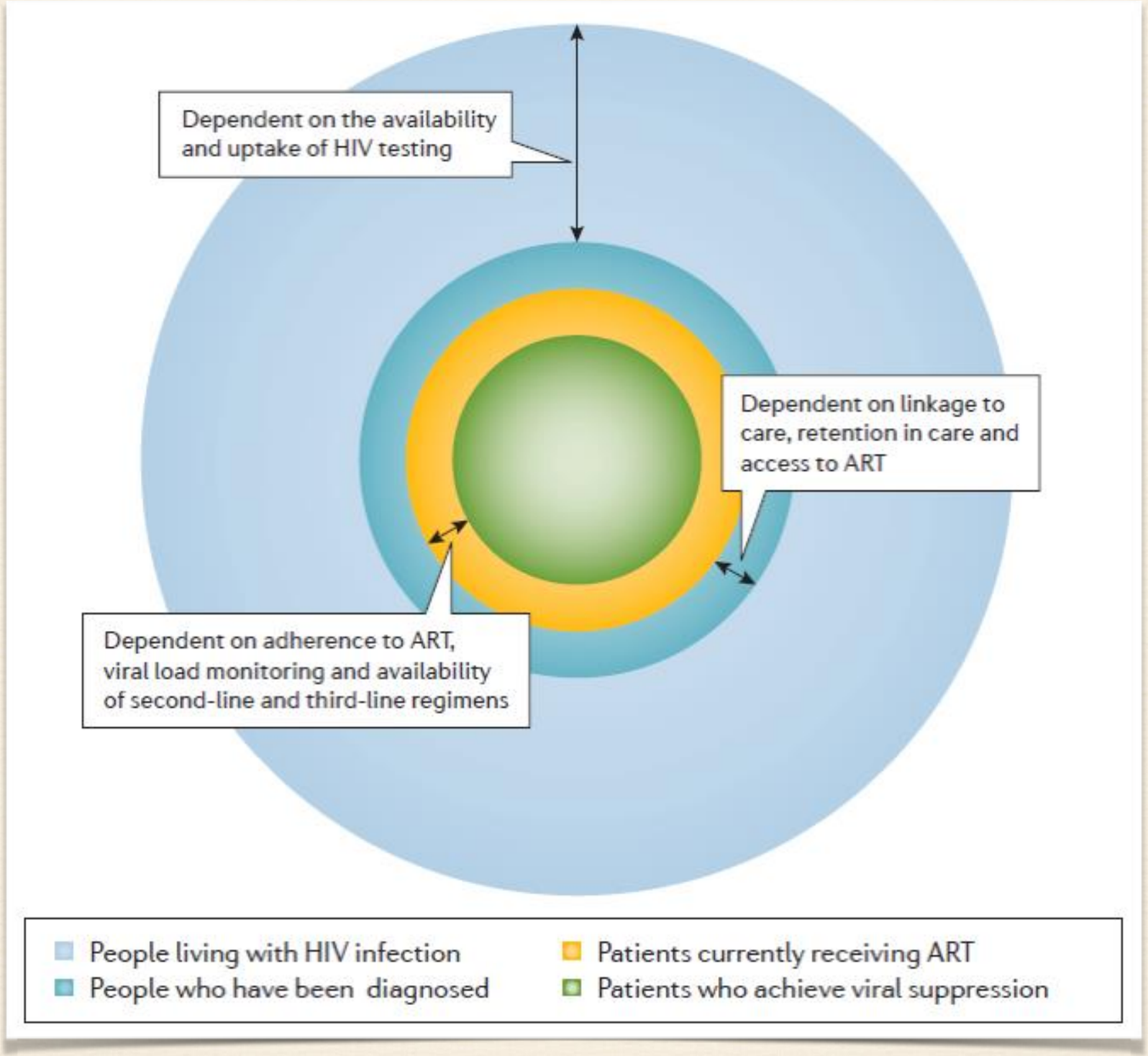

b
Primary infection
<350 cells per µl
The risk for several infectious complications begins to rise, including varicella zoster infection, severe bacterial infections and tuberculosis
<200 cells per µl
Increased risk of more-serious opportunistic infections — particularly pneumocystis pneumonia and oesophageal candidiasis
<100 cells per µl
Increased risk of coccidioidomycosis, cryptococcosis, cryptosporidiosis, cytomegalovirus disease (particularly retinitis), encephalopathy, histoplasmosis, disseminated mycobacterium avium complex, progressive multifocal leukoencephalopathy, toxoplasmosis of brain and HIV-associated wasting syndrome
CD4+ T cell count (cells per µl) in blood
1,200
1,100
1,000
900
800
700
600
500
400
300
200
100
0
0
6 weeks
12 weeks
Years
Time


Acute phase
Mononucleosis-like syndrome:
Lymphadenopathy
Diarrhea, etc.
Asymptomatic phase
Often none, sporadically:
Fatigue,
Mild weight loss
Generalized lymphadenopathy
Thrush
Oral hairy leukoplakia
Shingles
Symptomatic phase
A. 200–500 CD4+ T cells/ml:
Oral lesions, shingles, skin lesions
Low platelet count
Basal cell carcinoma of the skin
Headache
Genital warts
Reactivation of latent Mycobacterium tuberculosis
B. Fewer than 200 CD4+ T cells/ml:
Protozoal, bacterial, and fungal infections
Viral infections and malignancies
Neurological symptoms
Establishment of reservoirs
Continuous, low virus production. Virus evolution

Quality of life Impairment



HIV Care Cascade



President's Emergency Plan for AIDS Relief (www.pepfar.gov)

Global Fund for AIDS, TB and Malaria (www.theglobalfund.org)

- AIDS related mortality has declined globally from a peak level of 2.4 Million Death in 2005, to approximately 1.5 Million deaths in 2013.

- In 2013 240,000 children were newly infected with HIV, 58% fewer than in 2002.

- 2.6 Million children under 15 (90%) are living in sub-Saharan Africa.

- Women have a lower viral load set point than men (0.4 log10), yet progress at about the same.

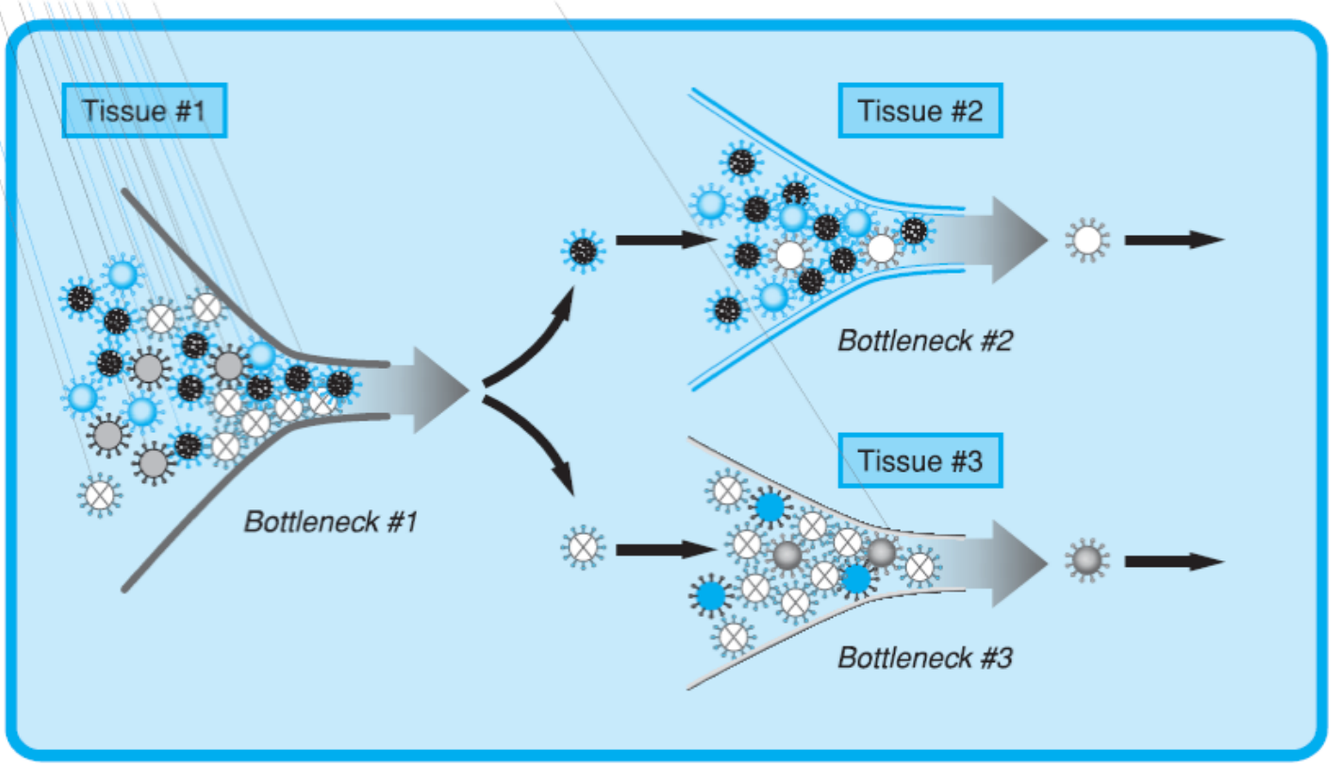
Pathogenesis

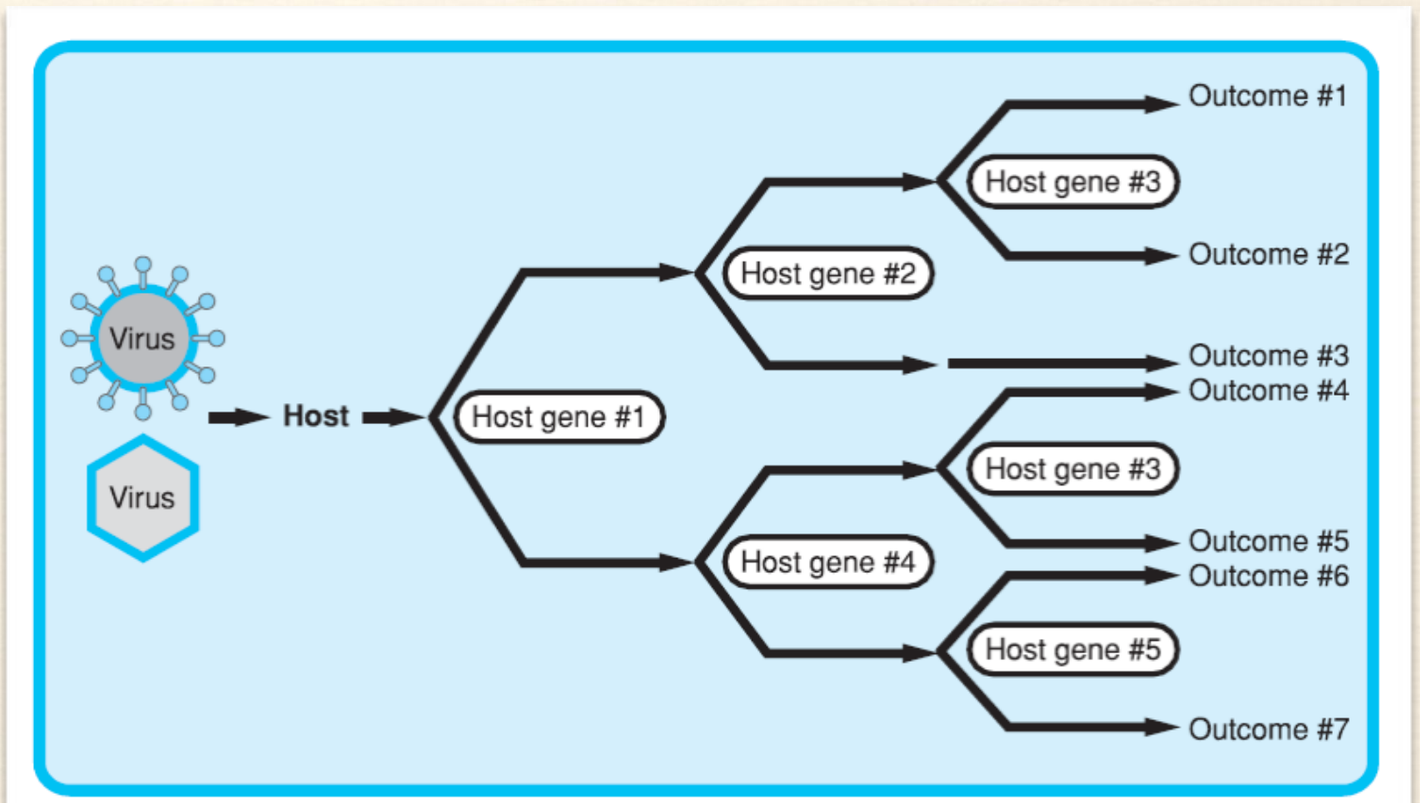
Definition of Viral Pathogenesis?

- As a series of stochastic events with the process of infection determined by strong selective pressures referred to as bottlenecks in infection.

- These bottlenecks can be thought of as analogous to the rate-limiting step.

- Stochastic events such as mutations or the random success of a given virus at a stage in infection provide variation in the substrates for these rate-limiting steps.


Tissue #1
Tissue #2
Bottleneck #2
Tissue #3
Bottleneck #1
Bottleneck #3

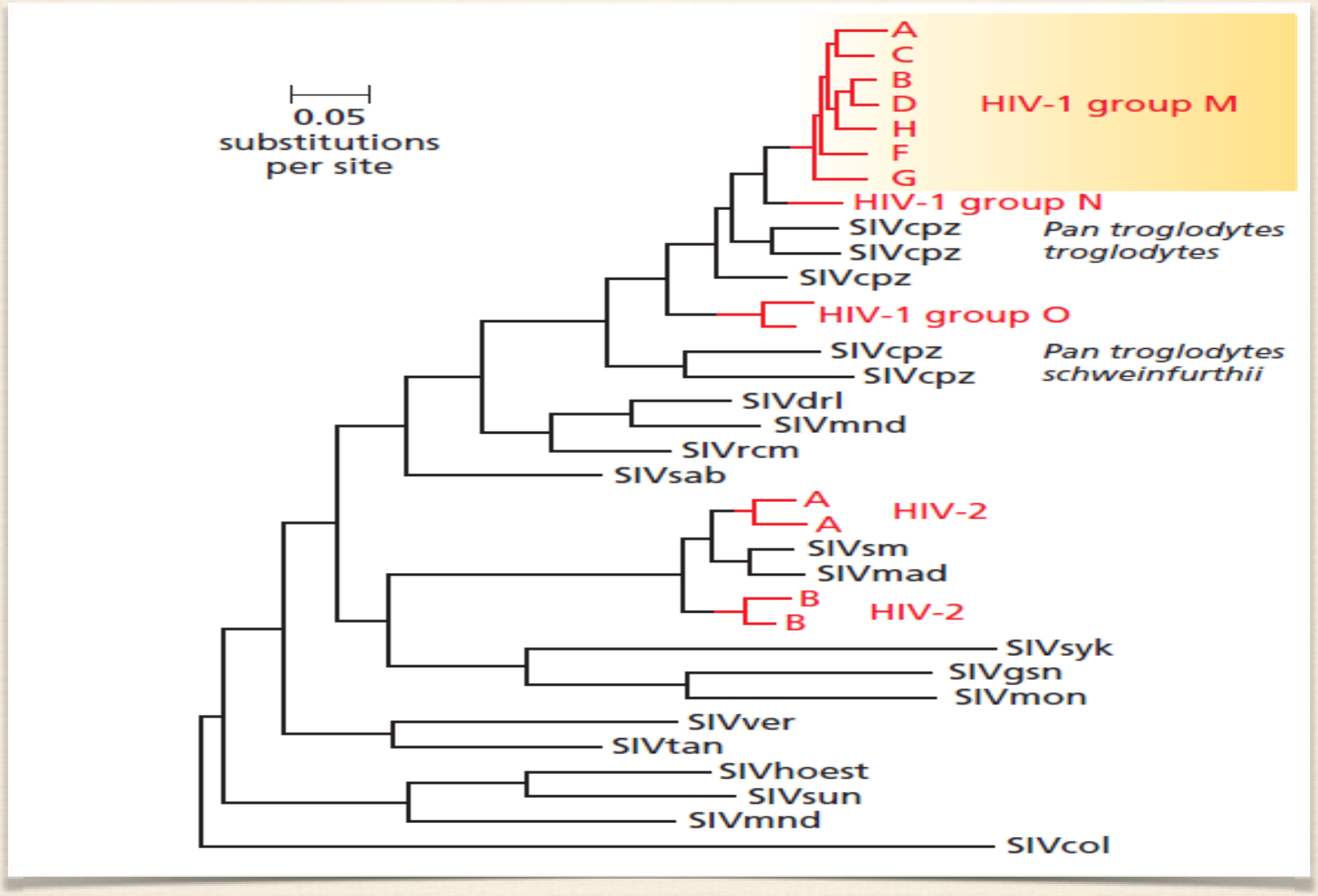

Virus
Virus
Host
Host gene #1
Host gene #2
Host gene #3
Host gene #4
Host gene #3
Host gene #5
Outcome #1
Outcome #2
Outcome #3
Outcome #4
Outcome #5
Outcome #6
Outcome #7

Faith of viral infection and disease

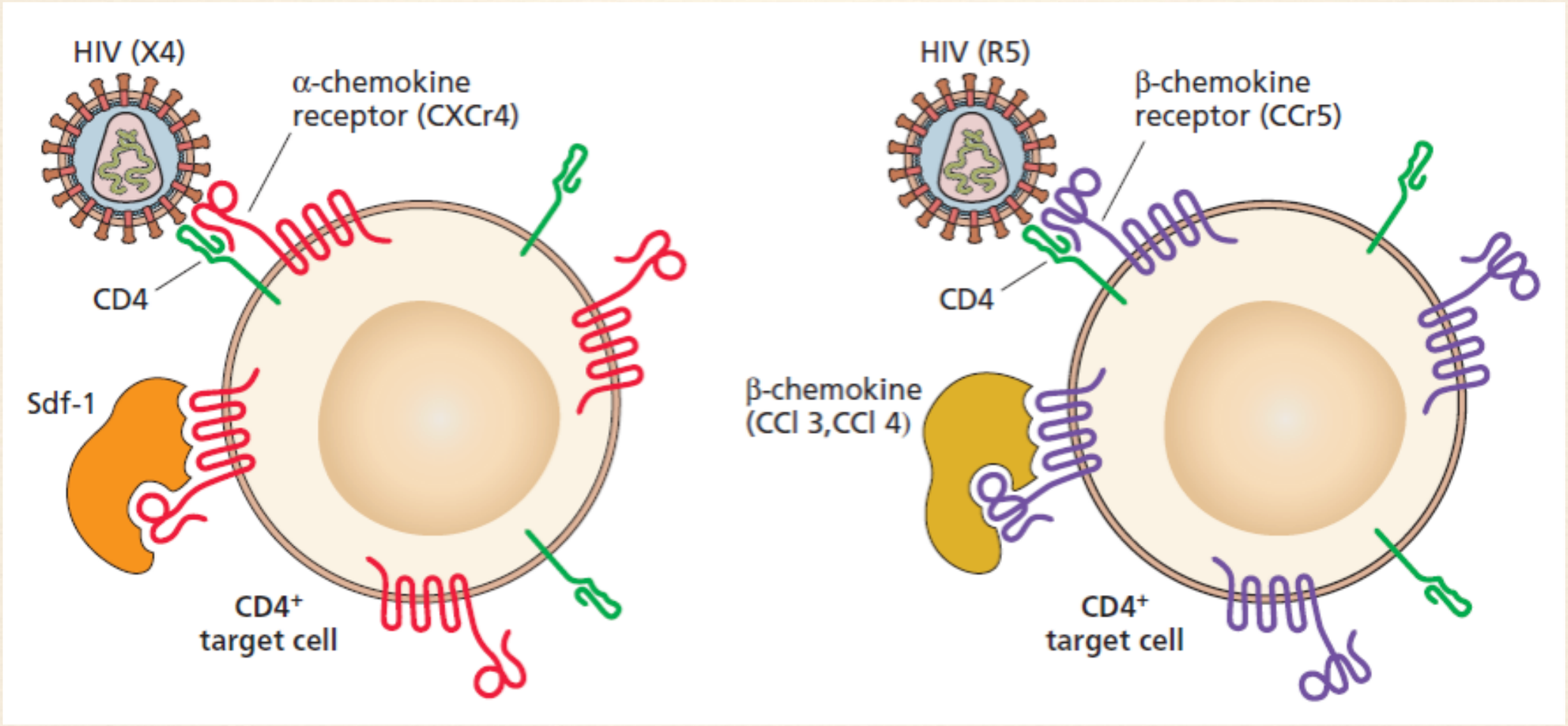
- Viral Bottlenecks?
- Host Bottlenecks?
- Human Induced Bottlenecks?!!

Viral Bottlenecks and Outcome

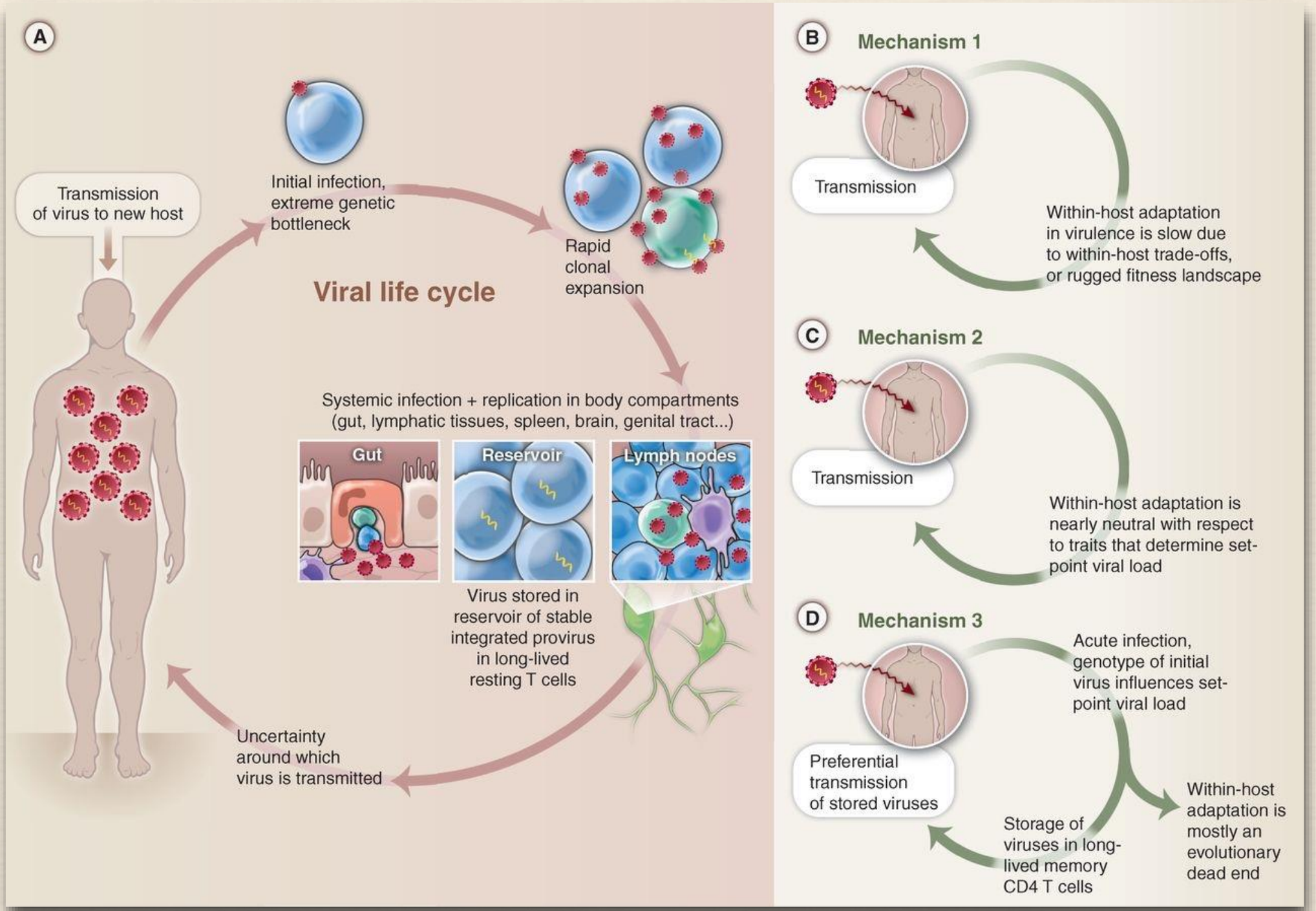
Viral Evolution and fitness

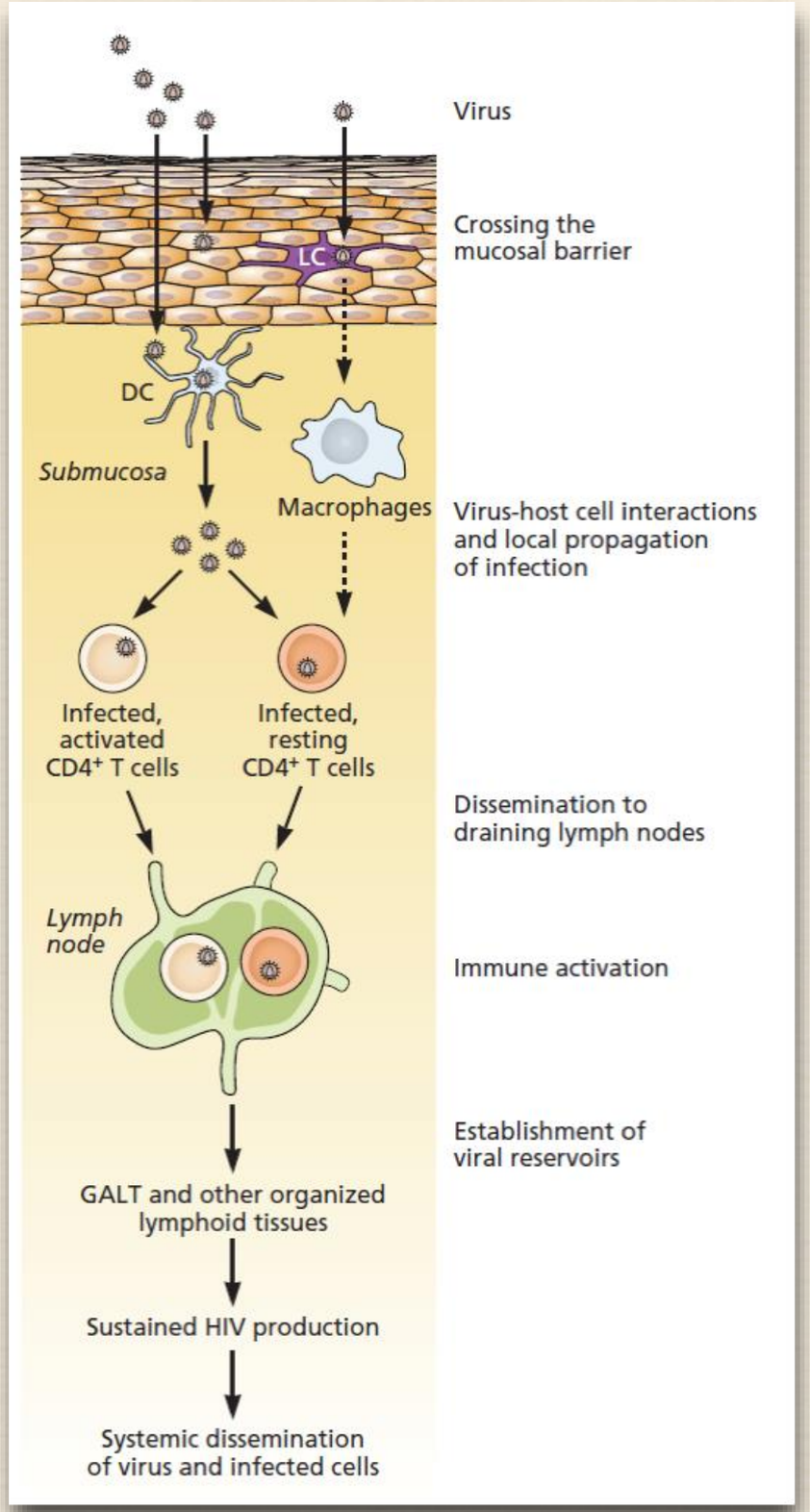


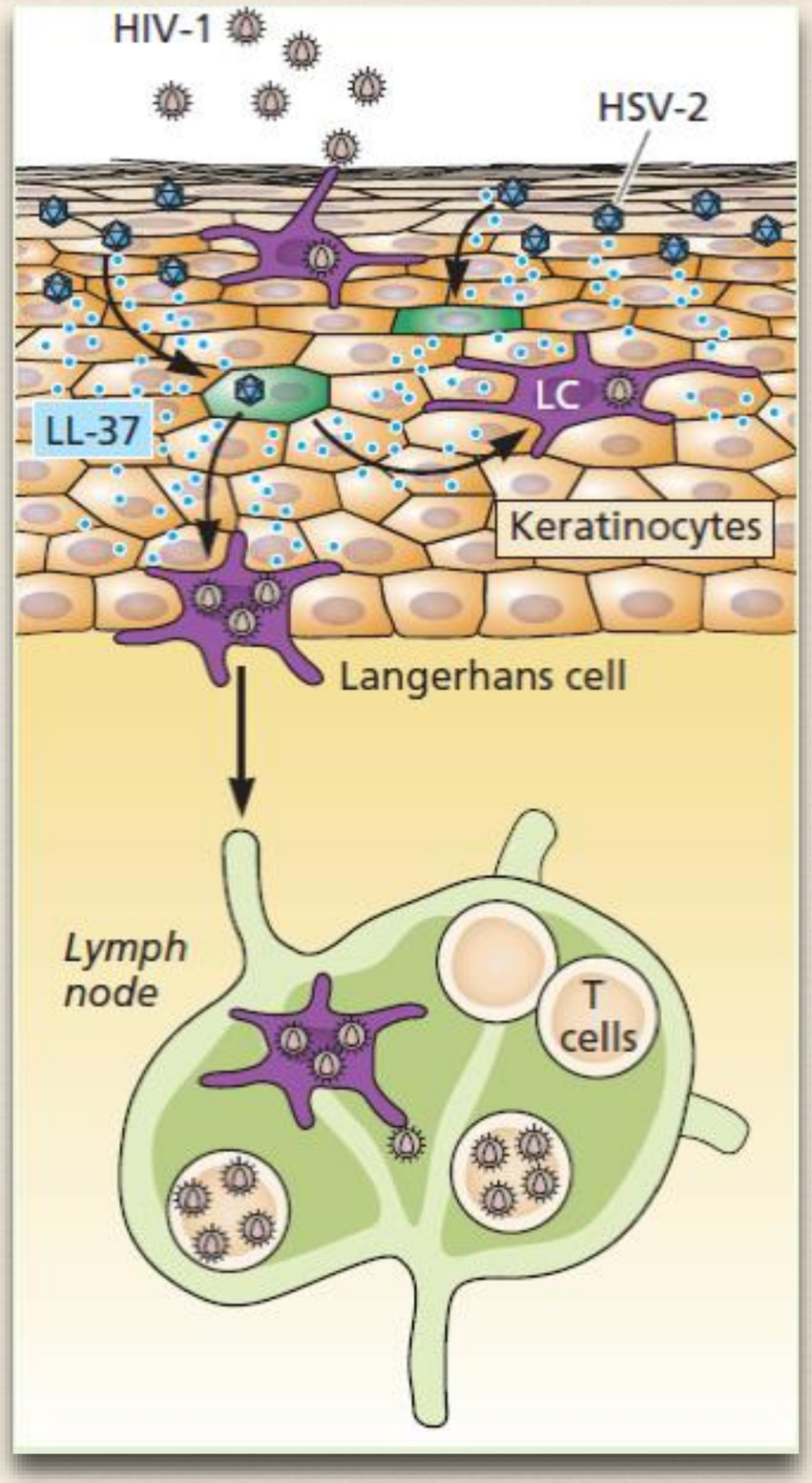
Viral Tropism and Strains

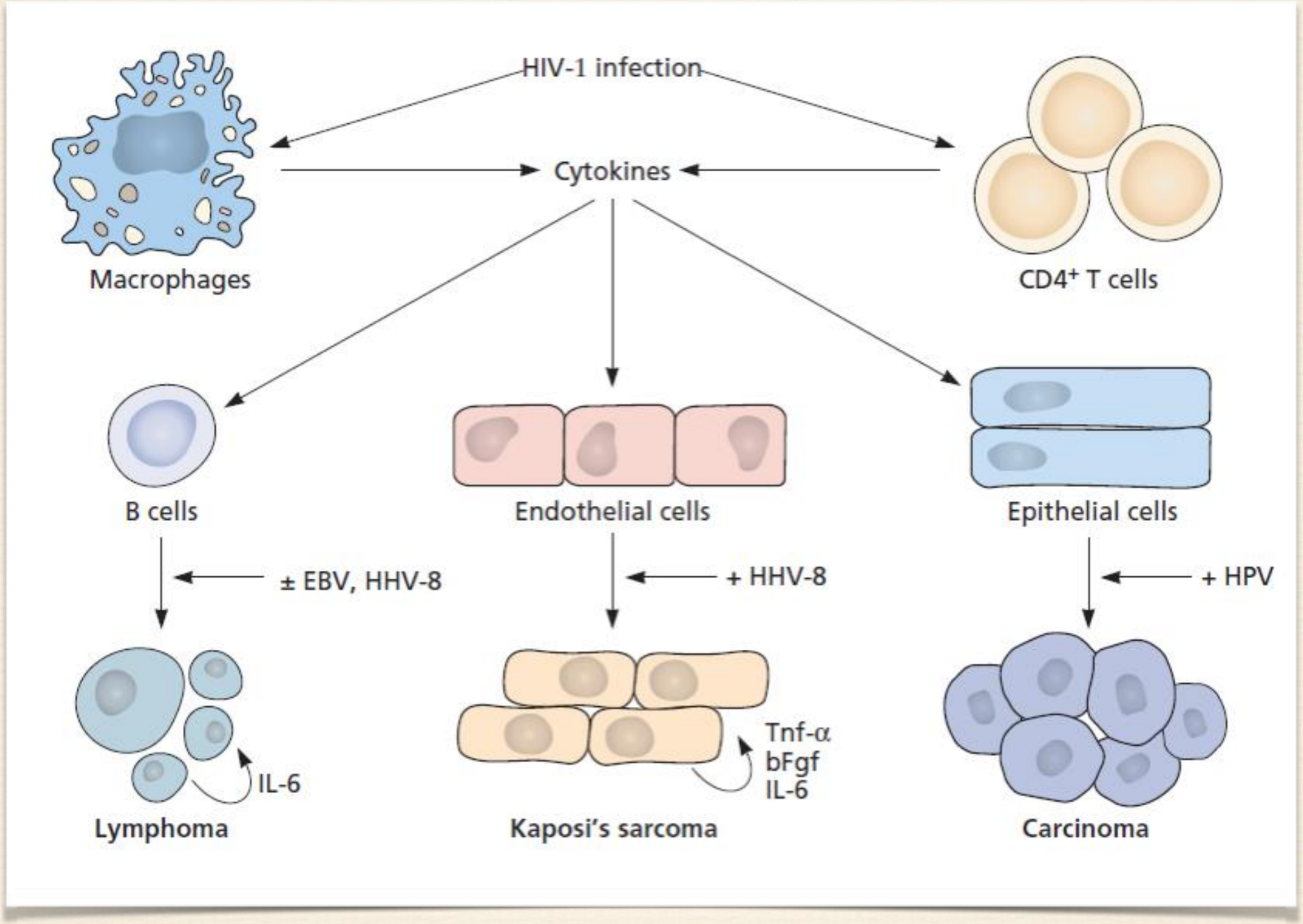


Viral-Host Fitness



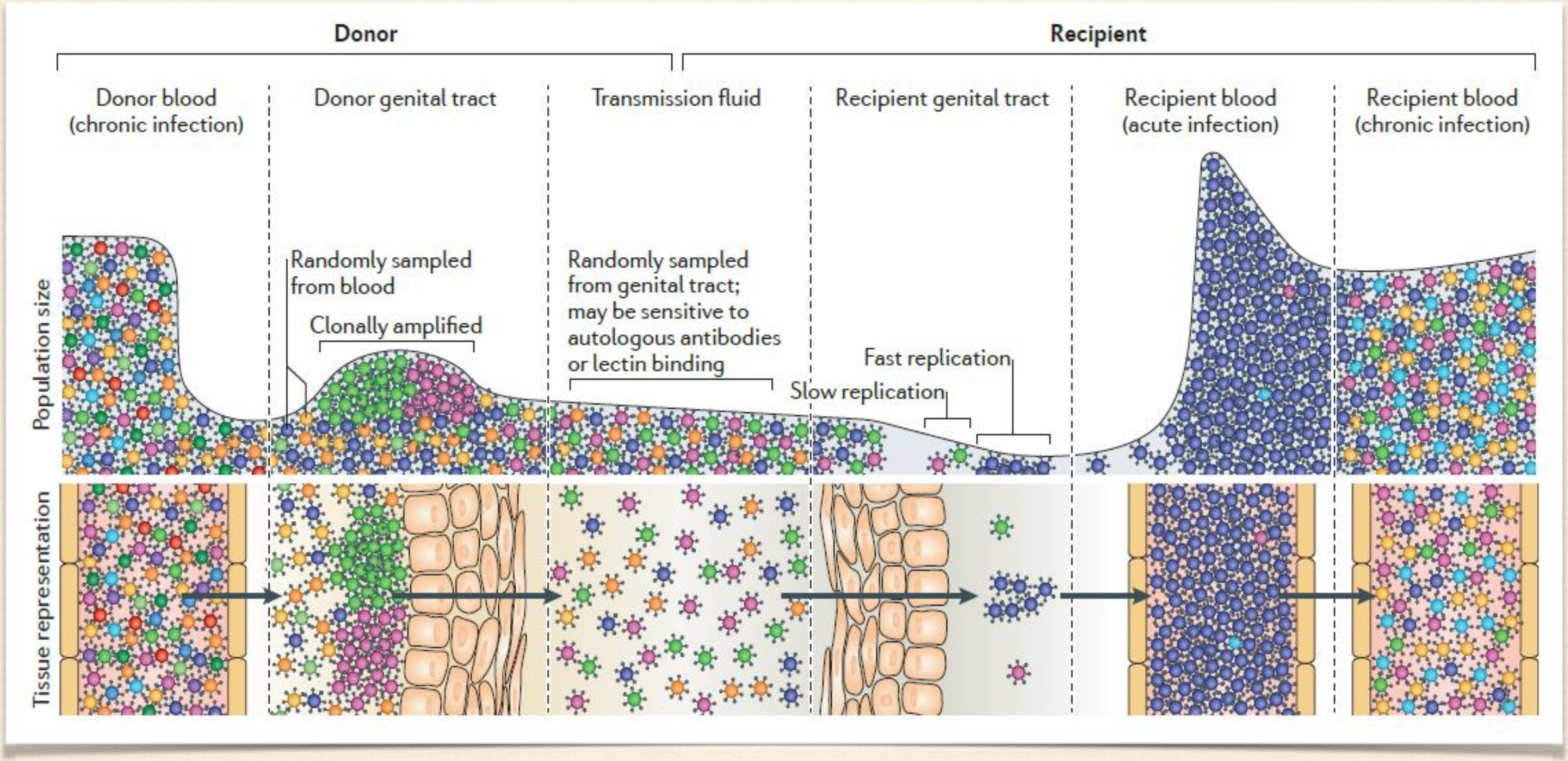

Virus
LC
Crossing the mucosal barrier
DC
Submucosa
Macrophages
Virus-host cell interactions and local propagation of infection
Infected, activated CD4+ T cells
Infected, resting CD4+ T cells
Dissemination to draining lymph nodes
Lymph node
Immune activation
GALT and other organized lymphoid tissues
Establishment of viral reservoirs
Sustained HIV production
Systemic dissemination of virus and infected cells

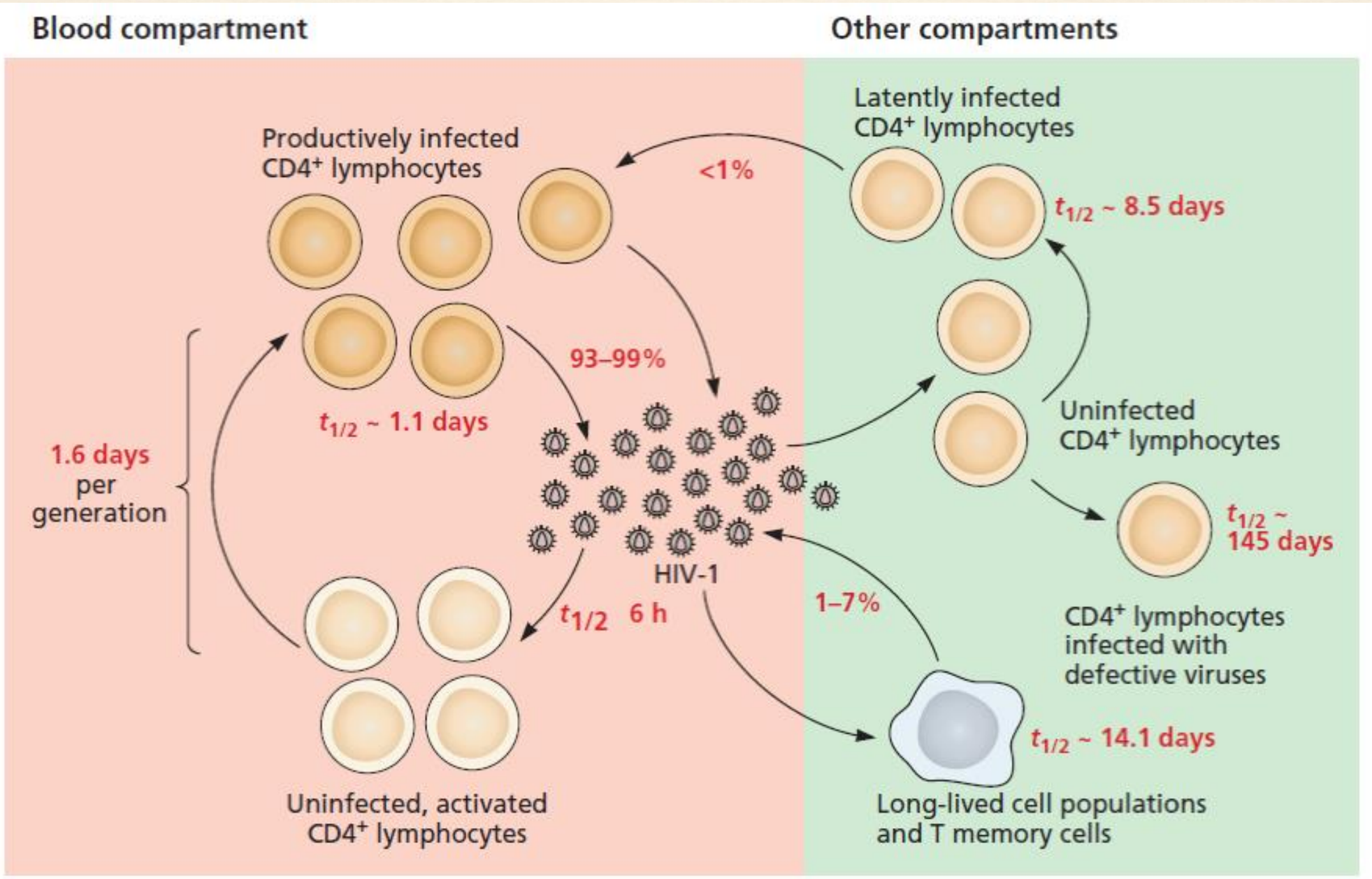

HIV-1
HSV-2
LL-37
LC
Keratinocytes
Langerhans cell
Lymph node
T cells


HIV-1 infection
Cytokines
Macrophages
CD4+ T cells
B cells
Endothelial cells
Epithelial cells
± EBV, HHV-8
+ HHV-8
+ HPV
IL-6
Tnf-α
bFgf
IL-6
Lymphoma
Kaposi's sarcoma
Carcinoma

Host Genetics / Epigenetic Bottlenecks

Host Bottlenecks




Blood compartment
Other compartments
Productively infected CD4+ lymphocytes
<1%
Latently infected CD4+ lymphocytes
t1/2 ~ 8.5 days
93–99%
t1/2 ~ 1.1 days
1.6 days per generation
Uninfected CD4+ lymphocytes
t1/2 ~ 145 days
HIV-1
t1/2 6 h
1–7%
CD4+ lymphocytes infected with defective viruses
t1/2 ~ 14.1 days
Uninfected, activated CD4+ lymphocytes
Long-lived cell populations and T memory cells

The Berlin Patient

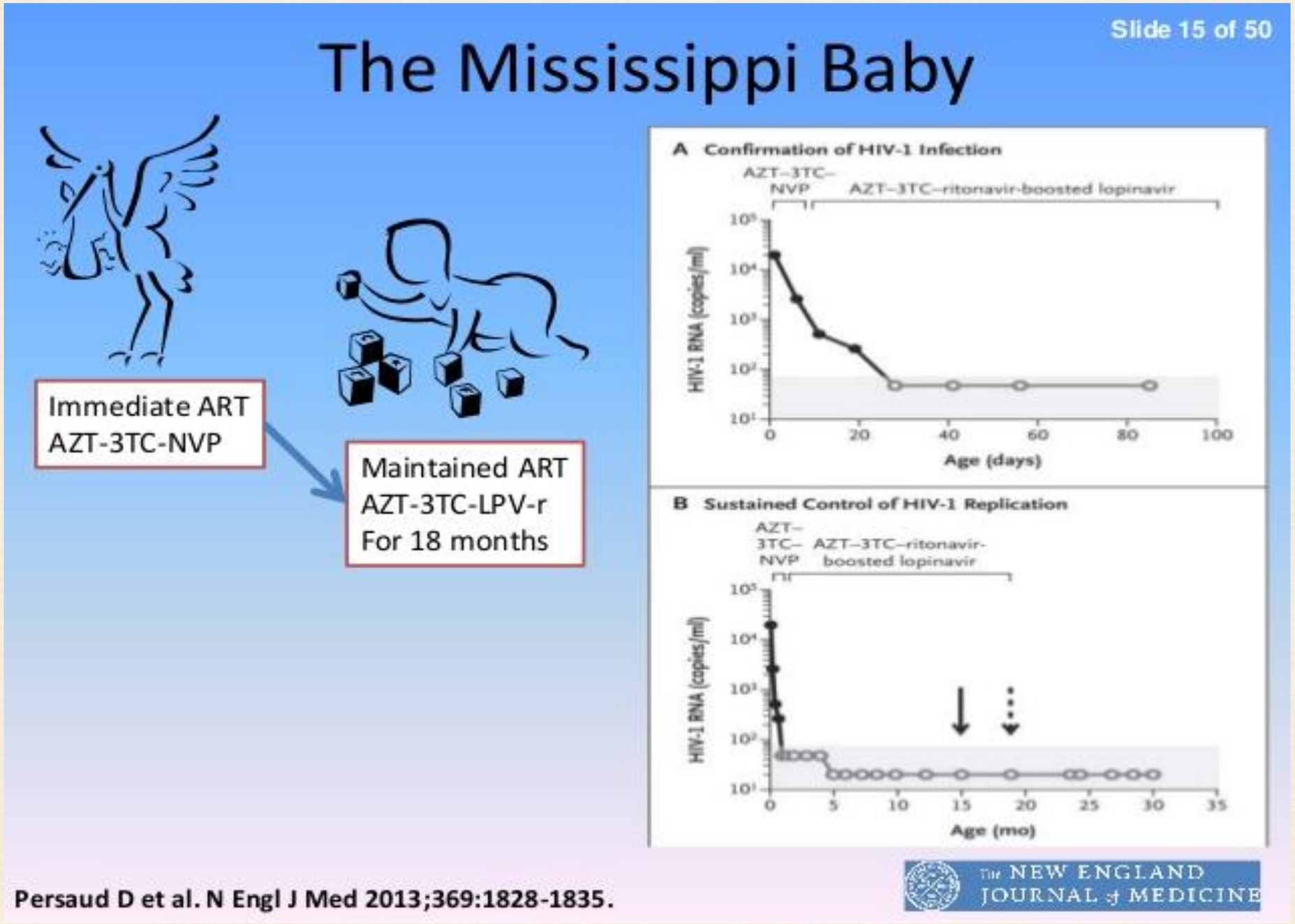
STOPPING AIDS IS IMPOSSIBLE

CHANGE THE STORY

Curing HIV – Only a Start

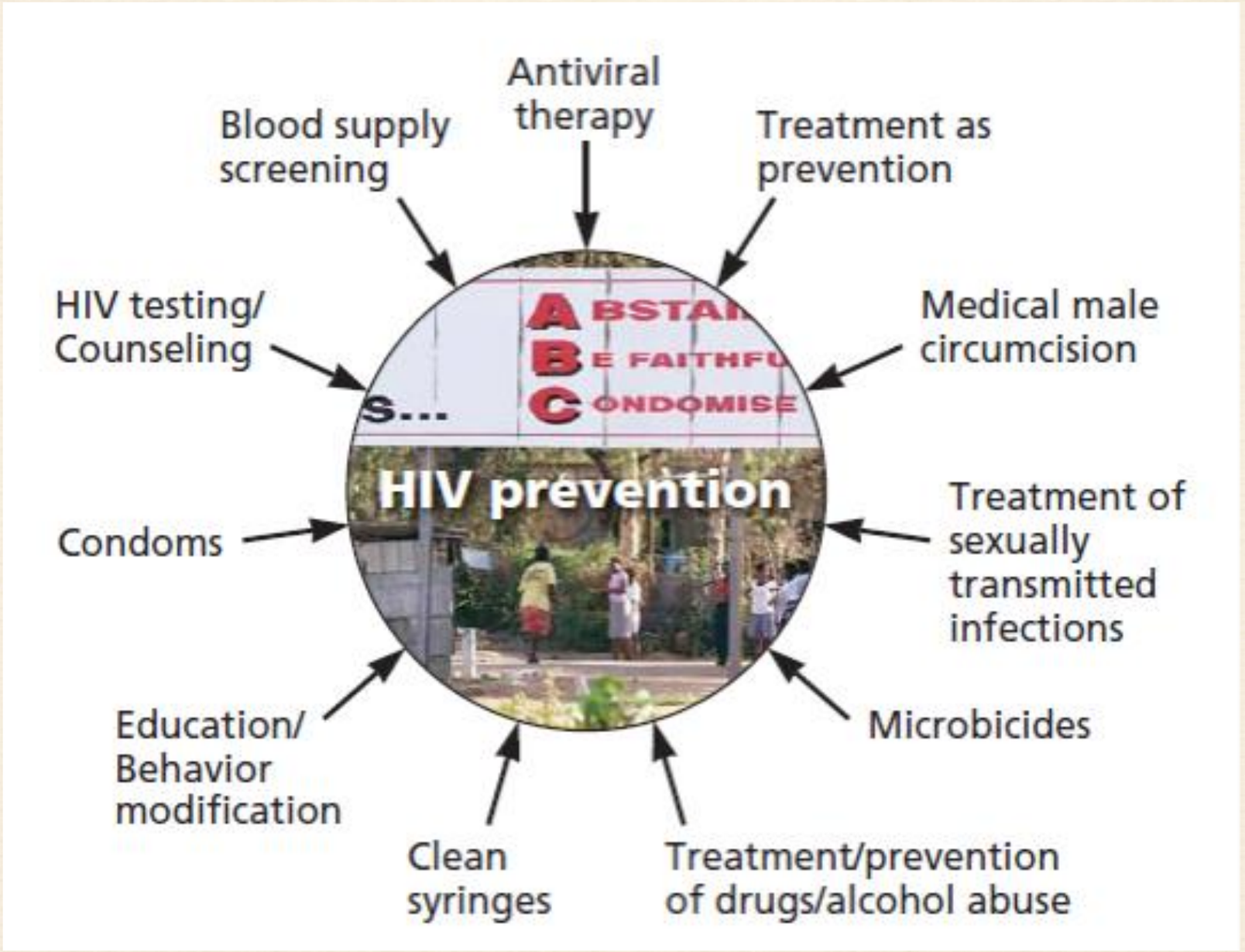
Community Forum on HIV Cure Research with Timothy Ray Brown, The Man Who Once Had HIV

Mississippi Baby



Boston Patients

Our Induced Bottlenecks



HARRT Therapy

- Highly Effective (Access and adherence)

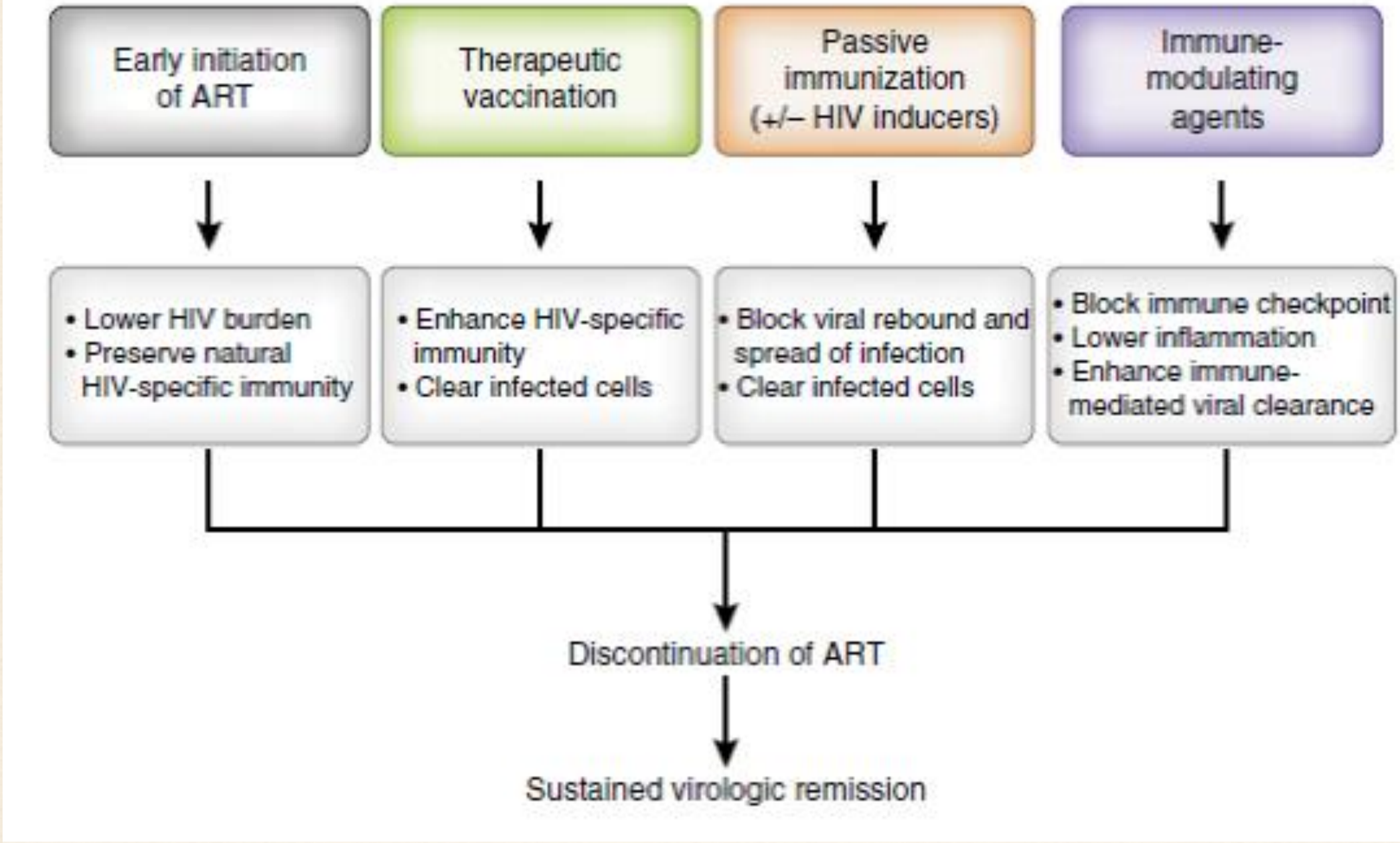
- Can virtually eliminate the risk of HIV transmission.

- Should be considered HIV Drug resistance (ARV)

The main Problem?!!!

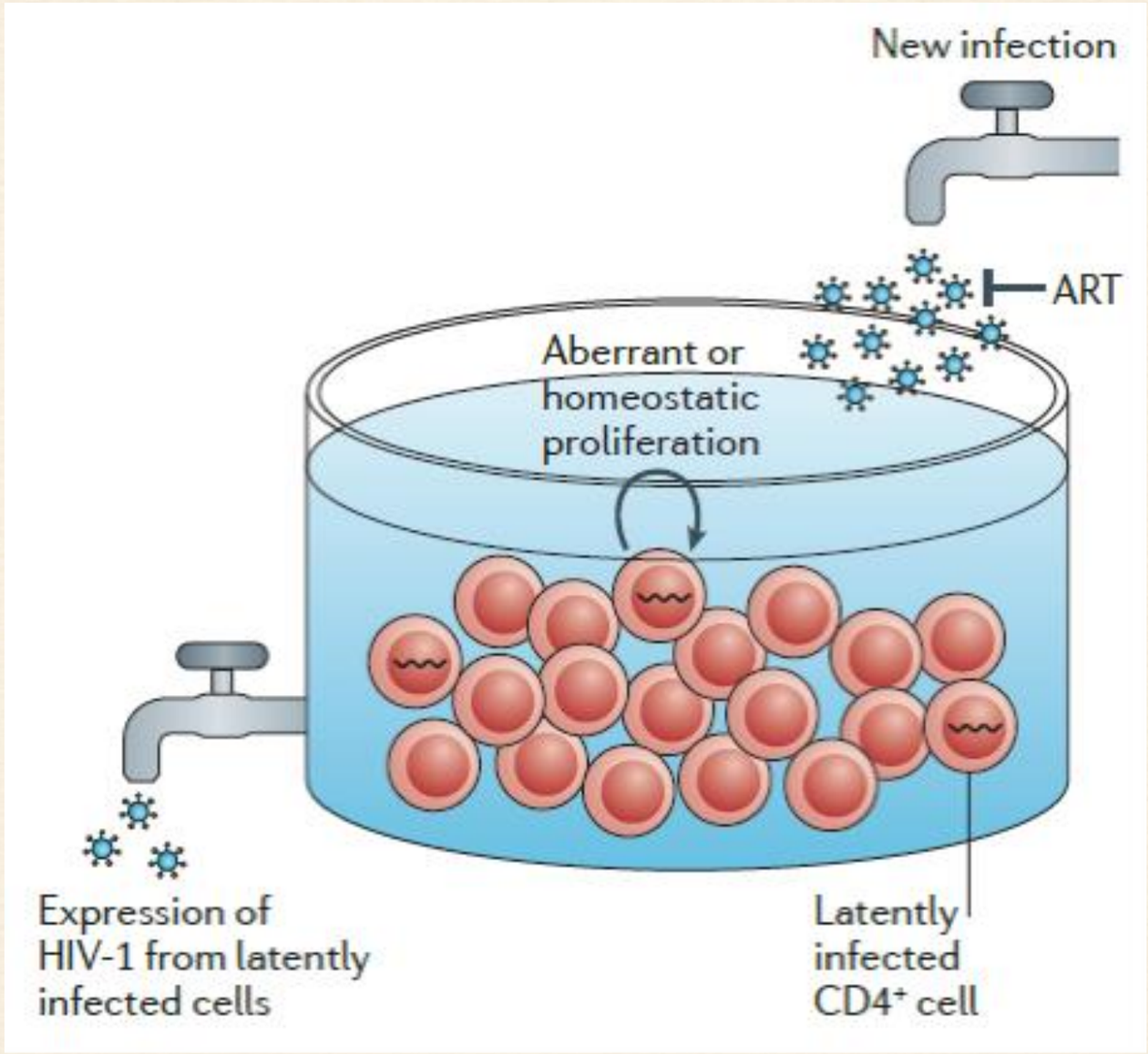
Cellular Reservoir of HIV

- Central Memory T cell.
- Transitional Memory T cell.
- CD34 hematopoietic progenitor.
- Naïve CD4 T cell.
- CD4 memory stem cell.

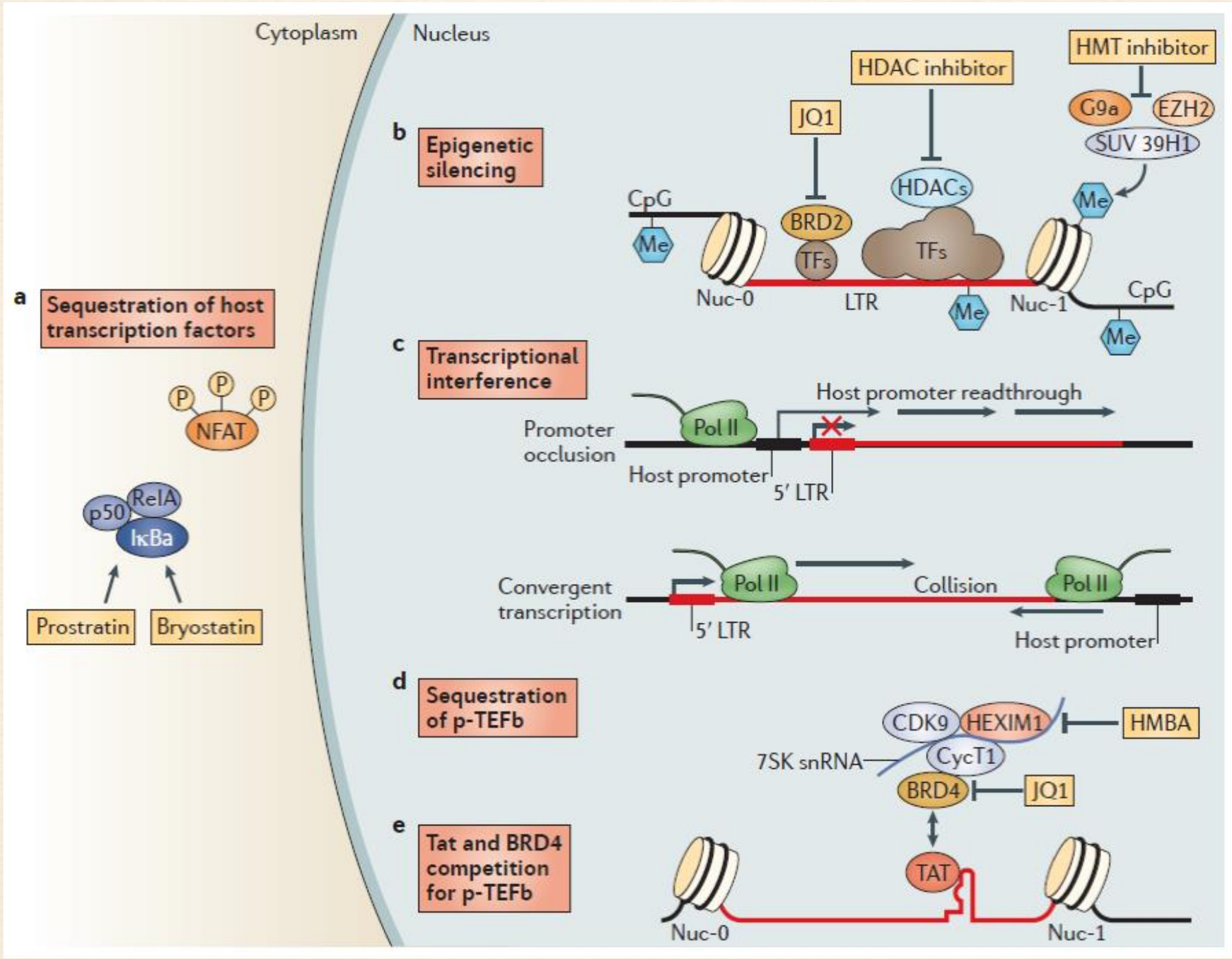

Early initiation of ART
Therapeutic vaccination
Passive immunization (+/– HIV inducers)
Immune-modulating agents
• Lower HIV burden
• Preserve natural HIV-specific immunity
• Enhance HIV-specific immunity
• Clear infected cells
• Block viral rebound and spread of infection
• Clear infected cells
• Block immune checkpoint
• Lower inflammation
• Enhance immune-mediated viral clearance
Discontinuation of ART
Sustained virologic remission

Future Therapies?

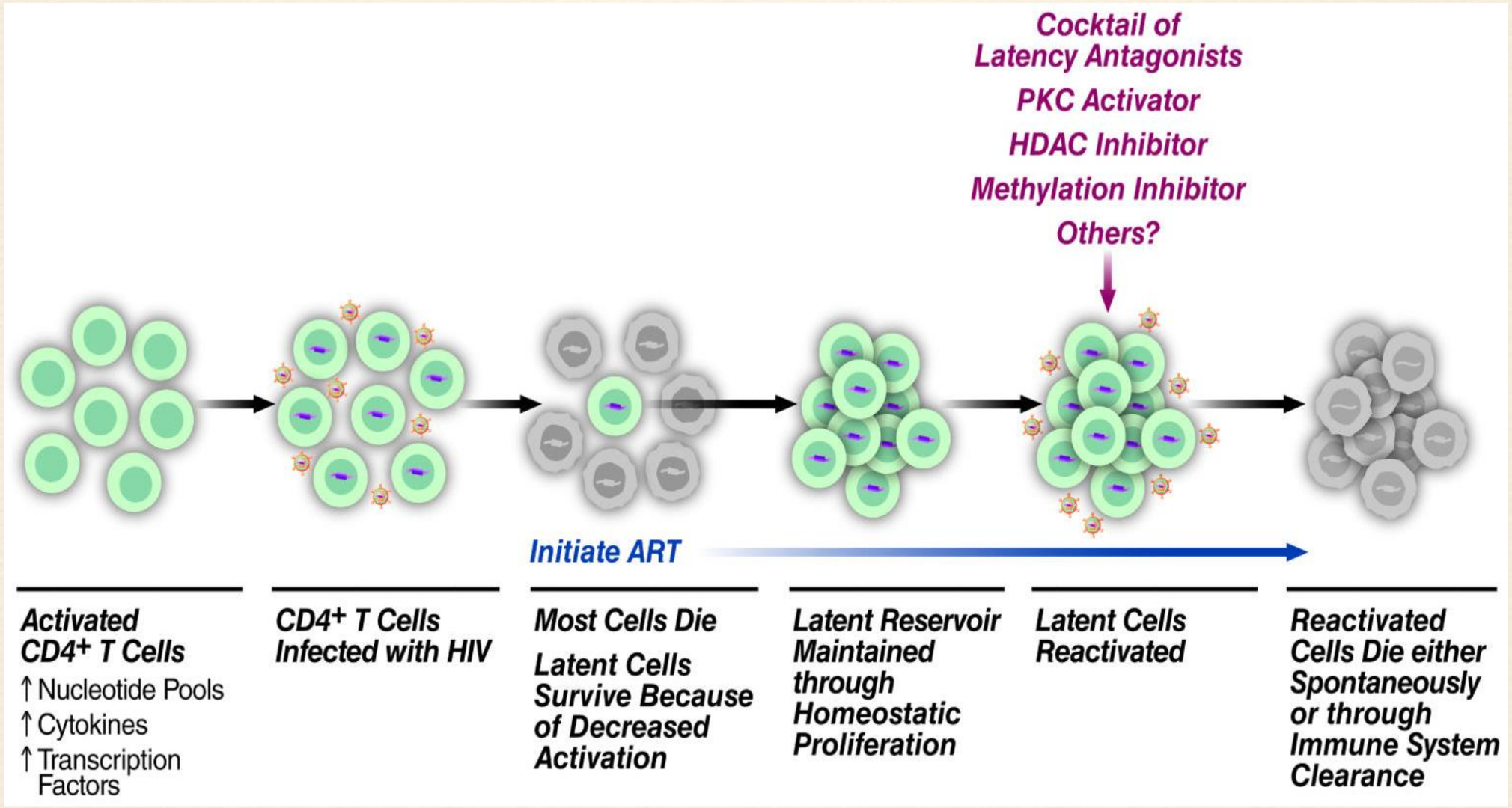
Barriers to HIV Eradication



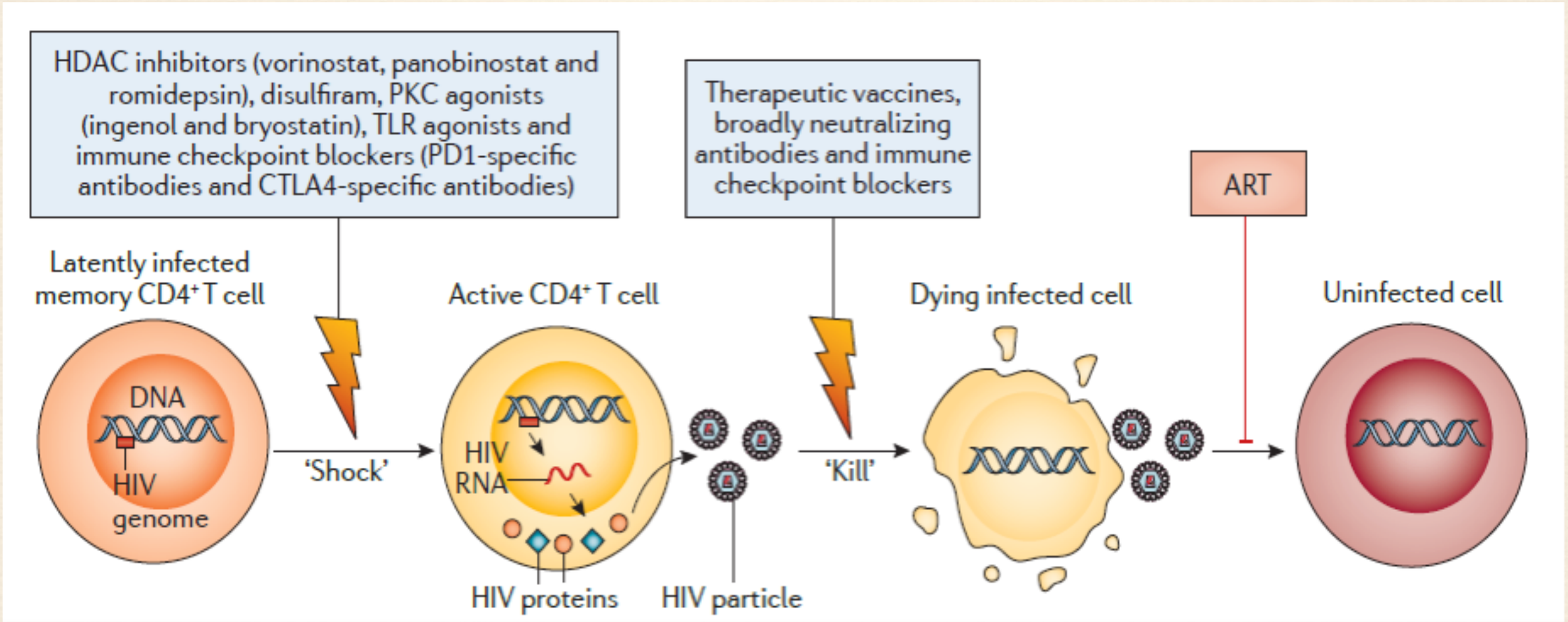
Mechanism involved in maintenance of HIV latency



Lytic-Induction Therapy



Lytic-induction therapy



Mechanism to disrupt latency	Compound	Clinical trials*	Comments
PTEN inhibitor	Disulfiram	Short-term disulfiram administration to accelerate the decay of the HIV-1 reservoir in antiretroviral-treated HIV-1 infected individuals (NCT01286259)	Completed: a transient increase in single-copy assay viraemia was observed in six patients at different times after disulfiram dosing; however, the size of the HIV-1 latent reservoir remained unaffected[123]
HDAC inhibitor	Romidepsin	Evaluating the safety and efficacy of single-dose romidepsin in combination with antiretroviral therapy in HIV-1-infected adults with suppressed viral load (NCT01933594)	Enrolling
HDAC inhibitor	Romidepsin	Safety and efficacy of romidepsin and the therapeutic vaccine vacc-4x for reduction of the latent HIV-1 reservoir (REDUC; NCT02092116)	Ongoing
HDAC inhibitor	Panobinostat (Novartis)	Safety and effect of panobinostat on HIV-1 expression in patients on suppressive HAART (CLEAR; NCT01680094)	Completed: a 2.1–14.4-fold increase in cell-associated RNA was observed in all patients and remained increased 4 weeks after panobinostat administration; however, no change in integrated HIV-1 DNA was observed[132]
HDAC inhibitor	Vorinostat	The effect of vorinostat on HIV-1 RNA expression in resting $CD4^+$ T cells of HIV-1-infected patients on stable ART (NCT01319383)	Enrolling
HDAC inhibitor	Vorinostat	A pilot study to assess the safety and effect of vorinostat on HIV-1 transcription in patients receiving suppressive combination anti-retroviral therapy (NCT01365065)	Completed: a significant increase in cell-associated RNA was observed in 88% of patients during vorinostat dosing; no significant change in DNA was observed[133]

* The clinicaltrials.gov identifier is given in brackets. ART, antiretroviral therapy; HAART, highly active ART; HDAC, histone deacetylase; PTEN, phosphatase and tensin homologue.

Clearing Persistently infected cells

- Therapeutic Vaccine.
- Cell based therapies.
- Gene therapy.
- Reversing immune exhaustion.
- Immunotoxins and Radio immunotherapy.

Cell Based Therapy

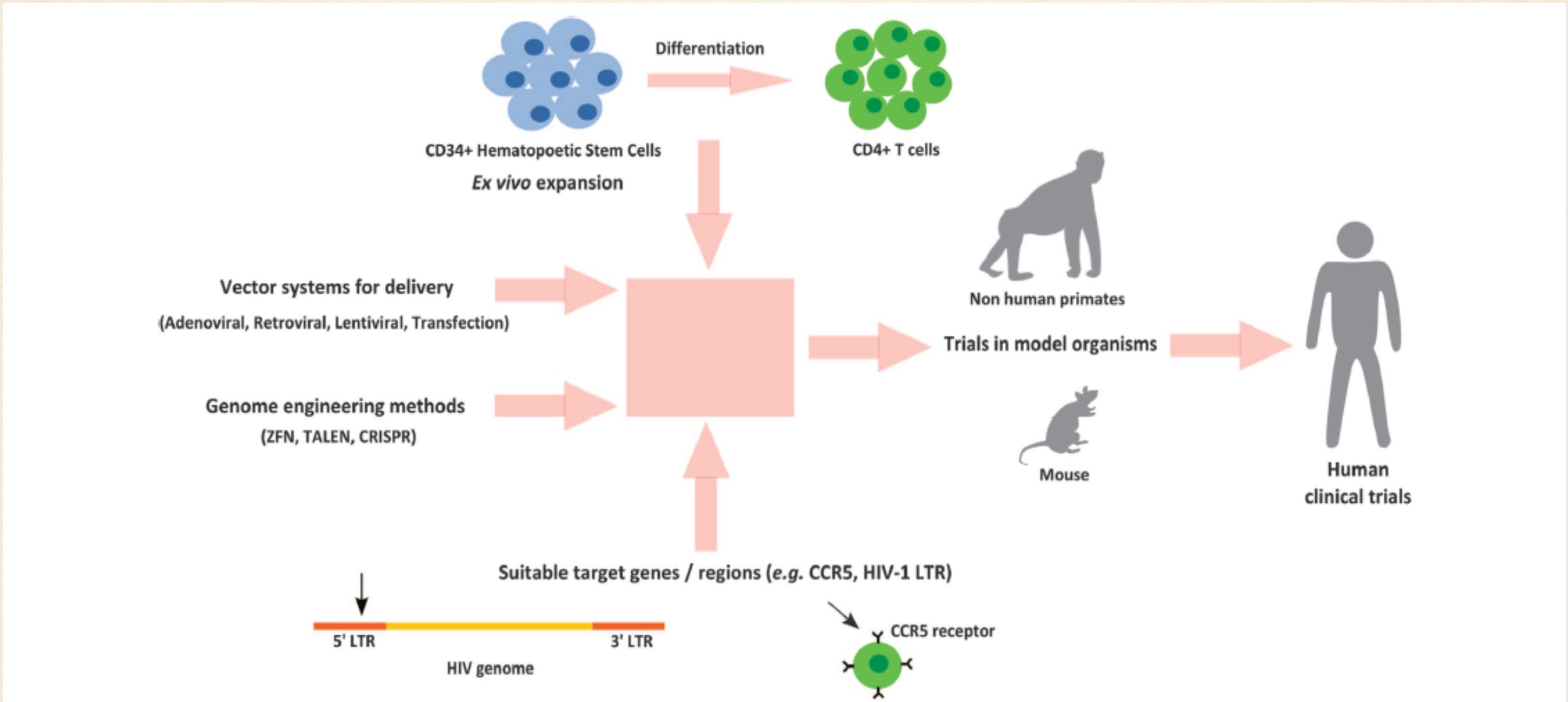


Figure 1. Critical factors in designing cell-based therapy for HIV-1: stem cells, vector systems, genome engineering methods and the choice of the target genes are essential prerequisites that require to be tackled in the laboratory before trials in model organisms or in humans can be initiated.

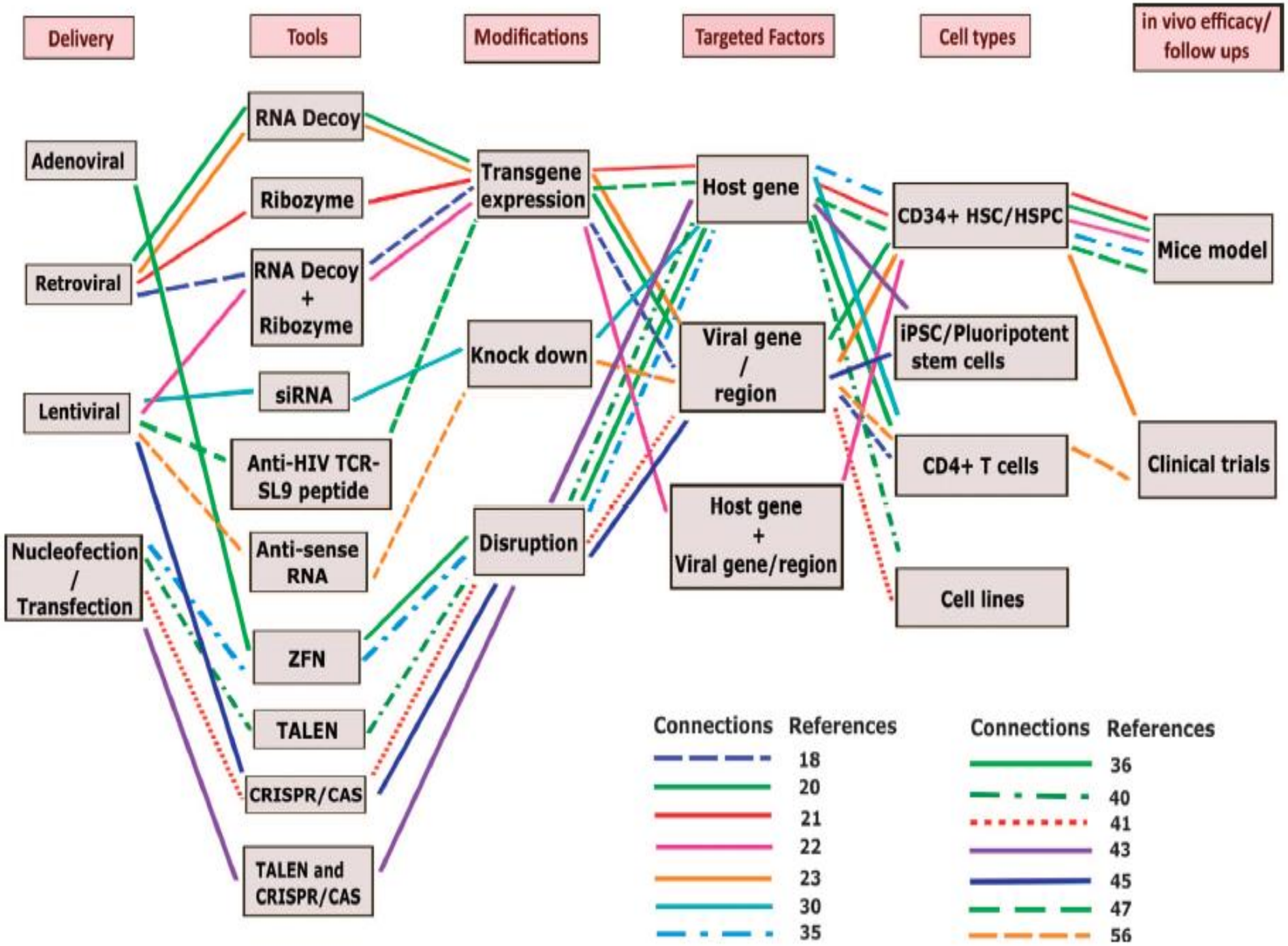


Figure 2. An overview of attempts at cell-based HIV therapy: Each column corresponds to a key step in development of cell-based therapies. Colored lines corresponding to individual publications connect the specific cell types tested, delivery methods and genetic engineering tools used and genes targeted, listed in the six columns.


Thank
you!