HIV-1 infection: When the virus and the host play hide and seek

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HIPer
HIV, Inflammation and Persistence

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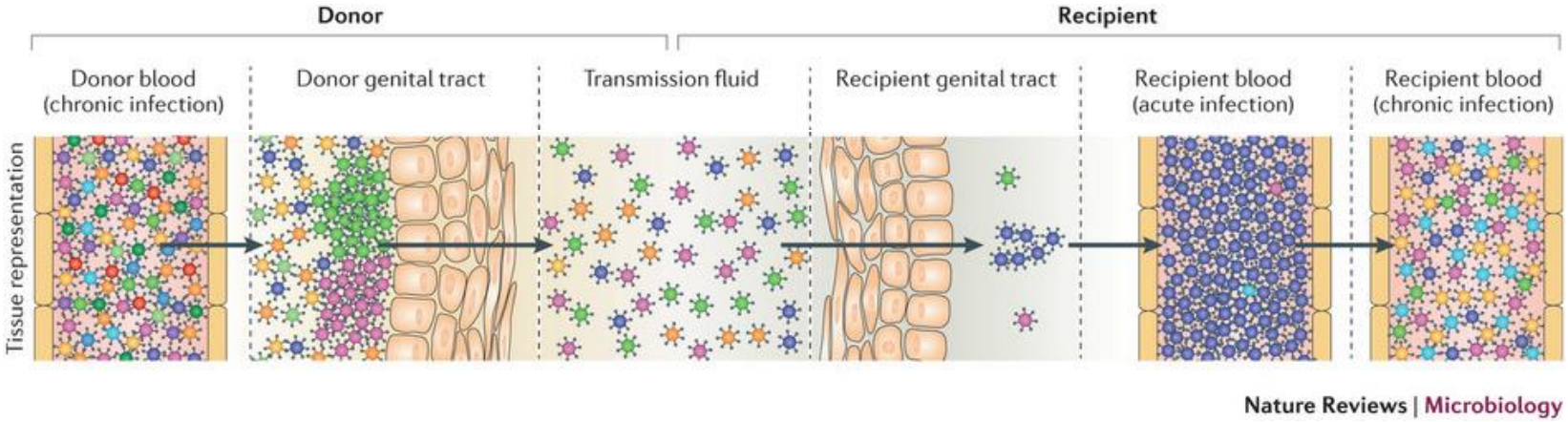
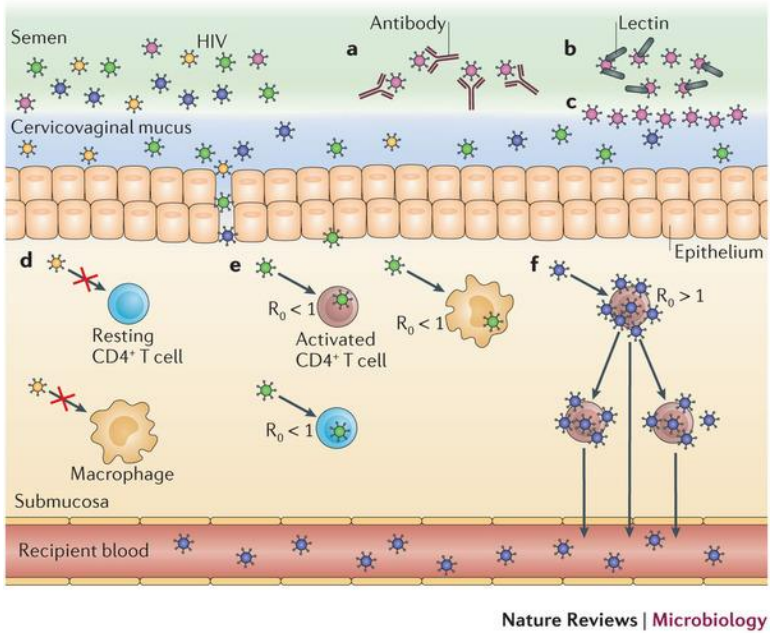
HIViera
Remission of HIV infection era

HIV-1 infection starts with transmission of limited number of founder viruses

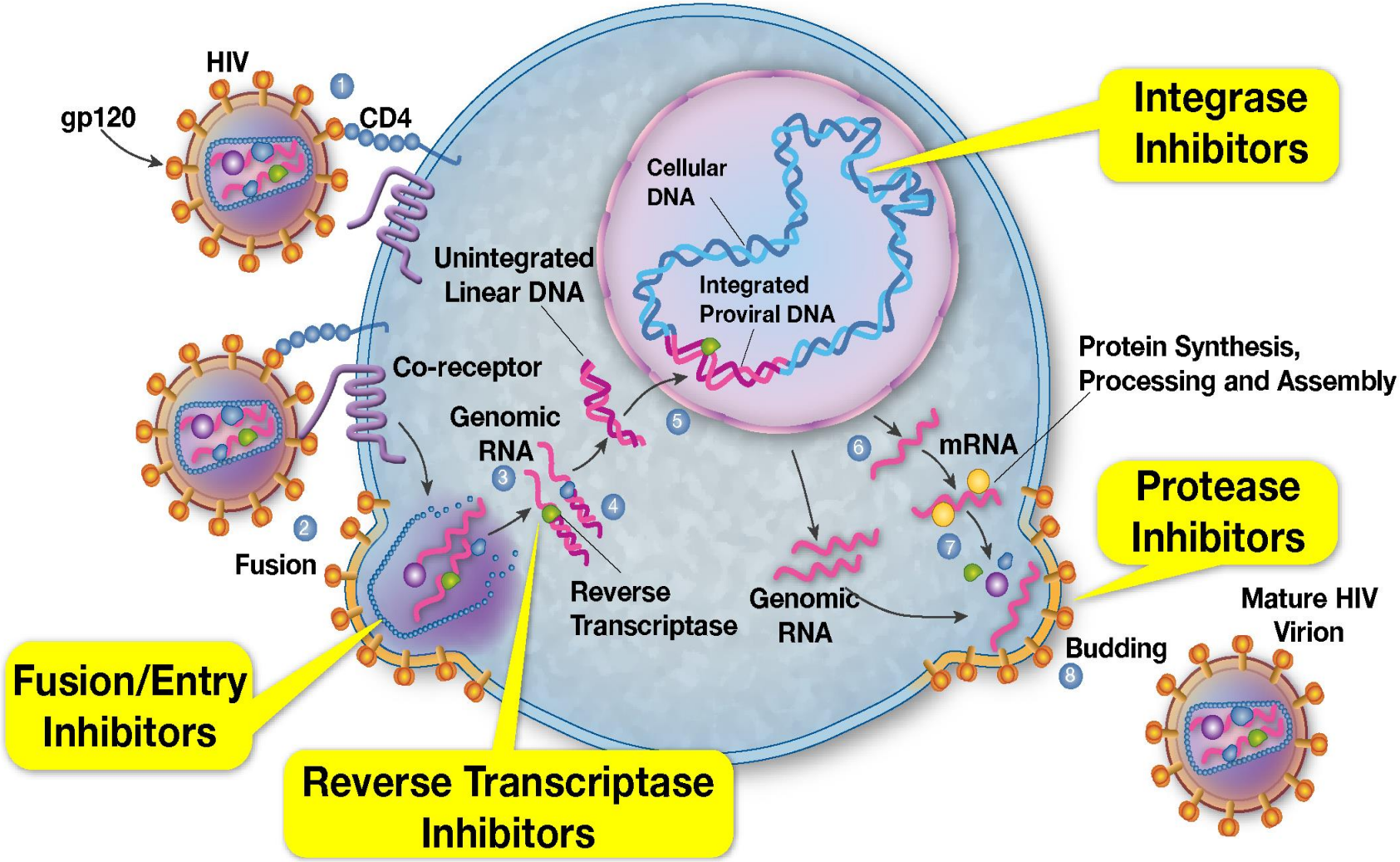




Several factors determine the selection of the founder viruses:
- Sensitivity to autologous antibodies
- Sensitivity to IFN
- Level of glycosylation
- Fitness to infect target cells

Joseph et al *Nat Rev Microb 2015* 13, 414–425

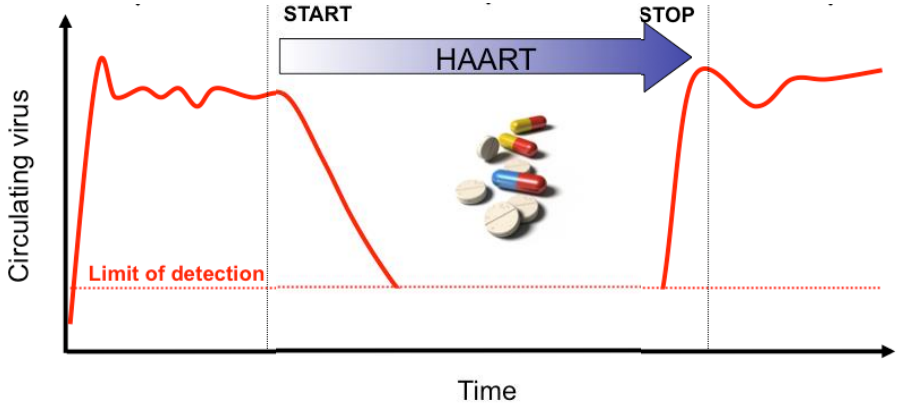
HIV-1 replication cycle: multiple targets for antiretroviral therapy

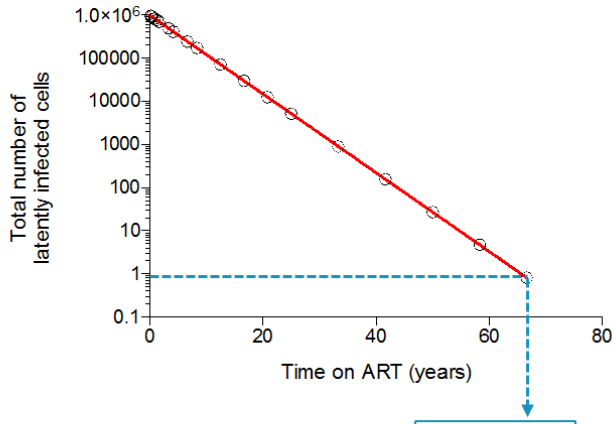


However antiretroviral therapy does not target the integrated provirus

Adapted from A Fauci

HIV persists in cellular reservoirs despite durable antiretroviral treatment





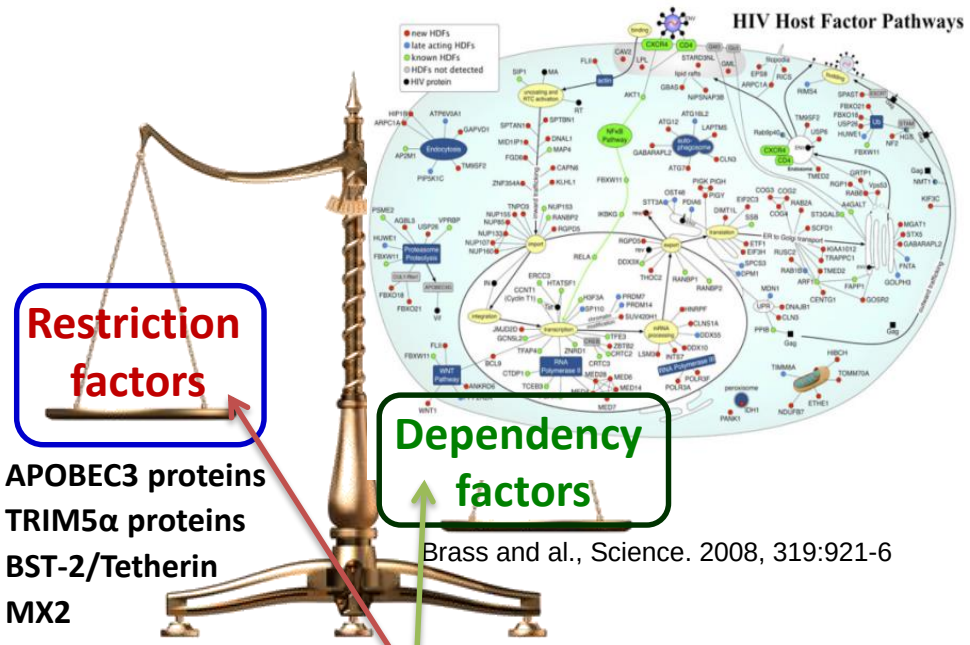
Time on treatment : **65.7 year**

Chomont et al unpublished

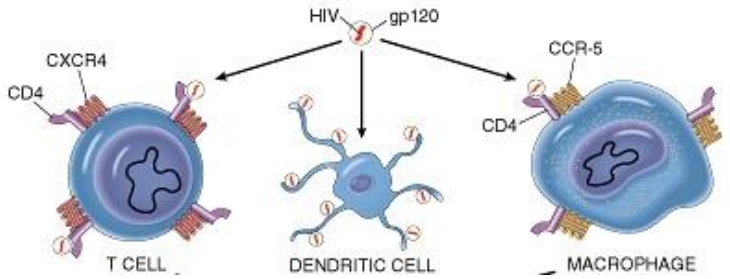
Establishment of HIV reservoir is a multifaceted process

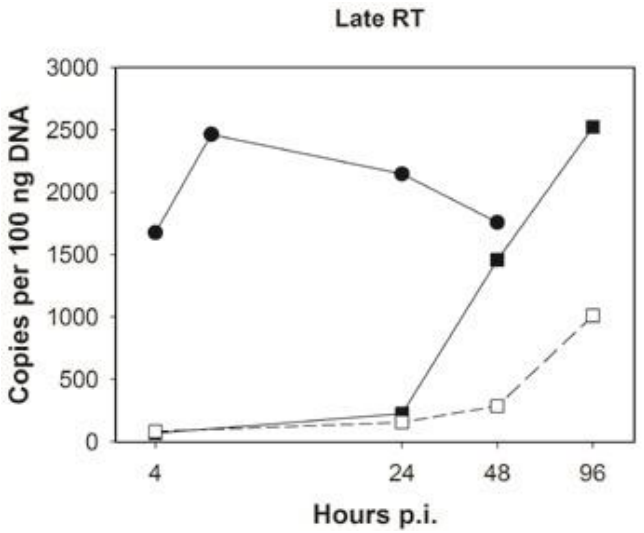
Cell susceptibility to infection

Balance between restriction and dependency factors



Brass and al., Science. 2008, 319:921-6





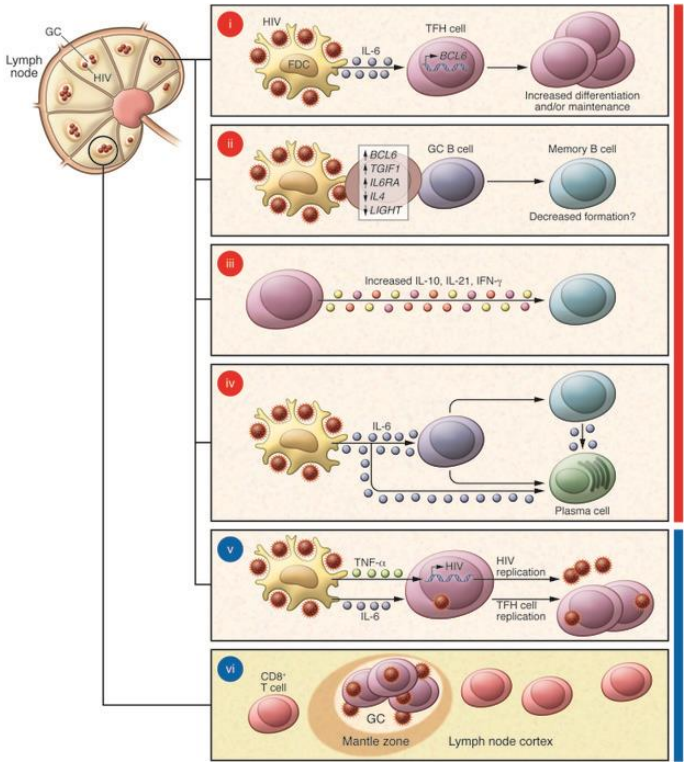
Establishment of HIV reservoir is a multifaceted process

Cell susceptibility to infection

Survival to HIV infection

Resistance to HIV induced apoptosis

Escape immune surveillance



FDC cytokines ➔ enhance HIV replication in TFH cells and increase proliferative rate of infected TFH cells viral persistence, since germinal centers are relatively devoid of cytolytic $CD8^+$ T cells.

Vinuesa J Clin Invest. 2012

Establishment of HIV reservoir is a multifaceted process

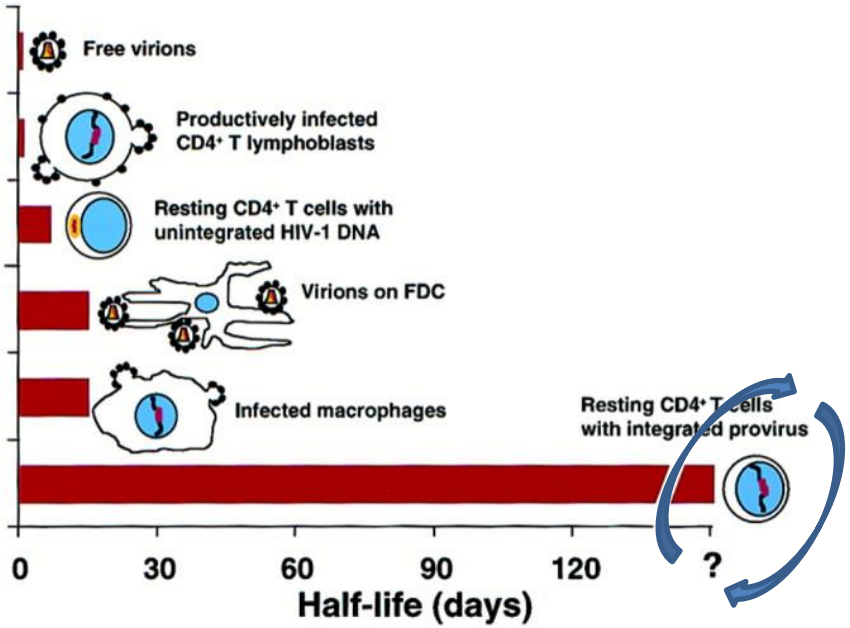
Cell susceptibility to infection

Survival to HIV infection

Cell Persistence

Half life

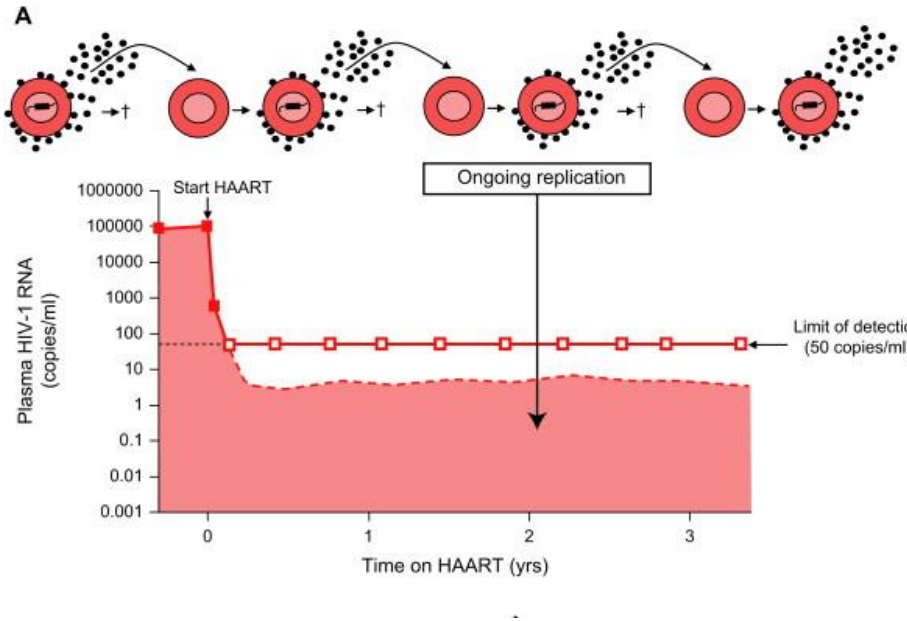
Turnover



Finzi et al. Cells 1997

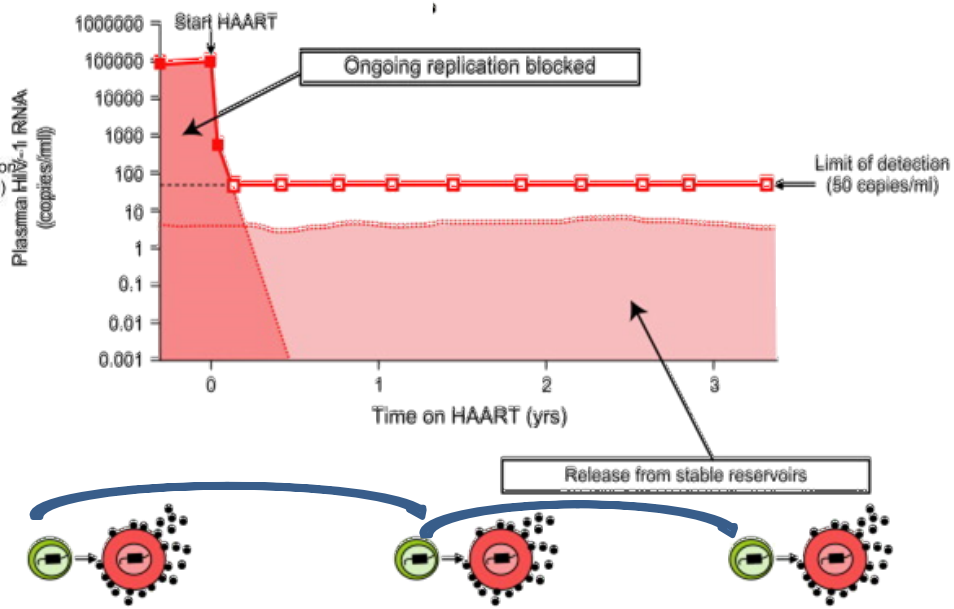
Two models to explain persistence on cART

Low level HIV replication



cART does not completely block viral replication (and in particular cell-to-cell transmission)

Survival and cell proliferation



Viral particles are released by infected cells that persist by homeostatic proliferation

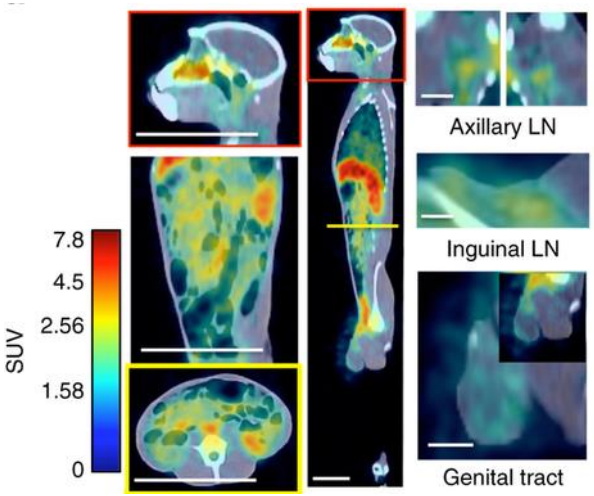
Adapted from Shen and Siliciano. JACI 2008

HIV infects cells from the immune system that contribute to spread and persistence

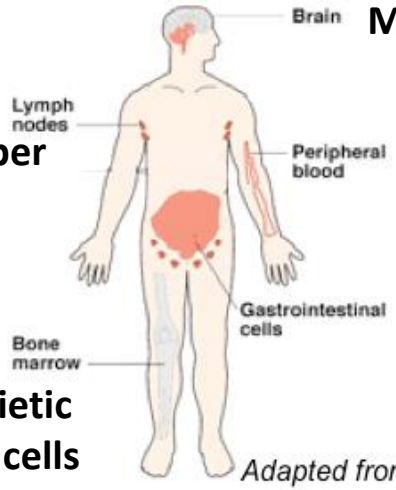
Dendritic cells

CD4⁺ T lymphocytes
(incluidng HIV-specific cells)

Monocytes/macrophages



Follicular DCs
T Follicular Helper



Microglial cells

T cells

T cells ($\alpha 4\beta 7$, CCR6+)

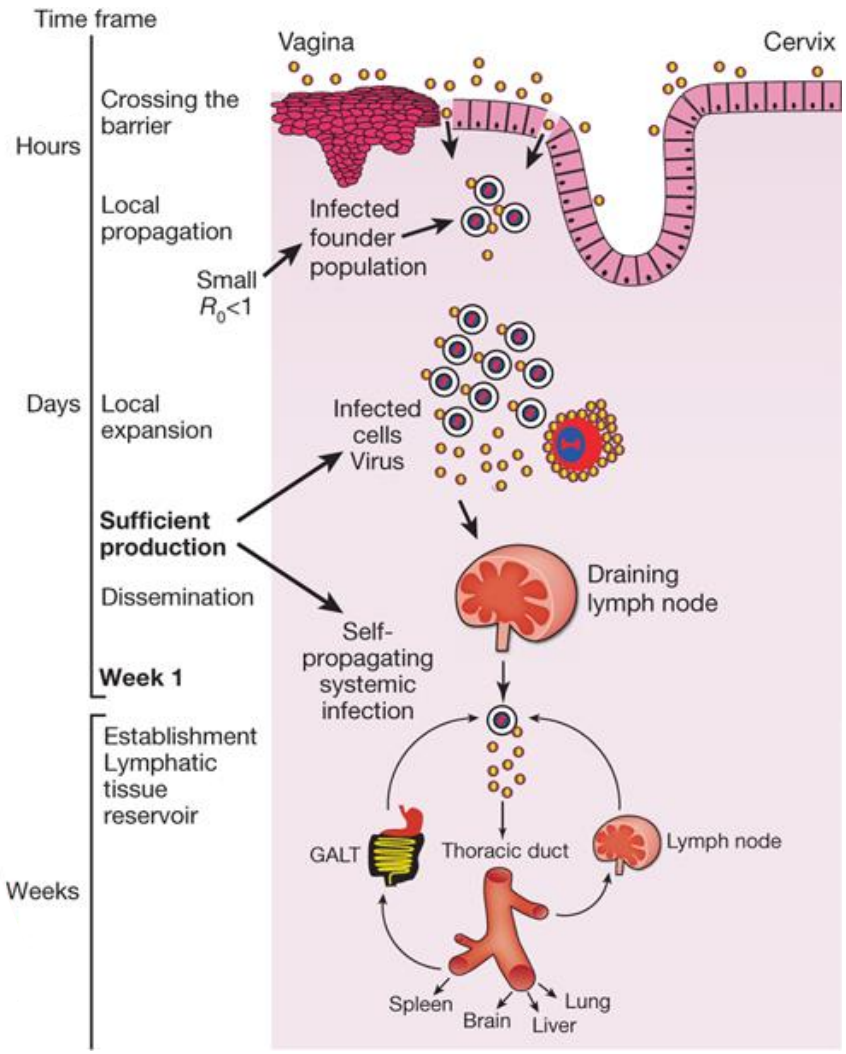
macrophages

hematopoietic progenitor cells

Santangelo et al Nat Methods 2015

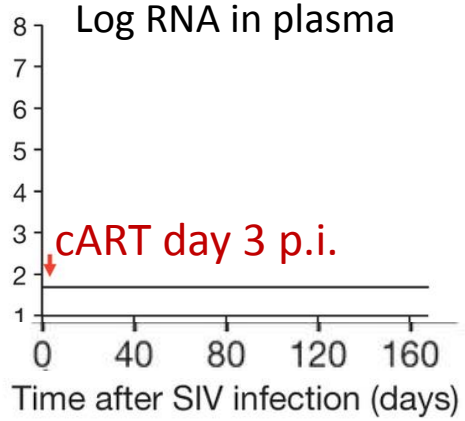
HIV replication is compartmentalized

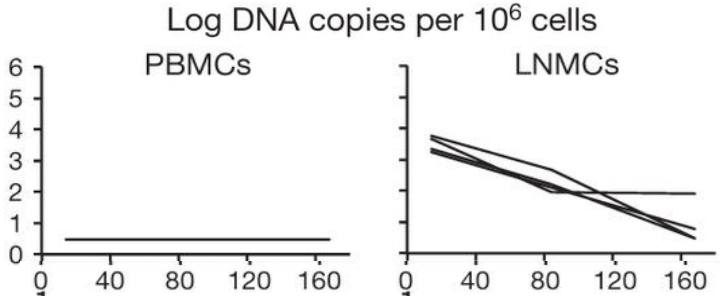
Spread and establishment of reservoirs is a fast process

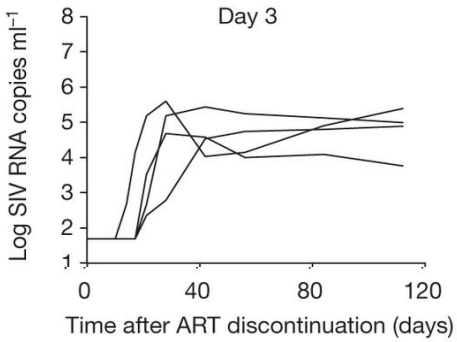


Haase Nature 2010

SIV reservoir established within 3 days?



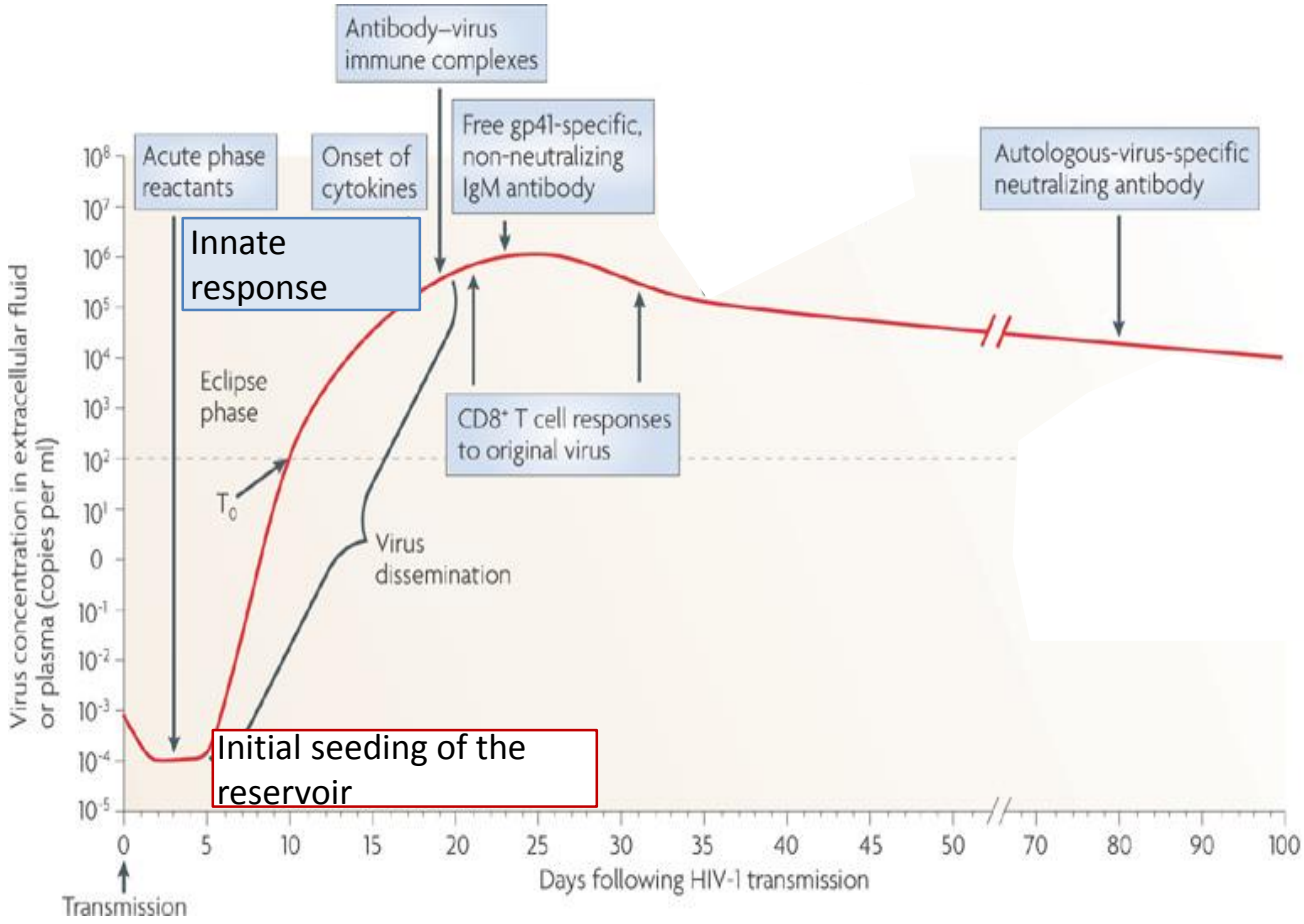




Whitney et al Nature 2014

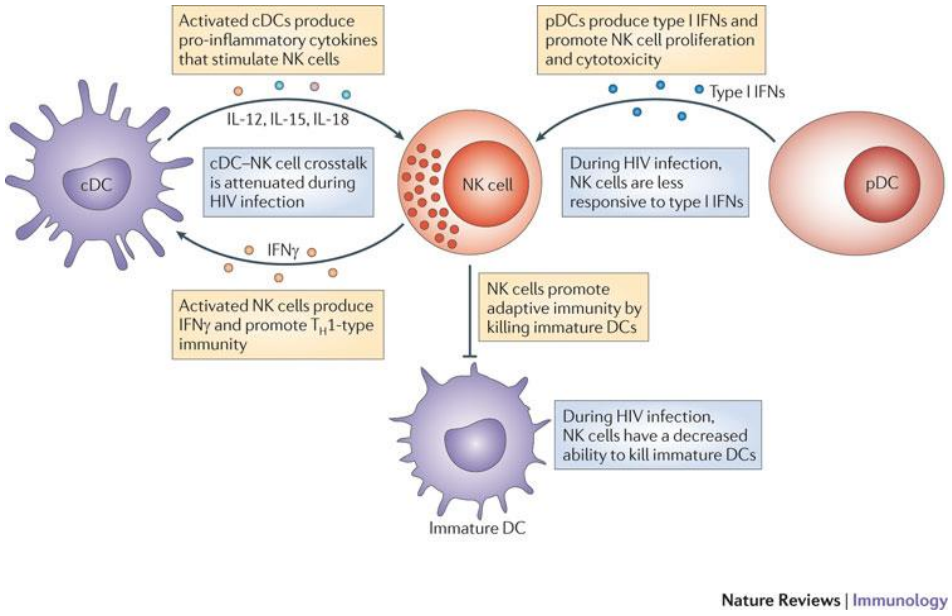
Development of Immune responses during acute HIV-1 infection

Concomitant establishment of viral reservoirs and development of immune responses

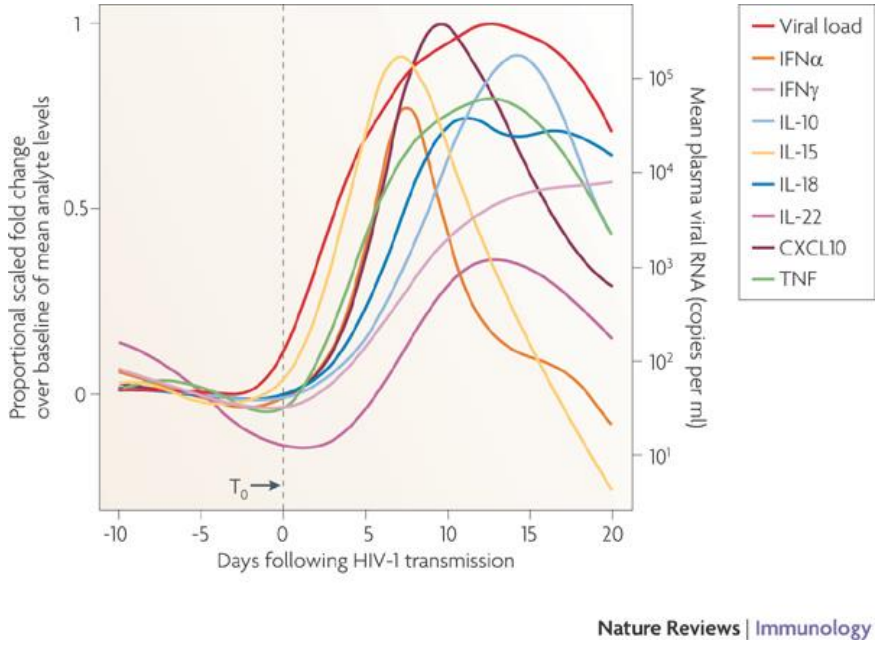


Adapted from McMichael et al Nat Rev Immunol 2010

Very early events and innate immunity



M.Altfeld, et al, 2011, Nat Rev Immunol



McMichael et al 2010 Nat Rev Immunol

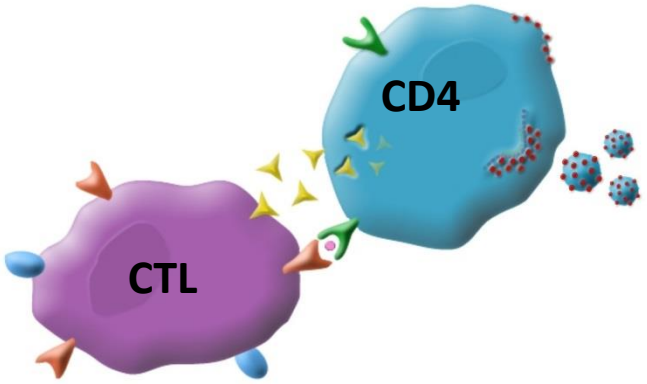
-Innate immunity constitutes a first barrier of defense against HIV infection:

NK cells have direct antiviral activity and promote adaptive immunity

Type I IFN production by pDCs

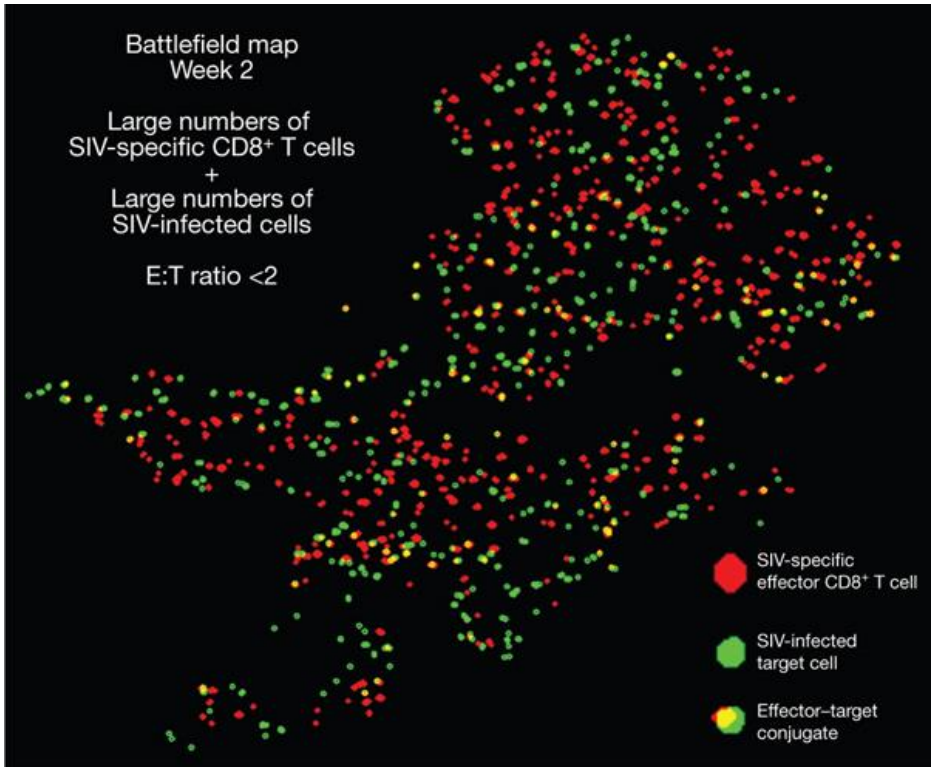
-Early and strong cytokine response may contribute to viral dissemination, establishment of reservoir and may decide the fate of immune responses

The CD8+ T cell response contributes to partially control HIV infection



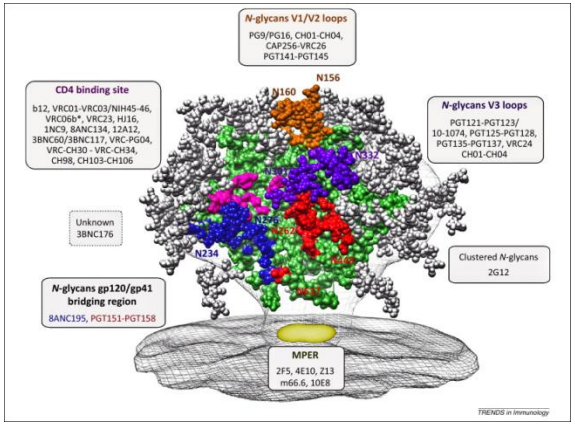
CD8+ T cells produce soluble anti-HIV factors (b-chemokines, CAF(?)) and eliminate infected cells through cytotoxic mechanisms.

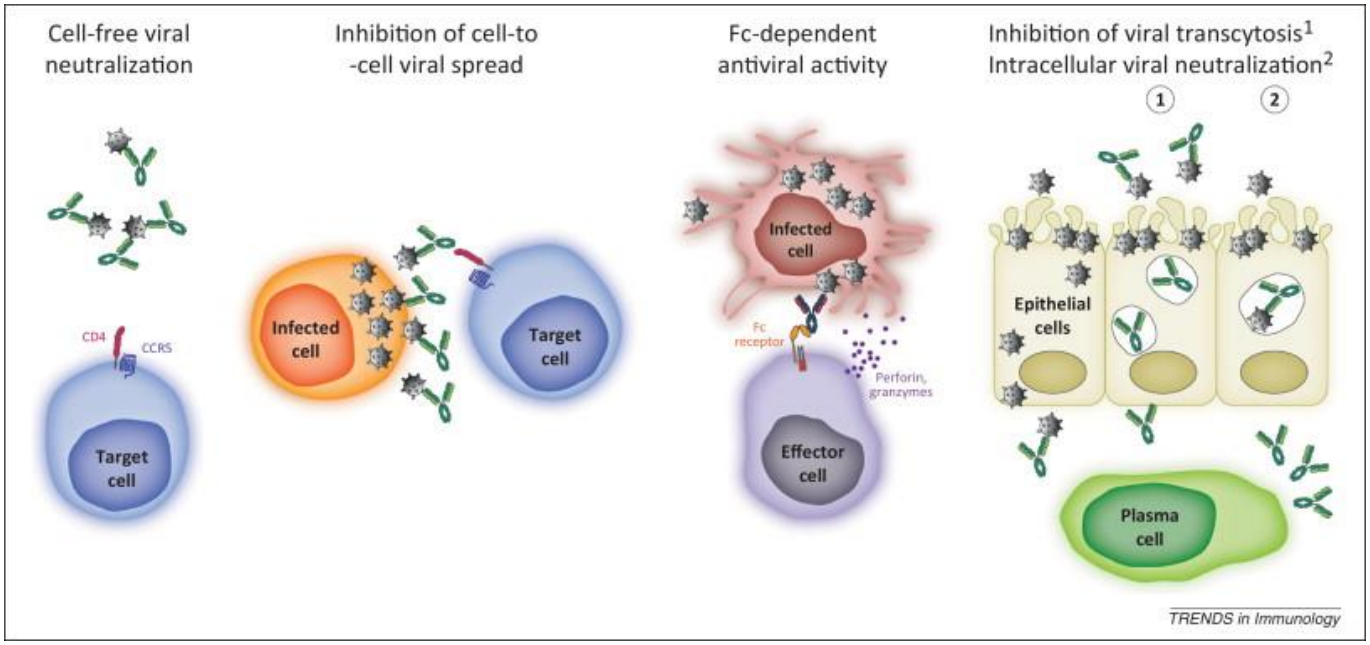
-Coincidence between the appearance of HIV specific CD8+ T cells and control of primary infection.
-Depletion of CD8+ T cells during SIV infection leads to increased viral load.
-Association between Class I HLAs and level of viremia



Haase, Nature, 2010, 464, 217-223

Antibodies against HIV: multiple ways to tackle the infection

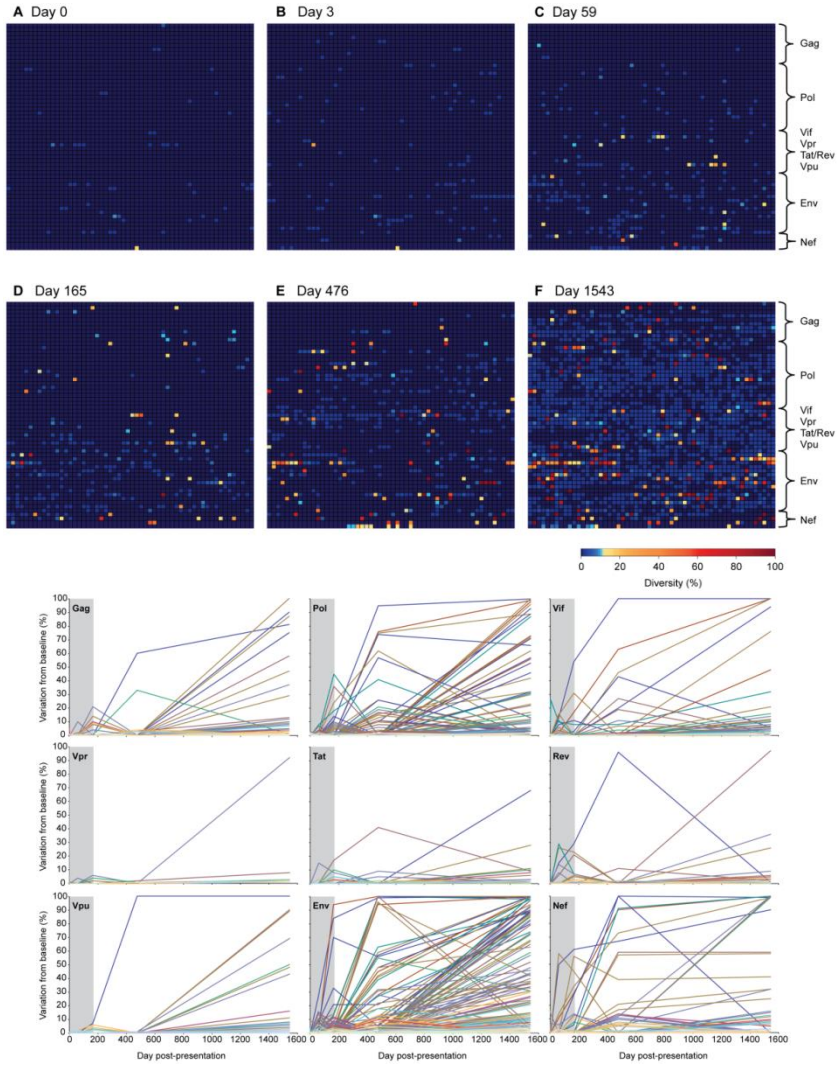




H Mouquet Trends Immunol 2014

Ultimately these defenses are inefficient to control the virus

Virus evolves to escape immune responses



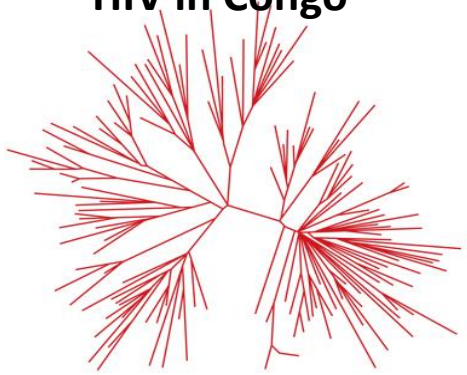
Henn et al, PLoS Path, 2012

1% of variability/year in each infected individual

Global flu

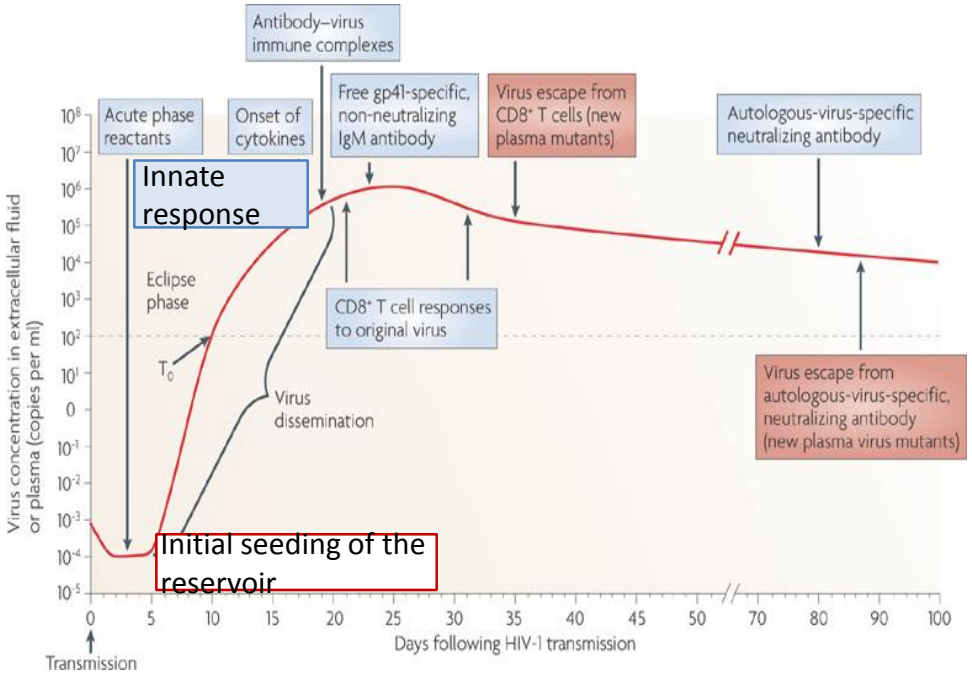
HIV one patient

HIV in Congo



Viral diversity 1996

Adapted from R Weiss Nature 2003 and B Korber Br Med Bull 2001



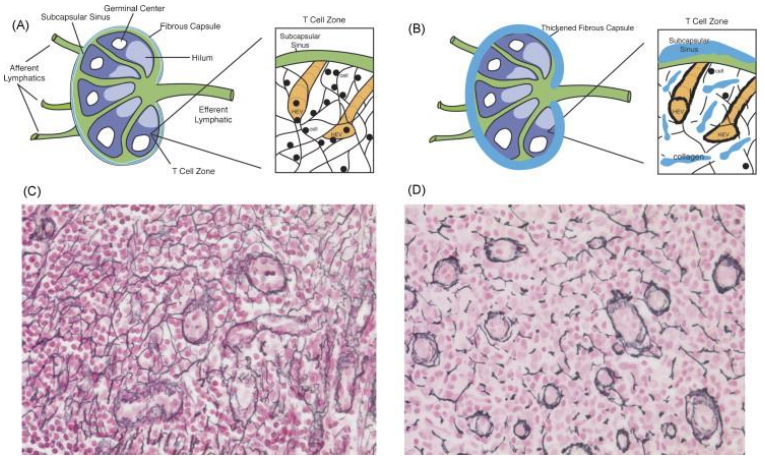
Inefficient control of infection leads to exhaustion of immune responses and damage of lymphoid structures

JEM

	IFN-γ	TNF-α	IL-2	CTL	Proliferative potential	Apoptosis	Antigen load	CD4 help	PD-1 expression
							Low	High	Low
Functional T cell	+++	+++	+++	+++	+++	–			
Partial exhaustion I	++	+/–	–	–	++	+/–			
Partial exhaustion II	+	–	–	–	+	++			
Full exhaustion	–	–	–	–	–	+++			
Deletion	–	–	–	–	–	++++	High	Low	High

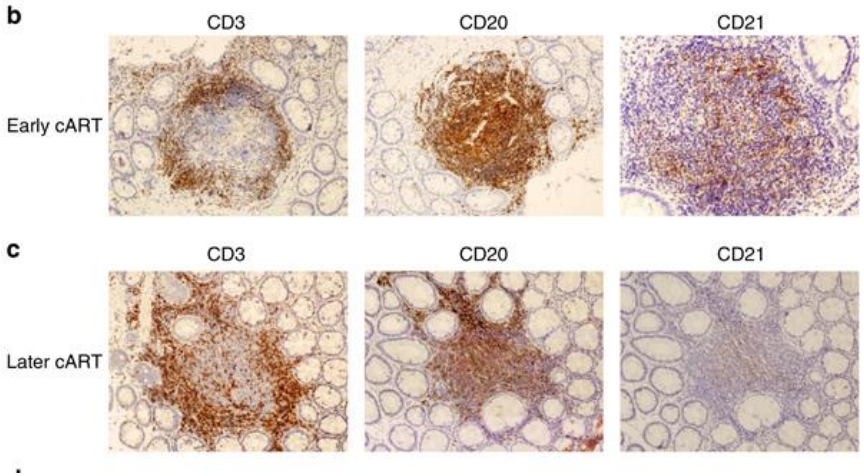
Freeman et al JEM, 2006, 203, 2223-2227

Disruption of reticulin network in T cell zone



Estes et al. Seminars Immunol 2008, 20, 181-86

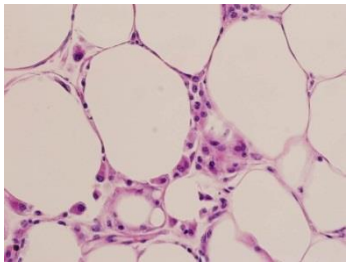
Loss of organized B cell follicles



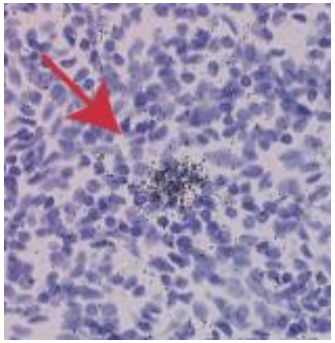
Kök et al. Mucosal Immunol 2015, 8, 127-40

HIV associated chronic inflammation

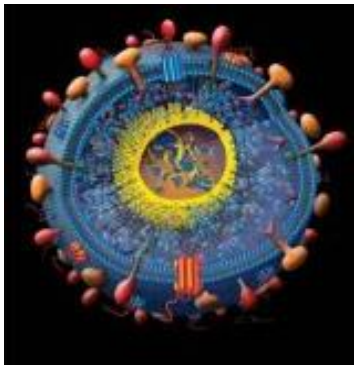
HIV-associated fat
Metabolic syndrome



HIV production
HIV replication

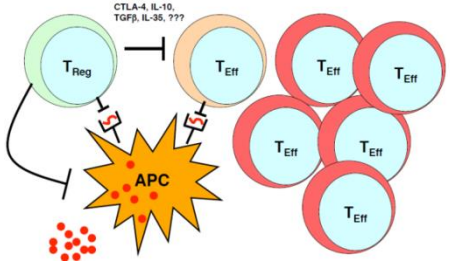


CMV
Excess pathogens

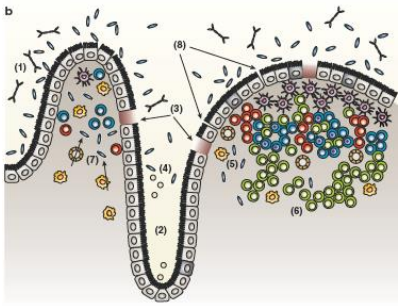


Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

Loss of regulatory cells



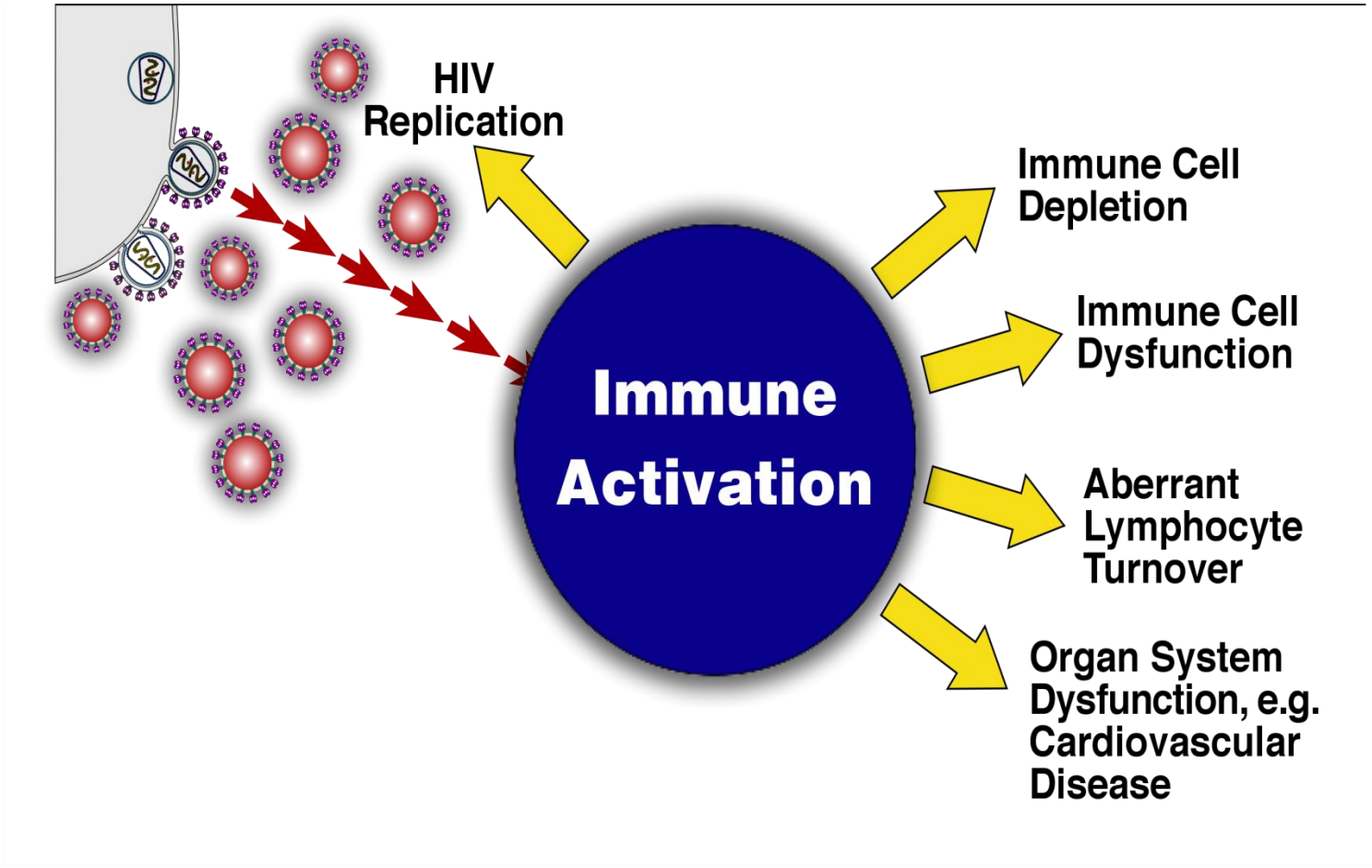
Microbial translocation



Co-morbidities
Aging

Steven Deeks, IAS 2013, KL

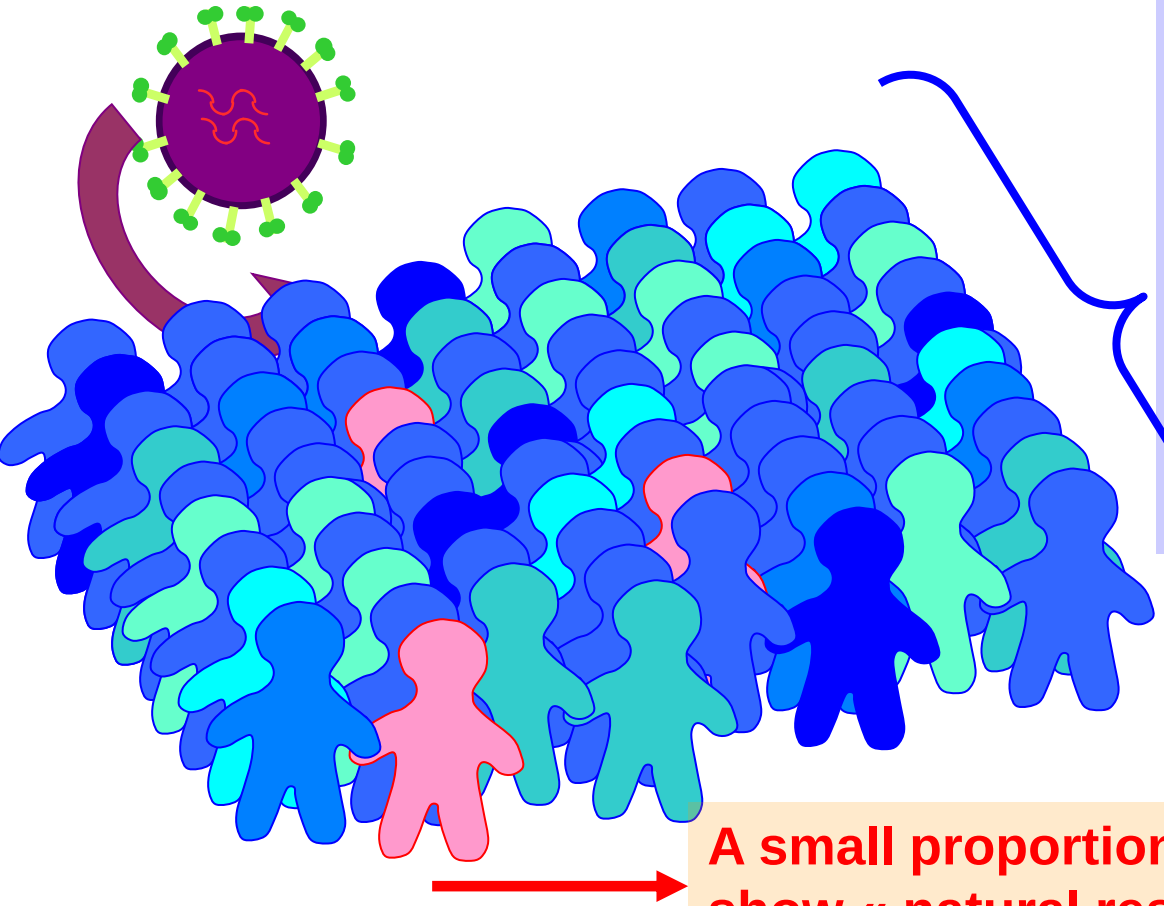
Immune activation and HIV pathogenesis



A Fauci. 30 years of HIV infection. 2013

All the same, but all different in response to HIV

Extensive interindividual variability in response to HIV *(susceptibility to virus, transmission and disease progression…*)

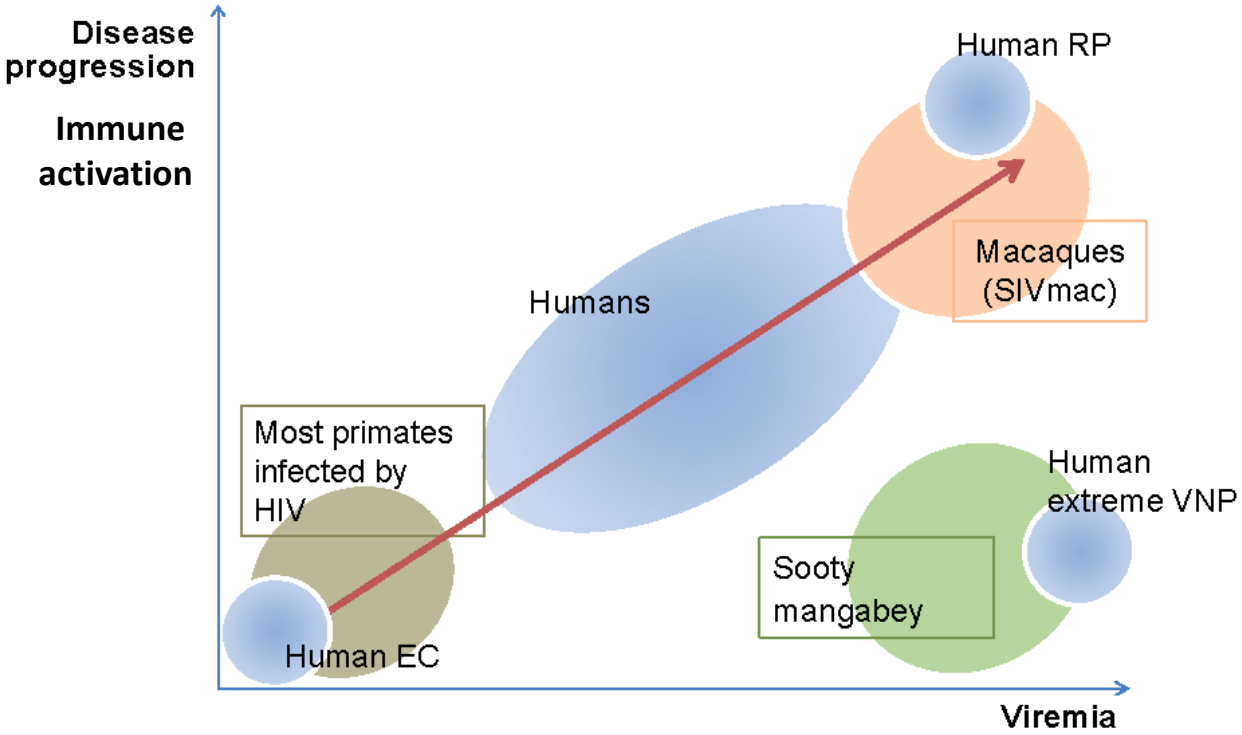


Differences in viral set points, rates of CD4 T cells decline, levels of viremia, inflammation/immune activation, emergence of CTL escape mutants or development of opportunistic infections

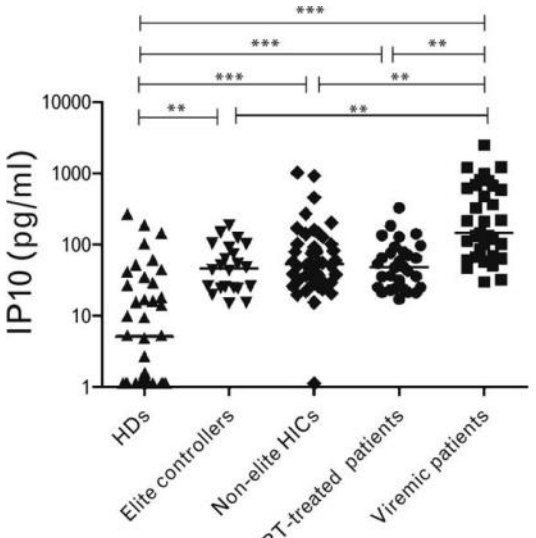
A small proportion of HIV-1 infected people show « natural resistance » to infection (HESN) or to disease progression (HIC,LTNP)

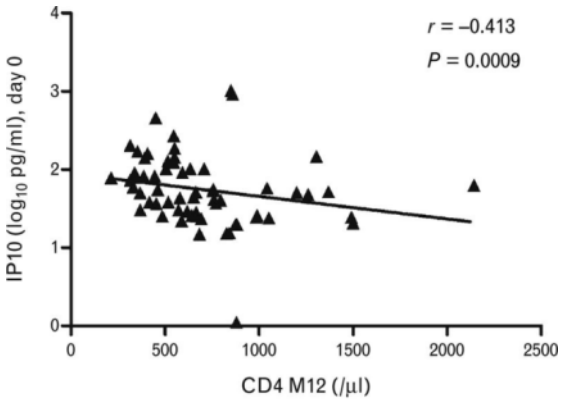
F Barré-Sinoussi

Distinct HIV/SIV infection outcomes



Adapted from G. Silvestri





Noel et al AIDS 2014

Three steps to control HIV-1 infection

1- Limit viral reservoirs
2- Develop efficient mechanisms to control viral rebound
3- Restrain immune activation/inflammation

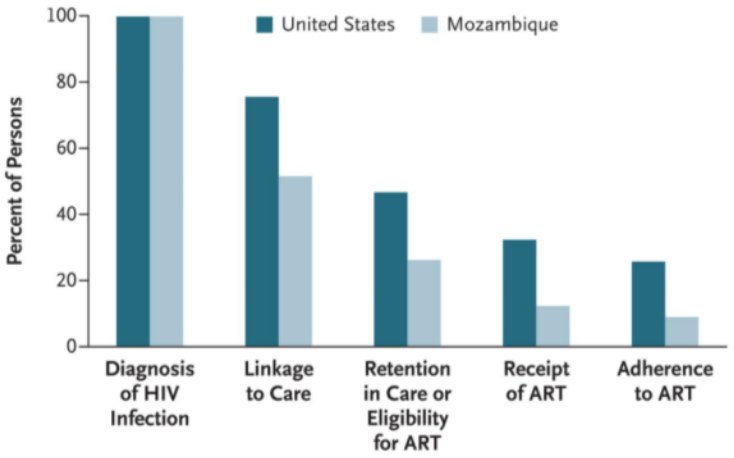
HIV/AIDS: an outstanding global health problem

~ 36.9 million people living with HIV

cART introduction changed the face of the epidemic, however:

- 2.0 million new infections/year
- 1.2 million deaths/year
- 60% of patients still in need of life-long cART

Patients request alternative strategies



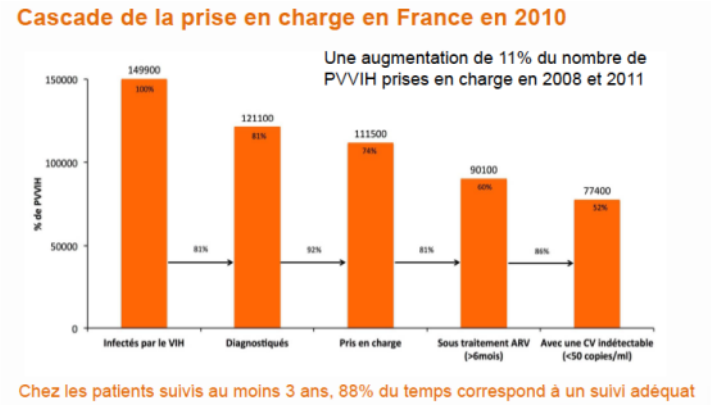


Fig. 2 : Nombre de découvertes de séropositivité VIH, France, 2003-2012
(Source : Déclaration obligatoire du VIH, données corrigées au 31/12/2012, InVS)

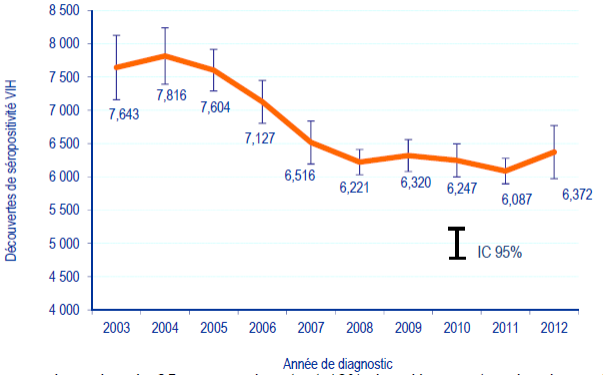


Fig. 4 : Nombre de découvertes de séropositivité VIH par mode de contamination et par pays de naissance, France, 2003-2012 (Source : Déclaration obligatoire du VIH, données corrigées au 31/12/2012, InVS)