

# PATHOGENESIS OF AIDS

how does HIV cause AIDS?

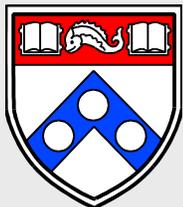
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- **Definitions**
- **Structure of HIV**
- **HIV entry and cell tropism**
- **HIV-cell interactions**
- **Course of HIV infection and AIDS**
- **HIV variants during infection**
- **HIV persistence**
- **How does HIV cause immunodeficiency?**

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## DEFINITIONS

- **HIV: human immunodeficiency virus**  
HIV is a member of the lentivirus family, a subgroup of retroviruses, RNA viruses that replicate via a DNA intermediate
- **AIDS: acquired immunodeficiency syndrome**  
AIDS is defined by a loss of CD4 T lymphocytes or the occurrence of opportunistic infections or cancers

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## STRUCTURE OF HIV

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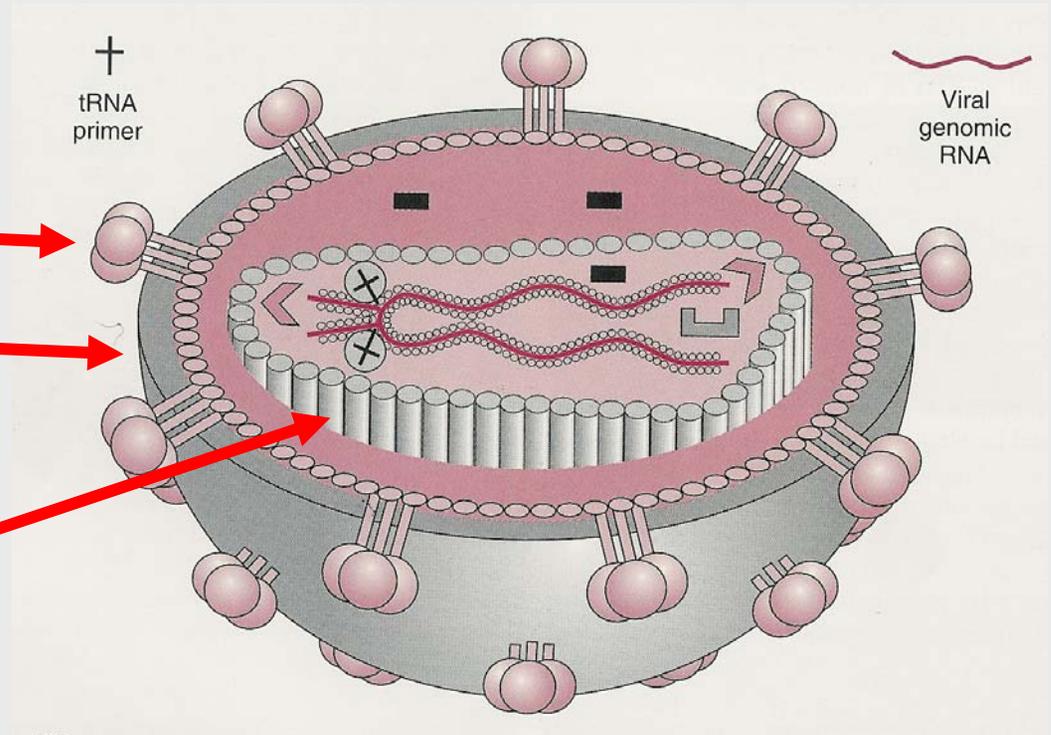
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A diagram of the virus particle to show the internal structure (after Brooks et al, 1998)

**VIRUS SPIKE  
CONSISTING OF  
TWO ENVELOPE PROTEINS  
gp120 and gp 41**

**VIRUS ENVELOPE  
(LIPID BILAYER)**

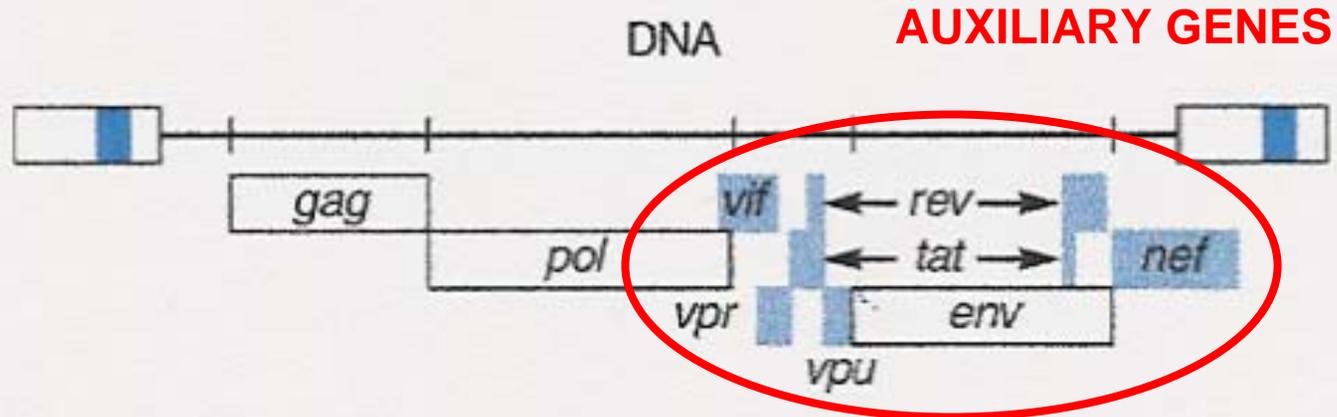
**VIRUS CAPSID  
CONTAINING THE  
RNA GENOME**



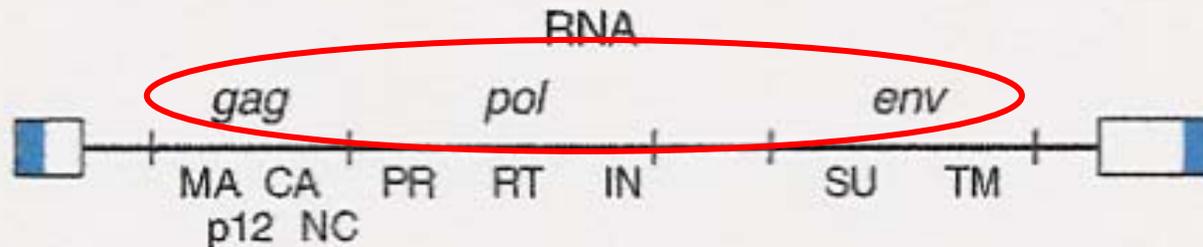
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The genes of HIV in the virion (RNA) and integrated into host cell genome (DNA)



**STRUCTURAL GENES**



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## HIV ENTRY INTO CELLS AND CELL TROPISM

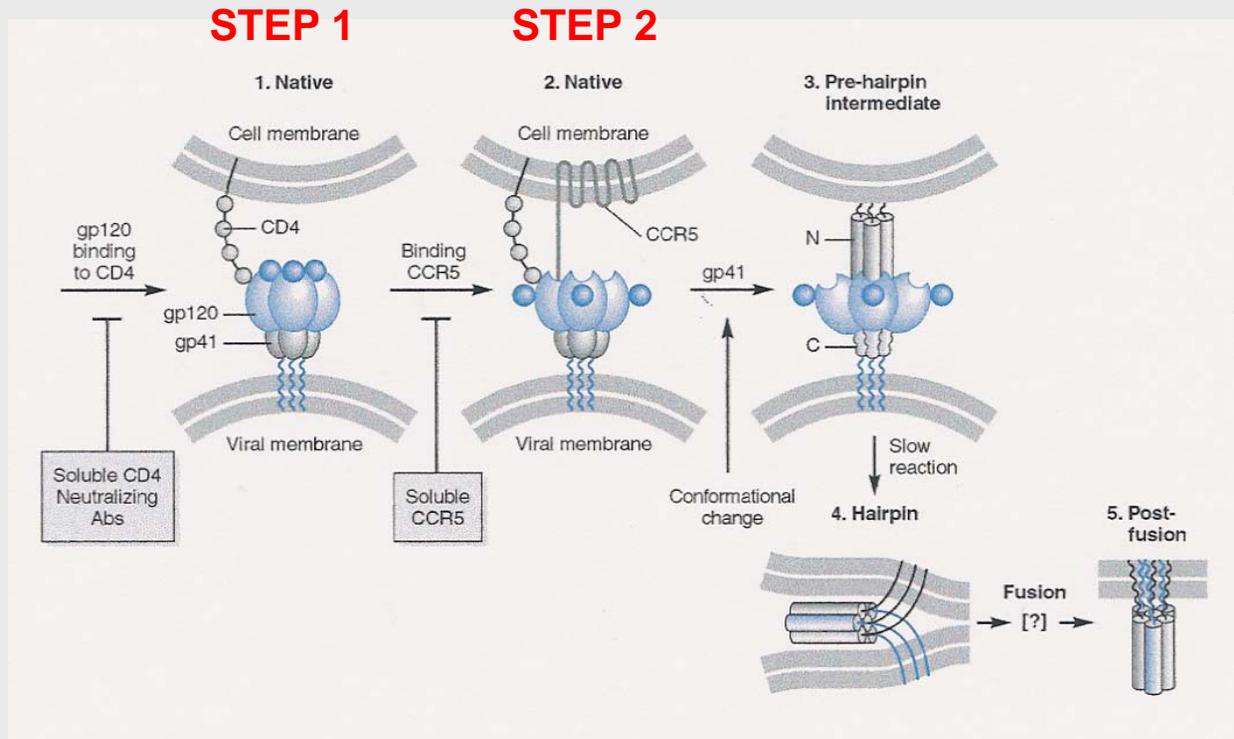
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## how does HIV cause AIDS?

HIV attaches to cells in two steps

**STEP 1** HIV attaches to its primary receptor, CD4

**STEP 2** HIV attaches to a co-receptor, either CCR5 or CXCR4



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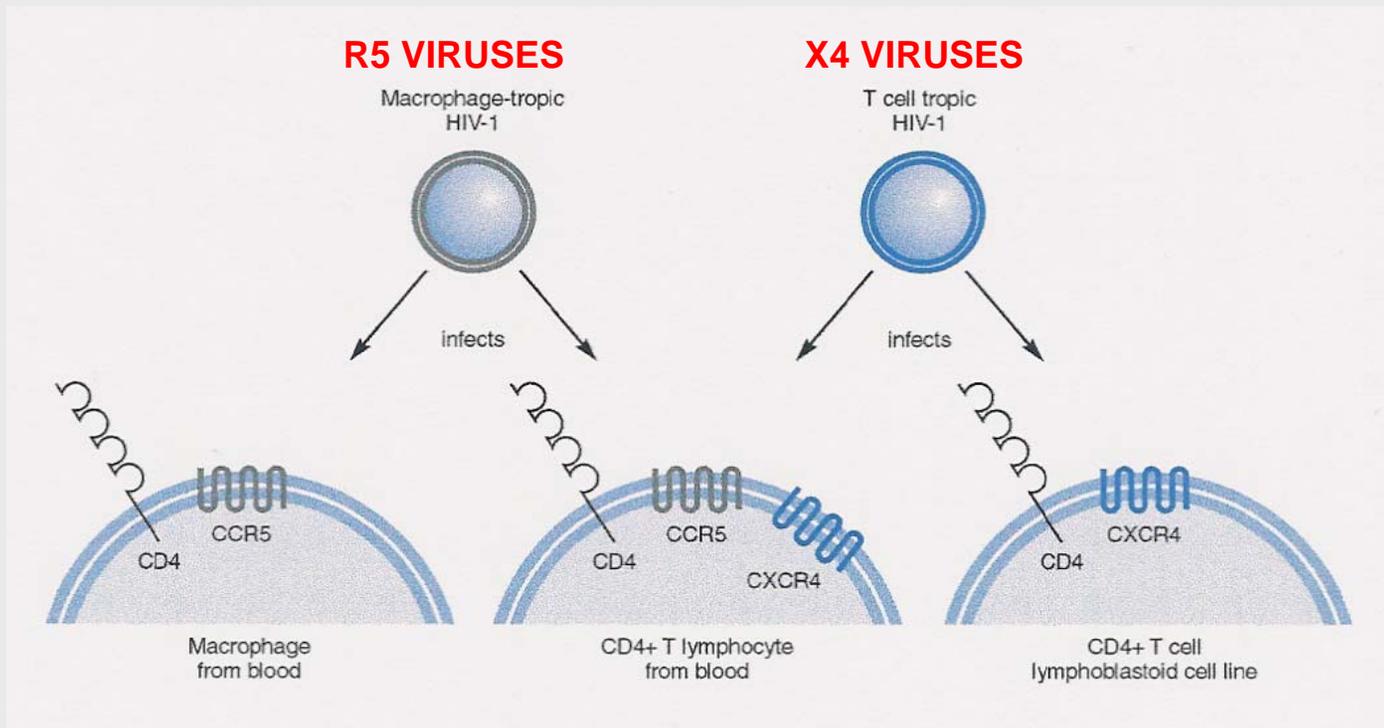
## how does HIV cause AIDS?

**HIV infects cells that carry the receptor and co-receptor**

**CD4** Expressed on the surface of CD4 T lymphocytes (helper T lymphocytes) and macrophages (including dendritic cells)

**CCR5** Expressed on CD4+ T lymphocytes and on macrophages

**CXCR4** Expressed on CD4+ T lymphocytes and T cell lines



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## HIV-CELL INTERACTIONS

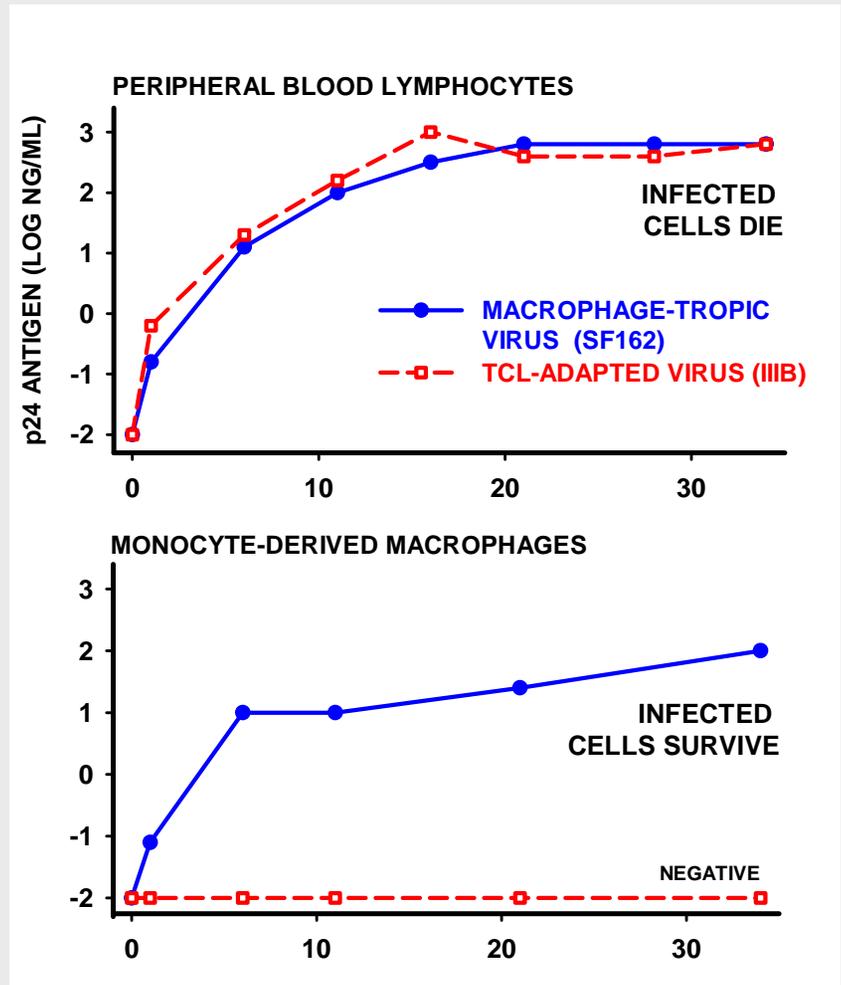
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HIV infection of cultured cells shows (Collman, 1989)

both R5 and X4 viruses infect and kill CD4 T lymphocytes

Only R5 viruses infect macrophages and they are not killed



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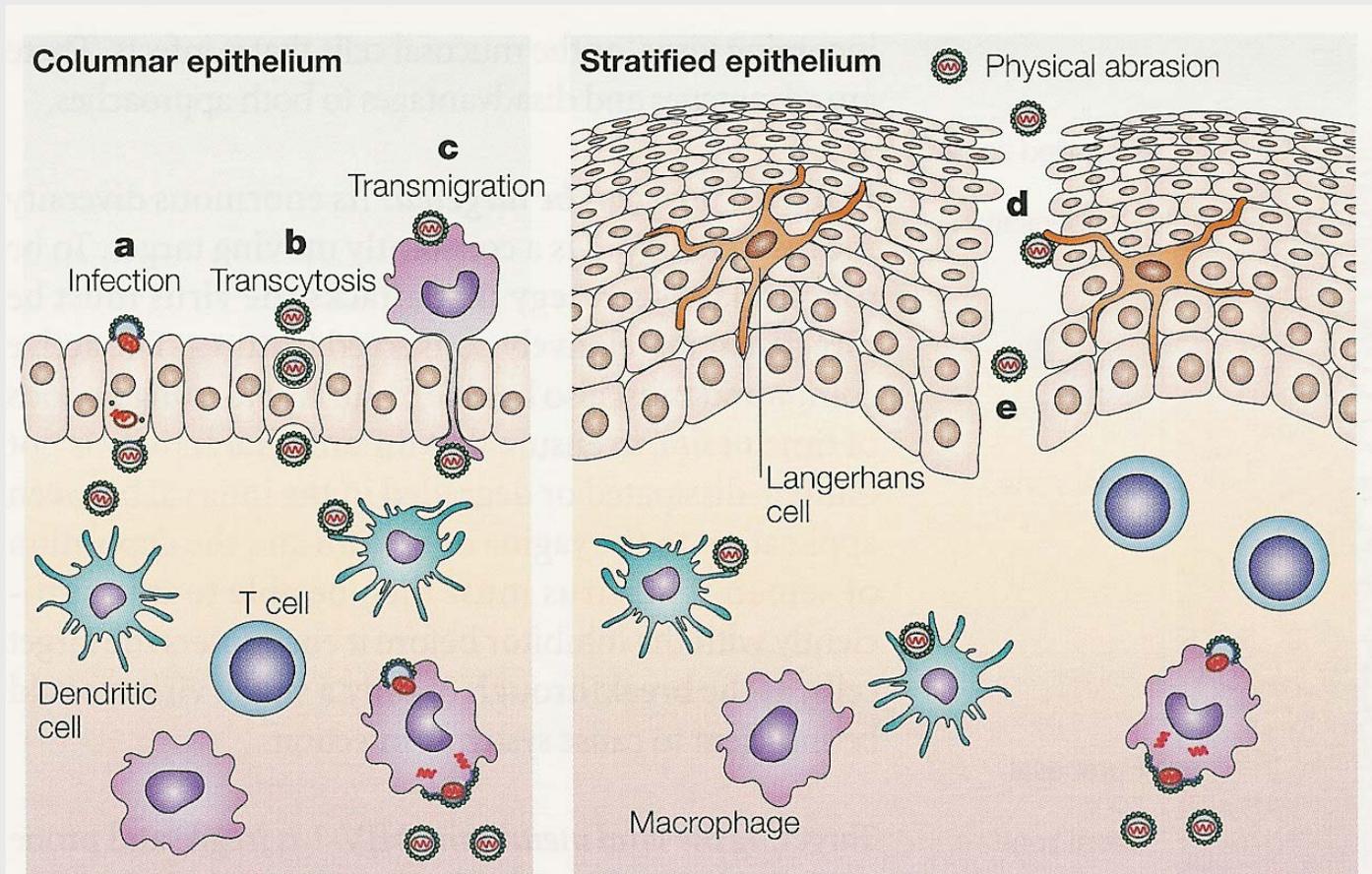
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## COURSE OF HIV INFECTION AND AIDS

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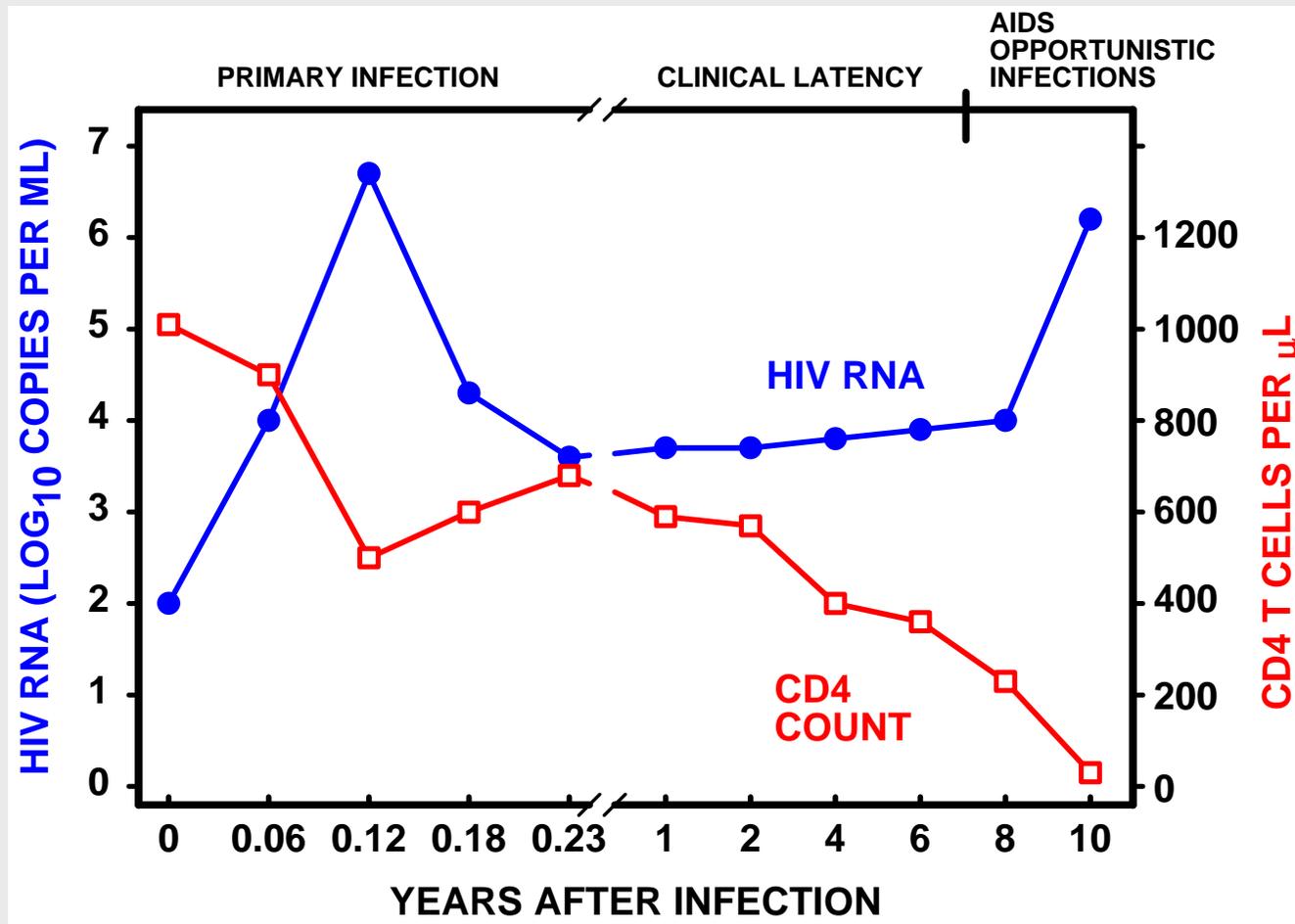
## HOW HIV INITIATES HETEROSEXUAL INFECTION (Shattock, 2003)



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THE COURSE OF HIV INFECTION AND AIDS (After Fauci, 1993)



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HIV VIREMIA BY STAGE OF HIV INFECTION (Bagasra, 1993; Pan, 1993)

STAGE OF INFECTION	CD4 CELL COUNT	PLASMA HIV (TCID PER ML)	% CD4+ CELLS INFECTED
ASYMPTOMATIC	>500	100	3%
GENERAL LYMPHADENOPATHY	300-499	200	20%
	200-299	400	
CLINICAL AIDS	<200	1,500	30%

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## **HIV VARIANTS DURING INFECTION**

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VIRUS VARIATION IS OFTEN SEEN DURING THE COURSE OF HIV INFECTION

BIOLOGICAL PHENOTYPE	VIRUS ISOLATED FROM PATIENTS WITH	
	ASYMPTOMATIC EARLY INFECTION	AIDS
REPLICATION KINETICS	SLOW/LOW	HIGH/RAPID
SYNCYTIUM INDUCTION	NON SI	SI
CELLULAR HOST RANGE	DUO-TROPIC	T CELL-TROPIC
CO-RECEPTOR USAGE	R5	X4

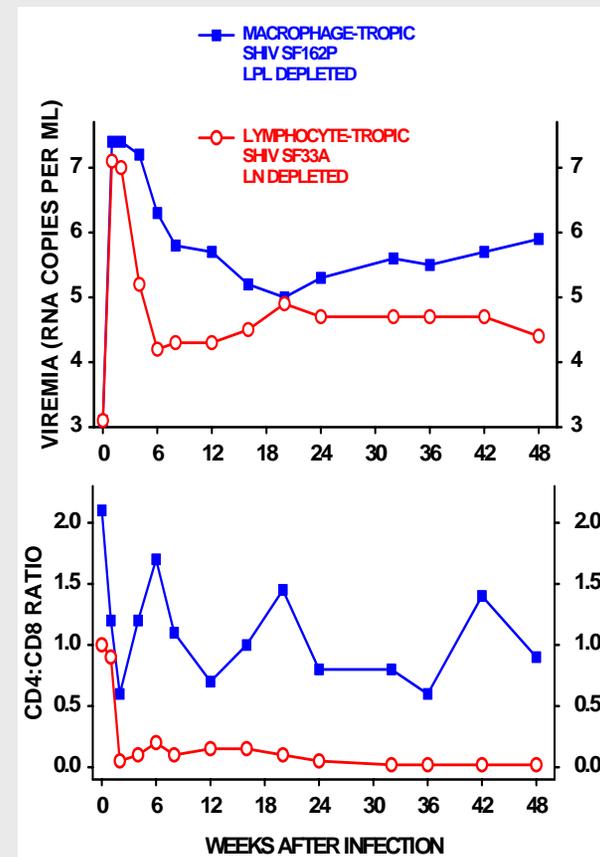
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DIFFERENTIAL INFECTION OF MONKEYS BY CO-RECEPTOR USAGE (Harouse, 1999)

**MACROPHAGE-TROPIC (R5) SHIV  
INFECTS GUT-ASSOCIATED  
LYMPHOID TISSUE PREFERENTIALLY  
WITH MODEST REDUCTION OF CD4  
CELLS IN CIRCULATION**

**T CELL-TROPIC (X5) SHIV INFECTS  
LYMPH NODES PREFERENTIALLY  
WITH SEVERE REDUCTION OF  
CIRCULATING CD4 CELLS**



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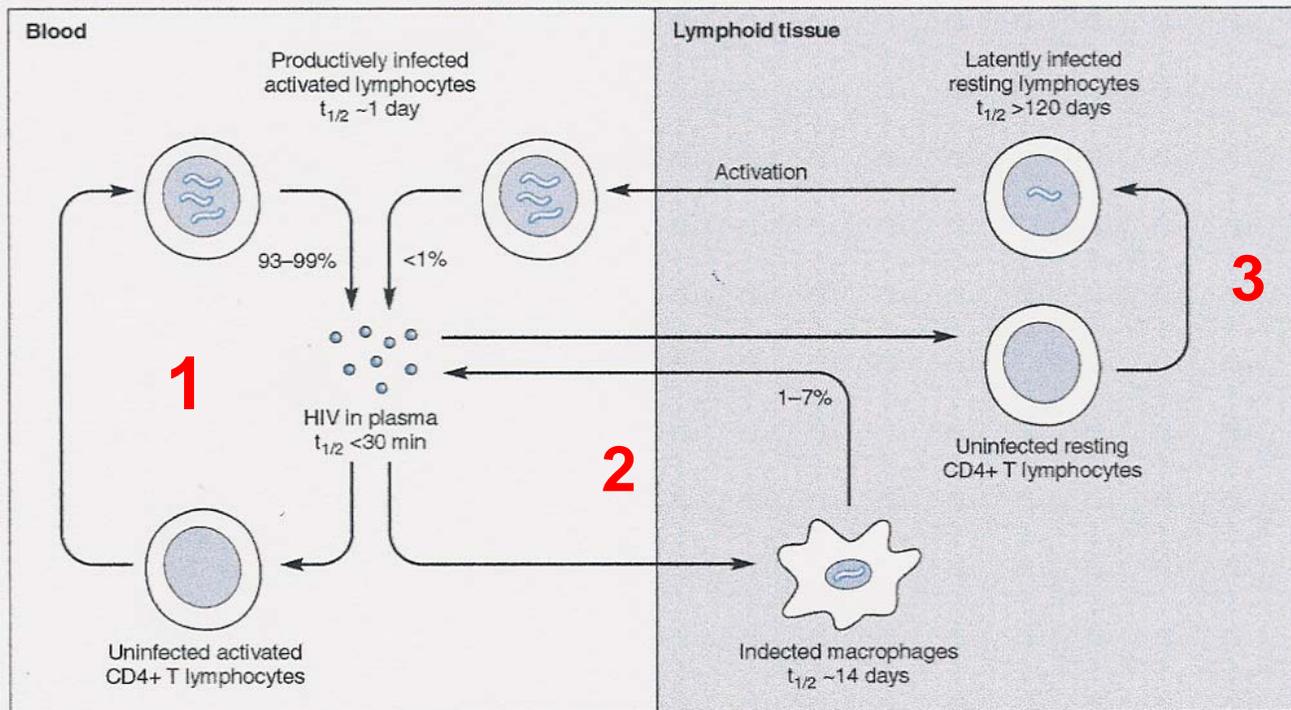
## HIV PERSISTENCE

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### HIV INFECTION IN VIVO INCLUDES (Ho, 1999)

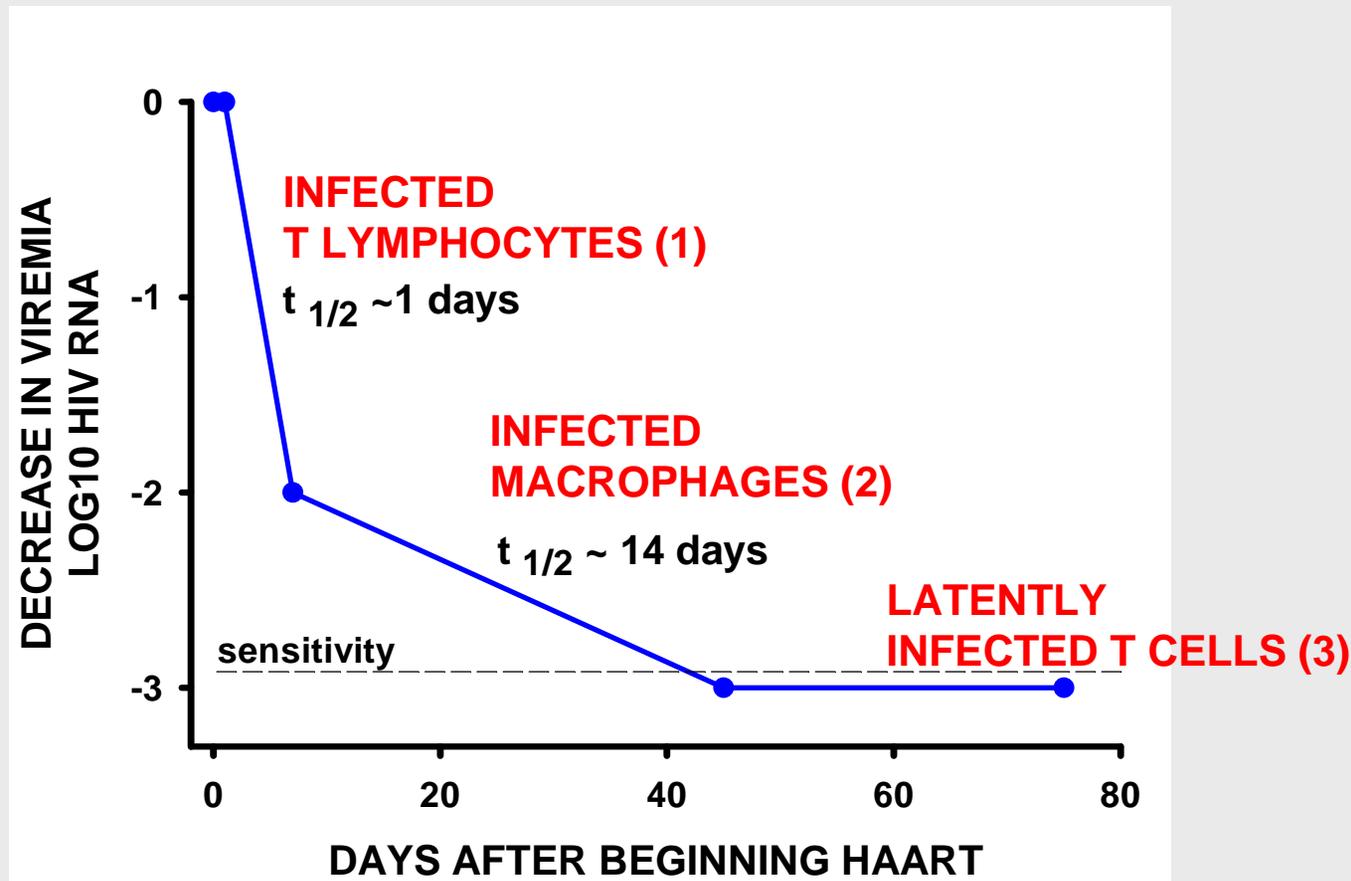
- Replication in activated T lymphocytes (1)
- Replication in macrophages (2)
- Latency in resting lymphocytes (3)



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ANTI-RETROVIRAL TREATMENT REFLECTS THE THREE HIV IN VIVO INFECTION CYCLES  
(Mittler, 1999; and others)



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**HOW DOES HIV CAUSE  
IMMUNODEFICIENCY?**

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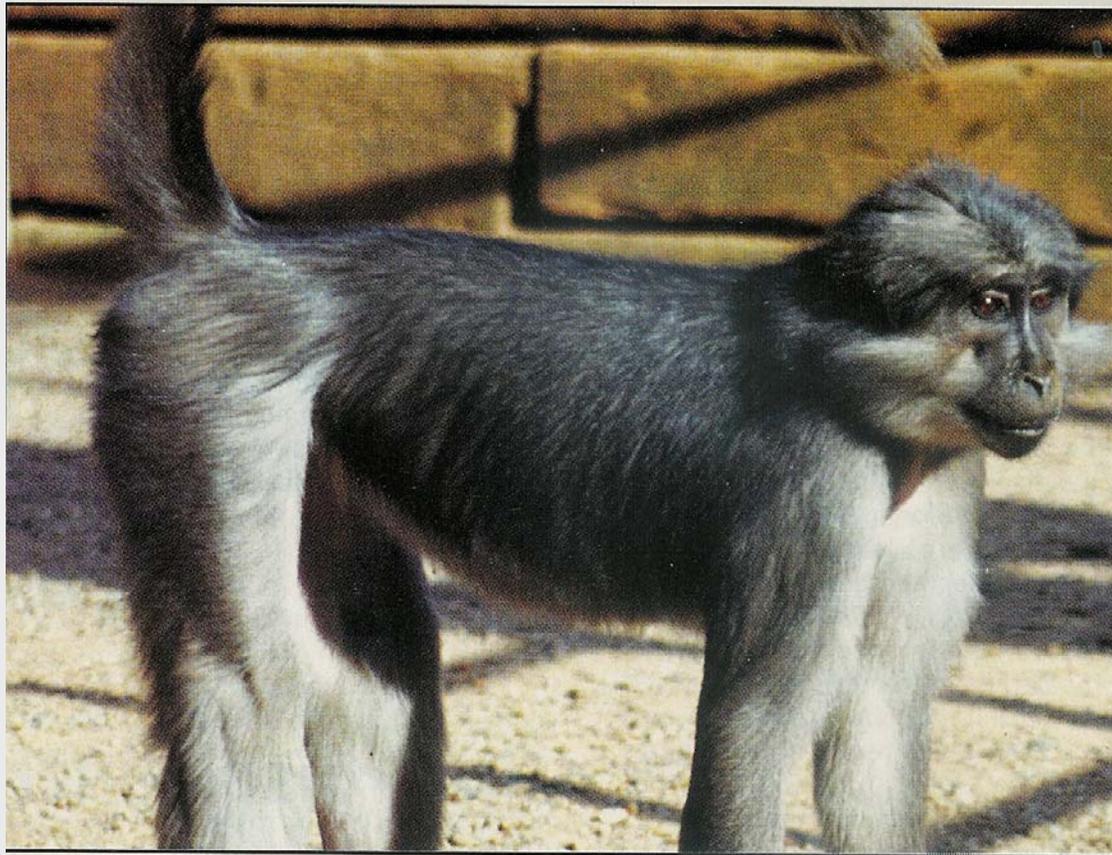
## CD4 AND CD8 T LYMPHOCYTES: A CENTRAL PARADOX IN THE PATHOGENESIS OF AIDS

- **Opportunistic infections are mainly due to the activation of existing latent infections**
- **Control of latent infections is mediated by parasite-specific CD8 effector T lymphocytes, which are NOT the direct target of HIV**
- **Indirect mechanisms must be responsible for the depletion of effector CD8 cells, including**
  - ∞ **Hyperactivation of T cells leading to apoptosis and premature cell death**

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Still an enigma?



📌 PICTURE OF HEALTH? *This 15-year-old mangabey at the Yerkes National Primate Research Center in Atlanta has been SIV-infected for at least 10 years.*

**FINIS**