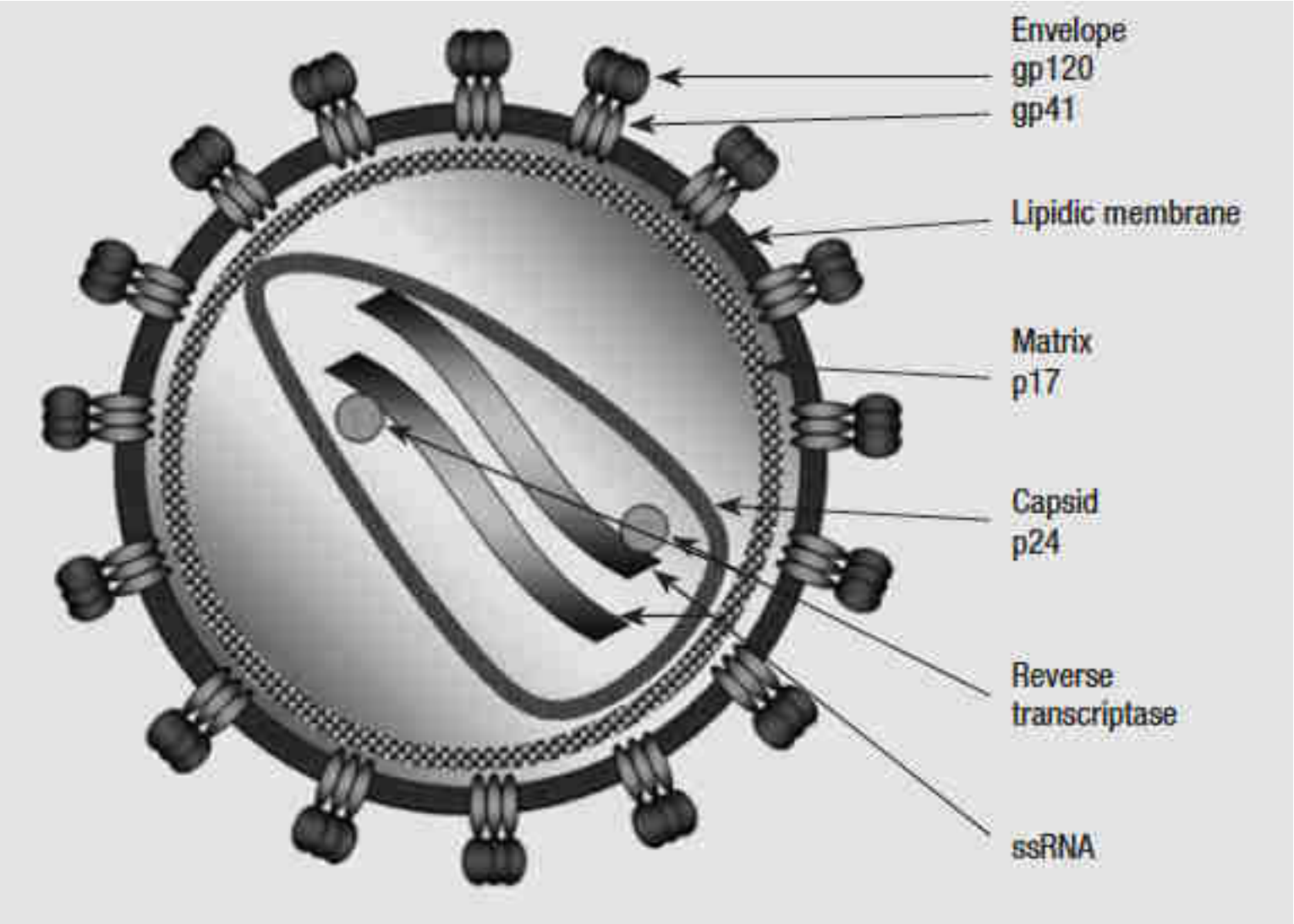
1. **Biologia di HIV, HBV e HCV: quali similitudini, quali differenze, quali implicazioni cliniche**

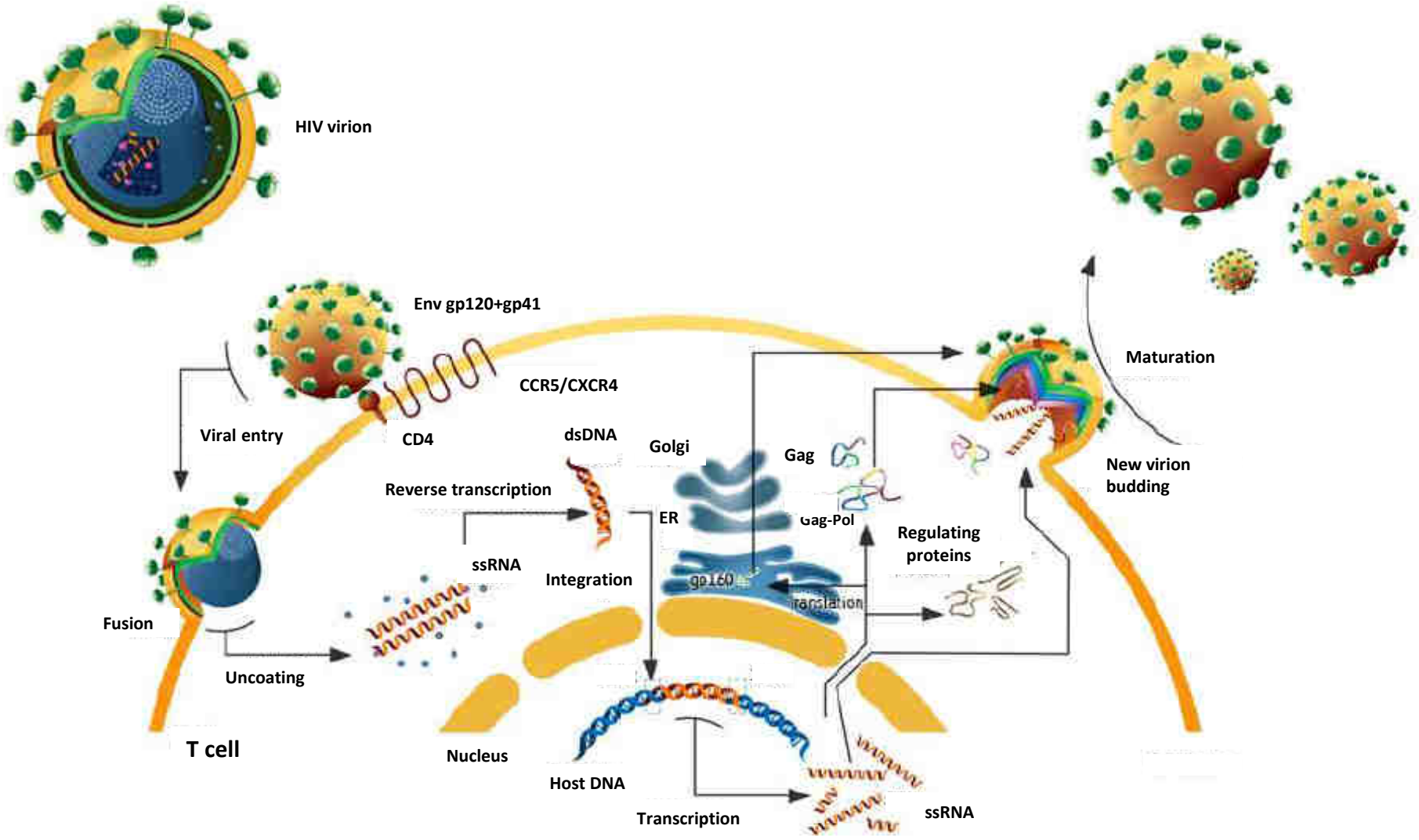
1. **Patogenesi dell'infezione da HIV: implicazioni terapeutiche e vaccinali**

1. **Diagnostica dell'infezione di HIV**

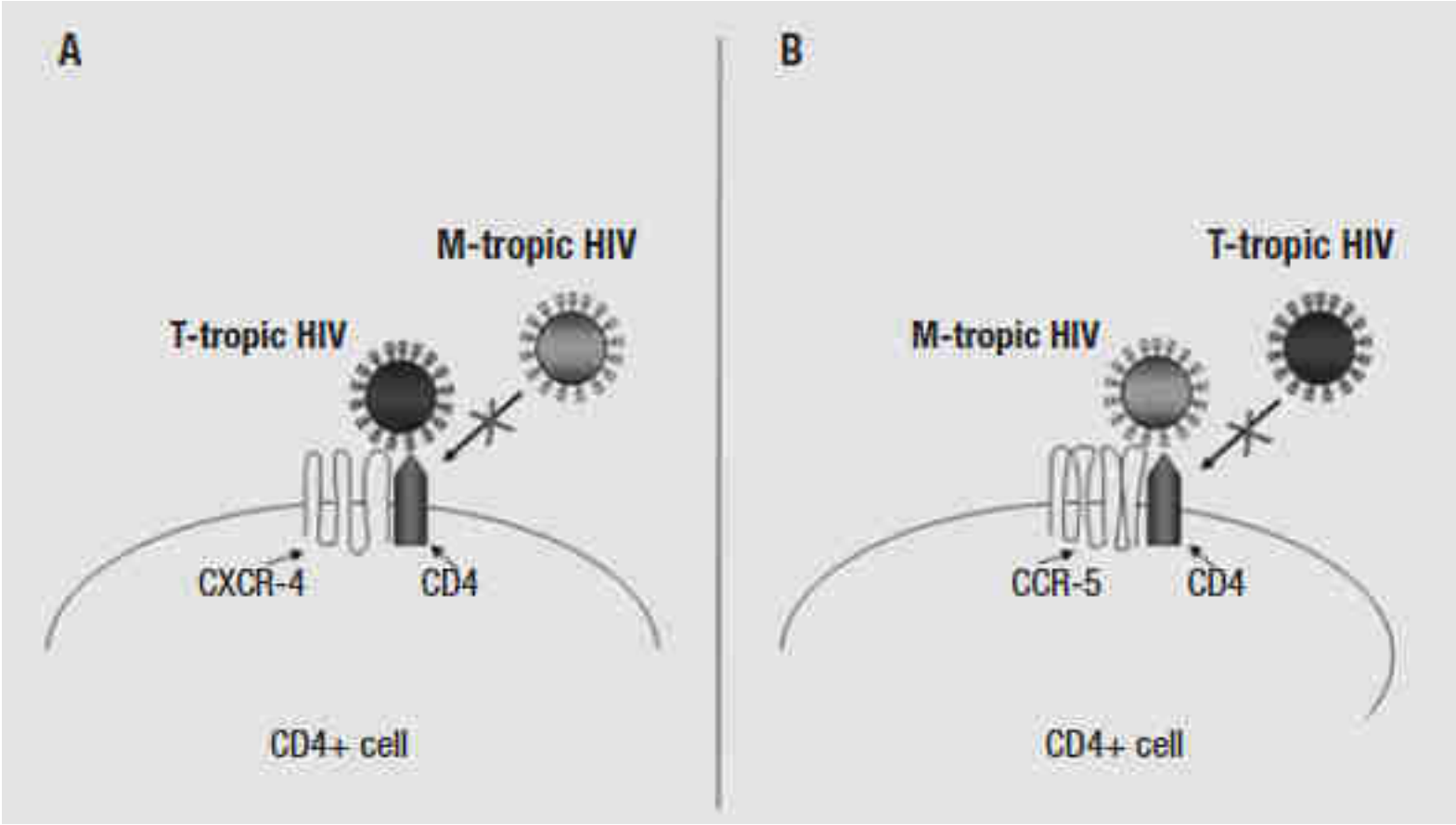
HIV virion


Envelope
gp120
gp41
Lipidic membrane
Matrix
p17
Capsid
p24
Reverse
transcriptase
ssRNA

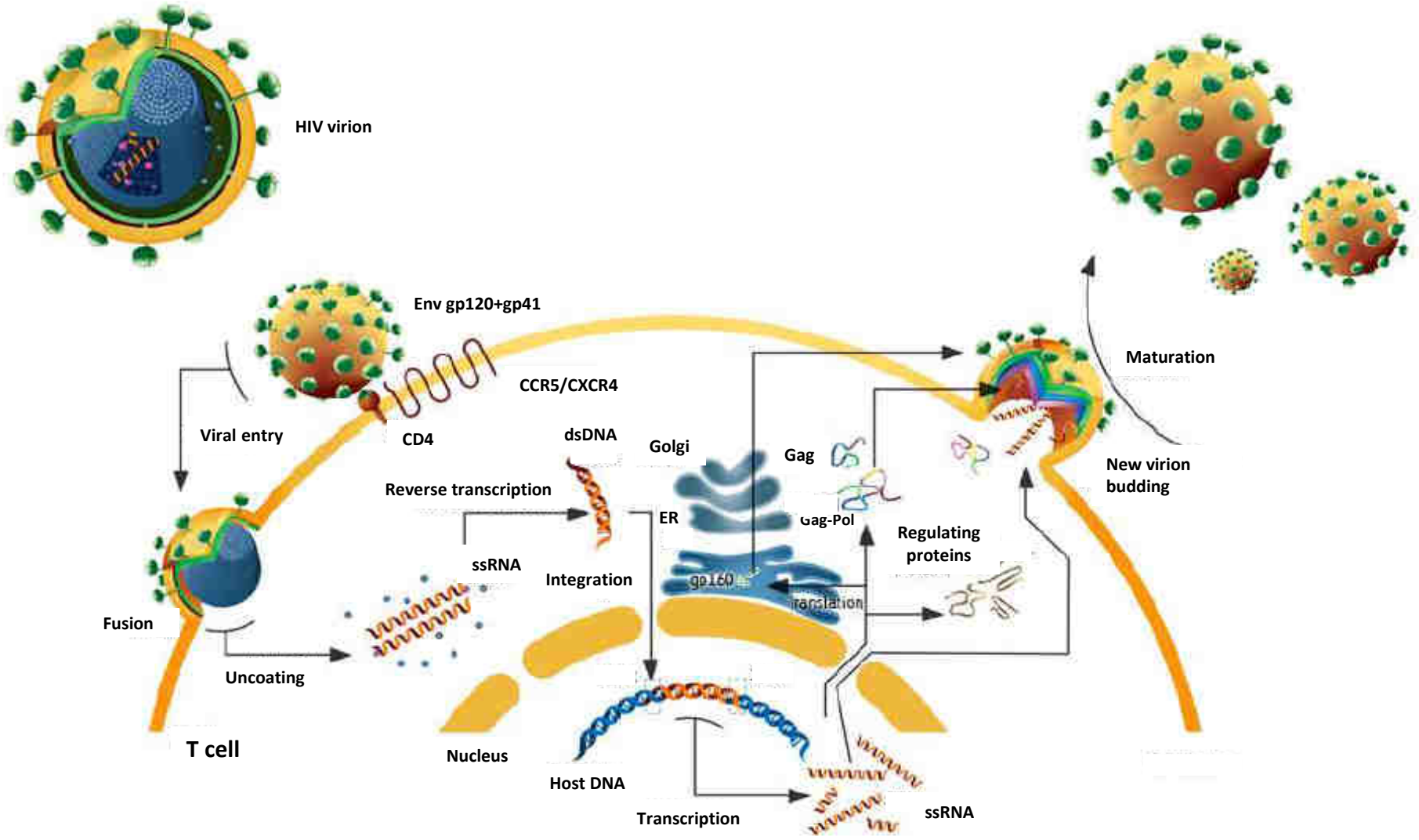
HIV replicative cycle



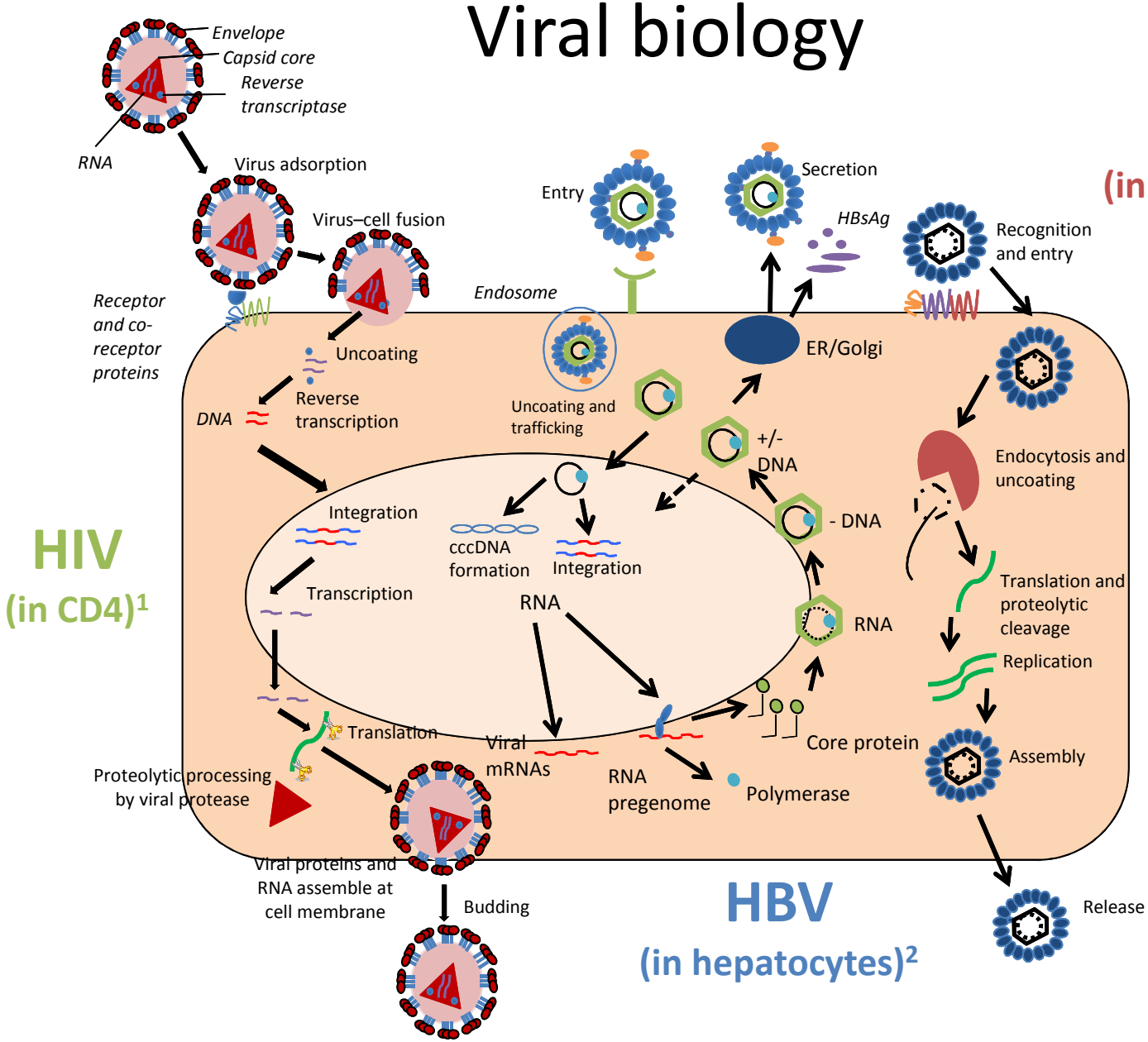
HIV tropism


A
M-tropic HIV
T-tropic HIV
CXCR-4
CD4
CD4+ cell
B
T-tropic HIV
M-tropic HIV
CCR-5
CD4
CD4+ cell

HIV replicative cycle



Viral biology



HIV
(in CD4)[1]

HCV
(in hepatocytes)[3]

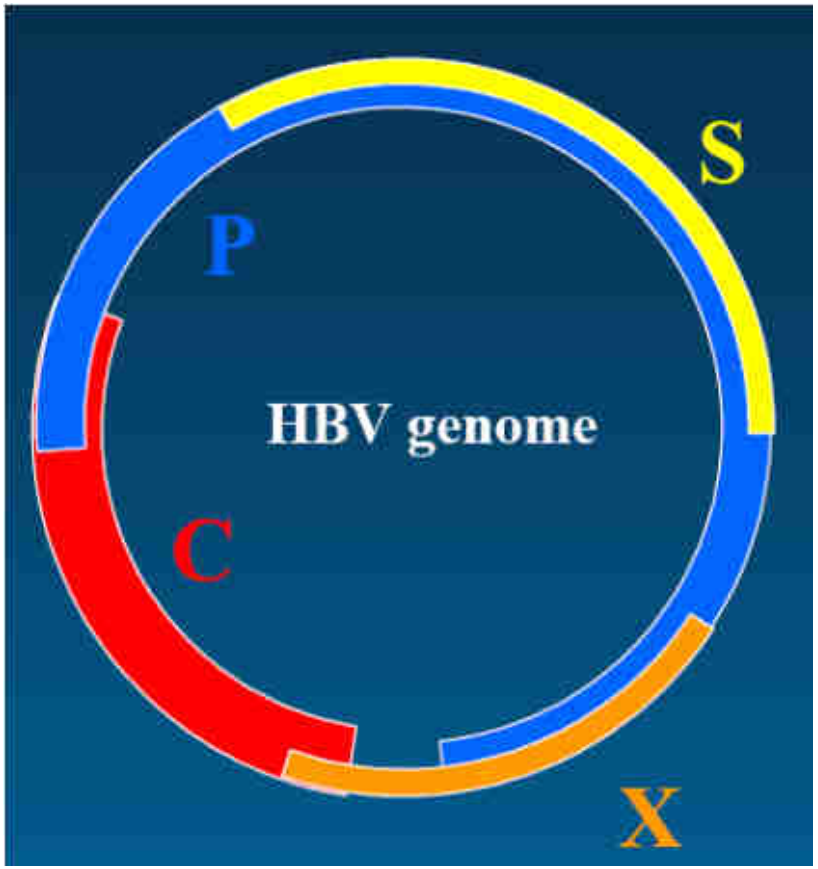
HBV
(in hepatocytes)[2]

1. De Clercq E. Nat Rev Drug Discov 2002;1(1):13-25. 2. Zoulim F, et al. Antiviral Res 2012;96(2):256-9. 3. Schaefer E, Chung R. Gastroenterology 2012;142(6):1340-50. Covalently closed-circular HBV DNA, cccDNA

Extensive overlapping of HBV open reading frames

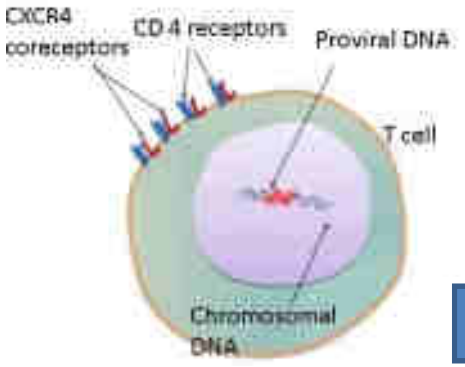
Thanks to this unique genome organization

- The HBV genome contains all the information necessary for its life cycle
- a single nucleotide substitution can change the function of multiple HBV proteins, and thus can affect multiple steps of HBV life cycle

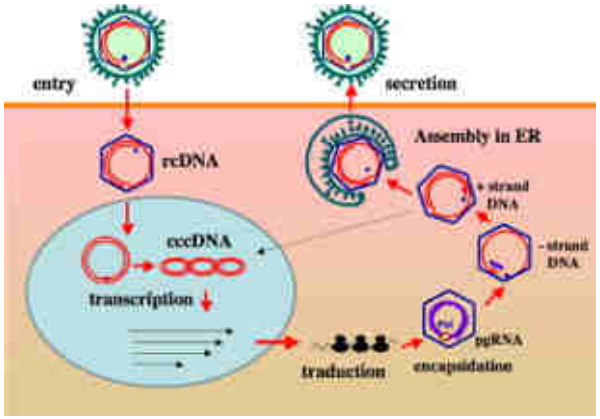


Infected cell death is required for complete HIV and HBV but NOT for HCV clearance

HIV proviral DNA

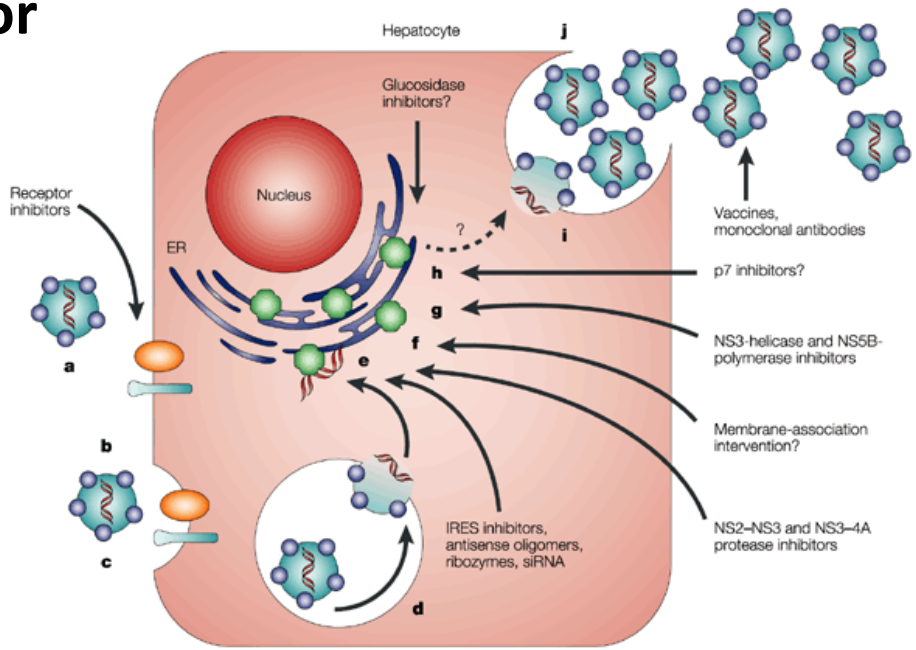


HBV cccDNA

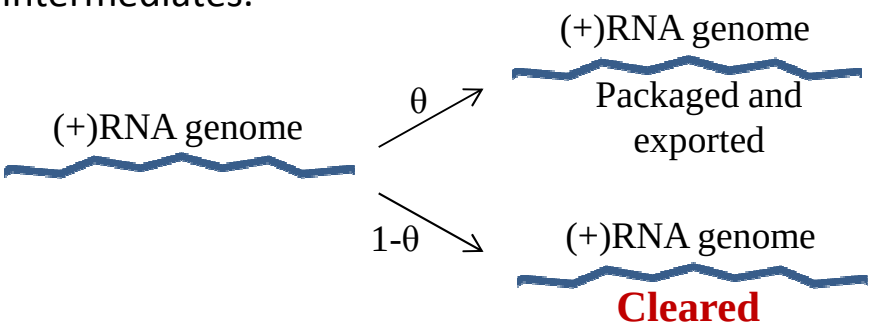


Long-term survival in quiescent cells

HCV

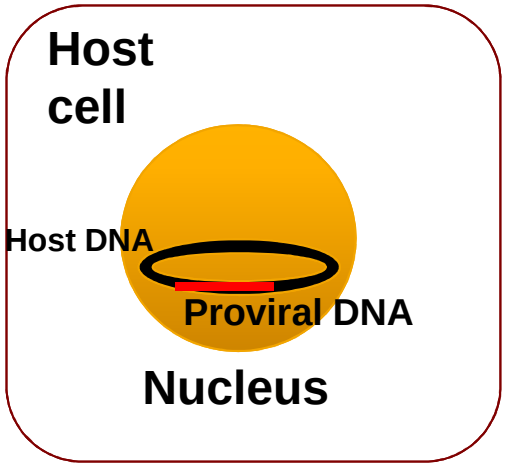


DAAs have the ability to reduce the synthesis of new intracellular HCV RNA, and also to enhance its degradation → "cell cure" by loss of replicative intermediates.



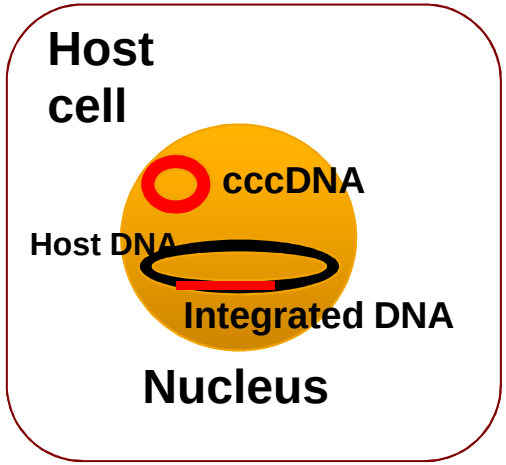
HIV, HBV e HCV

HIV[1]



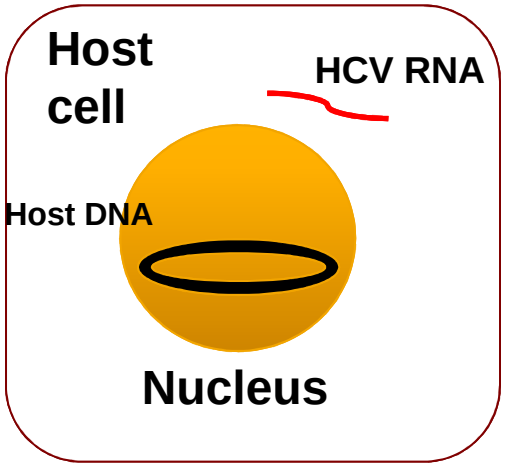
Life-long suppression of viral replication

HBV[1,2]



Long-term suppression of viral replication

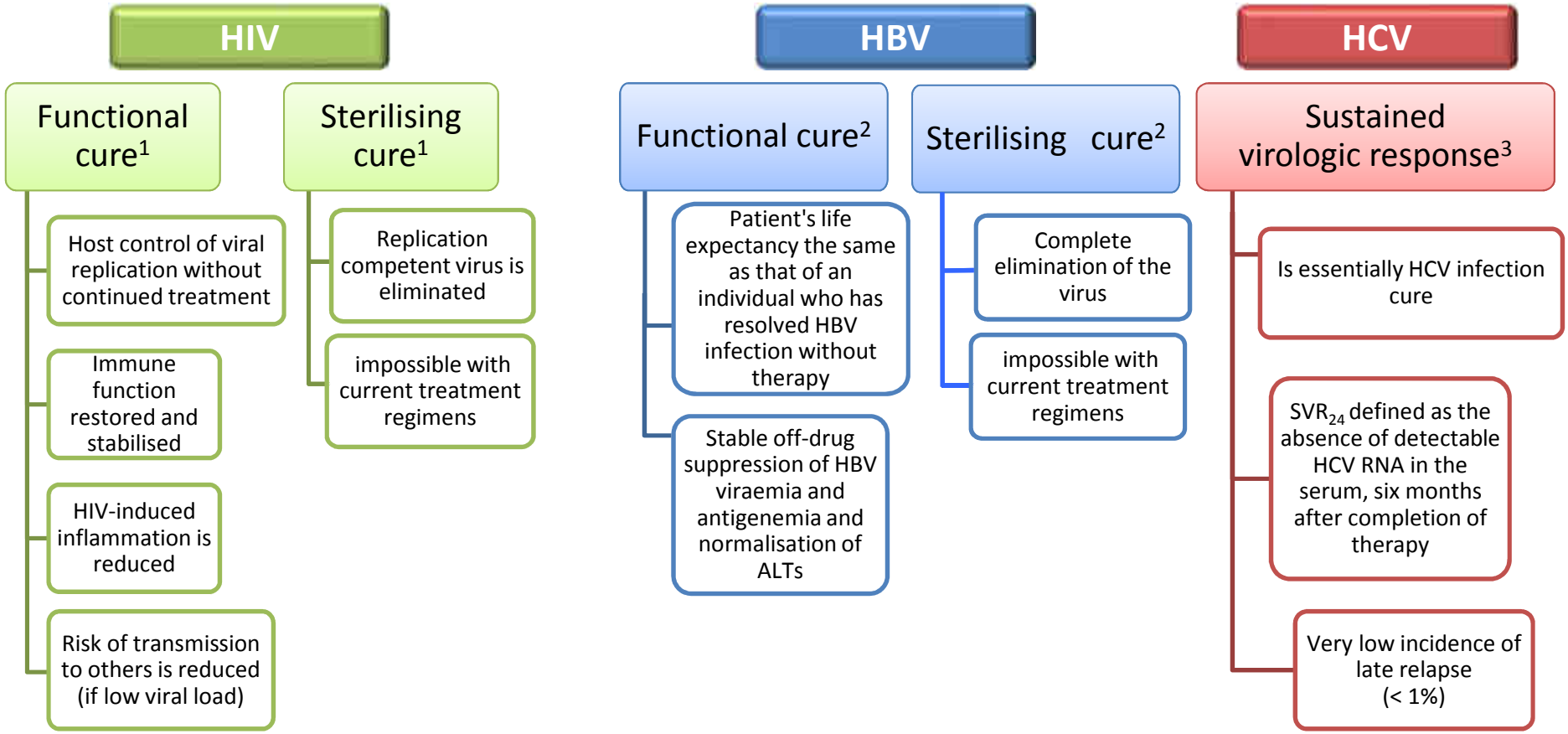
HCV[1,3]



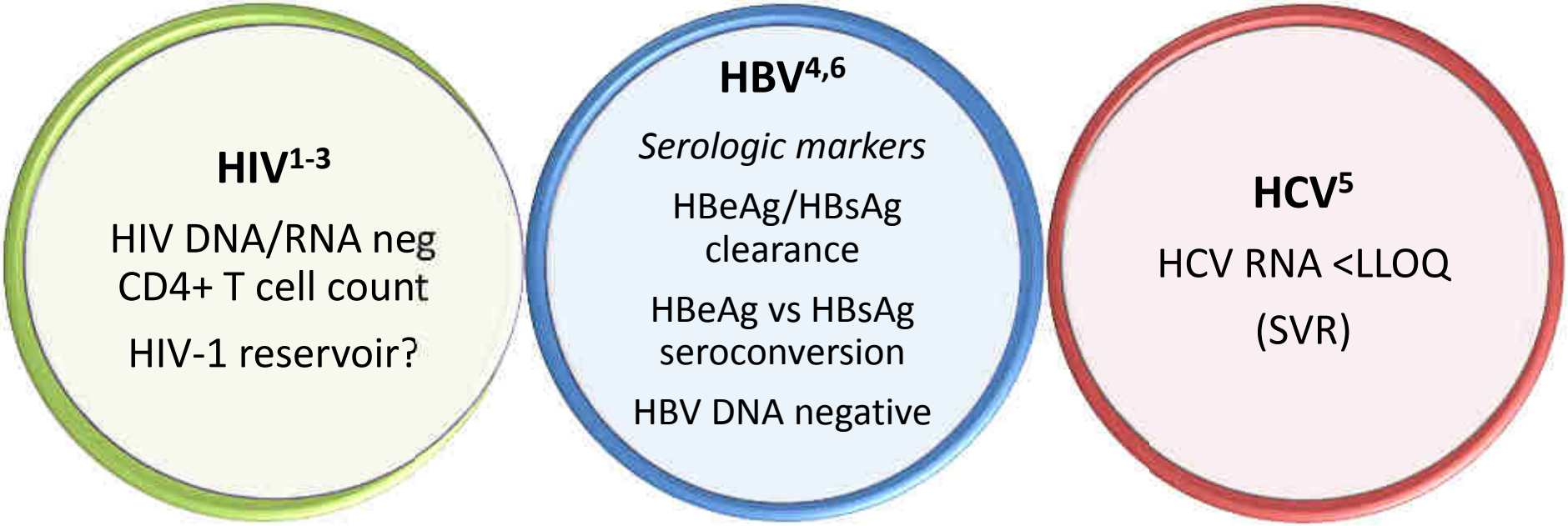
Definitive viral clearance and SVR

Adapted from 1. Soriano V, et al. J *Antimicrob Chemother* 2008;62:1-4. 2. Locarnini S and Zoulim F. *Antiviral Therapy* 2010;15 (suppl 3):3-14. 3. Sarrazin C and Zeuzem S. *Gastroenterology* 2010;138:447-462.

Objectives of treatment differ depending on the virus



Endpoints for cure also vary



LLOQ, lower limit of quantification.

1. Katlama C, et al. Lancet 2013;381(9883):2109-17. 2. Deeks SG, et al. Nat Rev Immunol 2012;12(8)607–14. 3. Li Q, et al. PLoS ONE 7(9): e46026. 4. Yuen et al. J Gastroenterol Hepatol 2011;26(S1):138-43. 5. Pearlman et al. Clin Infect Dis 2011;52:889-900.
6. Block TM, et al. Antiviral Res 2013;98(1):27–34

Long-term non-progressors

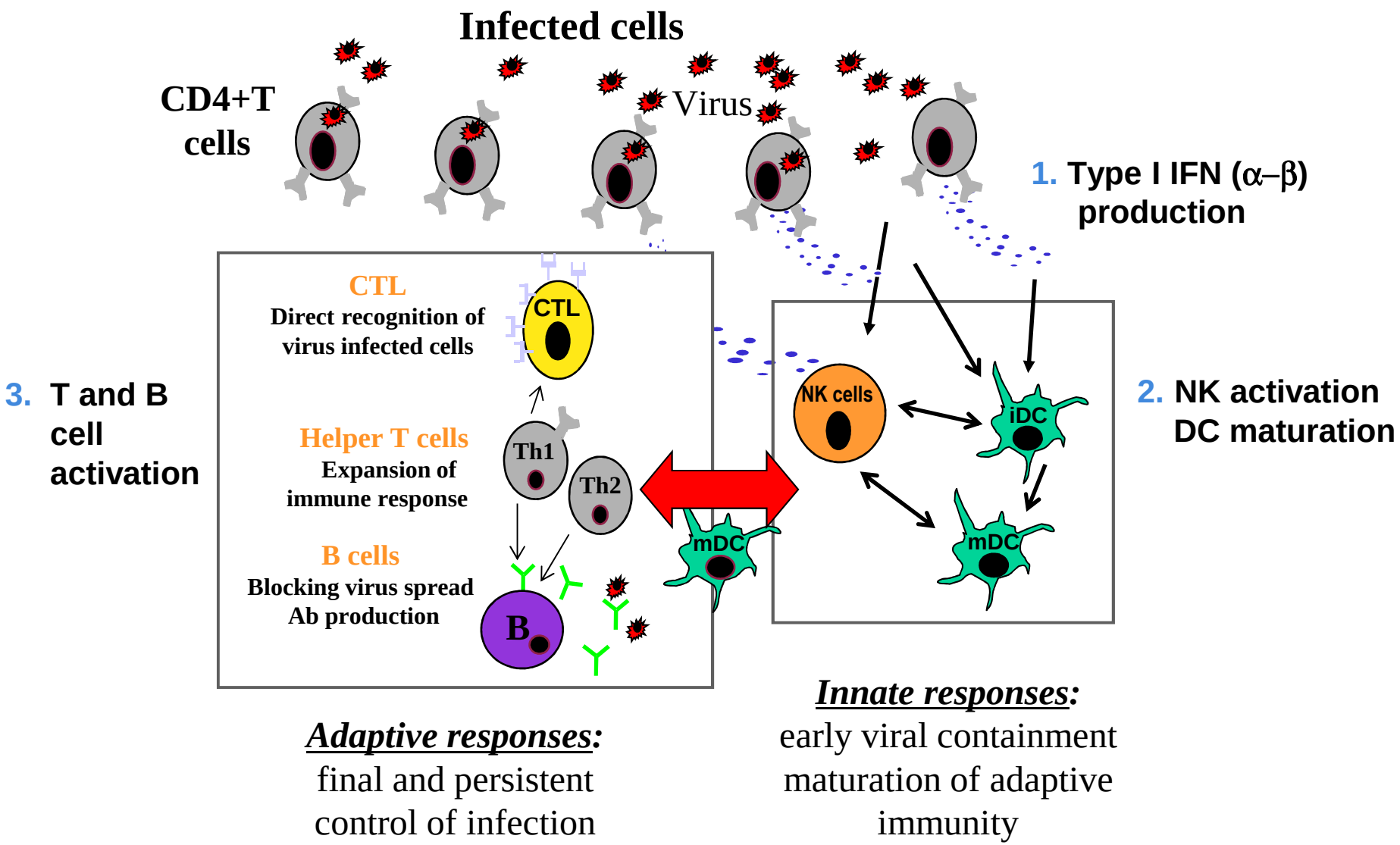
1. **Elite controllers**: a small number of untreated HIV-1-positive patients (estimated to be about 1 in 300 infected people) who have undetectable viral loads with commercial PCR assays (HIV-1 replication below the level of detection on at least three separate occasions during a 12-month period).

1. **Viraemic controllers**: patients who maintain low-level viraemia in the absence of treatment and typically have less than 2,000 copies of viral RNA per millilitre of plasma (7% of all HIV-1-positive patients)

Elite controllers

1. **Viral genetics**
   - Lack of gross sequence alterations
   - Transmission of replication-competent viruses from elite controllers to other patients who then developed progressive disease

2. **Host genetics:** no clear data


Infected cells
CD4+T cells
Virus
1. Type I IFN (α–β) production
CTL
Direct recognition of virus infected cells
CTL
Helper T cells
Expansion of immune response
Th1
Th2
B cells
Blocking virus spread
Ab production
B
NK cells
iDC
mDC
mDC
2. NK activation DC maturation
3. T and B cell activation
Adaptive responses:
final and persistent control of infection
Innate responses:
early viral containment
maturation of adaptive immunity

Elite controllers

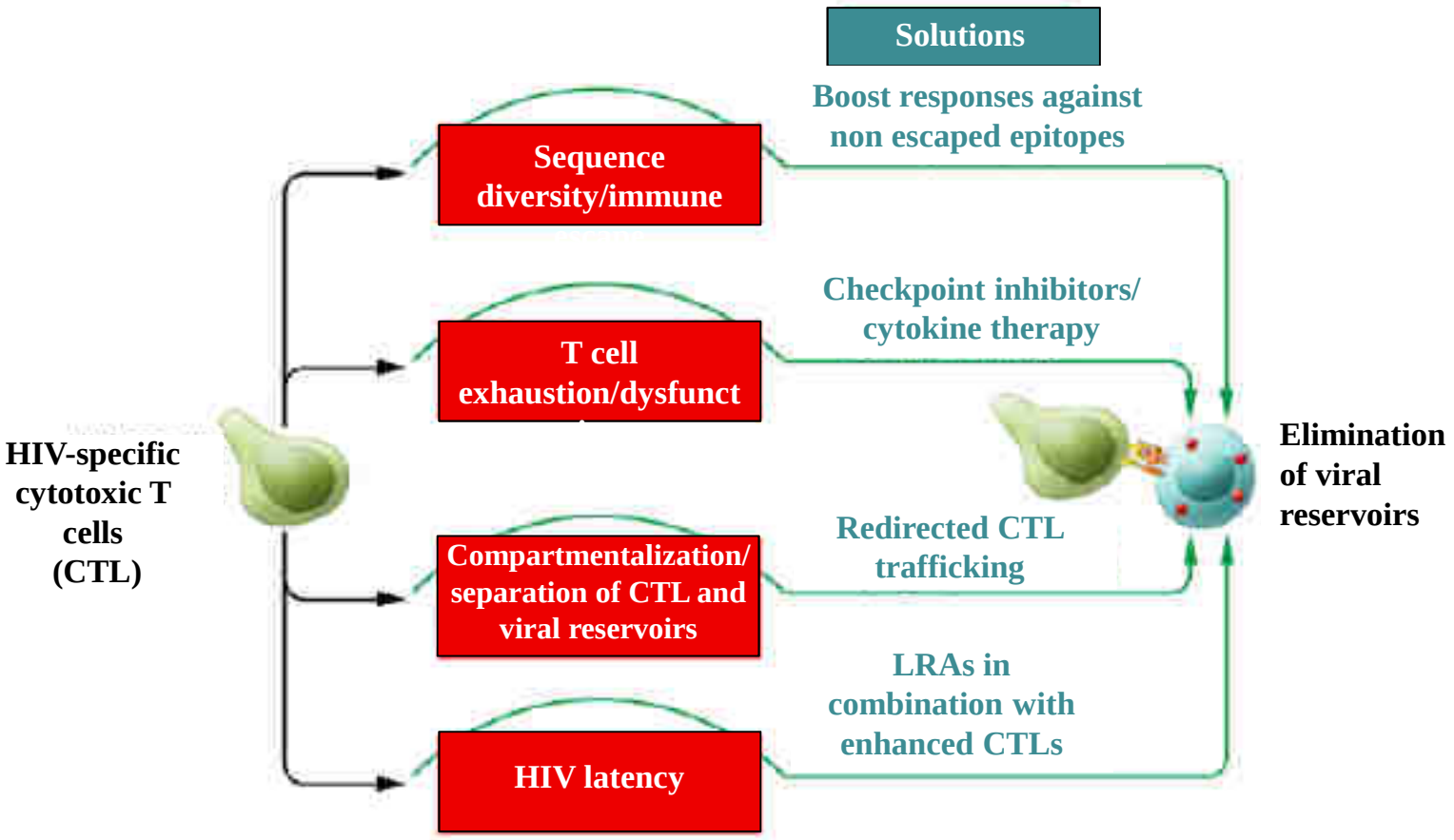
Adaptive immunity

- **CD8 T cells**
  - more efficient in virus inhibition in vitro
  - more efficient in anti-viral function (high capacity to express cytolytic activity, to proliferate, to simultaneously execute multiple effector functions)

- **CD4 T cells**
  - Capacity to secrete multiple cytokines enhancing the anti-viral activity of HIV-specific CD8 cells

- **Antibodies**
  - Neutralizing antibodies are less frequently found in elite controllers than in viraemic progressors

Barriers to elimination of HIV infected cells

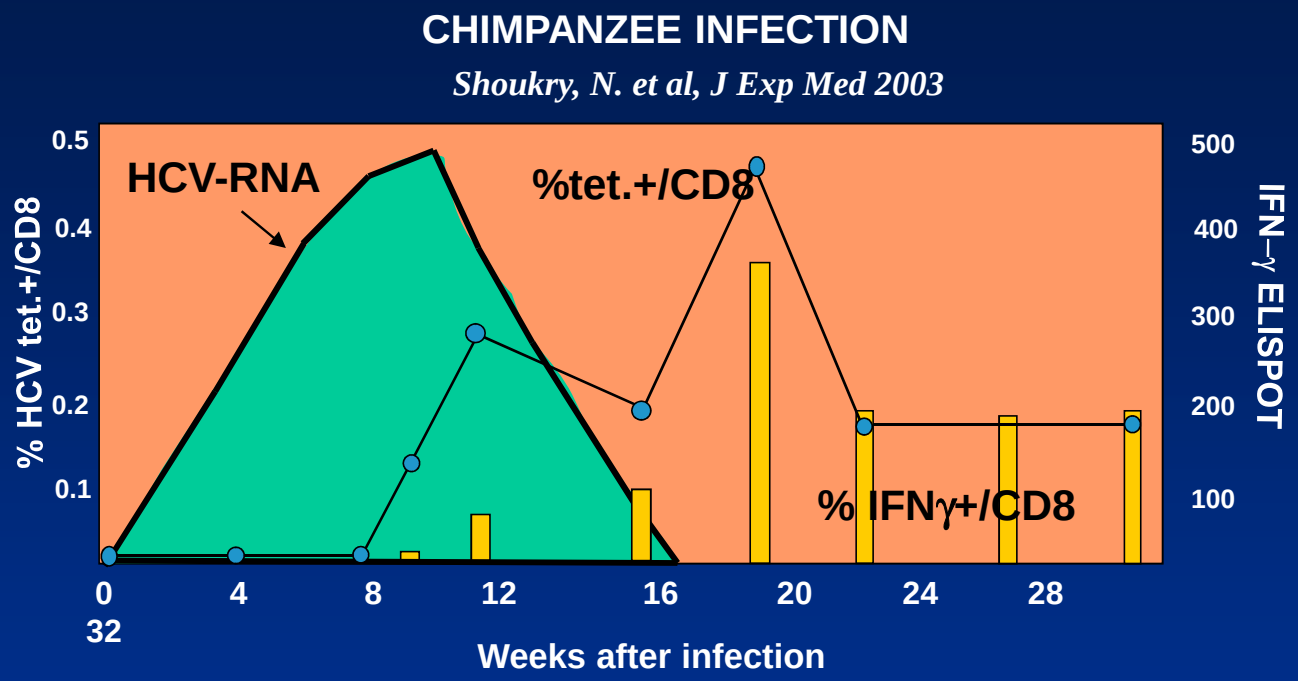


ADDITIONAL PROBLEMS LIMITING THE POSSIBLE DEVELOPMENT OF PROTECTIVE VACCINES

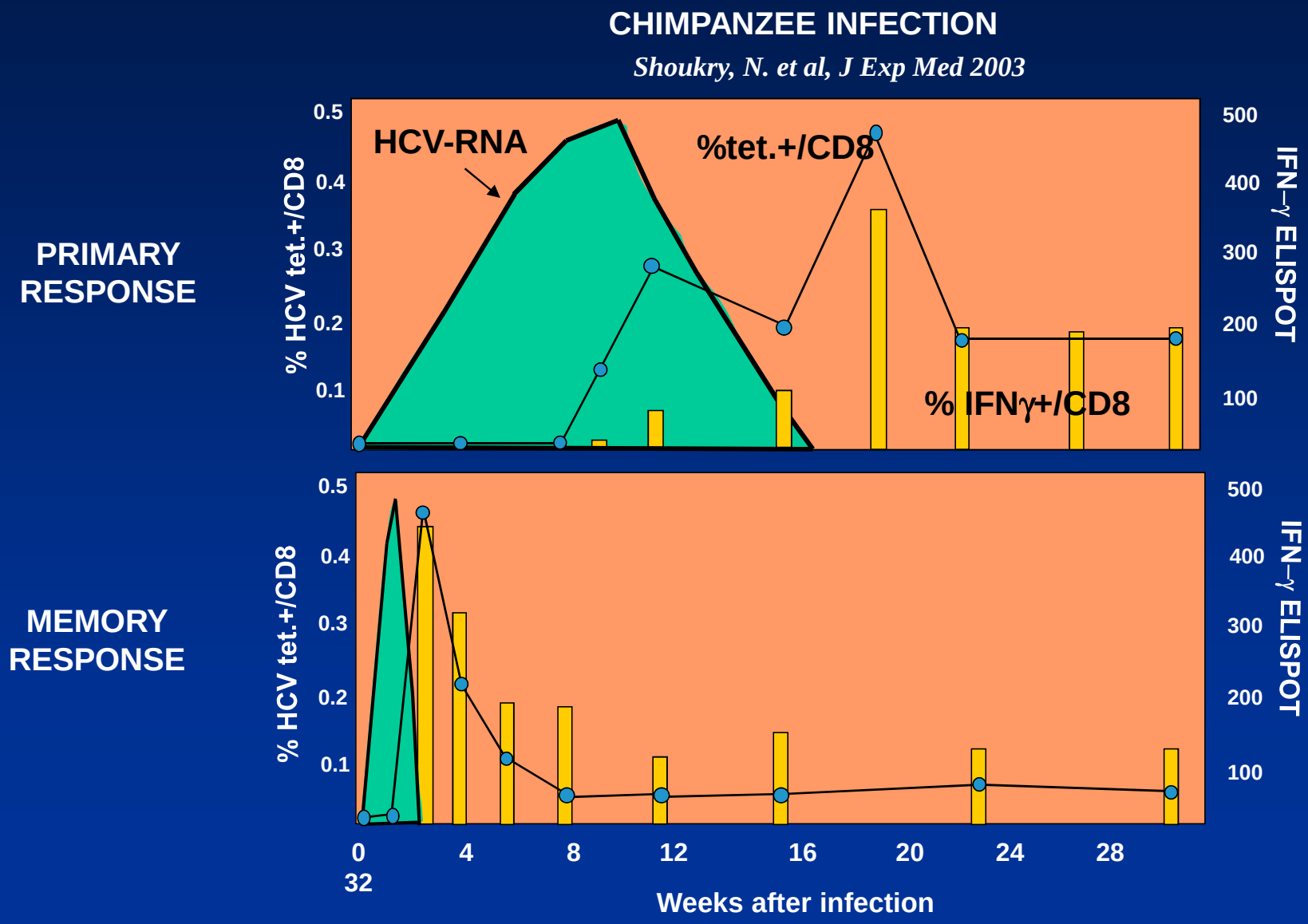
Why the development of an anti-HCV and HIV-vaccines is such a great challenge to the scientific community?

Kinetics of primary and memory T cell responses in HCV infection

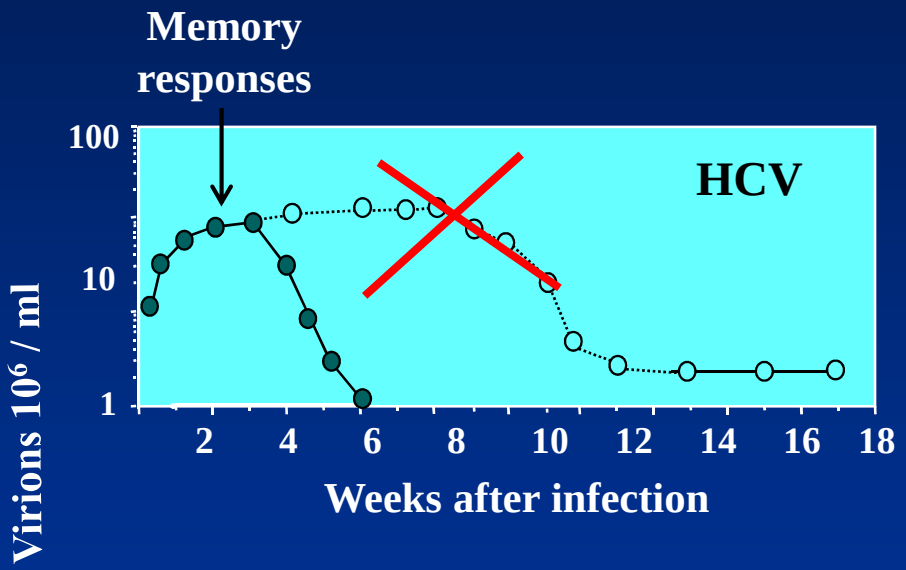
PRIMARY RESPONSE



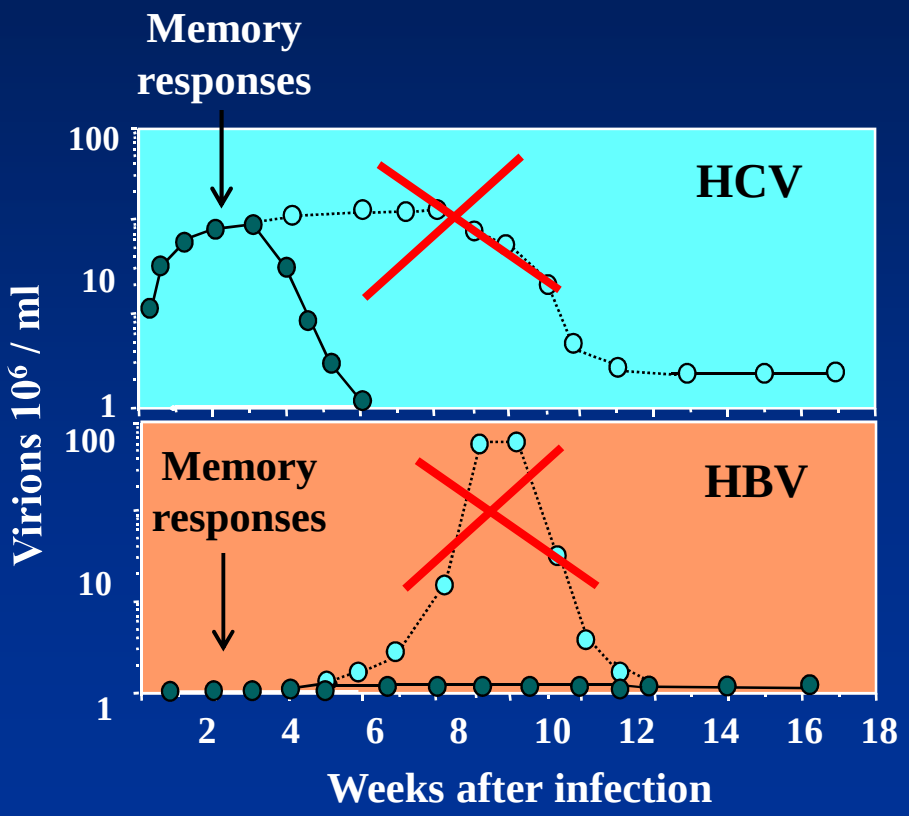
Kinetics of primary and memory T cell responses in HCV infection



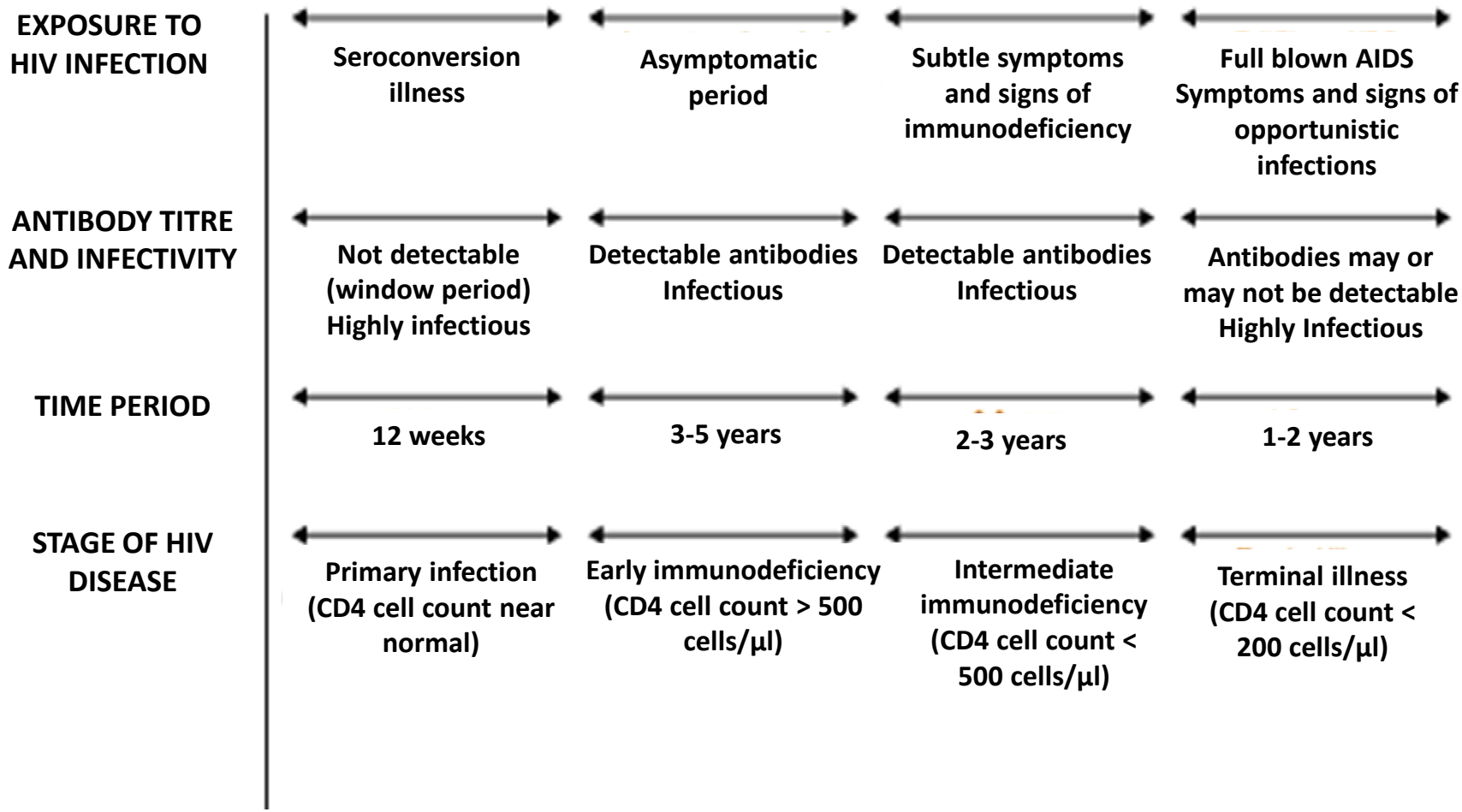
IMPLICATIONS FOR ANTI-HCV AND ANTI-HBV VACCINES

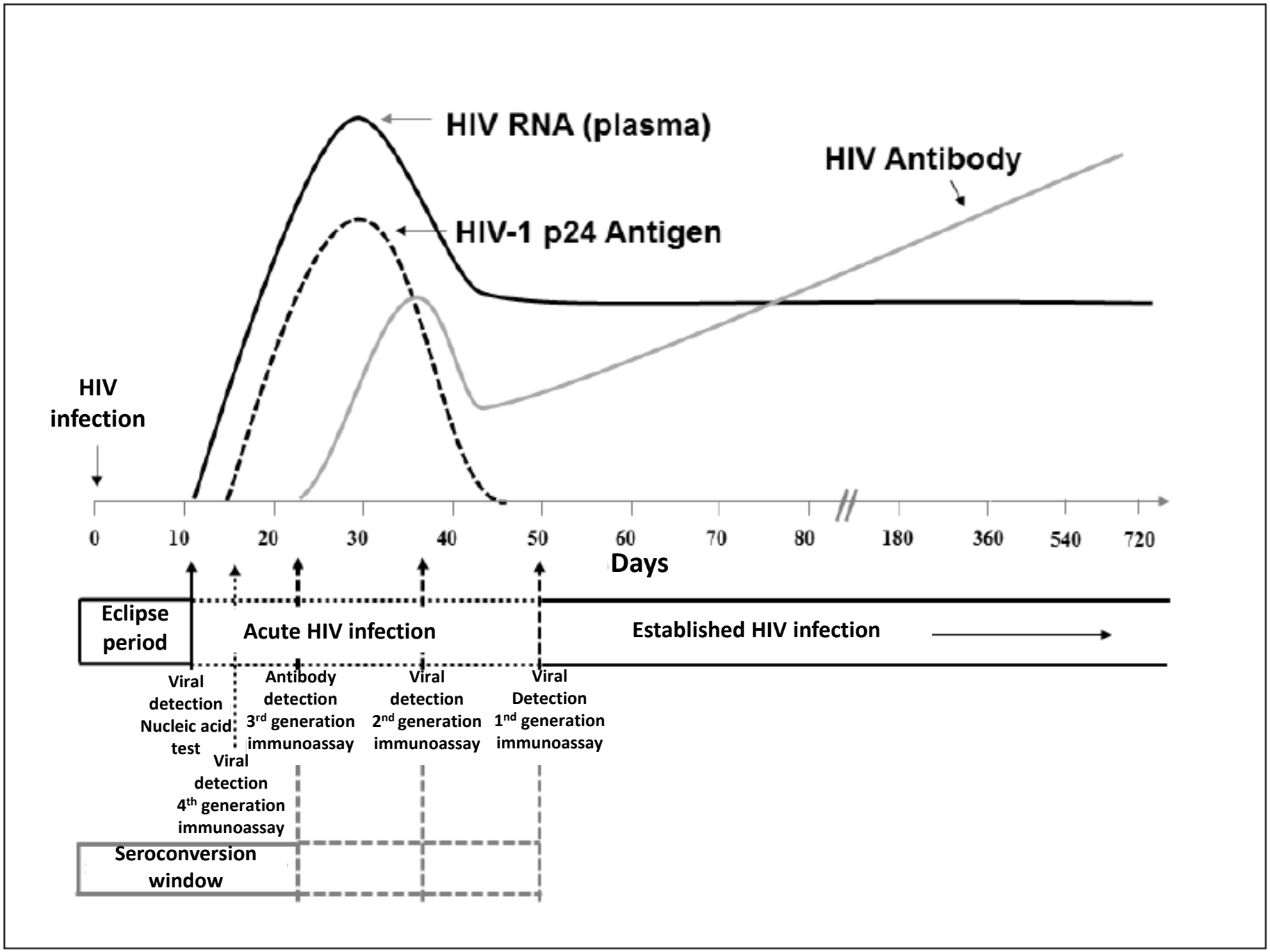


IMPLICATIONS FOR ANTI-HCV AND ANTI-HBV VACCINES

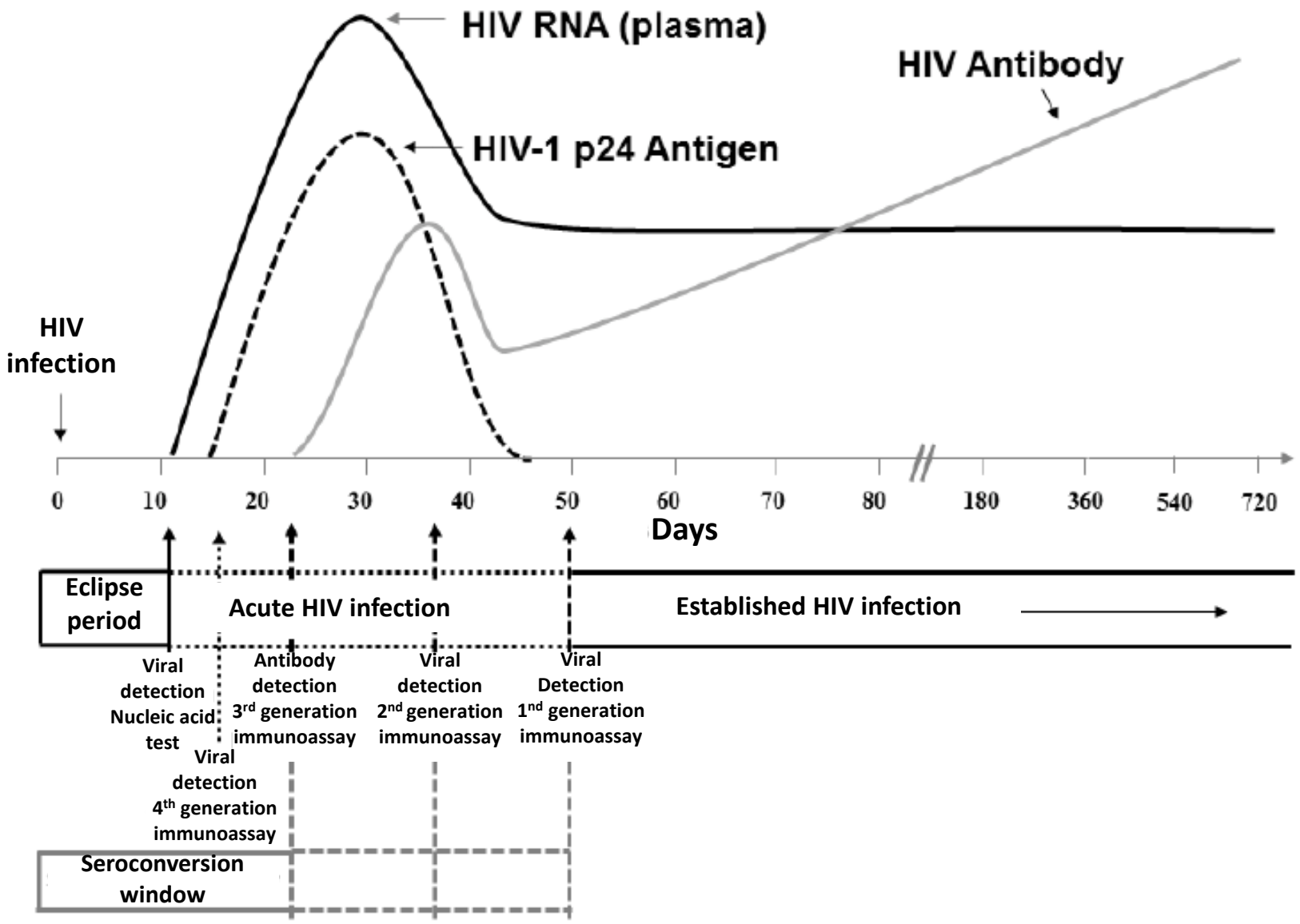


Natural history of HIV infection

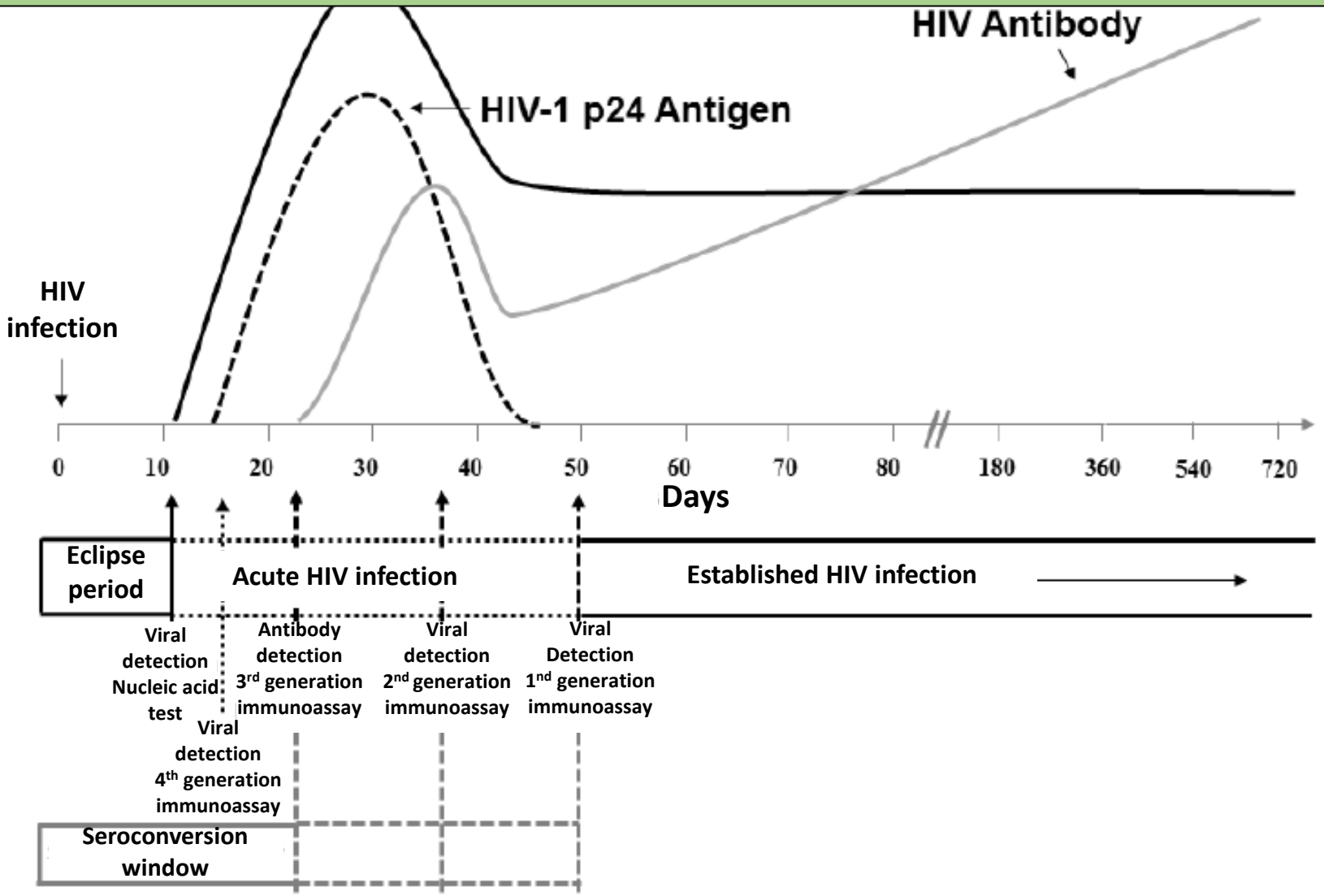



HIV RNA (plasma)
HIV Antibody
HIV-1 p24 Antigen
HIV infection
0
10
20
30
40
50
60
70
80
180
360
540
720
Days
Eclipse period
Acute HIV infection
Established HIV infection
Viral detection Nucleic acid test
Antibody detection 3rd generation immunoassay
Viral detection 2nd generation immunoassay
Viral Detection 1nd generation immunoassay
Viral detection 4th generation immunoassay
Seroconversion window

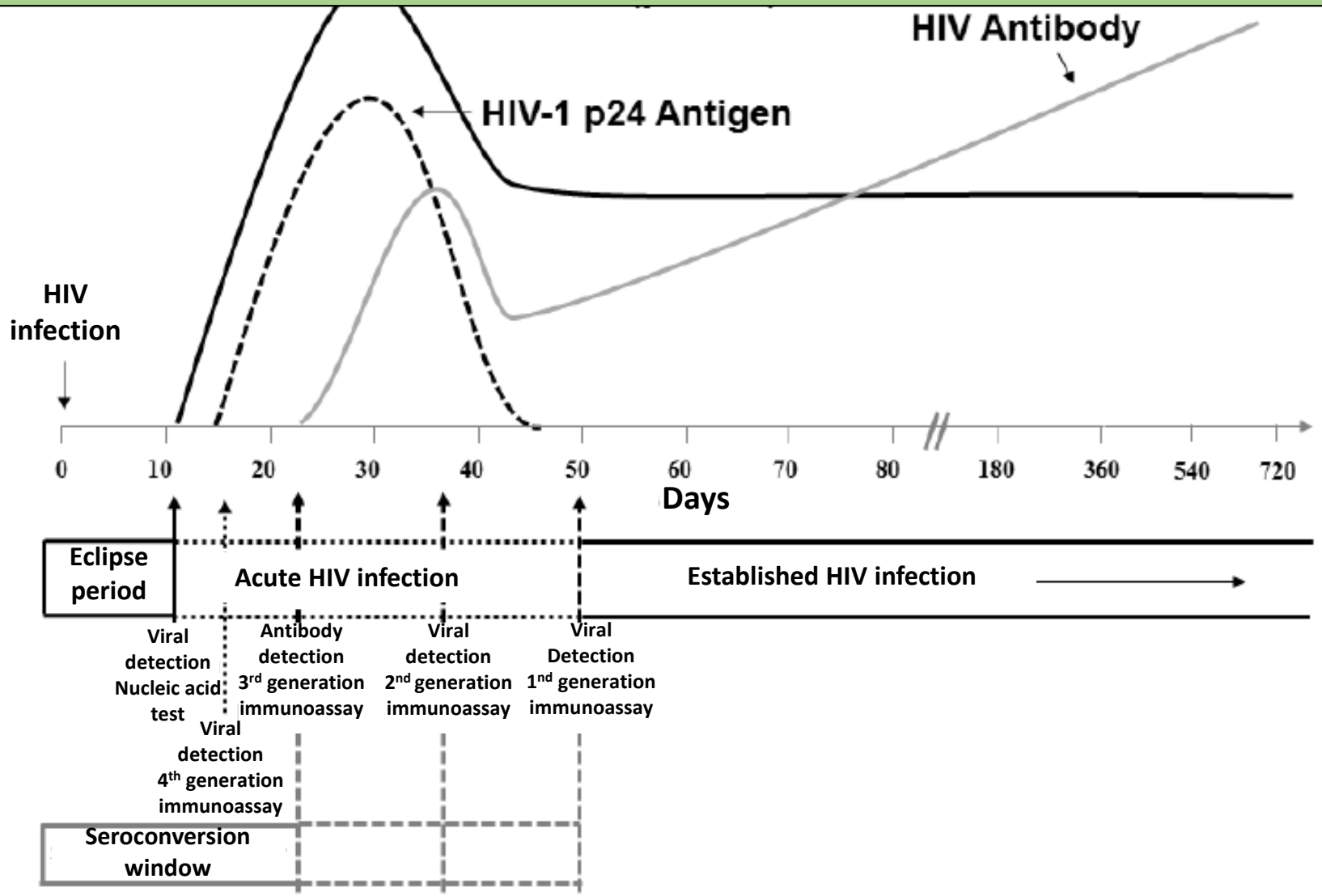
Approximately 10 days after infection, HIV-1 RNA becomes detectable by NAT in plasma and quantities increase to very high levels



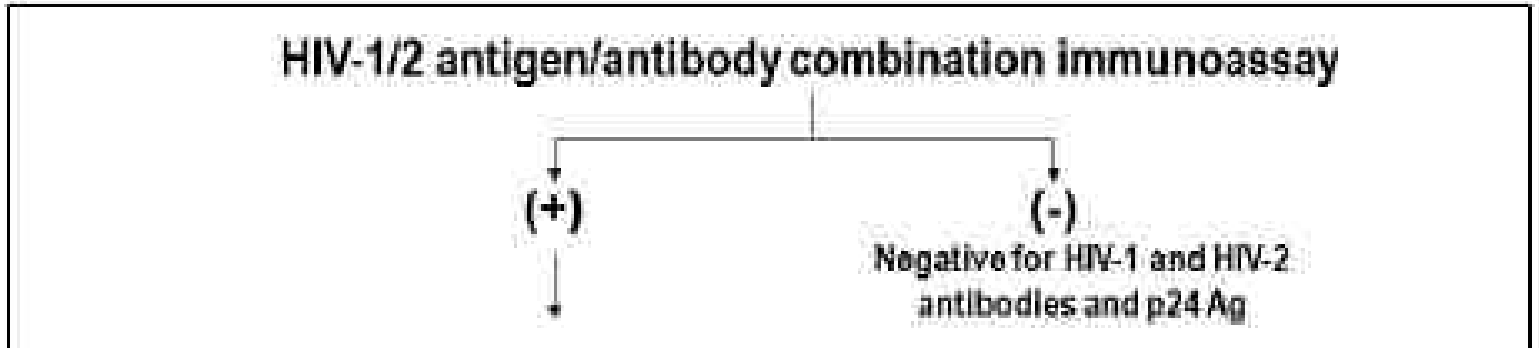
Next, HIV-1 p24 antigen is expressed and quantities rise to levels that can be detected by 4th generation immunoassays within 4 to 10 days after the initial detection of HIV-1 RNA



Next, IgM antibodies are expressed which can be detected by 3rd and 4th generation immunoassays 3 to 5 days after p24 antigen is first detectable, 10 to 13 days after the appearance of viral RNA

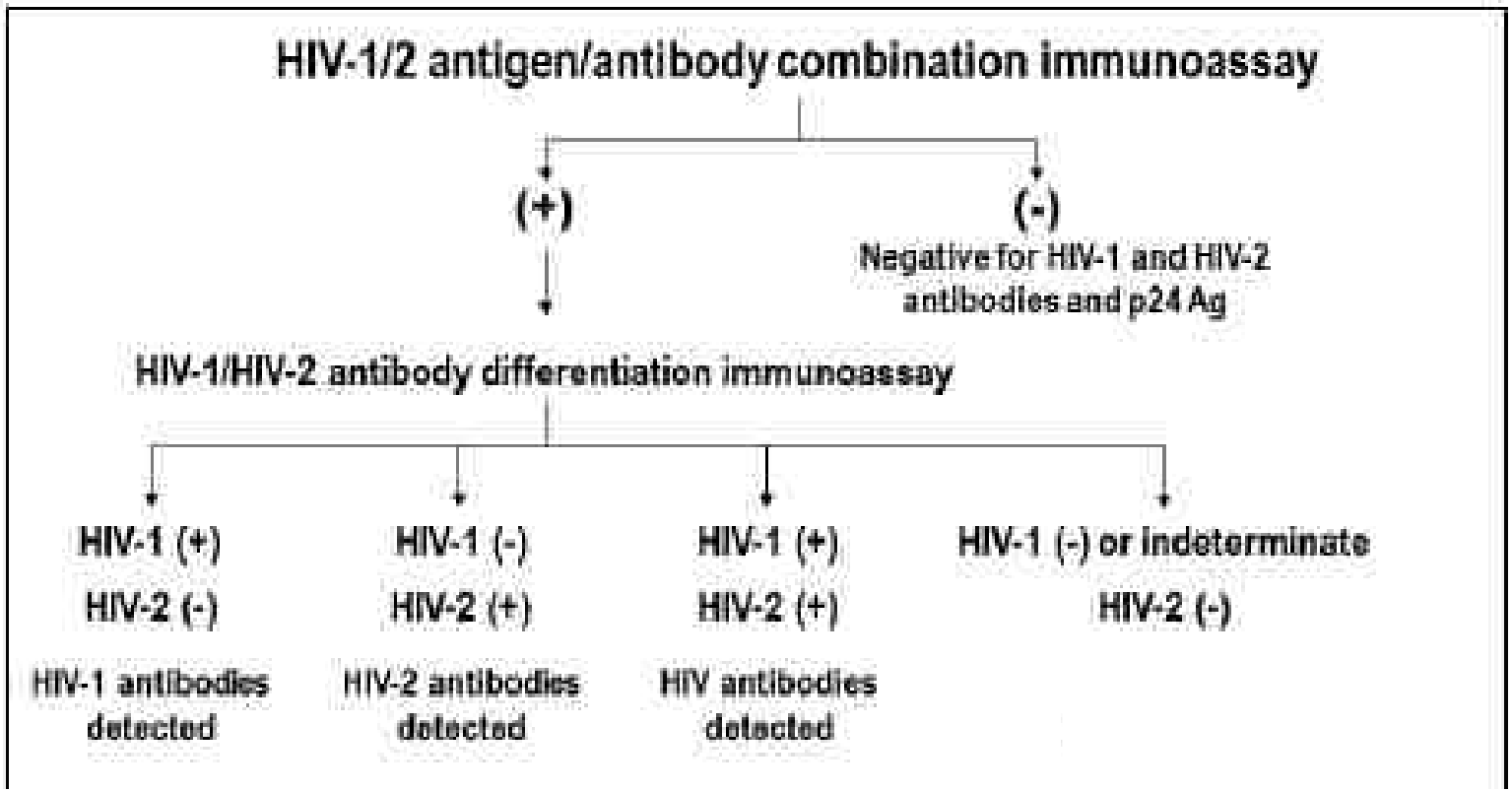


Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens



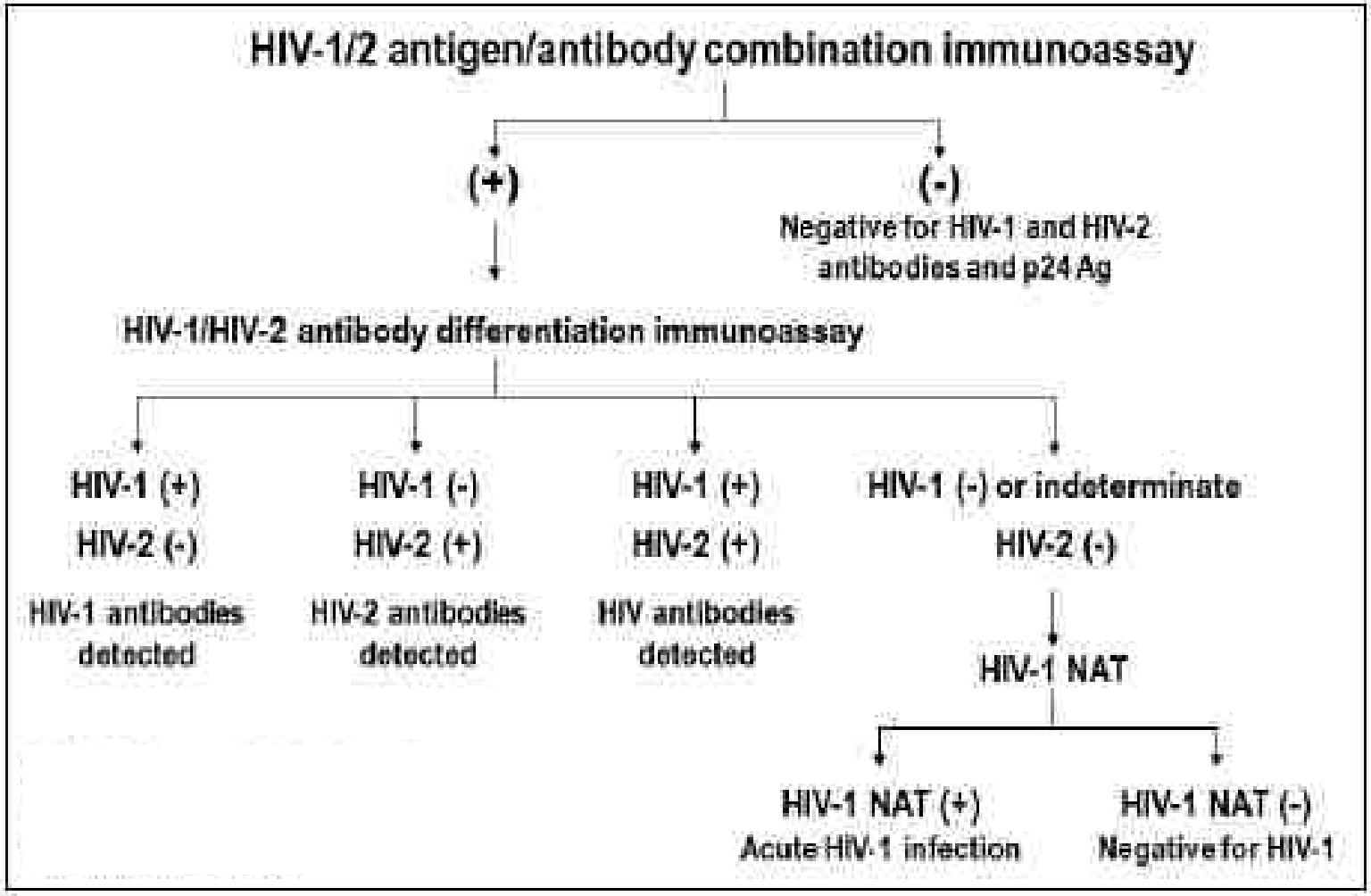
Laboratories should conduct initial testing for HIV with an FDA-approved antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection. No further testing is required for specimens that are nonreactive on the initial immunoassay.

Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens



Specimens with a reactive antigen/antibody combination immunoassay result should be tested with an FDA-approved antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies. Reactive results on the initial antigen/antibody combination immunoassay and the HIV-1/HIV-2 antibody differentiation immunoassay should be interpreted as positive for HIV-1 antibodies, HIV-2 antibodies, or HIV antibodies, undifferentiated.

Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens



Specimens that are reactive on the initial antigen/antibody combination immunoassay and nonreactive or indeterminate on the HIV-1/HIV-2 antibody differentiation immunoassay should be tested with an FDA-approved HIV-1 nucleic acid test (NAT).