HIV DRUG RESISTANCE

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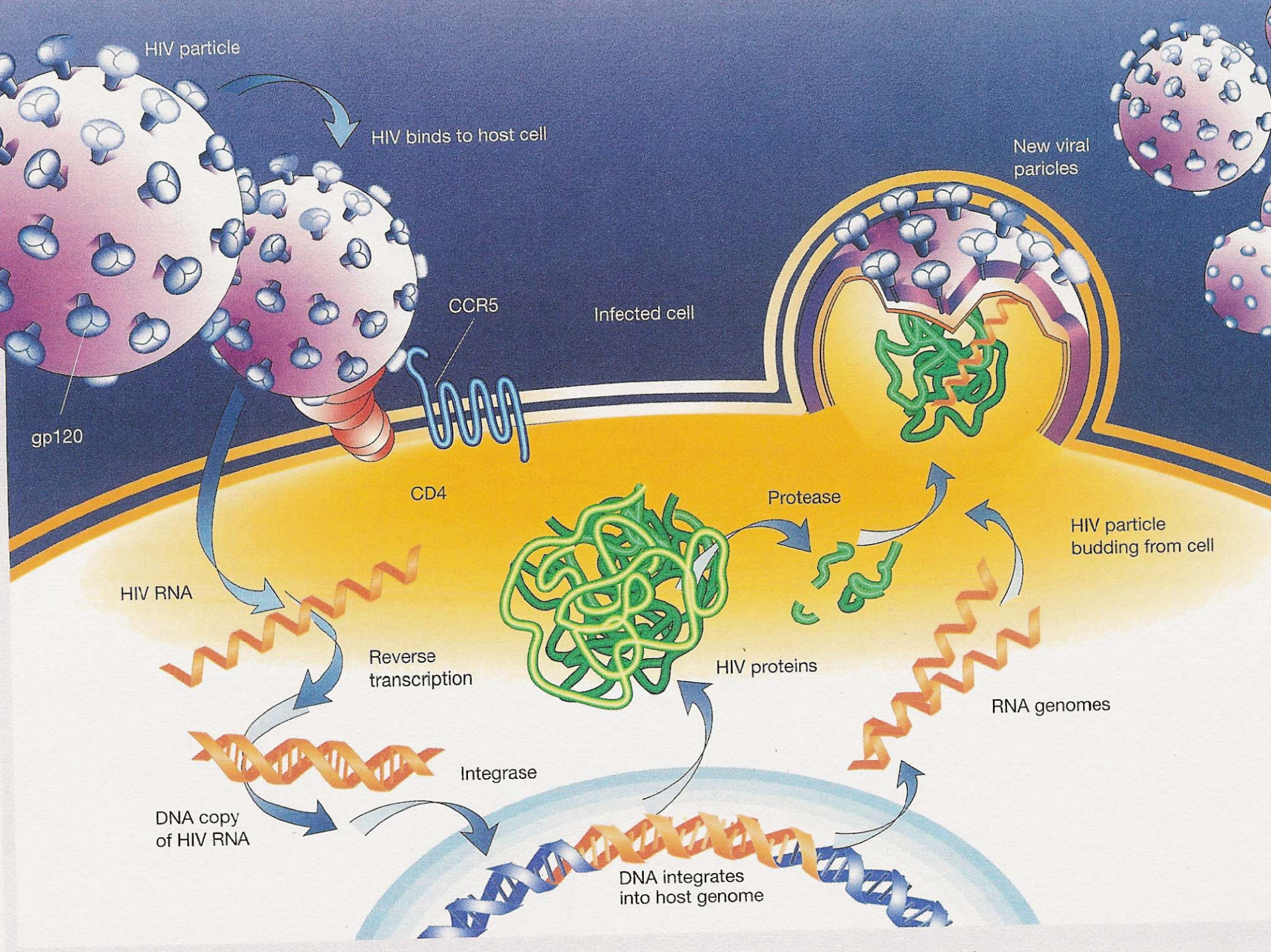
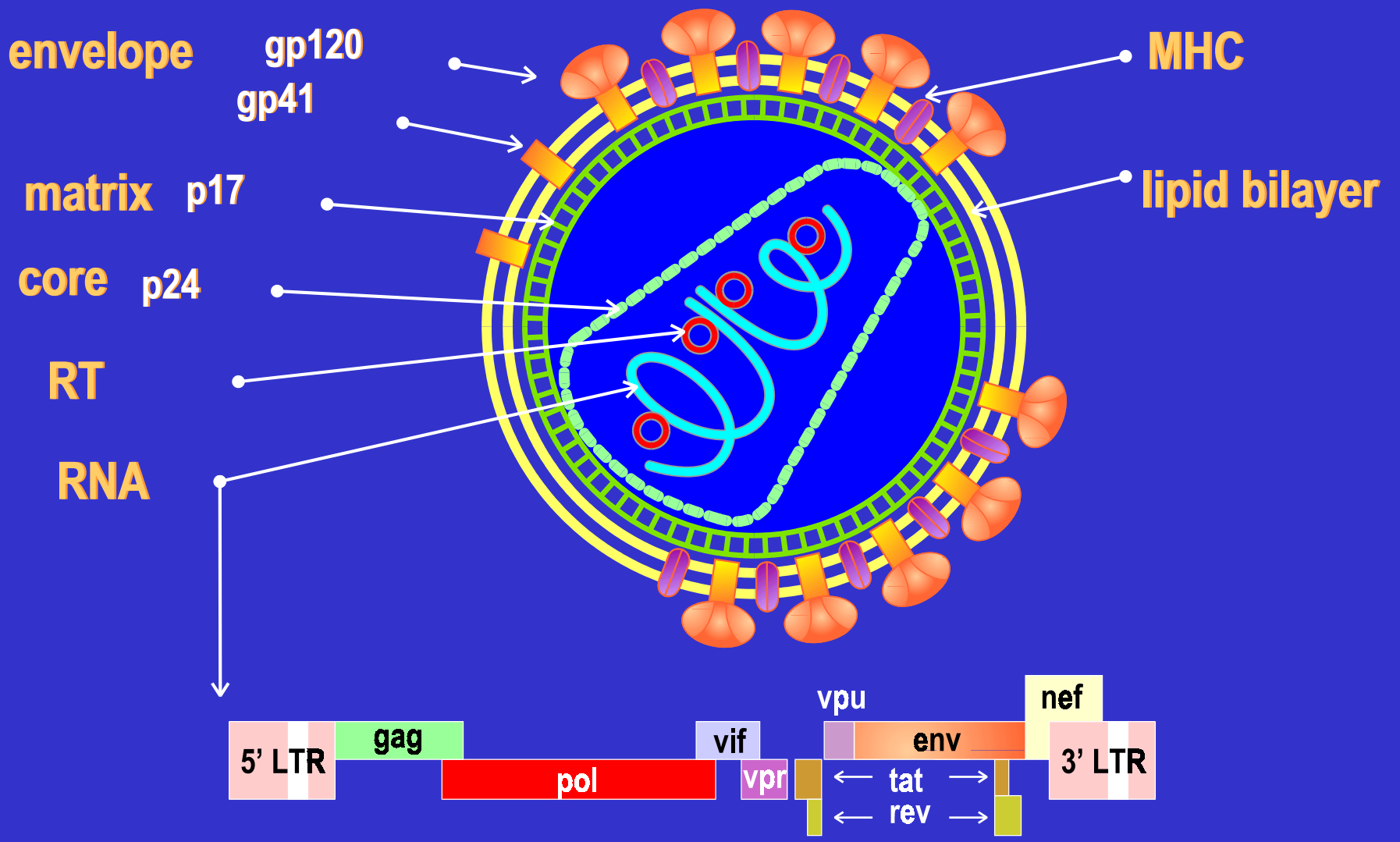
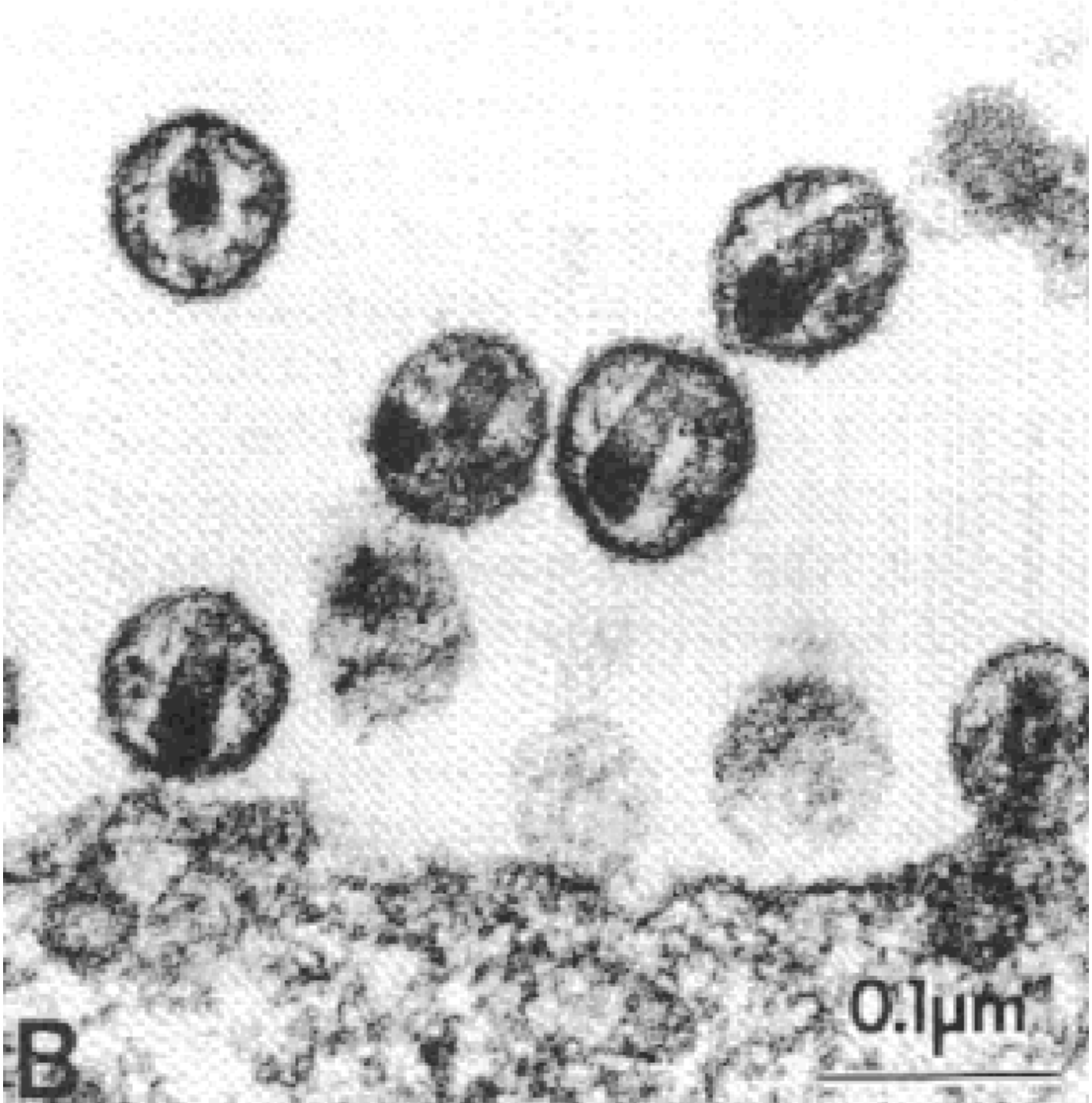
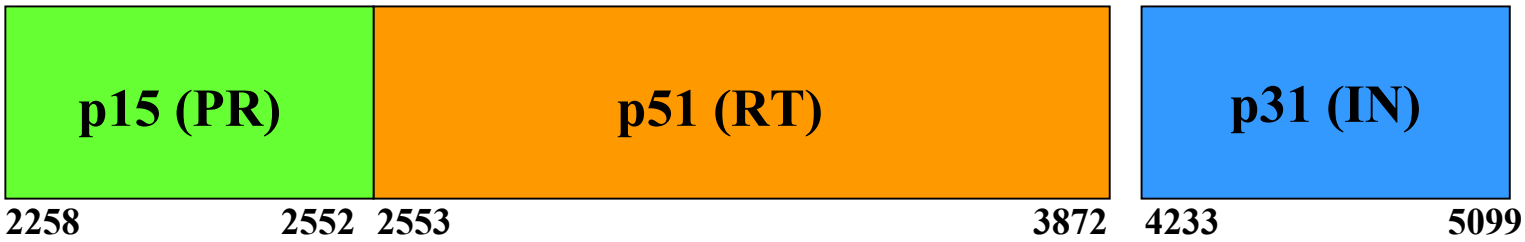

HIV particle
HIV binds to host cell
New viral
paricles
CCR5
Infected cell
gp120
CD4
Protease
HIV particle
budding from cell
HIV RNA
Reverse
transcription
HIV proteins
RNA genomes
Integrase
DNA copy
of HIV RNA
DNA integrates
into host genome

HIV PARTICLE AND GENOME



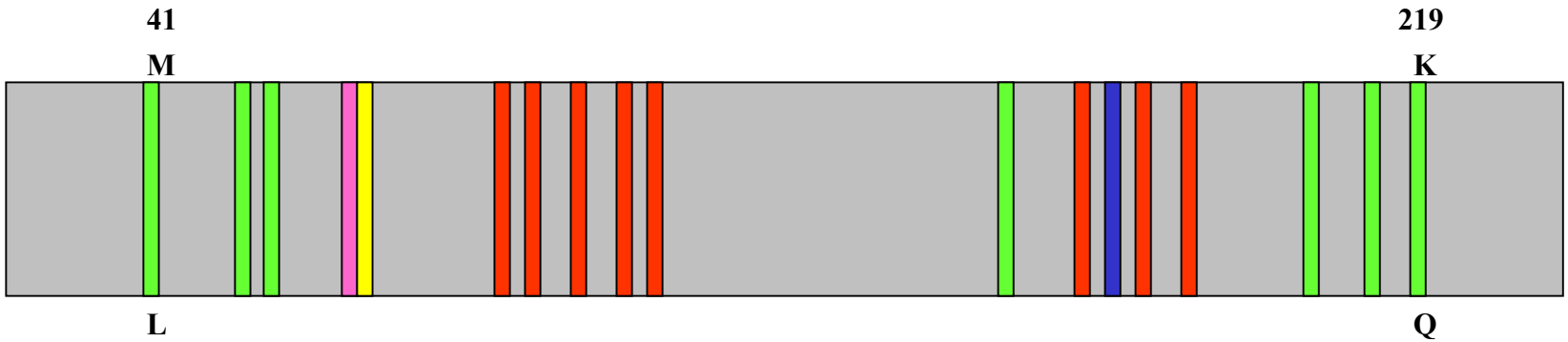

B
0.1µm

HIV-1 *polymerase (pol)* gene



p15 protease (PR) - gag/pol cleavage and maturation
p66 reverse transcriptase – RT and RNase H activity
p31 integrase (IN) - DNA provirus integration

DRUG RESISTANCE MUTATIONS IN RT GENE



ZDV – M41L, D67N, K70R, Q151M, L210W, T215Y, K219Q

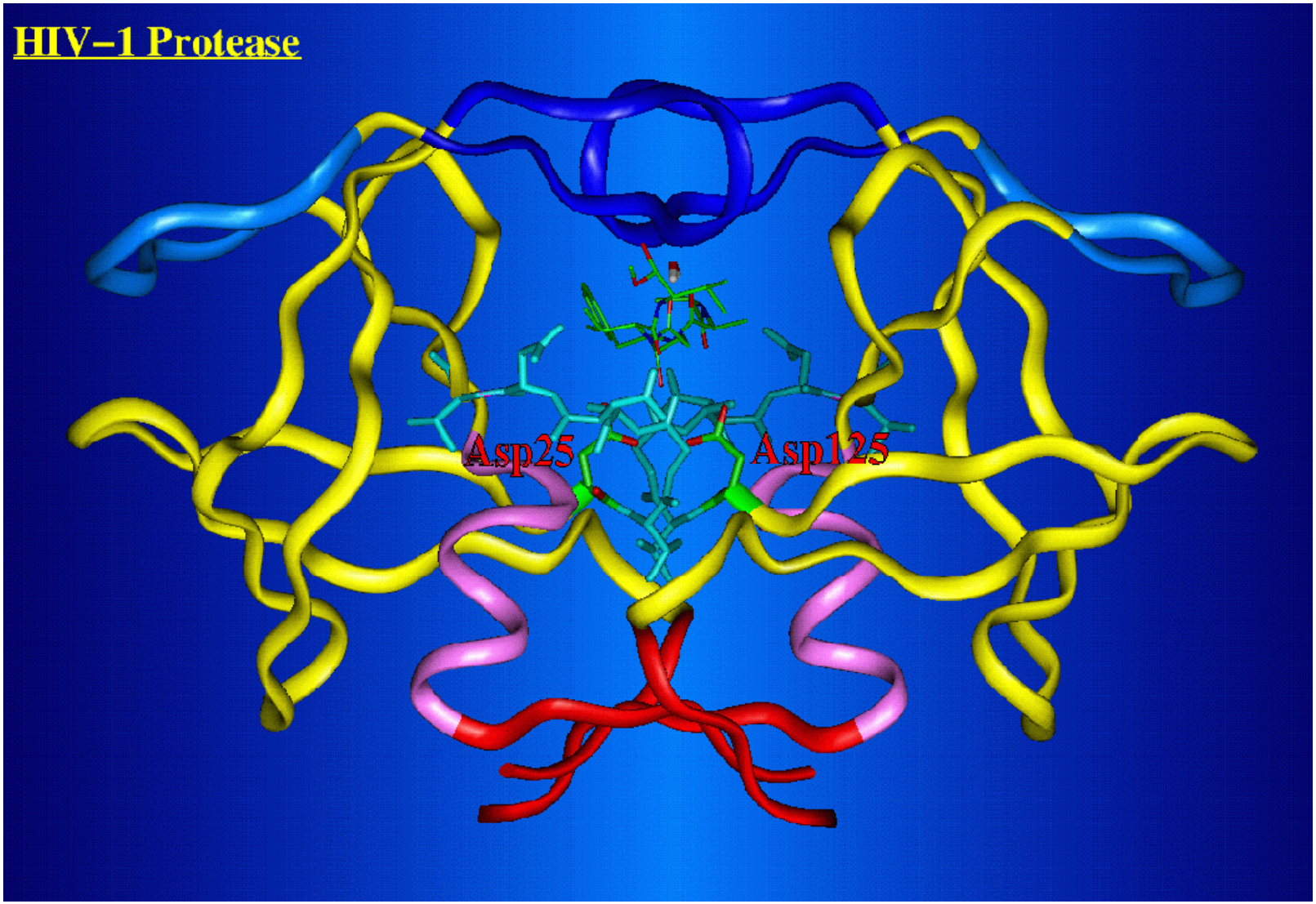
3TC – M184V/I/T

ddI – L74V

d4T – V75T

NVP – A98G, L100I, K103N, V106A, V108I, Y181C, Y188C, G190A

HIV–1 Protease



Drug resistance- a predetermined agenda

HIV consists of viral swarm (quasispecies).
High turnover – an estimated 1-10 billion viral particles/day.
RT highly error-prone, makes one mistake every replication cycle

Mutations conferring drug resistance involve genetic changes that result in alterations to the structure and function of RT and/or protease. Such changes often reduce fitness of the variant and thus they exist only as a minority population in the absence of drug pressure.

Some rare variants are naturally resistant to a particular drug which may be selected for under drug selection pressure.

Reverse transcriptase inhibitors

Nucleoside RT inhibitors (NRTIs)

AZT, ddI, d4T, ddC, 3TC, ABC

Derivatives of natural nucleosides. Phosphorylated by cellular enzymes. Competitive inhibitors of natural dNTPs/chain terminators

Non-nucleoside RT inhibitors (NNRTIs)

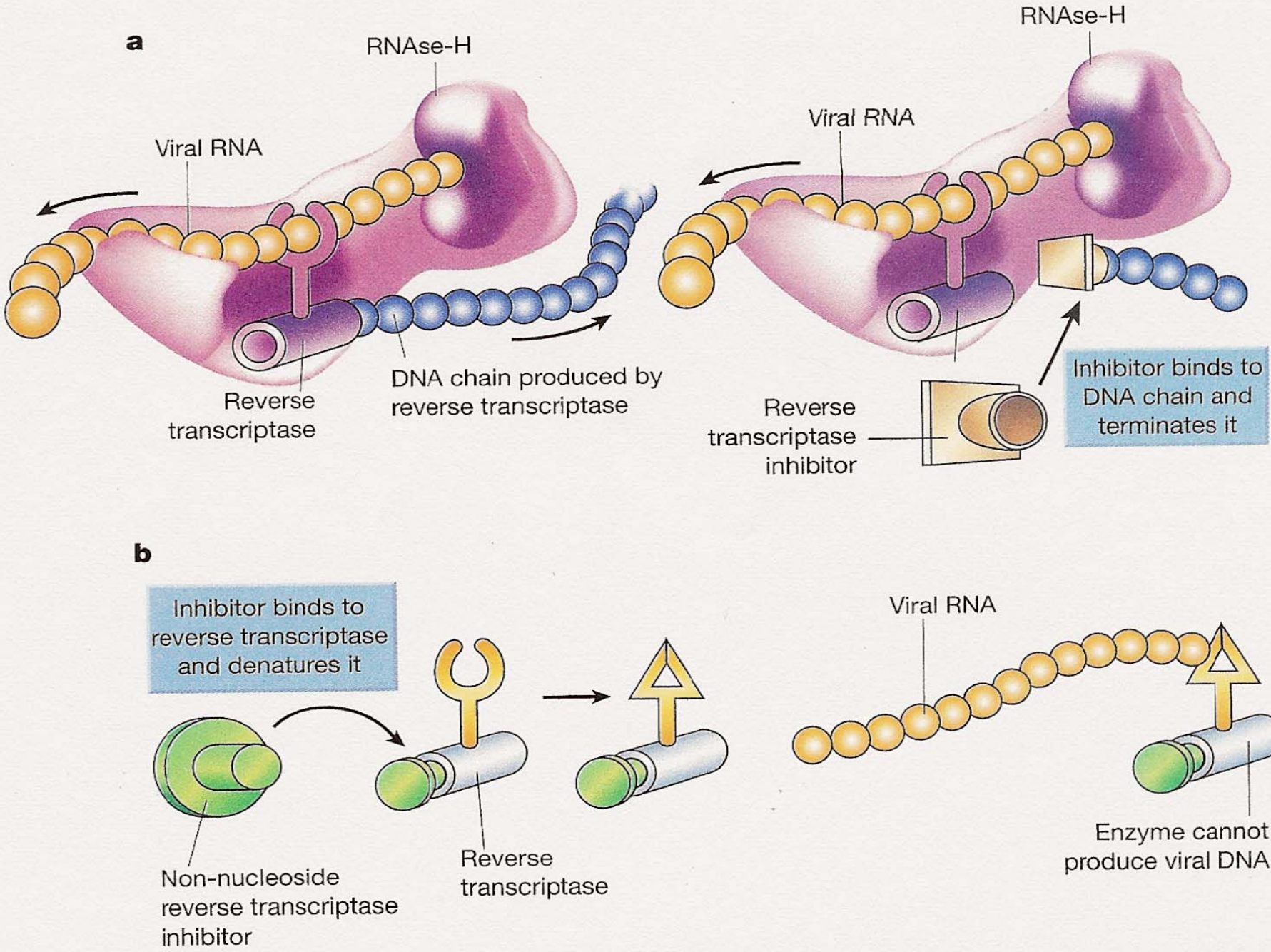
NVP, Efavirenz, Delavirdine

Bind directly to enzyme

Protease inhibitors

Saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir

Bind to protease active site and inhibit proteolytic cleavage of the gag and gag-pol precursors


a
RNAse-H
Viral RNA
Reverse transcriptase
DNA chain produced by reverse transcriptase
RNAse-H
Viral RNA
Reverse transcriptase inhibitor
Inhibitor binds to DNA chain and terminates it
b
Inhibitor binds to reverse transcriptase and denatures it
Non-nucleoside reverse transcriptase inhibitor
Reverse transcriptase
Viral RNA
Enzyme cannot produce viral DNA

Rate of emergence of resistance

Low genetic barrier to resistance

Single mutation confers resistance
eg 3TC, NNRTI's
Resistance occurs rapidly when used as monotherapy

High genetic barrier to resistance

Require accumulation of several sequential mutations
eg Indinavir and abacavir require 3 mutations

Cross-resistance

Resistance to one drug conferred by genetic mutations that were selected by another drug

Factors affecting the emergence of drug-resistant HIV variants

- **Prior treatment** – previous drug history, archived resistance
- **Stage in disease** – resistance develops more readily in patients with more advanced disease (higher viral turnover)
- **Drug potency** – incomplete inhibition eg dual nucleosides
- **Patient adherence** – sub-optimal dosing
- **Achievable drug levels** – rates of drug metabolism and pharmaco-dynamic parameters
- **Drugs with low genetic barrier to resistance** – eg NVP monotherapy
- **Infection with drug resistant virus** – compromises treatment options and could lead to more rapid emergence of resistance

Recommendations on HIV Drug Resistance Testing

EuroGuidelines/IAS/US DHHS

- **Primary HIV-1 infection**
  - **strongly considered due to increased rates of primary HIV-1 drug resistance**
- **Established HIV-1 infection**
  - **not generally recommended**
- **First regimen failure**
  - **recommended as resistance may not have developed to all drugs in a combination**
- **Multiple regimen failure**
  - **recommend testing to optimize the number of active drugs in the next regimen**
- **Pregnancy**
  - **recommend testing to optimize maternal treatment and prophylaxis for neonate**
- **Post-exposure prophylaxis**
  - **recommended but treatment should not be delayed for result**

Methods for drug resistance testing

Genotypic testing

Detects genotypic changes associated with resistance to particular drugs. Accessory mutations confer resistance in presence of other mutations
Two commercial assays Visible genetics TRUGENE Applied BioSystems ViroSeq

Phenotypic (drug susceptibility) testing

Measures drug inhibition of HIV-1 *in vitro*
Two commercial sources Virco and ViroLogic
Costly, labor-intensive, antiviral effects of NRTI differ *in vivo* and *in vitro* e.g ddI poorly phosphorylated *in vitro*

Benefits of resistance testing

Four of 5 prospective studies have shown the benefits of resistance testing. Patients whose physicians have access to drug resistance data, particularly genotypic resistance data respond better to therapy than control patients whose physicians do not have access to the same data.

Can assist in the choice of a combination treatment regimen but cannot predict the successful use of a given drug.

Resistance data needs to be interpreted together with treatment and clinical profile.

Resistance to single dose NVP

HIVNET 006 and 012 trial to PMTCT in Uganda
NVP highly efficacious - reduces transmission by 50%
20% of mothers developed resistance
46% of infants developed resistance

- **Resistance did not compromise the ability of NVP to PMTCT**
- **Mutations arose *de novo* in mothers and infants ie not transmitted**
- **K103N in mothers and Y181C in infants**
- **Mutations faded with time (12-18 months)**
- **Higher frequency in infants - due to higher VL in infants?**
- **Compromise treatment options for mother and infant???**

<u>WHO RECOMMENDATION</u>
NVP RESISTANCE SHOULD NOT DELAY THE IMPLEMENTATION OF PMTCT PROGRAMS