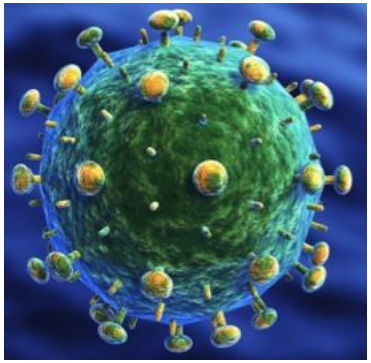
HIV, HBV, HCV Virology

Anna Maria Geretti

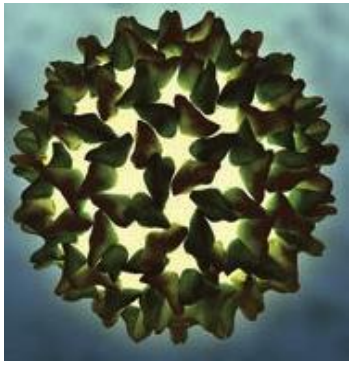
Institute of Infection & Global Health

University of Liverpool

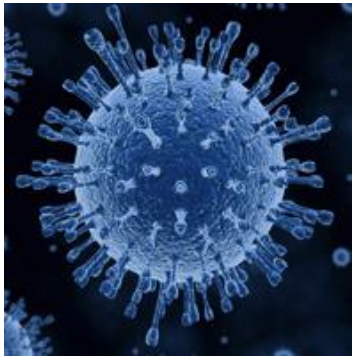
HIV



HBV

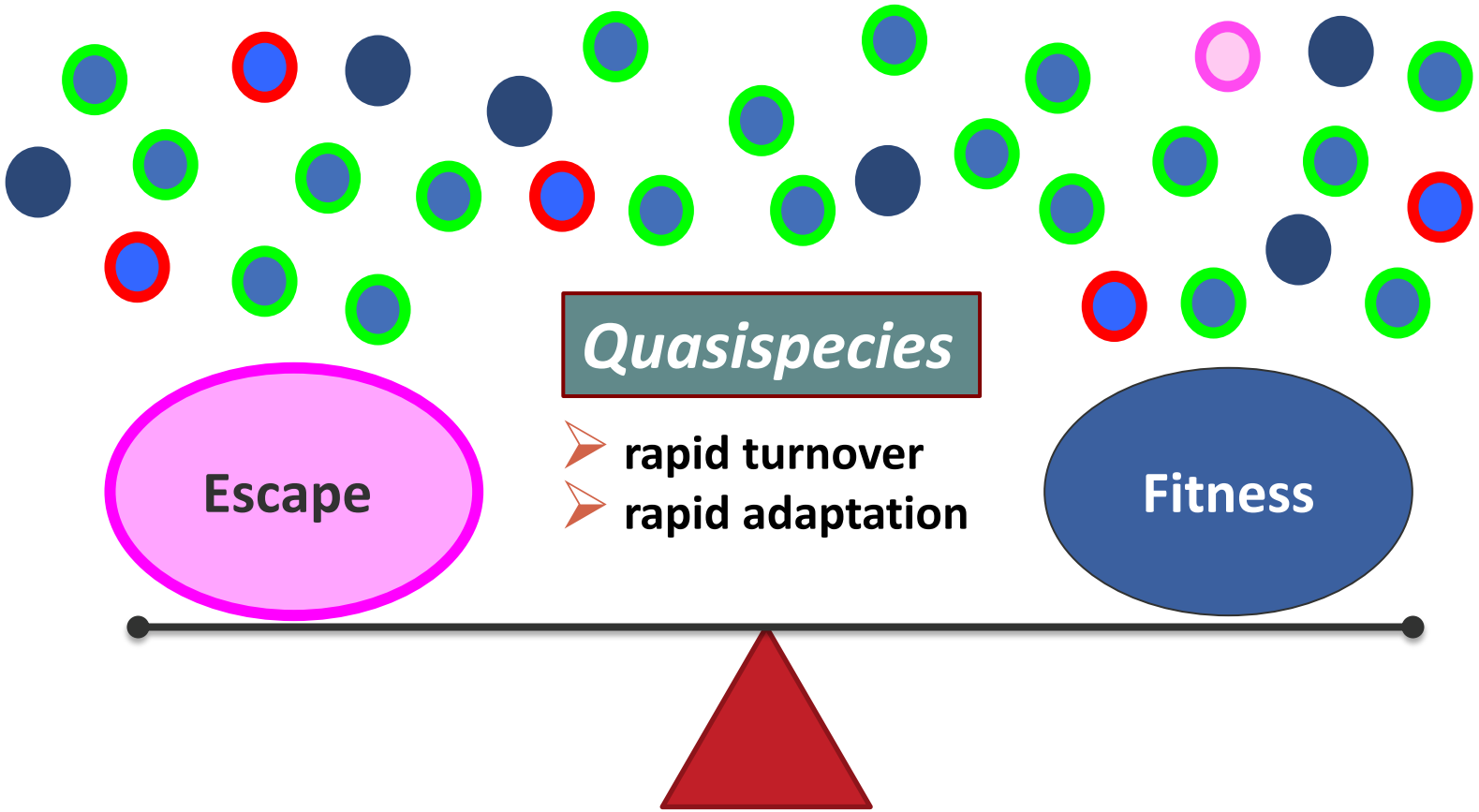


HCV



- **Many similarities**
- **Several fundamental differences**

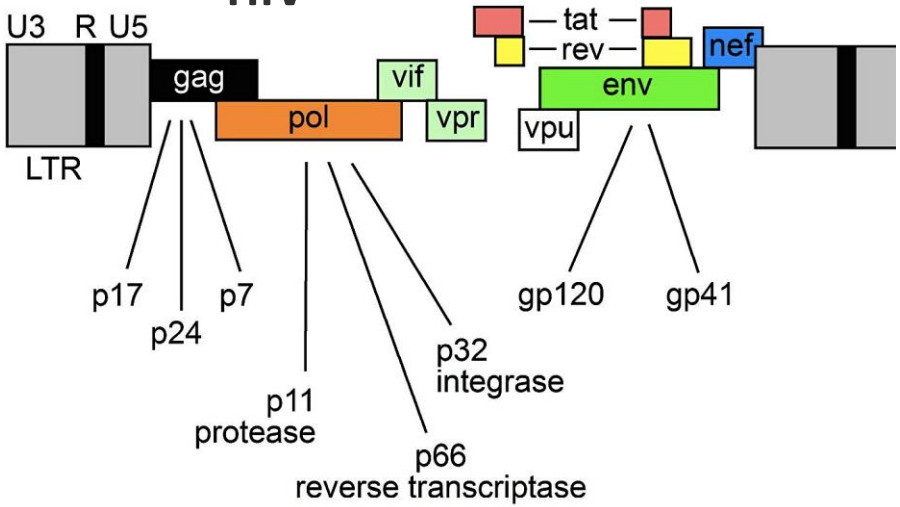
- High-level replication: **HIV 10^{10}, HBV 10^{11}, HCV 10^{12} particles/day**
- Rapid clearance of newly produced virus
- High mutation rate ⟶ quasispecies
- Some mutations detrimental, some allow escape



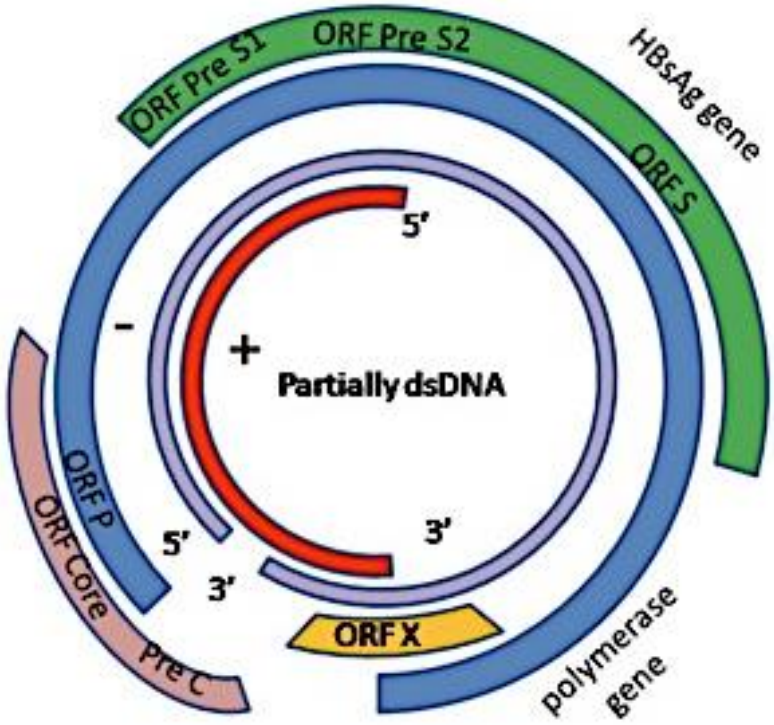
Antiviral resistance

- Drug resistant variants are **produced spontaneously** during virus replication
  - Single, double, and even triple mutants emerge daily in untreated patients – *persistence as replicating variants directly related to the fitness cost of the mutations*
  - "Tolerance" for mutations is HCV > HIV > HBV

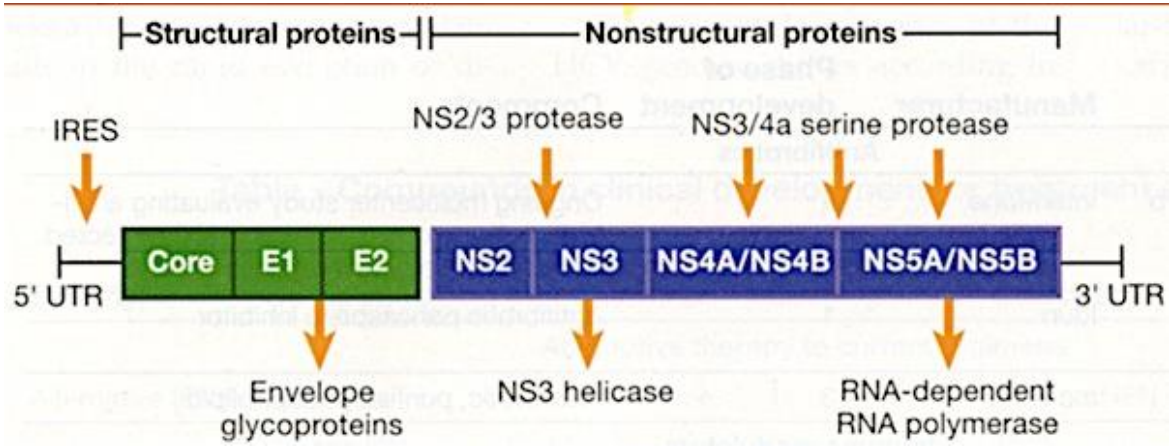
HIV


U3
R
U5
LTR
gag
pol
vif
vpr
tat
rev
nef
env
vpu
p17
p24
p7
p11
protease
p32
integrase
p66
reverse transcriptase
gp120
gp41

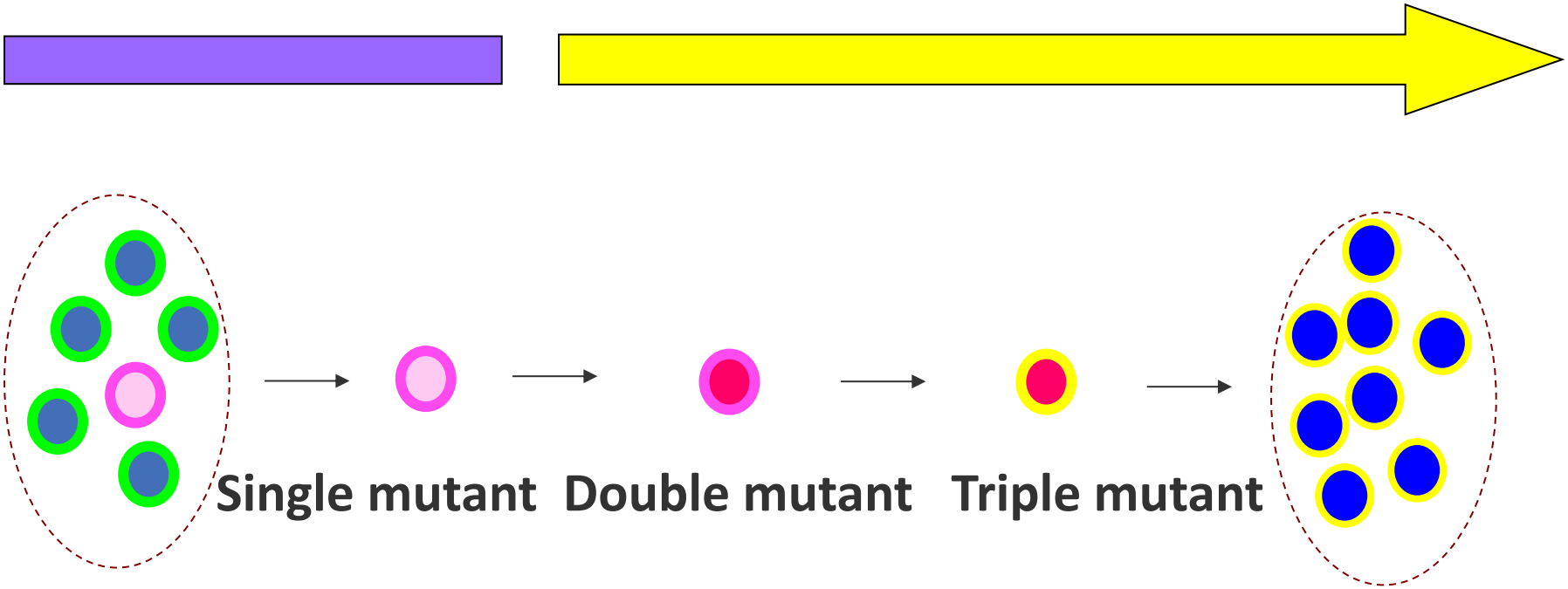
HBV

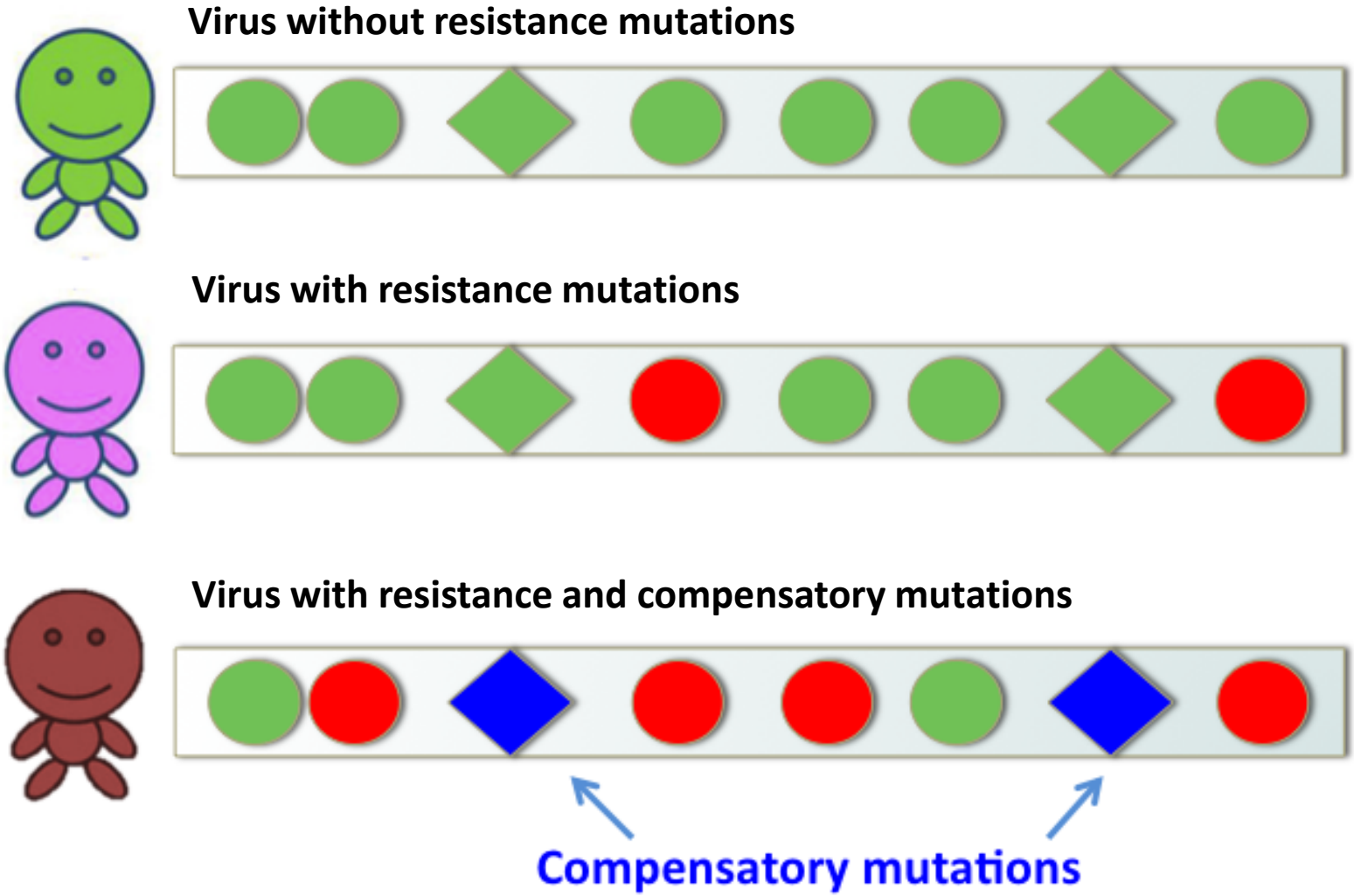

ORF Pre S1
ORF Pre S2
HBsAg gene
ORF S
5'
-
+
Partially dsDNA
ORF P
ORF Core
Pre C
5'
3'
3'
ORF X
polymerase gene

HCV

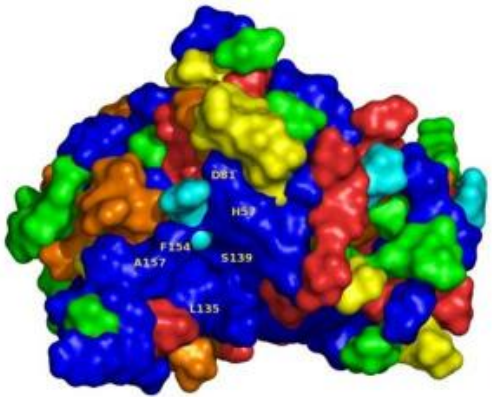

Structural proteins
Nonstructural proteins
IRES
NS2/3 protease
NS3/4a serine protease
5' UTR
Core
E1
E2
NS2
NS3
NS4A/NS4B
NS5A/NS5B
3' UTR
Envelope glycoproteins
NS3 helicase
RNA-dependent RNA polymerase

Emergence & evolution of HIV drug resistance

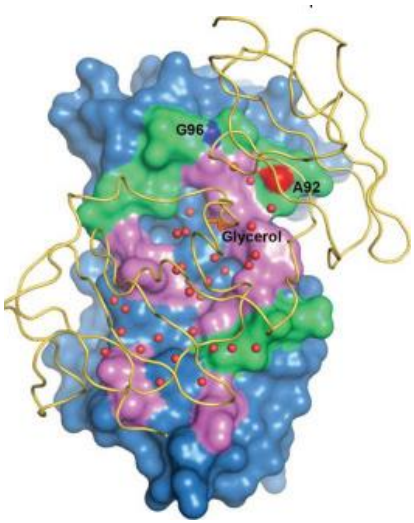



Virus without resistance mutations
Virus with resistance mutations
Virus with resistance and compensatory mutations
Compensatory mutations

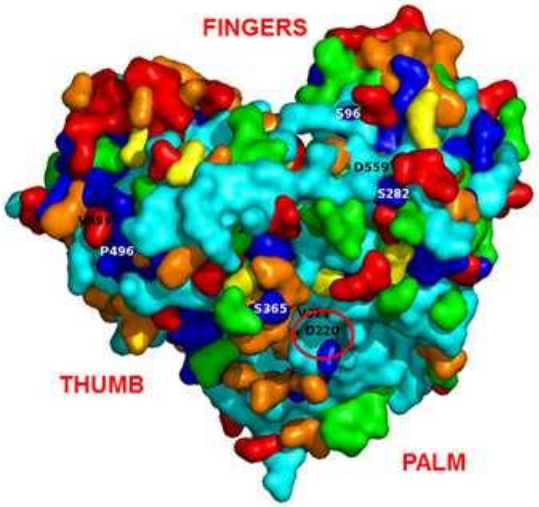
HCV genetic variability



NS3: 42% of amino acid conserved among all genotypes



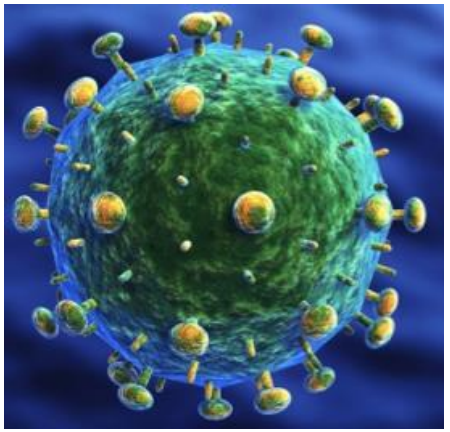
NS5A: 46% of amino acid conserved among all genotypes



NS5B: 55% of amino acid conserved among all genotypes

HIV

RNA virus	• Chronic infection • Without treatment, most people develop AIDS and die within ~10 years (7.5 to 11.6)[1,2] • Non-AIDS HIV-related disease	• Latent reservoir as integrated provirus • Antiviral therapy controls but does not eradicate HIV • Life-long therapy required to suppress virus replication • PrEP and PEP



1. Todd AIDS 2007; 2. Laskey Nature Rev Microbiol 2014

The HIV virology timeline

HIV-1 isolated

HIV-1 genome sequenced

HIV replicates at high levels throughout the infection

HIV replication drives immune compromise

Highly active antiretroviral therapy

Plasma HIV RNA ('viral load') suppression as goal of therapy

HIV replication causes disease through immune activation & inflammation

HIV eradication research

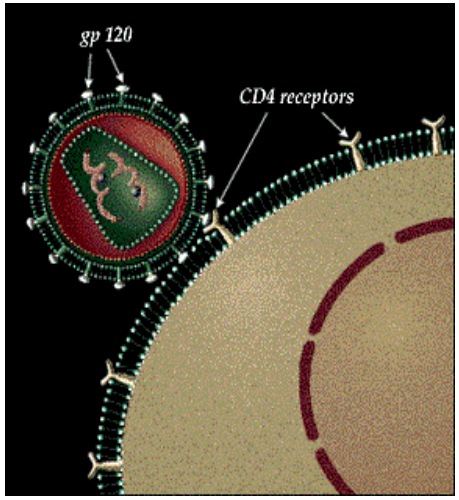
1982 1985 1991 1995 1996 2009 2010 →

Primary HIV infection

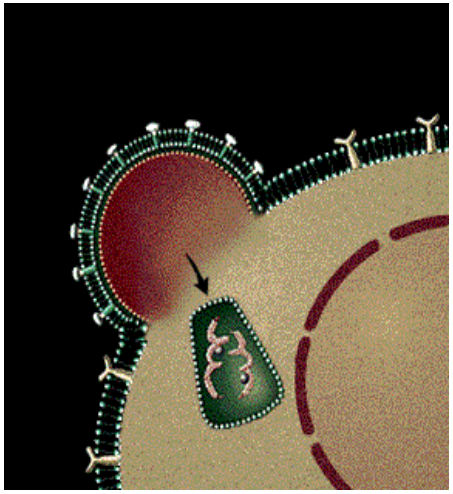
- Encompasses the first **6 months** after infection
- Presents symptomatically in **23-92%** of individuals[1-14]
  - *Usually clinically mild, temporary and self-limited*
- Characterised by **high levels of virus replication**[15]
- High risk of onward **transmission**
  - *Can contribute to >50% of all transmissions within focussed epidemics*[16]
  - *Exacerbated by concomitant acquisition of STIs*[17]
- Viral dissemination and establishment of long-lived **viral reservoir** occurs rapidly after HIV acquisition[18-21]

STIs = Sexually Transmitted Infections

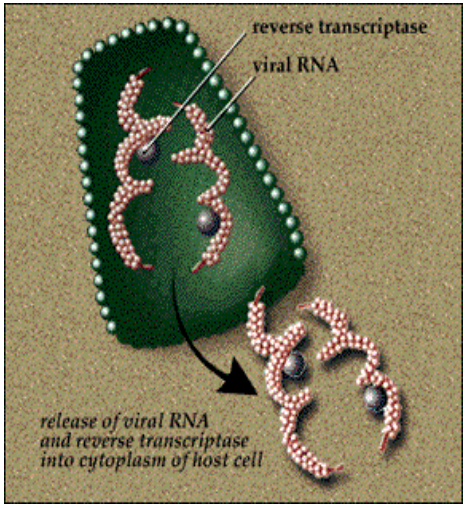
1. Cooper et al. Lancet 1985; 2. Fox et al. AIDS 1987; 3. Quinn TC. JAMA 1997; 4. Tindall et al. Arch Intern Med 1988; 5. Gaines et al. BMJ 1988; 6. Kinloch-de Loes et al. Clin Infect Dis 1993; 7. Dorrucci et al. AIDS 1995; 8. Schacker et al. Ann Intern Med 1996; 9. Bollinger et al. JAMA 1997; 10. Hofer et al. J Acquir Immune Defic Syndr 2000; 11. Lavreys et al. Clin Infect Dis 2000; 12. Vanhems et al. J Acquir Immune Defic Syndr 2002; 13. Daar et al. Curr Opin HIV AIDS 2008; 14. Braun et al. Clin Infect Dis 2015; 15. Quinn et al. N Engl J Med 2000; 16. Phillips et al. AIDS 2015; 17.Ward et al. Curr Opin HIV AIDS 2010; 18. Lodi et al. Clin Infect Dis 2011; 19. Katlama et al. Lancet 2013; 20. Kulpa et al. J Virus Erad 2015; 21. Ananworanich et al. J Virus Erad 2016



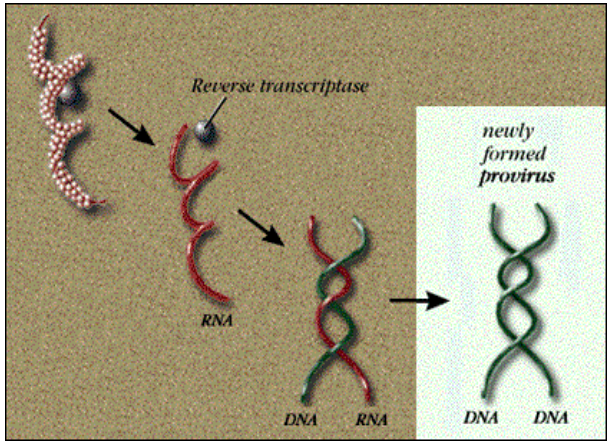
Attachment



Fusion

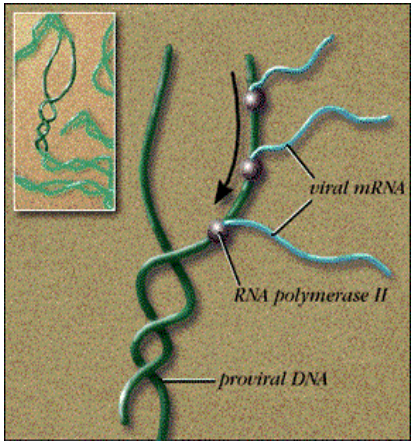


Release of RNA

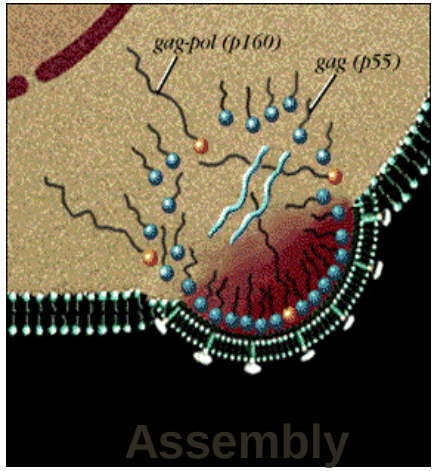


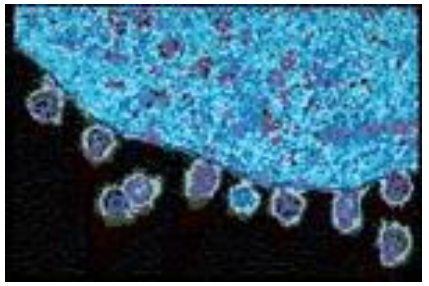
Reverse transcription

Integration



Transcription

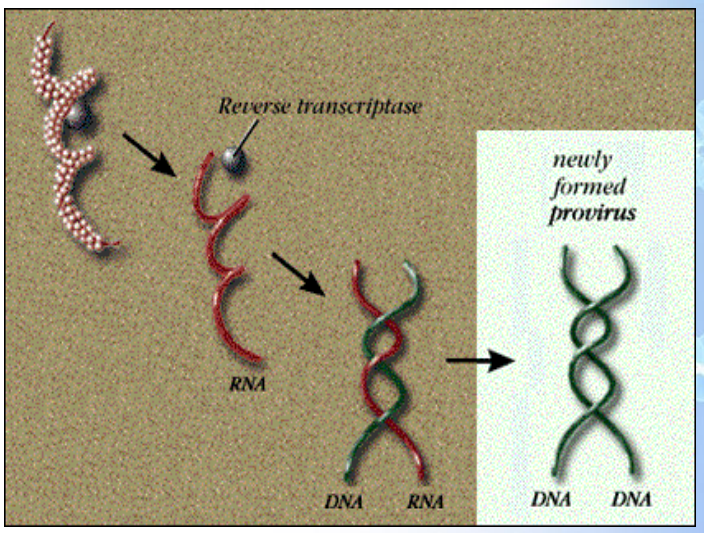




Maturation
& budding

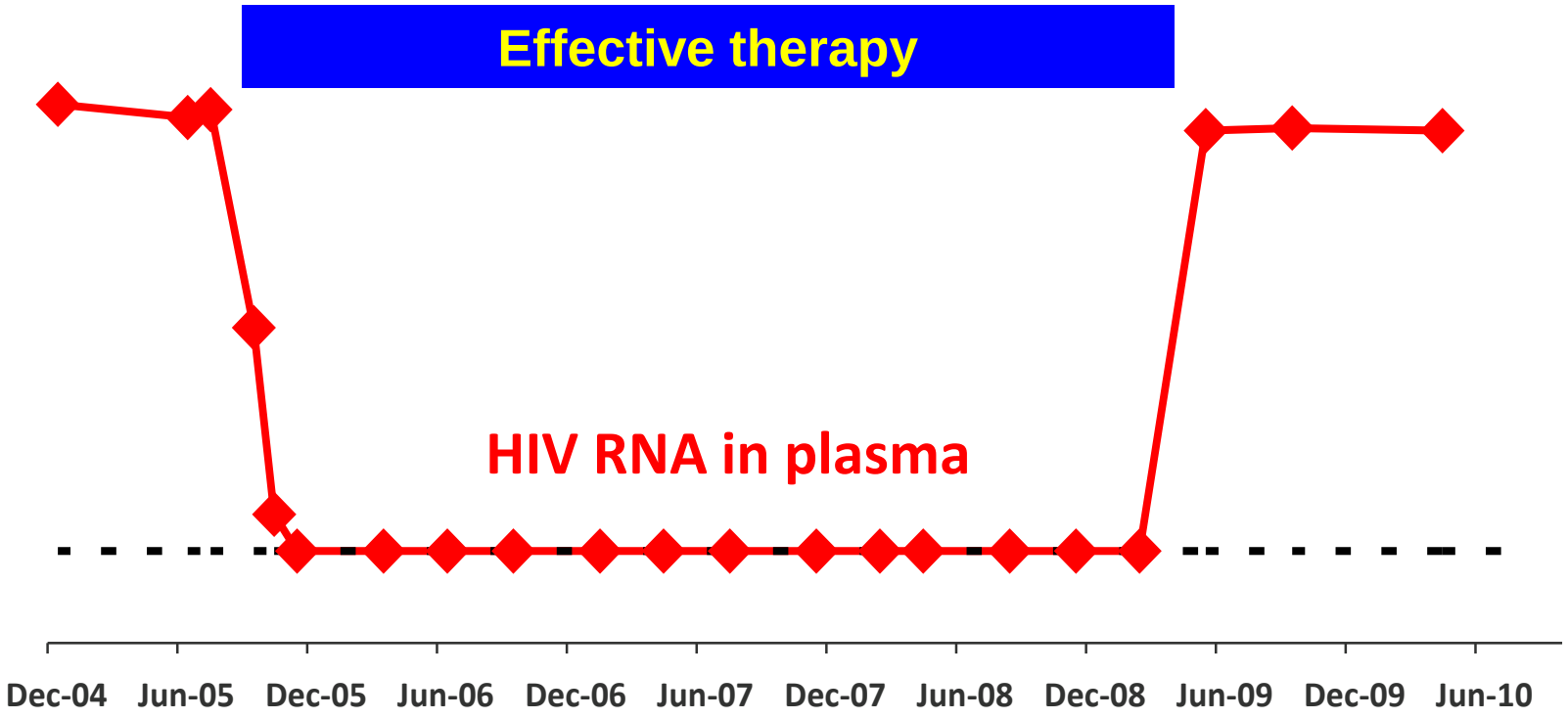
HIV replication

Mechanisms of HIV genetic evolution



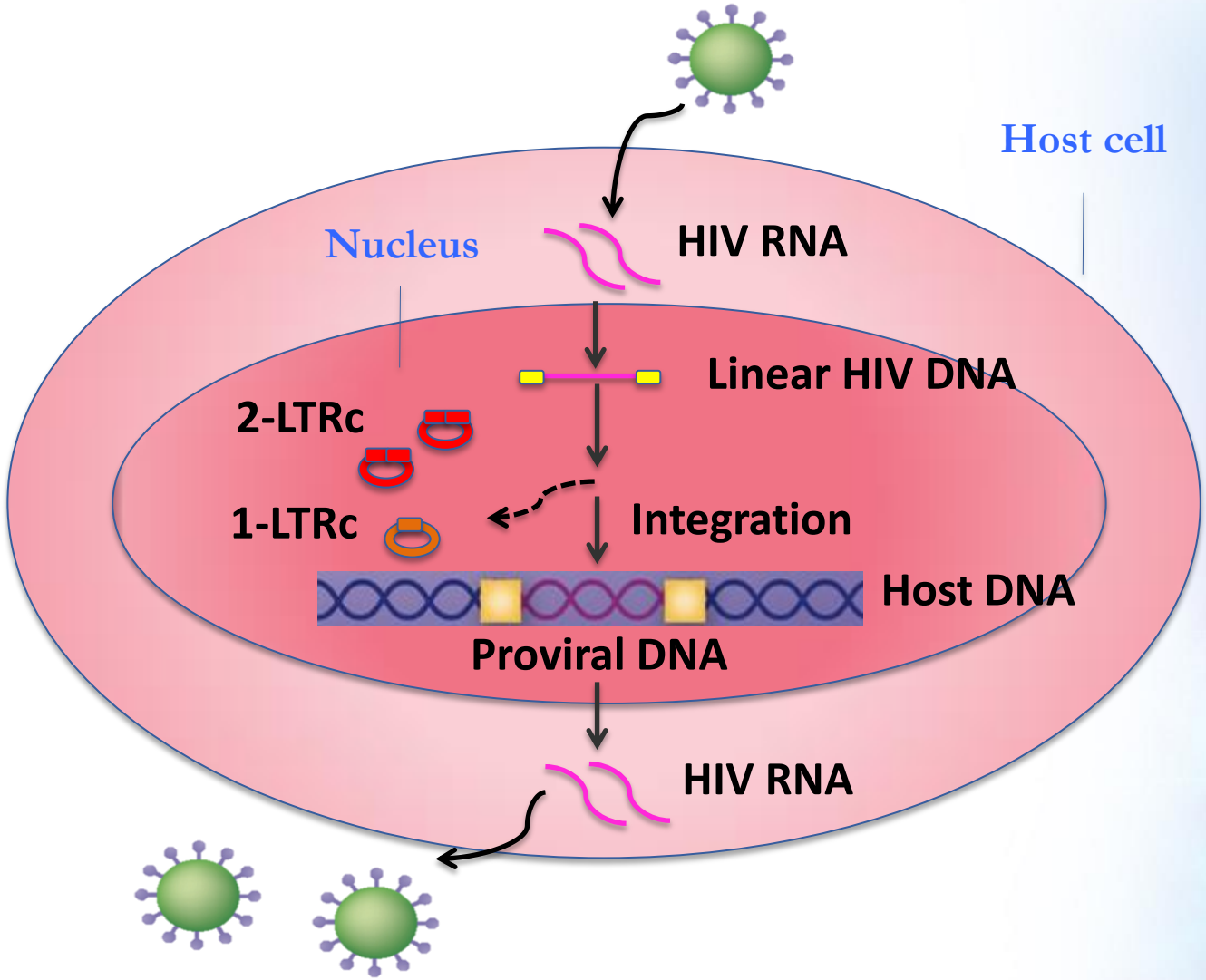
1. **Errors by viral reverse transcriptase**
   - ***~1 mis-incorporation per genome round***
2. Errors by cellular RNA polymerase II
3. APOBEC-driven G➔A hypermutation
   - *Deamination of cytosine residues in nascent DNA*
4. Recombination between HIV strains

HIV replication resumes if therapy is stopped

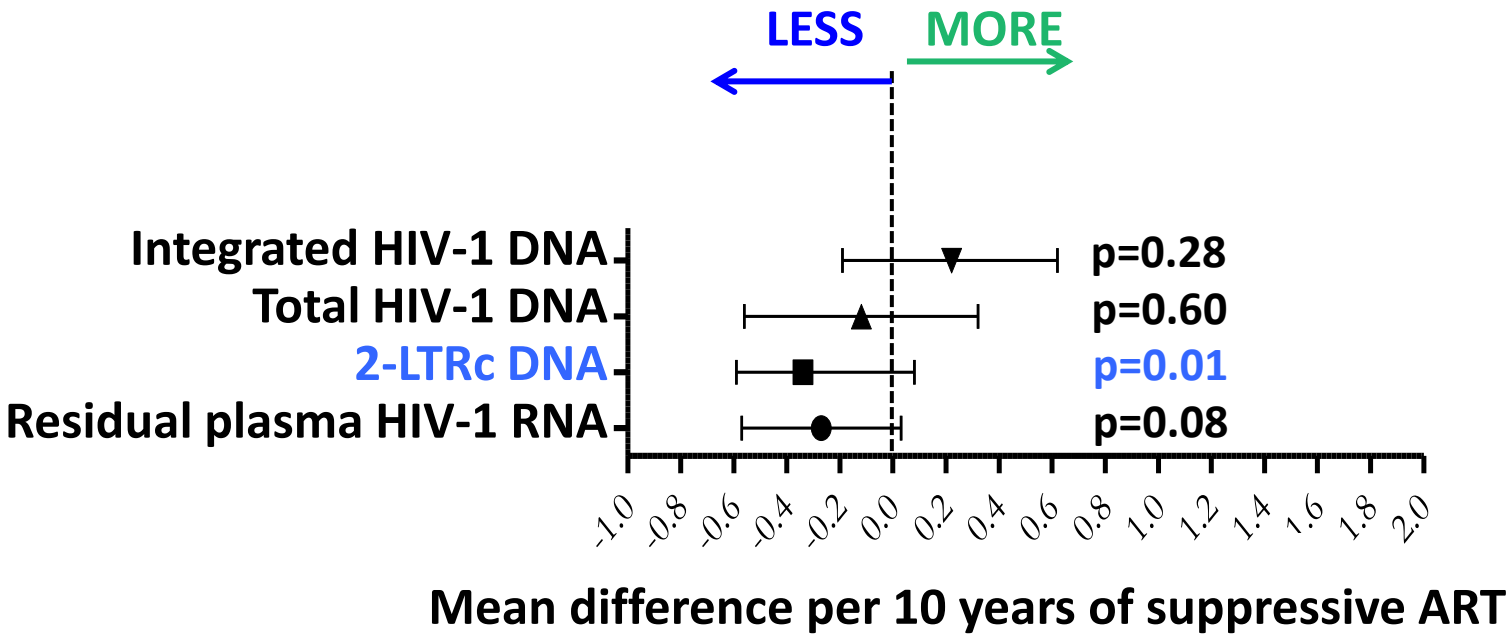


- Antiretroviral therapy cannot achieve HIV eradication
- After stopping therapy HIV replication resumes to pre-treatment levels
- A few exceptions exist

HIV DNA forms



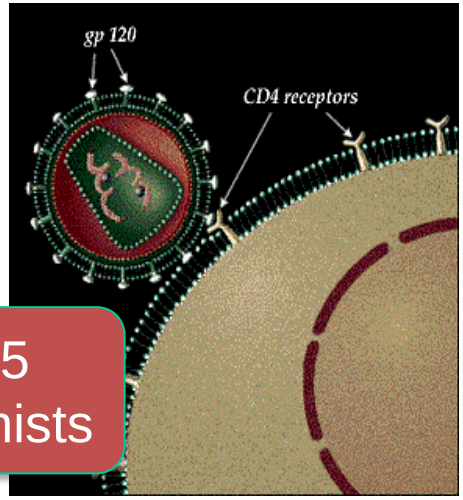
Effect of fully suppressive ART on markers of HIV persistence



log-transformed variables

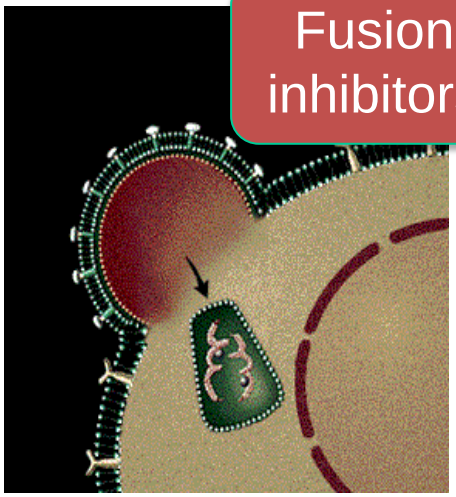
Ruggiero. EBiomed 2015

Targets of therapy



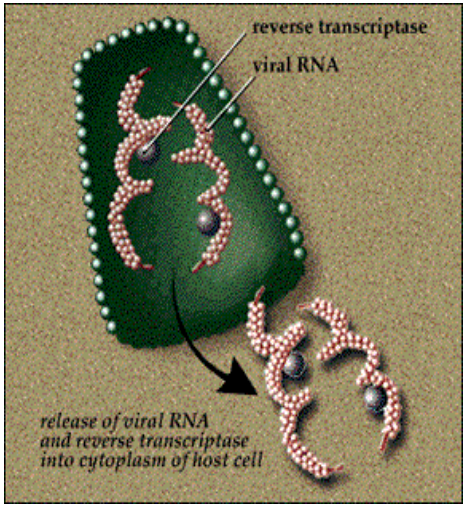
CCR5 antagonists

Attachment

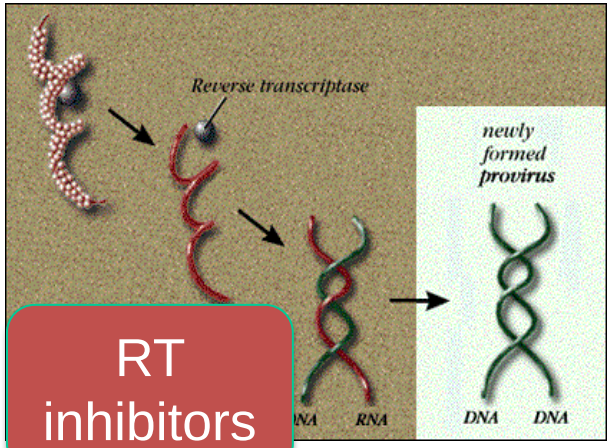


Fusion inhibitors

Fusion



Release of RNA

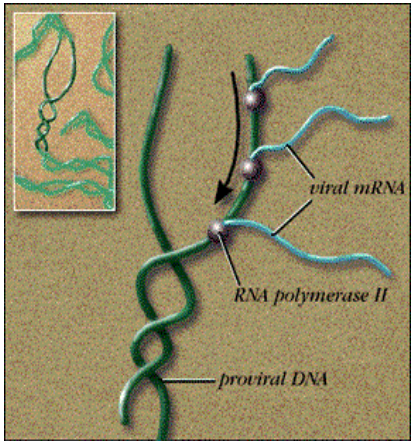


RT inhibitors

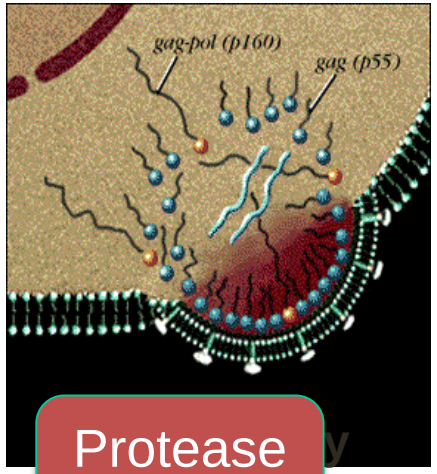
Reverse transcription

Integrase inhibitors

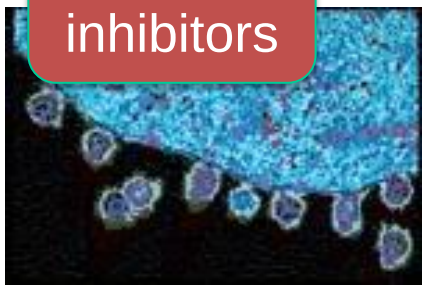
Integration



Transcription

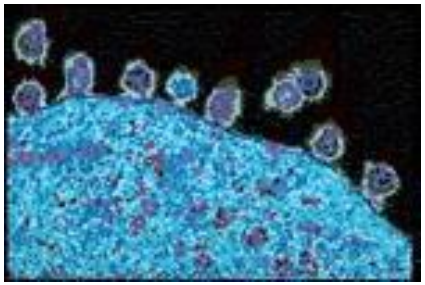


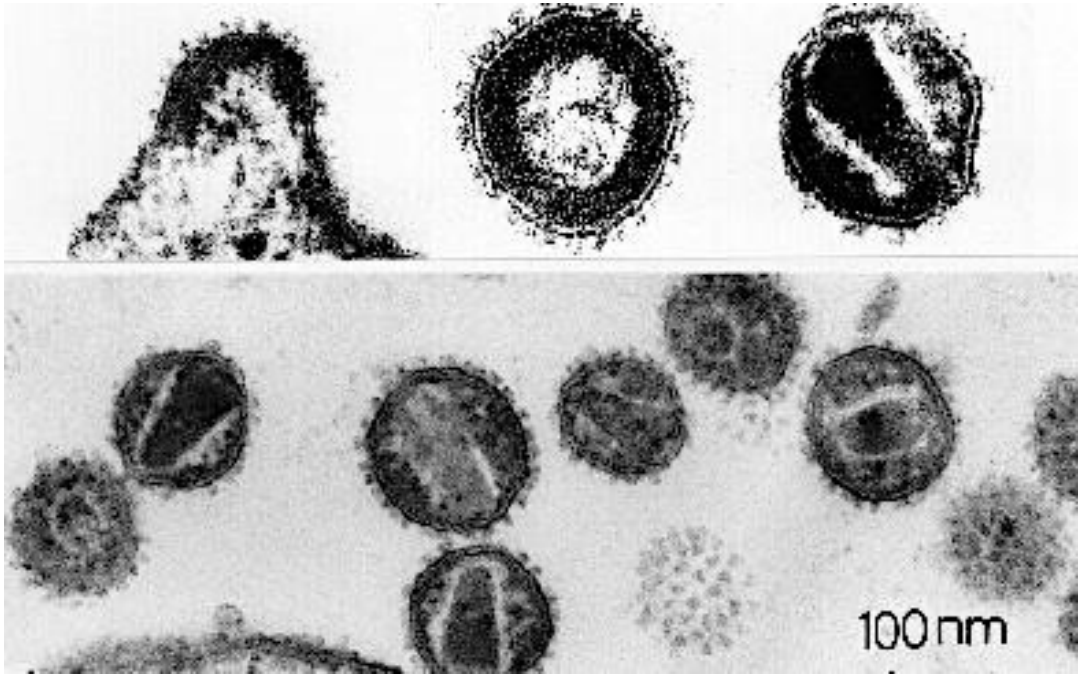
Protease inhibitors

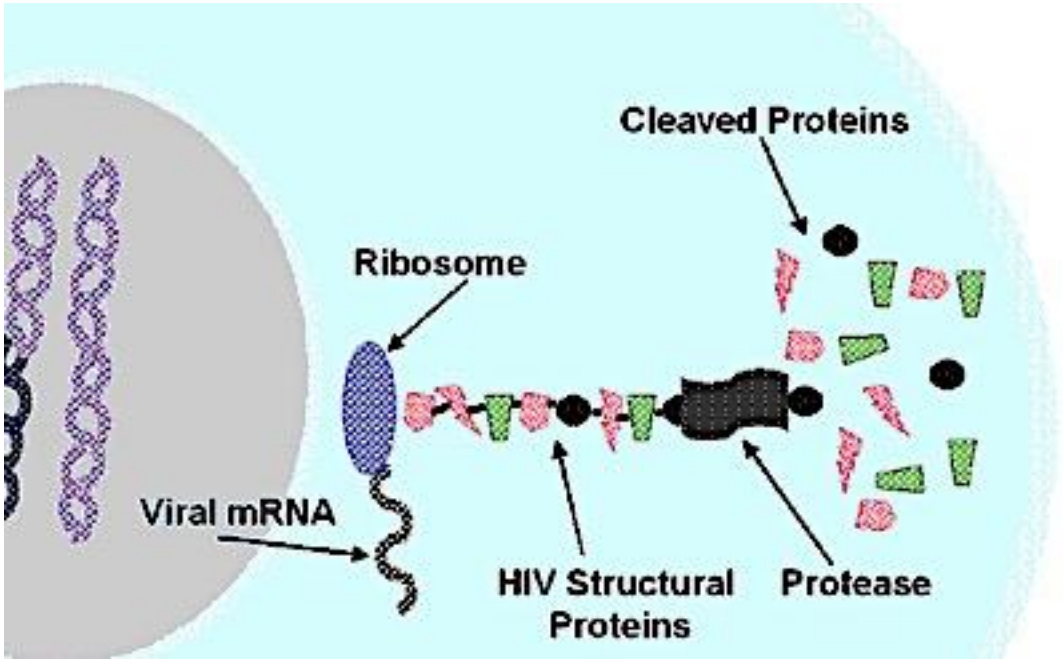


Maturation & budding

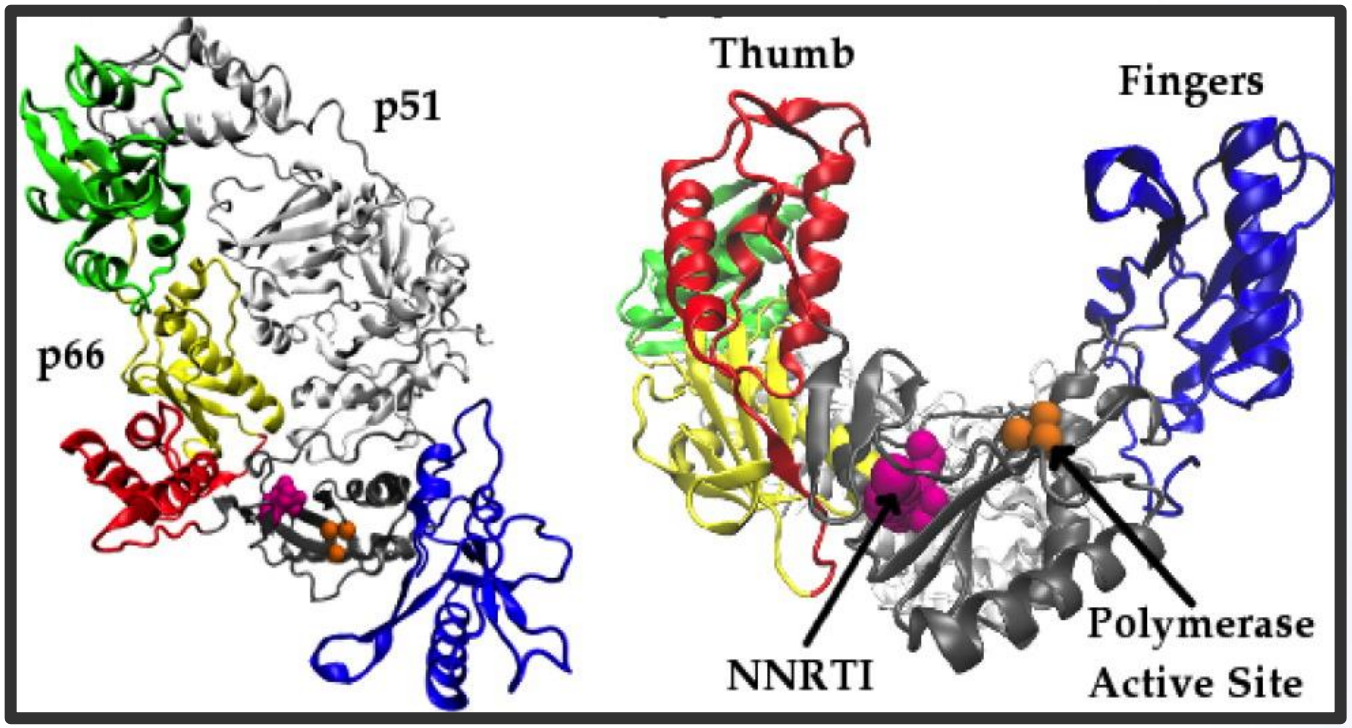
Maturation & budding







Polyprotein

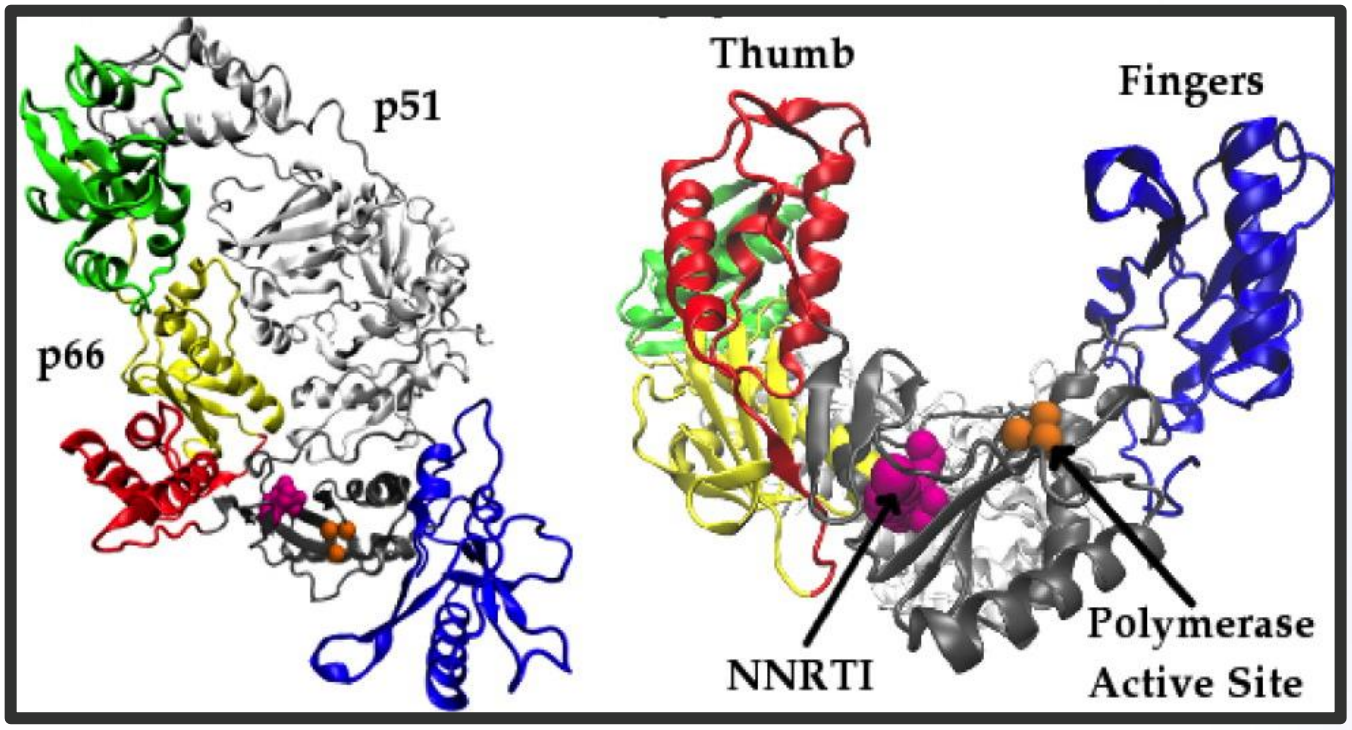


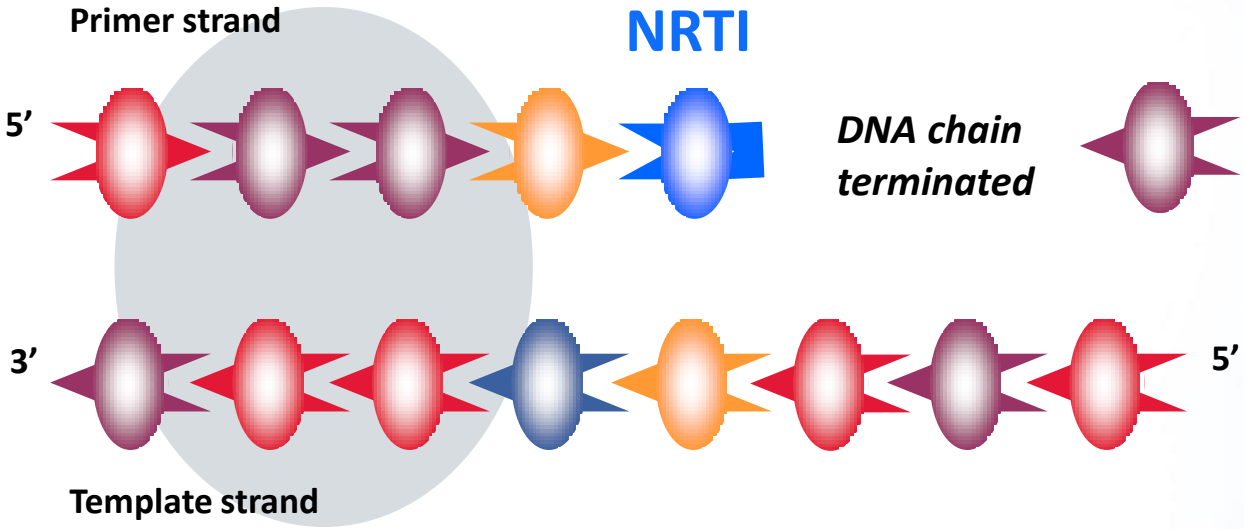
- **HIV Reverse transcriptase/Polymerase**

Two mechanisms of inhibition

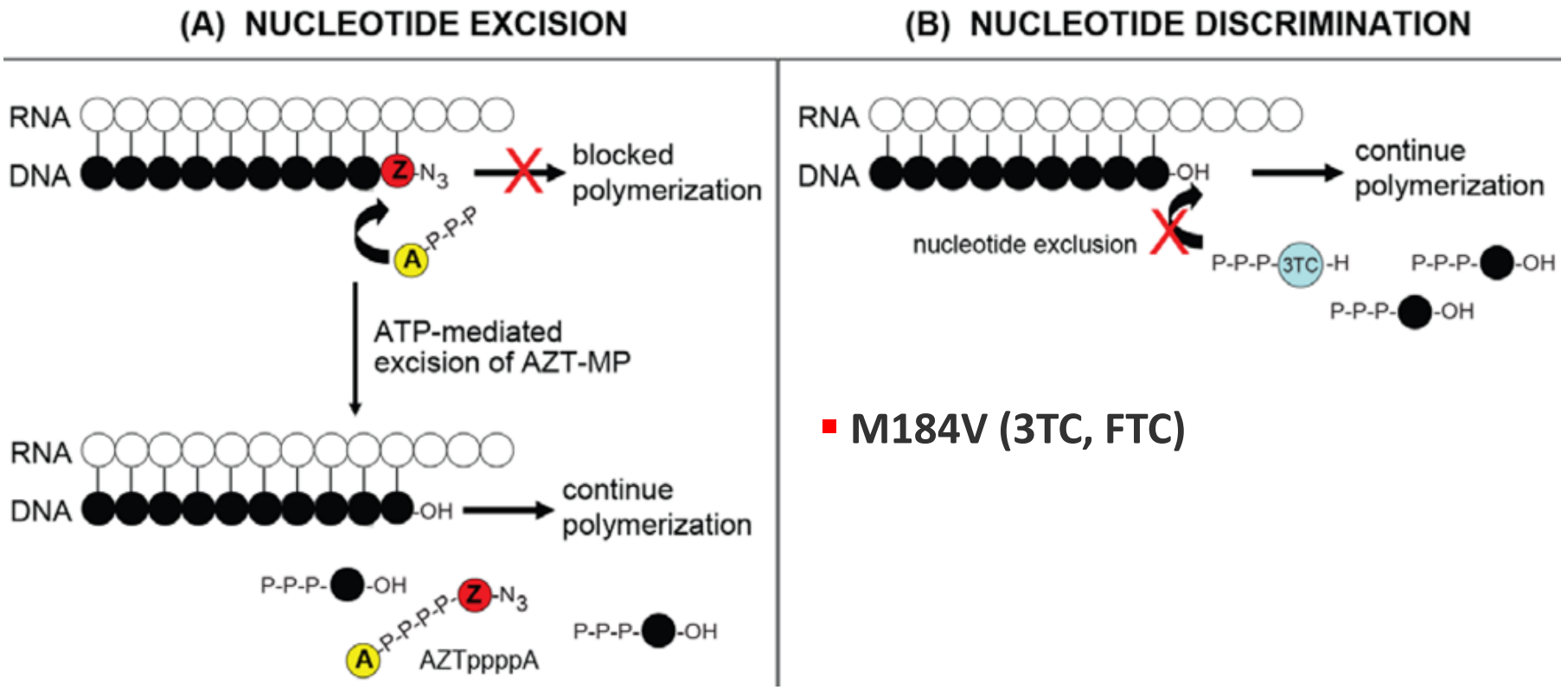
- **Competitive – NRTIs**
- **Allosteric – NNRTIs**

Wright et al. Biology 2012


p51
p66
Thumb
Fingers
NNRTI
Polymerase
Active Site


Primer strand
NRTI
5’
DNA chain
terminated
3’
5’
Template strand

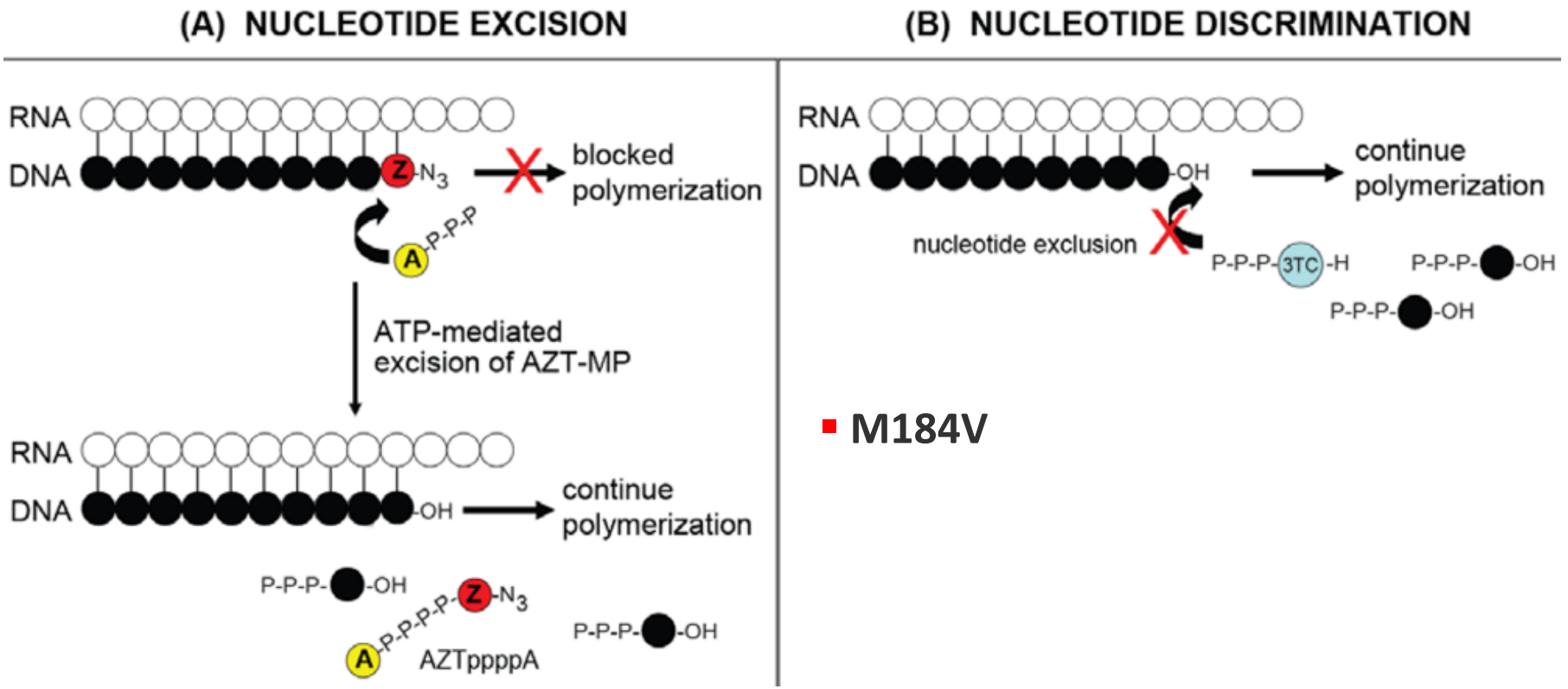
Mechanisms of NRTI resistance



- M184V (3TC, FTC)

- T215Y (AZT, ABC, ddI, d4T, TDF)

Mechanisms of NRTI resistance

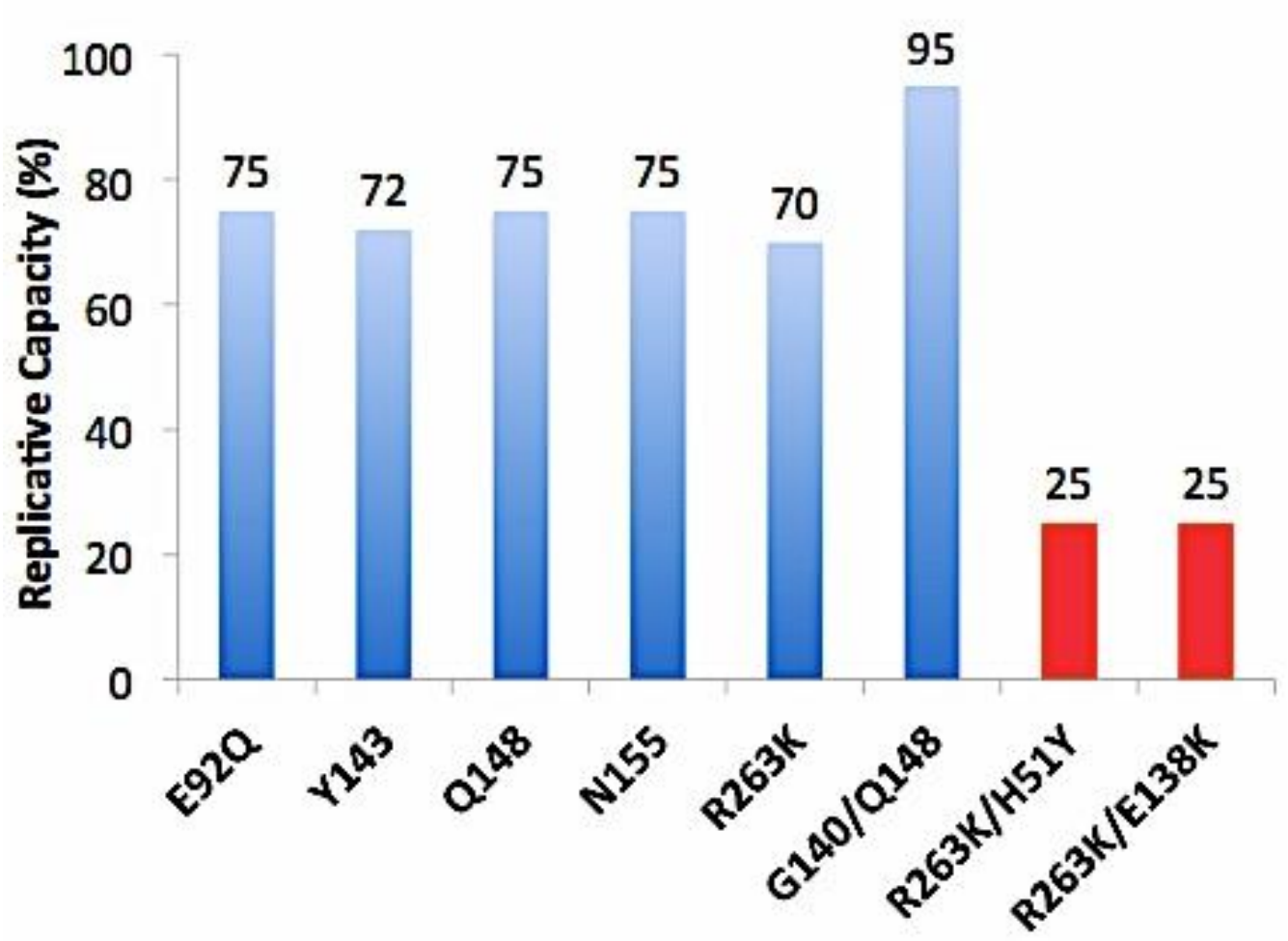


- M184V

- T215Y

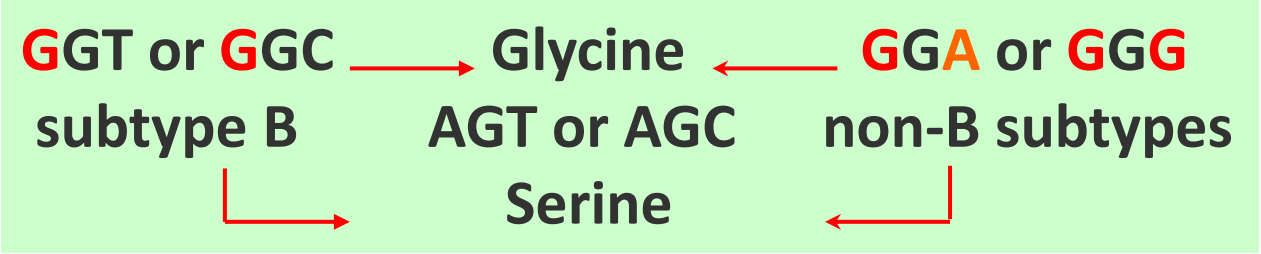
Antagonised by M184V

Replicative capacity ("fitness") of integrase resistant mutants



Hightower Antimicrob Agents Chemother 2011; Quashie J Virol 2012; Wainberg ISHEID Conference 2014

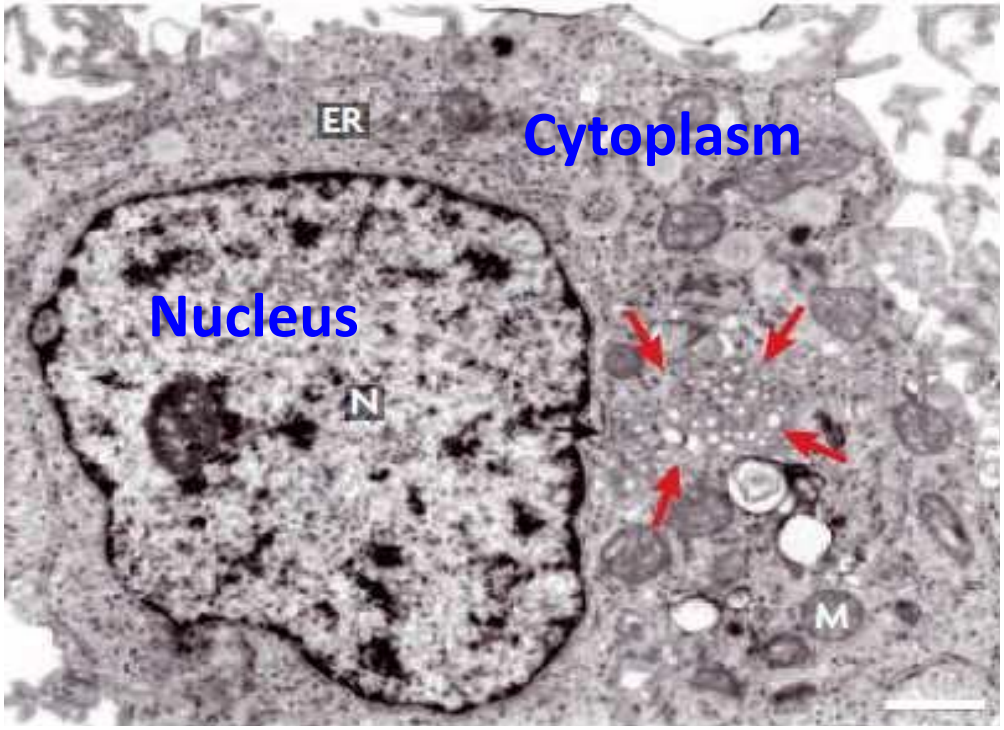
Codon usage at integrase position 140 in B vs. non-B subtypes

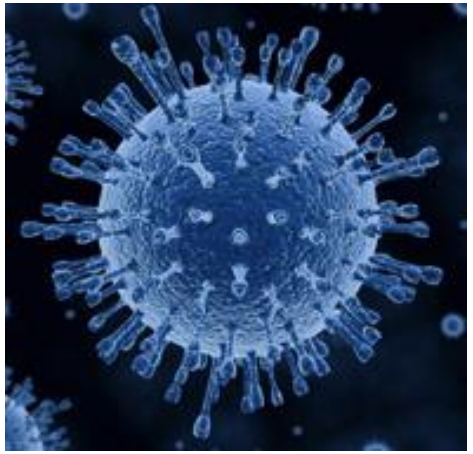


Doyle JAC 2015

HCV

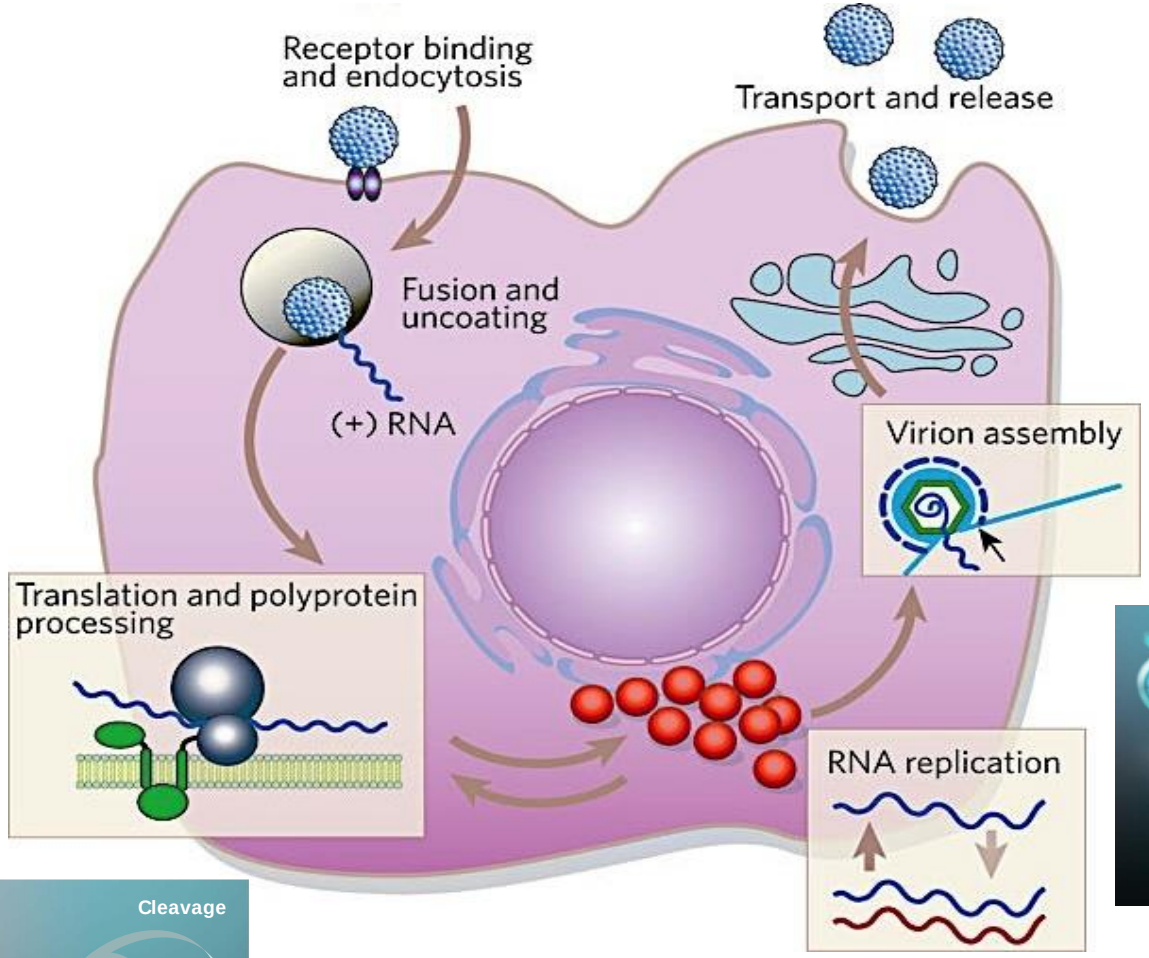
RNA virus	• Chronic infection ~75-80% • Cirrhosis (41% over 30 years), hepatocellular carcinoma • Extra-hepatic disease increasingly recognised[1,2]	• No stable or latent reservoir • Simple life cycle • Curable with antiviral therapy

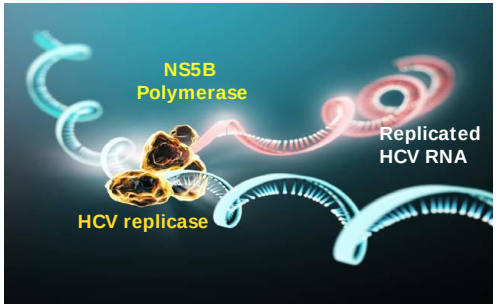


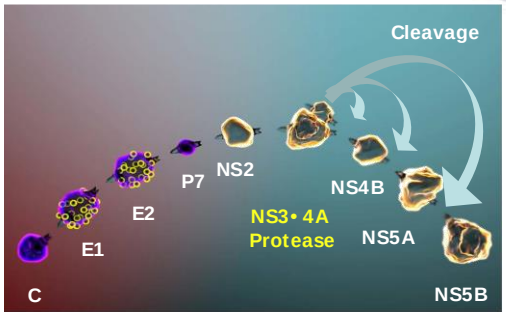


1. Giordano JAMA 2007; 2. Lee JID 2012

HCV replication

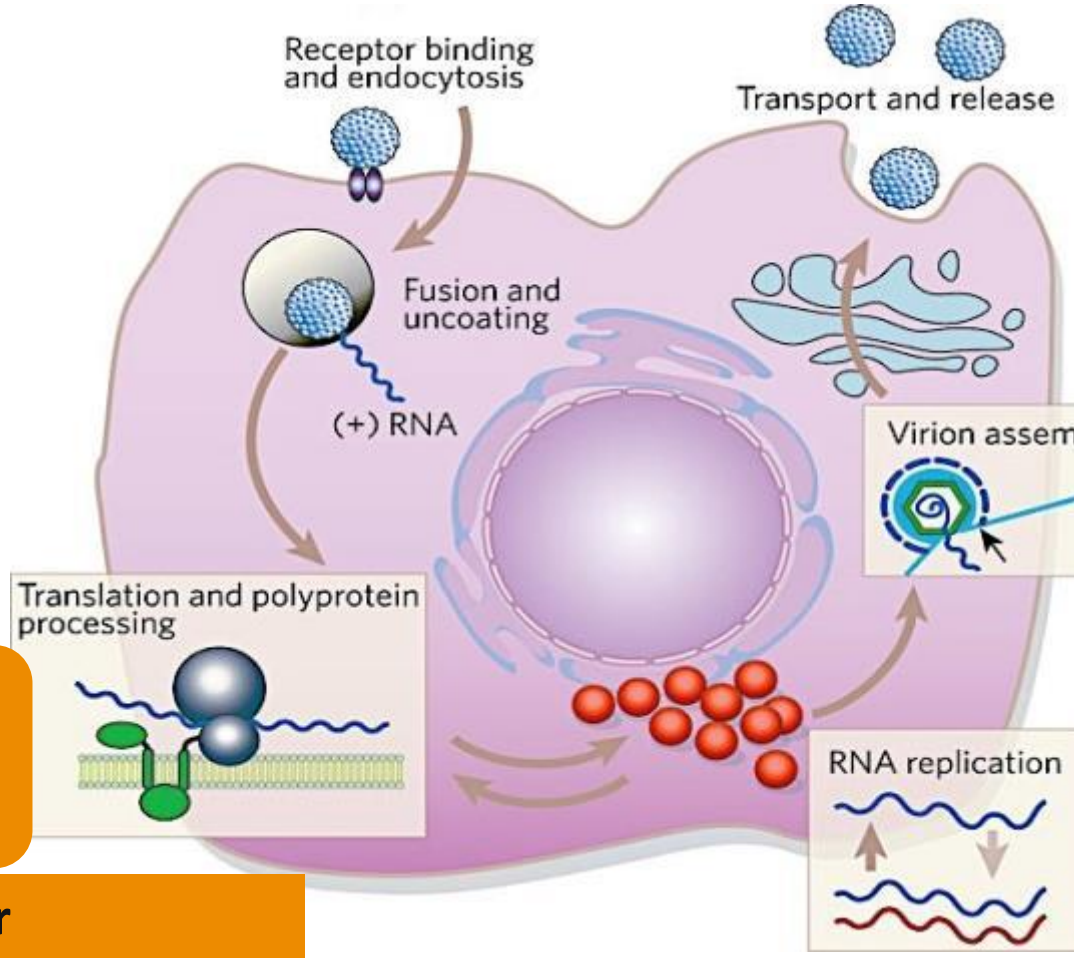






Brett Nature 2005

Antiviral targets & drug classes



Ledipasvir
Daclatasvir
Ombitasvir
Elbasvir
Velpatasvir

NS5A Inhibitors

NS3 Protease Inhibitors

Telaprevir
Boceprevir
Simeprevir
Paritaprevir/ritonavir
Grazoprevir

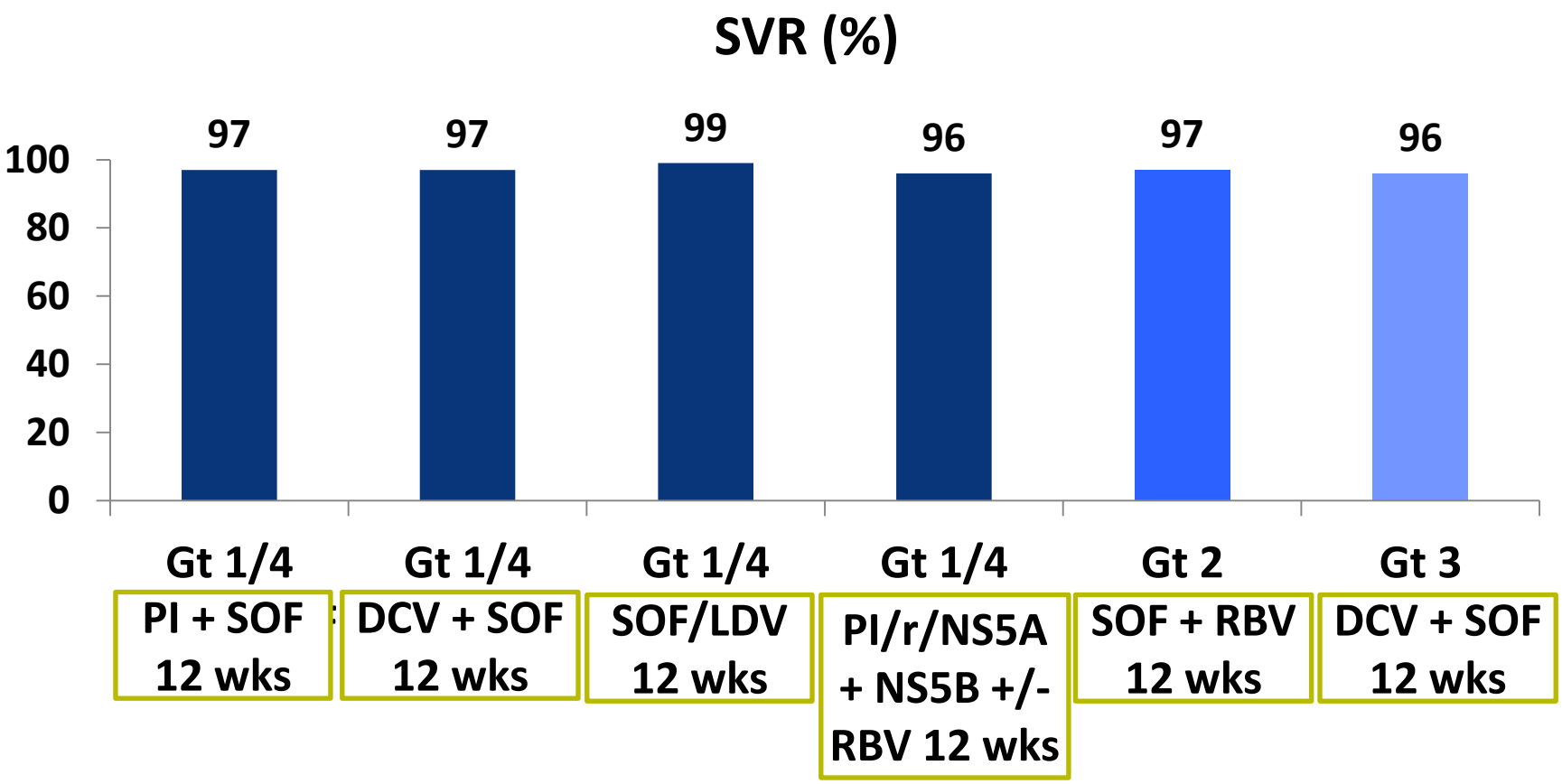
NS5B Polymerase Inhibitors

Nucleoside/nucleotide analogues: Sofosbuvir
Non-nucleoside analogues: Dasabuvir

Efficacy of antiviral therapy: Overview

SVR rates in patients <u>without</u> cirrhosis

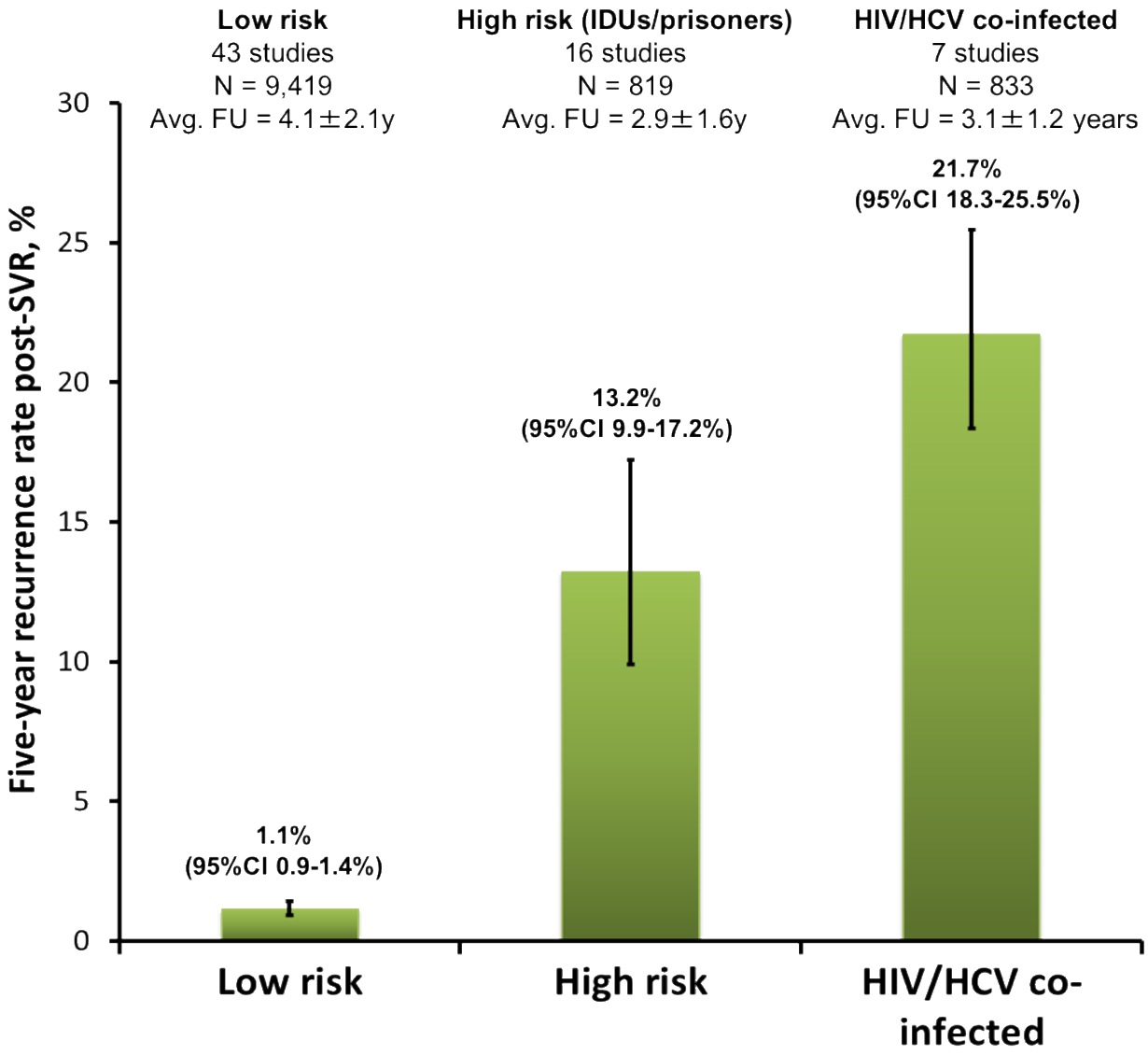
(NB: no head-to-head studies)



SVR = Sustained Virological Response; Gt = Genotype;
PI = protease Inhibitor (r = ritonavir); SOF = sofosbuvir; DCV = daclatasvir; LDV = ledipasvir; RBV = ribavirin

Kwo. EASL 2015; Wyles. EASL 2015;
Afdhal. NEJM 2014; Feld. NEJM 2014; Zeuzem. NEJM 2014; Gane. NEJM 2013. Nelson. Hepatology 2015

Risk of re-infection after SVR[1]



Relapse of IDU predicts risk of re-infection[2]

1. Hill. CROI 2015; 2. Midgard. J Hepatol 2016

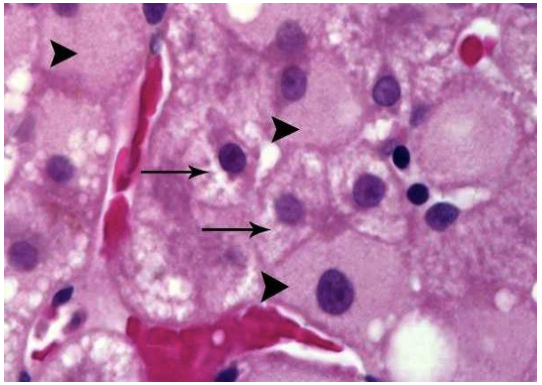
Characteristics of current DAAs

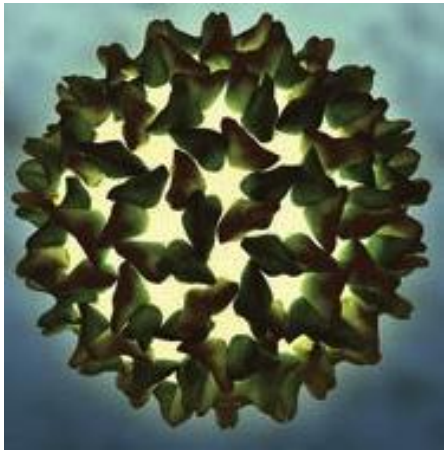
DAA Class	Potency	BL RAS	TE RAS	Agents
NS3 Protease	+++ to ++++	Relatively common	Highly common	Simeprevir Paritaprevir Grazoprevir
NS5B Polymerase *NA*	++ to ++++	Rare	Rare to uncommon	Sofosbuvir
NS5B Polymerase *Non-NA*	++ to +++	Common	Highly common	Dasabuvir
NS5A	++++	Common	Highly common	Ledipasvir Daclatasvir Ombitasvir Elbasvir

BL = Baseline; TE = Treatment-Emergent; RAS = Resistance-Associated Substitutions
NA = Nucleoside / Nucleotide Analogue; Non-NA = Non-Nucleoside Analogue

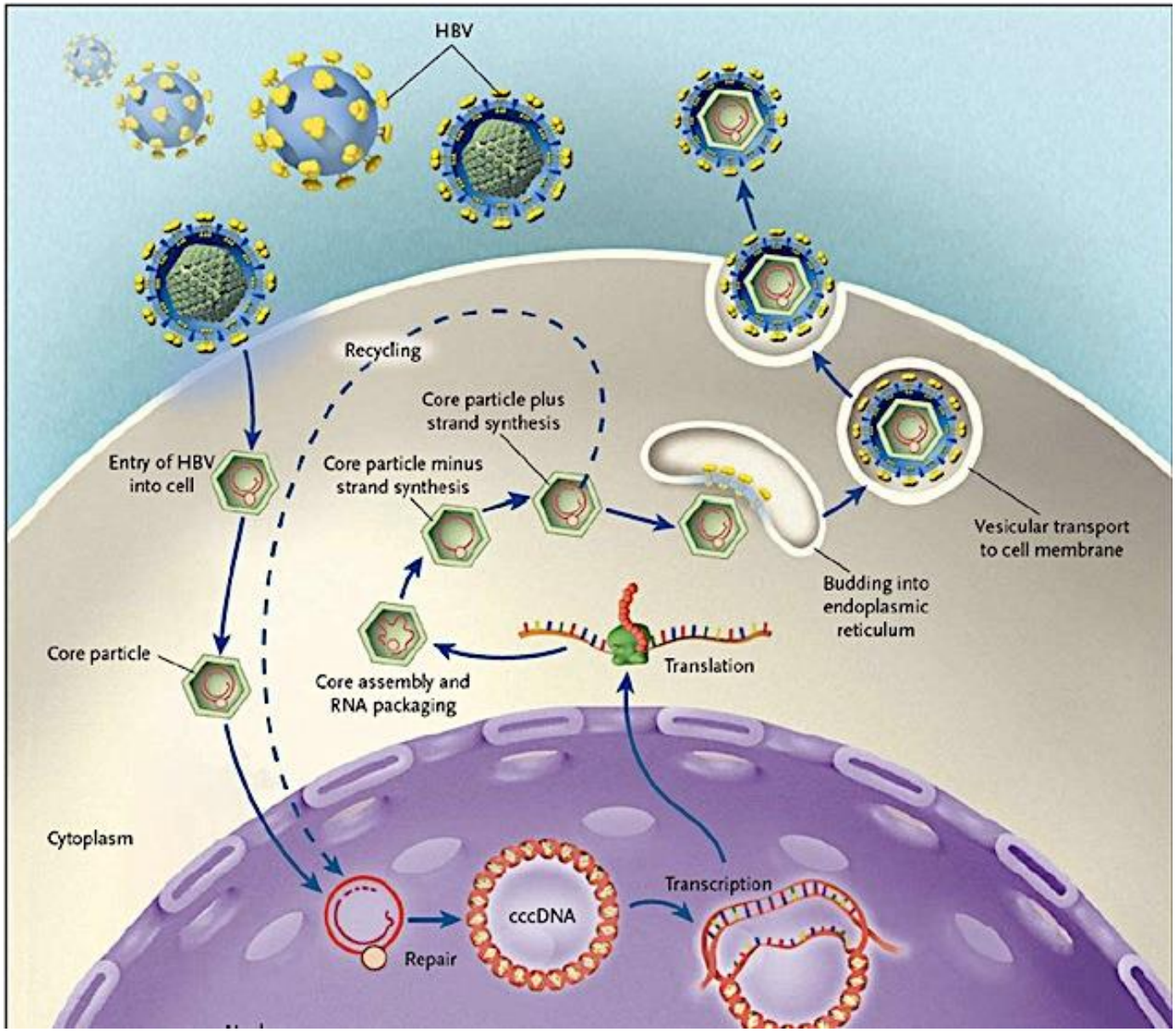
HBV

DNA virus	• Vaccine • Chronic infection in >90% children, <5% adults • Cirrhosis (~30%) • Hepatocellular carcinoma (with/without cirrhosis) • Extra-hepatic disease	• Persistence as cccDNA, may integrate • Several replicative states • Antiviral therapy not always required, controls but does not eradicate HBV, probably life-long • Antivirals work as PrEP

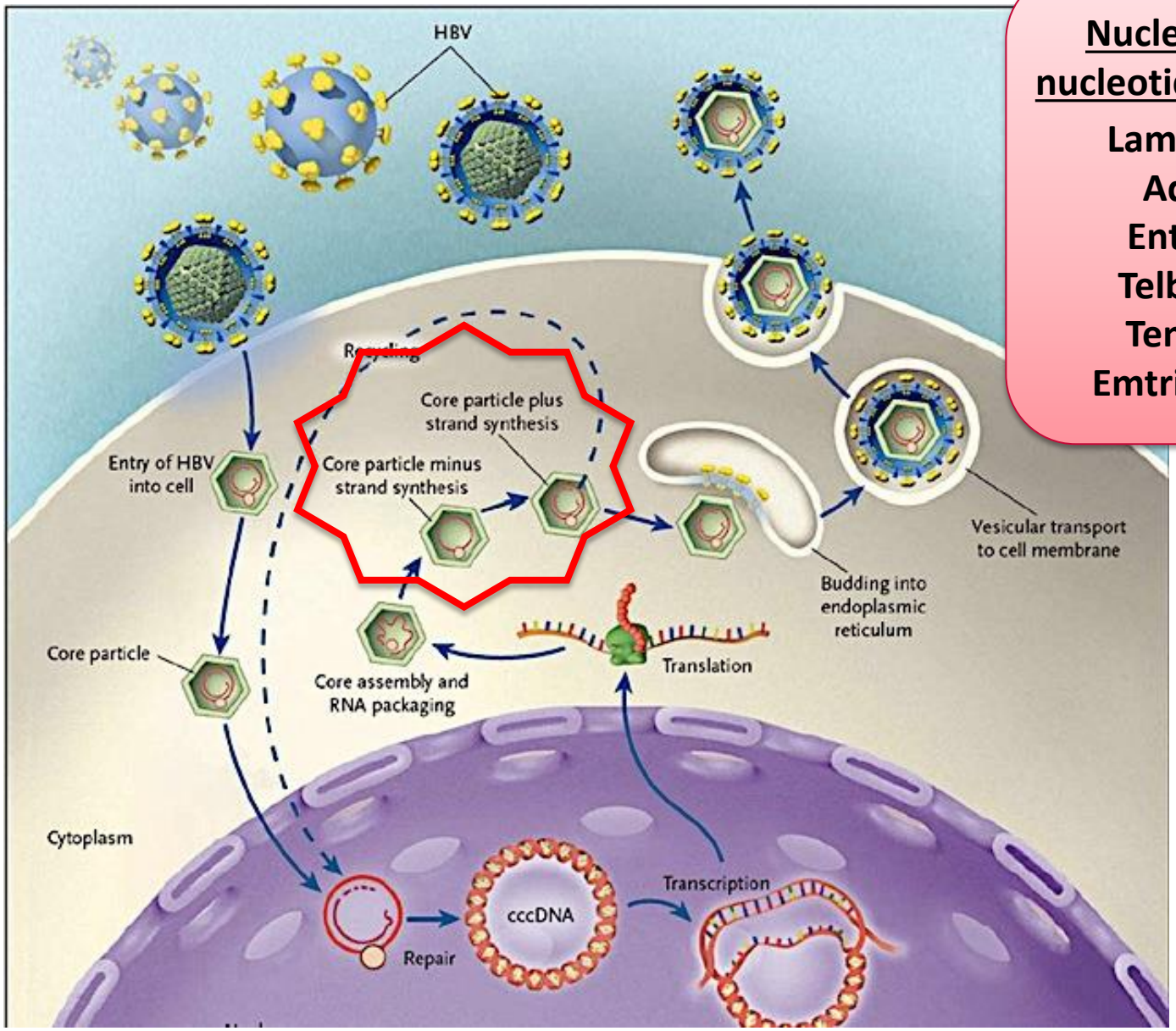




HBV replication



HBV drug targets

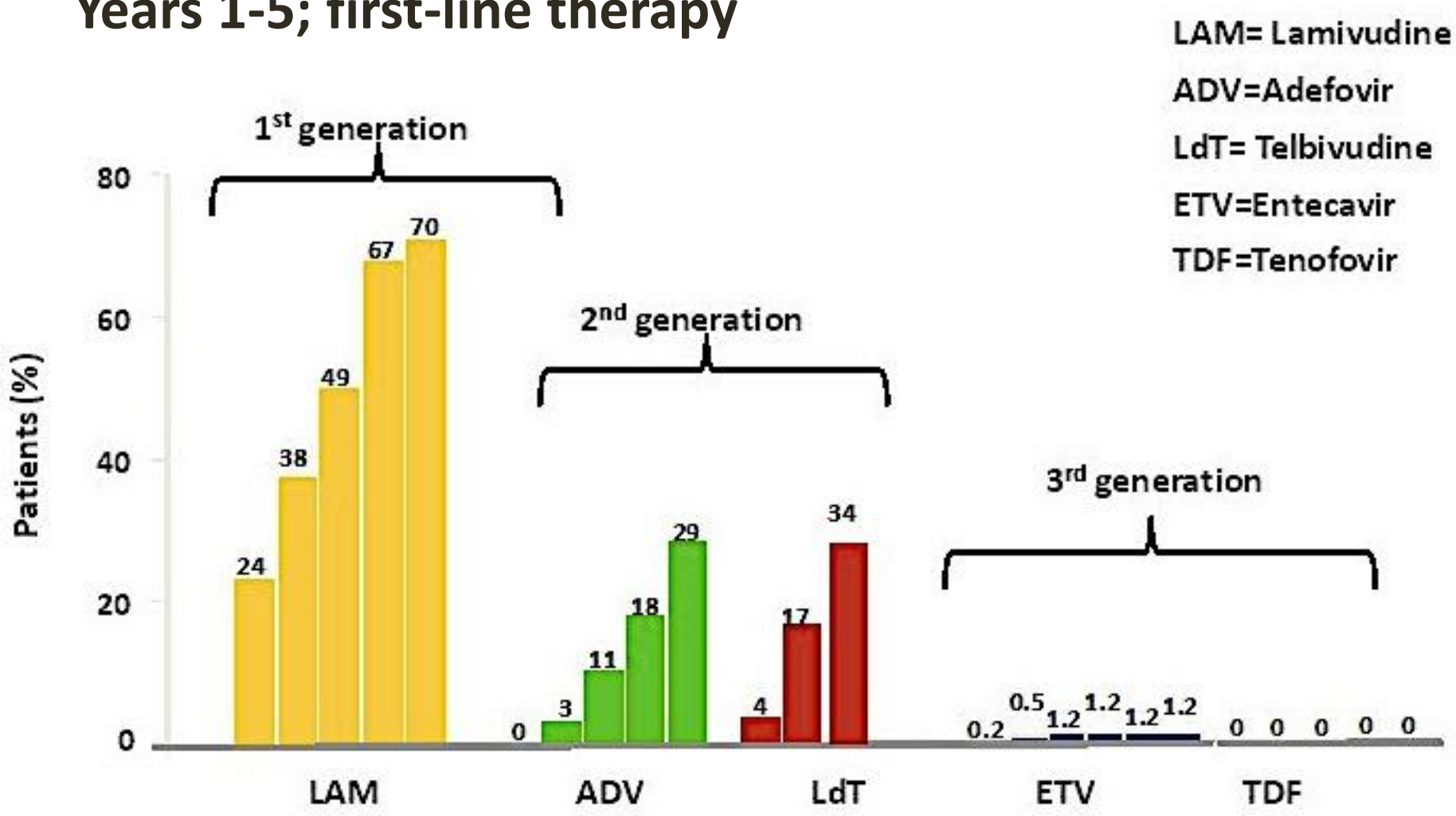


Nucleoside and nucleotide analogues

Lamivudine*
Adefovir
Entecavir*
Telbivudine
Tenofovir*
Emtricitabine*

Incidence of HBV drug resistance

Years 1-5; first-line therapy



Drug resistance with HIV, HBV, HCV

- Drug-resistant mutants emerge ”spontaneously “ during virus replication
- Tolerance for mutation is HCV > HIV > HBV
- Virus replication under drug pressure drives expansion of the mutants – *Natural evolution* ➔ *increasing resistance & fitness*
- If therapy is stopped, drug susceptible virus tends to outgrow resistant mutants selected by therapy – *mutants persist as enriched minority species*
- Mutants are archived in HIV DNA provirus and HBV cccDNA
- No archive for HCV

The barrier to resistance is expression of multiple interacting factors

- Virus sequence
- Phenotypic effect of individual mutations
- No. of mutations required to reduce drug susceptibility
- Fitness cost of the mutation
- Ease of emergence of compensatory adjustments

- Drug potency
- Mode of interaction between drug and target
- Drug concentration
- Drug combination
- Antagonism or synergism between resistance pathways

- Viral load
- Host genetics
- Host immune function
- Reservoirs of replications
- Disease stage

More than the sum of each drug in a regimen

Your turn ☺

Which of the following correctly describes HIV?

1. **RNA virus, high replication during AIDS phase only**
2. **RNA virus, high replication, stable genetic make-up**
3. **RNA virus, high replication, rapid genetic evolution**

Your turn ☺

Which of the following correctly describes HIV?

1. **RNA virus, high replication during AIDS phase only**
2. **RNA virus, high replication, stable genetic make-up**
3. **RNA virus, high replication, rapid genetic evolution**

Your turn ☺

Which of the following correctly describes HBV?

1. **HBV polymerase lacks reverse transcriptase activity**
2. **The genomic structure favours rapid emergence of resistance**
3. **Resistance is less of a problem with 3rd gen drugs**

Your turn ☺

Which of the following correctly describes HBV?

1. **HBV polymerase lacks reverse transcriptase activity**
2. **The genomic structure favours rapid emergence of resistance**
3. **Resistance is less of a problem with 3rd gen drugs**

Your turn ☺

Which of the following correctly describes HCV?

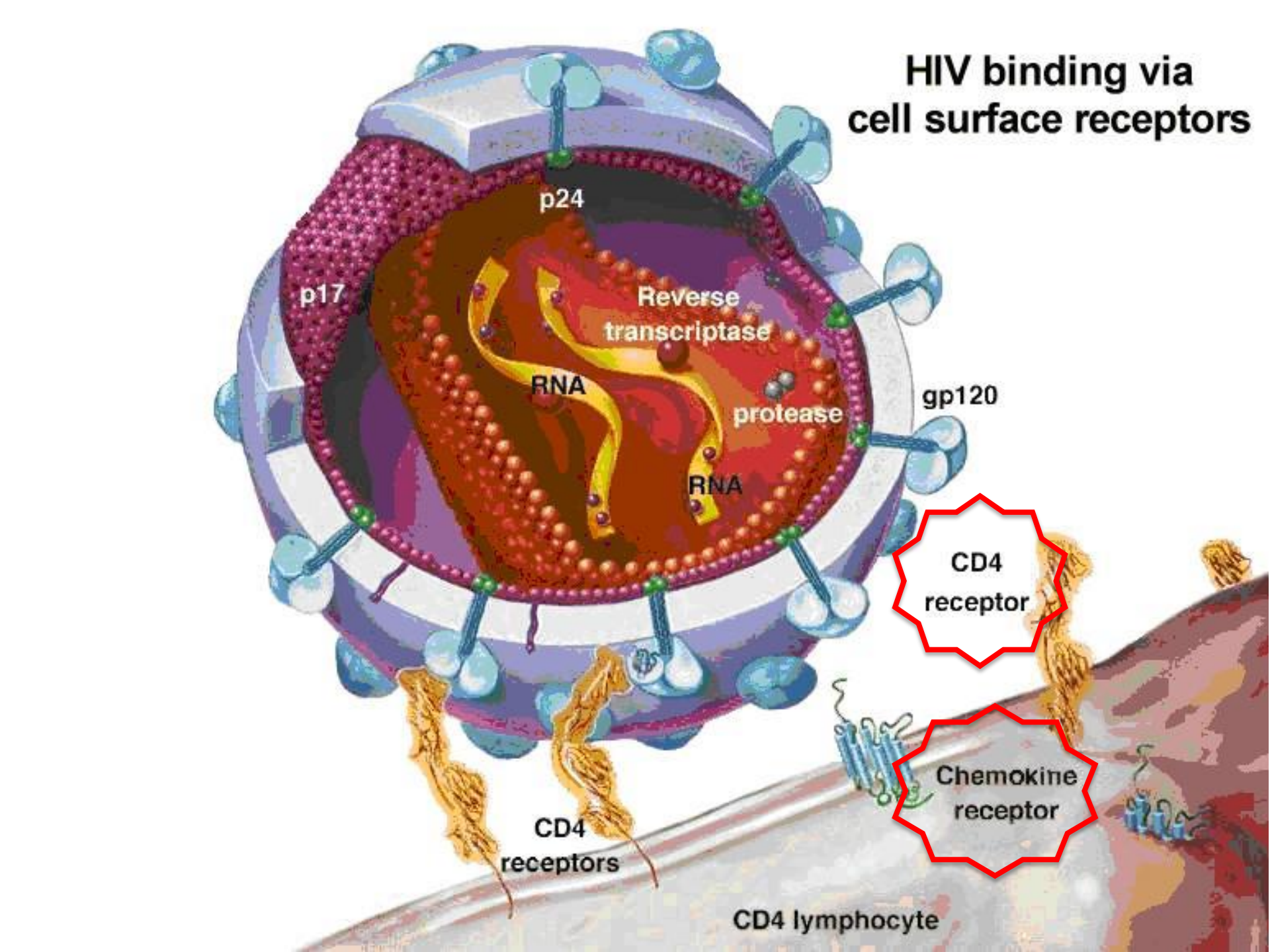
1. **Resistance is created by suboptimal therapy**
2. **Resistance is selected by suboptimal therapy**
3. **Resistance is archived in the nucleus of hepatocytes**

Your turn ☺

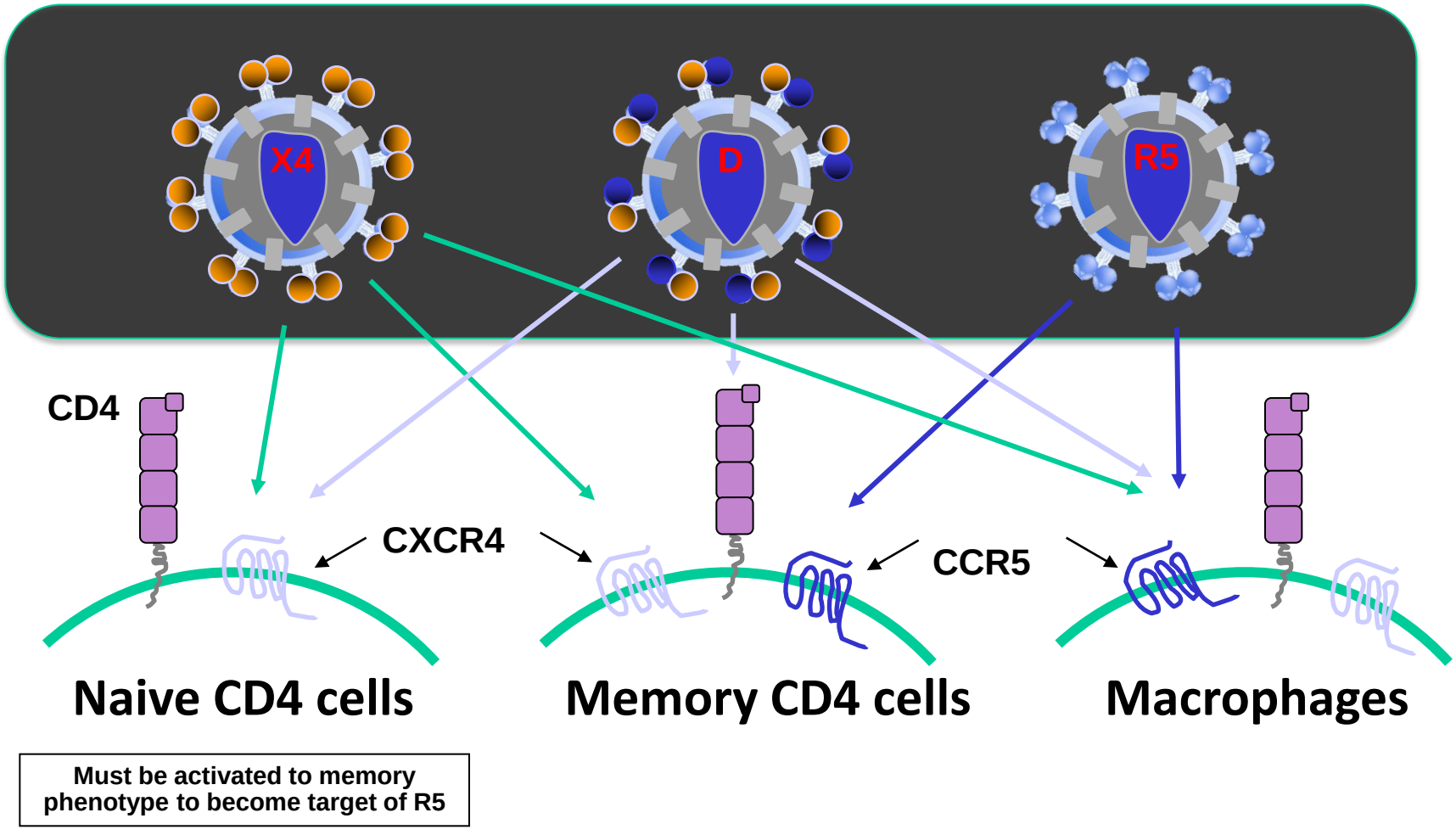
Which of the following correctly describes HCV?

1. **Resistance is created by suboptimal therapy**
2. **Resistance is selected by suboptimal therapy**
3. **Resistance is archived in the nucleus of hepatocytes**


Well
done!


HIV binding via
cell surface receptors
p24
p17
Reverse
transcriptase
RNA
protease
RNA
gp120
CD4
receptor
Chemokine
receptor
CD4
receptors
CD4 lymphocyte

HIV tropism defined by co-receptor use



Esté Lancet 2007