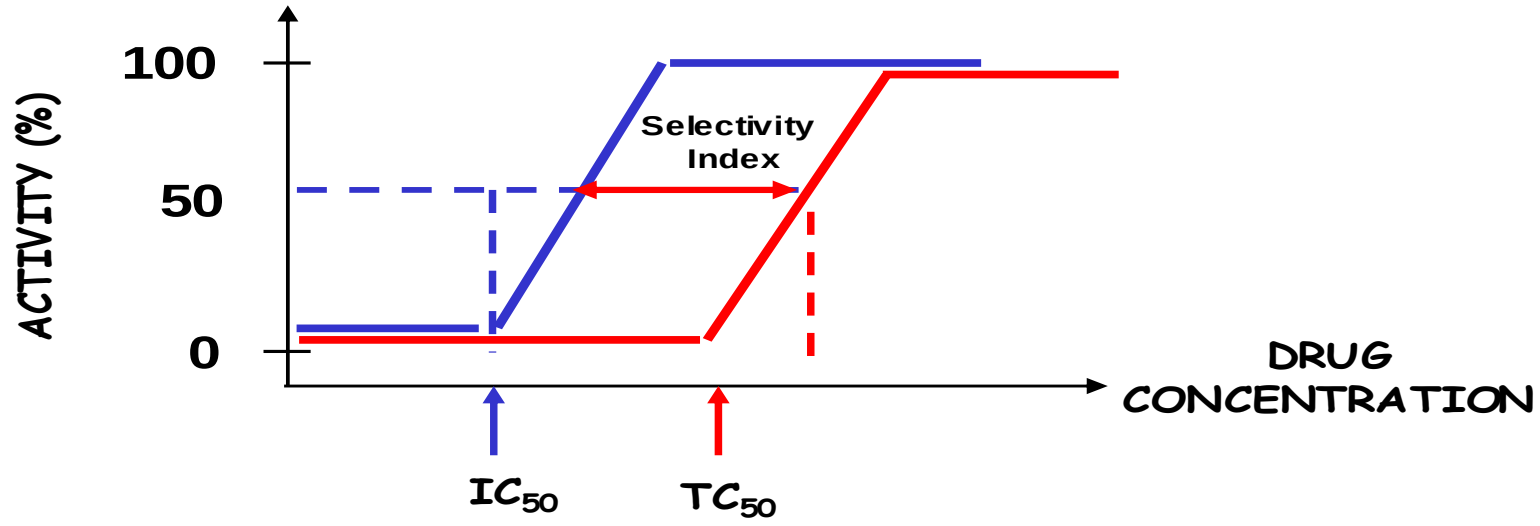
ANTIVIRAL CHEMOTHERAPYand VIRUS DRUG RESISTANCE

Any antiviral compound must possess
a good selectivity index

$$\text{SELECTIVITY INDEX} = \frac{\text{TOXIC CONCENTRATION}}{\text{ACTIVE CONCENTRATION}}$$

SELECTIVITY INDEX

Selectivity Index = TC_{50}/IC_{50}



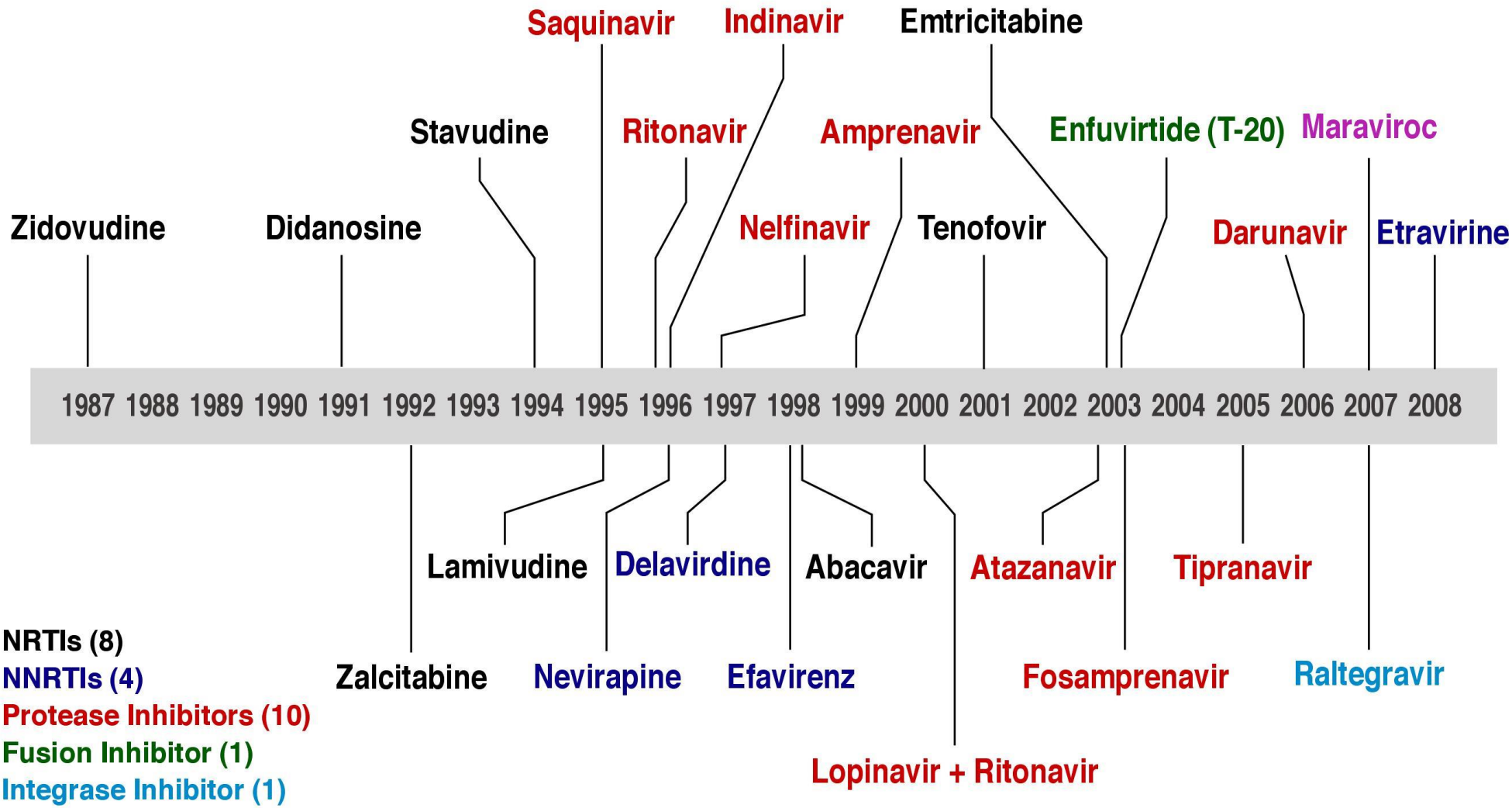
IC_{50} = 50% Inhibitory Concentration

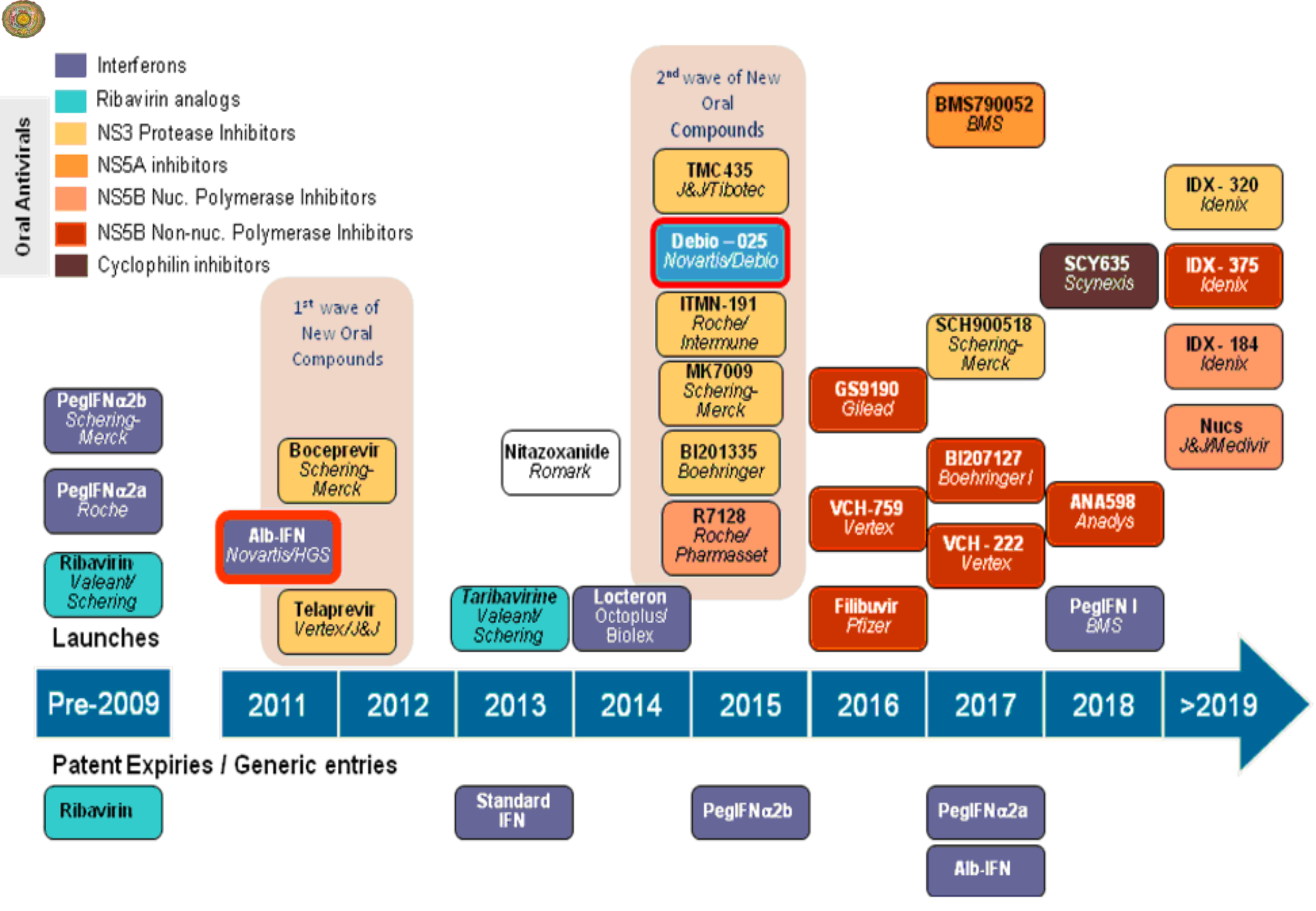
TC_{50} = 50% Toxic Concentration

MILESTONES IN ANTIVIRAL DRUG DEVELOPMENT

DISCOVERY (years)	COMPOUND	ACTIVITY VS
Hamre et al. (1950)	Thiosemicarbazone	Poxvirus
Davies et al.(1964)	Amantadine	Orthomixovirus
Isaacs et al.(1957)	Interferon	Many viruses
Prusof, (1959)	Iododeoxyuridine	Herpesvirus
Kaufman, (1964)	Trifluorothymidine	Herpesvirus
Elion et al.(1971)	Acyclovir	Herpesvirus

30 FDA-Approved Antiretroviral Drugs




Oral Antivirals
Interferons
Ribavirin analogs
NS3 Protease Inhibitors
NS5A inhibitors
NS5B Nuc. Polymerase Inhibitors
NS5B Non-nuc. Polymerase Inhibitors
Cyclophilin inhibitors
1st wave of New Oral Compounds
2nd wave of New Oral Compounds
PegIFNα2b Schering-Merck
PegIFNα2a Roche
Ribavirin Valeant/ Schering
Launches
Boceprevir Schering-Merck
Alb-IFN Novartis/HGS
Telaprevir Vertex/J&J
Nitazoxanide Romark
Taribavirine Valeant/ Schering
Locteron Octoplus/ Biolex
TMC435 J&J/Tibotec
Debio – 025 Novartis/Debio
ITMN-191 Roche/ Intermune
MK7009 Schering-Merck
BI201335 Boehringer
R7128 Roche/ Pharmasset
BMS790052 BMS
GS9190 Gilead
SCH900518 Schering-Merck
VCH-759 Vertex
BI207127 Boehringer I
VCH - 222 Vertex
Filibuvir Pfizer
ANA598 Anadys
PegIFN I BMS
SCY635 Scynexis
IDX - 320 Idenix
IDX - 375 Idenix
IDX - 184 Idenix
Nucs J&J/Medivir
Pre-2009
2011
2012
2013
2014
2015
2016
2017
2018
>2019
Patent Expiries / Generic entries
Ribavirin
Standard IFN
PegIFNα2b
PegIFNα2a
Alb-IFN

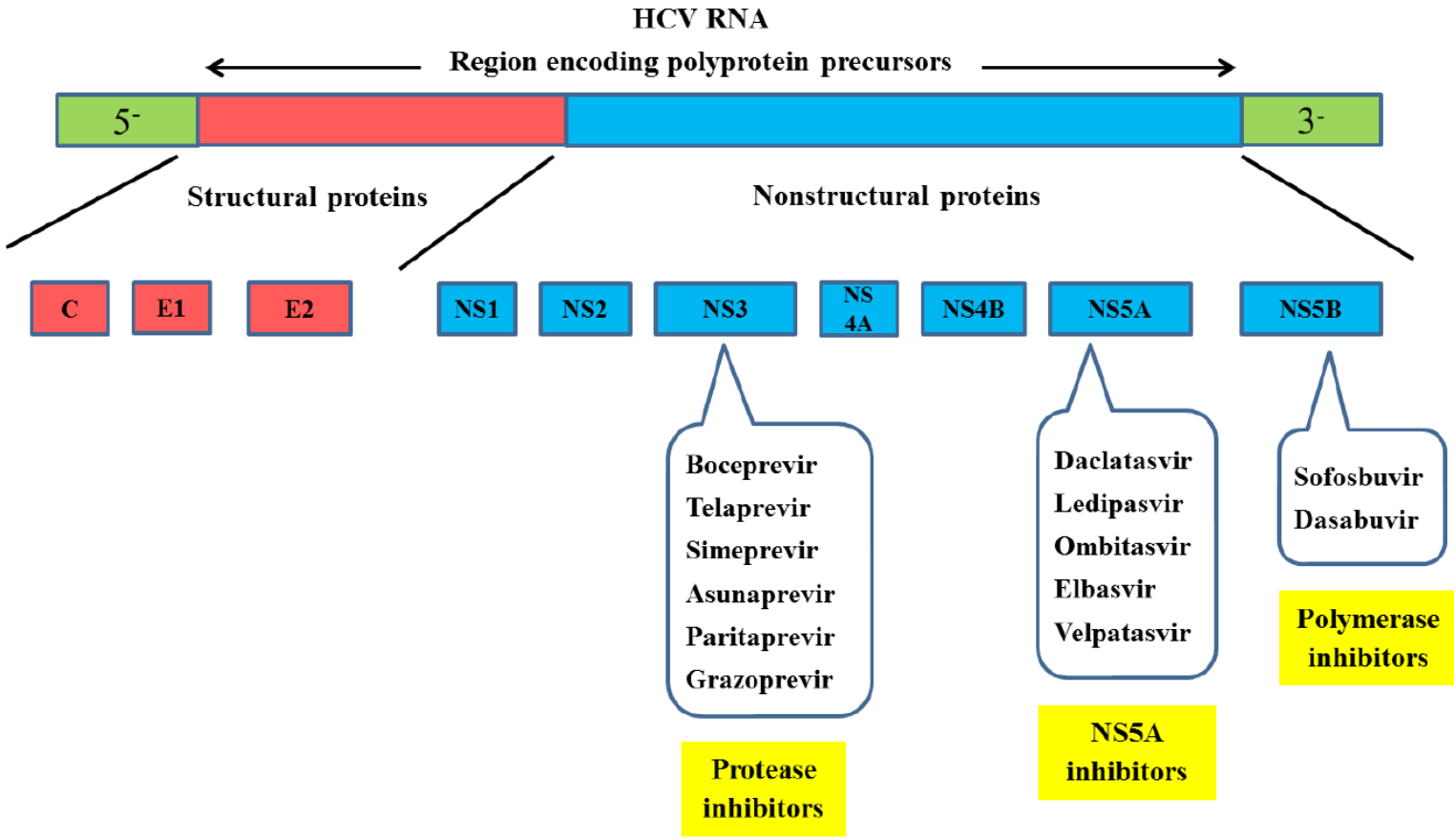


Figure 1: Proteins encoded by the hepatitis C virus genome as targets for direct acting antiviral agents.

APPROVED ANTIVIRAL DRUGS (2019)

Main Approved Antiviral Drugs and Their Mechanism of Action**	
Anti-HIV	**Mechanism of action (Main)**
Entry inhibitors	
Enfuvirtide	It interferes with glycoprotein 41-dependent membrane fusion blocking virus entry.
Ibalizumab	It binds CD4 extracellular domain, preventing conformational changes in the CD4–gp120 complex essential for viral entry.
Maraviroc	Negative allosteric modulator of the CCR5 receptor that is an essential co-receptor for the entry process of HIV.
Reverse transcriptase inhibitors	
Nucleoside analogs	Active as triphosphate derivates which prematurely terminate DNA synthesis.
Abacavir	
Emtricitabine	
Lamivudine	
Stavudine	
Zidovudine	
Nucleotide analog	
Tenofovir	
Non-nucleoside inhibitors	They bind to a hydrophobic pocket of HIV-1 reverse transcriptase, blocking polymerization of viral DNA.
Doravirine	
Efavirenz	
Etravirine	
Nevirapine	
Rilpivirine	
Protease inhibitors	
Atazanavir	They bind to the active site of viral protease.
Fosamprenavir	
Lopinavir	
Darunavir	They bind strongly and selectively to the HIV-1 protease.
Tipranavir	
Pharmacodynamic enhancer	
Cobicistat	These drugs inhibit CYP3A4 leading to higher drug exposure
Ritonavir	
Integrase inhibitor	
Dolutegravir	They bind viral integrase inhibiting the strand transfer step of HIV-1 integration
Bictegravir[a]	
Elvitegravir[a]	
Raltegravir	

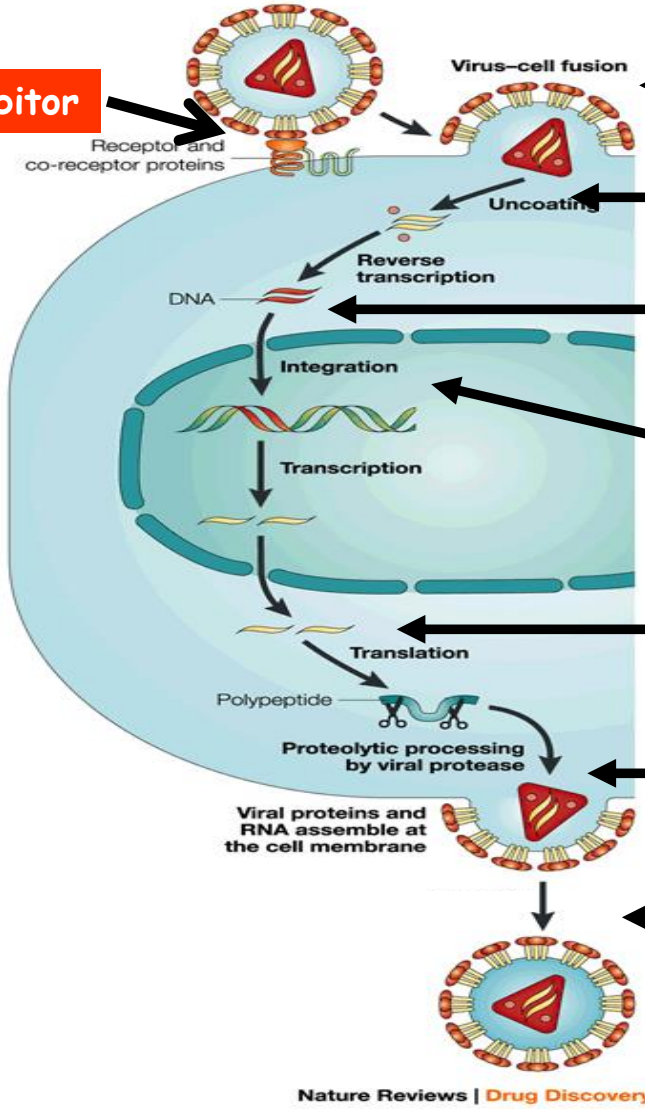
Anti-Herpes viruses	
DNA polymerase inhibitors	
Nucleoside analogs	
Aciclovir	Active as triphosphate derivates, which prematurely terminate DNA synthesis.
Brivudine[b]	
Famciclovir	
Ganciclovir	
Valaciclovir	
Valganciclovir	
	It selectively inhibits the pyrophosphate binding site on viral DNA polymerases.
DNA maturation and packaging inhibitor	
Letermovir	It inhibits CMV replication by binding to components of the terminase complex
Anti HBV	
Reverse transcriptase inhibitors	
Nucleoside analogs	
Entecavir	Active as triphosphate derivates, which prematurely terminate viral DNA synthesis
Telbivudine	
Lamivudine	
Nucleotide analog	
Tenofovir	

Anti-HCV	
NS5B RNA polimerase inhibitor	
Non nucleoside inhibitor	
Dasabuvir	It binds HCV NS5B polymerase and blocks viral RNA synthesis and replication.
Nucleotide analog	
Sofosbuvir	Potent inhibitor of the NS5B polymerase. It blocks viral RNA synthesis and replication.
Nucleoside analog	
Ribavirin	Active as triphosphate derivates, which prematurely terminate viral nucleic acid synthesis[e]
NS5A protein inhibitor	
Elbasvir	They bind to the replication complex protein NS5A, disrupting HCV RNA replication and virion assembly
Ledipasvir	
Ombitasvir	
Pibrentasvir	
Velpatasvir	
NS3/4A protease inhibitor	
Glecaprevir	They prevent viral replication by inhibiting the NS3/4A serine protease of HCV
Grazoprevir	
Paritaprevir	
Voxilaprevir	

APPROVED ANTIVIRAL DRUGS (2019)

Anti-influenza virus	
Encoating inhibitor	
Amantadine	Inhibitors of the viral M2 channel. The activity of channel is required for uncoating
Rimantadine	
Neuraminidase inhibitors	
Oseltamivir	Block influenza neuraminidase and prevent the cleavage of sialic acid residues, thus interfering with progeny virus release
Peramivir	
Zanamivir	
Endonuclease inhibitor	
Baloxavir marboxil	It inhibits cap-dependent endonuclease, a key enzyme involved in the initiation of influenza virus mRNA synthesis.
Anti-RSV	
Entry inhibitors	
Palivizumab[c]	It Binds to RSV F protein, which plays a role in virus attachment and fusion.
RNA inhibitor	
Ribavirine	It interferes with viral RNA synthesis[e]

THE VIRAL LIFE CYCLE (EXEMPLIFIED BY HIV) AND TARGET FOR ANTIVIRAL THERAPY



CCR5 inhibitor

T20

AMANTADINE, RIMANTADINE

AZT, d4t, 3TC, ABC, ddI, ddC, FTC, ACV, PCV, FCV, VGCV, HPMPC, TFT, PMEA, PMPA, BVDU, GCV, Foscarnet, DLV, EFV, NVP

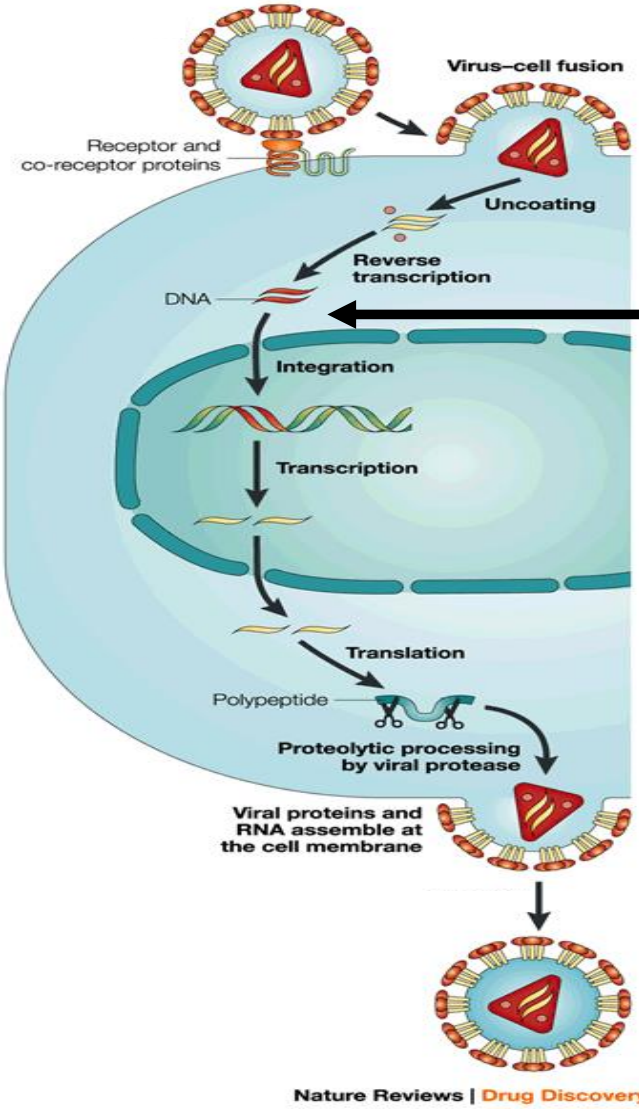
Raltegravir, Elvitegravir, Dolutegravir

FOMIVIRSEN

NFV, APV, ATV, LPV, SQV, RTV, IDV

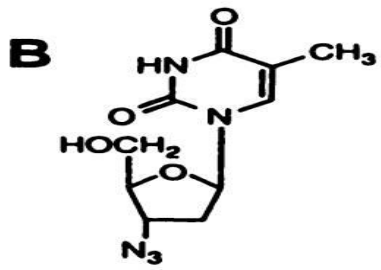
OSELTAMIVIR
ZANAMIVIR

THE VIRAL LIFE CYCLE (EXEMPLIFIED BY HIV) AND TARGET FOR ANTIVIRAL THERAPY

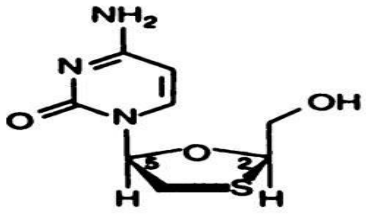


AZT, d4t, 3TC, ABC, ddI, ddC, FTC, ACV, PCV, FCV, VGCV, HPMPC, TFT, PMEA, PMPA, BVDU, GCV, Foscarnet, DLV, EFV, NVP

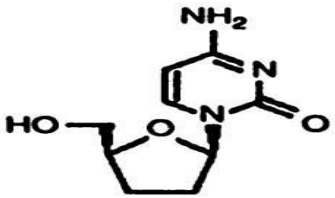
MAIN NUCLEOSIDE ANALOGUES USED TO TREAT HIV INFECTION



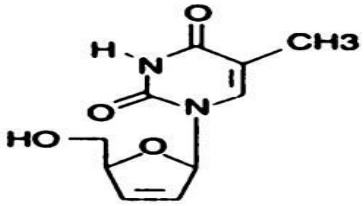
Zidovudine



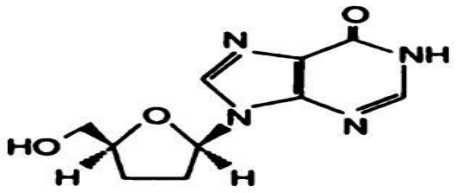
Lamivudine



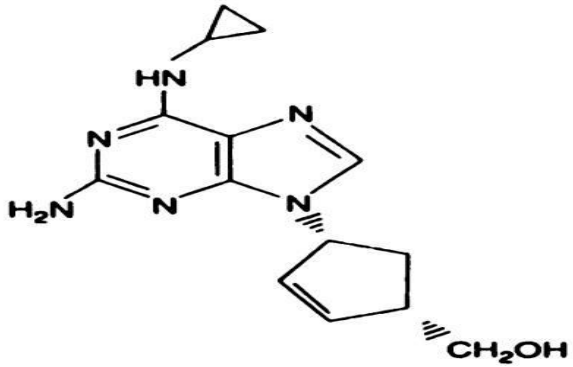
Zalcitabine



Stavudine

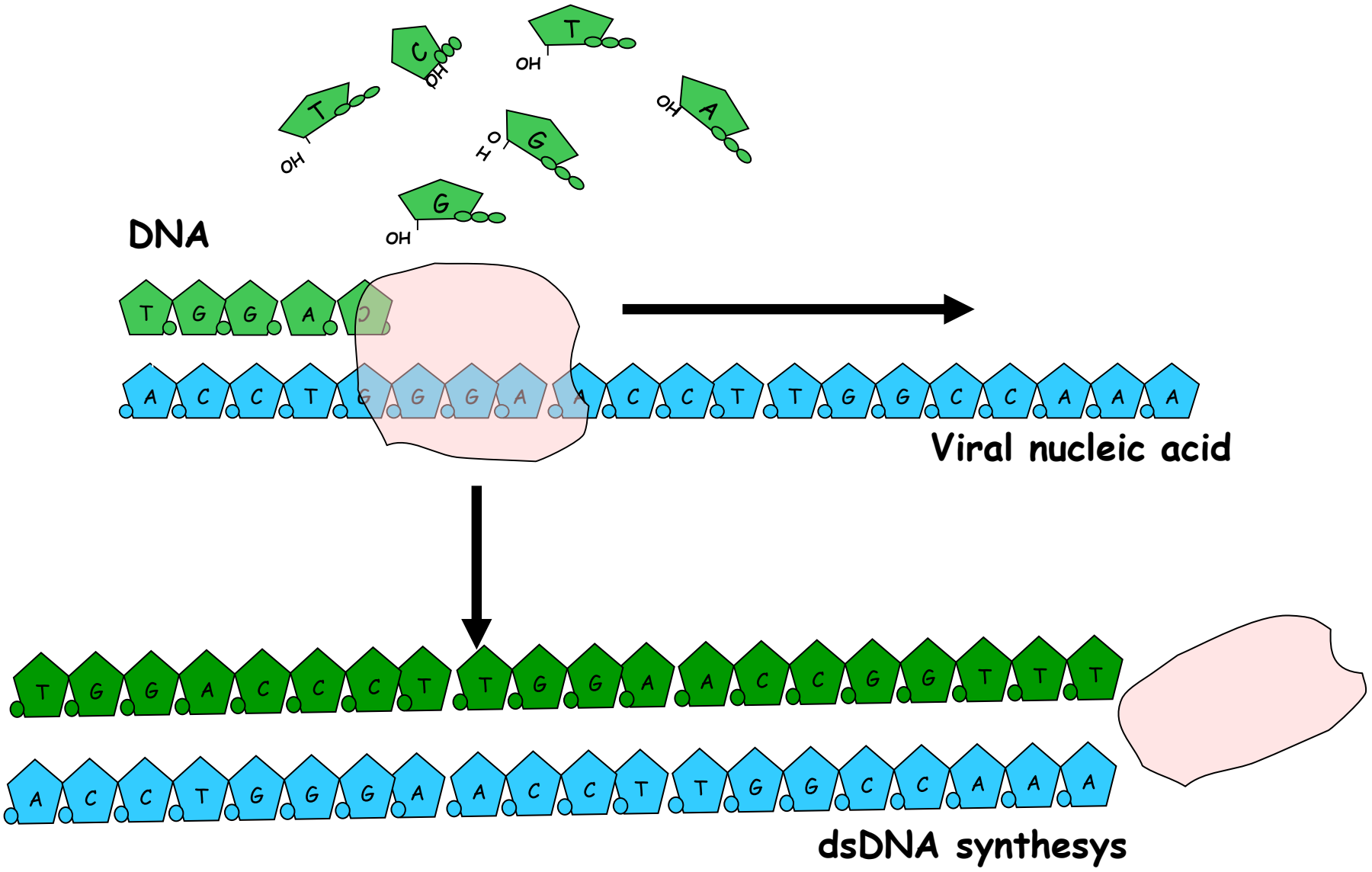


Didanosine

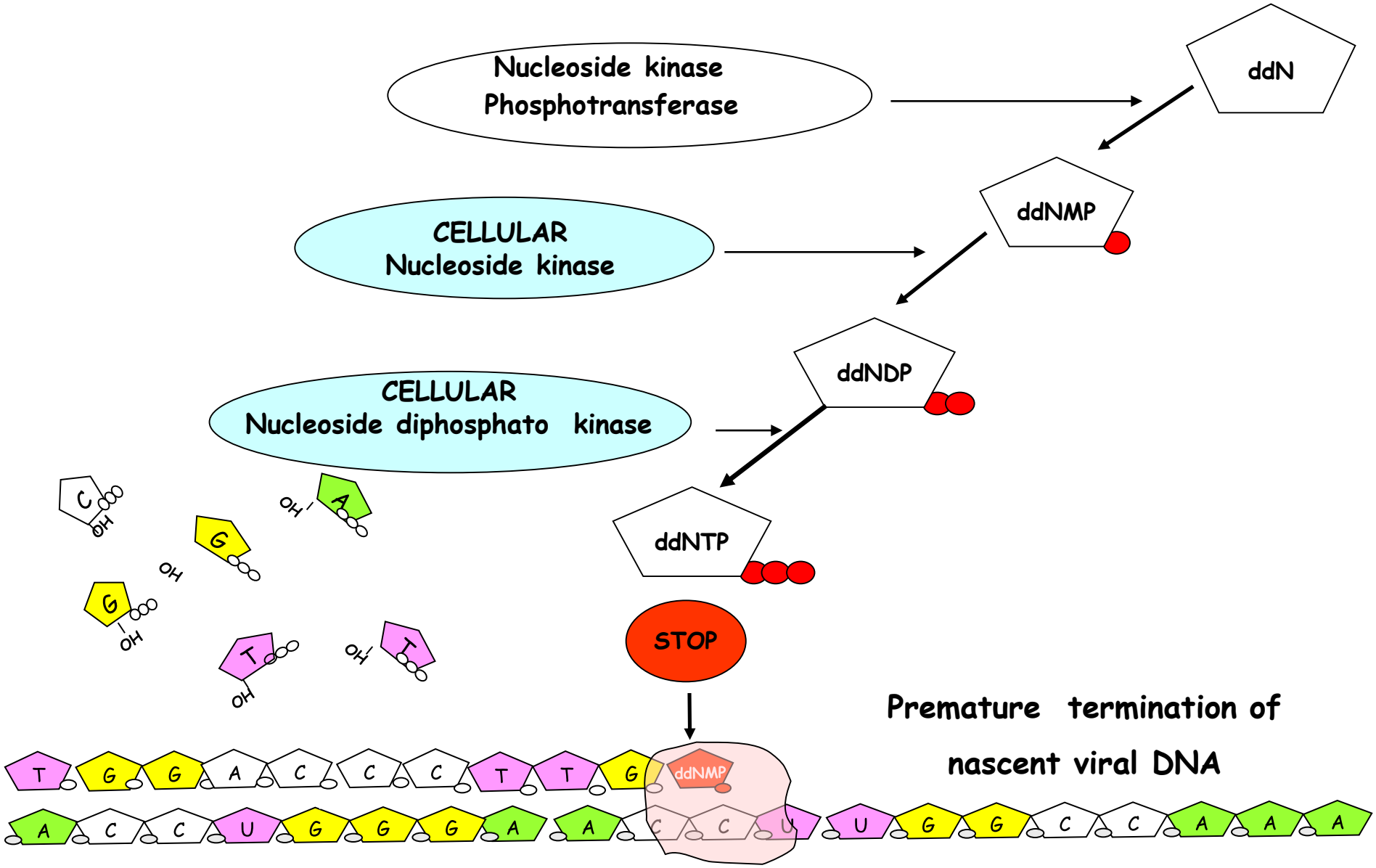


Abacavir

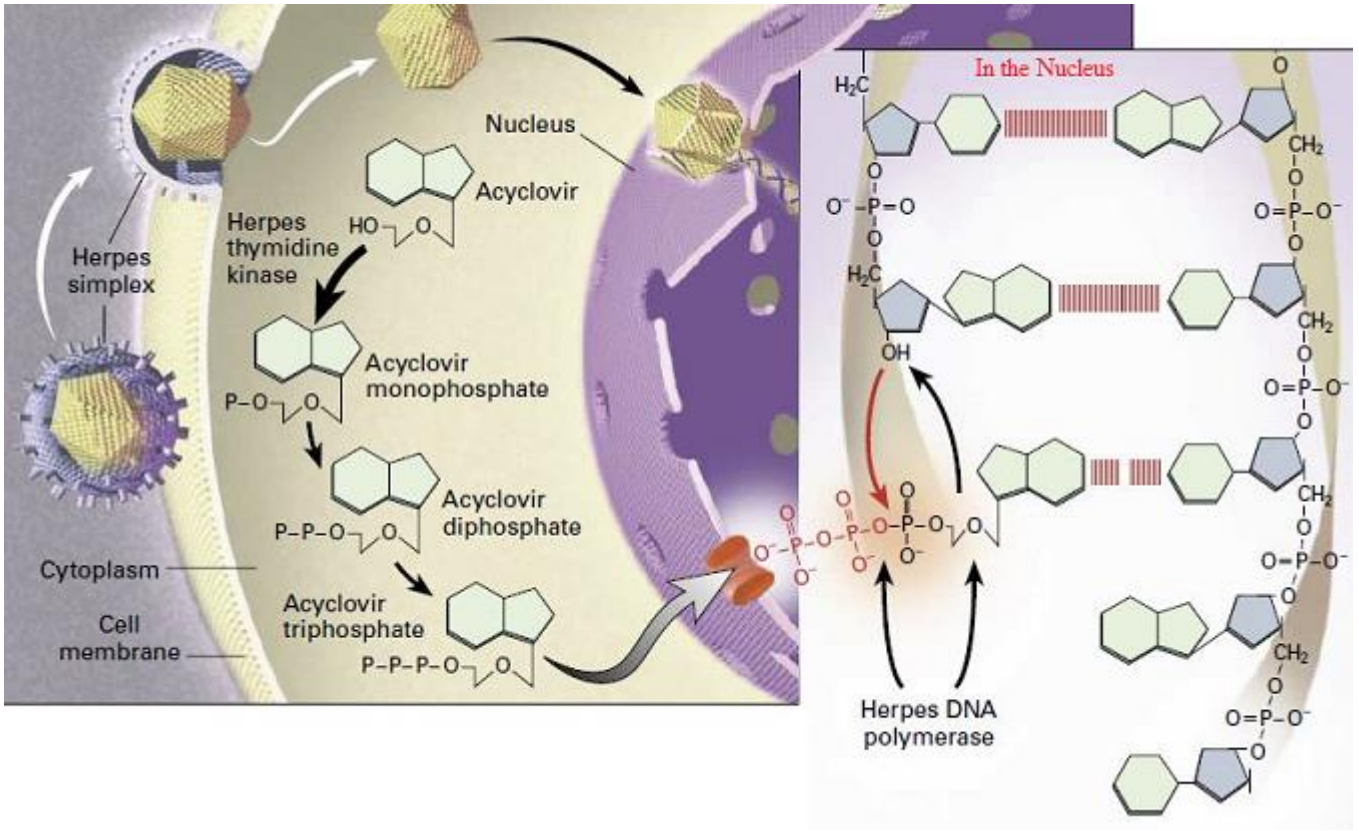
MECHANISM OF ACTION OF NUCLEOSIDE ANALOGS



MECHANISM OF ACTION OF NUCLEOSIDE ANALOGS

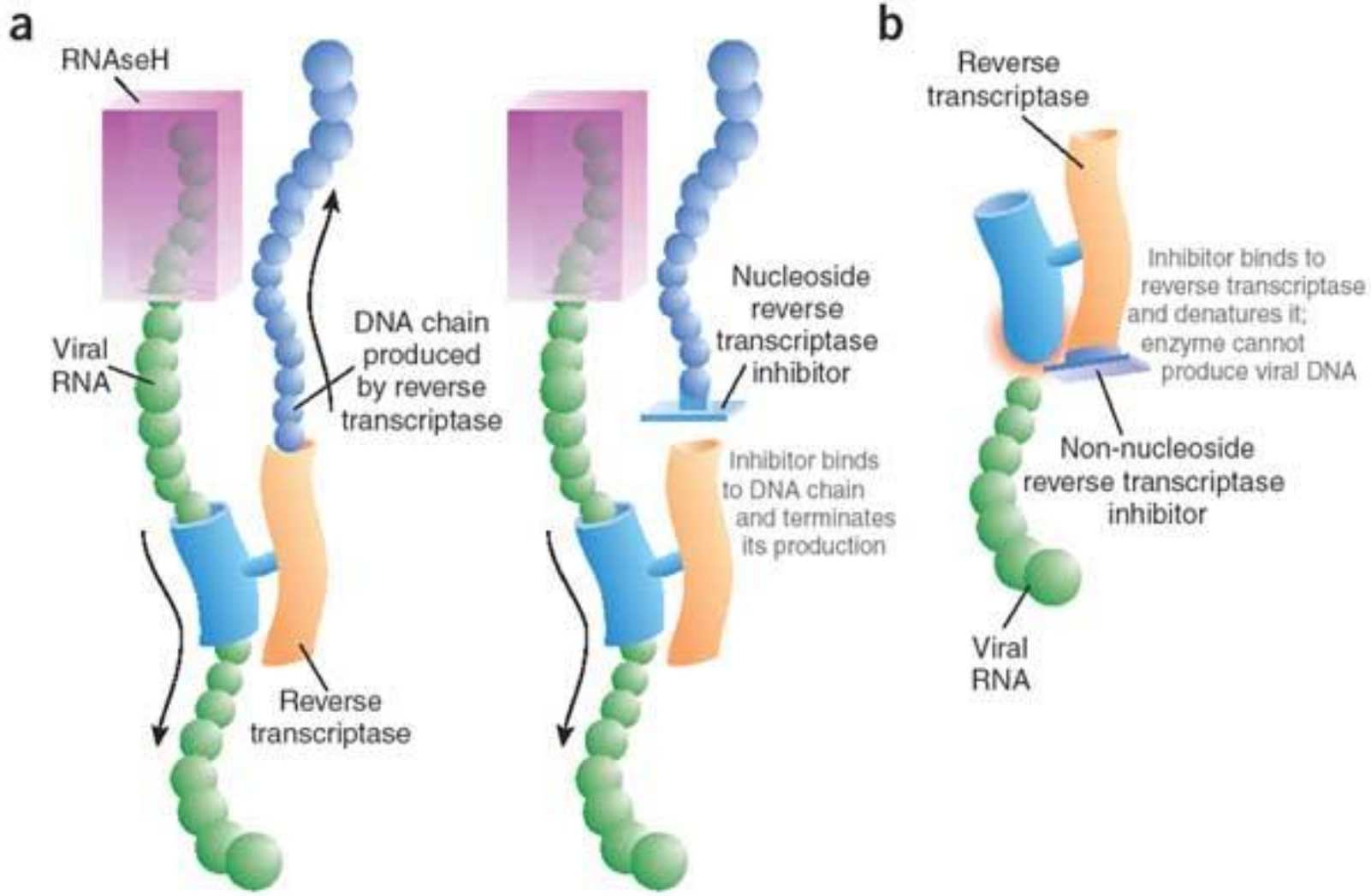


Mechanism of Action of Acyclovir

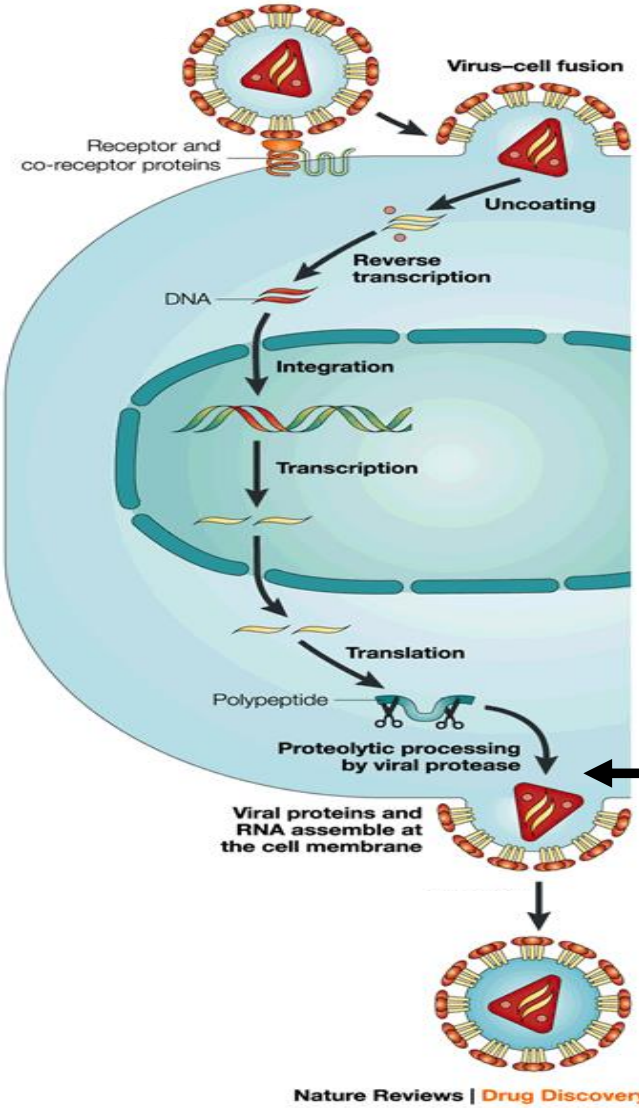


From: Medical Pharmacology: Antiviral Drugs

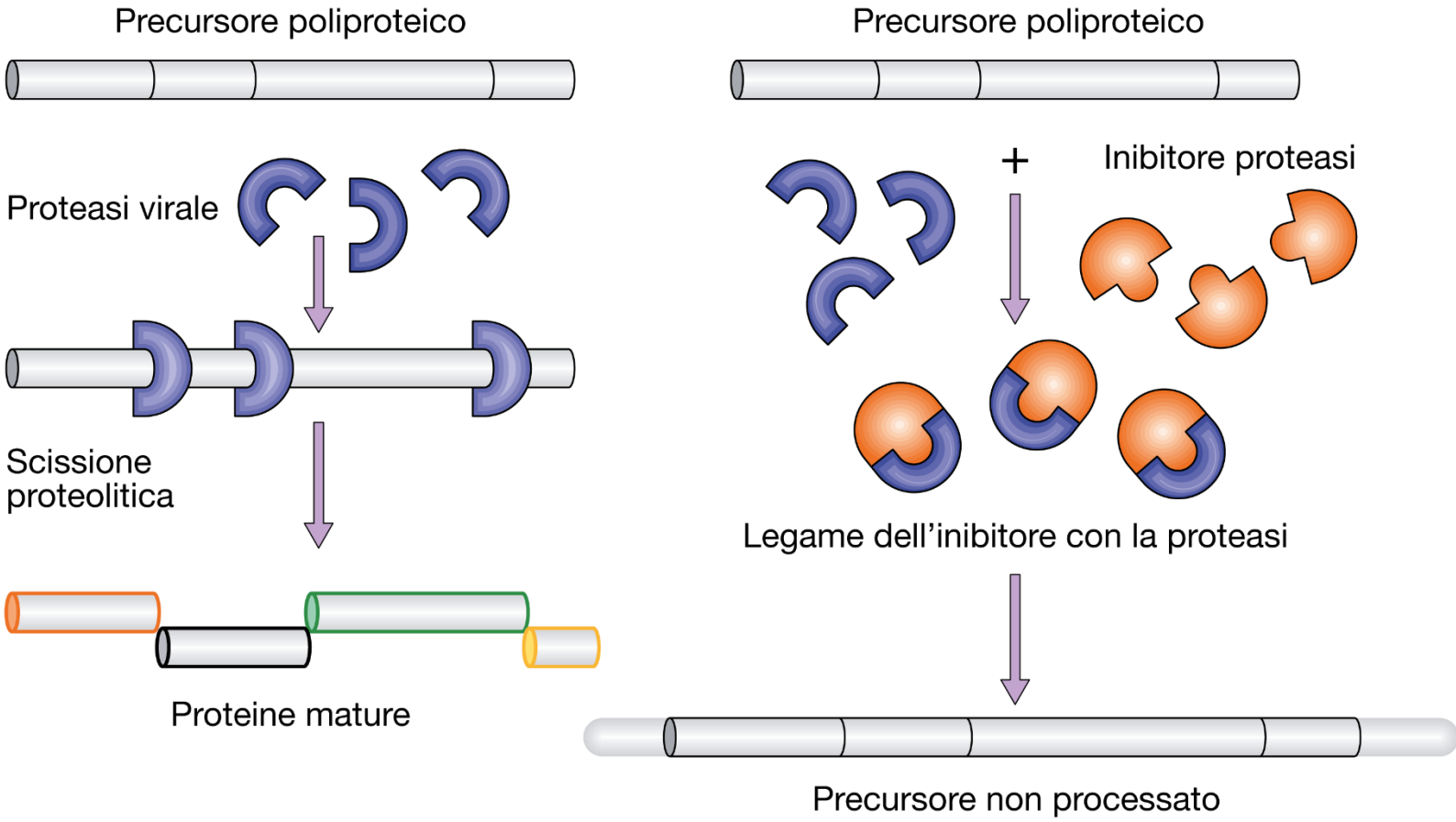
NRTIS AND NNRTIs: MECHANISMS OF ACTION



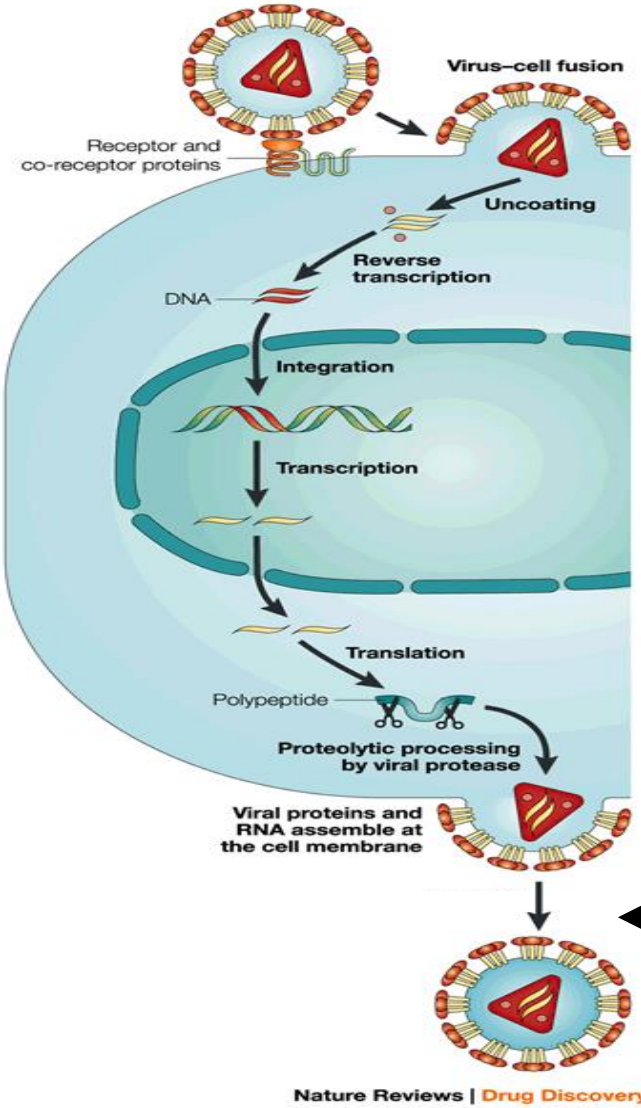
THE VIRAL LIFE CYCLE (EXEMPLIFIED BY HIV) AND TARGET FOR ANTIVIRAL THERAPY



APV, ATV, LPV, SQV, RTV, IDV,TPV, DRV, etc.


Precursore poliproteico
Proteasi virale
Scissione proteolitica
Proteine mature
Precursore poliproteico
+
Inibitore proteasi
Legame dell'inibitore con la proteasi
Precursore non processato

THE VIRAL LIFE CYCLE (EXEMPLIFIED BY HIV) AND TARGET FOR ANTIVIRAL THERAPY



OSELTAMIVIR
ZANAMIVIR

Antiviral drugs	Characteristics
Adamantane derivatives	
Rimantadine Amantadine	Prevention of the uncoating of the virus's protective shells, which are the envelope and capsid of influenza virus Activity limited on influenza A virus Poor tolerability Emergence of resistance No longer recommended starting from 2004 to 2005
Neuraminidase inhibitors (NAIs)	
Oseltamivir Zanamivir Laninamavir Peramivir	Reduction of viral release from the infected cells Activity on influenza A and B viruses Good tolerability Emergence of resistant strains without cross-resistance between the drugs Laninamavir and peramivir are used only in Japan, Chin South Korea, and the USA
Polymerase inhibitors	
Baloxavir marboxil Favipiravir	Inhibition of viral replication Activity on influenza A and B viruses Efficacy on NAIs-resistant strains Effective on avian influenza subtypes Good safety and tolerability More expensive Problem of resistance still unknown

REVIEW article

Front. Med., 28 May 2019

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Volume 6 - 2019 | https://doi.org/10.3389/fmed.2019.00109

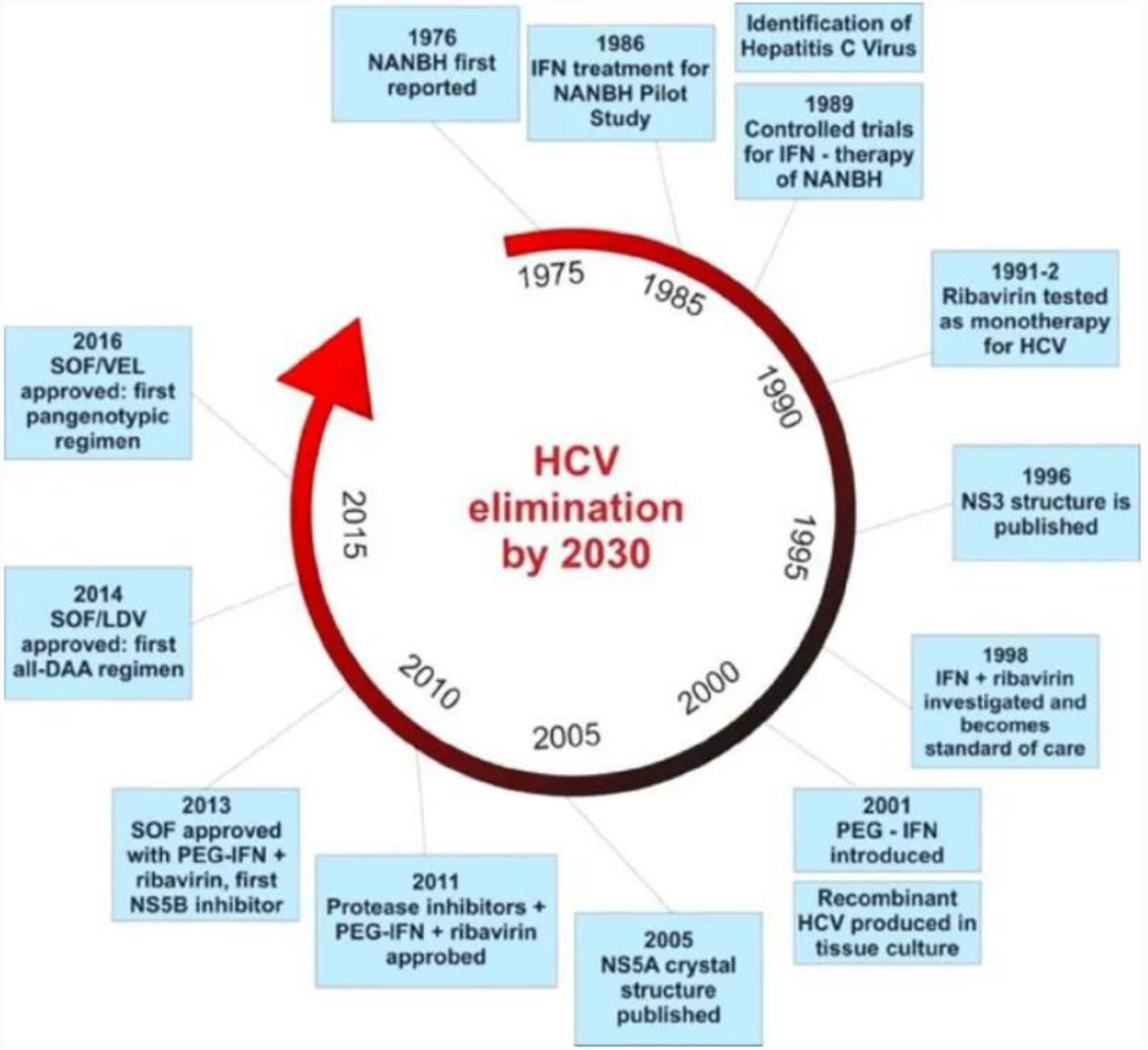


Figure 2. The evolution of hepatitis C drugs. The first available treatment used alpha interferon ... [+] OANCEA

Int. J. Mol. Sci. **2023**, *24*(10), 8867; **https://doi.org/10.3390/ijms24108867**

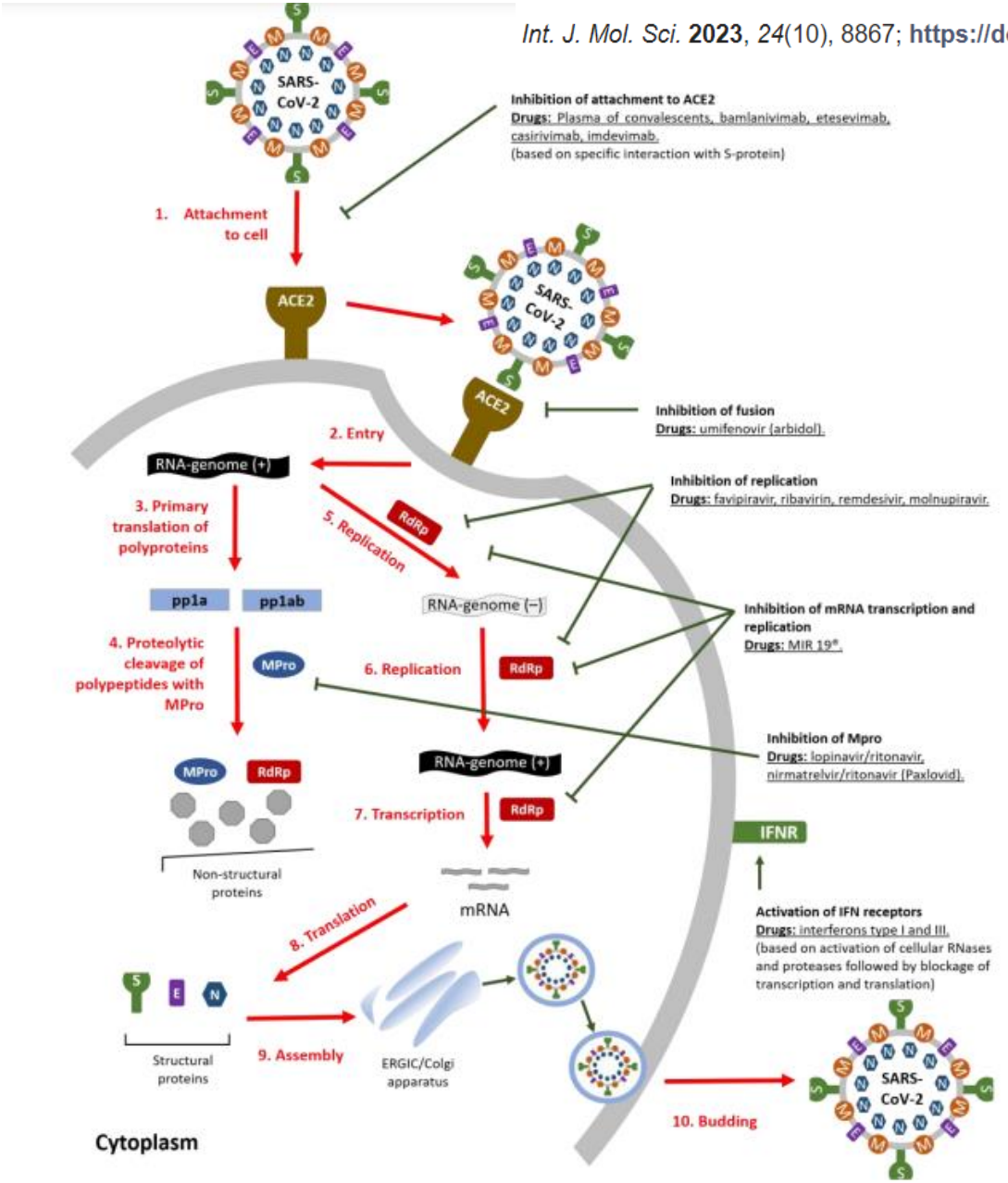
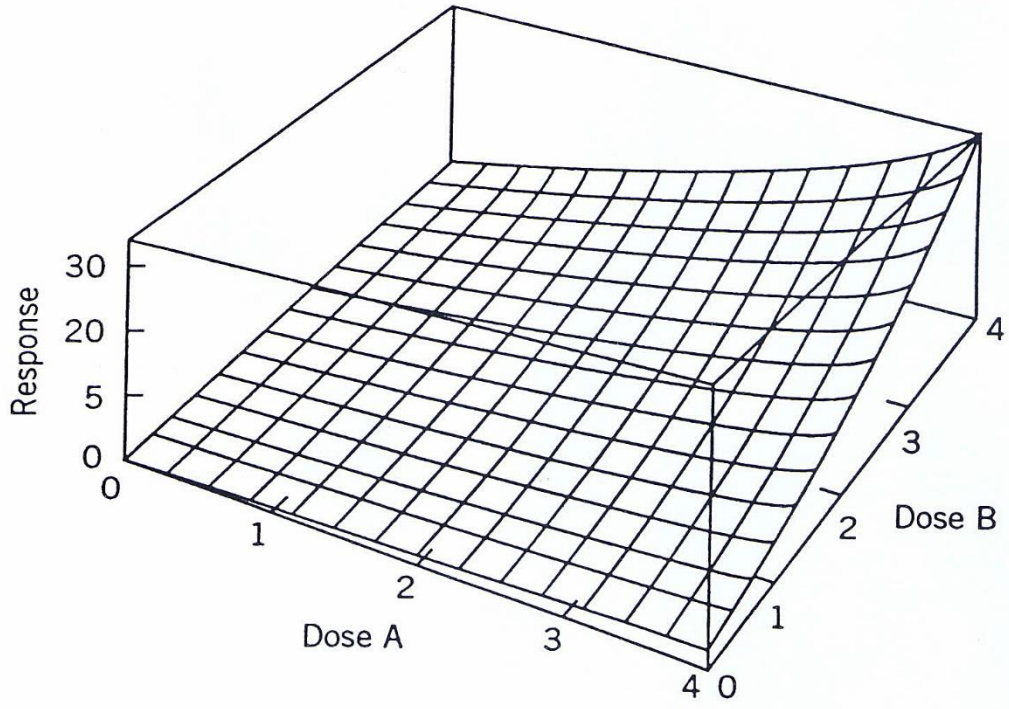
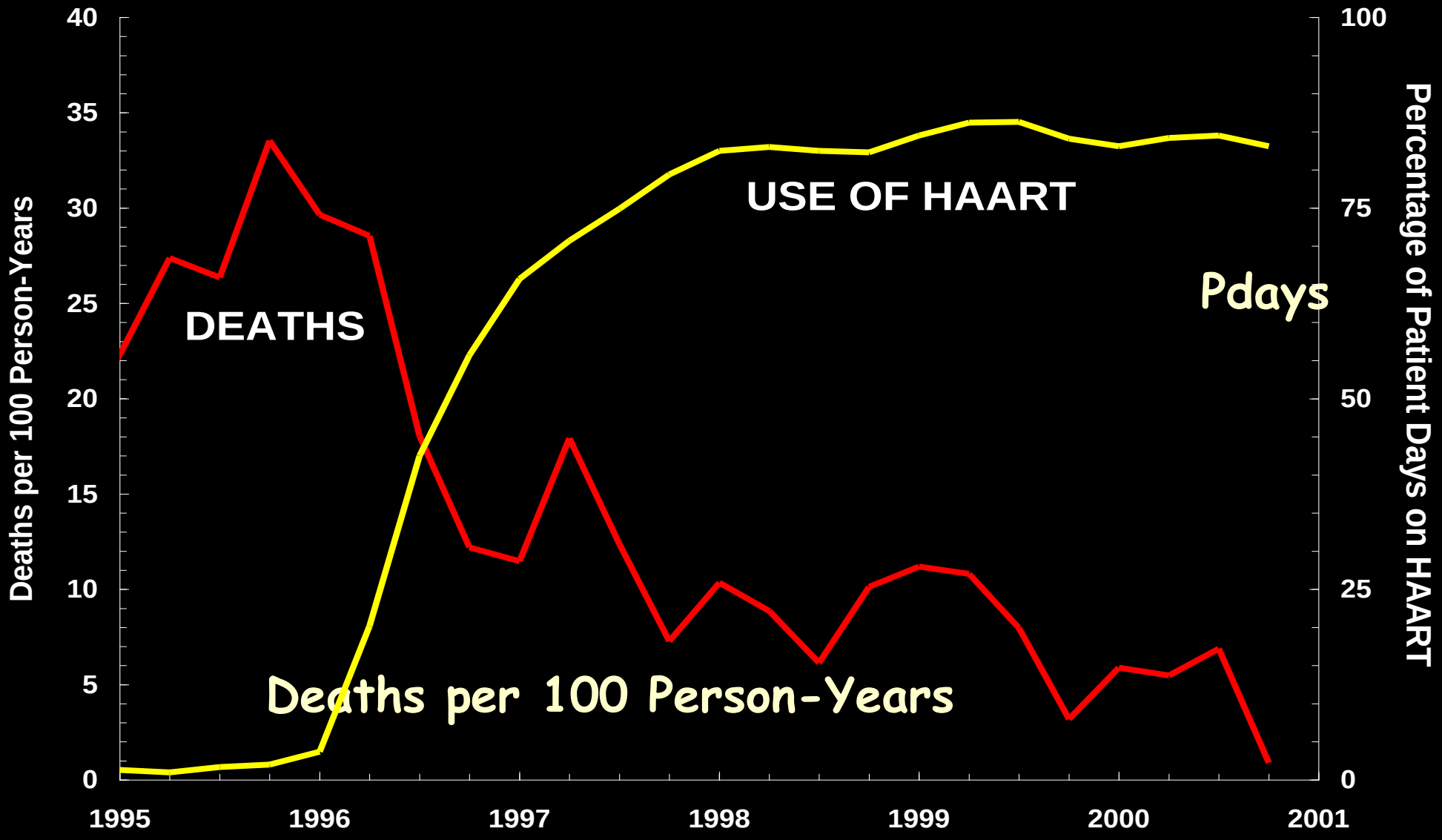


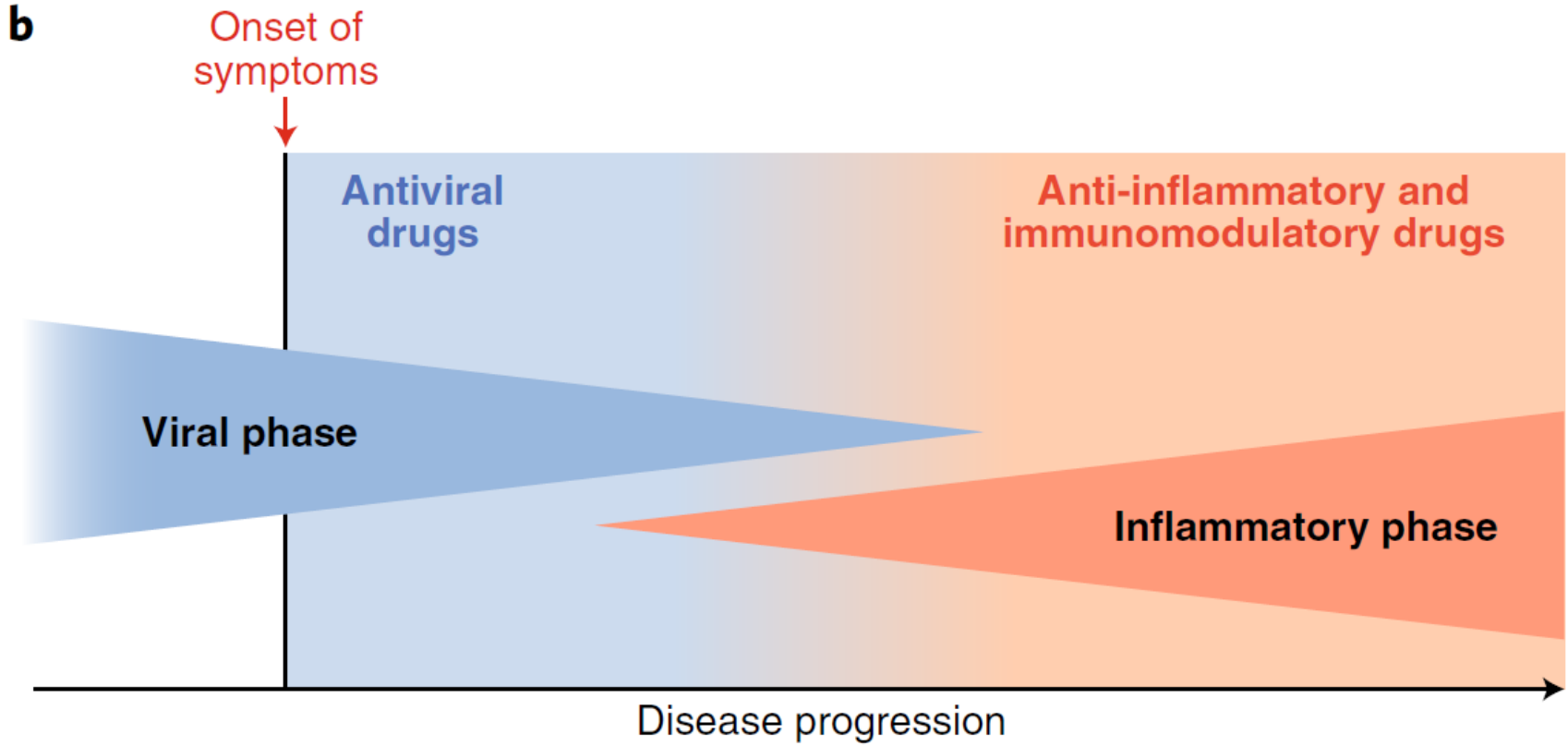
Figure 1. SARS-CoV-2 life cycle and mechanisms of antiviral drugs action.


Response
30
20
5
0
0
1
2
3
4
Dose A
0
1
2
3
4
Dose B

Mortality vs. HAART Utilization



Palella F et al, HOPS Study


b
Onset of symptoms
Antiviral drugs
Anti-inflammatory and immunomodulatory drugs
Viral phase
Inflammatory phase
Disease progression

INTERFERONs

IFN Protective effects in viral infection

IFN Detrimental effects in viral infection

(Persistent viral infections)

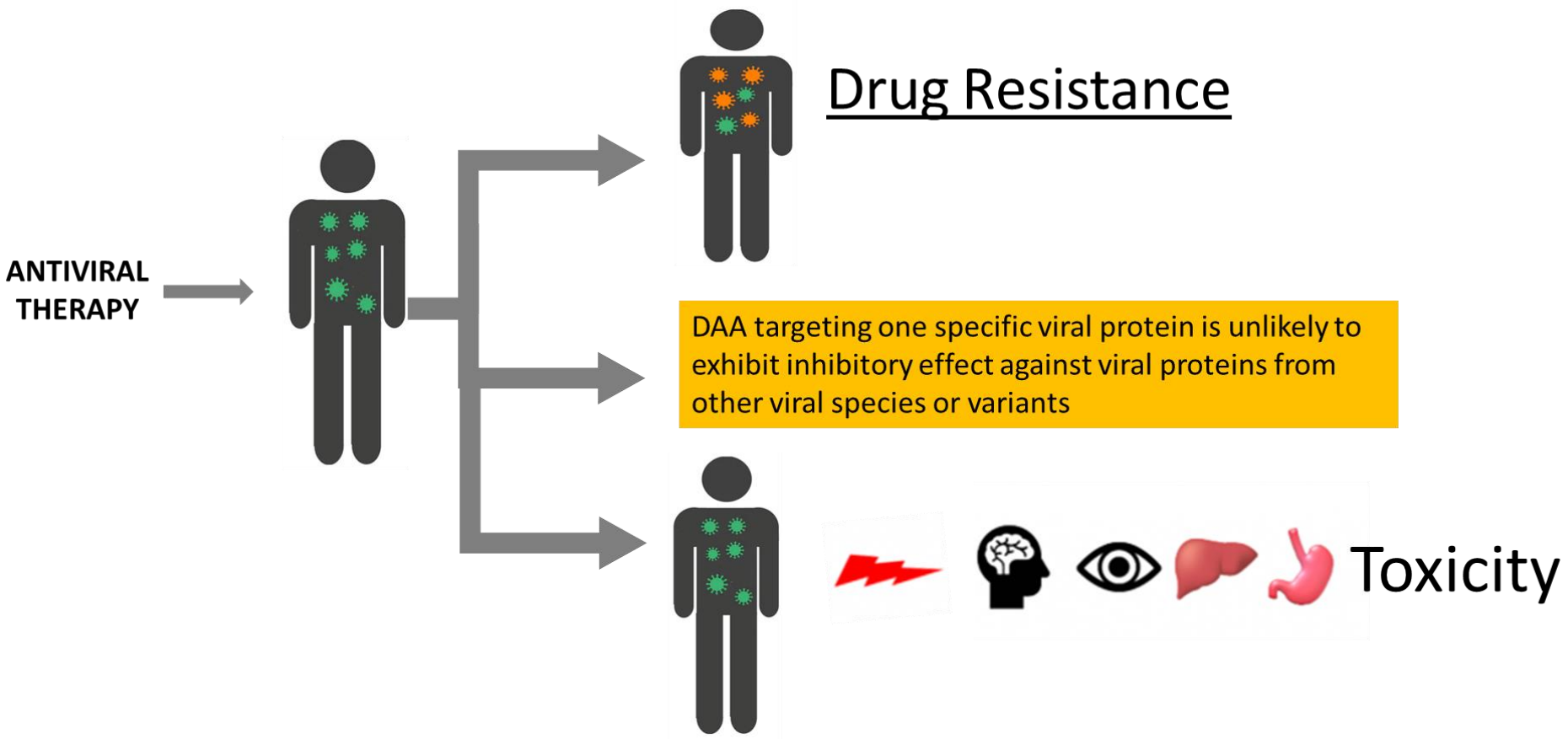
(Acute viral infections)

Antiviral therapy: further issues

New issues in antiviral therapy

- **Toxicity**
- **The emergence of resistant viral variants**
- **Residual viremia and eradication of chronic infection**
- **Antiviral therapy as prevention.**
- **Pharmacogenetics**
- **Therapeutical drug monitoring**
- **New class of antiviral drugs**

DAA limitations



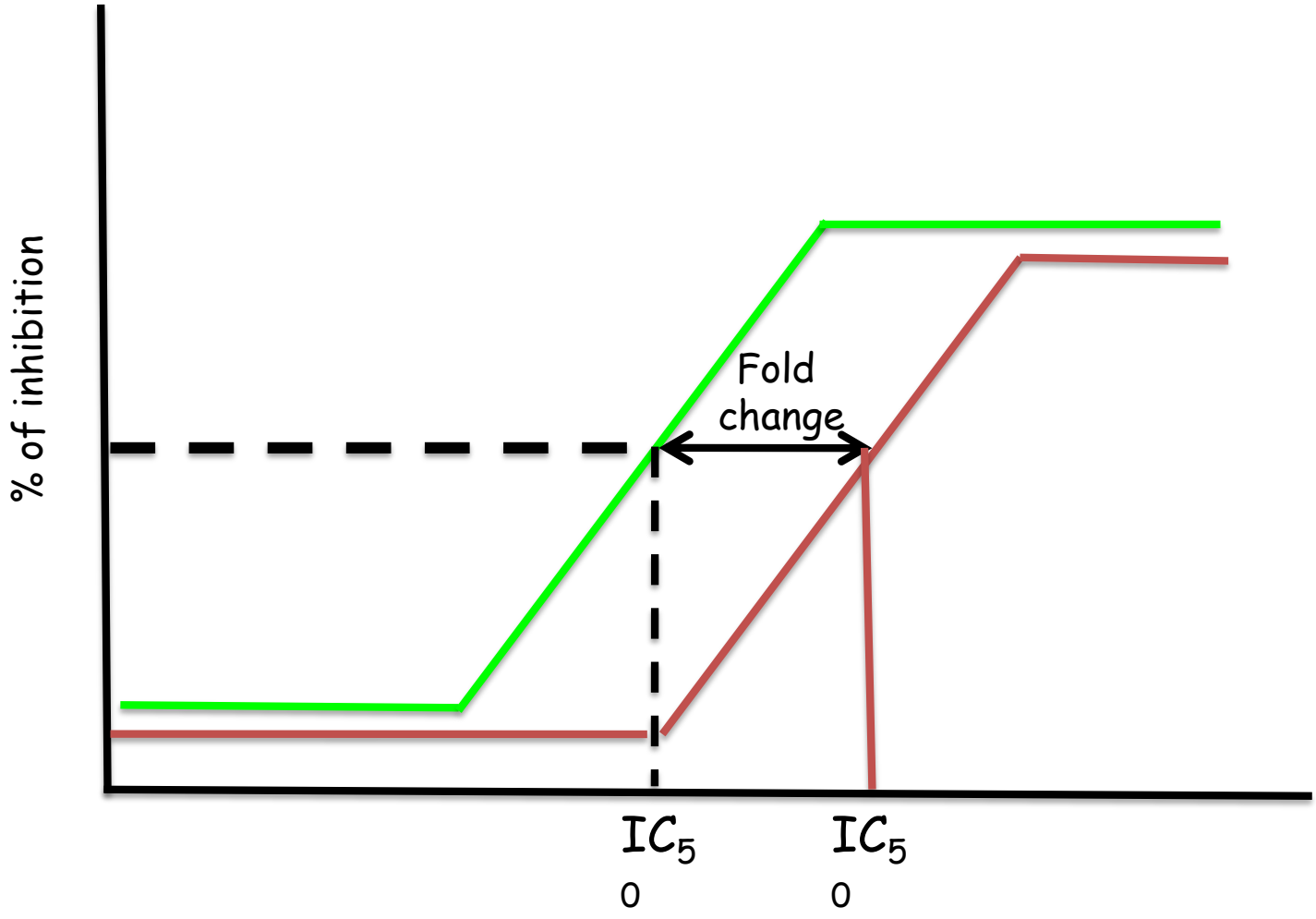
VIRUS DRUG-RESISTANCE

VIRUS	COMPOUND	REFERENCE
POLIOVIRUS	Guanidine hydrochloride	*Melnick JL et al. Science 1961*
INFLUENZA A	Amantadine	*Oxford et al. Nature 1970*
HERPESVIRUS	Acyclovir	*Schnipper & Crumpacker, PNAS 1980*
POLIOVIRUS	Arildone	*Schrom M et al. Virology 1982*
VARICELLA ZOSTER	Acyclovir	*Pahwa S et al. AIDS 1988*
CITOMEGALOVIRUS	Ganciclovir	*Erice A et al. N Engl J Med 1989*
HUMAN IMMUNODEFICIENCY VIRUS	Zidovudine	*Larder BA et al. Science 1989*

VIRUSES AND DRUG RESISTANCE

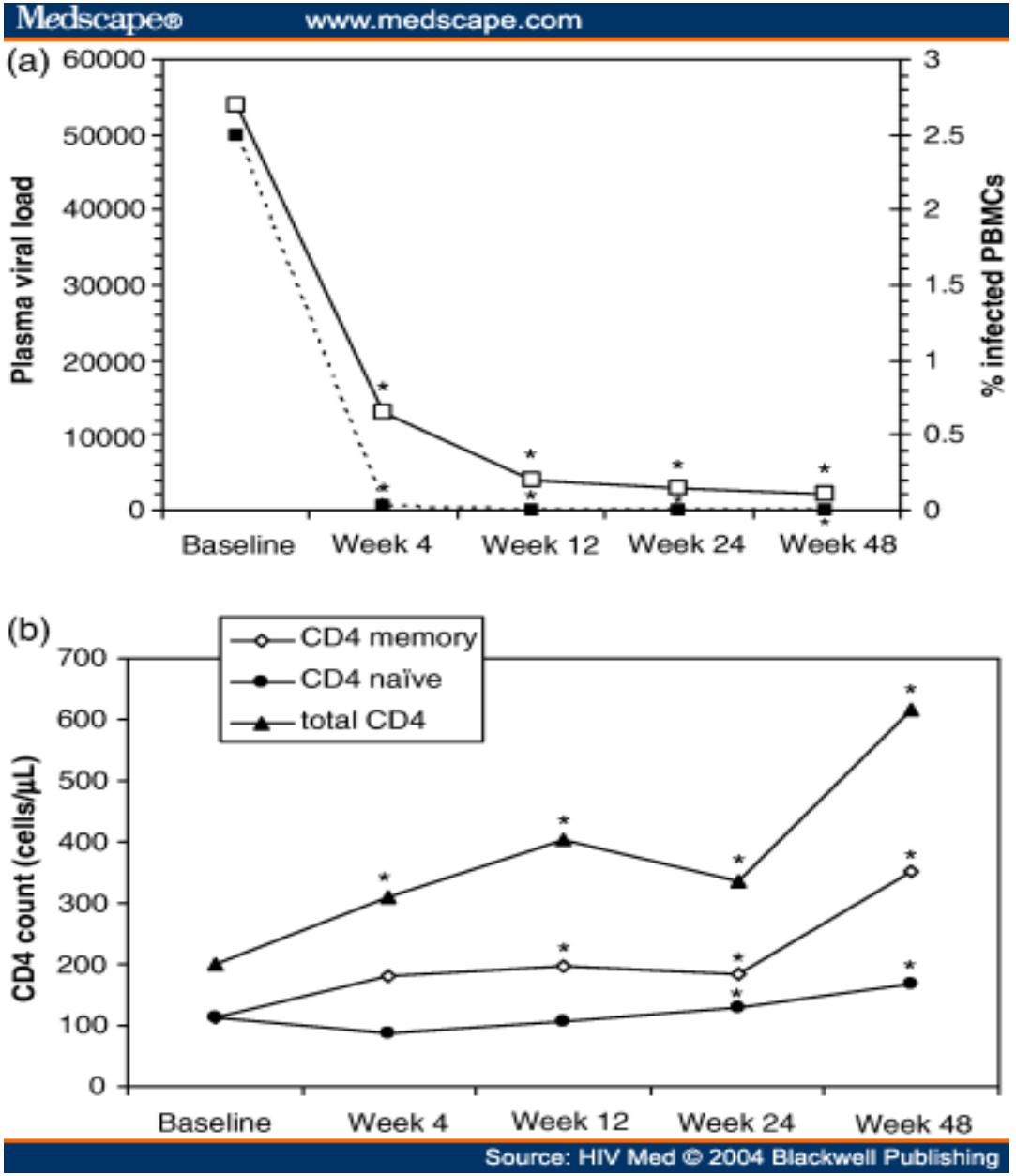
VIRUS	DRUG	mutated region
HSV	ACICLOVIRV/PENCICLOVIR, CIDOFOVIR, FOSCARNET, ADEFOVIR	TK, DNA polimerase
CMV	GANCICLOVIR, CIDOFOVIR, FOSCARNET	UL97 Kinase, DNA polimerase
INFLUENZA VIRUS	OSELTAMIVIR, ZANAMIVIR, AMANTADINE	Neuraminidase, M2
HBV	LAMIVUDINE, ADEFOVIR, ENTECAVIR, TELBUVIDINE, TENOFOVIR	Reverse transcriptase
HCV	RIBAVIRIN, BOCEPREVIR, TELAPREVIR,	Polymerase, Protease
HIV	NRTIs, NNRTIs, PIs, INI,	Reverse transcriptase, Protease, Integrase.

DRUG RESISTANCE PHENOMENON

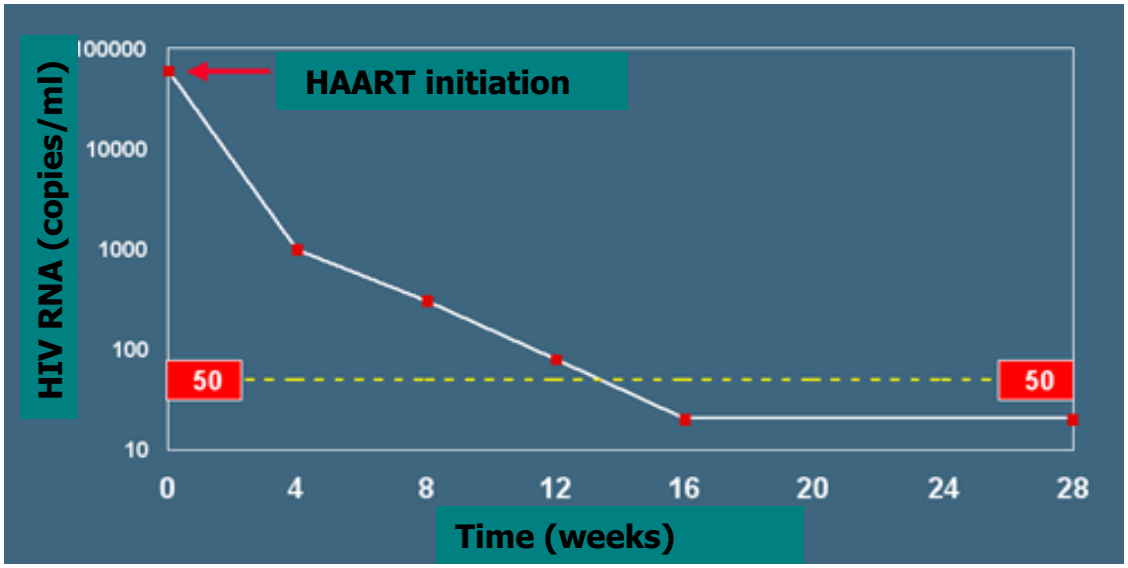


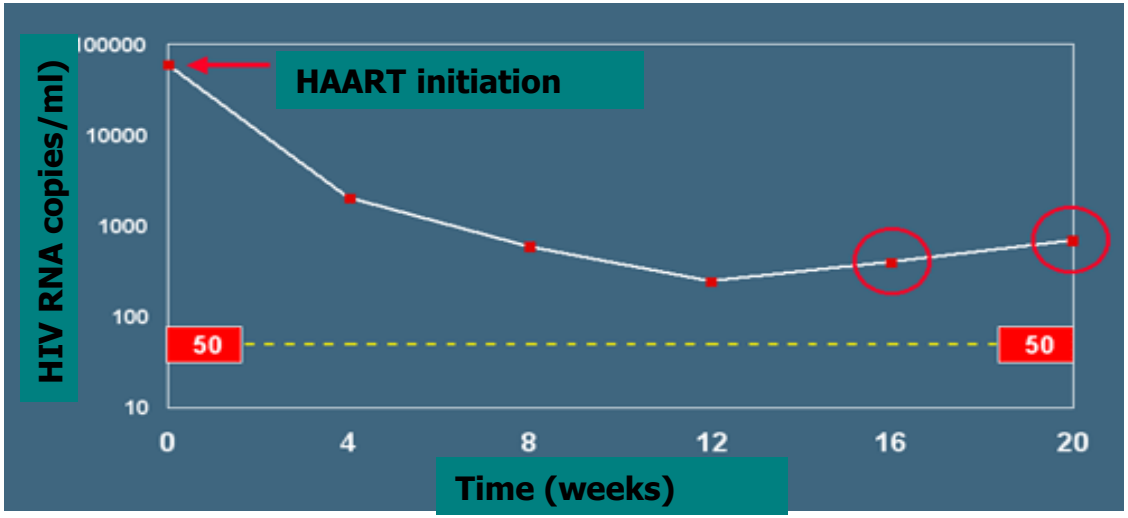
Decline of plasma viral load and percentage of infected PBMC following HAART

Kinetics of CD4 change

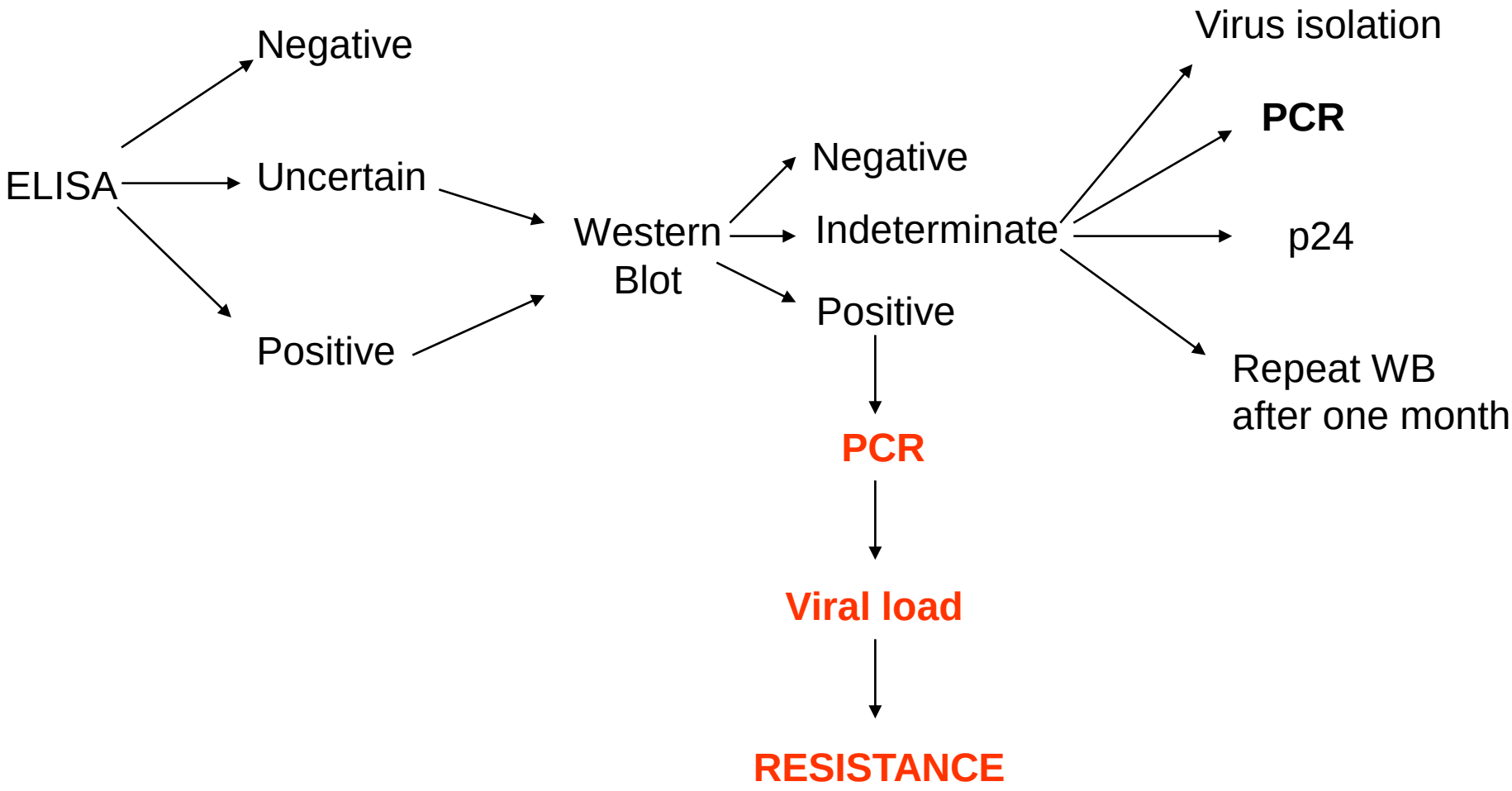


Effect of antiretroviral therapy on viral load





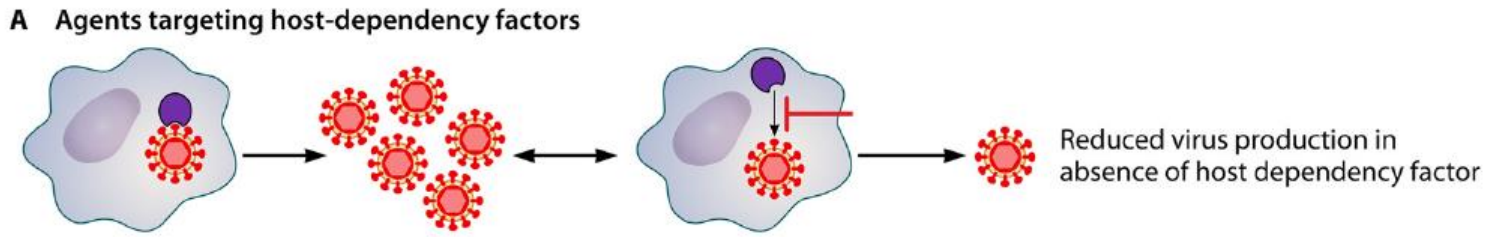
Diagnostic Algorithm for HIV Diagnosis in adults



New issues in antiviral therapy

- **Toxicity**
- **The emergence of resistant viral variants**
- **Residual viremia and eradication of chronic infection**
- **Antiviral therapy as prevention.**
- **Pharmacogenetics**
- **Therapeutical drug monitoring**
- **New class of antiviral drugs**

Novel strategies of antiviral drug development



HOST TARGETS

- Cyclophillins
- Eucaryotic initiation factor 2α
- α-glucosidase
- inosine-5’-monophosphate dehydrogenase
- Kinase
- lipid biosynthesis
- Heat shock protein 90 e 70
- ……