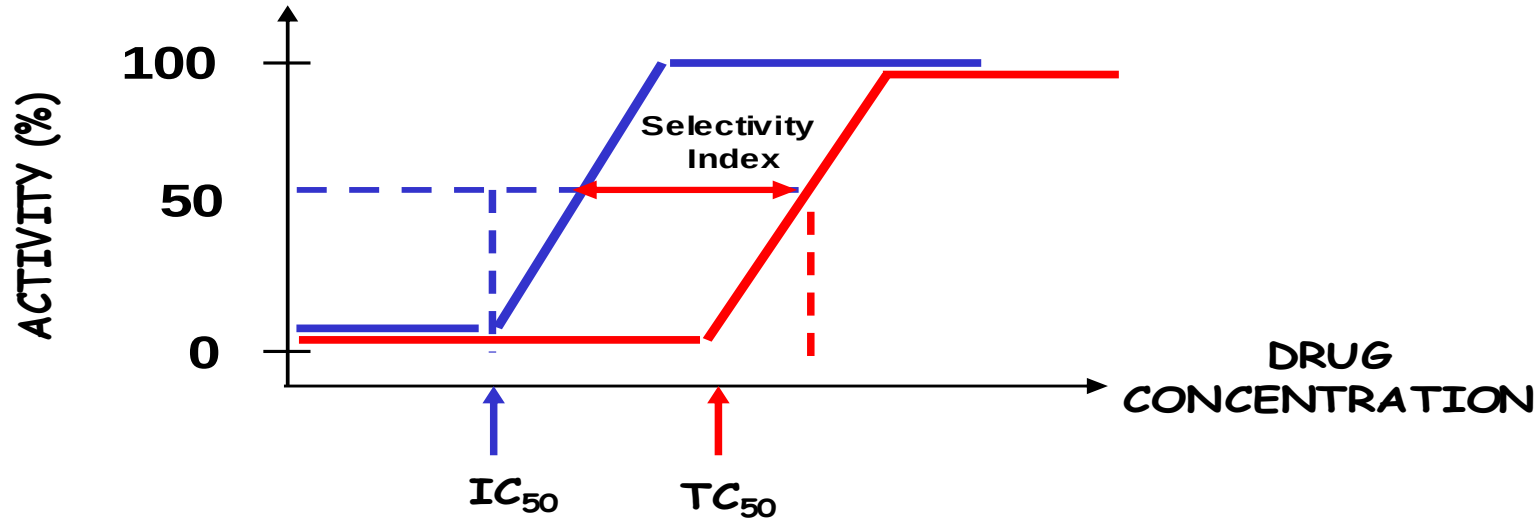
ANTIVIRAL CHEMOTHERAPYand VIRUS DRUG RESISTANCE

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}



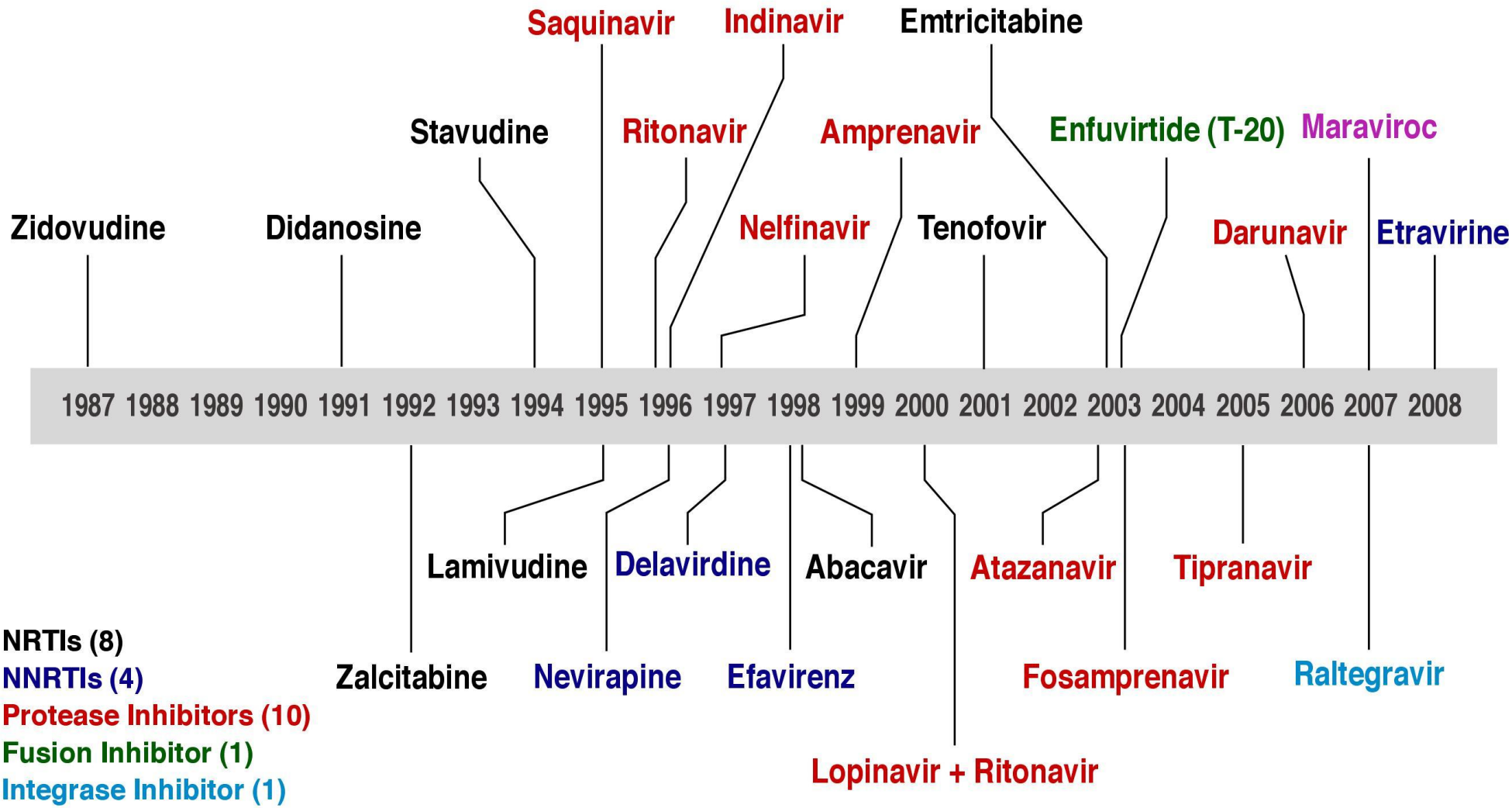
IC_{50} = 50% Inhibitory Concentration

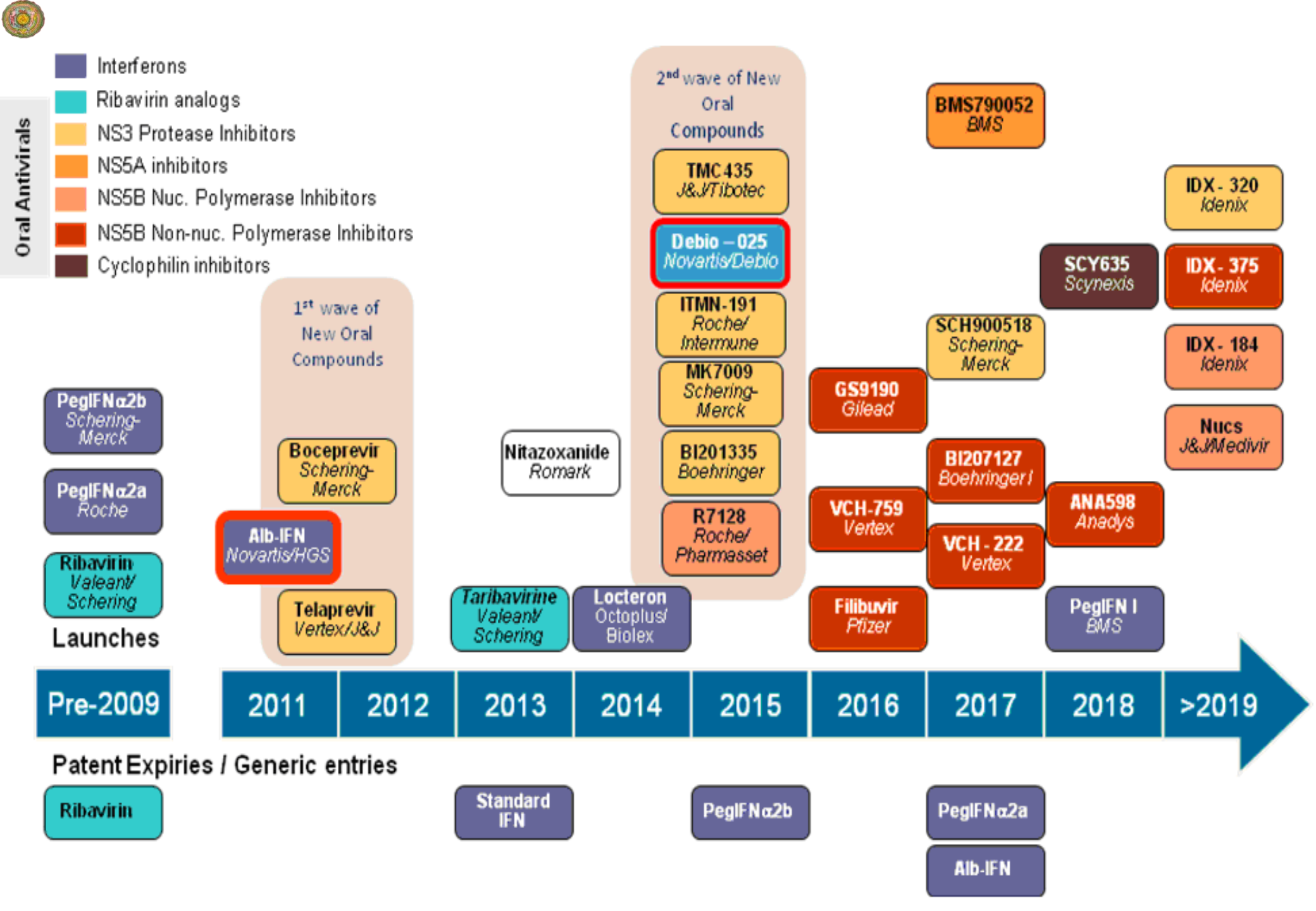
TC_{50} = 50% Toxic Concentration

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

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	

APPROVED ANTIVIRAL DRUGS (2019)

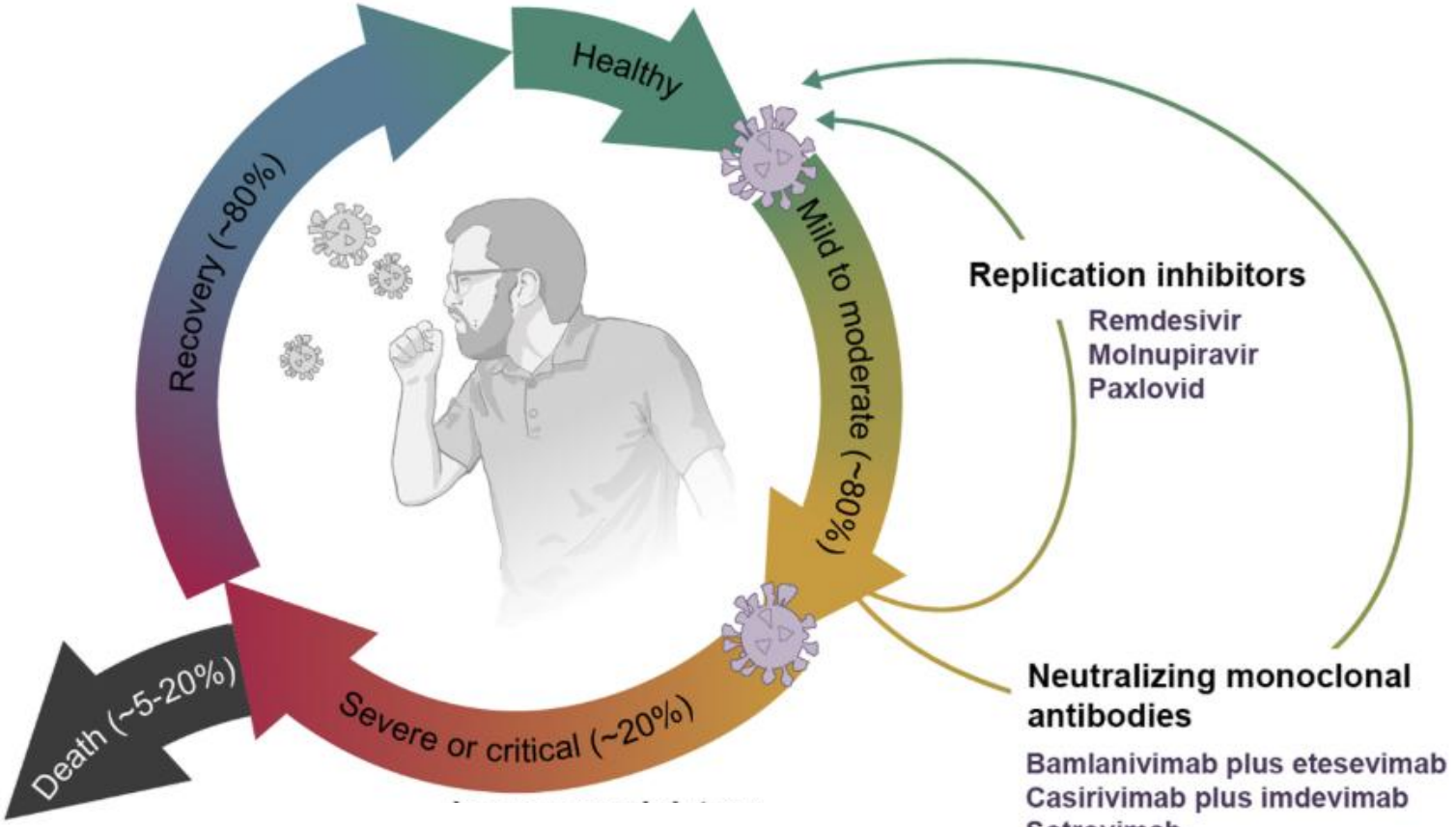
Anti-HCV	
NS5B RNA polimerase inhibitor	
Non nucleoside inhibitor	
Dasabuvir	It binds HCV NS5B polymerase and blocks viral RNA synthesis and replication.
Nucleotide analog	
Sofosbuvir	Potent inhibitor of the NS5B polymerase. It blocks viral RNA synthesis and replication.
Nucleoside analog	
Ribavirin	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)

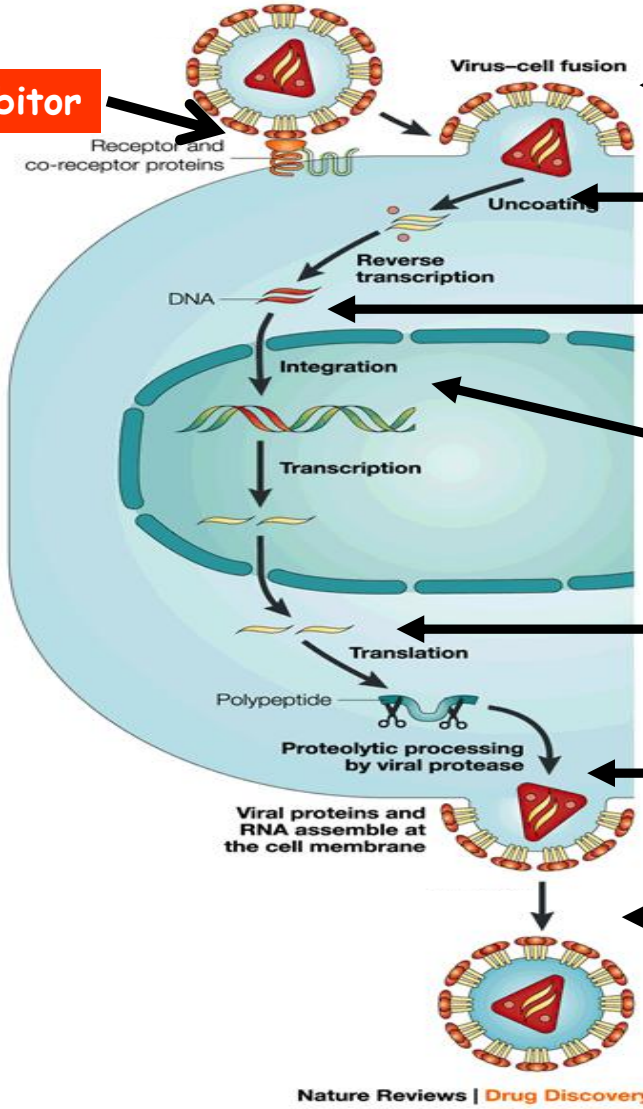
APPROVED ANTIVIRAL DRUGS (2019)

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]

Antiviral agents for the treatment of COVID-19



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

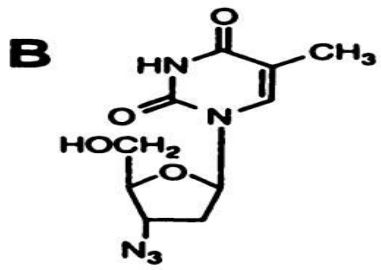
Raltegravir, Elvitegravir, Dolutegravir

FOMIVIRSEN

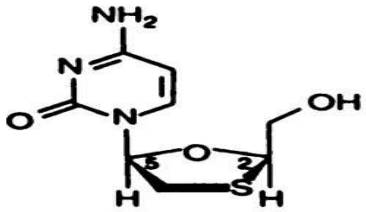
NFV, APV, ATV, LPV, SQV, RTV, IDV

OSELTAMIVIR
ZANAMIVIR

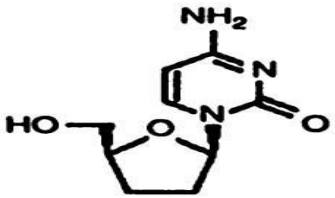
MAIN NUCLEOSIDE ANALOGUES USED TO TREAT HIV INFECTION



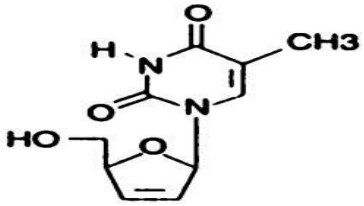
Zidovudine



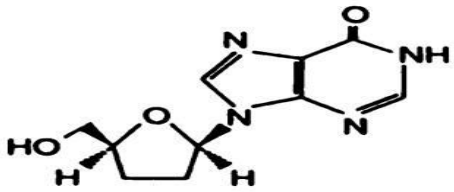
Lamivudine



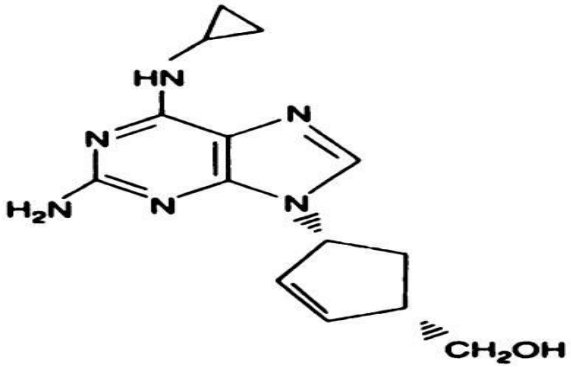
Zalcitabine



Stavudine

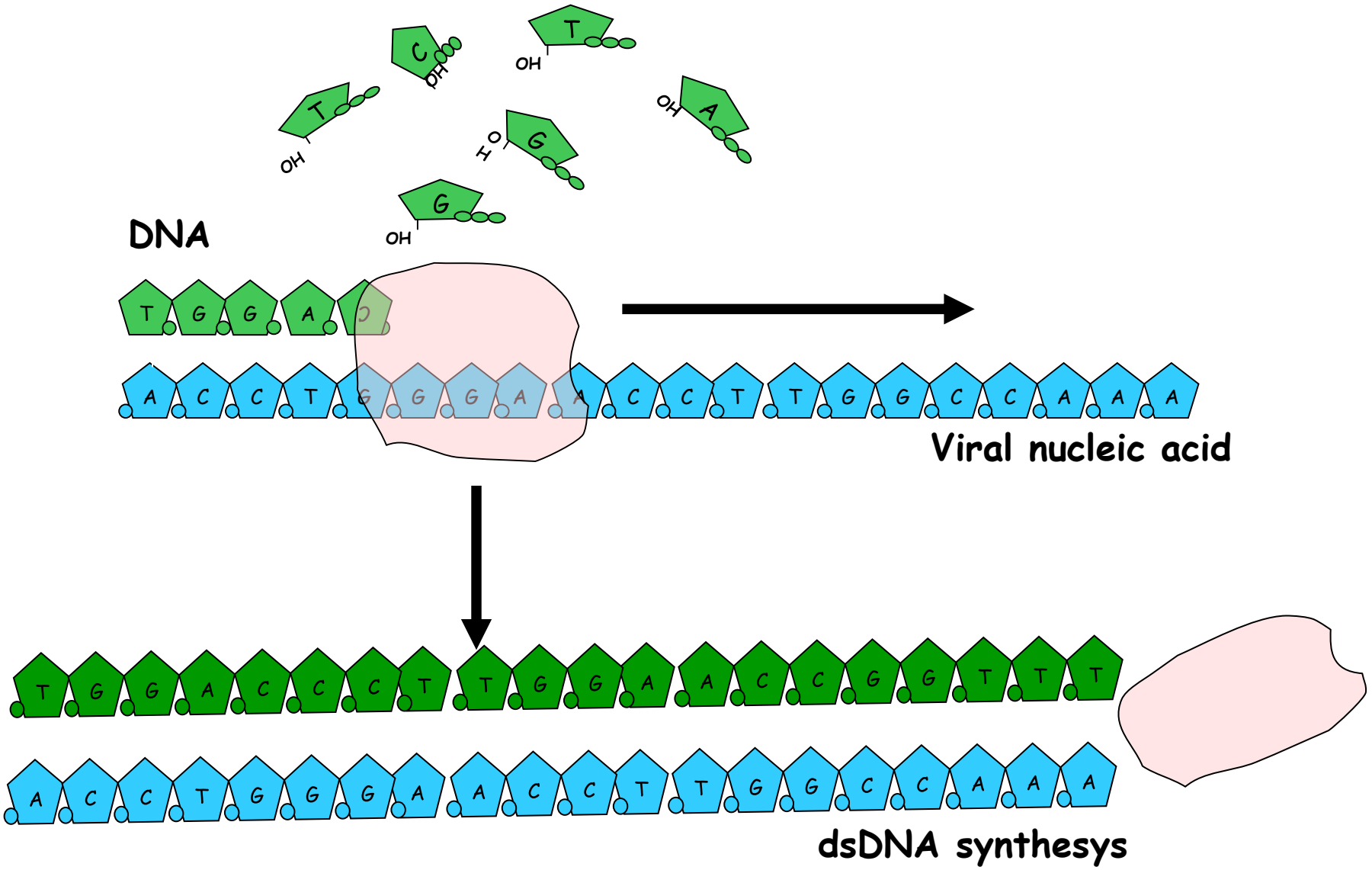


Didanosine



Abacavir

MECHANISM OF ACTION OF NUCLEOSIDE ANALOGS



MECHANISM OF ACTION OF NUCLEOSIDE ANALOGS