Specific virus families: **Picornaviridae,** Caliciviridae, Astroviridae, Bunyaviridae, Filoviridae, **Hepeviridae (HEV**), **Coronaviridae (SARS), Togaviridae, Flaviridae (HCV), Rabdoviridae**, **Paramyxoviridae, Orthomyxoviridae**, Arenaviridae, Reoviridae, **Retroviridae (HIV, HTLV-1),** Polyomaviridae, **Papillomaviridae**, **Adenoviridae,** Parvoviridae (B19), **Herpesviridae, Hepadnaviridae (HBV),** Viroids (HDV), Prions.

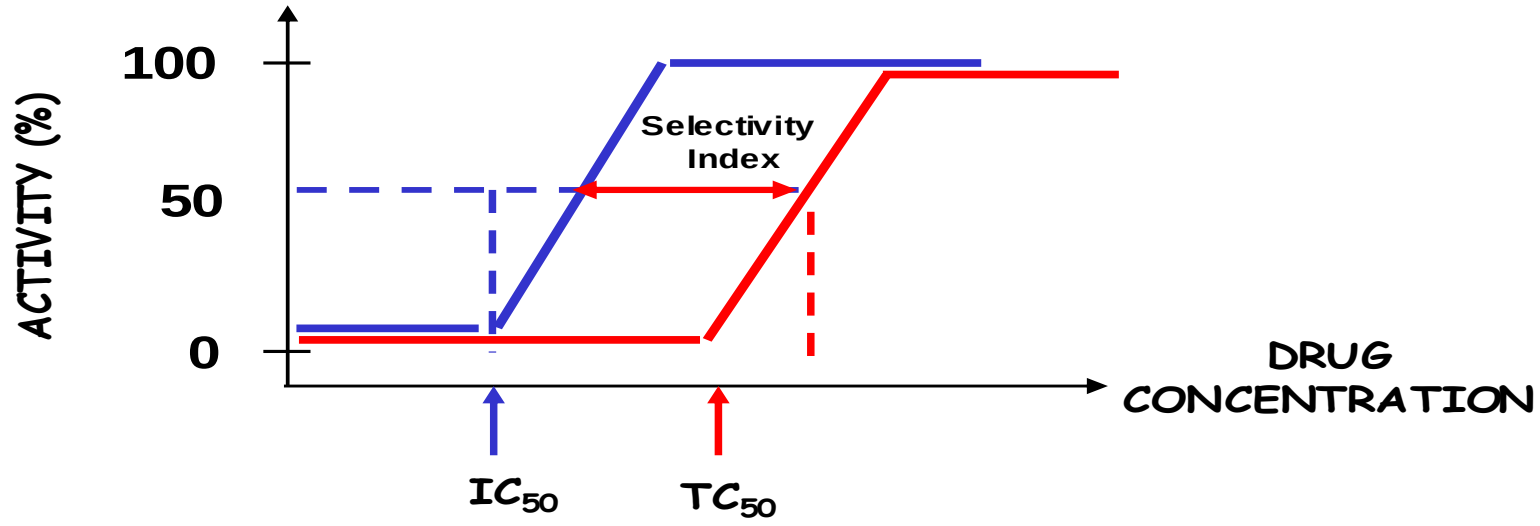
ANTIVIRAL CHEMOTHERAPY

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}



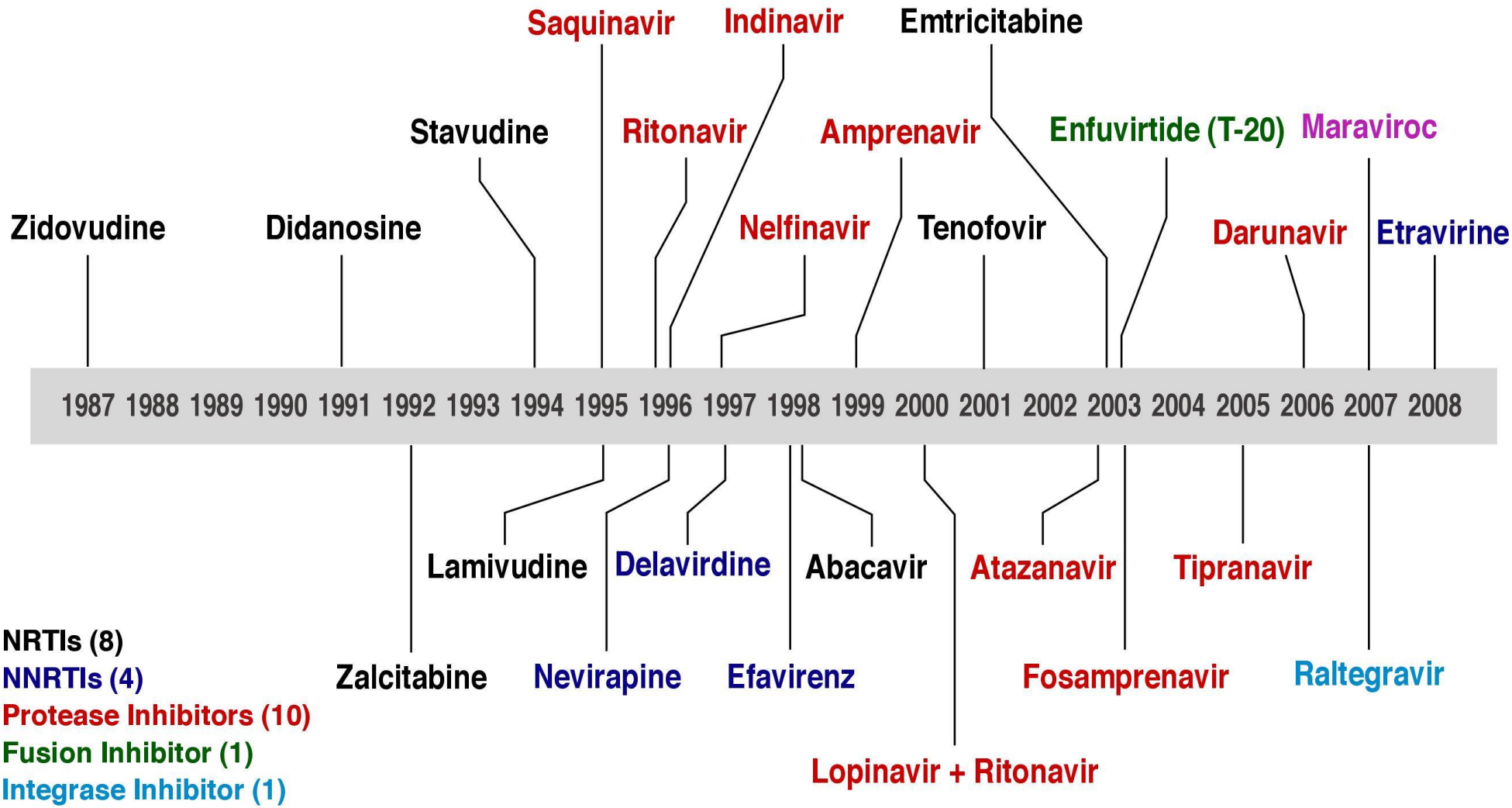
IC_{50} = 50% Inhibitory Concentration

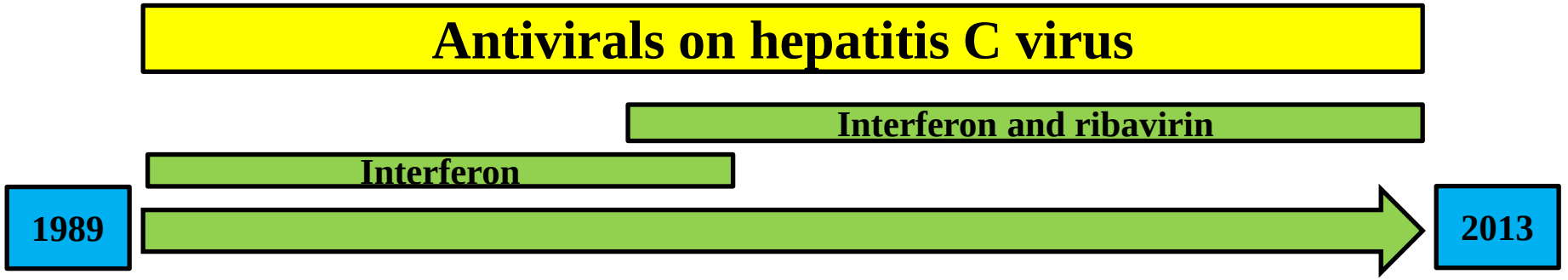
TC_{50} = 50% Toxic Concentration

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



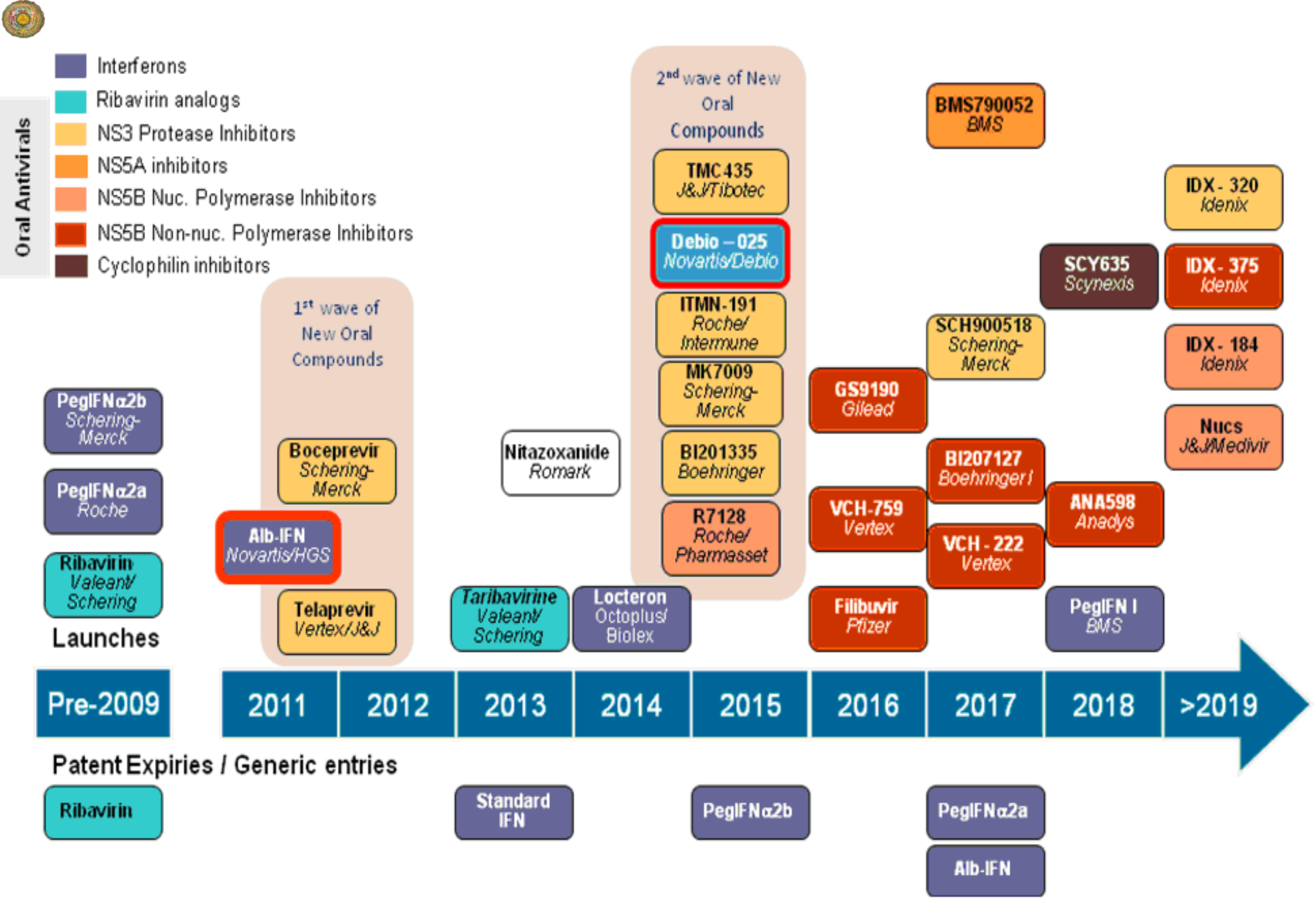


Direct acting antivirals on hepatitis C virus

Table 1: Timeline for DAA approval

Date of approval	Drug
On May 13th, 2011	**Boceprevir was approved by the FDA** for the treatment of chronic HCV to be used, in combination with peginterferon alfa and ribavirin, in adult patients.
On May 23th, 2011	**Telaprevir was approved by the FDA** to be used in combination with peginterferon alfa and ribavirin for the treatment of HCV infection in adults.
In November, 2013	**Simeprevir was approved by the FDA** to be used in combination with peginterferon alfa and ribavirin or in combination with sofosbuvir.
In December, 2013	**Sofosbuvir was approved to be used** in combination with ribavirin or with pegylated interferon and ribavirin.
In October, 2014	**(Ledipasvir/Sofosbuvir) were approved by the FDA in one tablet.**
In December, 2014	**FDA approved a combination (ombitasvir/paritaprevir/ritonavir and dasabuvir)** for the treatment of patients with genotype 1.
In July, 2015	**Daclatasvir was approved to be** used with sofosbuvir. **A combination (ombitasvir, paritaprevir and ritonavir) in one tablet to be** used in combination with ribavirin for the treatment of HCV genotype 4 infections.
In January, 2016	**On January 28th FDA approved a combination of elbasvir and grazoprevir**, with or without ribavirin for treating **patients with genotype 4.**
In July, 2016	A combination of sofosbuvir plus velpatasvir were approved with or without ribavirin for treating adult patients in all genotypes.

DDA: direct acting antiviral agent; HCV: hepatitis C virus.


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	

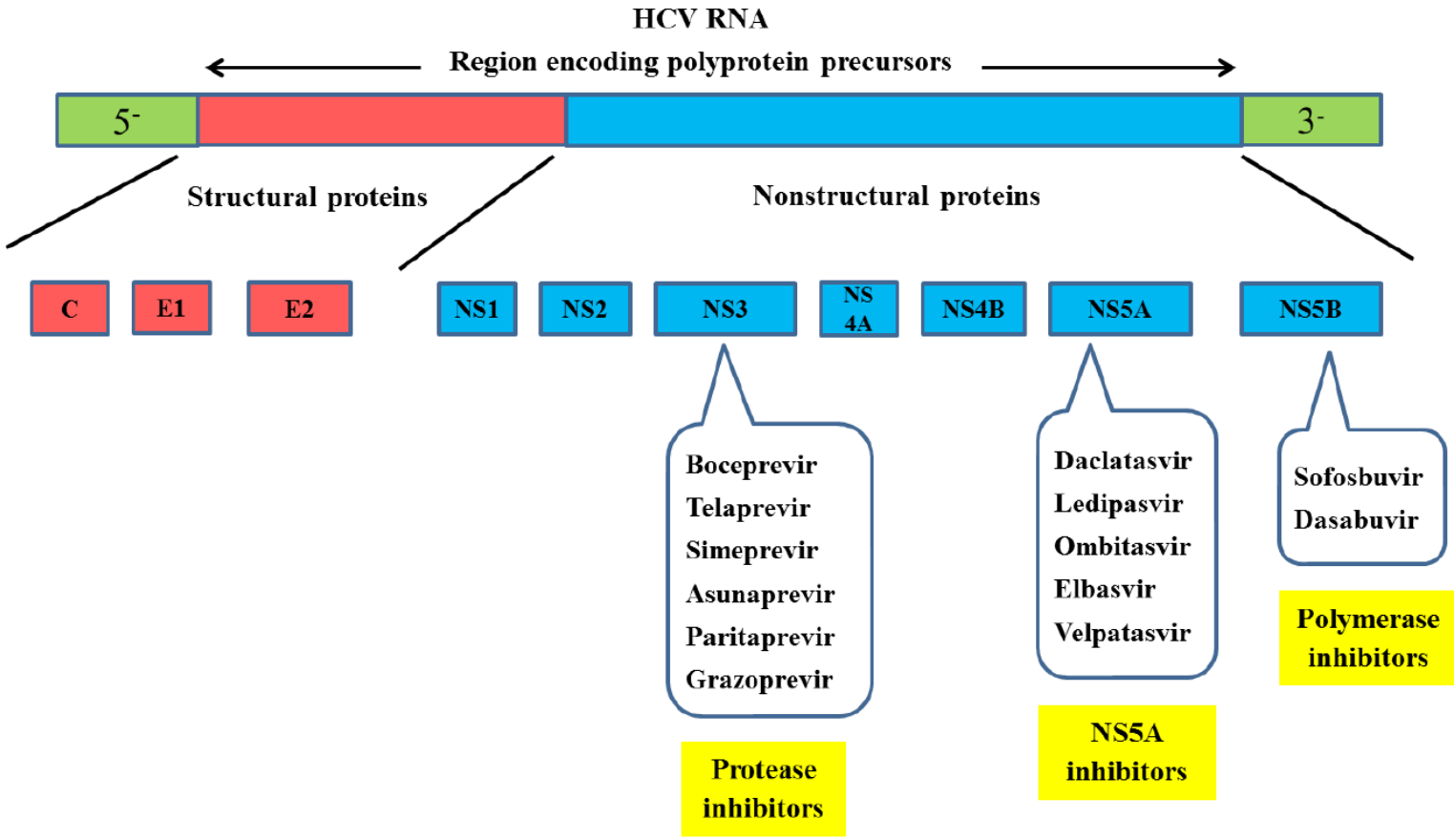


Figure 1: Proteins encoded by the hepatitis C virus genome as targets for direct acting antiviral agents.

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]

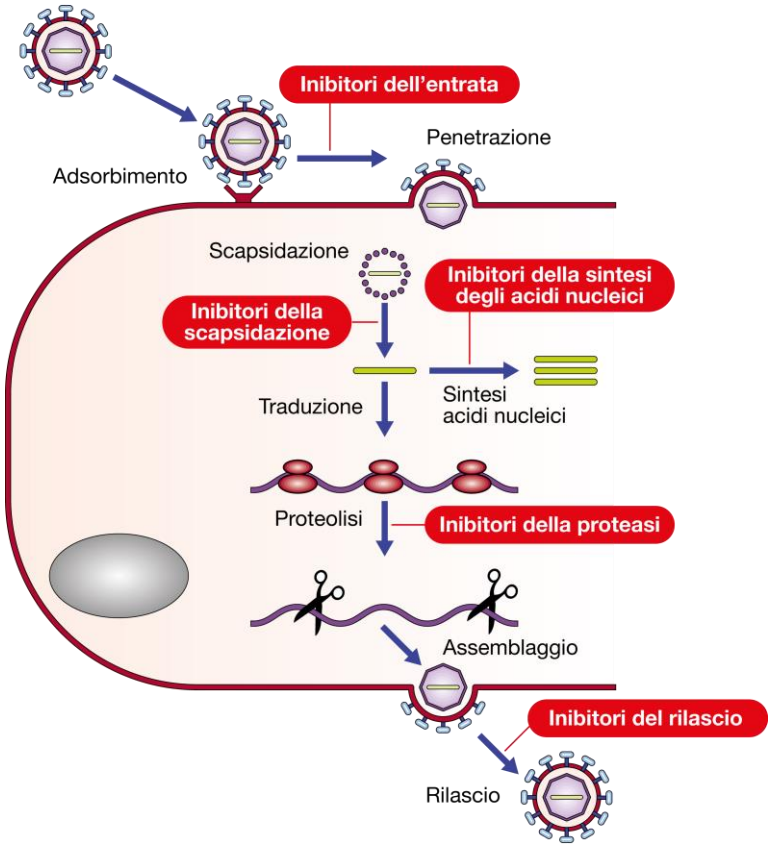
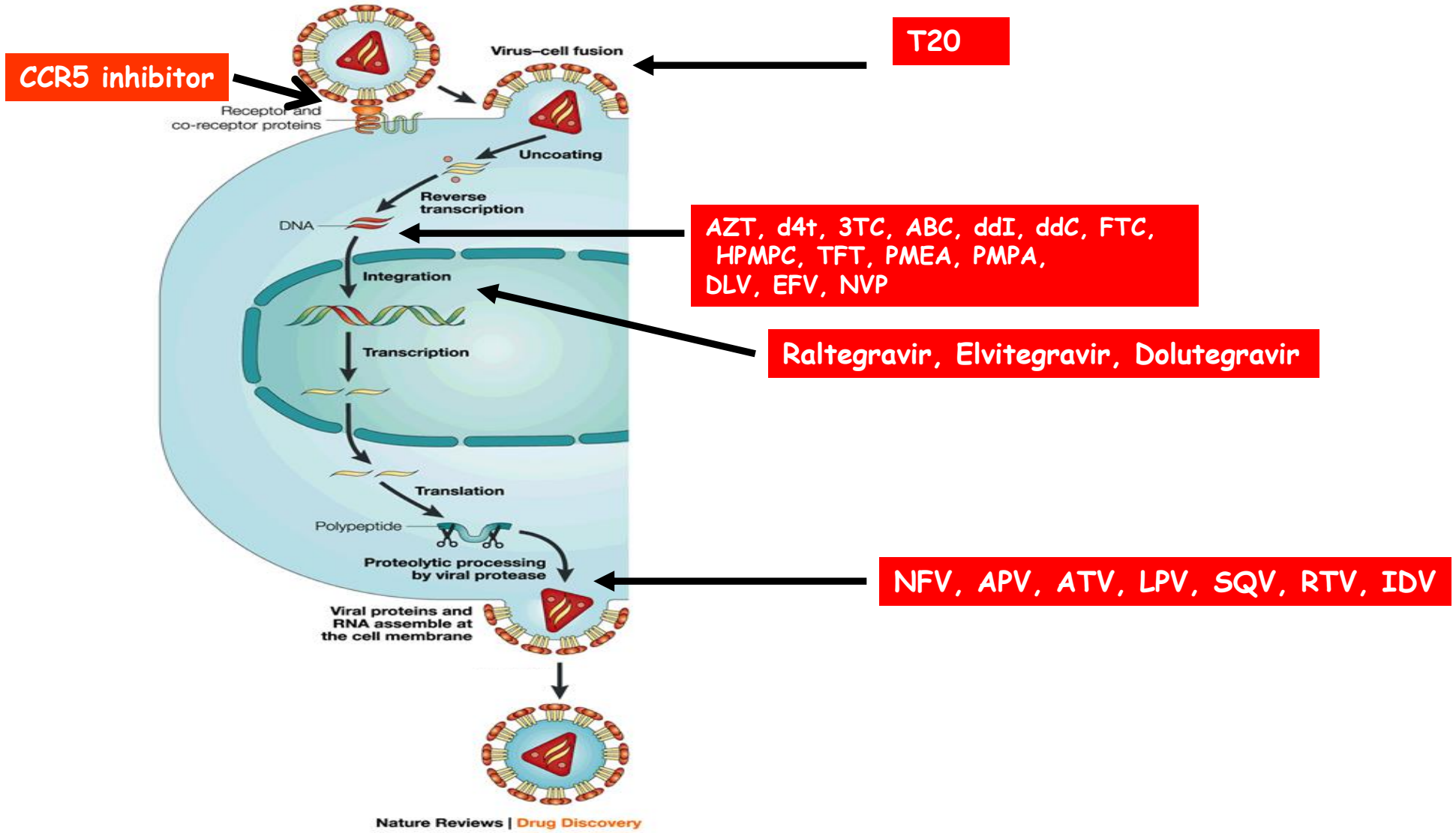
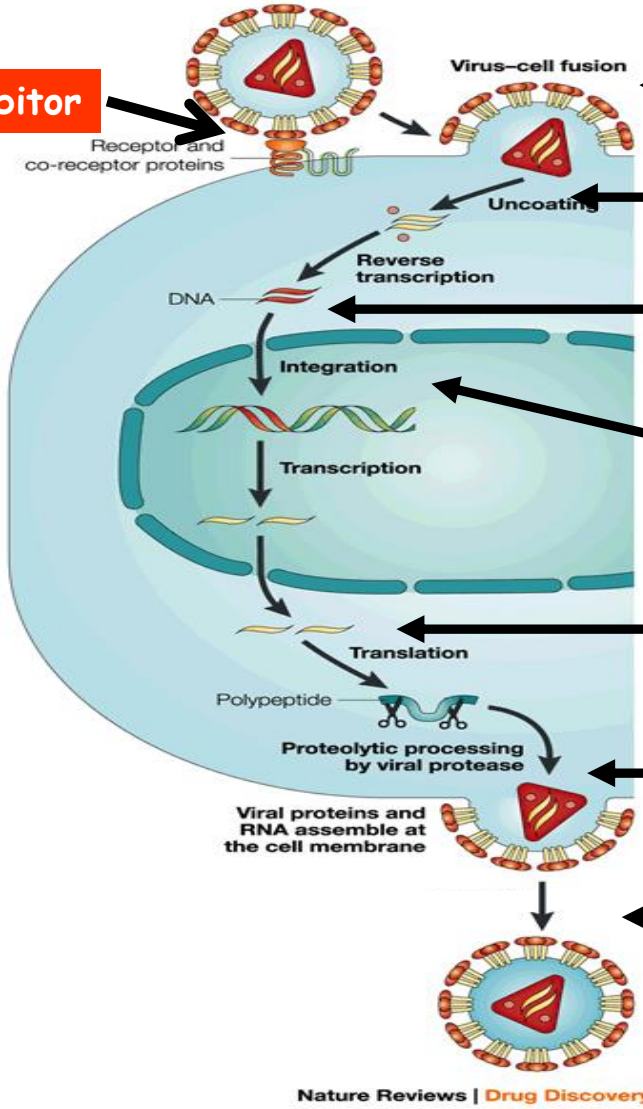


Figura 67.1 Principali tappe del ciclo di replicazione dei virus bersaglio dei farmaci antivirali.

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



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

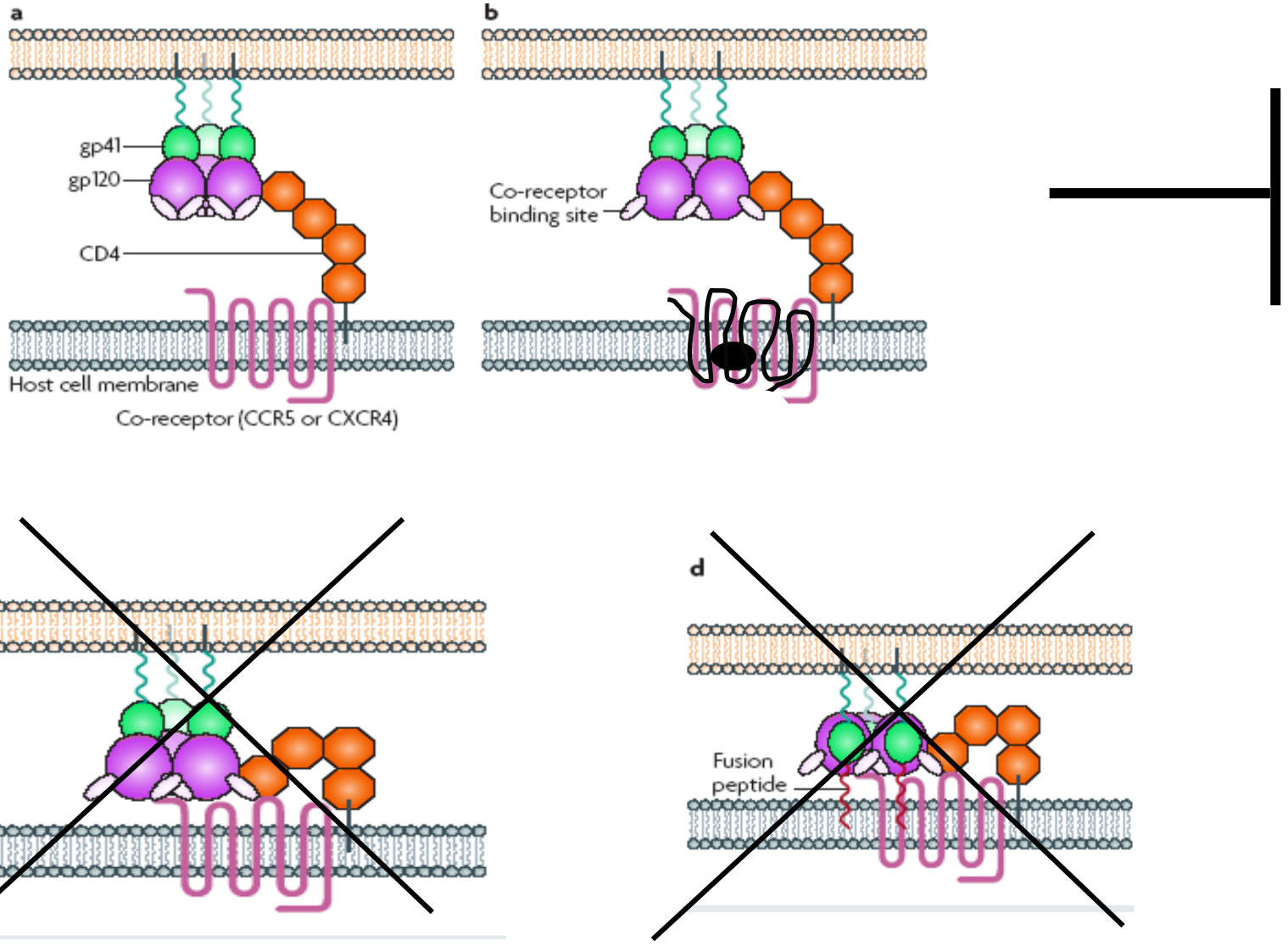
Raltegravir, Elvitegravir

FOMIVIRSEN

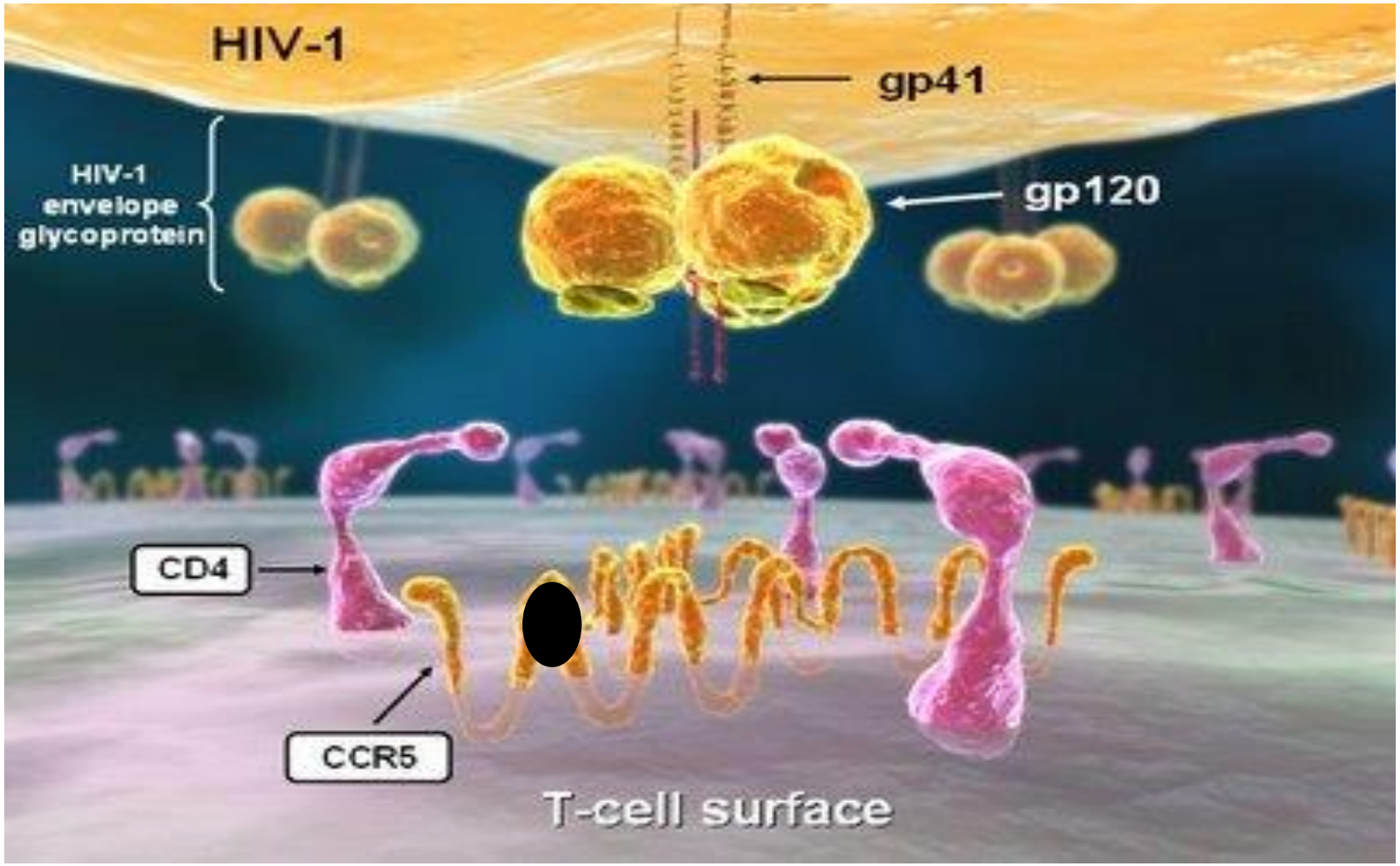
NFV, APV, ATV, LPV, SQV, RTV, IDV

OSELTAMIVIR
ZANAMIVIR

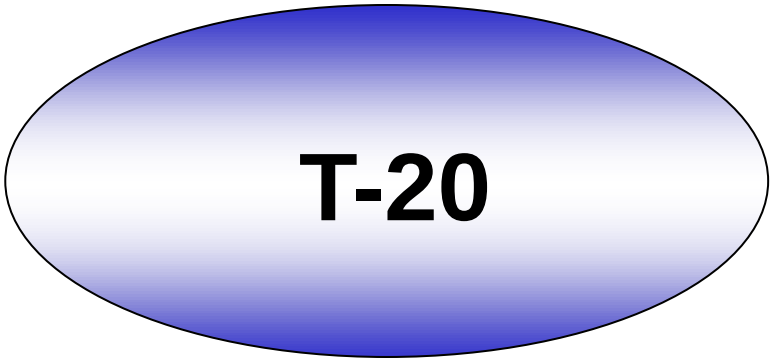
HUMAN IMMUNODEFICIENCY VIRUS CO-RECEPTOR ANTAGONIST

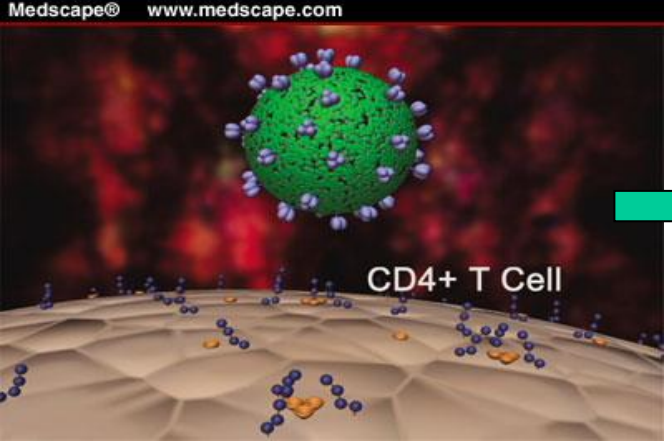


CCR5 INHIBITORS



FUSION INHIBITOR

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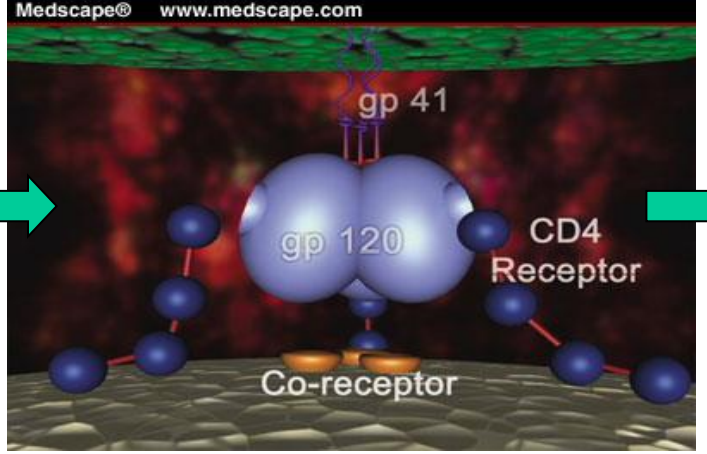
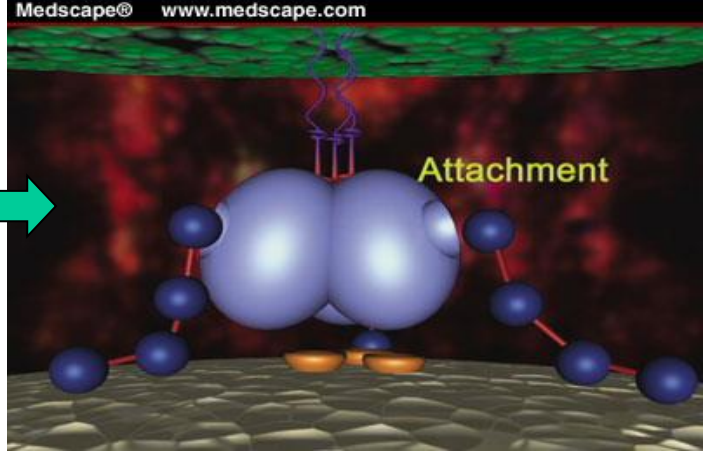
CD4+ T Cell


Medscape® www.medscape.com
gp 41
gp 120
CD4
Receptor
Co-receptor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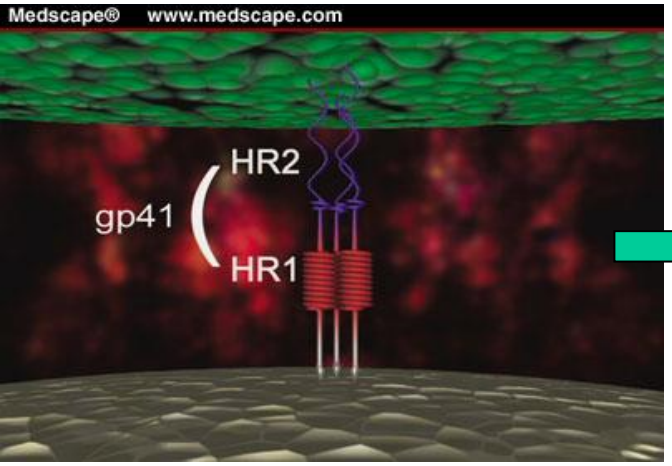
Attachment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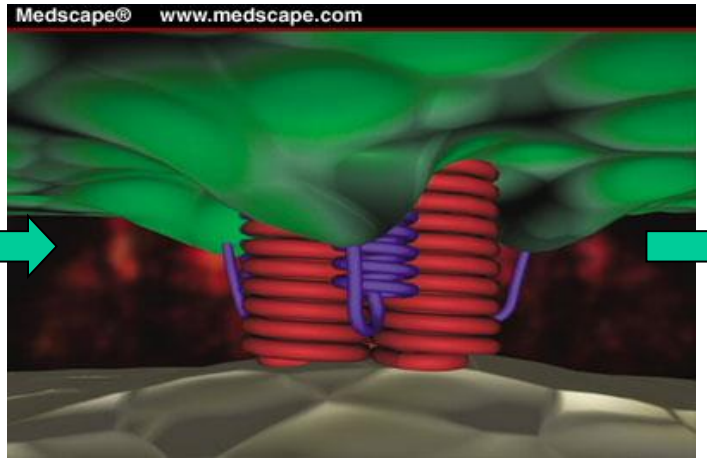
gp41
HR2
HR1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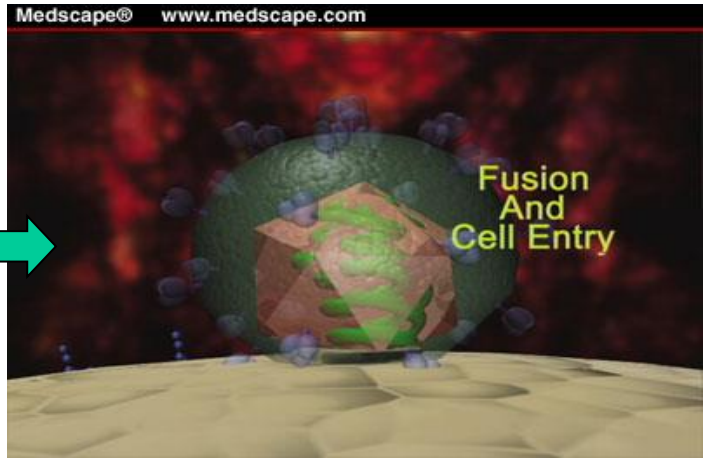
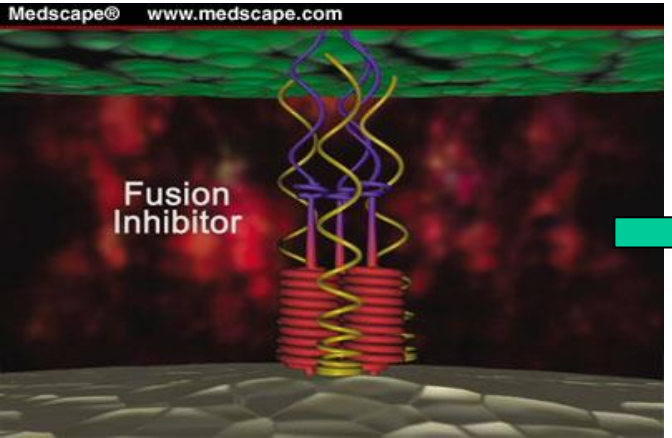

Medscape® www.medscape.com
Fusion
And
Cell Entry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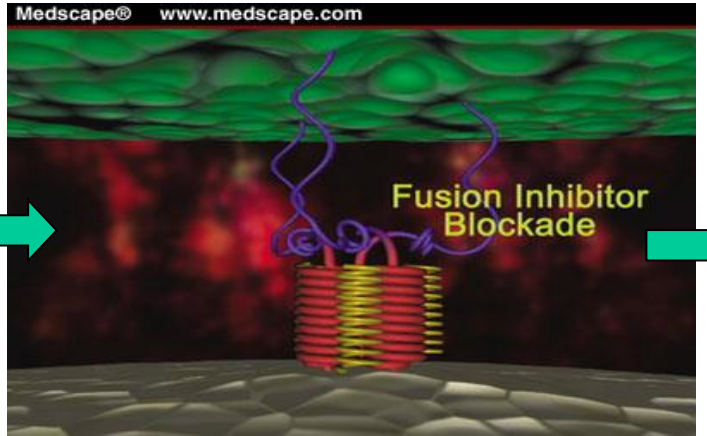
Fusion
Inhibitor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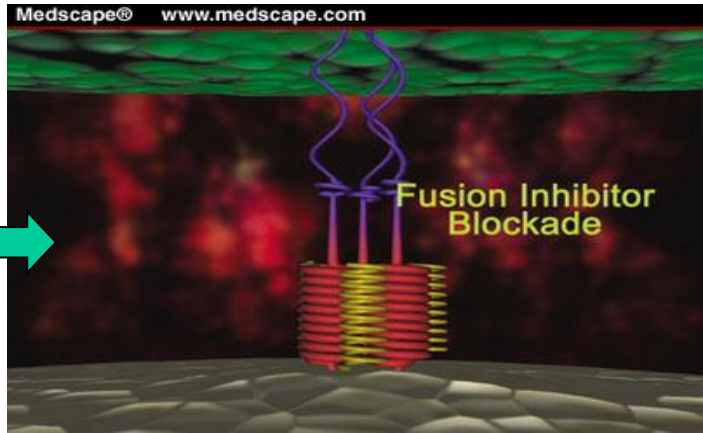
Fusion Inhibitor
Blockade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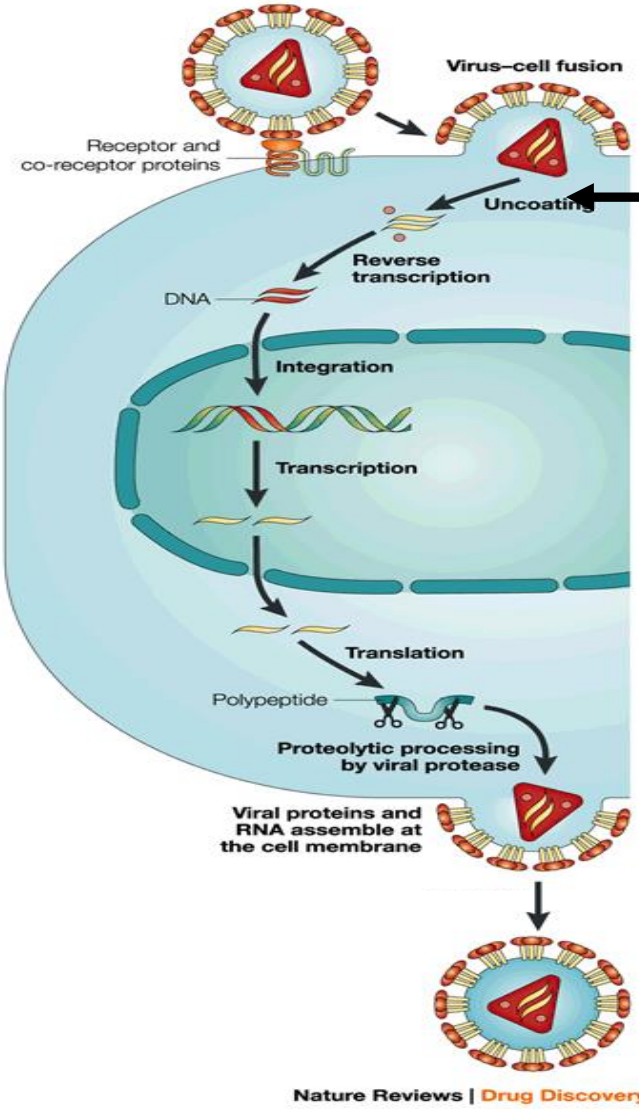
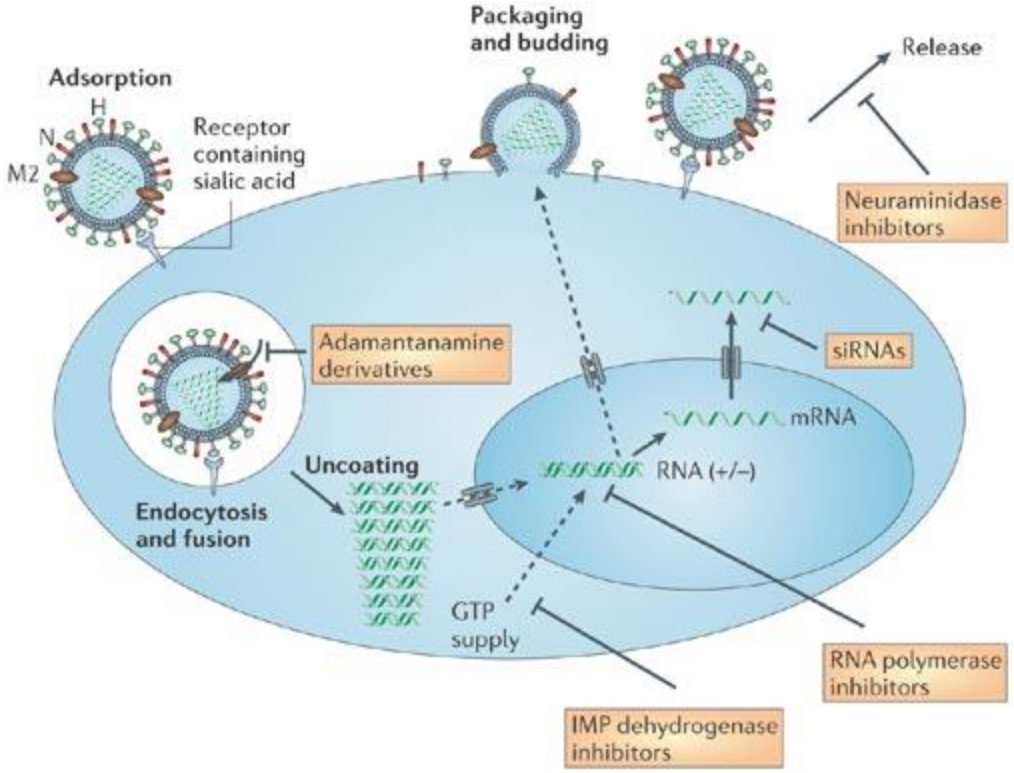
Fusion Inhibitor
Blockade

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

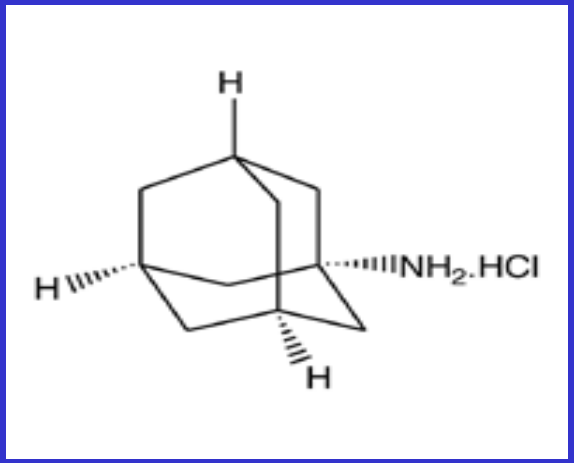


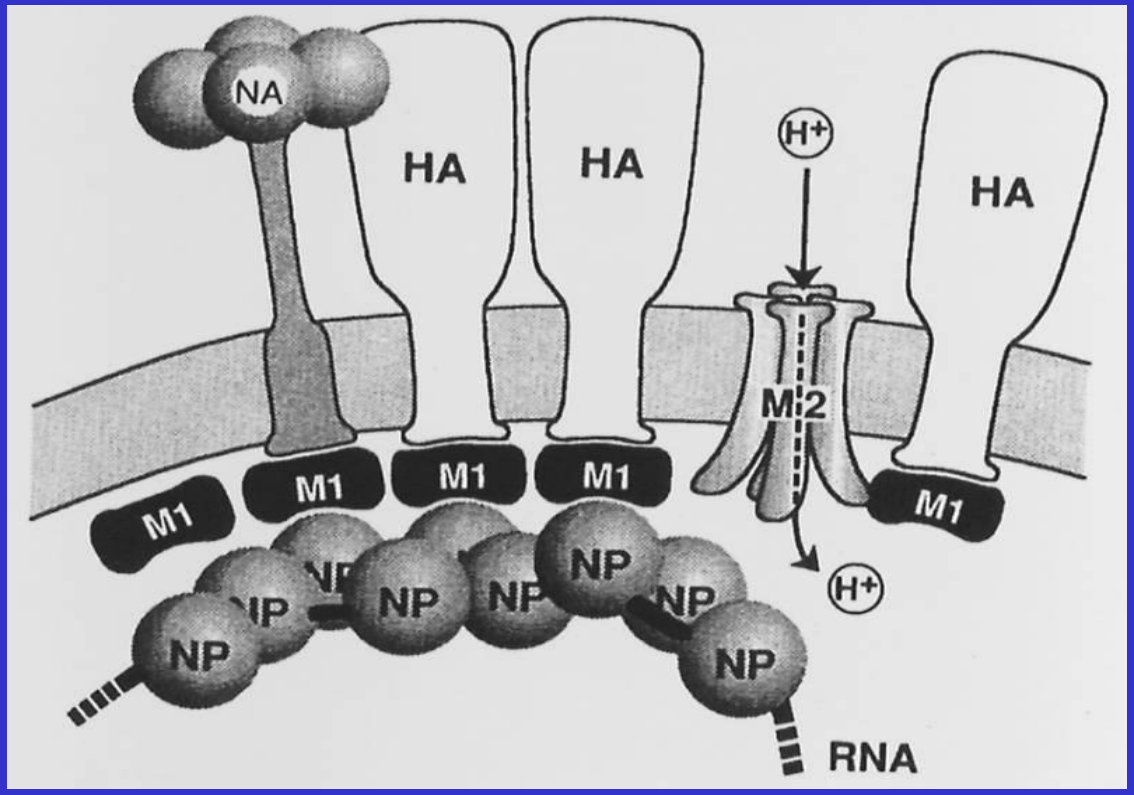
AMANTADINE, RIMANTADINE

Inhibition of the influenza-virus replication cycle by antiviral agents

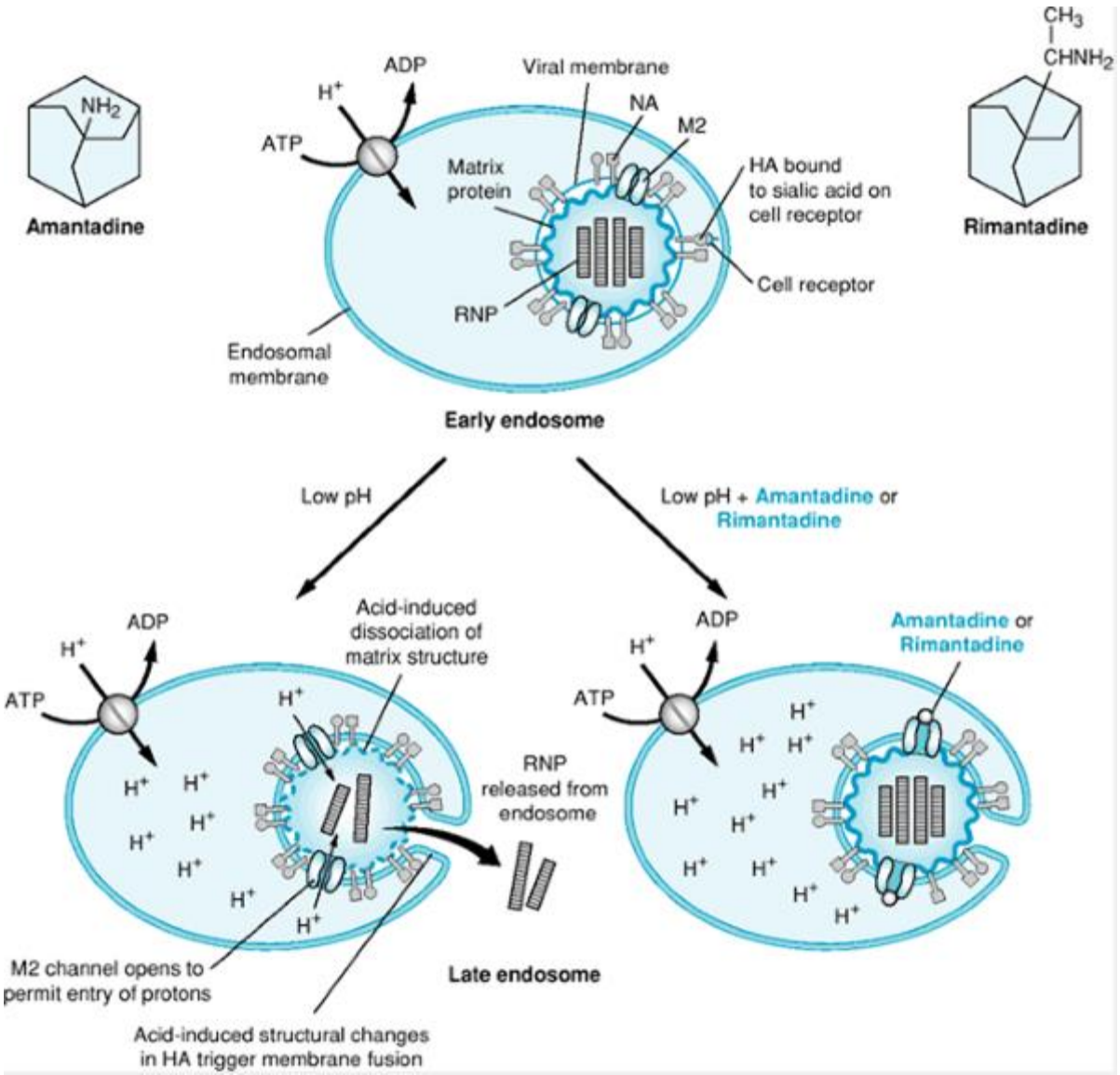


AMANTADINE

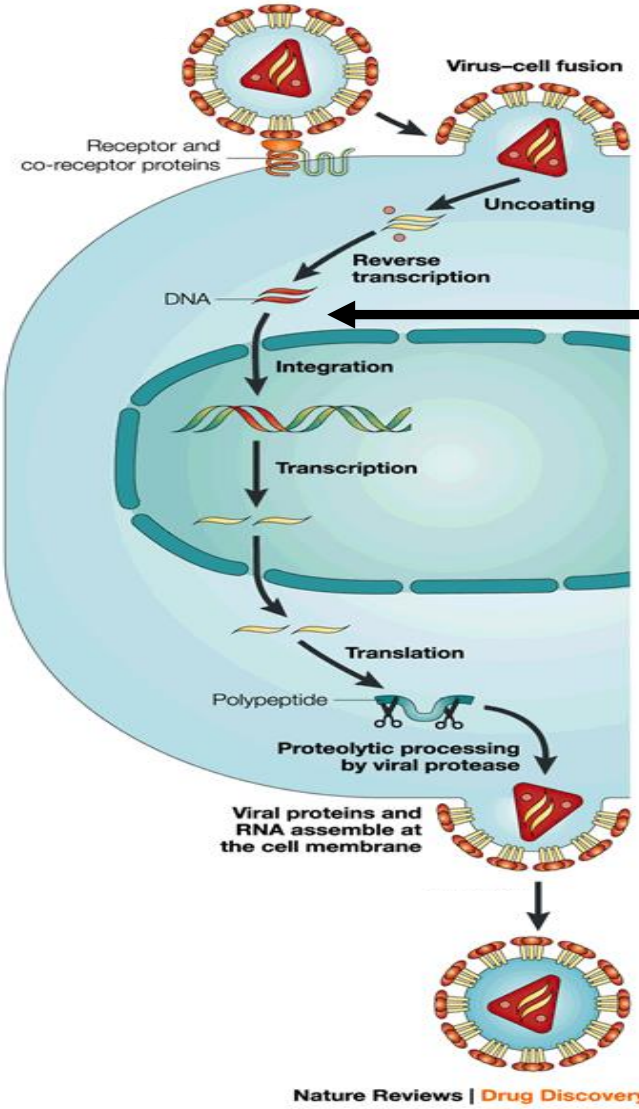




Model for uncoating of influenza A virus and effect of amantadine or rimantadine.

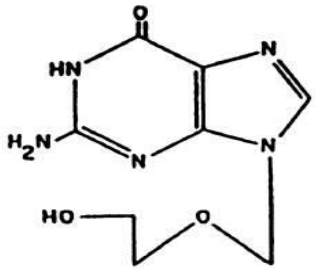


THE VIRAL LIFE CYCLE (EXEMPLIFIED BY HIV) AND TARGET FOR ANTIVIRAL THERAPY

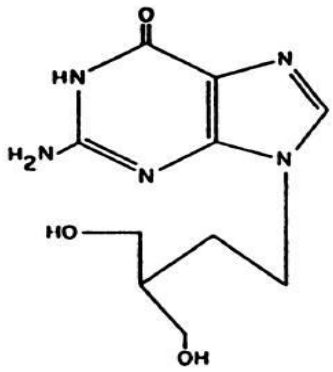


AZT, d4t, 3TC, ABC, ddI, ddC, FTC, ACV, PCV, FCV, VGCV, HPMPC, TFT, PMEA, PMPA, BVDU, GCV, Foscarnet, DLV, EFV, NVP

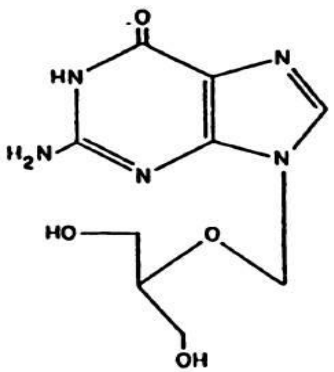
NUCLEOSIDE ANALOGUES



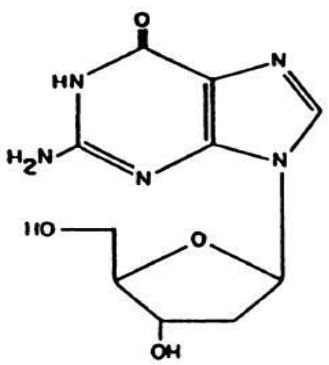
ACYCLOVIR



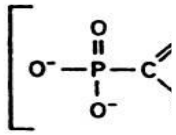
PENCICLOVIR



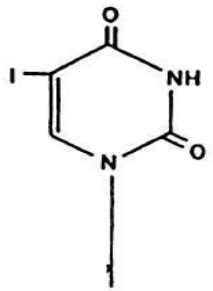
GANCICLOVIR



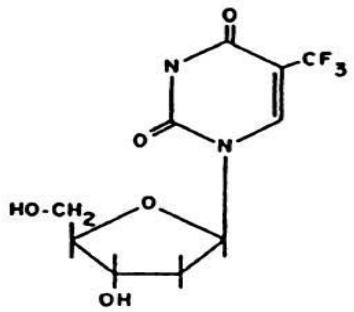
DEOXYGUANOSINE



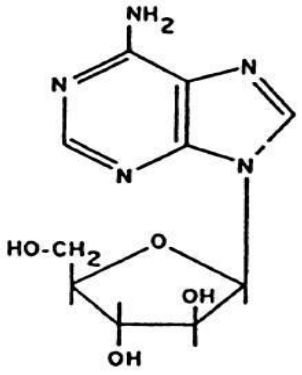
FOSCARNET



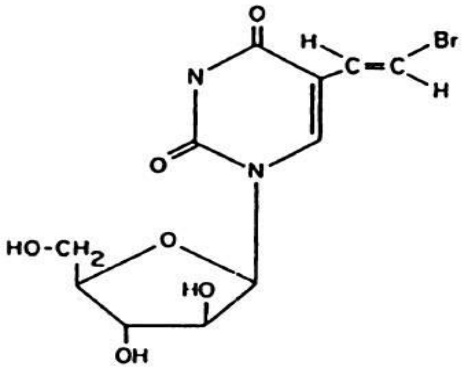
IDOXURIDINE



TRIFLUOROTHYMIDINE

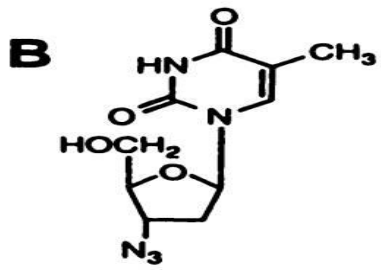


VIDARABINE

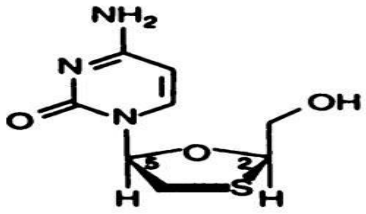


SORIVUDINE

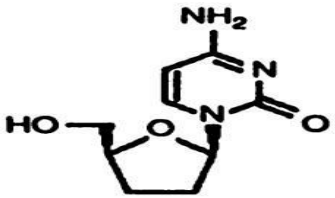
MAIN NUCLEOSIDE ANALOGUES USED TO TREAT HIV INFECTION



Zidovudine



Lamivudine



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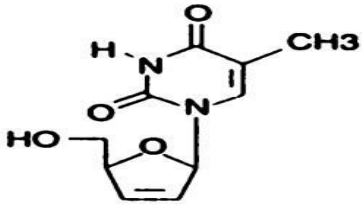
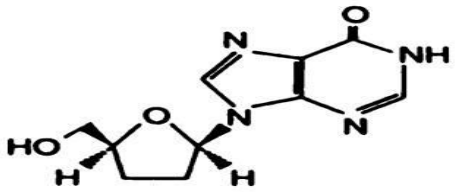
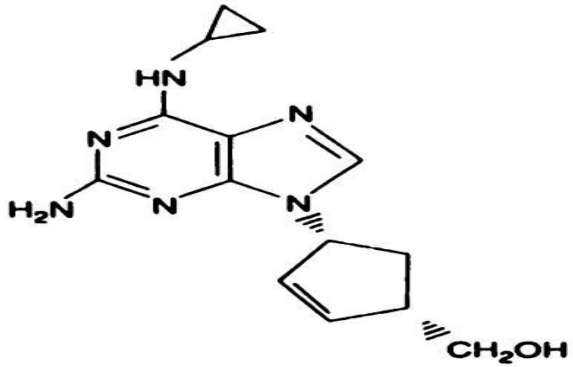


Stavudine

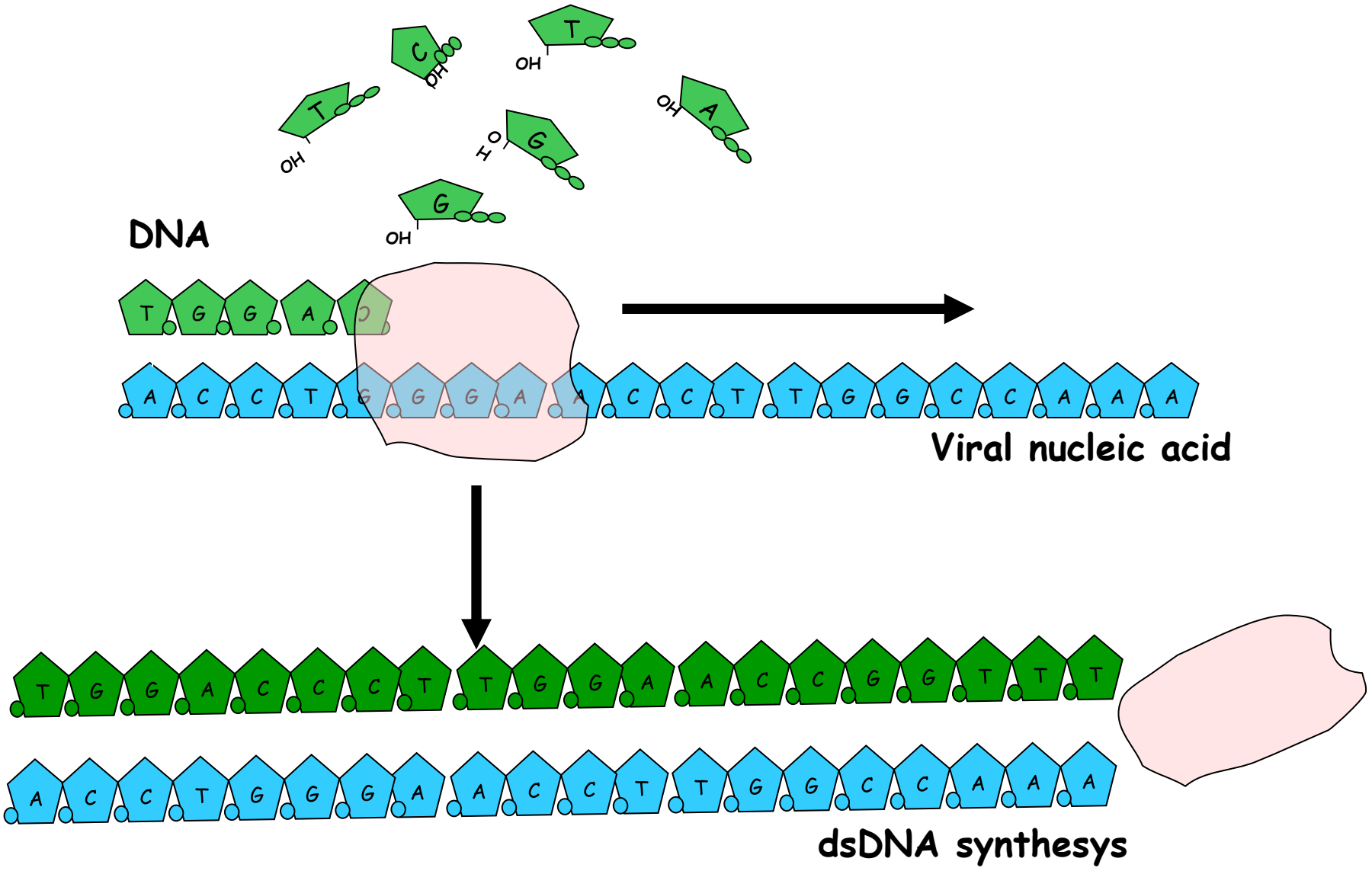


Didanosine

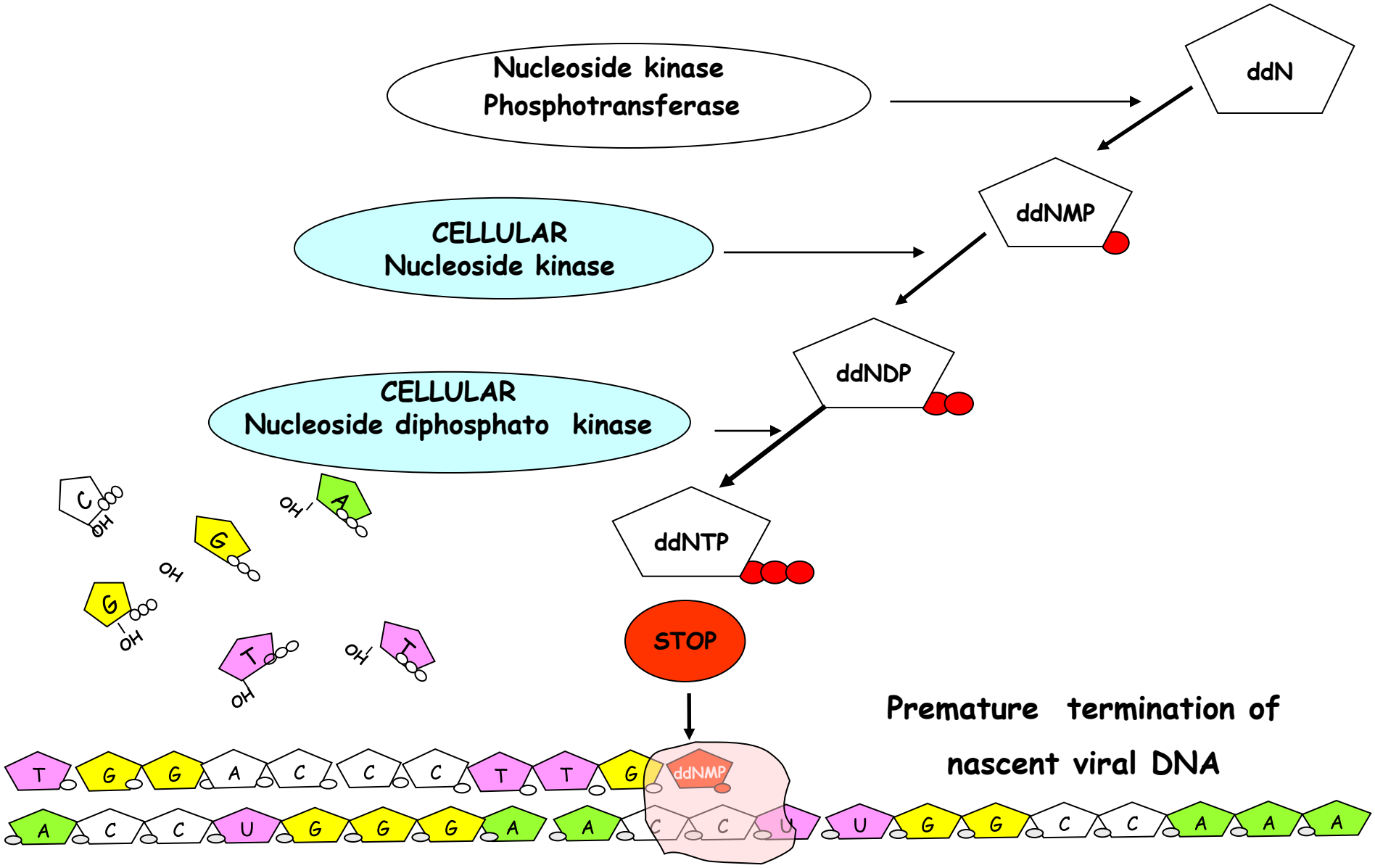


Abacavir

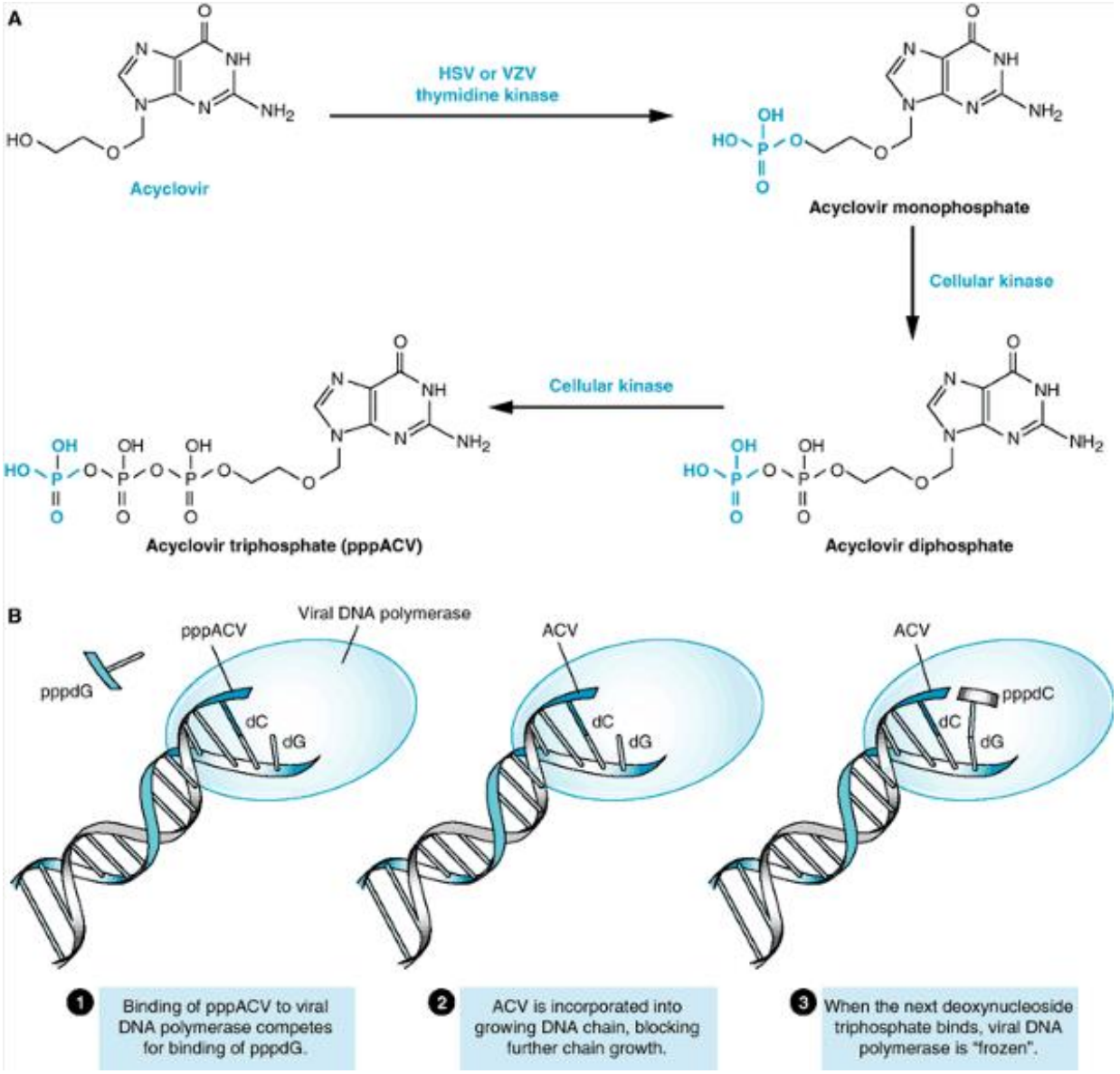
MECHANISM OF ACTION OF NUCLEOSIDE ANALOGS



MECHANISM OF ACTION OF NUCLEOSIDE ANALOGS

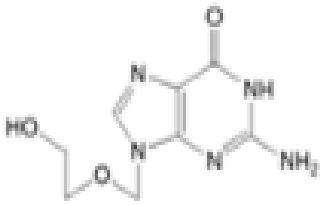


Mechanism of action of acyclovir (ACV)

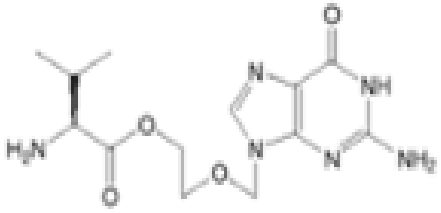


Fields Virology, V ed., Lippincott Williams and Wilkins

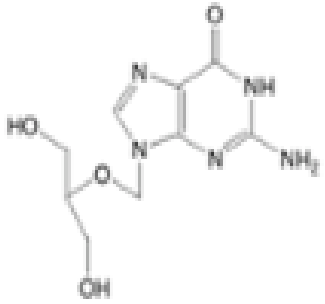
Anti-herpesvirus nucleoside and nucleotide analogues



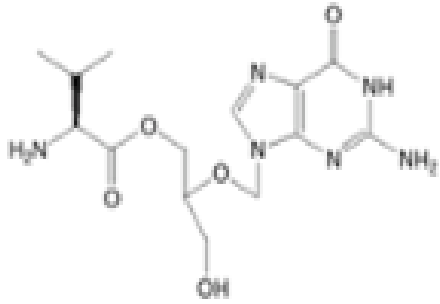
Acyclovir



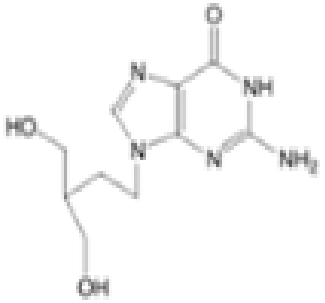
Valacyclovir
(prodrug)



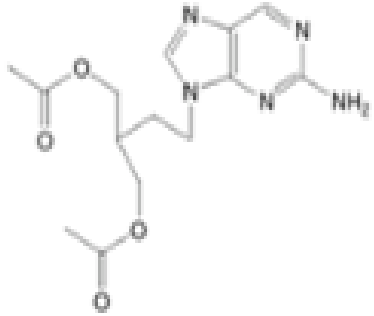
Ganciclovir



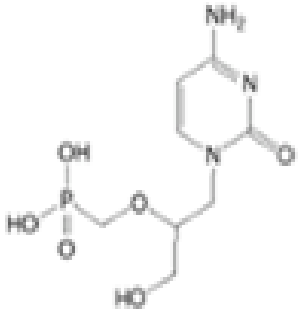
Valganciclovir
(prodrug)



Penciclovir



Famciclovir
(prodrug)



Cidofovir

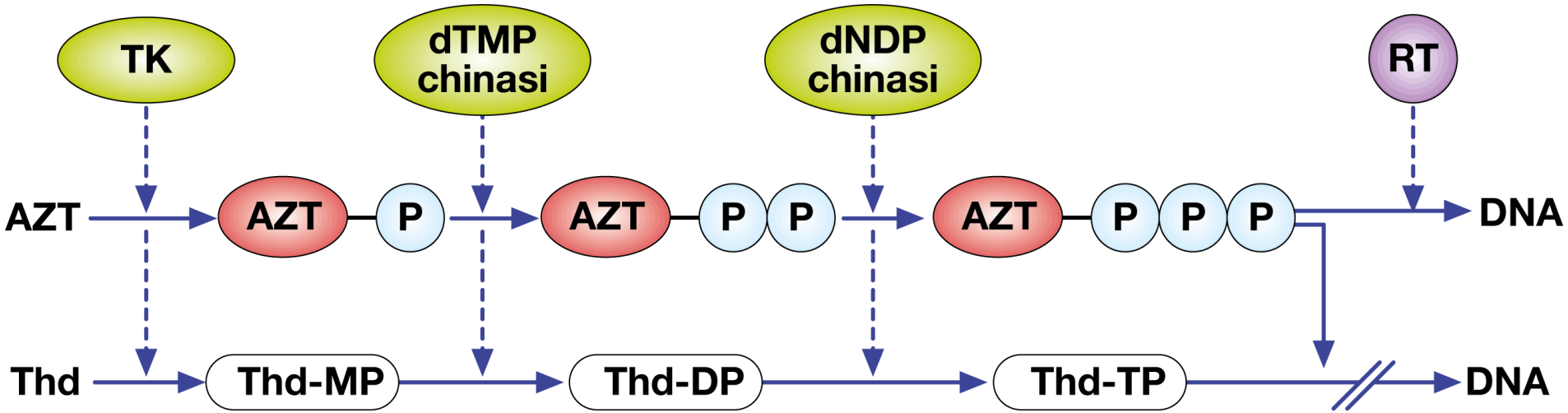
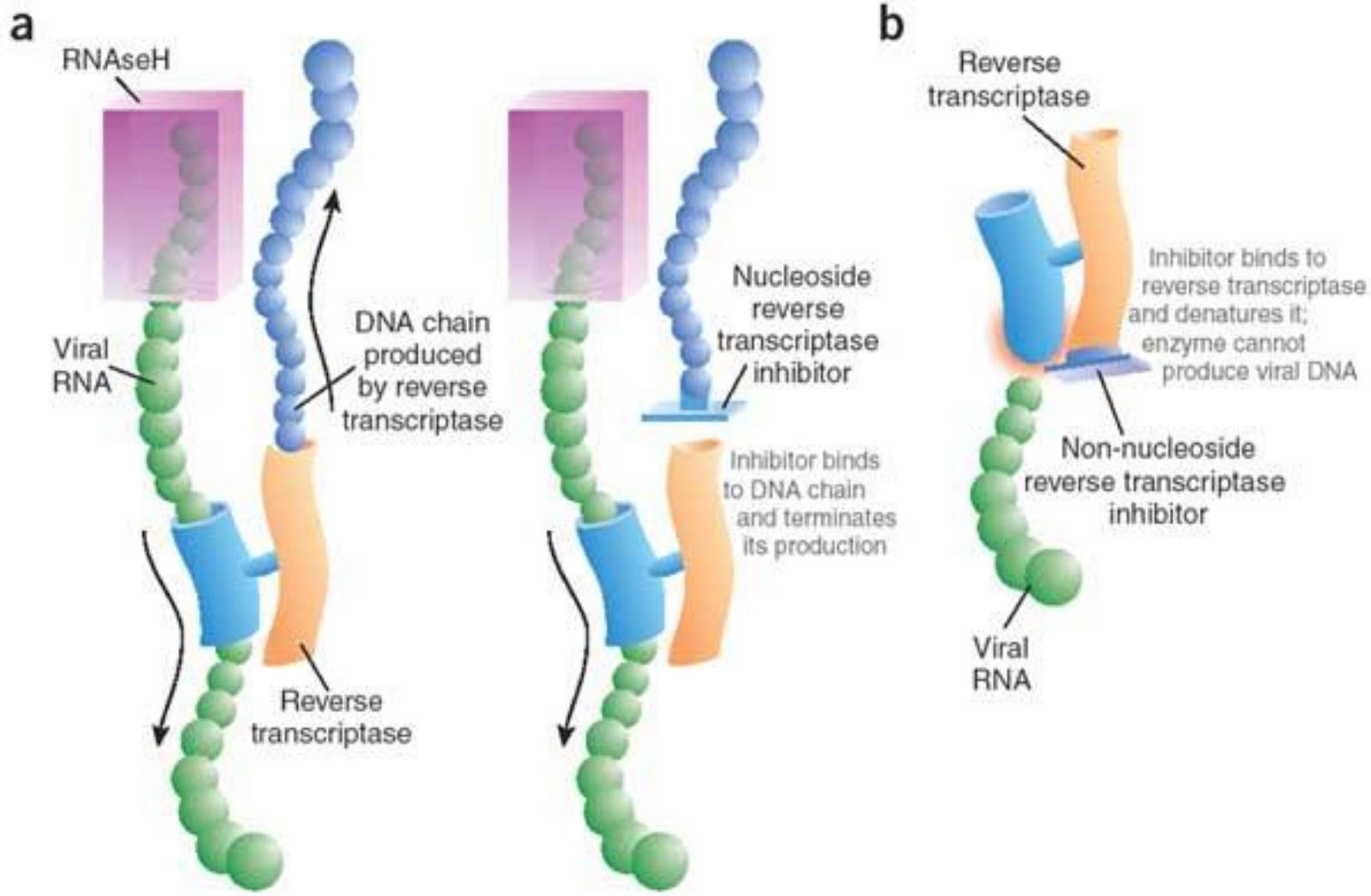


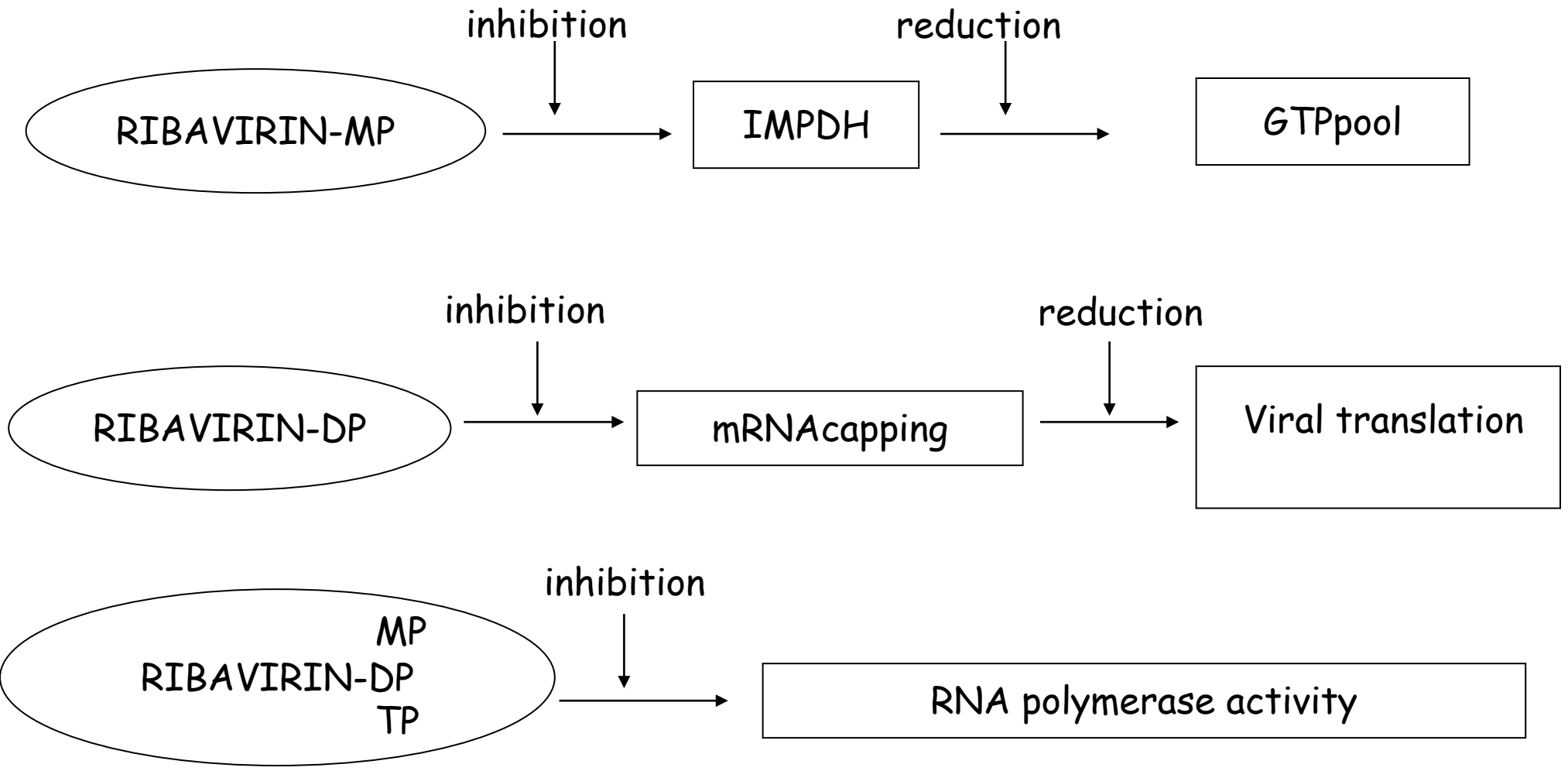
Figura 67.3 Meccanismo d'azione dell'azidotimidina (AZT). Questo composto, per poter esercitare la sua azione antivirale, deve essere fosforilato da chinasi cellulari. La timidina chinasi (TK) cellulare è responsabile della prima fosforilazione, successivamente intervengono la timidilato (dTMP) chinasi e la nucleotide (dNDP) chinasi. Le forme trifosfato possono così competere con la timidina trifosfato (Thd-TP).

978-88-08-18705-5

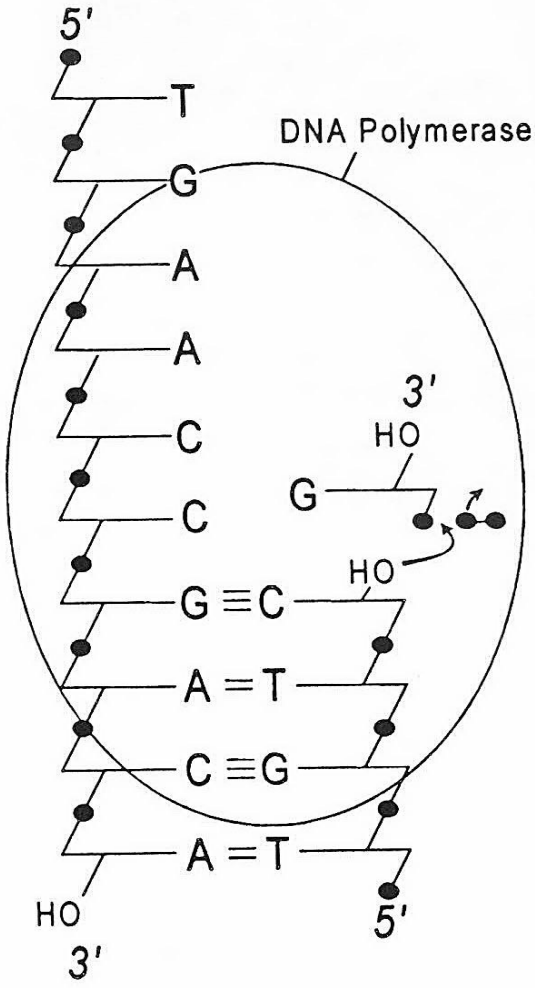
NRTIS AND NNRTIs: MECHANISMS OF ACTION



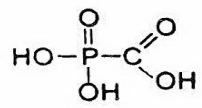
MECHANISMS OF ACTION OF RIBAVIRIN



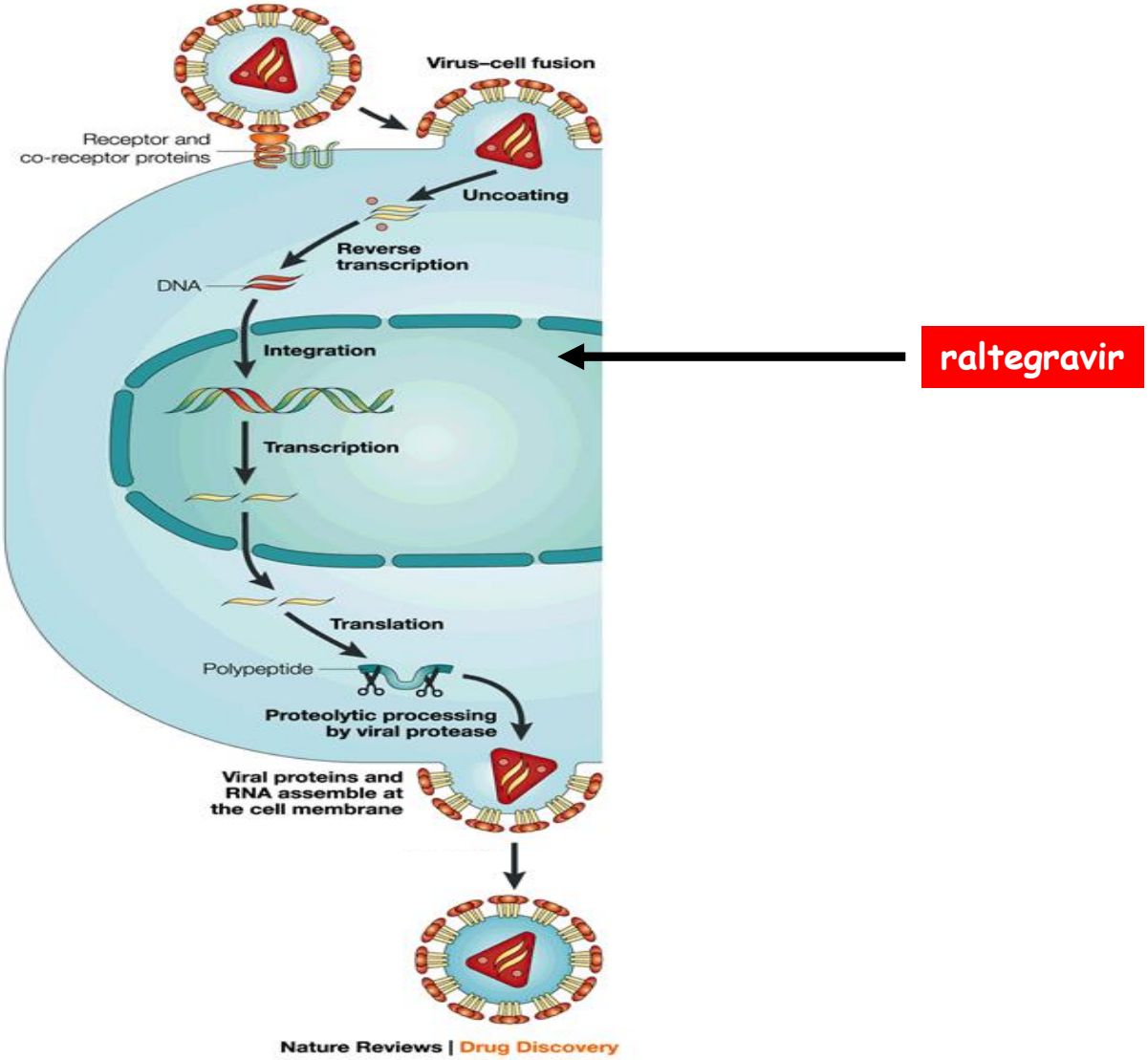
Non-nucleoside Inhibitors of Herpesvirus DNA Polymerase: Foscarnet

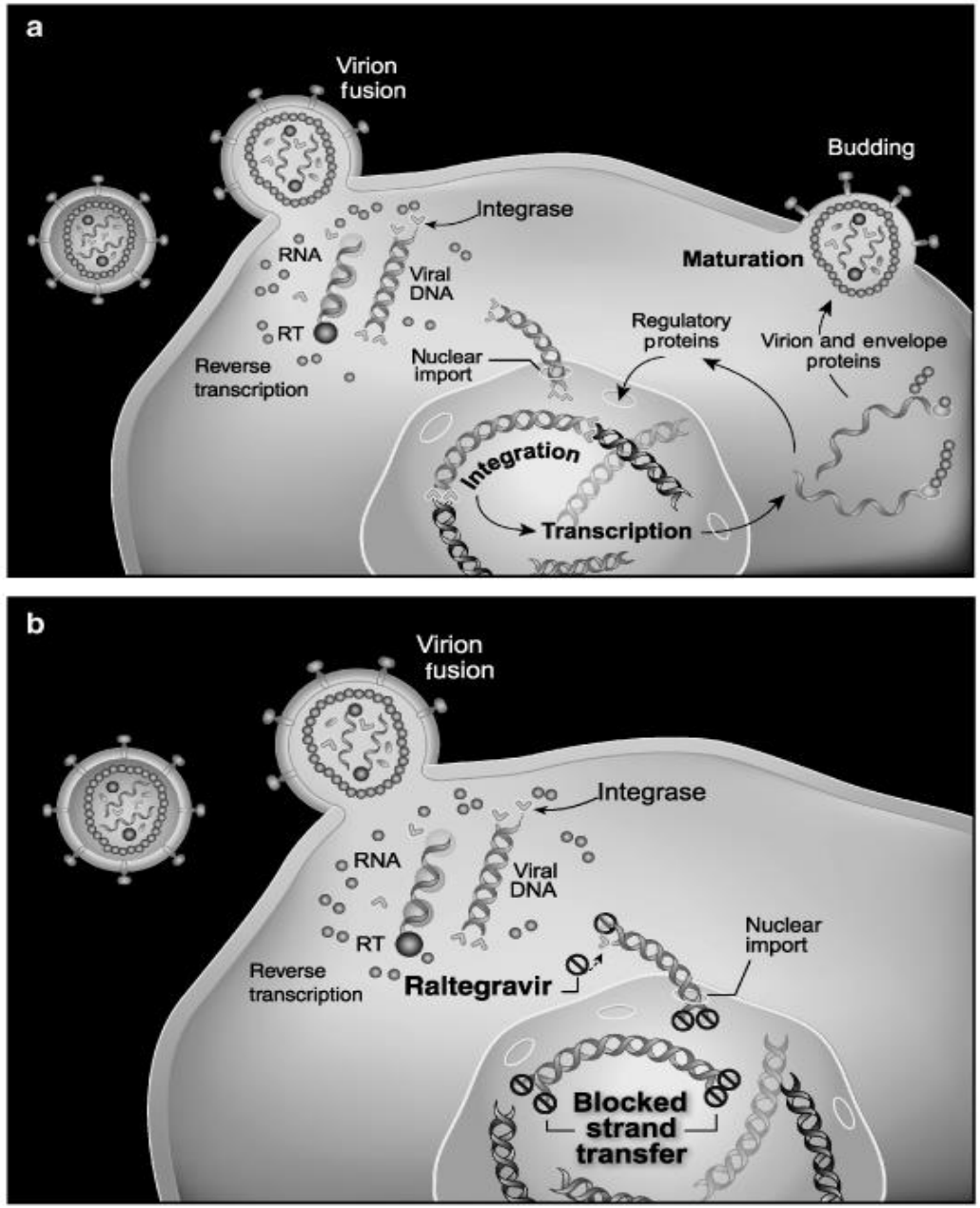


Foscarnet

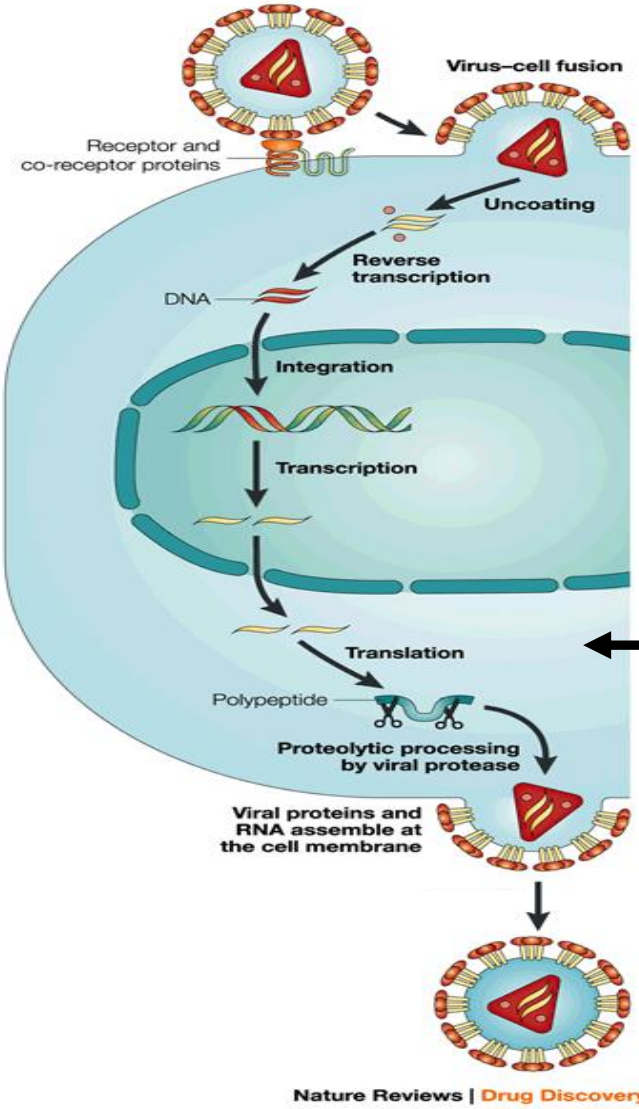


THE VIRAL LIFE CYCLE (EXEMPLIFIED BY HIV) AND TARGET FOR ANTIVIRAL THERAPY




a
Virion
fusion
Budding
Integrase
RNA
Viral
DNA
Maturation
RT
Reverse
transcription
Nuclear
import
Regulatory
proteins
Virion and envelope
proteins
Integration
Transcription
b
Virion
fusion
Integrase
RNA
Viral
DNA
RT
Reverse
transcription
Raltegravir
Nuclear
import
Blocked
strand
transfer

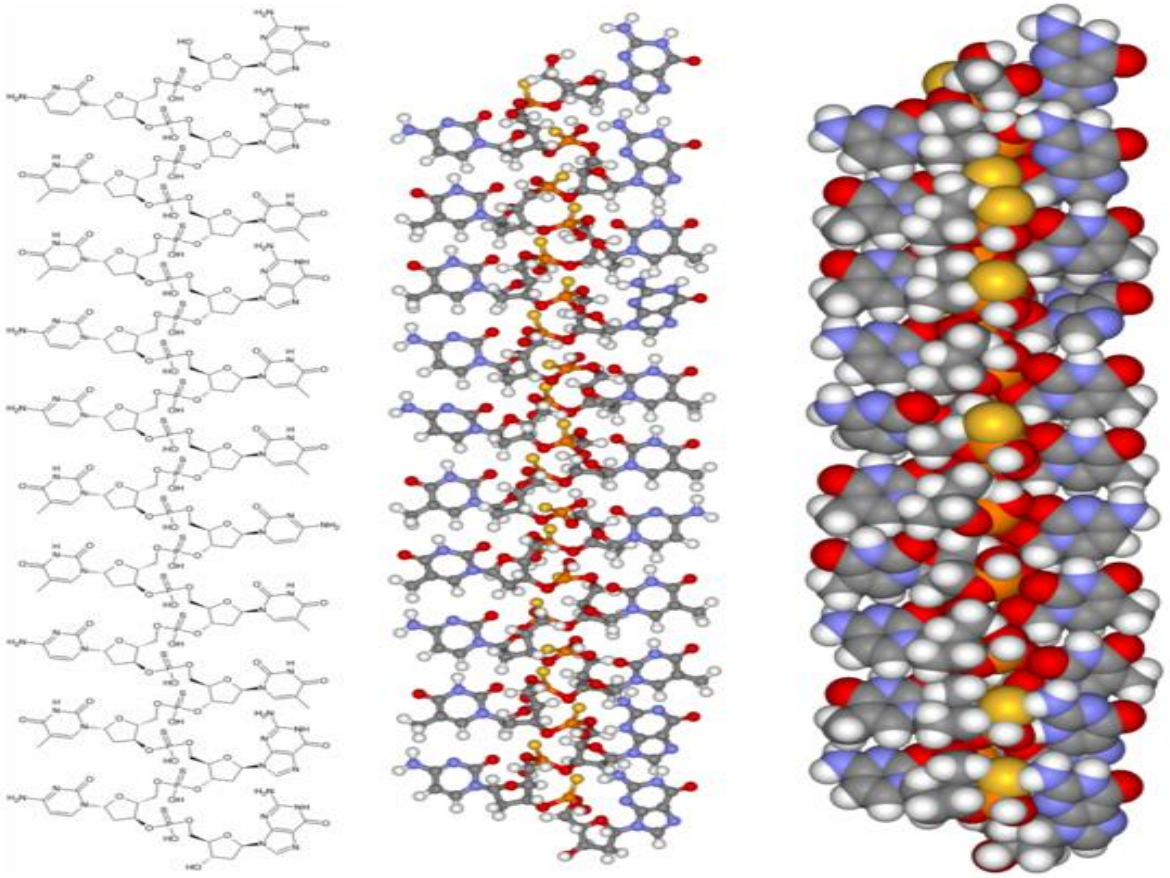
THE VIRAL LIFE CYCLE (EXEMPLIFIED BY HIV) AND TARGET FOR ANTIVIRAL THERAPY



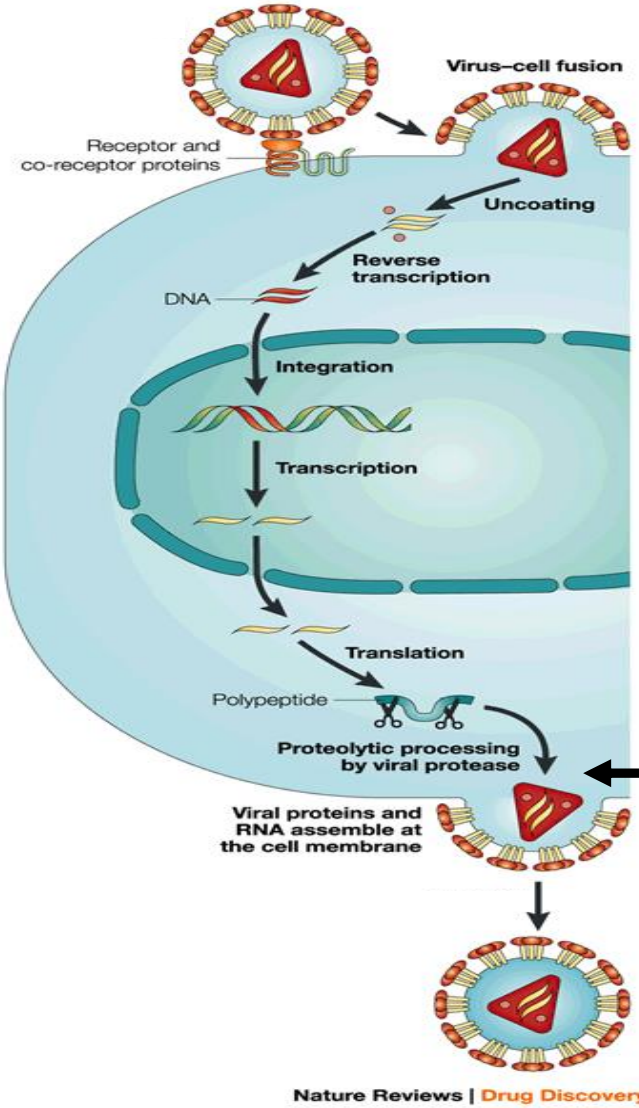
fomivirsen

Anti mRNA compound

Fomivirsen



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



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

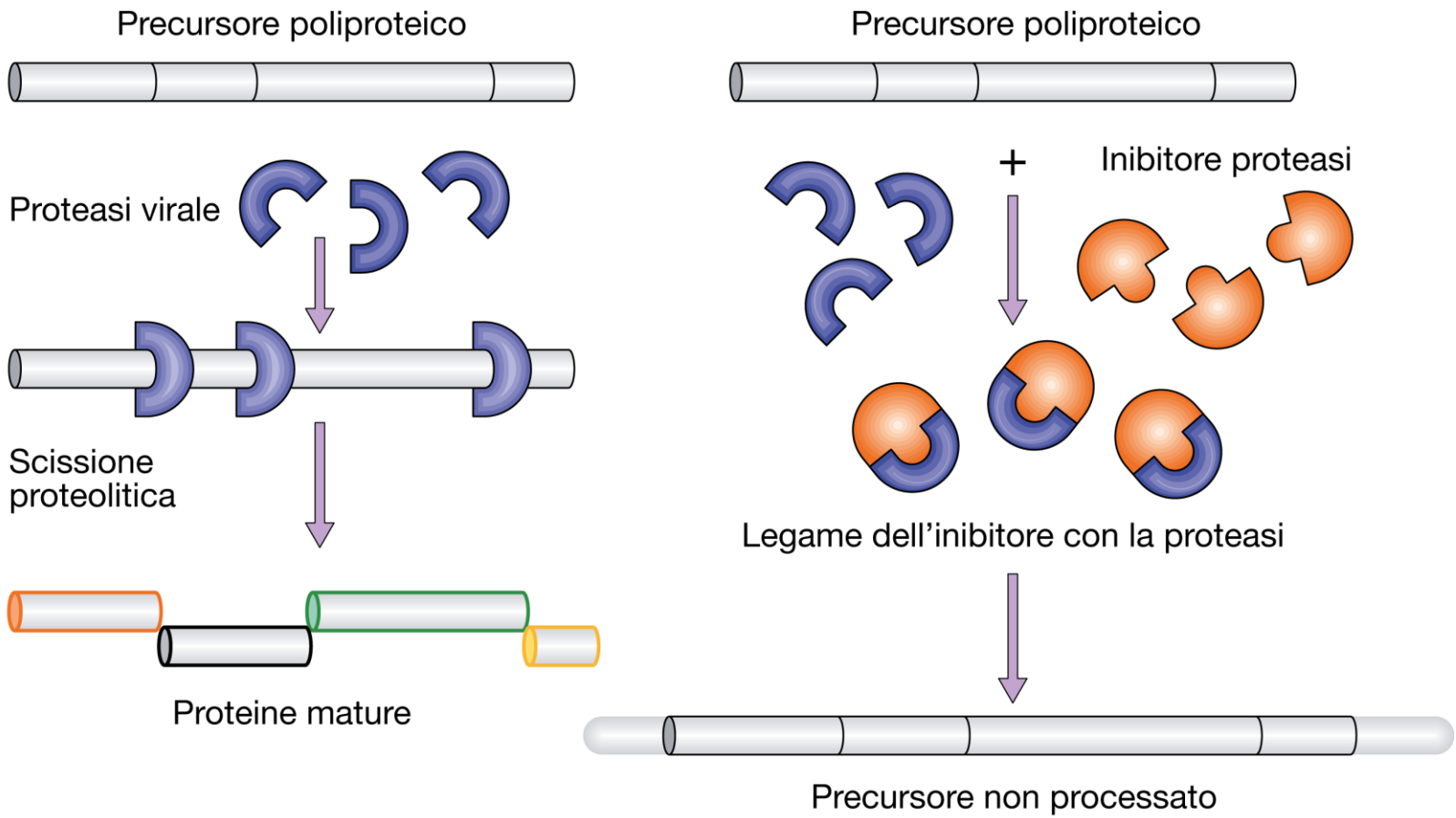
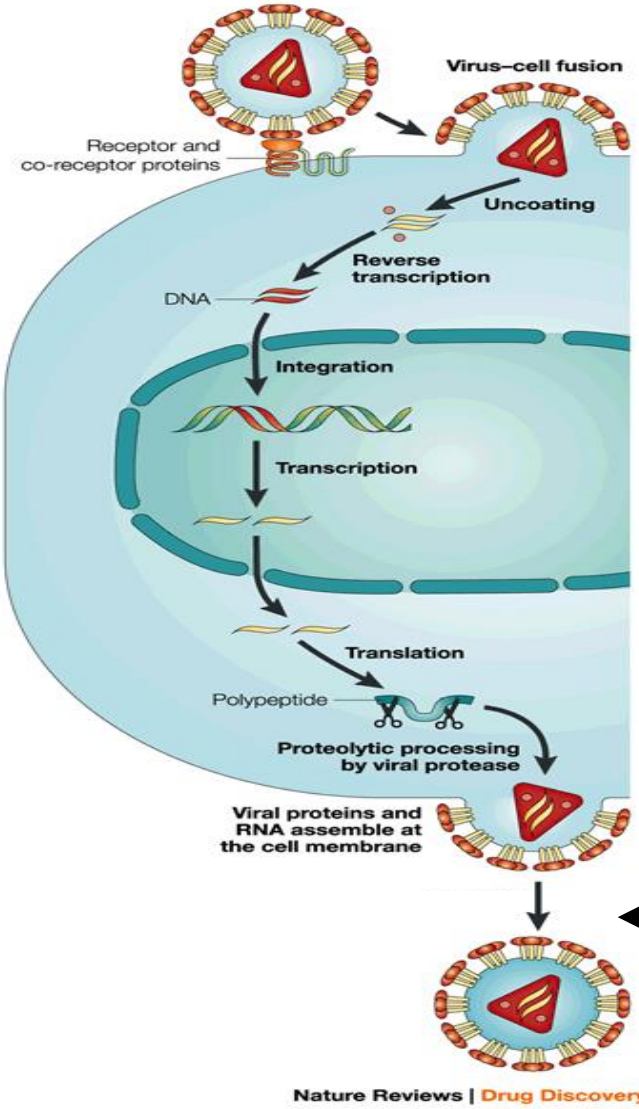


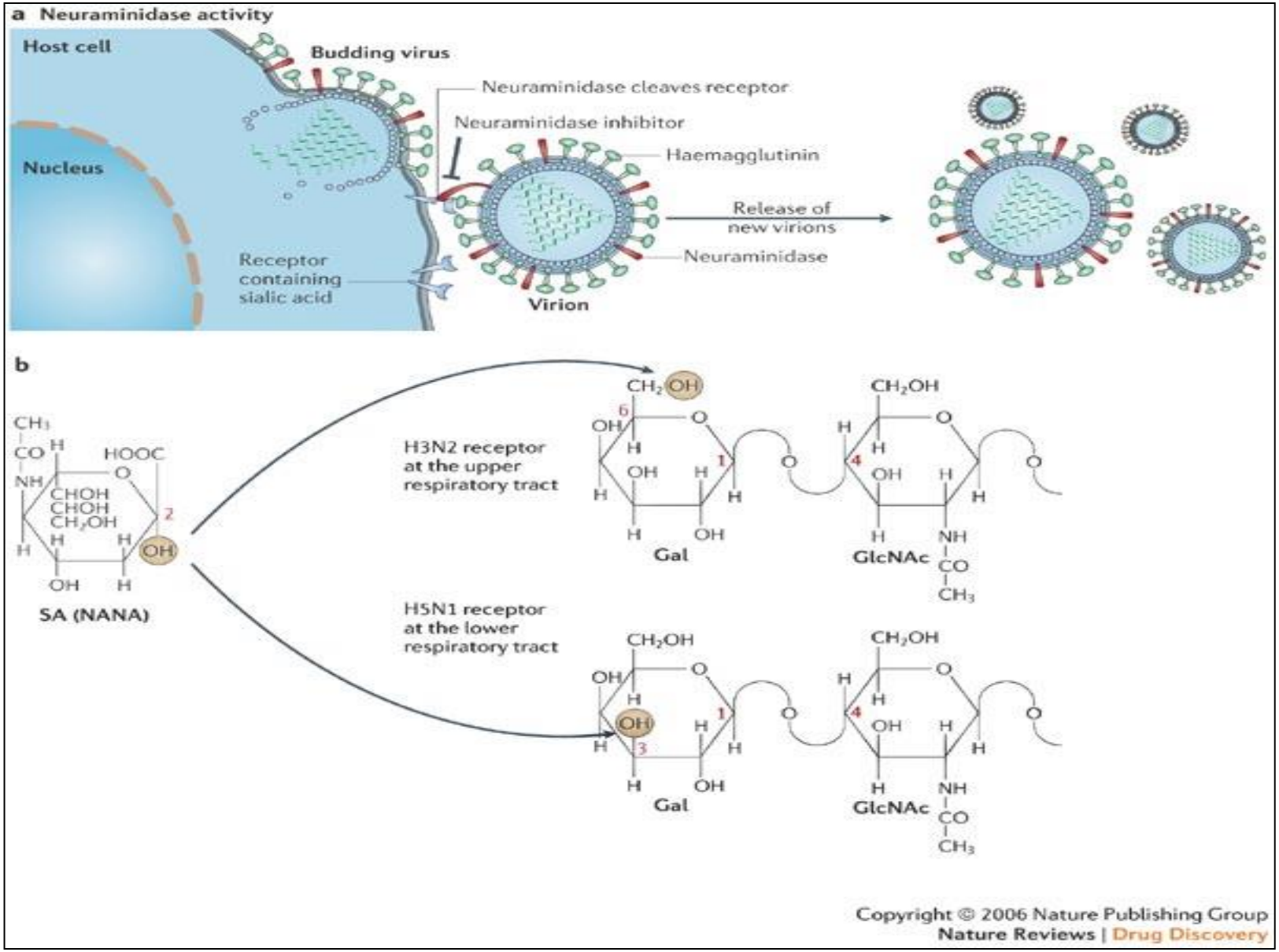
Figura 67.4 Meccanismo di azione degli inibitori della proteasi. La proteasi virale è responsabile della scissione proteolitica del precursore poliproteico. Gli inibitori di questo enzima impediscono la formazione delle proteine mature.

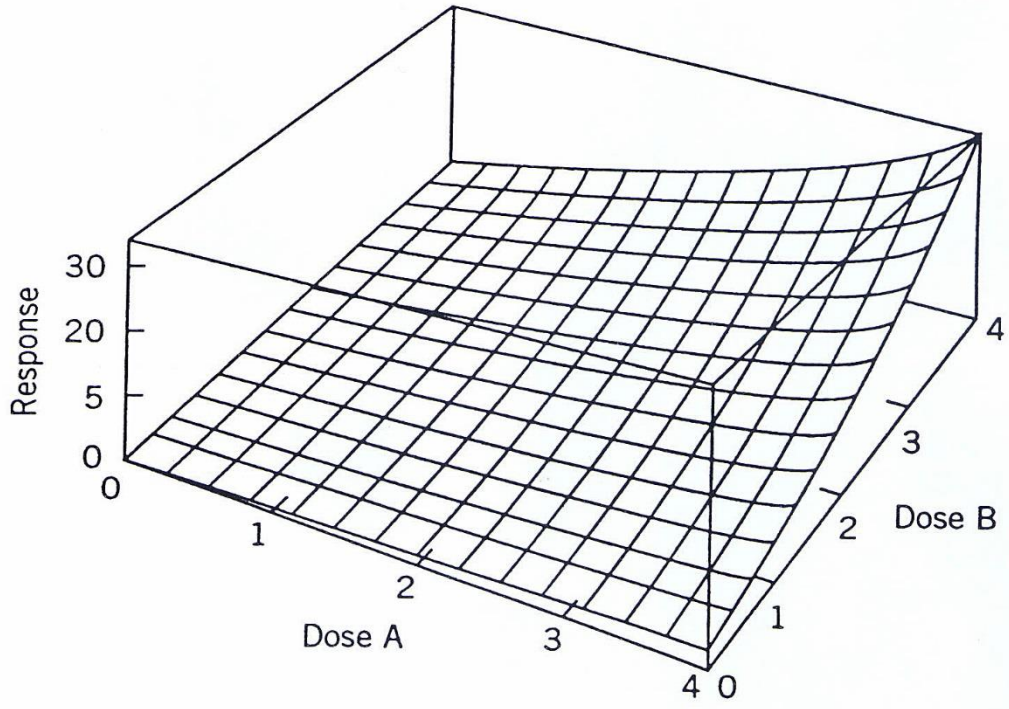
THE VIRAL LIFE CYCLE (EXEMPLIFIED BY HIV) AND TARGET FOR ANTIVIRAL THERAPY



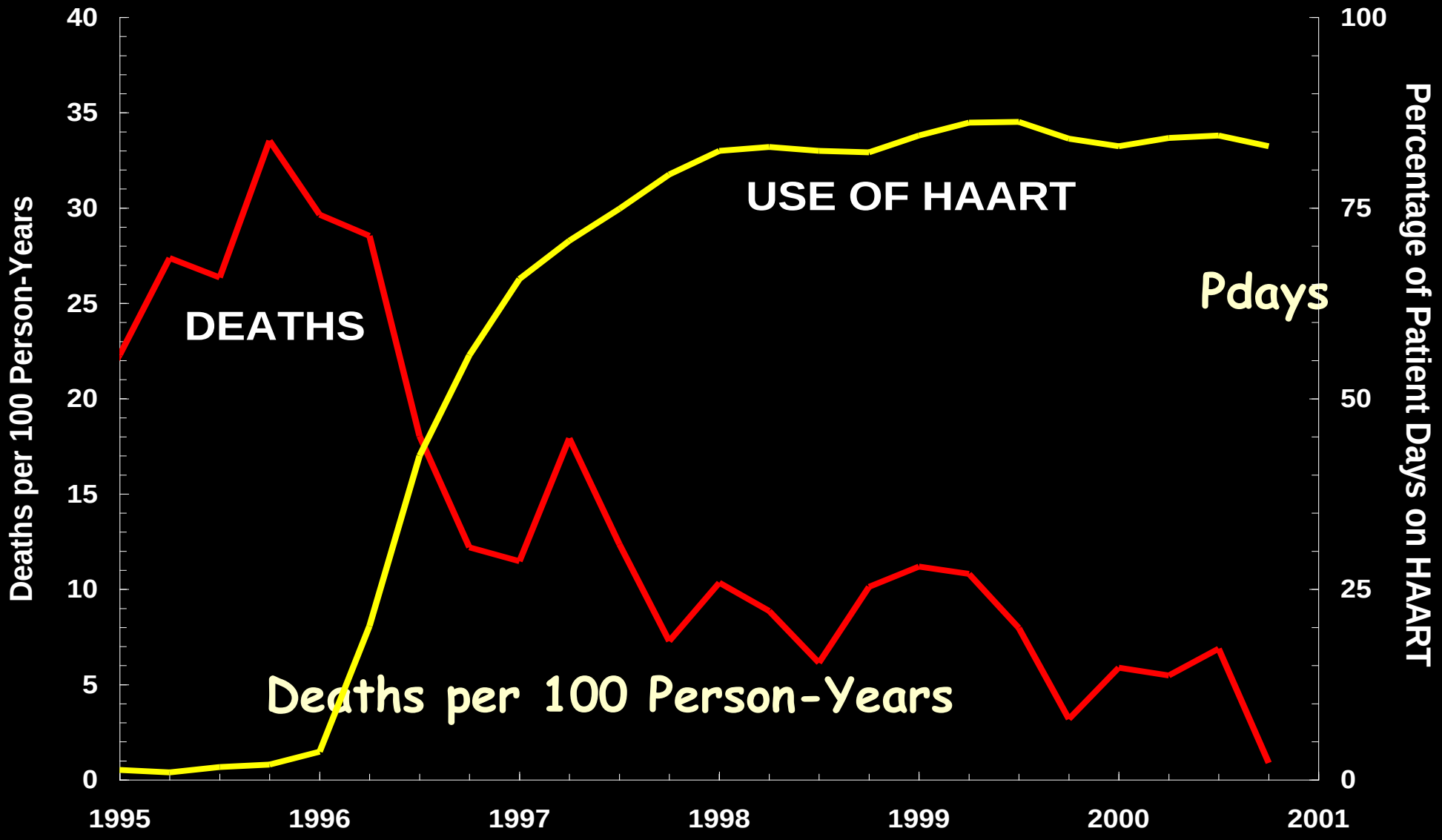
OSELTAMIVIR
ZANAMIVIR

Viral neuraminidase inhibition




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

Table 2: Role of DAA in HCV guidelines

Drug regimen	HCV genotype
Sofosbuvir/Ledipasvir +/-Ribavirin	Genotypes 1, 4, 5, and 6
Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir +/- Ribavirin:	Genotype 1
Sofosbuvir + Simeprevir +/- Ribavirin:	Genotypes 1 and 4
Sofosbuvir + Daclatasvir +/- Ribavirin:	All genotypes
Paritaprevir/Ritonavir/ombitasvir +/- Ribavirin:	Genotype 4
Sofosbuvir + Ribavirin	Genotypes 2 and 3

HCV: hepatitis C virus; DDA: direct acting antiviral agent.

INTERFERONs

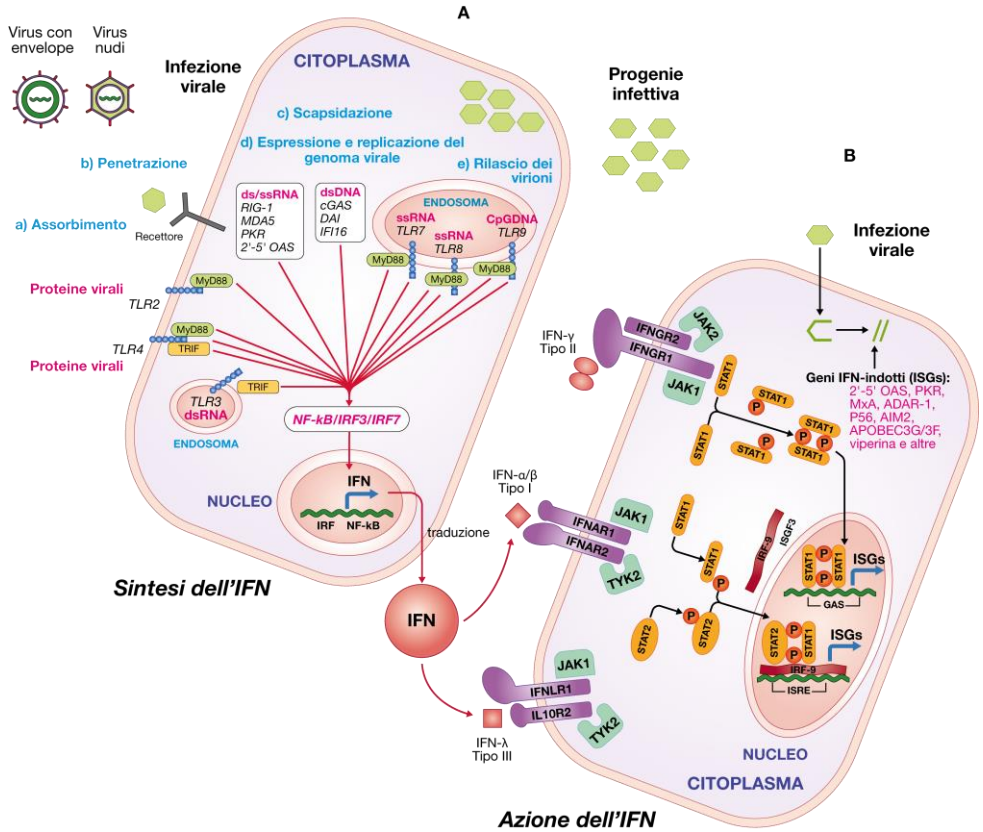


Figura 68.1 Produzione e meccanismo d'azione antivirale dell'IFN. A. Produzione dell'interferon (IFN) in risposta a una infezione virale. I PRRs coinvolti nella sintesi di IFN di tipo I/III durante un'infezione virale sono i TLR2/4, localizzati sulla membrana plasmatica, i TLR3/7/8/9, espressi sulle membrane degli endosomi e alcuni sensori citoplasmatici di acidi nucleici (cGAS, DAI, IFI16, RIG-1, MDA5, PKR, 2'5'OAS). La sintesi di IFN-α/β e di IFN-λs avviene in seguito al riconoscimento di proteine virali (TLR2 e TLR4), di polimeri di RNA a doppia (TLR3, RIG-1, MDA5, PKR, 2'5' OAS) o a singola elica (TLR7/8 e RIG-1), e di molecole di DNA (TLR9, cGAS, DAI, IFI16) prodotte durante il ciclo vitale del virus. Il signalling intracellulare, diversificato a seconda del PRR stimolato, porta all'attivazione di fattori di trascrizione (ad es. NF-κB, IRF7 e IRF3), che traslocando dal citoplasma al nucleo inducono la sintesi di numerosi mRNA codificanti citochine e IFNs. Mentre gli IFN di tipo I/III vengono sintetizzati dalla cellula dopo il legame di proteine o acidi nucleici virali ai PRRs, l'IFN-γ viene prodotto principalmente dalle cellule NK e dai linfociti T in risposta allo stimolo di microbi, mitogeni, antigeni o citochine. **B. Meccanismo d'azione antivirale dell'IFN.** L'IFN secreto dalle cellule infette si lega a specifici recettori situati sulla membrana plasmatica. Gli IFN di tipo I (α/β) legano un recettore costituito da due proteine strutturalmente correlate (IFNAR1 e IFNAR2), mentre gli IFN di tipo III (IFN-λ1-4) riconoscono un recettore formato da 2 subunità: IL28R o IFNLR1 e IL10R2. Ad entrambi i recettori sono ancorate le proteine Tyk2 e JAK1. Al contrario, l'IFN-γ attiva un recettore costituito da due catene polipeptidiche, IFNGR1 e IFNGR2, associato alle proteine JAK1 e JAK2. Il legame ad alta affinità degli IFN di tipo I-III con i recettori specifici attiva delle vie di trasduzione del segnale che portano alla traslocazione nel nucleo di complessi proteici che stimolano la trascrizione di centinaia di geni IFN-indotti (ISGs, *IFN stimulated gene*s) in seguito al legame a sequenze denominate ISRE (*IFN-stimulated response element*, per gli IFN α/β e IFNλs), o GAS (*IFN-gamma-activated sequence*, per l'IFN-γ).

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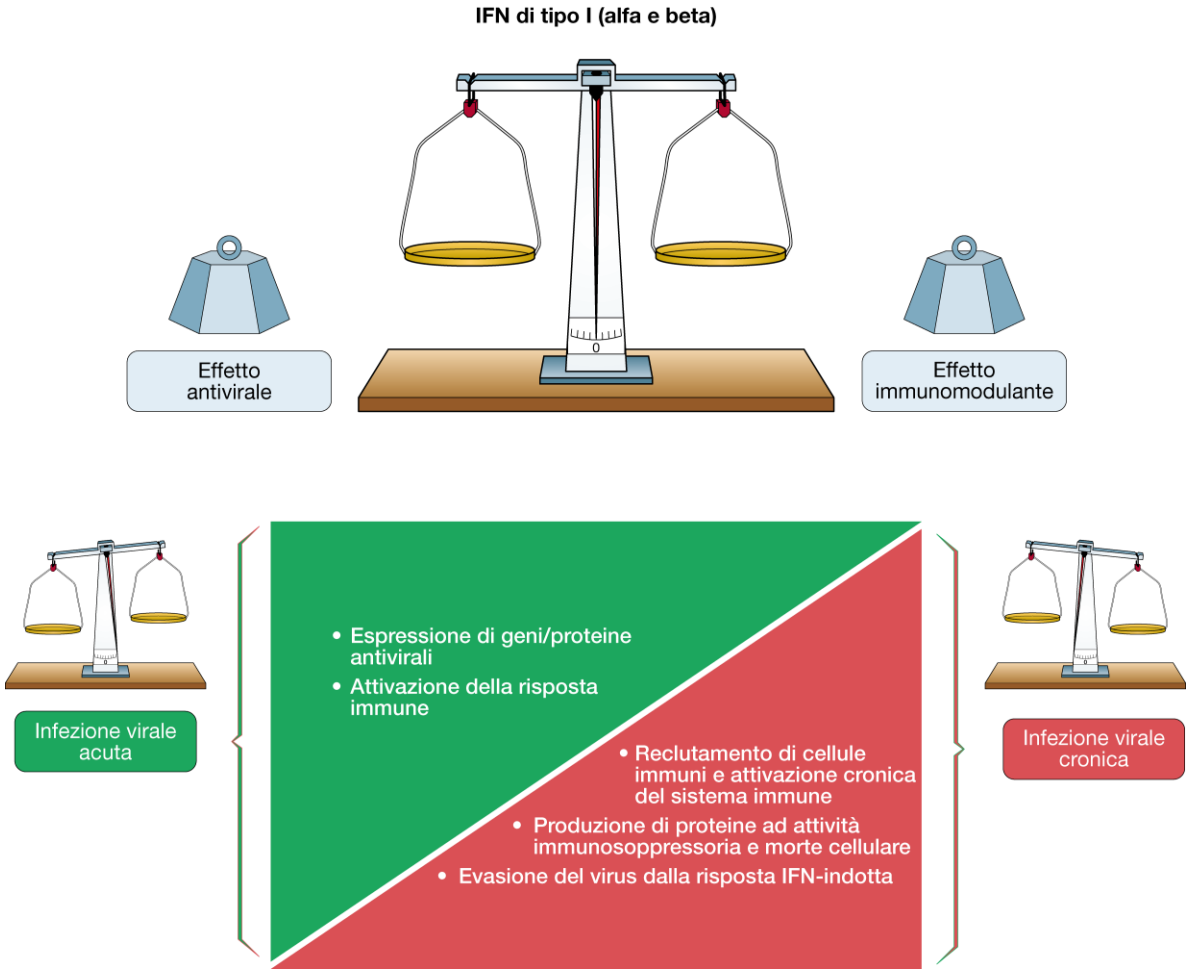


Figura 68.2 L'azione dell'IFN di tipo I (che comprende anche i più noti IFN alfa e beta) nei confronti delle infezioni virali. *Vedi* testo per maggiori infomazioni.

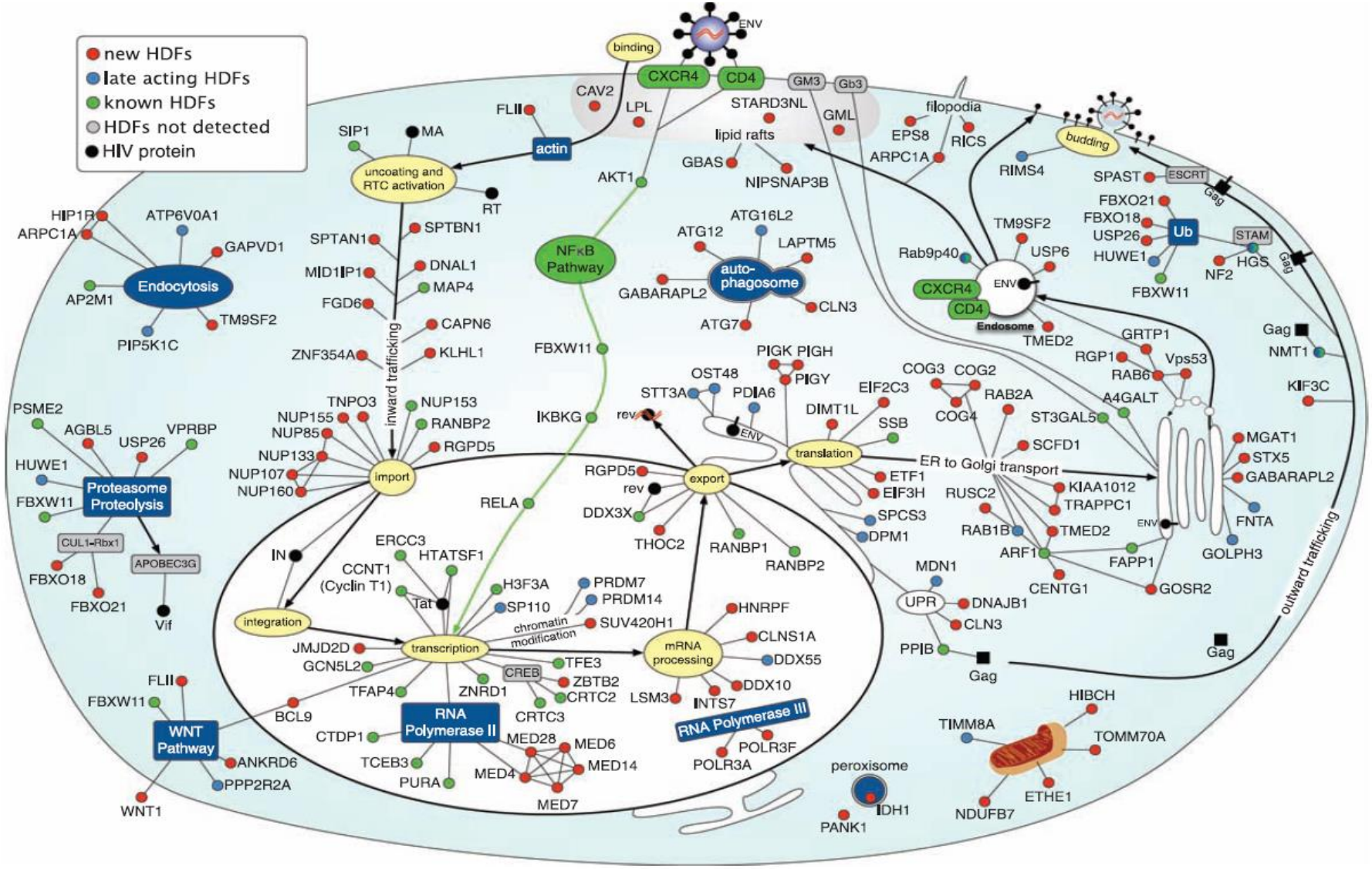
978-88-08-18705-5

New issues in antiviral therapy

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

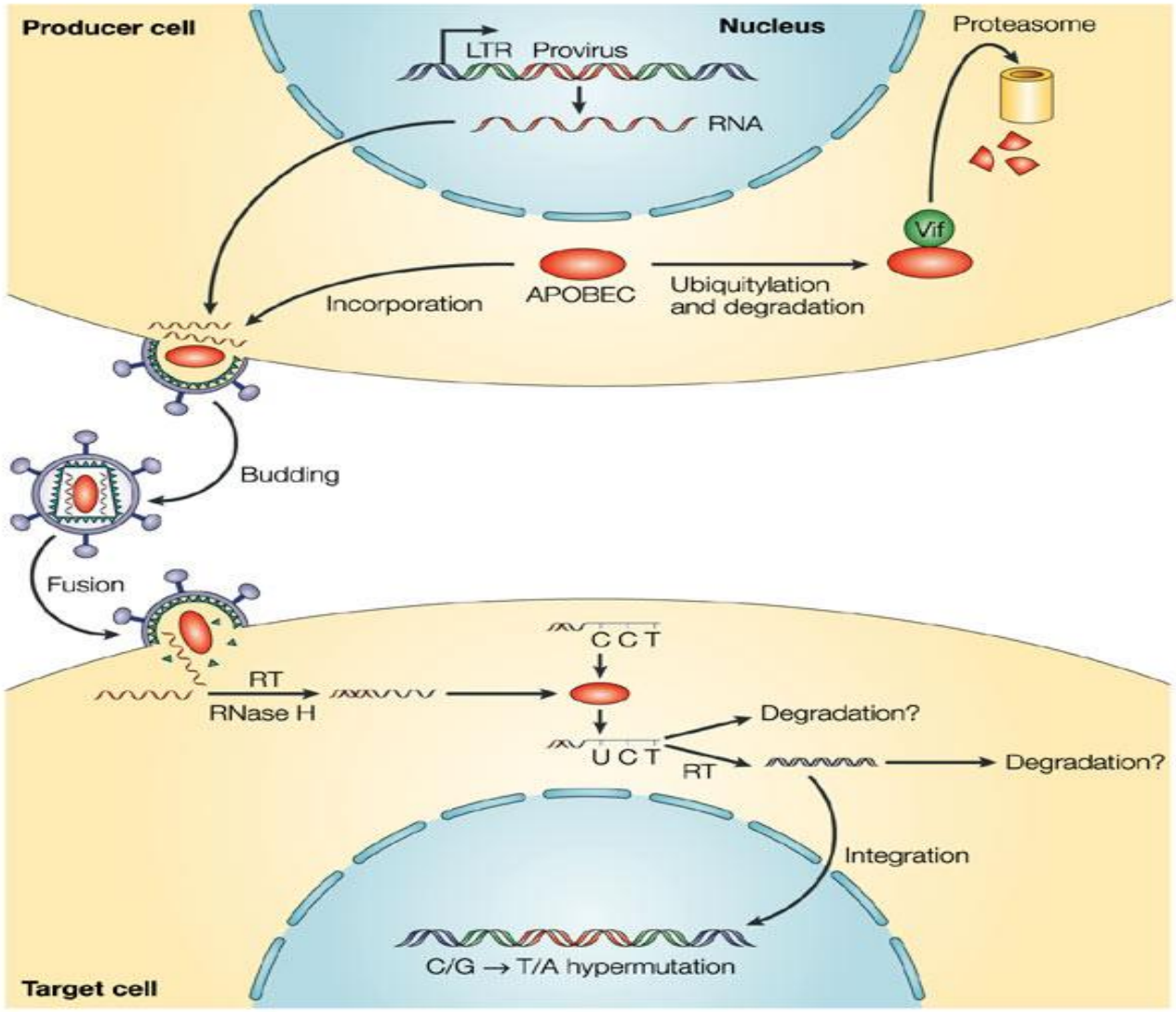
NEW TARGET

Model of HDF roles in the HIV life cycle. With the stages of the HIV life cycle as a framework, each HDF was placed at the position most likely to elicit HIV dependency. The function and subcellular location of HDFs were determined with the use of multiple databases (rationale, table S4). Some proteins are in multiple locations to represent more than one possible role in the HIV life cycle. Newly identified HDFs (red or blue, the latter if they inhibited HIV in part two only); previously implicated HDFs detected in the screen (green), or not detected but with a relevant interaction



Science 15 February 2008:Vol. 319. no. 5865, pp. 921 - 926
Identification of Host Proteins Required for HIV Infection Through a Functional Genomic Screen . Abraham L. Brass et al.

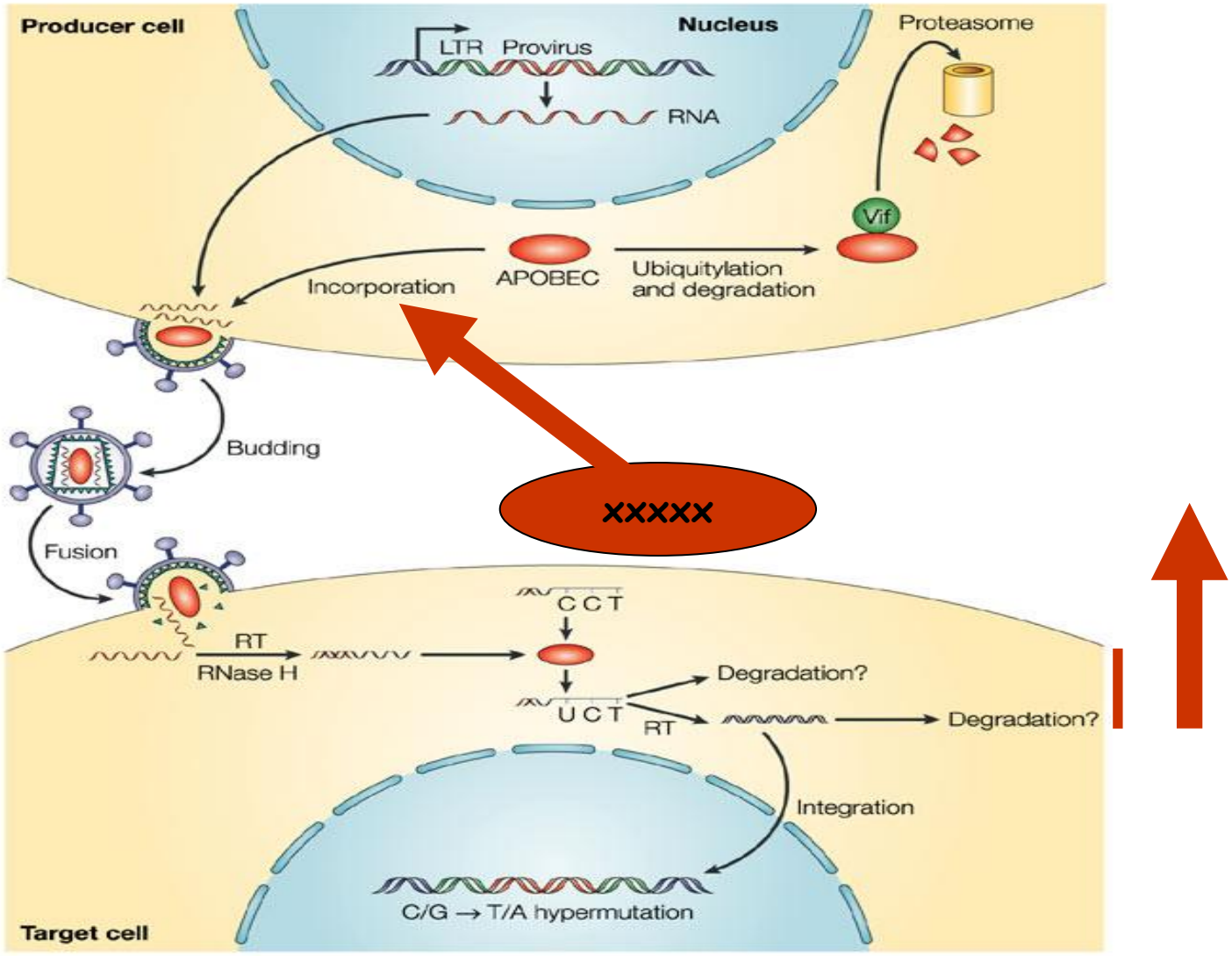
ABOBEC is a cytidine-deaminase that, when packaged into virions, causes extensive G-to-A hypermutation during reverse trascription compromising the stability and functionality of the viral cDNA



Nature Reviews | Immunology

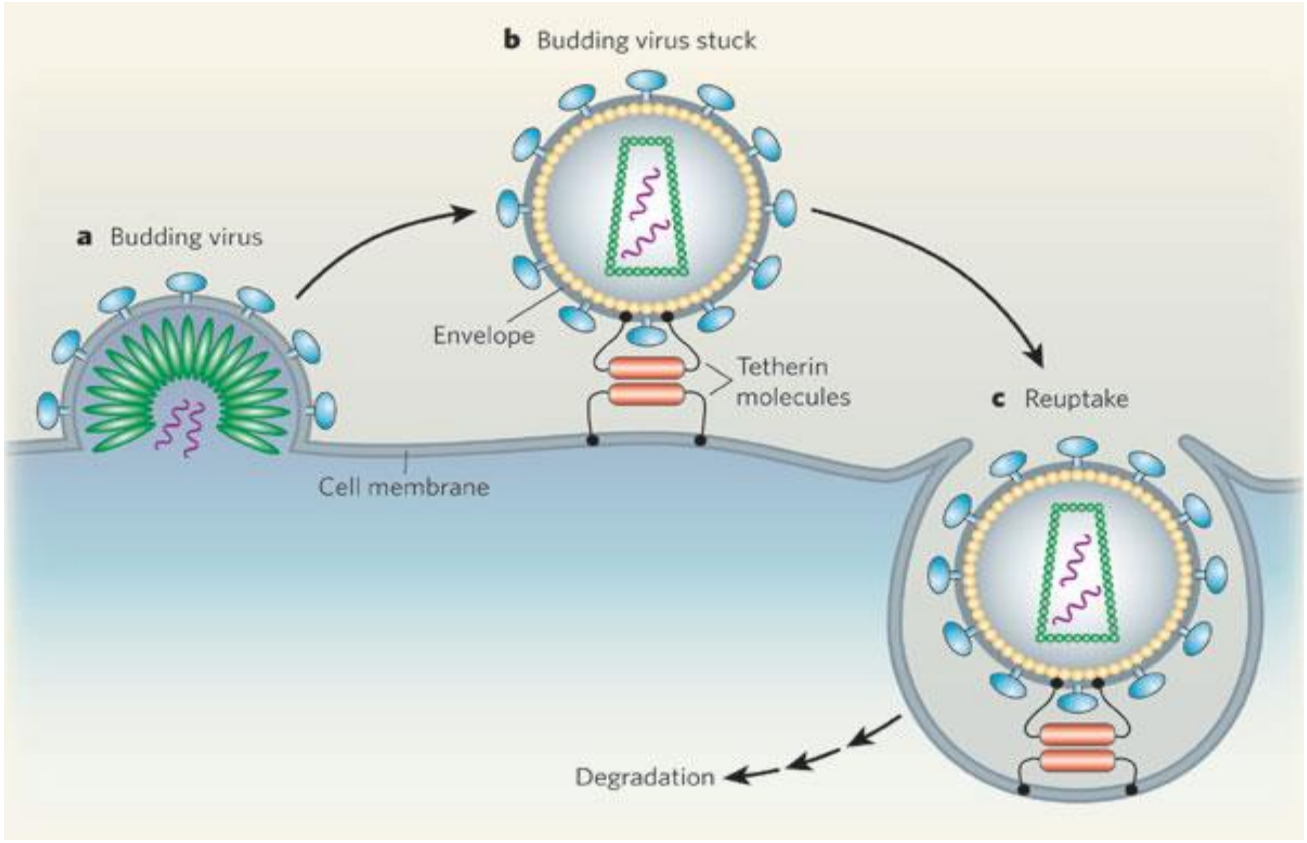
Harris and Liddament, 2004; Nature Reviews Immunology

ABOBEC is a cytidine-deaminase that, when packaged into virions, causes extensive G-to-A hypermutation during reverse trascription compromising the stability and functionality of the viral cDNA



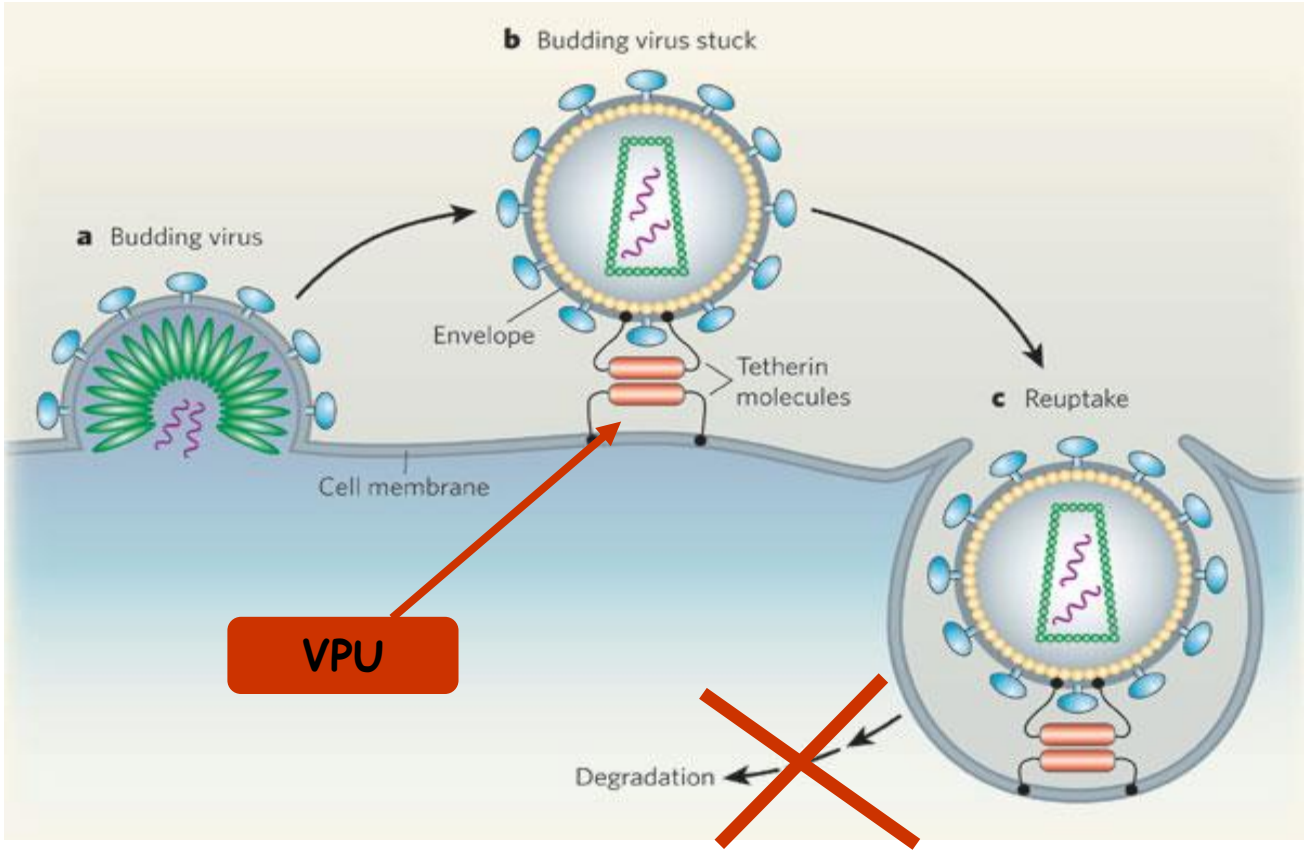
Harris and Liddament, 2004; Nature Reviews Immunology

Tetherin is an IFN-inducible protein that causes retention of viral particles on the cell surfaces
Neil, S. J. D., Zang, T. & Bieniasz, P. D. *Nature 451*,425–430 (2008).

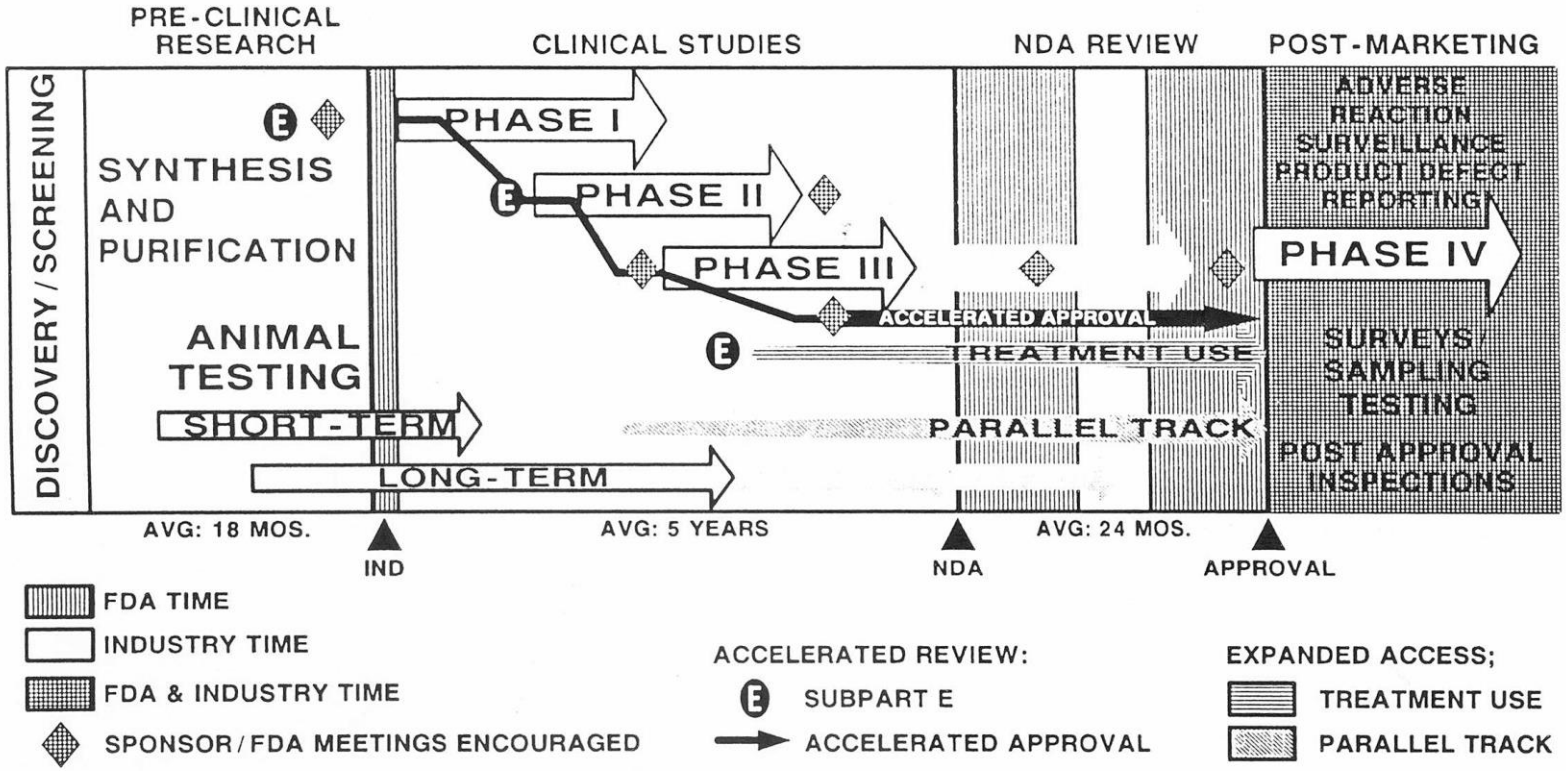


Heinrich G. Göttlinger
***Nature* 451**, 406-408(24 January 2008)

Tetherin is an IFN-inducible protein that causes retention
of viral particles on the cell surfaces – vpu counteract the action of tetherin
Neil, S. J. D., Zang, T. & Bieniasz, P. D. *Nature 451*,425–430 (2008).



Heinrich G. Göttlinger
***Nature* 451**, 406-408(24 January 2008)


PRE-CLINICAL RESEARCH
CLINICAL STUDIES
NDA REVIEW
POST-MARKETING
DISCOVERY / SCREENING
SYNTHESIS AND PURIFICATION
ANIMAL TESTING
SHORT-TERM
LONG-TERM
PHASE I
PHASE II
PHASE III
ACCELERATED APPROVAL
TREATMENT USE
PARALLEL TRACK
ADVERSE REACTION SURVEILLANCE PRODUCT DEFECT REPORTING
PHASE IV
SURVEYS / SAMPLING TESTING
POST APPROVAL INSPECTIONS
AVG: 18 MOS.
AVG: 5 YEARS
AVG: 24 MOS.
IND
NDA
APPROVAL
FDA TIME
INDUSTRY TIME
FDA & INDUSTRY TIME
SPONSOR / FDA MEETINGS ENCOURAGED
ACCELERATED REVIEW:
SUBPART E
ACCELERATED APPROVAL
EXPANDED ACCESS;
TREATMENT USE
PARALLEL TRACK