DEPARTAMENTO DE
MICROBIOLOGIA
UNIVERSIDADE DE SÃO PAULO

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Antivirais

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Desenvolvimento de antivirais

Existem relativamente poucas doenças para as quais tem sido desenvolvidas drogas antivirais eficientes.

- Existem menos alvos “óbvios” para vírus do que para bactérias.
- Os diferentes tipos de vírus apresentam um conjunto próprio de proteínas e estratégias de replicação variadas.
- Alguns vírus estabelecem latência e tratamento da infecção produtiva não cura a doença.
- Diferentes vírus podem causar sintomas semelhantes, dificultando o diagnóstico.
- Para muitos vírus o tratamento só é eficiente se aplicado na fase inicial da infecção (quando muitas vezes não há sintomas...)

Desenvolvimento de antivirais

Uma molécula pode agir como antiviral se inibe alguma etapa da replicação viral sem ser tóxica demais para o hospedeiro.

Os possíveis mecanismos de ação incluem:

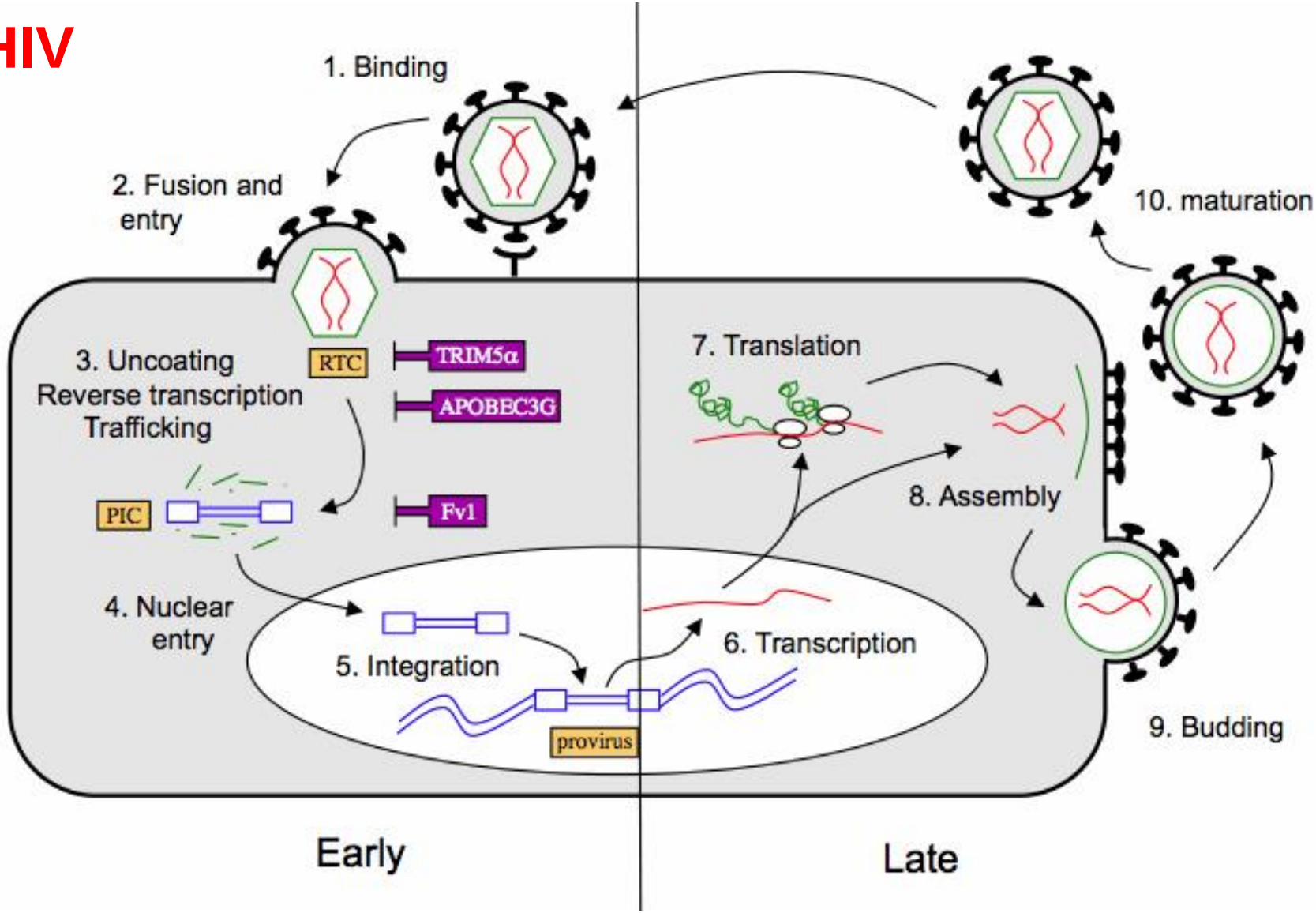
- A capacidade de inativar partículas virais extracelulares.
- Prevenir a união do vírus à celula e/ou sua entrada.
- Prevenir a replicação do genoma viral.
- Prevenir a síntese/função de proteínas virais específicas.
- Prevenir a montagem e/ou liberação de novos vírions.

O ciclo dos diferentes vírus apresenta etapas comuns

- Adsorção
- Penetração
- Desnudamento
- Síntese dos componentes virais:
  - Proteínas
  - Ácido nucléico
- Montagem
- Maturação
- Liberação

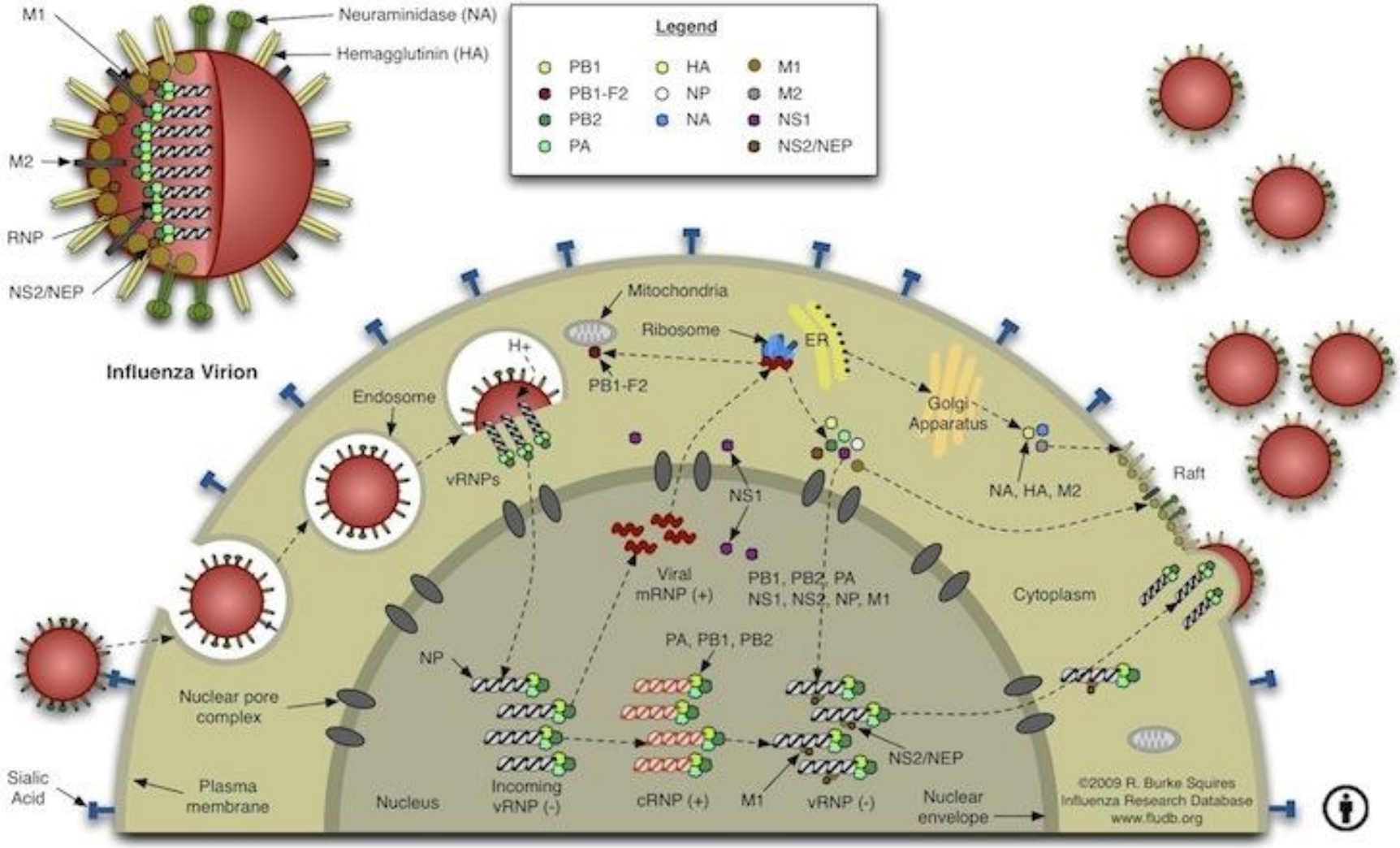
O ciclo de cada tipo viral apresenta características próprias

HIV

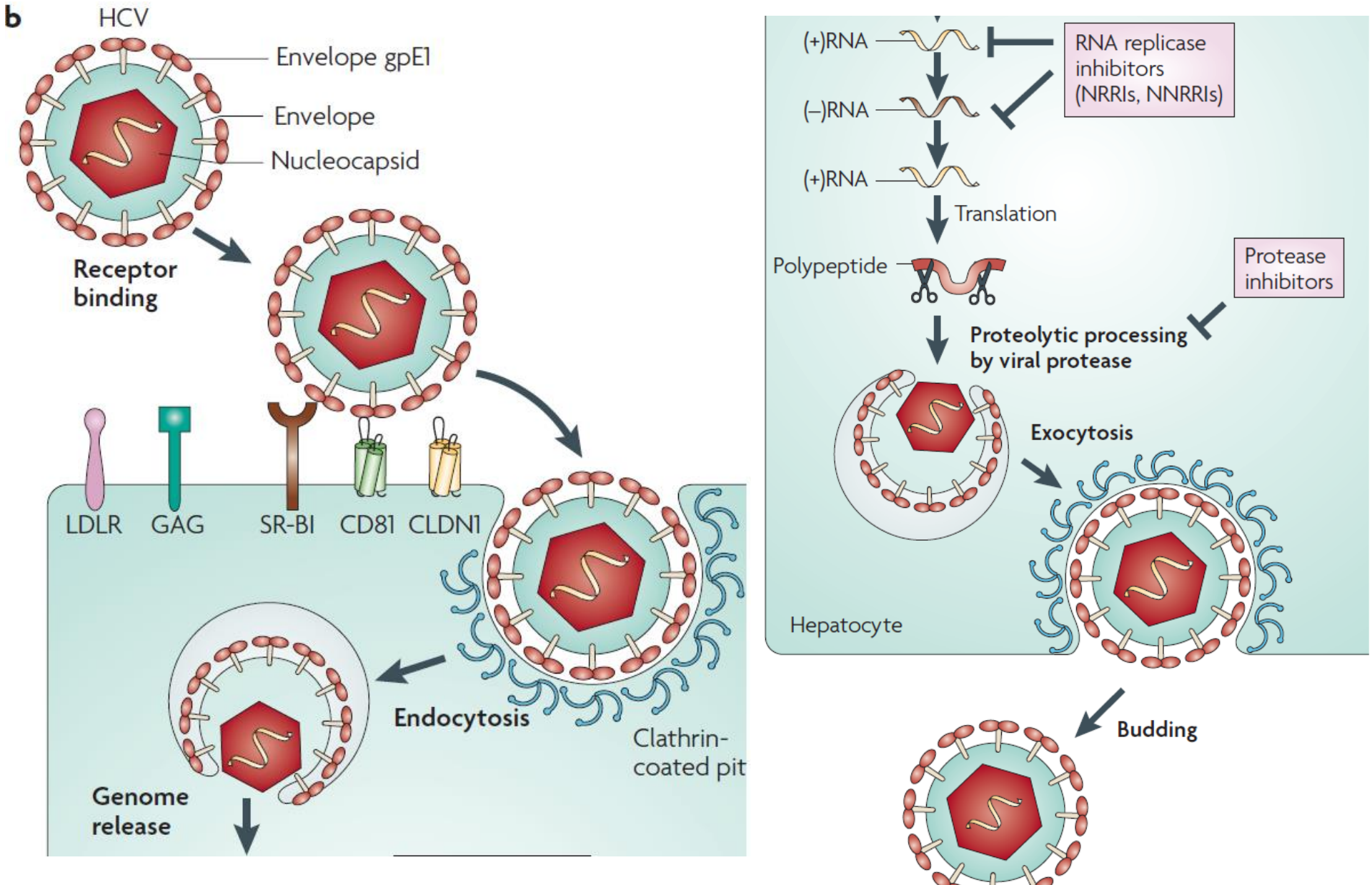


O ciclo de cada tipo viral apresenta características próprias

Influenza

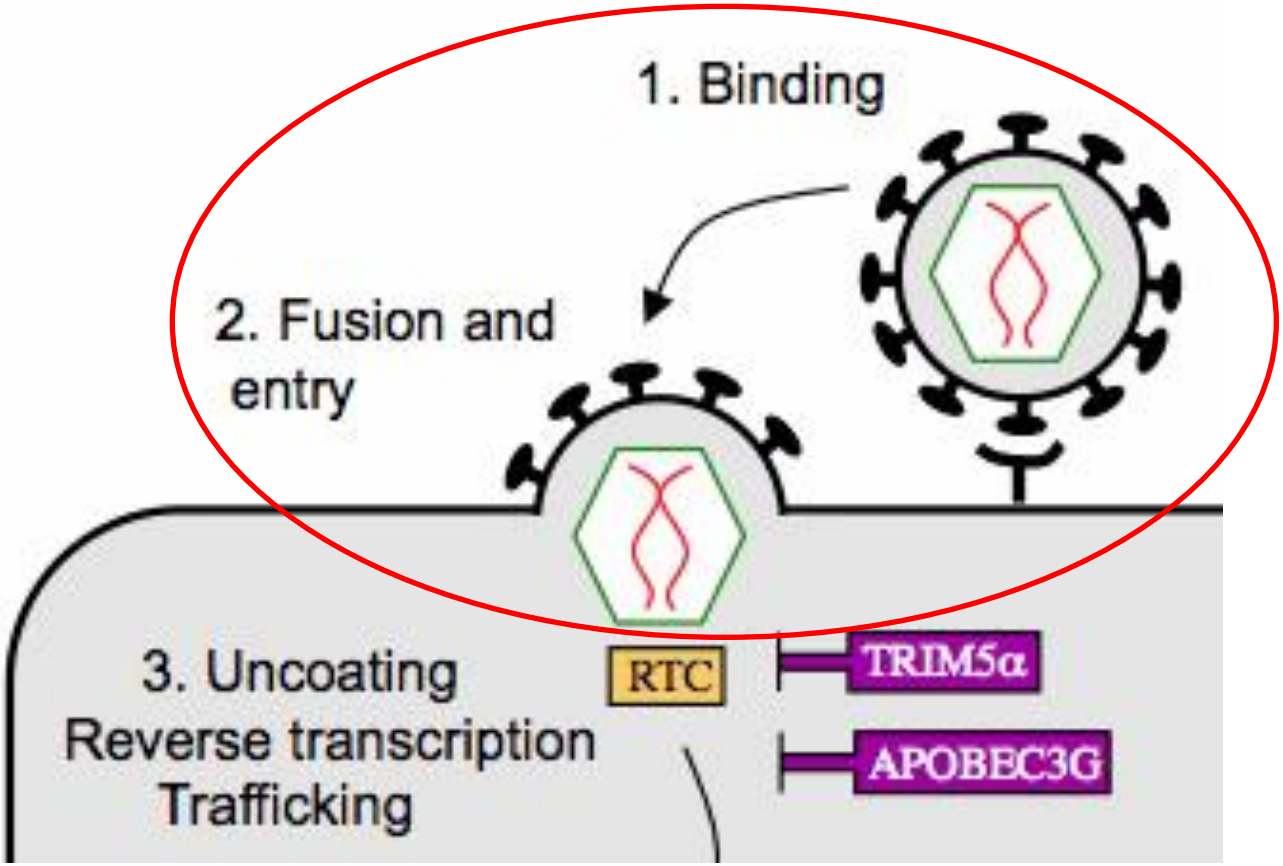


O ciclo de cada tipo viral apresenta características próprias

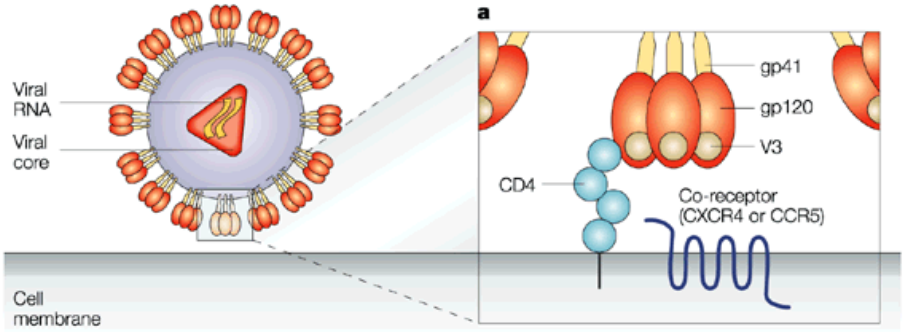


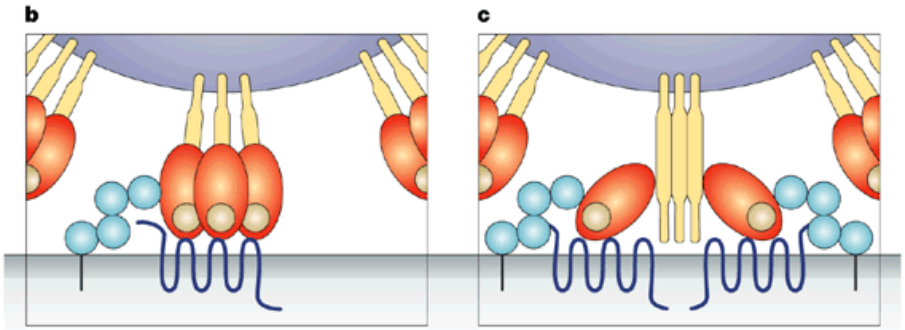
Inibidores de adsorção e fusão

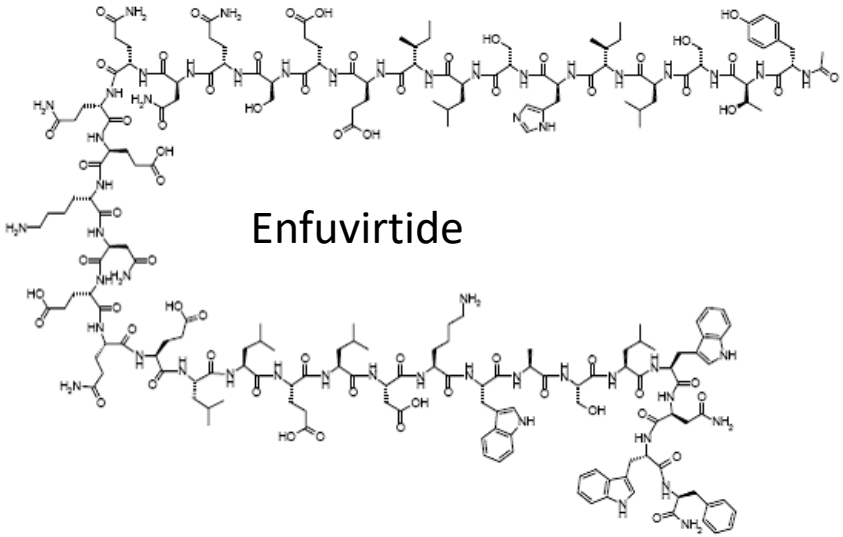
Inibidores de fusão



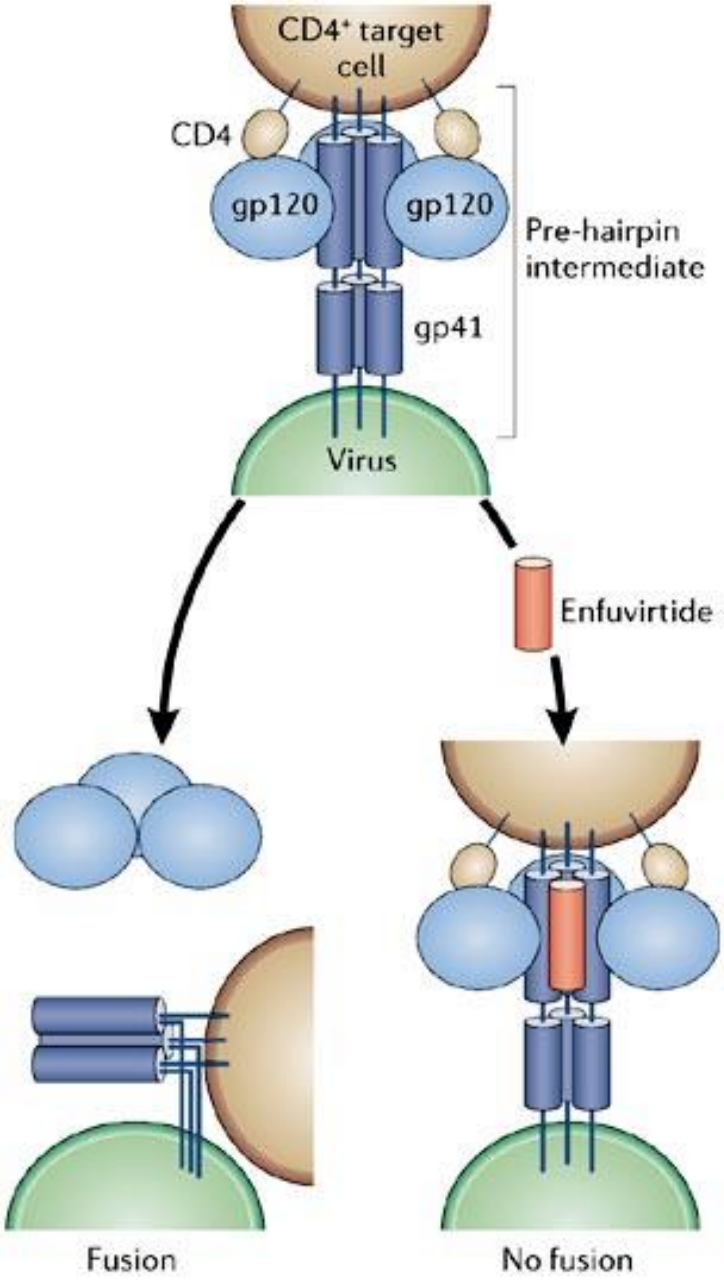
Inibidores de fusão





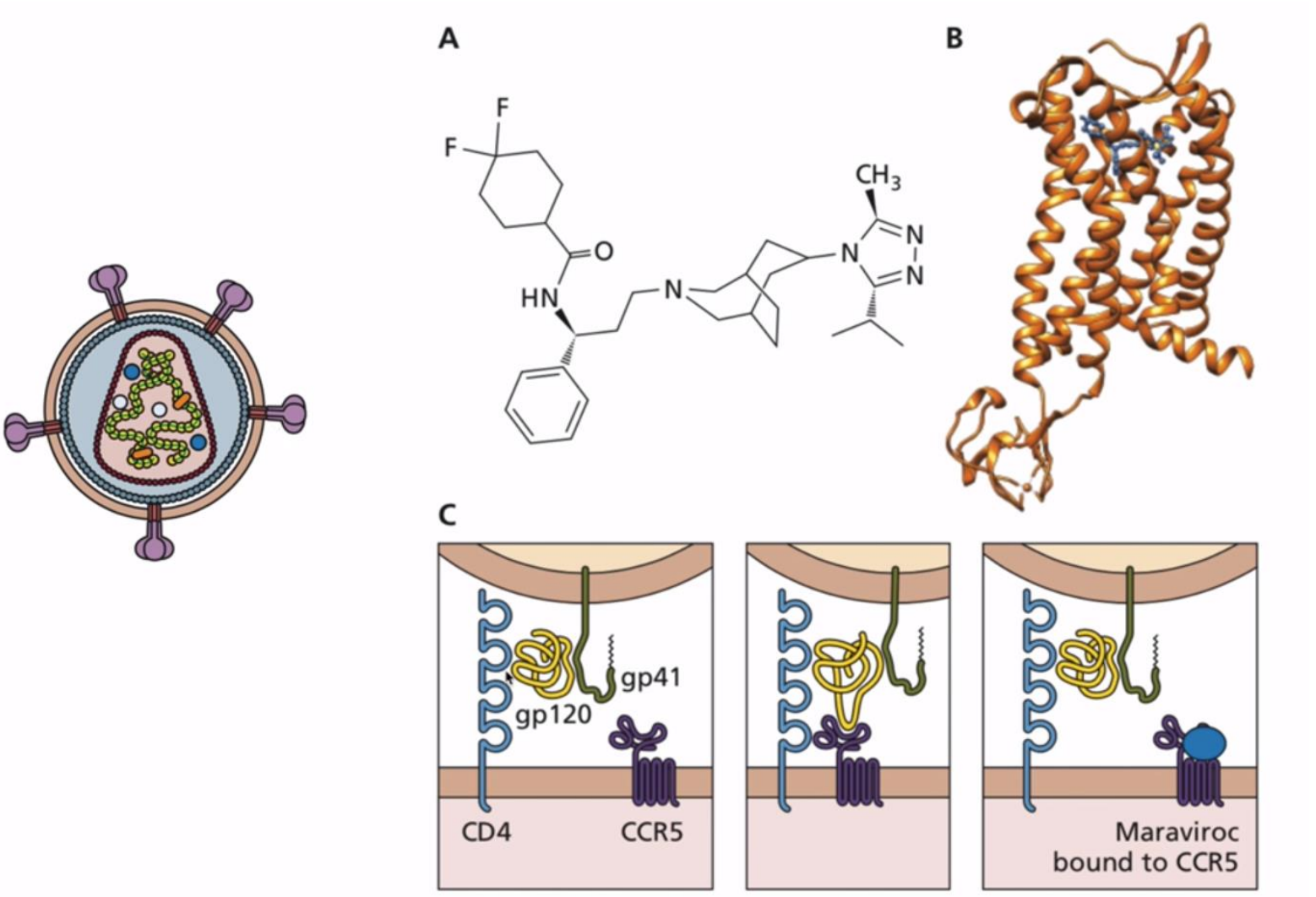


Enfuvirtide

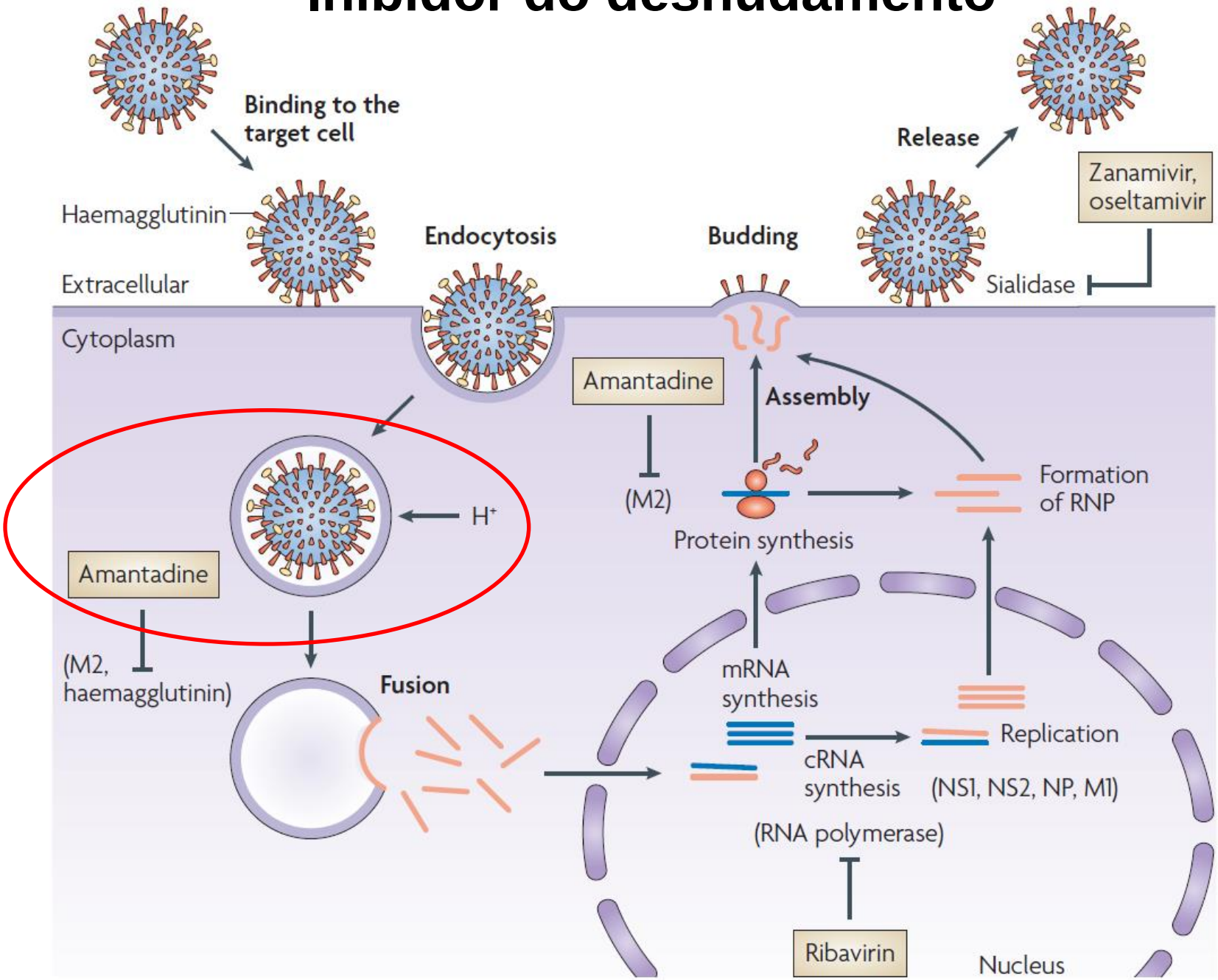


Inibidor de entrada

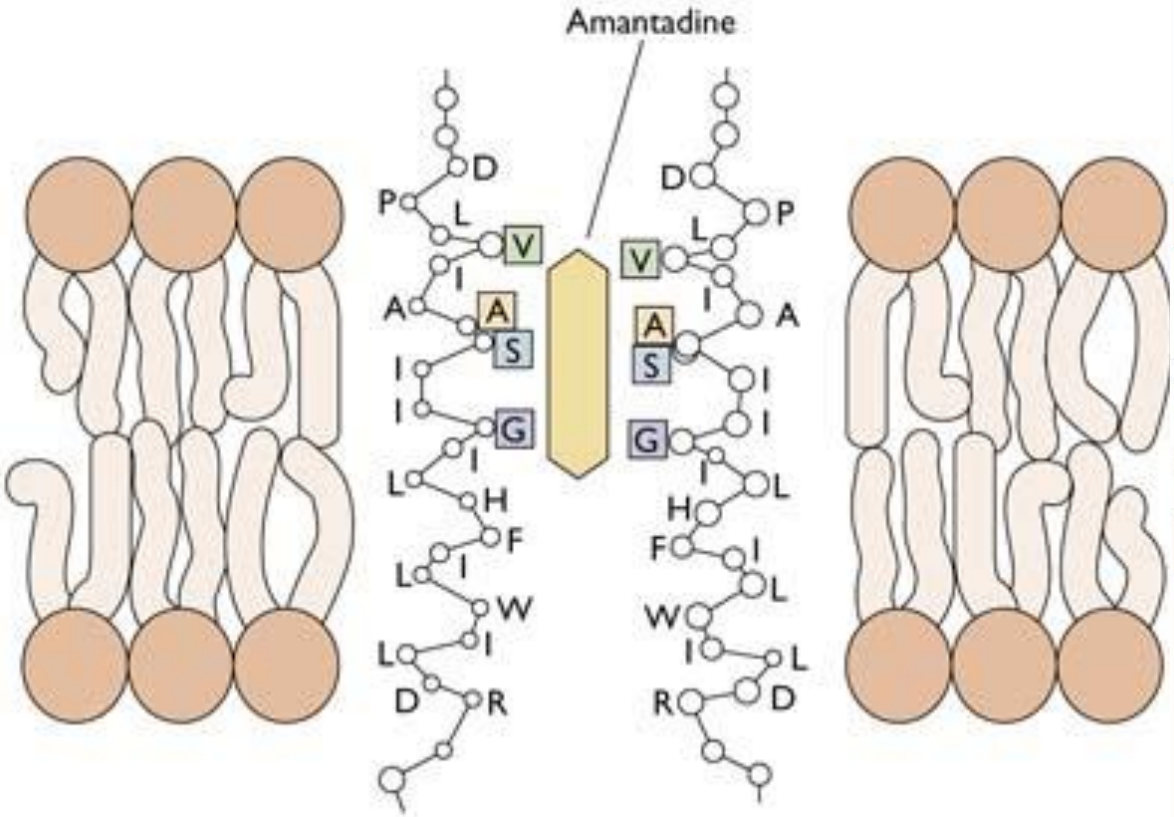
Maraviroc: inibidor de CCR5

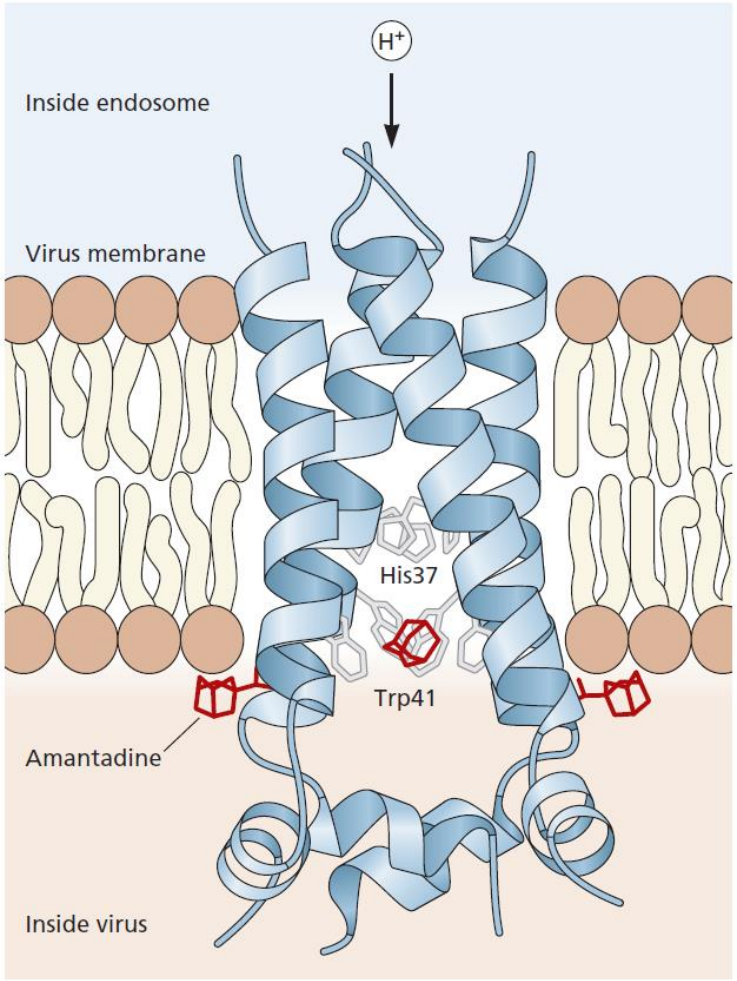


Inibidor do desnudamento



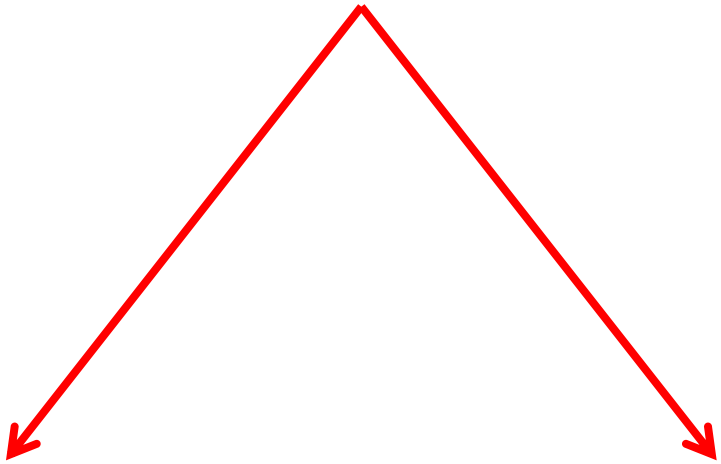
Inibidor do desnudamento





Inibidores das polimerases virais

Inibidores das polimerases virais

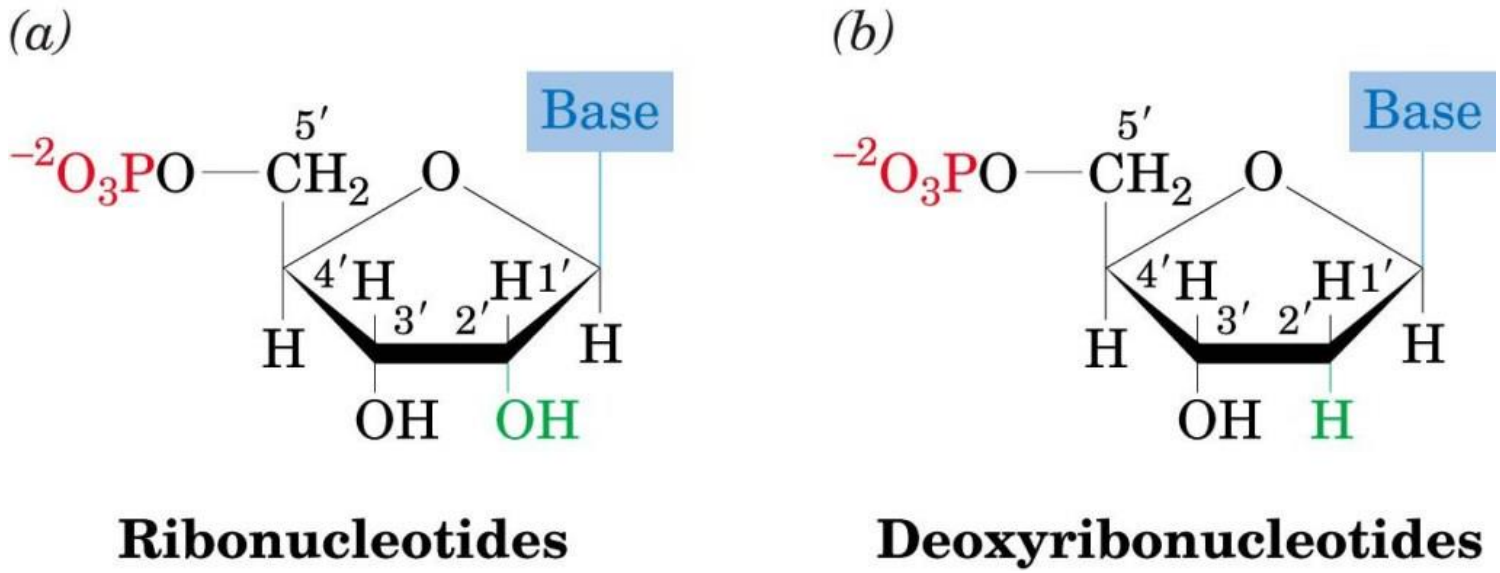


Análogos de nucleotídeos o de nucleosídeos.

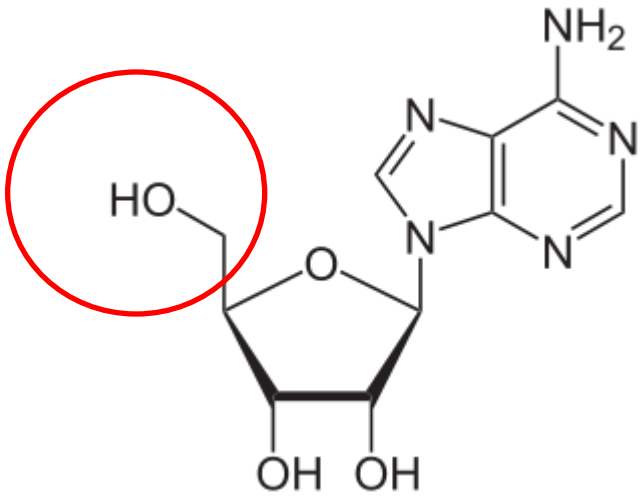
Não análogos de nucleotídeos o de nucleosídeos.

- Servem, exclusivamente, para tipos virias que codificam polimerases próprias.

Inibidores das polimerases virais



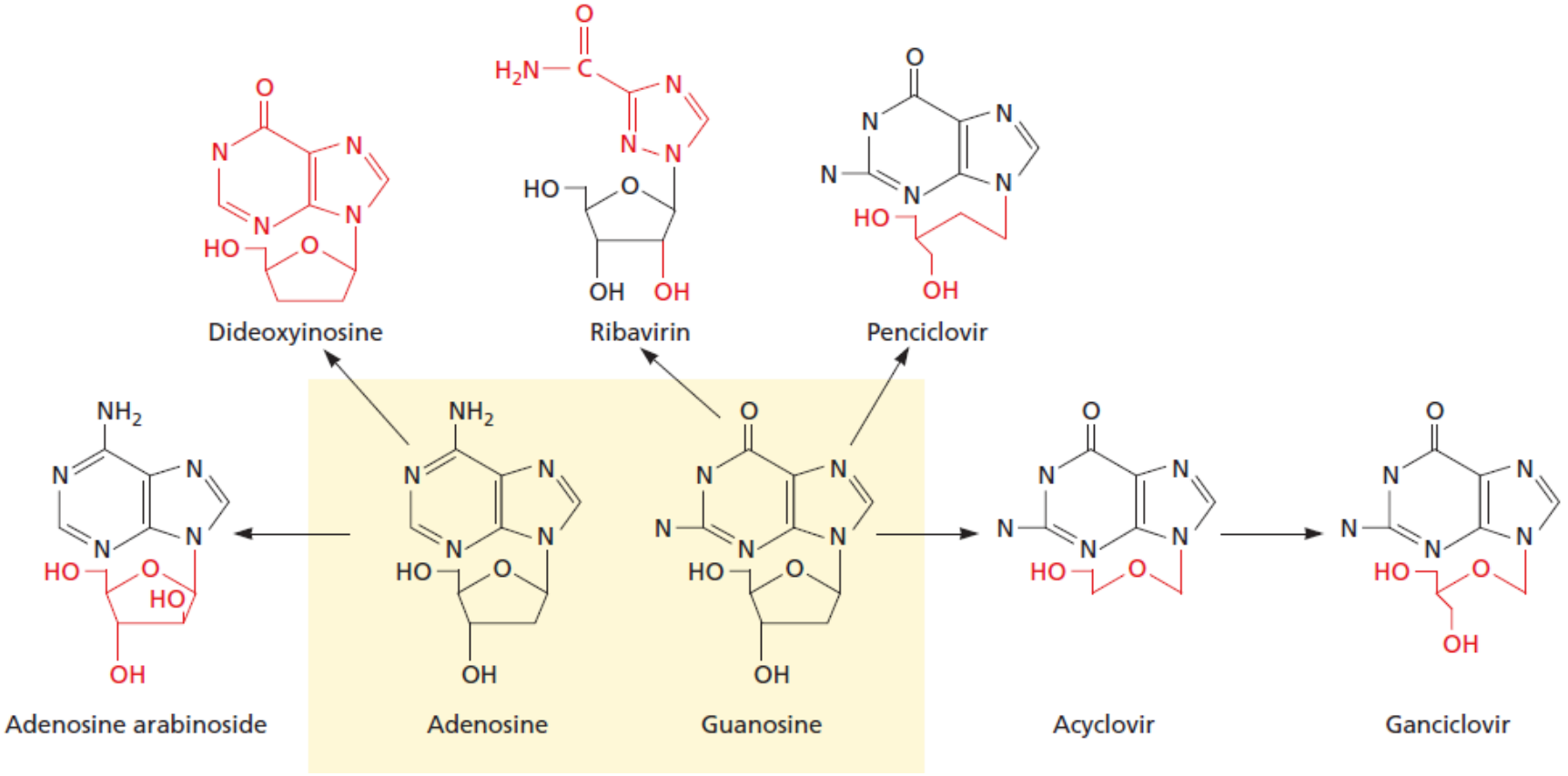
Ribonucleotides **Deoxyribonucleotides**



Nucleosídeo

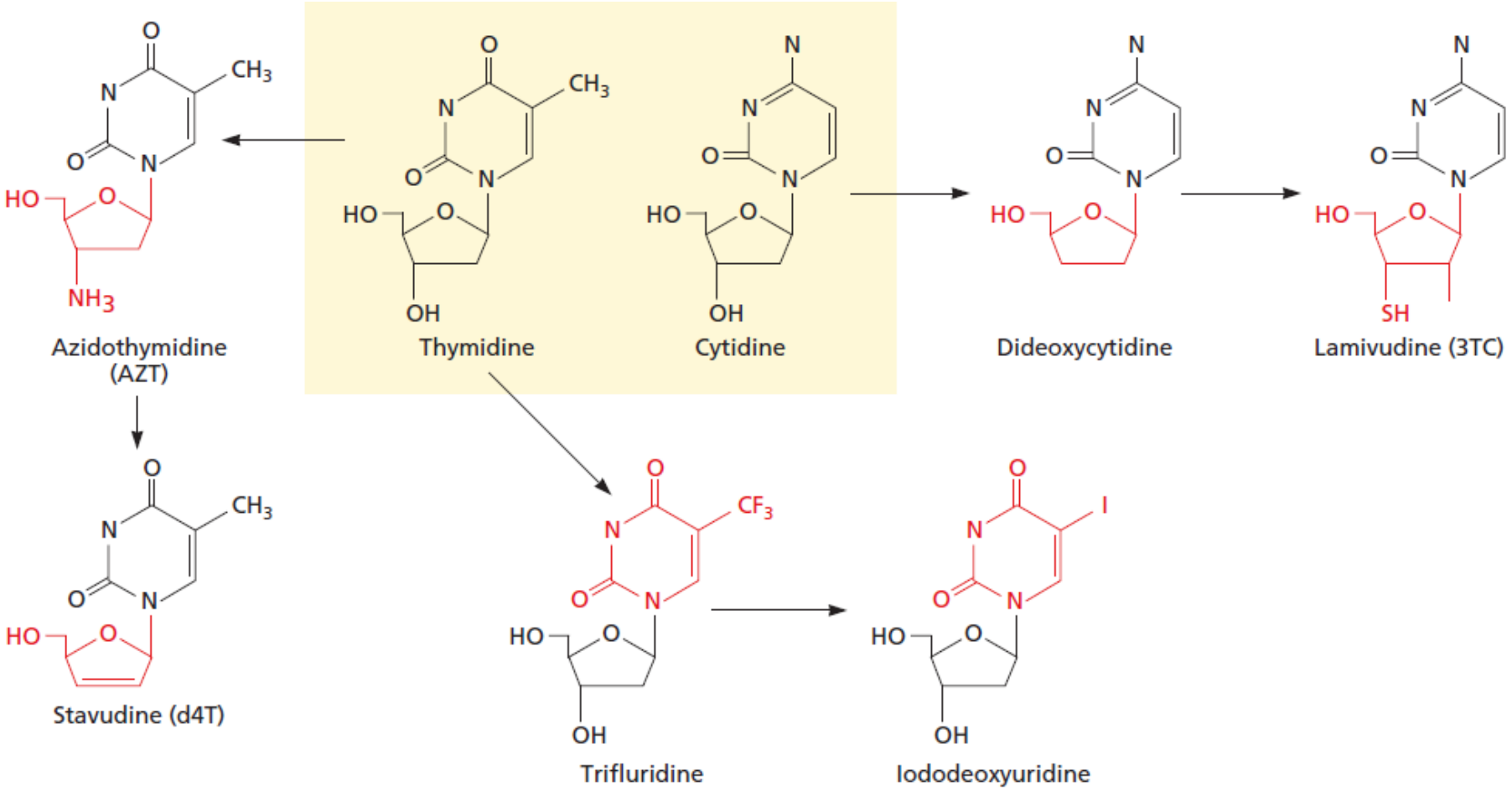
Inibidores das polimerases virais

Análogos de Nucleosídeos



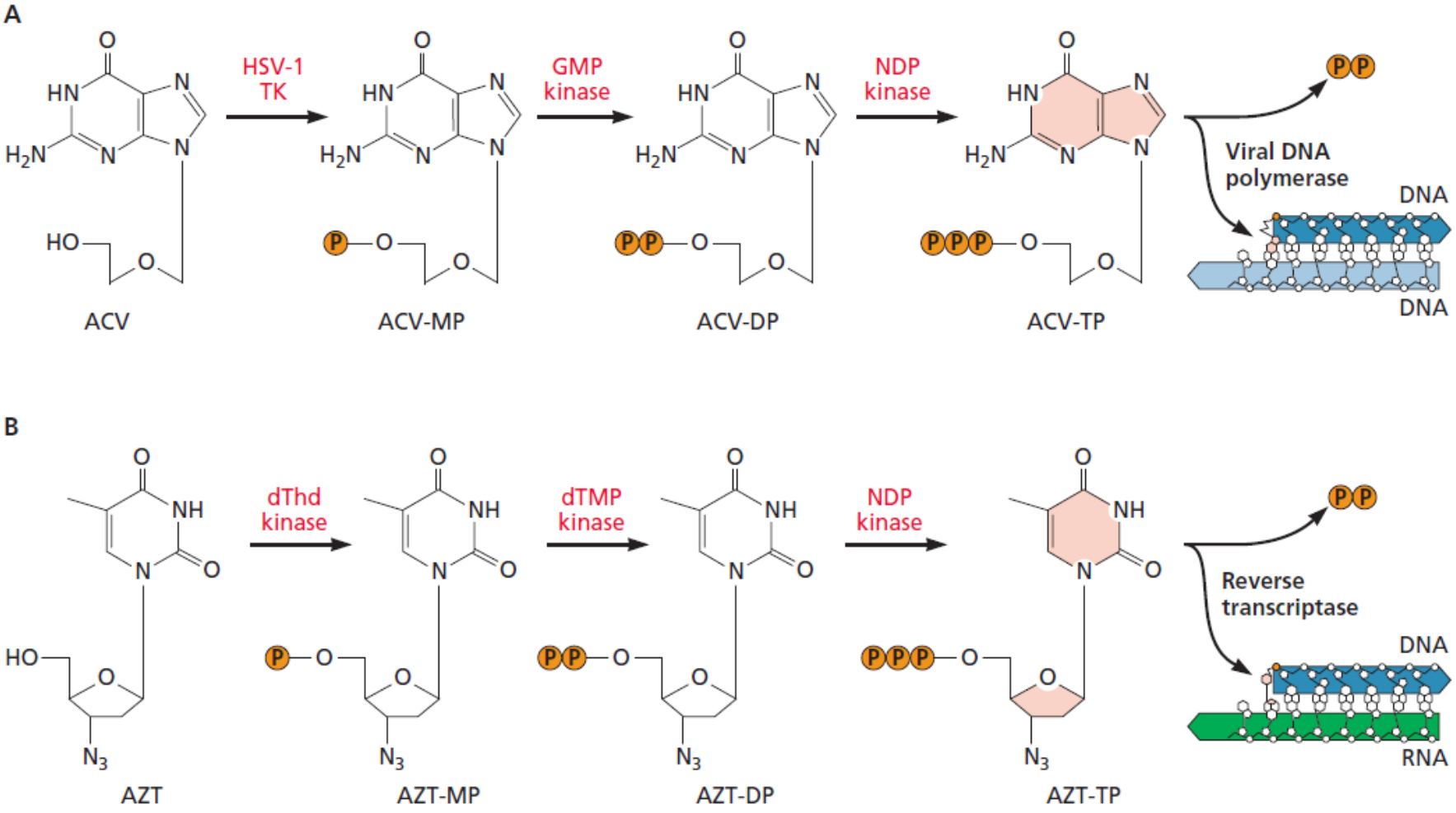
Inibidores das polimerases virais

Análogos de Nucleosídeos



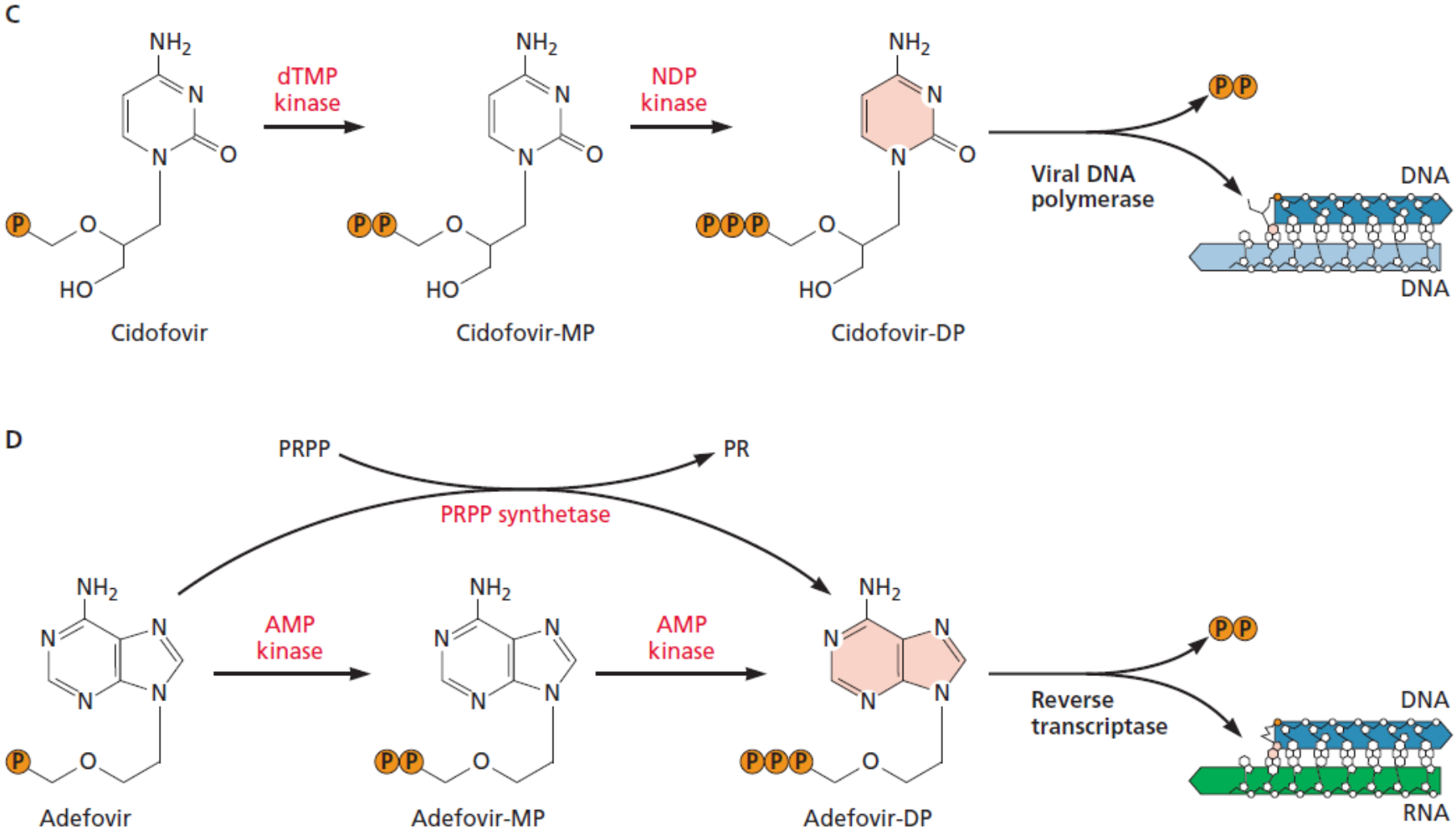
Inibidores das polimerases virais

Análogos de Nucleosídeos



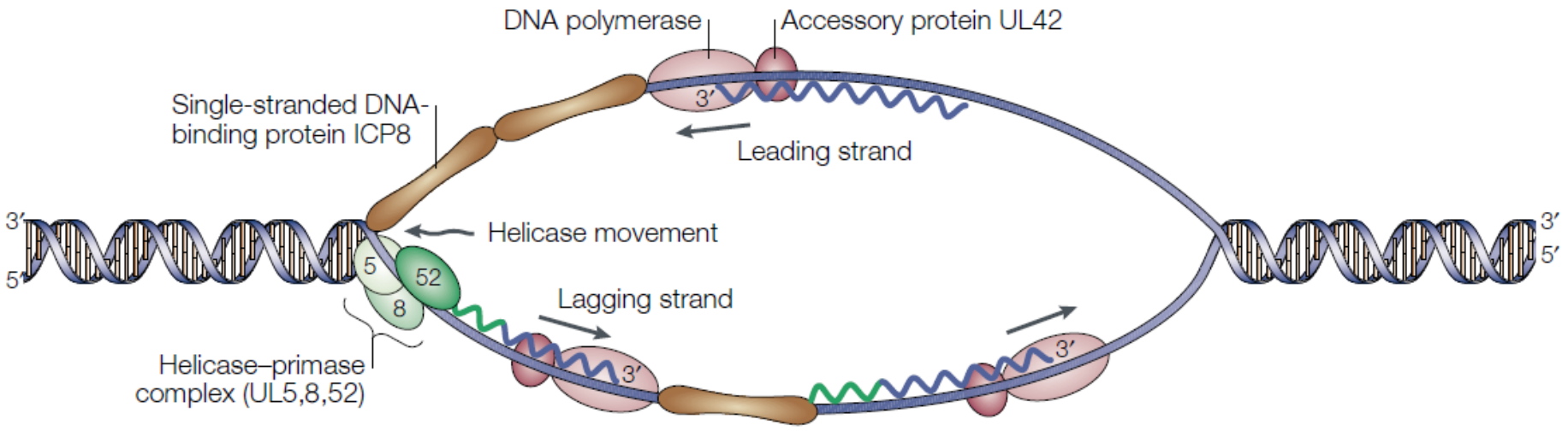
Inibidores das polimerases virais

Análogos de Nucleosídeos



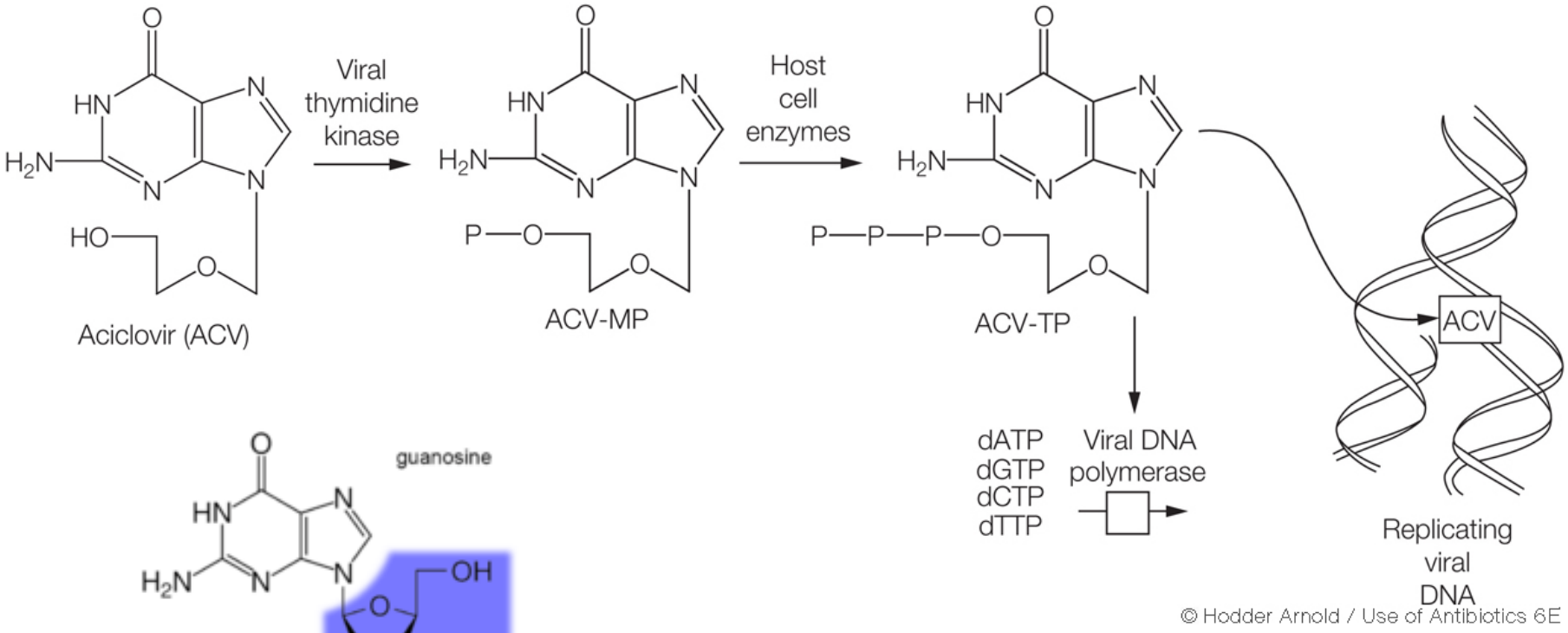
Inibidores da DNA polimerase de Herpesvírus

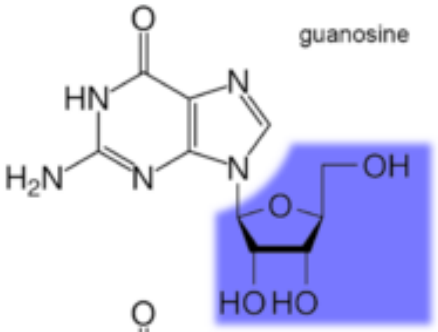
Inibidores da replicação de Herpesvírus

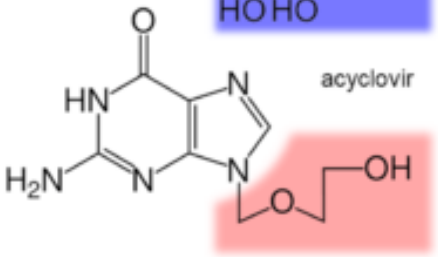


Inibidores da replicação de Herpesvírus

Inibidores das polimerases virais

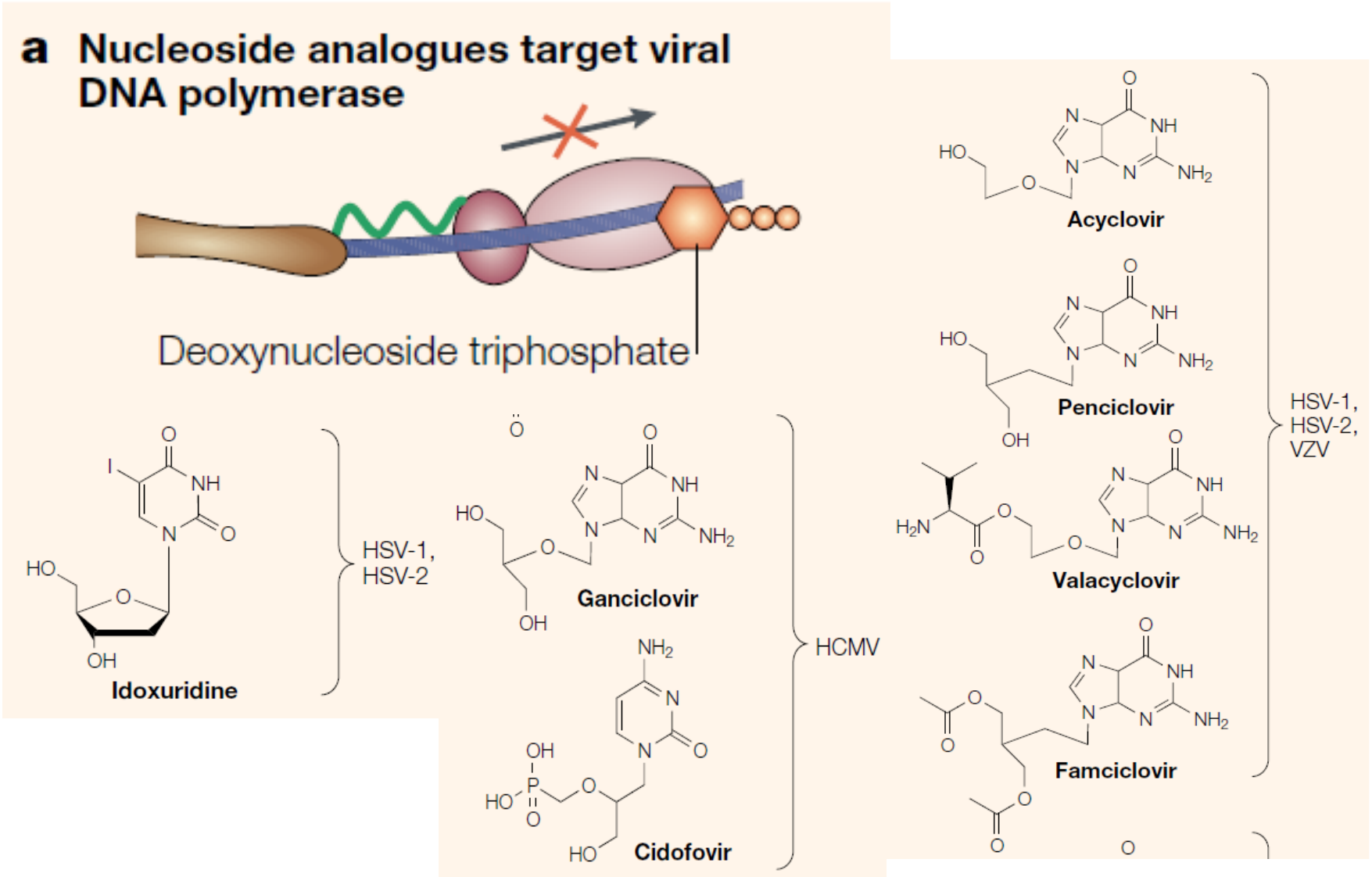






Inibidores da replicação de Herpesvírus

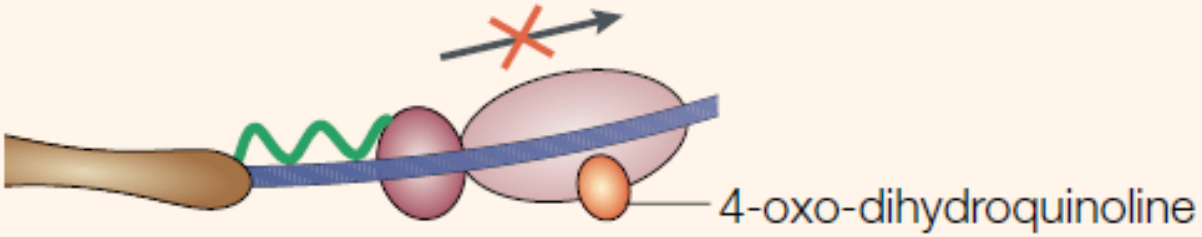
Inibidores das polimerases virais



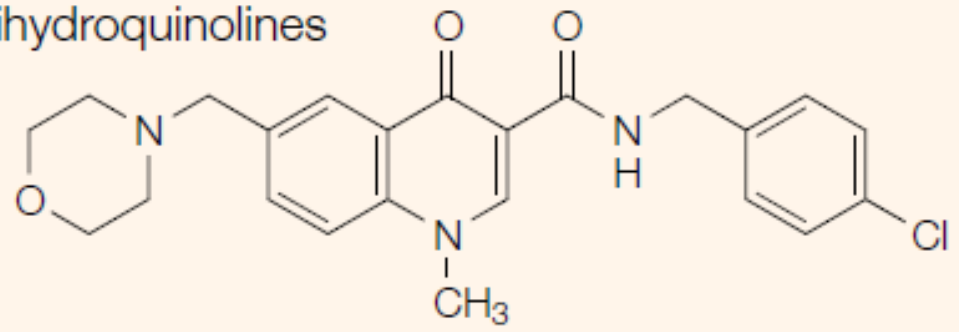
Inibidores da replicação de Herpesvírus

Inibidores das polimerases virais

b Non-nucleoside drugs that target viral DNA polymerase

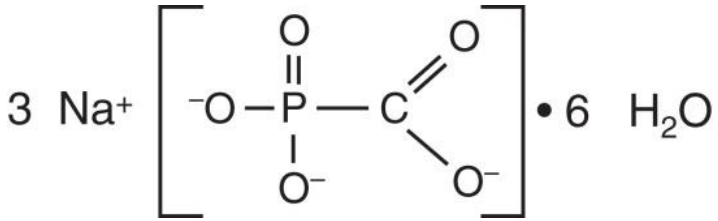


4-oxo-dihydroquinolines



PNU-183792

Multiple herpesviruses



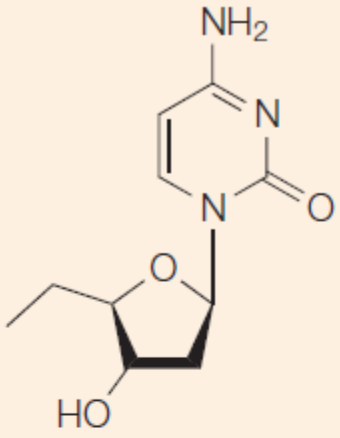
Foscarnet

Inibidores da DNA polimerase de Retrovírus

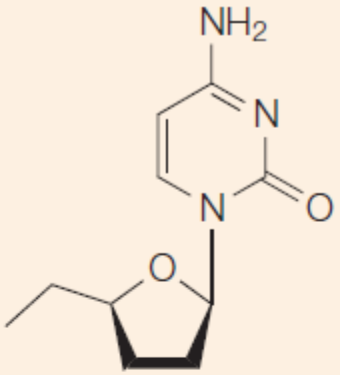
Inibidores da replicação de Retrovírus

Inibidores da transcriptase reversa

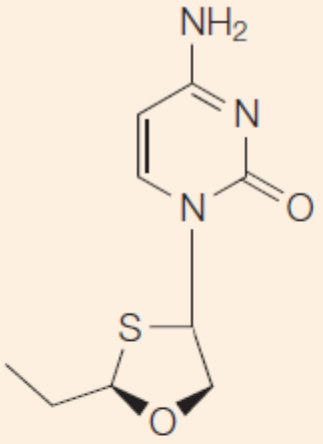
a



dC

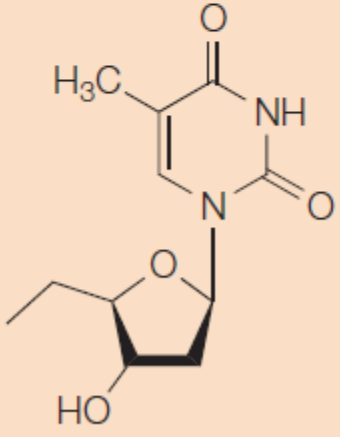


ddCTP (zalcitabine)

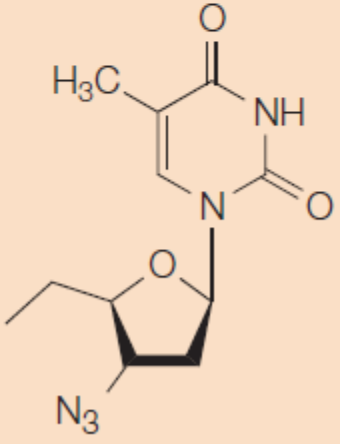


3TC (lamivudine)

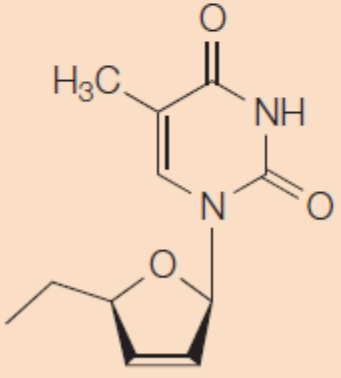
Análogos de nucleosídeos.



dT



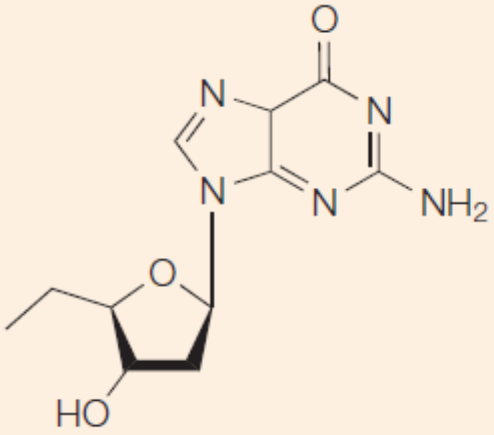
AZT (zidovudine)



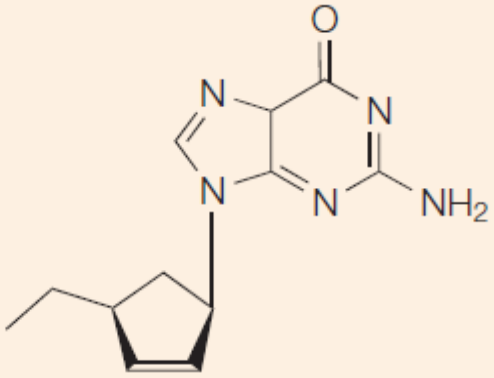
D4T (stavudine)

Inibidores da replicação de Retrovírus

Inibidores da transcriptase reversa

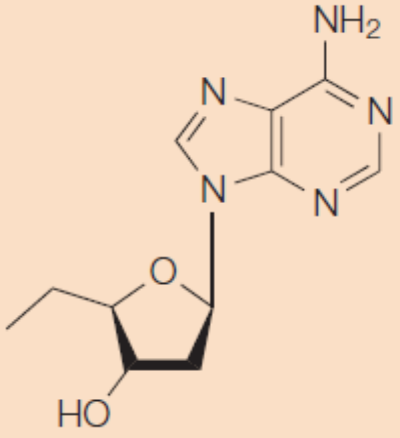


dG

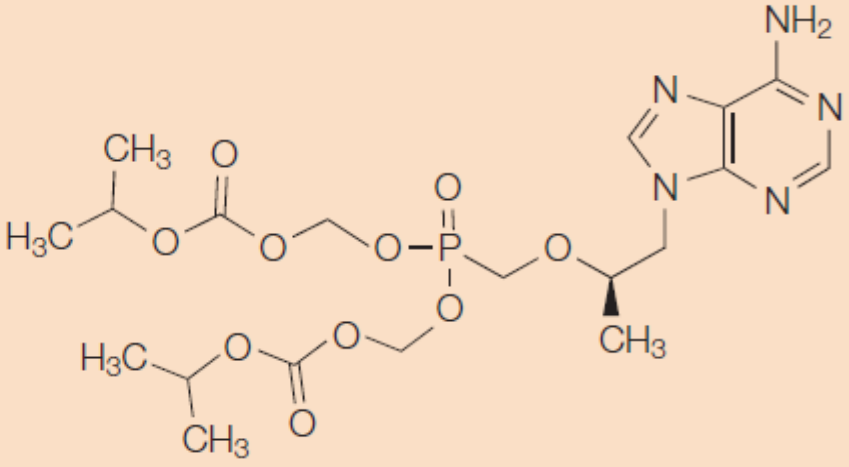


CBV (carbovir, active form of abacavir)

Análogos de nucleosídeos.



dA



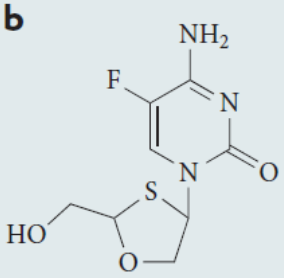
PMPA (tenofovir)

Inibidores da replicação de Retrovírus

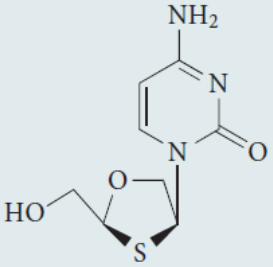
Inibidores da transcriptase reversa

Análogos de nucleosídeos.

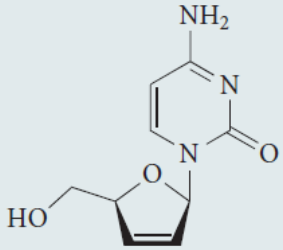
b



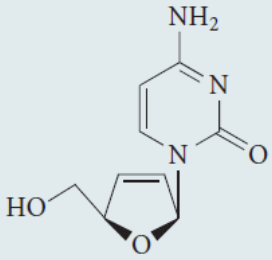
Racemic
(±)FTC (FdOTC)
Racivir



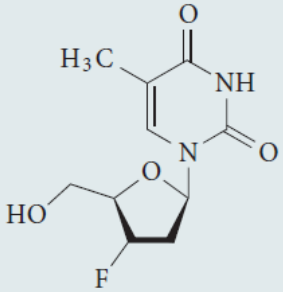
AVX-754 ((–)dOTC)
SPD-754
Apricitabine



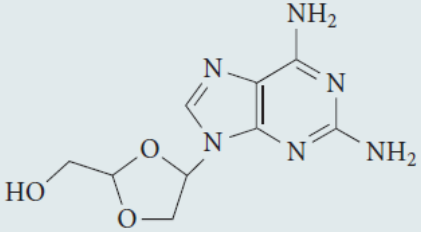
DPC-817 (β-D-Fd4C)
Dexelvucitabine
Reverset



ACH-126443 (β-L-Fd4C)
Elvucitabine



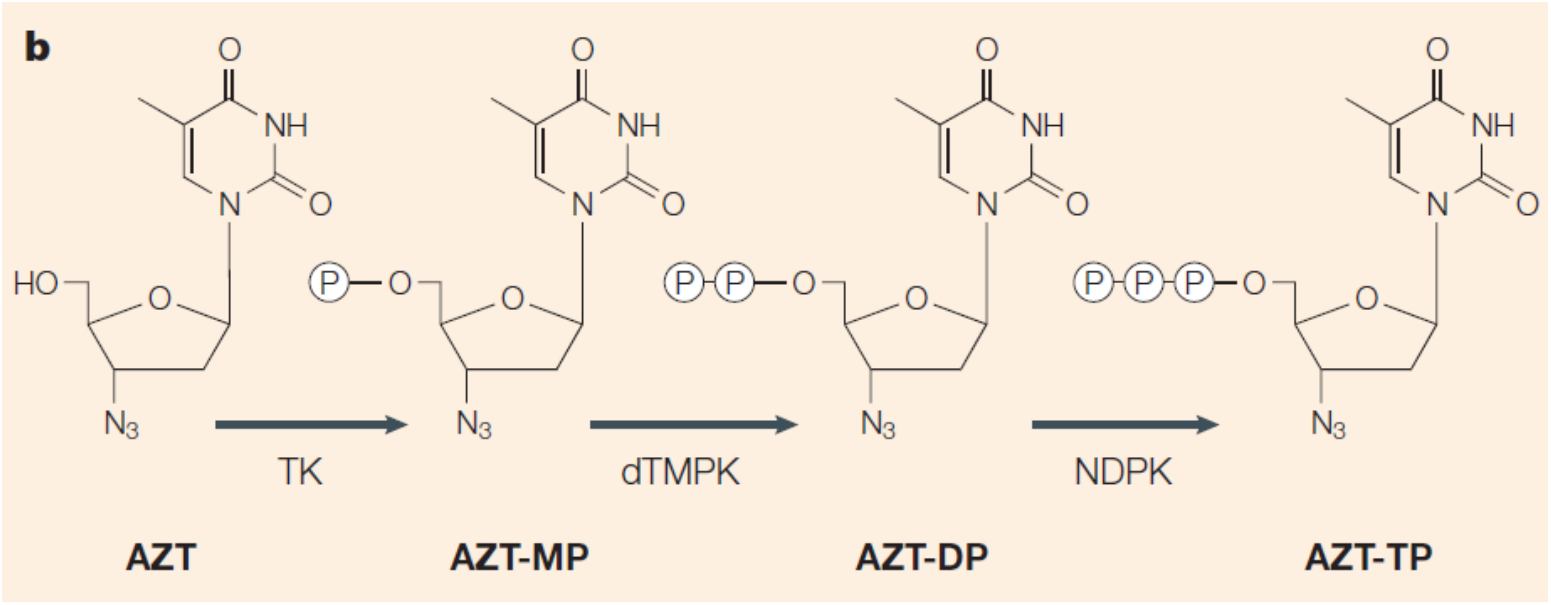
MIV-310 (FddThd, FLT)
Alovudine

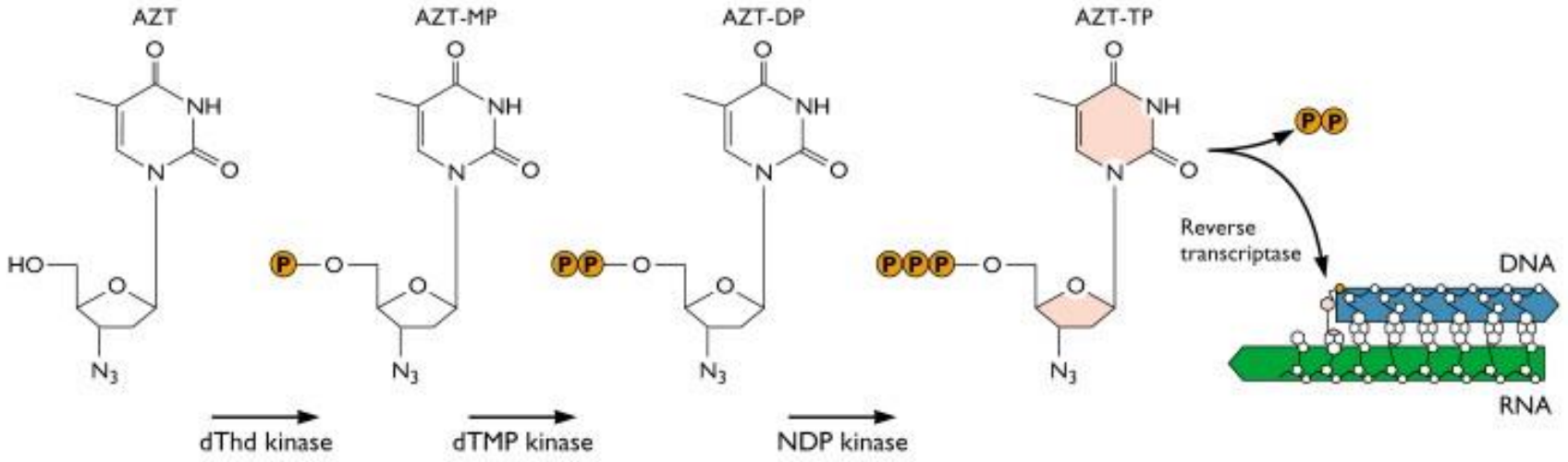


Diaminopurine
dioxolane (DAPD)
Amdoxovir

Inibidores da replicação de Retrovírus

Inibidores da transcriptase reversa



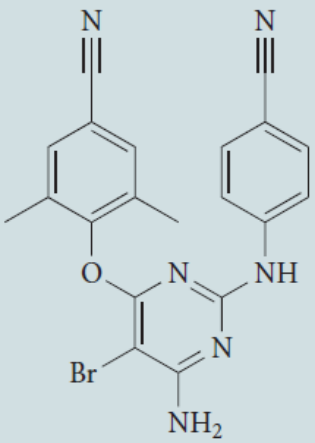


Inibidores da replicação de Retrovírus

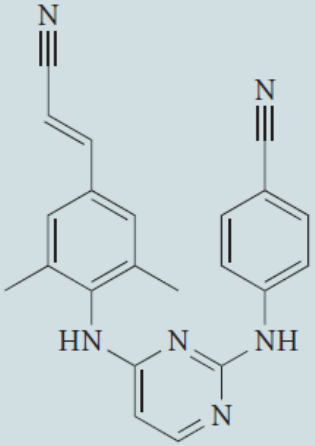
Inibidores da transcriptase reversa

Não análogos de nucleosídeos.

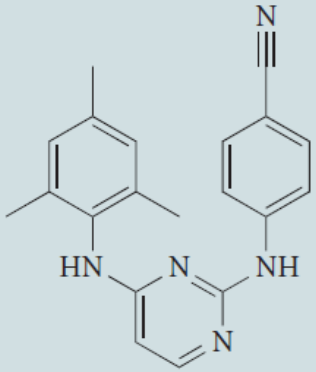
c



Etravirine
(TMC125, R165335)



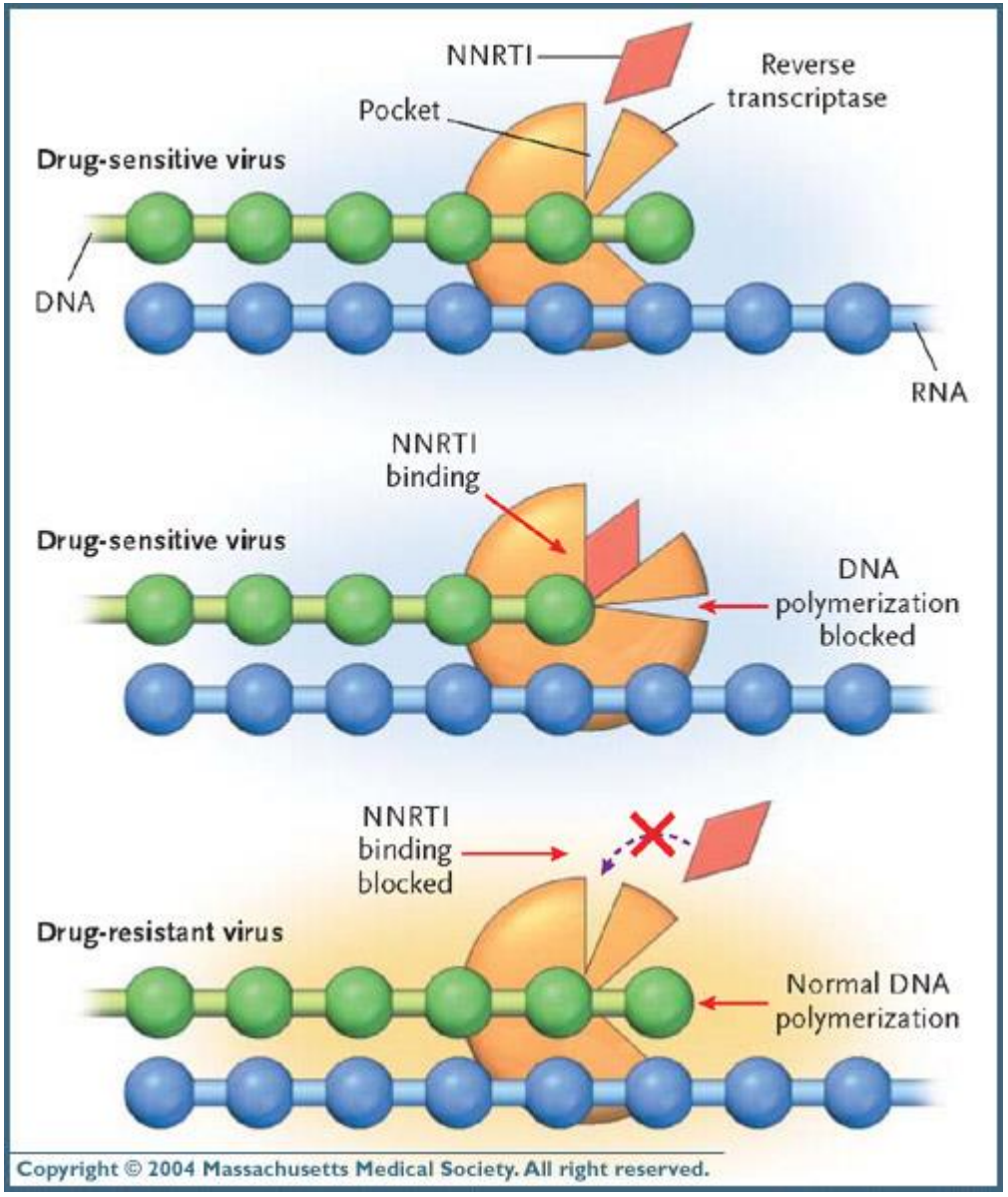
Rilpivirine
(TMC278, R278474)



Dapivirine
(TMC120, R147681)

Inibidores da replicação de Retrovírus

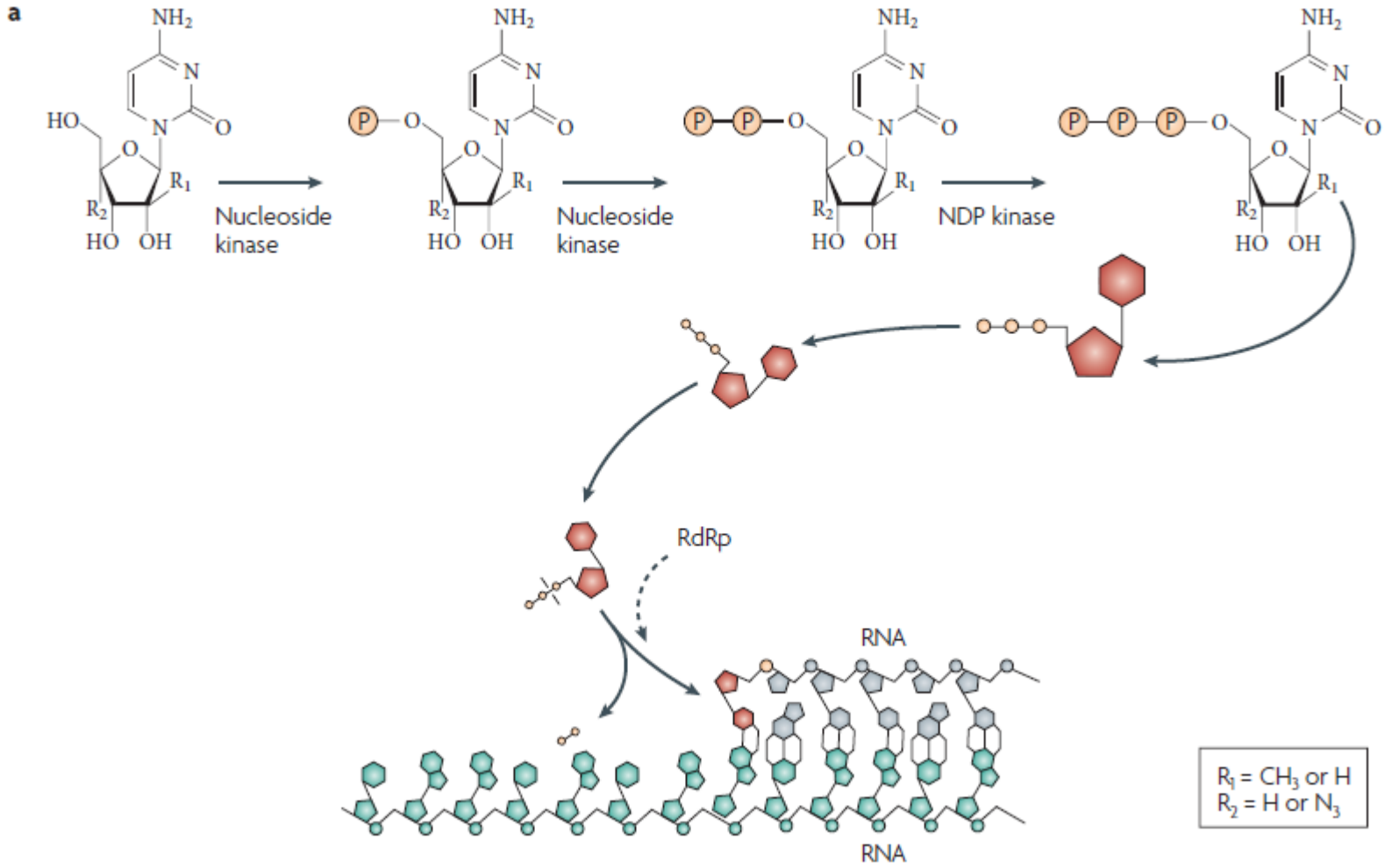
Inibidores da transcriptase reversa



Inibidores da RNA polimerase de flavivírus

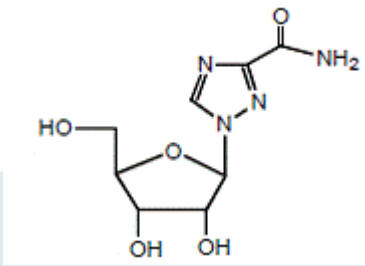
Inibidores da RNA polimerase dependente de RNA (*replicase inhibitors*)

Inibidores da NS5B de HCV



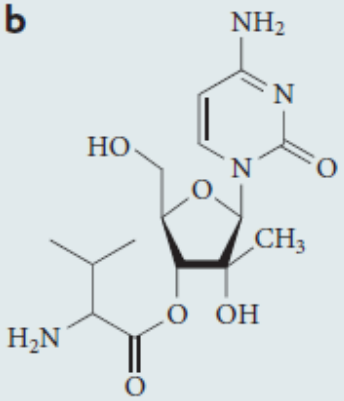
Inibidores da RNA polimerase dependente de RNA (*replicase inhibitors*)

Inibidores da NS5B de HCV análogos de nucleosídeos

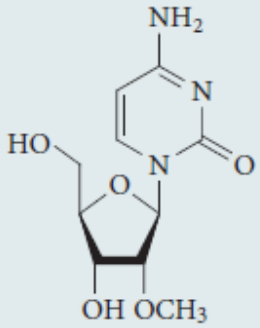


Ribavirina

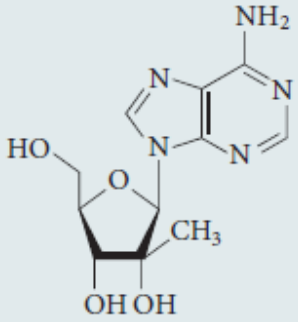
b



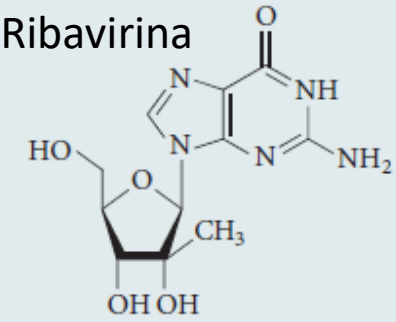
3′-valine ester of 2′-*C*-methylcytidine Valopicitabine (NM283)



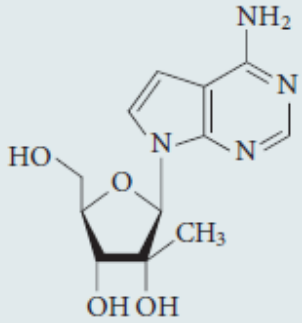
2′-*O*-methylcytidine



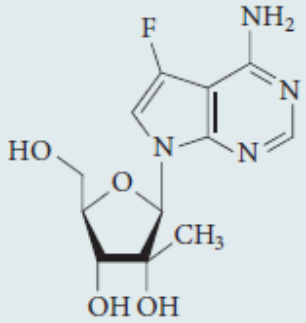
2′-*C*-methyladenosine



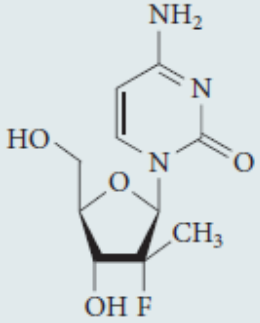
2′-*C*-methylguanosine



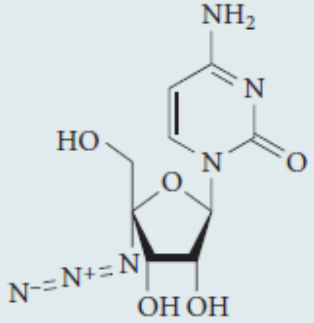
7-deaza-2′-*C*-methyladenosine



7-Deaza-7-fluoro-2′-*C*-methyladenosine



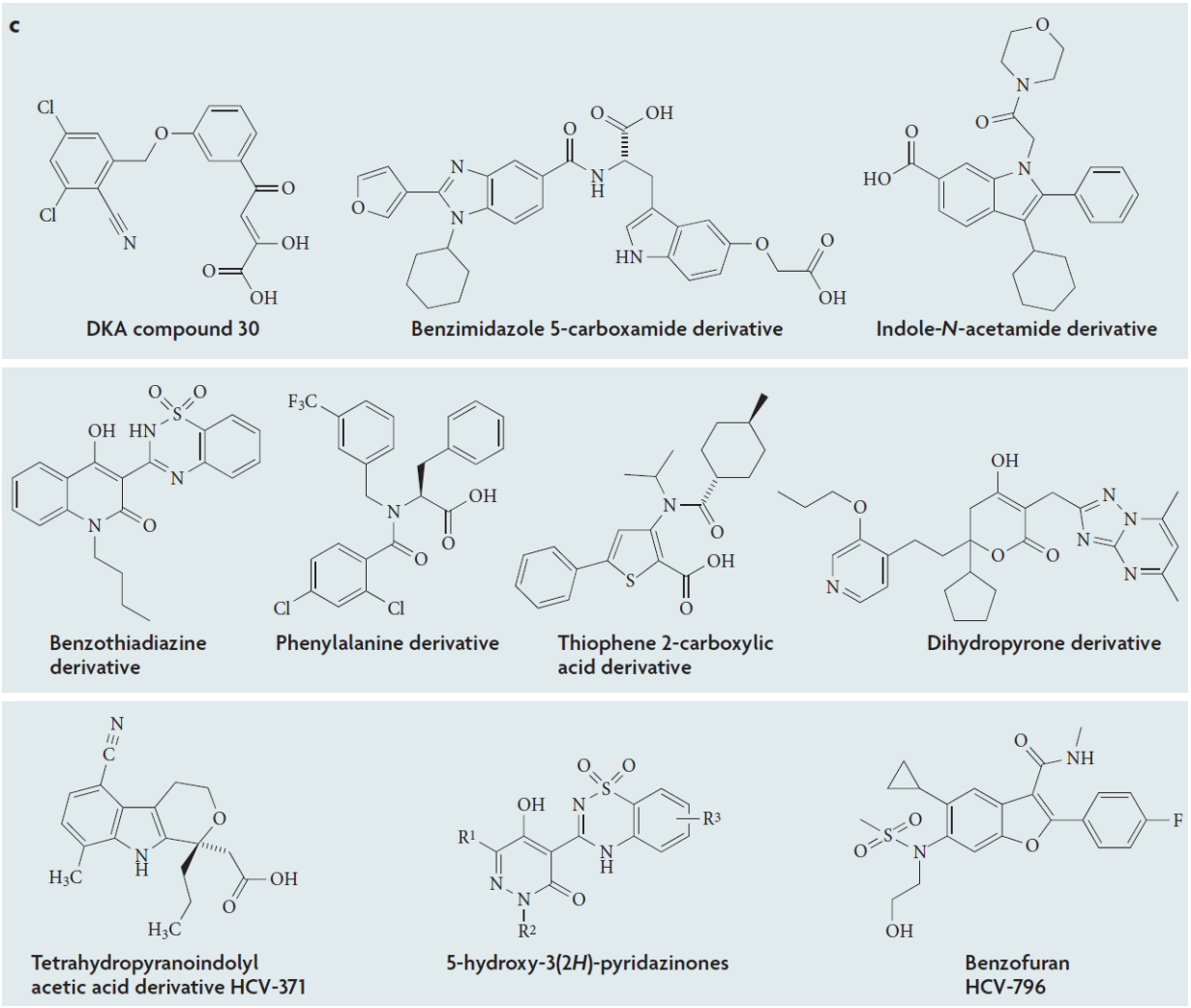
2′-Deoxy-2′-fluoro-2′-*C*-methylcytidine (PSI-6130)



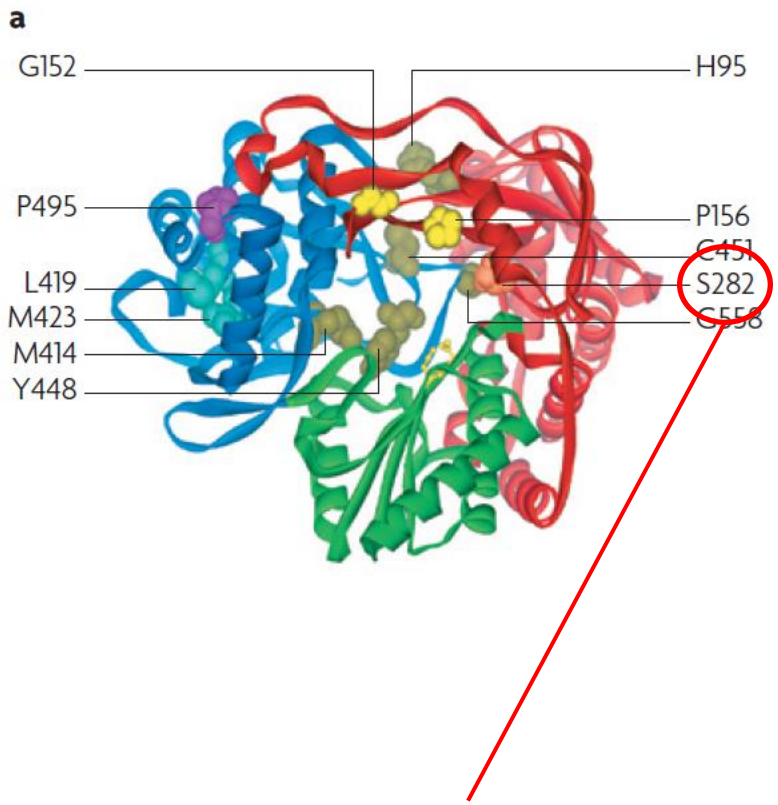
4′-Azidocytidine (R1479)

Inibidores da RNA polimerase dependente de RNA (*replicase inhibitors*)

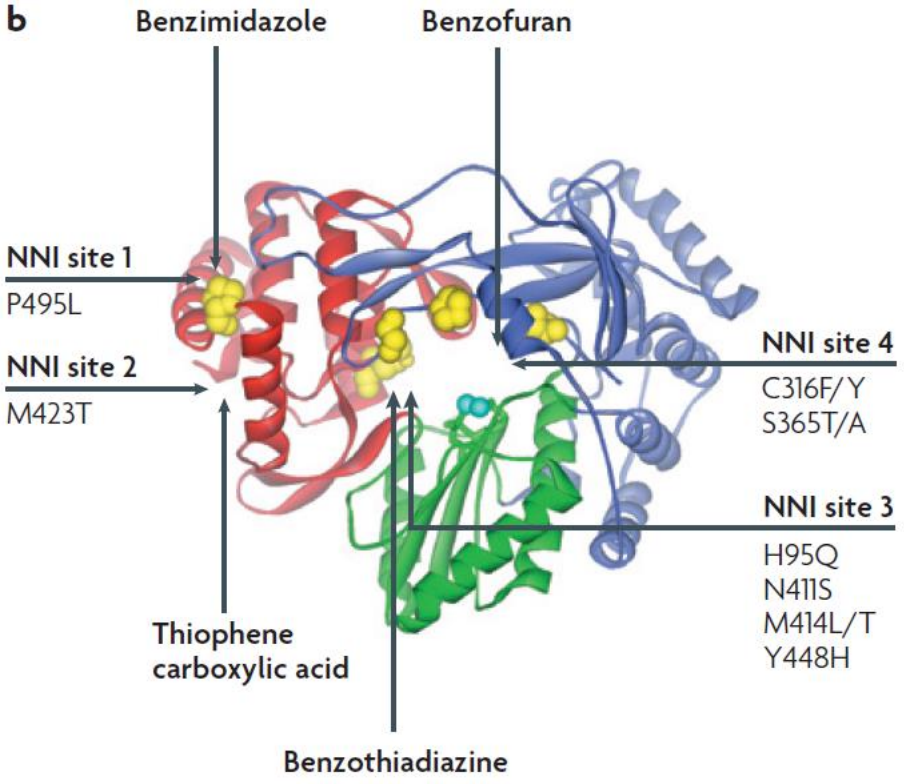
Inibidores da NS5B de HCV NÃO análogos de nucleosídeos



Inibidores da RNA polimerase dependente de RNA (*replicase inhibitors*)



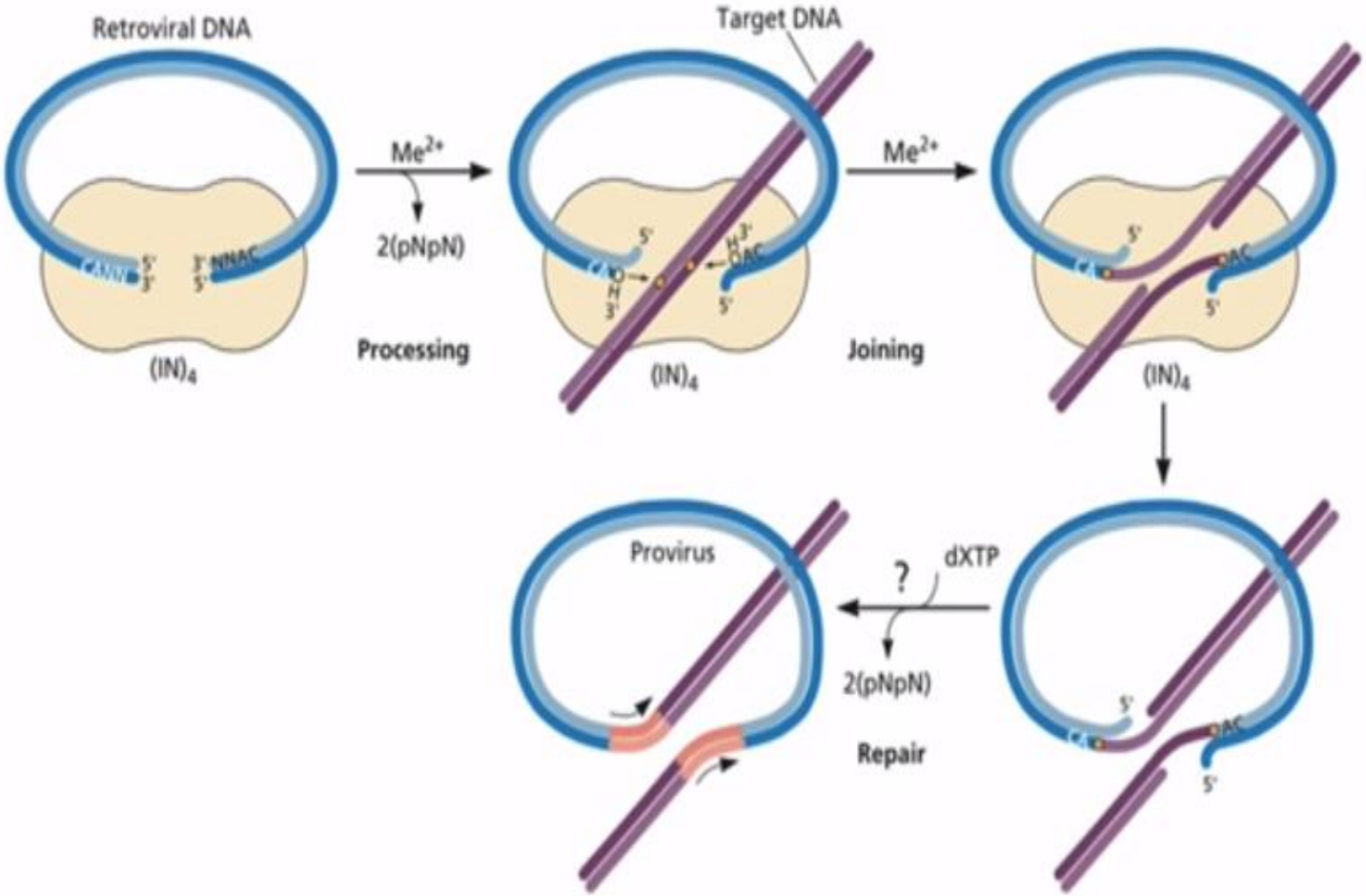
Único sítio de ligação de inibidores da replicase análogos de nucleosídeos



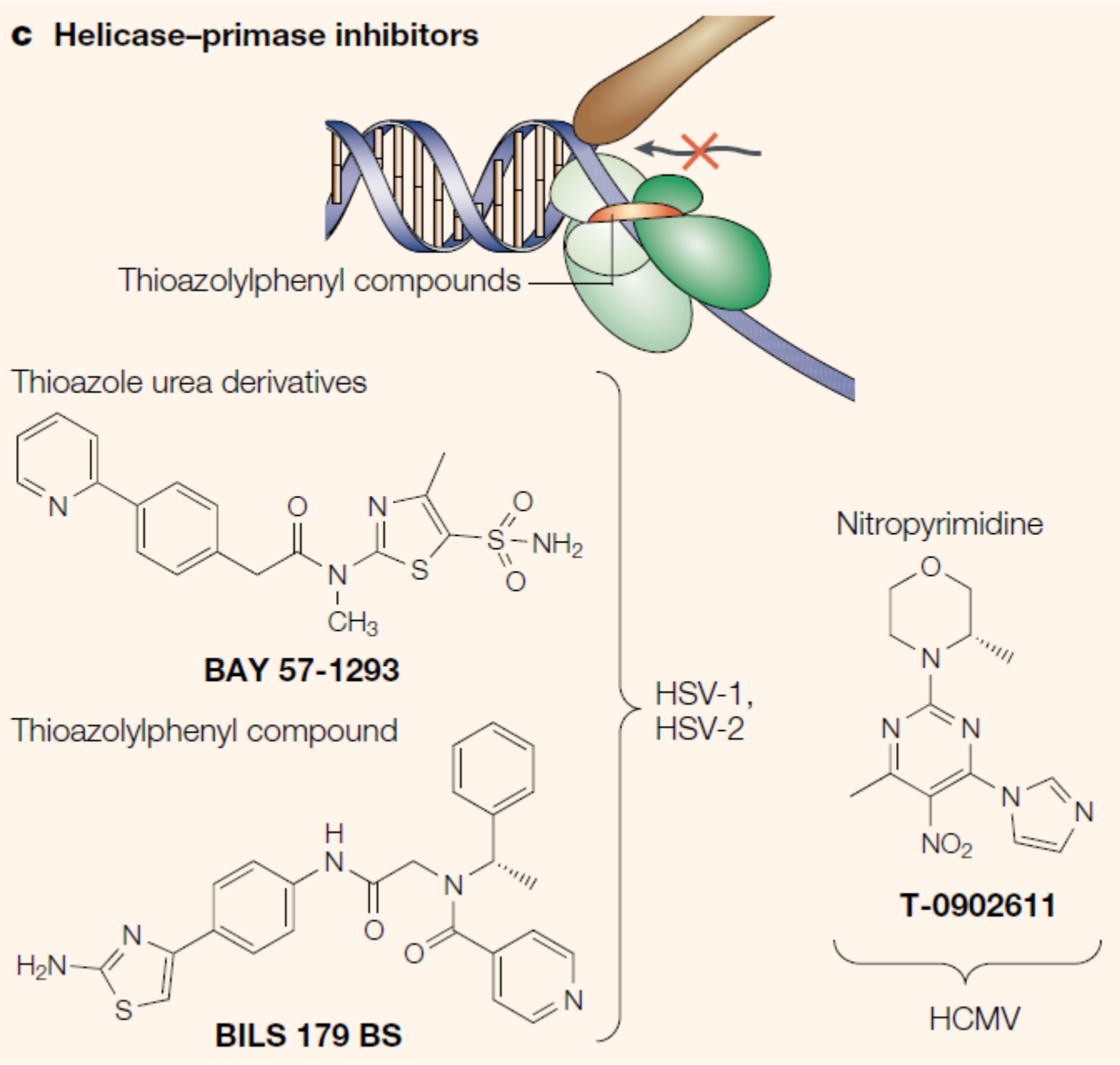
Existem 4 sítios de ligação de inibidores da replicase NÃO análogos de nucleosídeos

Inibidores de outras enzimas virais

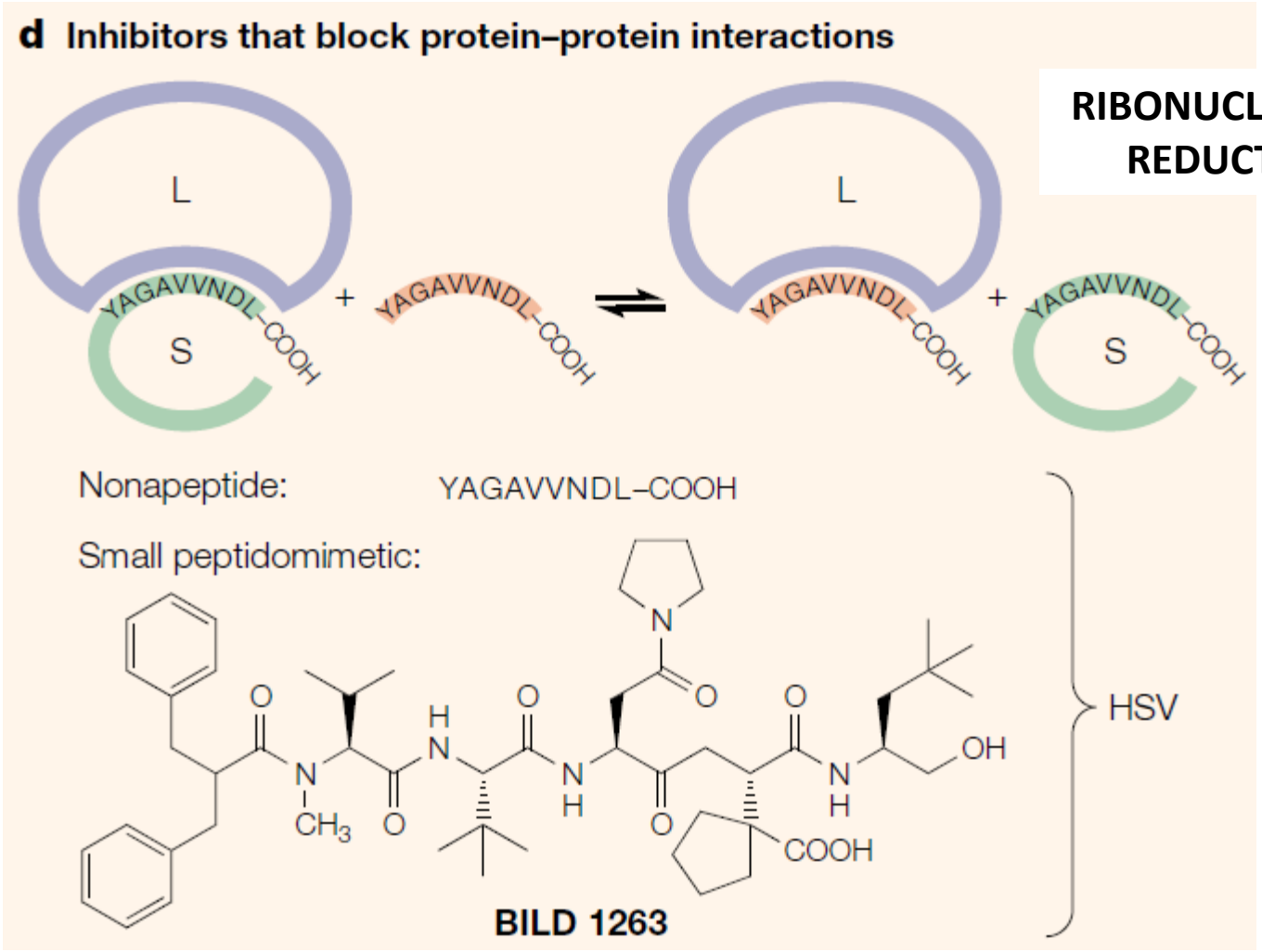
Inibidores da integrase de HIV



Inibidores da replicação de Herpesvírus



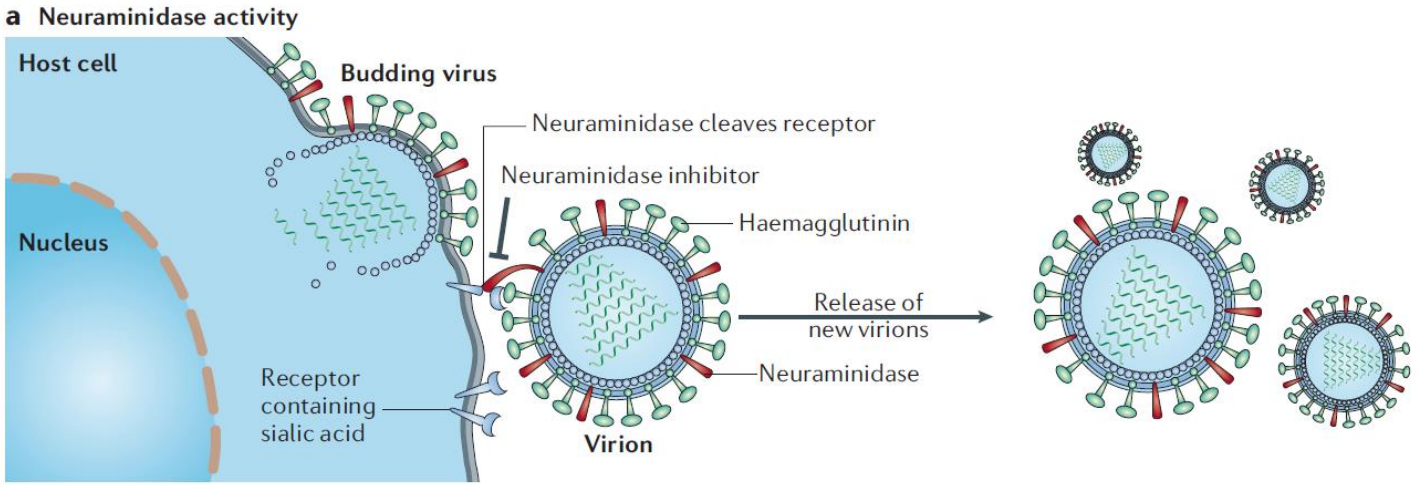
Inibidores da replicação de Herpesvírus

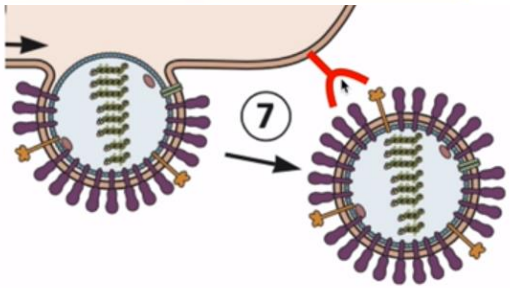


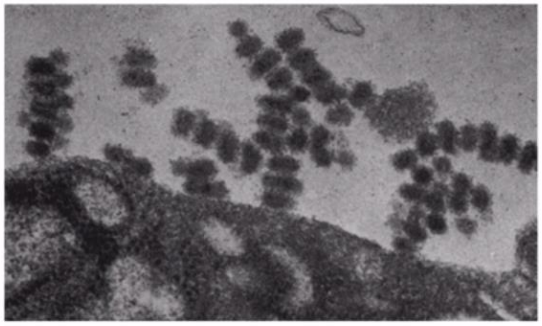
RIBONUCLEOTIDE REDUCTASE

Inibidores do brotamento

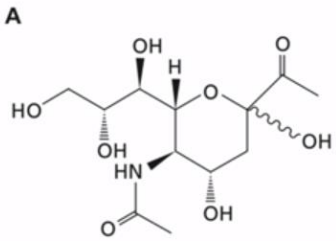
Influenza



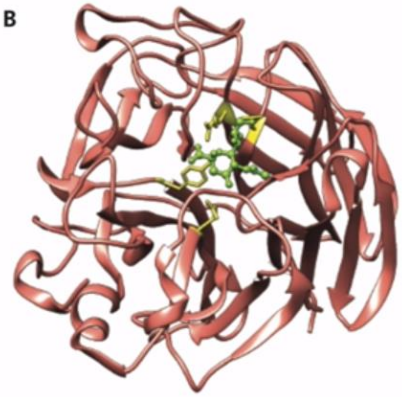


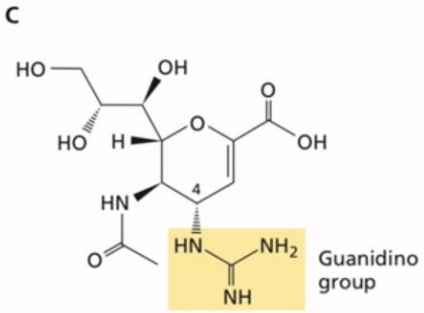


J Gen Virol. 1976 Oct;33(1):159-63.

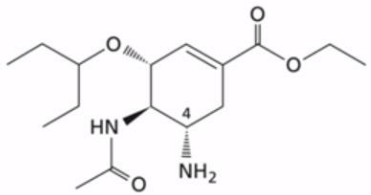


Sialic acid
(*N*-acetyl neuraminic acid)



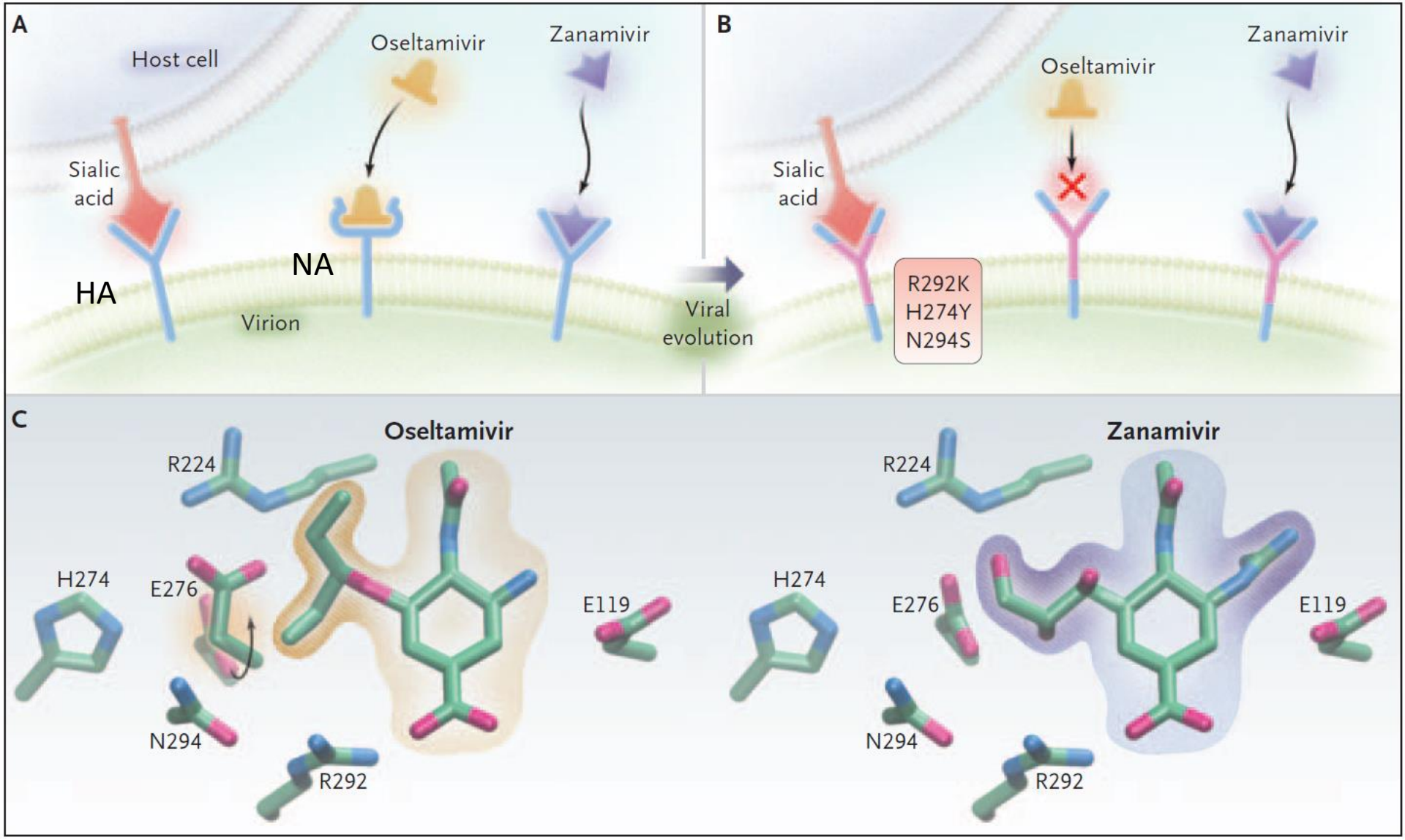


Zanamivir
"Relenza"



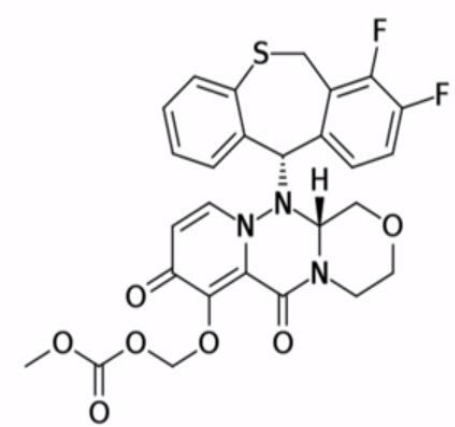
Oseltamivir
"Tamiflu"

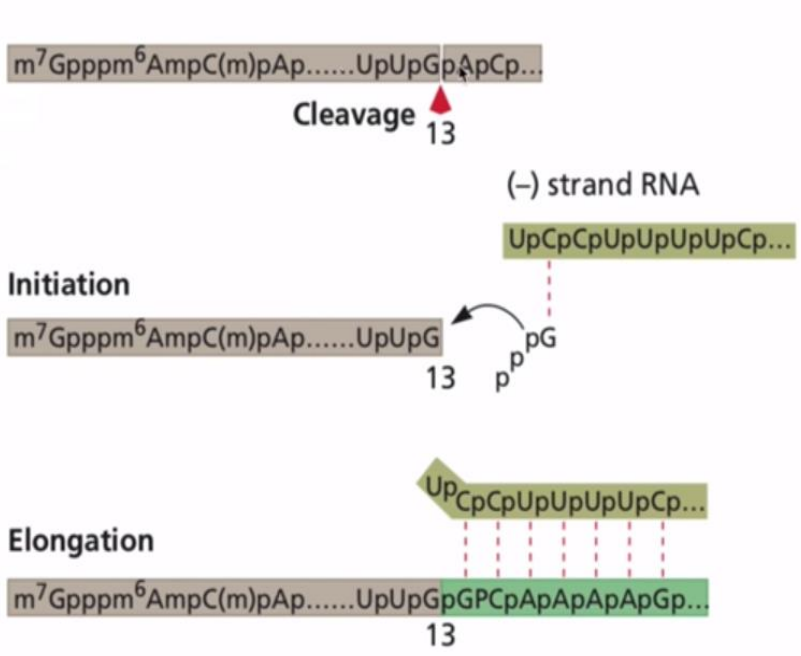
Inibidores do brotamento Influenza



Inibidores da endonuclease de influenza

- Baloxavir (aprovado em 2018)



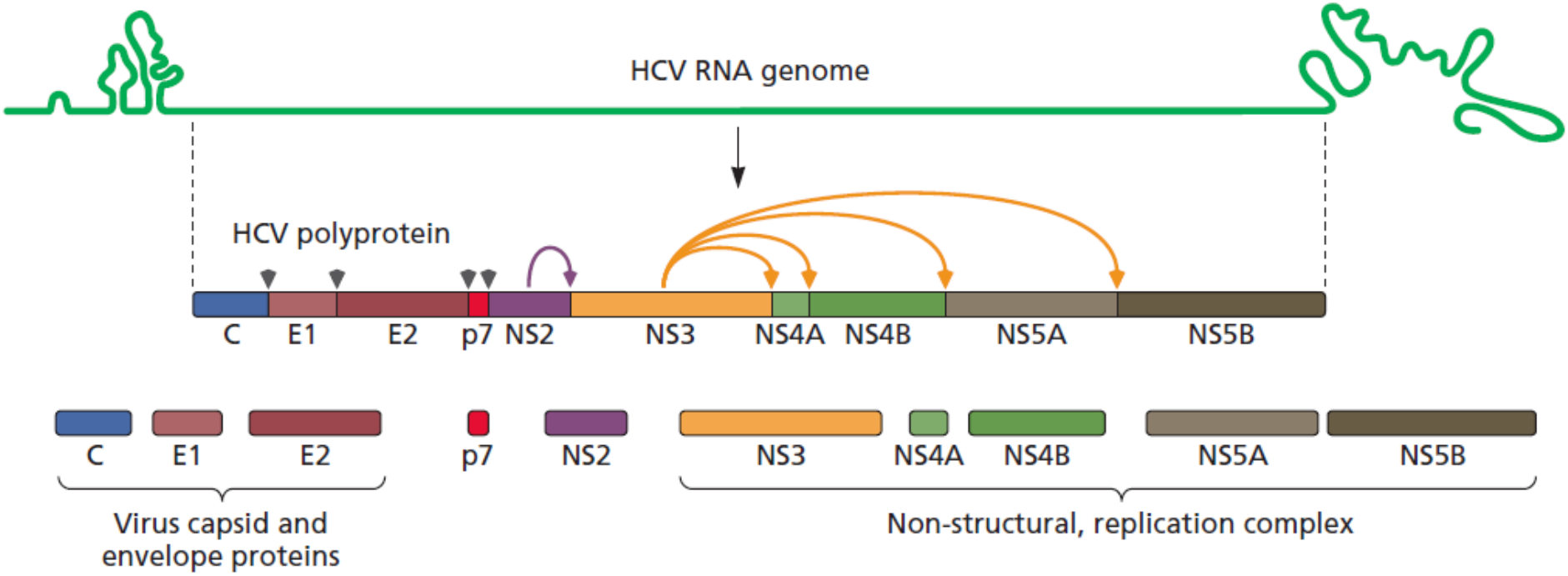


Inibidores de proteases

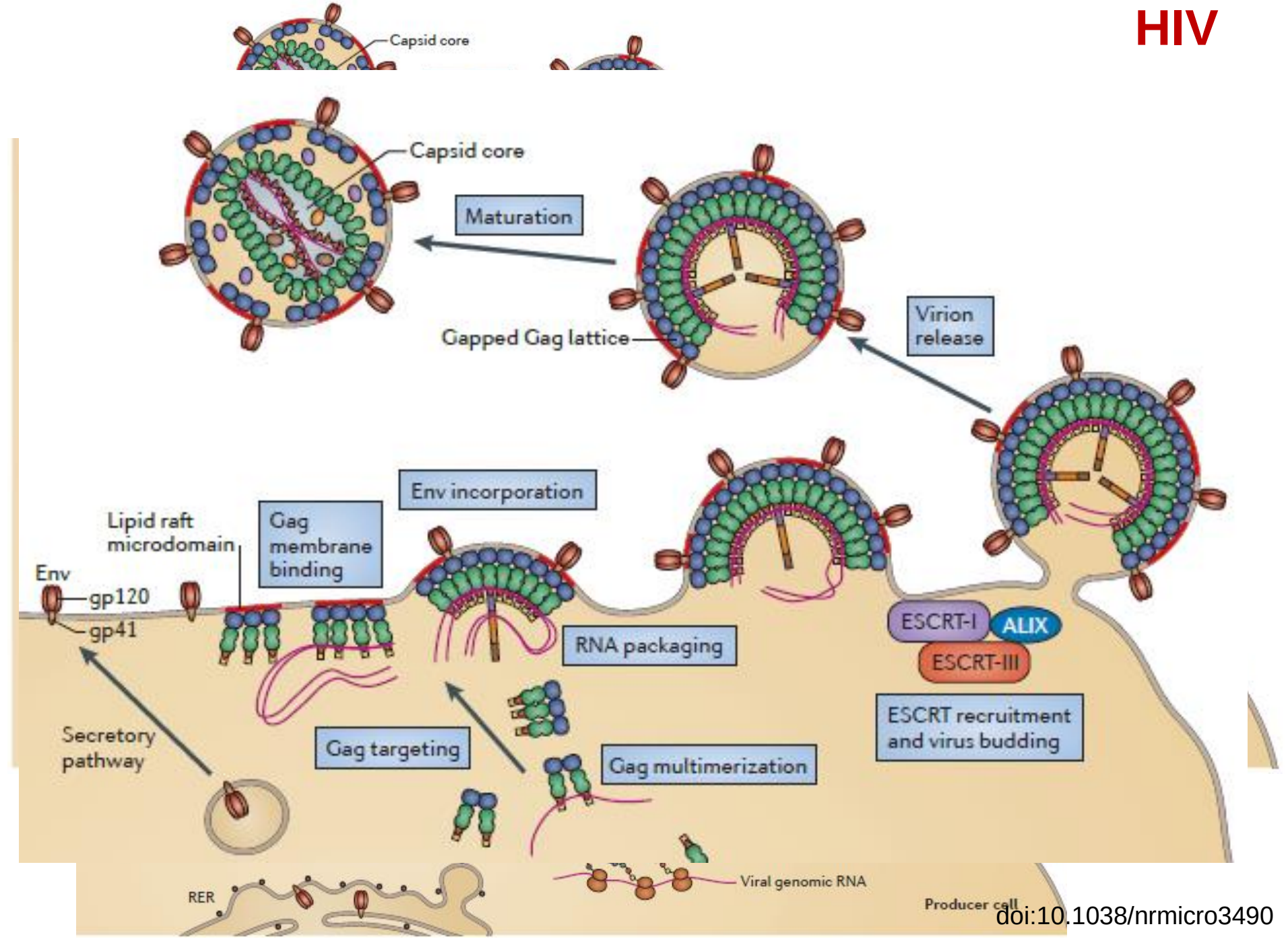
Inibidores de Protease

HCV

- Alguns vírus, por exemplo Retrovírus e Flavivírus produzem poliproteínas que precisam ser processadas.



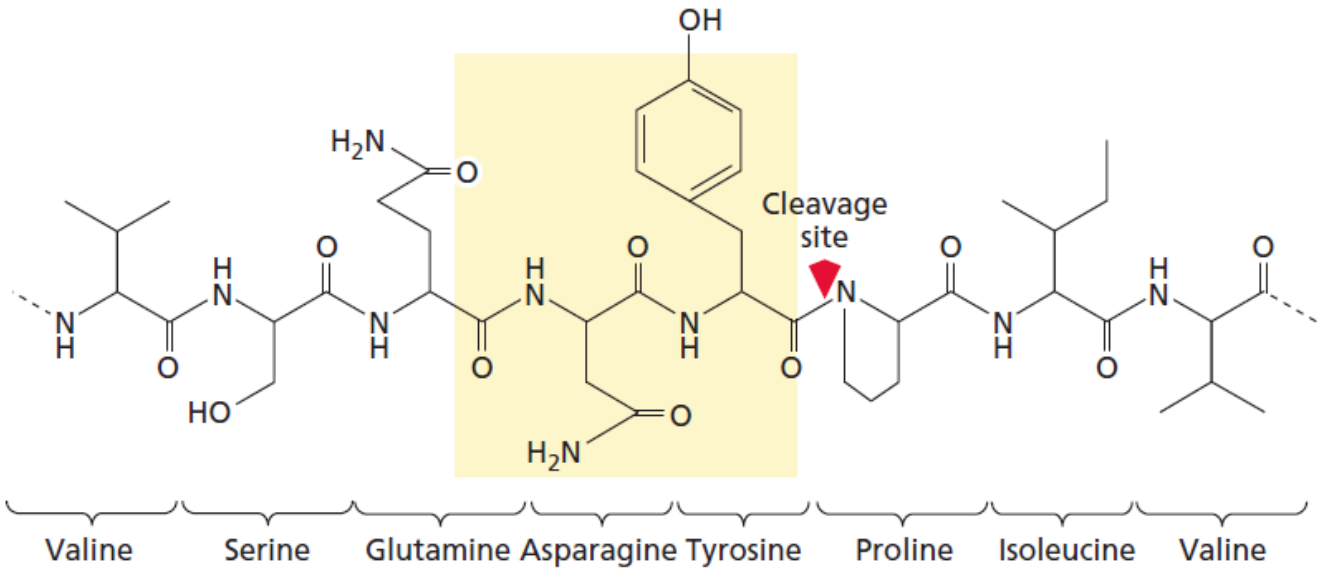
HIV



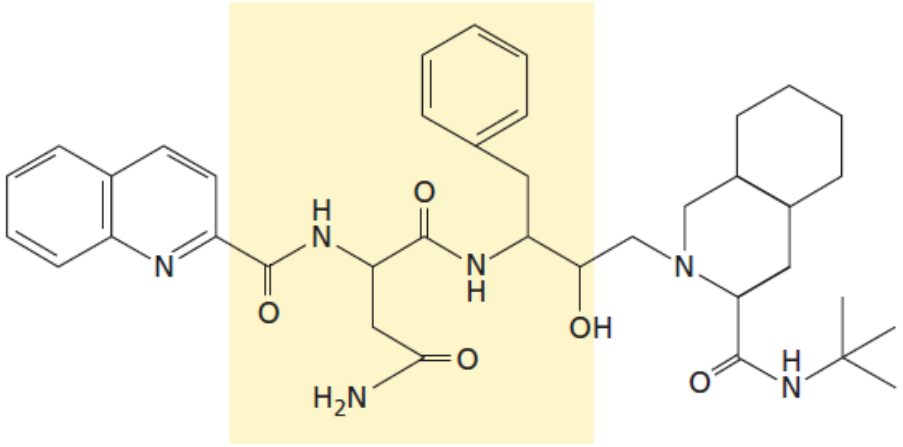
doi:10.1038/nrmicro3490

Inibidores de Protease

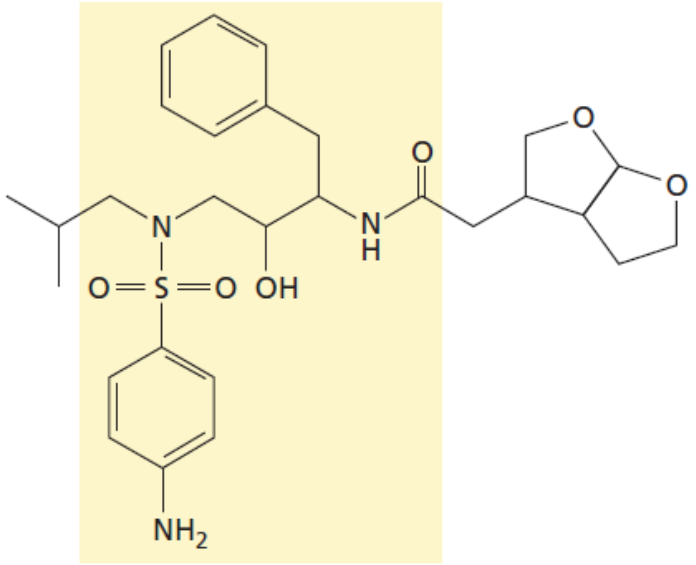
A Natural substrate of the HIV-1 protease



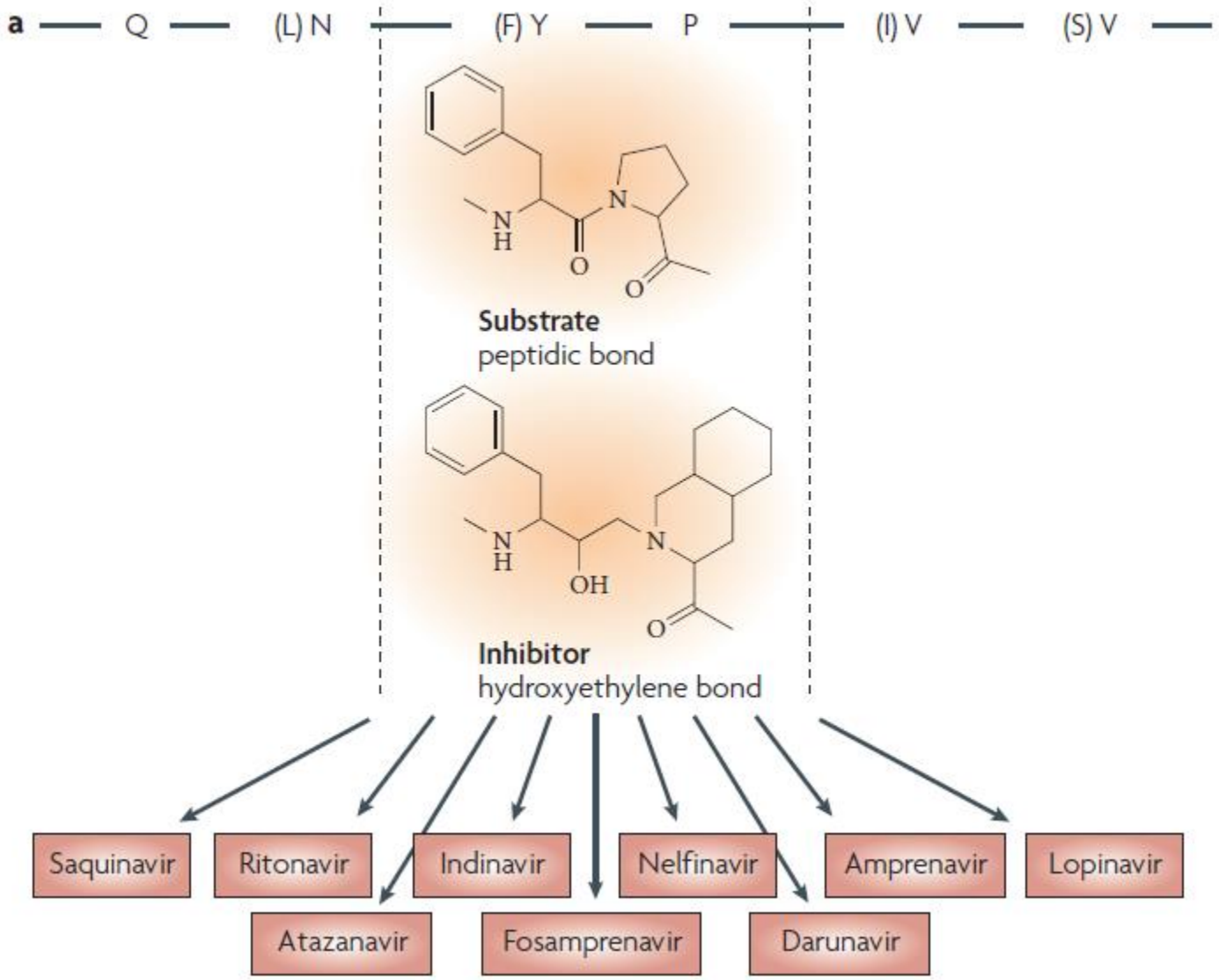
B Saquinavir



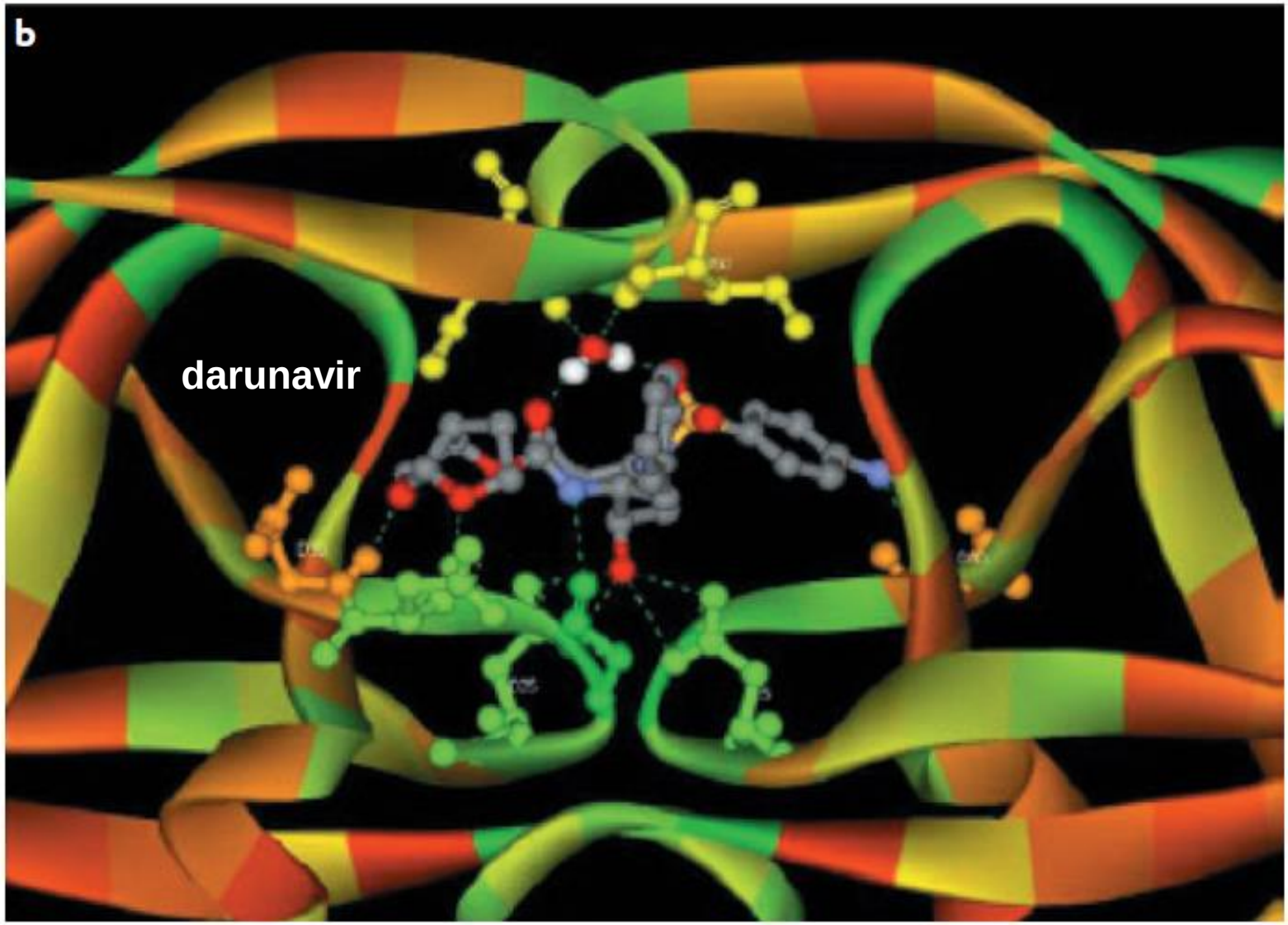
C Darunavir



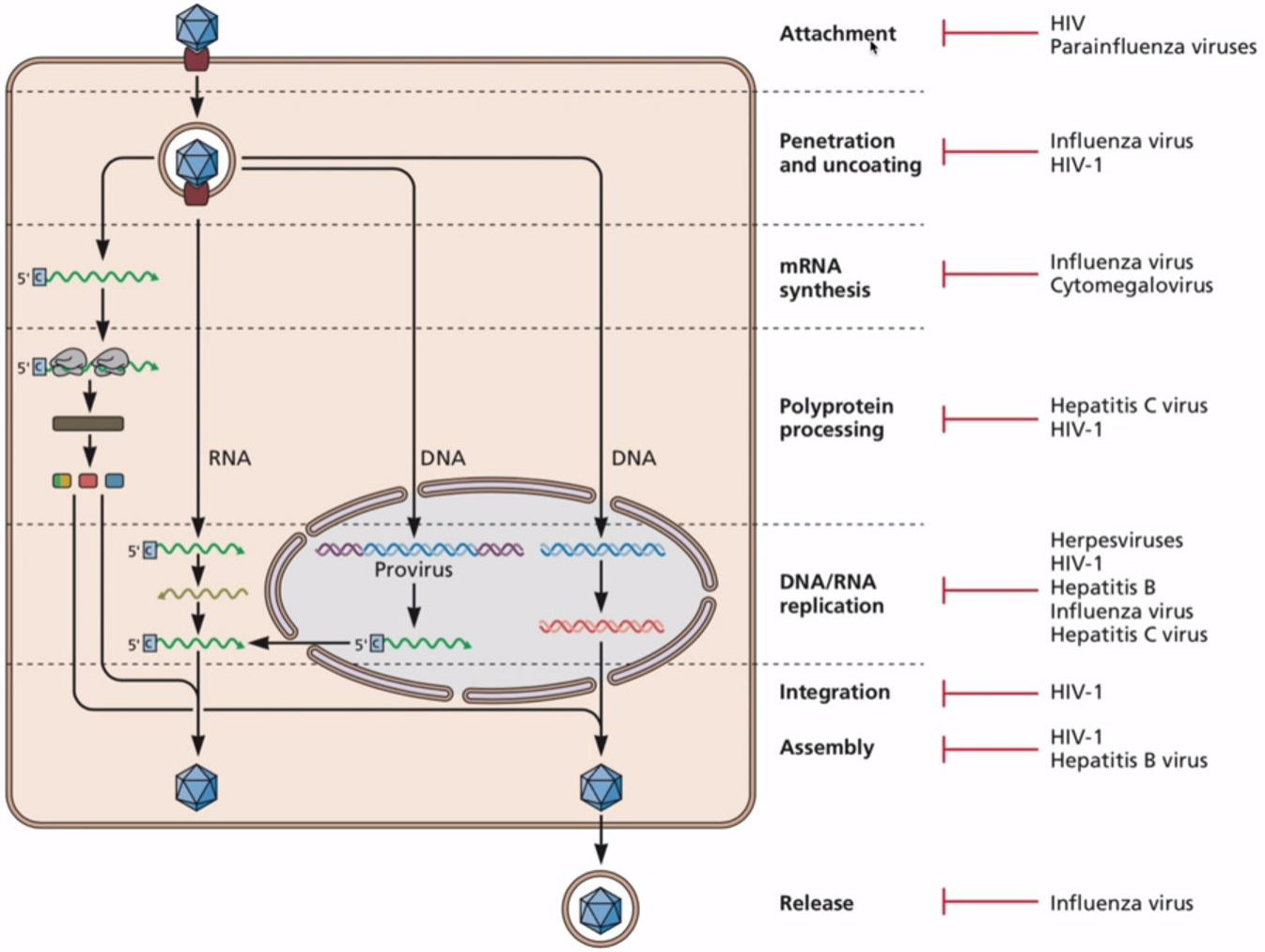
Inibidores de Protease



Inibidores de Protease



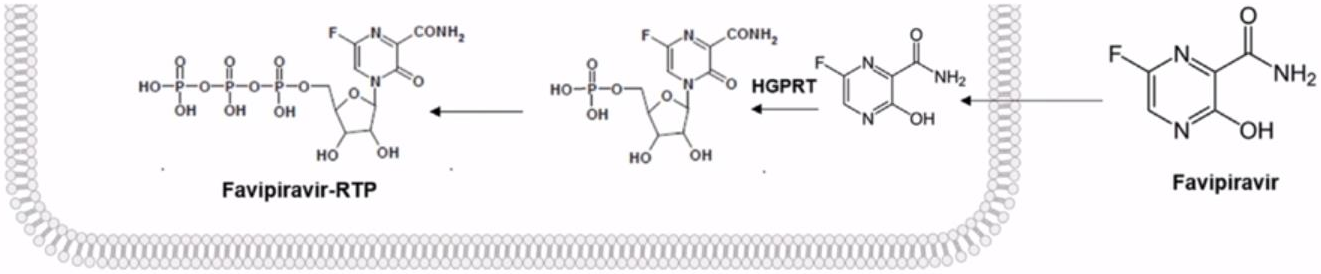
Resumindo...


RNA
DNA
DNA
Provirus
Attachment
HIV
Parainfluenza viruses
Penetration and uncoating
Influenza virus
HIV-1
mRNA synthesis
Influenza virus
Cytomegalovirus
Polyprotein processing
Hepatitis C virus
HIV-1
DNA/RNA replication
Herpesviruses
HIV-1
Hepatitis B
Influenza virus
Hepatitis C virus
Integration
HIV-1
Assembly
HIV-1
Hepatitis B virus
Release
Influenza virus

Outros inibidores...

É possível criar um antiviral de amplo espectro?

Favipiravir (Avigan)



- Broad-spectrum inhibitor of RNA viruses
- Target: RdRp, a nucleoside analog
- (+) RNA: WNV, YFV, ZIKV, WEEV, CHIKV, picornaviruses, norovirus
- (-) RNA: Lassa virus, EBOV, Rabies virus, measles virus, Pichinde, Junin, Rift Valley fever virus, Hantaviruses, Respiratory syncytial virus, parainfluenza virus
- Licensed in Japan to treat influenza

https://doi.org/10.1016/j.antiviral.2018.03.003

É possível criar um antiviral de amplo espectro?

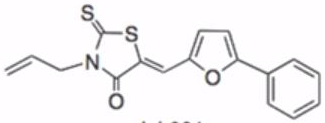
LJ001

Virus	Family	Genome type	Envelope (yes/no)	Activity
Ebola[L] (cat A)	Filoviridae	ssRNA(−)	Y	++
Marburg[L] (cat A)	Filoviridae	ssRNA(−)	Y	++
Influenza A[L] (cat A)	Orthomyxoviridae	ssRNA(−)	Y	+++
Junín[L] (cat A)	Arenaviridae	ssRNA(−)	Y	++
Rift Valley fever[L] (cat A)	Bunyaviridae	ssRNA(−)	Y	+++
LaCrosse[L] (cat B)	Bunyaviridae	ssRNA(−)	Y	+++
Nipah[L,P] (cat C)	Paramyxoviridae	ssRNA(−)	Y	++
Omsk hemorrhagic fever[L] (cat C)	Flaviviridae	ssRNA(+)	Y	++
RSSE[L] (cat C)	Flaviviridae	ssRNA(+)	Y	++
PIV-5[L]	Paramyxoviridae	ssRNA(−)	Y	++
HPIV-3[L]	Paramyxoviridae	ssRNA(−)	Y	++
Newcastle disease[L] *	Paramyxoviridae	ssRNA(−)	Y	++
HIV-1[L,P] *	Retroviridae	ssRNA(−)RT	Y	++
Murine leukemia[L]	Retroviridae	ssRNA(−)RT	Y	++
Yellow fever[L]	Flaviviridae	ssRNA(+)	Y	+++
Hepatitis C[L]	Flaviviridae	ssRNA(+)	Y	+++
West Nile[L]	Flaviviridae	ssRNA(+)	Y	+++
Vesicular stomatitis[L,P]	Rhabdoviridae	ssRNA(−)	Y	++
Cowpox[L]	Poxviridae	dsDNA	Y	+
Vaccinia[L]	Poxviridae	dsDNA	Y	++
Adenovirus[L] **	Adenoviridae	dsDNA	N	−
Coxsackie B[L] **	Picornaviridae	ssRNA(+)	N	−
Reovirus[L]	Reoviridae	dsRNA	N	−

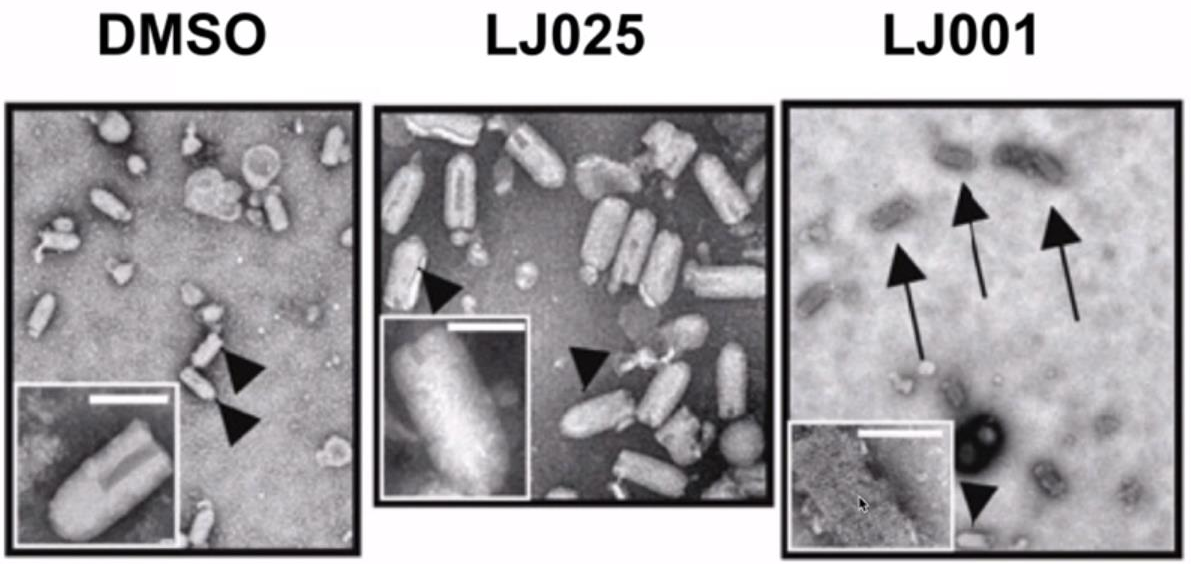
http://www.ncbi.nlm.nih.gov/pubmed/20133606

É possível criar um antiviral de amplo espectro?

LJ001

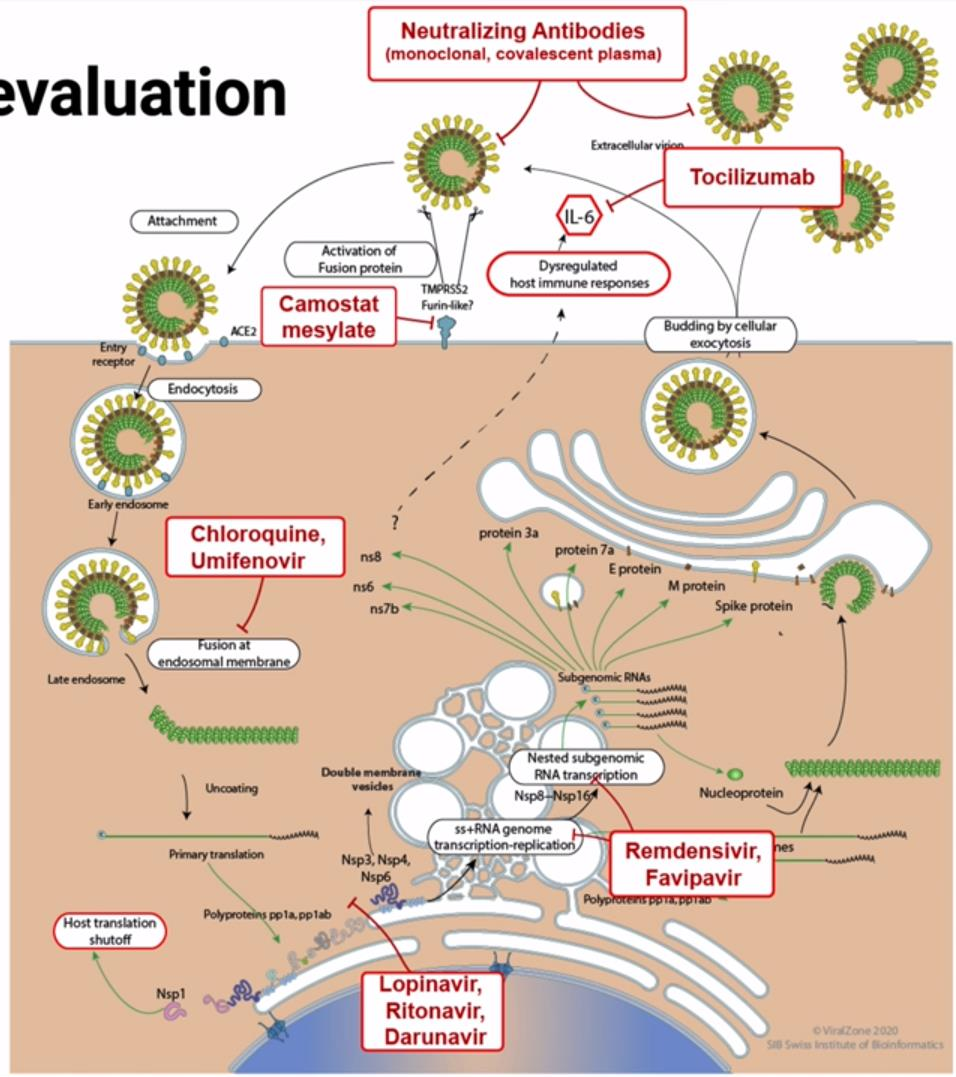


LJ-001



SARS-CoV-2 antivirals under evaluation

- Camostat mesylate - inhibitor of TMPRSS2 protease
- Chloroquine - raises endosomal pH
- Remdesivir, Favipiravir - nucleot/side analogs
- Lopinavir, Ritonavir, Darunavir - HIV-1 protease inhibitors
- 79 trials at clinicaltrials.gov



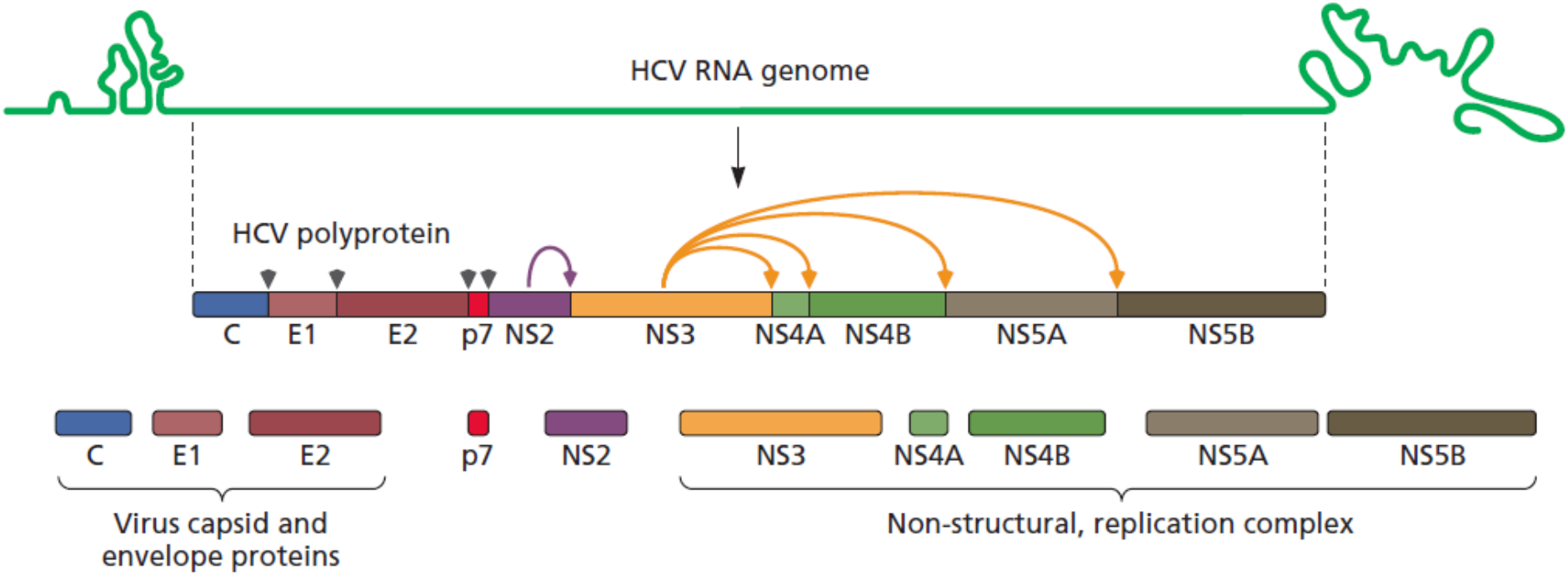
Virology Lectures 2020 • Prof. Vincent Racaniello • Columbia University

26/09/2022 --- **8269** clinical trials em andamento.

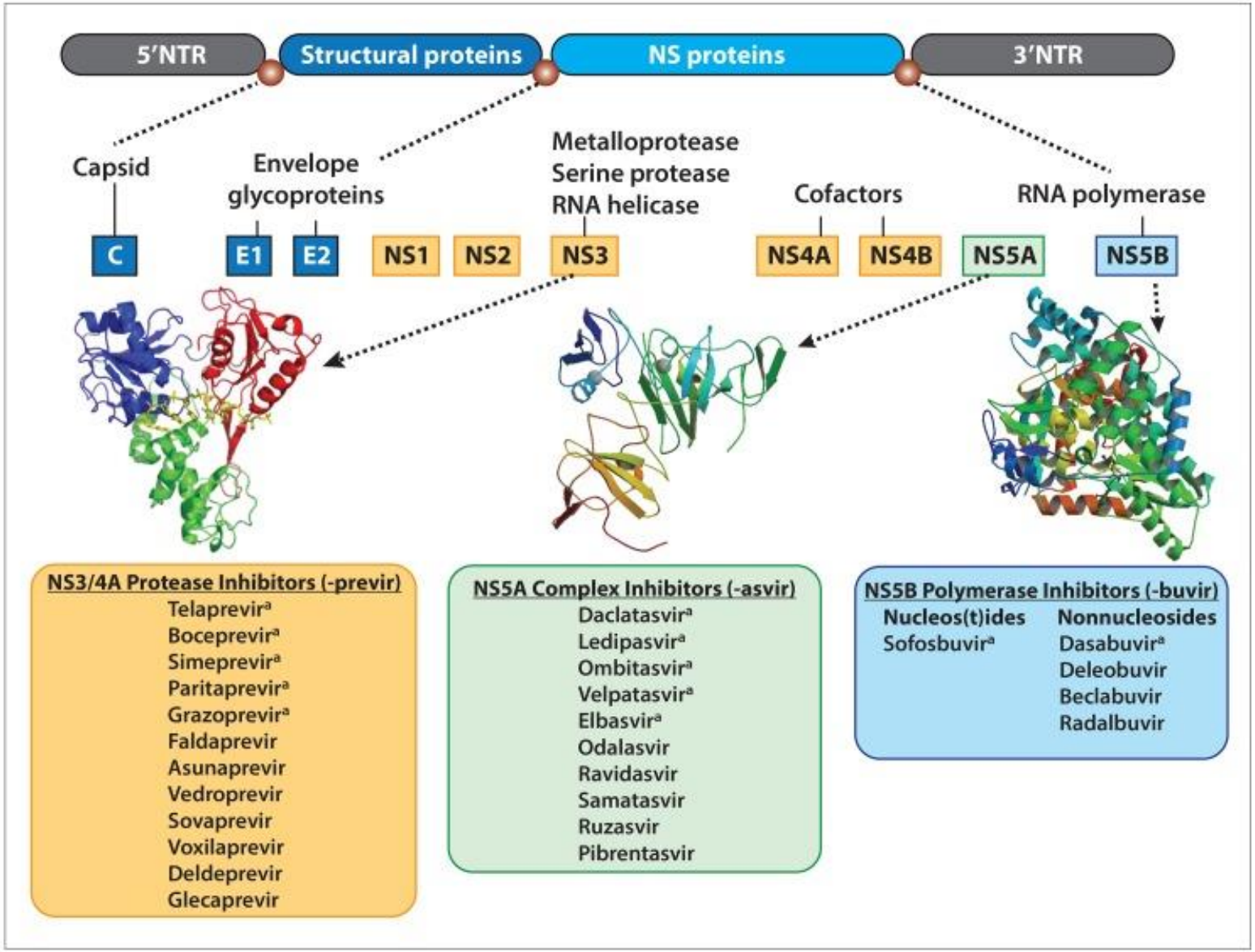
Duas histórias de sucesso.

Vírus da Hepatite C

- Várias atividades enzimáticas.



Vírus da Hepatite C



Gastroenterol Hepatol (N Y). 2017 Jan;13(1):22-31.

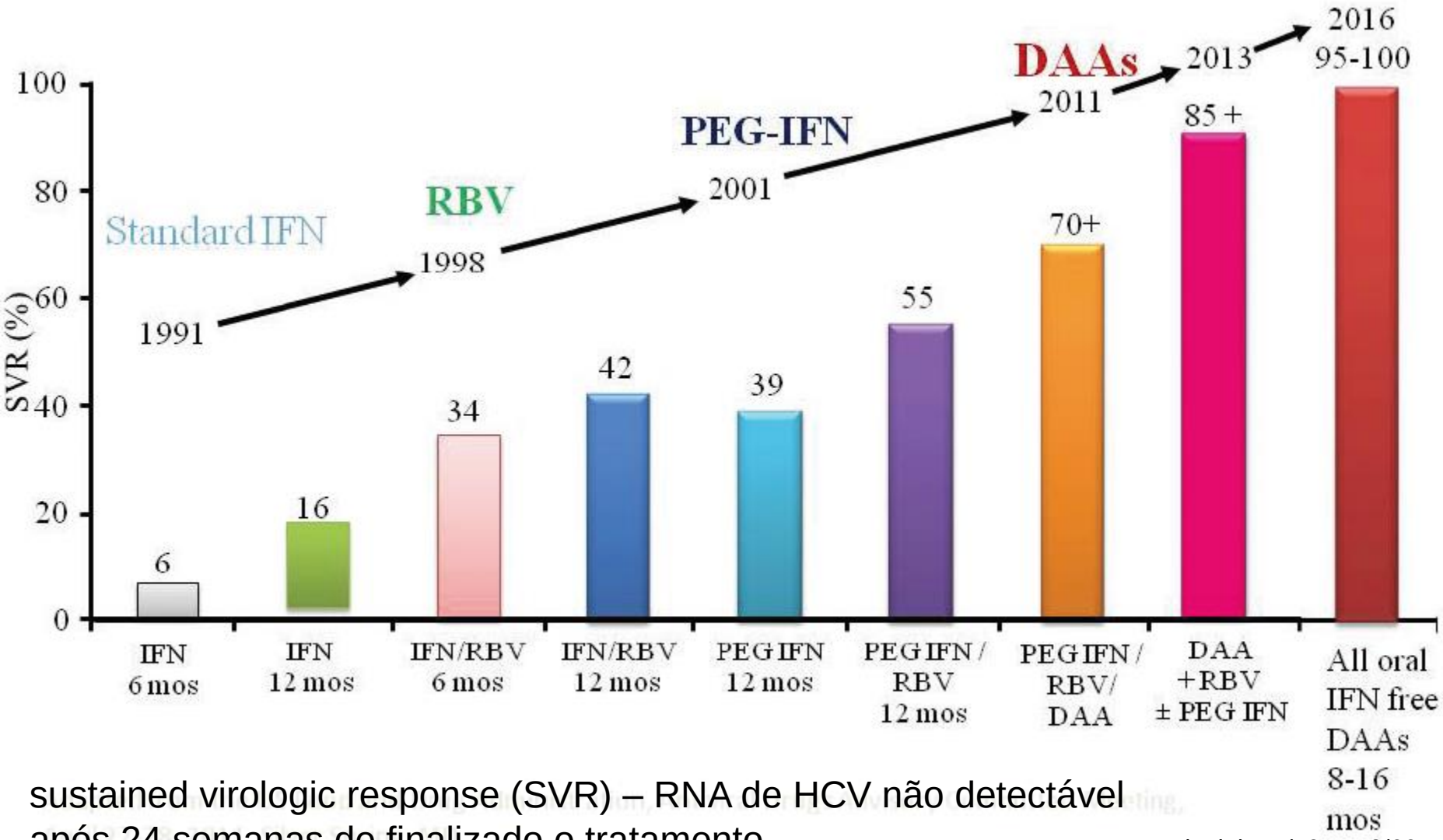
Vírus da Hepatite C

Table 9.2 Examples of drugs targeted against HCV proteins

Target	Generic name	Brand name	Developer	Date approved/ Trial phase
Polymerase (NS5B)	Sofosbuvir	Sovaldi	Gilead Sciences	2013
Nucleoside	Mericitabine		Roche	II
Nonnucleoside	Deleobuvir		Boehringer Ingelheim	III
	ABT-333		Abbott	III
RNA binding (NS5A)	Ledipasvir		Gilead Scienes	III (filed)
	Daclatasvir		Bristol-Myers Squibb	III
	ABT-267		Abbott	III
Protease (NS3/4A)	Telaprevir	Incivek	Vertex/Johnson & Johnson	2011
	Boceprevir	Victrelis	Merck	2011
	Simeprevir	Olysio	Janssen/Tibotec/Medivir	2013
	Faldaprevir		Boehringer Ingelheim	III
	Vaniprevir		Merck	III
	Samatasvir		Idenix	II
Combinations	Sofosbuvir + ledipasvir		Gilead Sciences	III
	Faldaprevir + deleobuvir		Boehringer Ingelheim	III
	Simeprevir + samatasvir + TMC647055/r		Janssen	II
	ABT-450/r + ABT-267 and ABT-333		Abbott	II
	MK-8742 + MK-5172		Merck	II

Vírus da Hepatite C

Evolução das terapias: Maior eficâcia.

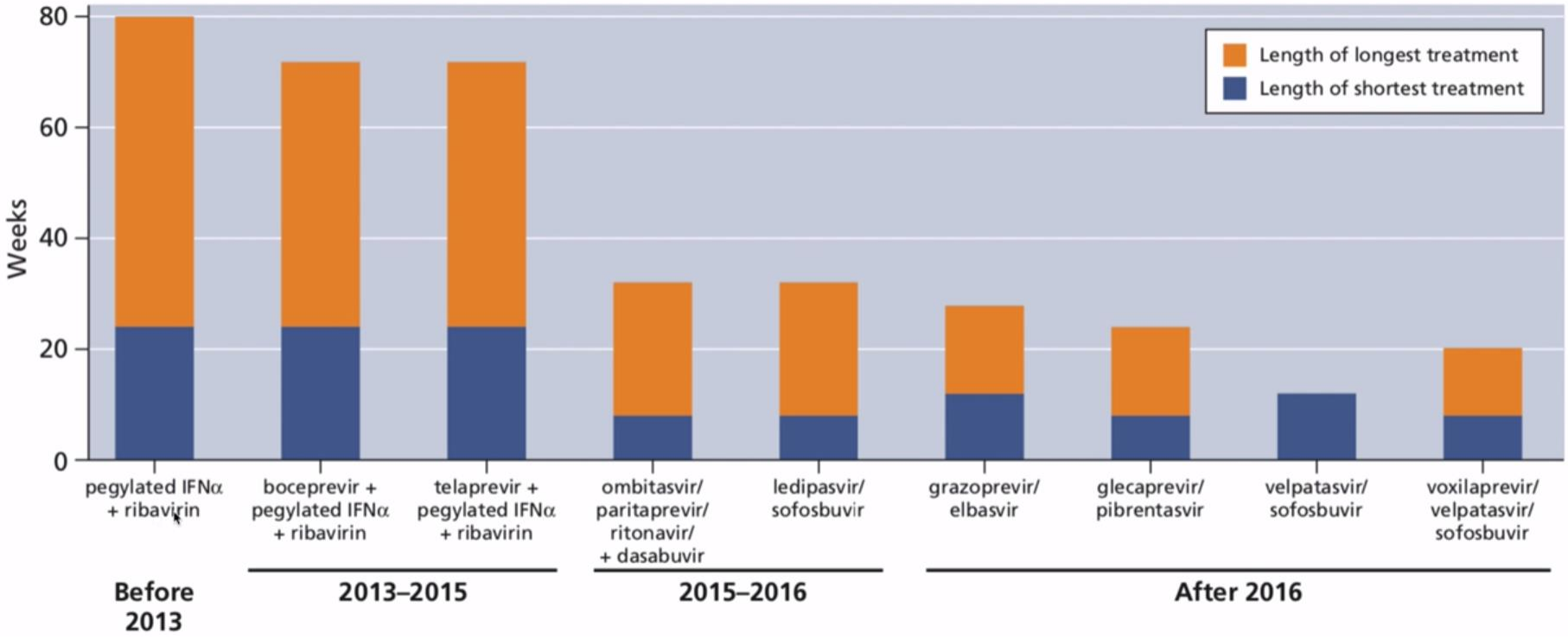


sustained virologic response (SVR) – RNA de HCV não detectável após 24 semanas de finalizado o tratamento.

dx.doi.org/10.5772/66719

Vírus da Hepatite C

Evolução das terapias: menor tempo.



HIV

HAART ***Highly active antiretroviral therapy***

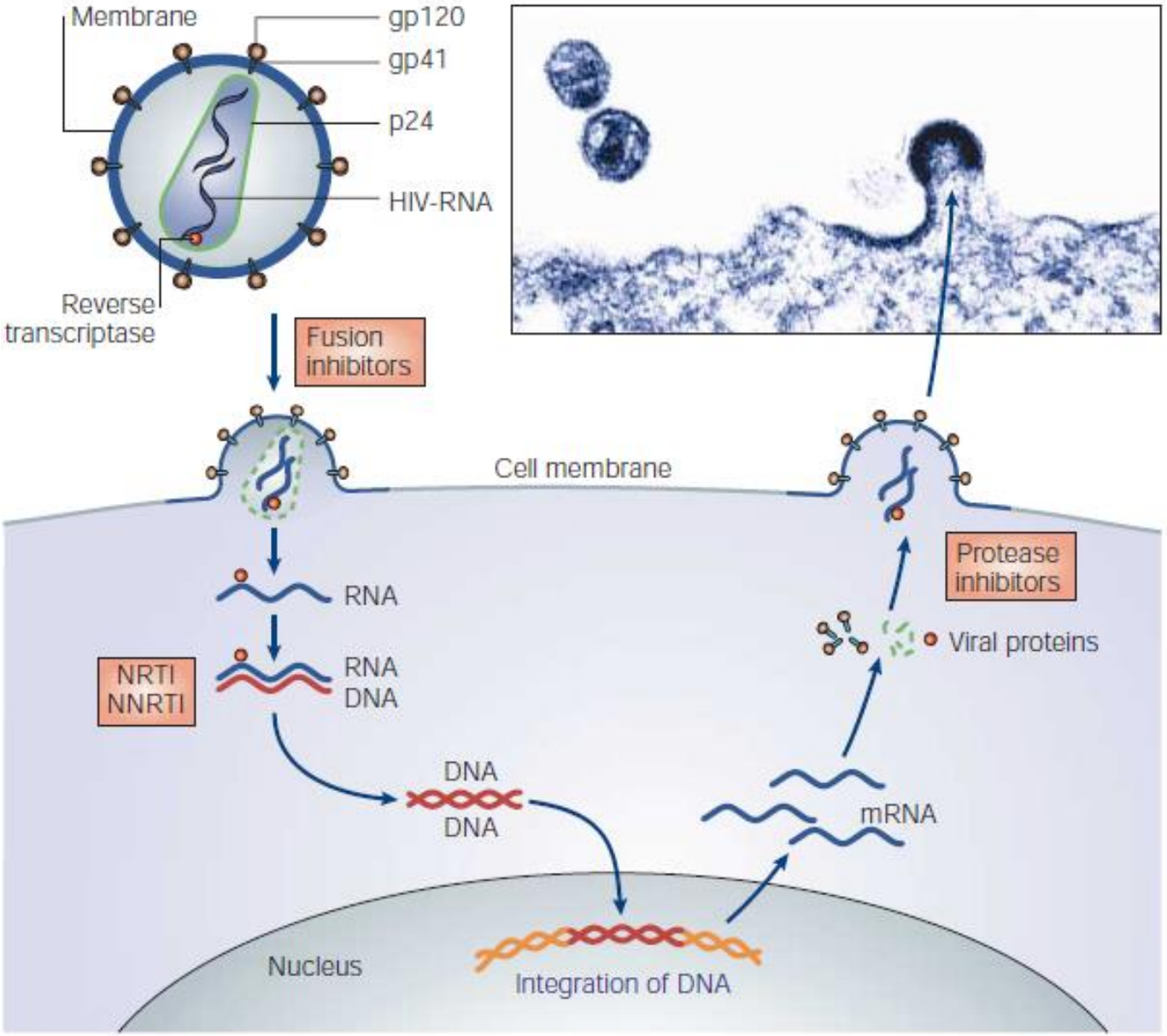
HAART Highly active antiretroviral therapy

- Drogas anti-retrovirais que inibem a reprodução do HIV no sangue;
- Terapia anti-retroviral, também chamada de coquetel;
- Atualmente, são dezenas de medicamentos divididos em cinco classes.

HAART Highly active antiretroviral therapy

- inibidores de transcriptase reversa análogos de nucleosídeos
- inibidores de transcriptase reversa não análogos de nucleosídeos
- Inibidores de protease
- Inibidores de fusão
- Inibidores da integrase

HAART Highly active antiretroviral therapy



HAART Highly active antiretroviral therapy

Target	Generic name	Brand name	Manufacturer	Year
Reverse transcriptase	Zidovudine (AZT)	Retrovir	GlaxoSmithKline	1987
Nucleos(t)ide inhibitors	Didanosine (ddI)	Videx	Bristol-Myers Squibb	1991
	Zalcitabine (ddC)	Hivid	Hoffmann-La Roche	1992
	Stavudine (d4T)	Zerit	Bristol-Myers Squibb	1994
	Lamivudine (3TC)	Epivir	GlaxoSmithKline	1995
	Abacavir (ABC)	Ziagen	GlaxoSmithKline	1998
	Tenofovir (TDF)	Viread	Gilead Sciences	2001
	Emtricitabine (FTC)	Emtriva	Bristol-Myers Squibb	2003
Nonnucleoside inhibitors	Nevirapine (NVP)	Viramune	Roxane	1996
	Delavirdine (DLV)	Rescriptor	Pfizer	1997
	Efavirenz (EFV)	Sustiva	DuPont	1998
	Etravirine (ETR)	Intelence	Tibotec	2008
	Rilpivirine (RPV)	Edurant	Tibotec	2011
Protease	Saquinavir (SQV)	Invirase	Hoffmann-La Roche	1995
	Ritonavir (RTV)	Norvir	Abbott	1996
	Indinavir (IDV)	Crixivan	Merck	1996
	Nelfinavir (NFV)	Viracept	Agouron	1997
	Amprenavir (APV)	Agenerase	GlaxoSmithKline	1999
	Lopinavir/RTV	Kaletra	Abbott	2000
	Atazanavir (ATV)	Revataz	Bristol-Myers Squibb	2003
	Fosamprenavir (FPV)	Lexia	ViiV	2003
	Tipranavir (TPV)	Aptivus	Boehringer Ingelheim	2005
	Darunavir (DRV)	Prezista	Tibotec	2006
Integrase	Raltegravir (RAL)	Isentress	Merck	2007
	Elvitegravir (EVG)	Vitekta	Gilead Sciences	2012
	Dolutegravir (DTG)	Tivicay	GlaxoSmithKline	2013
Entry	Enfuvirtide (T20)	Fuzeon	Genentech	2003
	Maraviroc (MVC)	Selzentry	Pfizer	2007
Combinations	3TC/AZT	Combivir	ViiV	1997
	ABC/3TC/AZT	Trizivir	ViiV	2000
	TDF/FTC	Truvada	Gilead Sciences	2004
	DRV/cobicistat (COBI)	Prezcobix	Janssen	2006
	TDF/FTC/EFV	Atripla	Bristol-Myers Squibb/ Gilead Sciences	2006
	TDF/FTC/RPV	Complera	Gilead Sciences	2011
	TDF/FTC/EVG/COBI	Stribild	Gilead Sciences	2012
	DTG/ABC/3TC	Triumeq	Gilead Sciences	2014
	RAL/3TC	Dutrebis	Merck	2015
	ATV/COBI	Evotaz	ViiV	2015
	TAF[a]/COBI/FTC/EVG	Genvoya	Gilead Sciences	2015
	TAF/RPV/FTC	Odefsey	Gilead Sciences	2016
	TAF/FTC	Descovy	Gilead Sciences	2016
	DTG/RPV	Juluca	ViiV	2017
	Bictegravir/FTC/TAF	Biktarvy	Gilead Sciences	2018

FDA Approval of HIV Medicines

1981: First AIDS cases are reported in the United States.

'85-'89

1987
Zidovudine (NRTI)

'90-'94

1991
Didanosine (NRTI)

1992
Zalcitabine (NRTI)

1994
Stavudine (NRTI)

'95-'99

1995
Lamivudine (NRTI)
Saquinavir (PI)

1996
Indinavir (PI)
Nevirapine (NNRTI)
Ritonavir (PI)

1997
Combivir (FDC)
Delavirdine (NNRTI)
Nelfinavir (PI)

1998
Abacavir (NRTI)
Efavirenz (NNRTI)

1999
Amprenavir (PI)

'00-'04

2000
Didanosine EC (NRTI)
Kaletra (FDC)
Trizivir (FDC)

2001
Tenofovir DF (NRTI)

2003
Atazanavir (PI)
Emtricitabine (NRTI)
Enfuvirtide (FI)
Fosamprenavir (PI)

2004
Epzicom (FDC)
Truvada (FDC)

'05-'09

2005
Tipranavir (PI)

2006
Atripla (FDC)
Darunavir (PI)

2007
Maraviroc (CA)
Raltegravir (INSTI)

2008
Etravirine (NNRTI)

'10-'14

2011
Complera (FDC)
Nevirapine XR (NNRTI)
Rilpivirine (NNRTI)

2012
Stribild (FDC)

2013
Dolutegravir (INSTI)

2014
Cobicistat (PE)
Elvitegravir (INSTI)
Triumeq (FDC)

'15-'19

2015
Evotaz (FDC)
Genvoya (FDC)
Prezcobix (FDC)

2016
Descovy (FDC)
Odefsey (FDC)

2017
Juluca (FDC)

2018
Biktarvy (FDC)
Cimduo (FDC)
Delstrigo (FDC)
Doravirine (NNRTI)
Ibalizumab-uiyk (PAI)
Symfi (FDC)
Symfi Lo (FDC)
Symtuza (FDC)
Temixys (FDC)

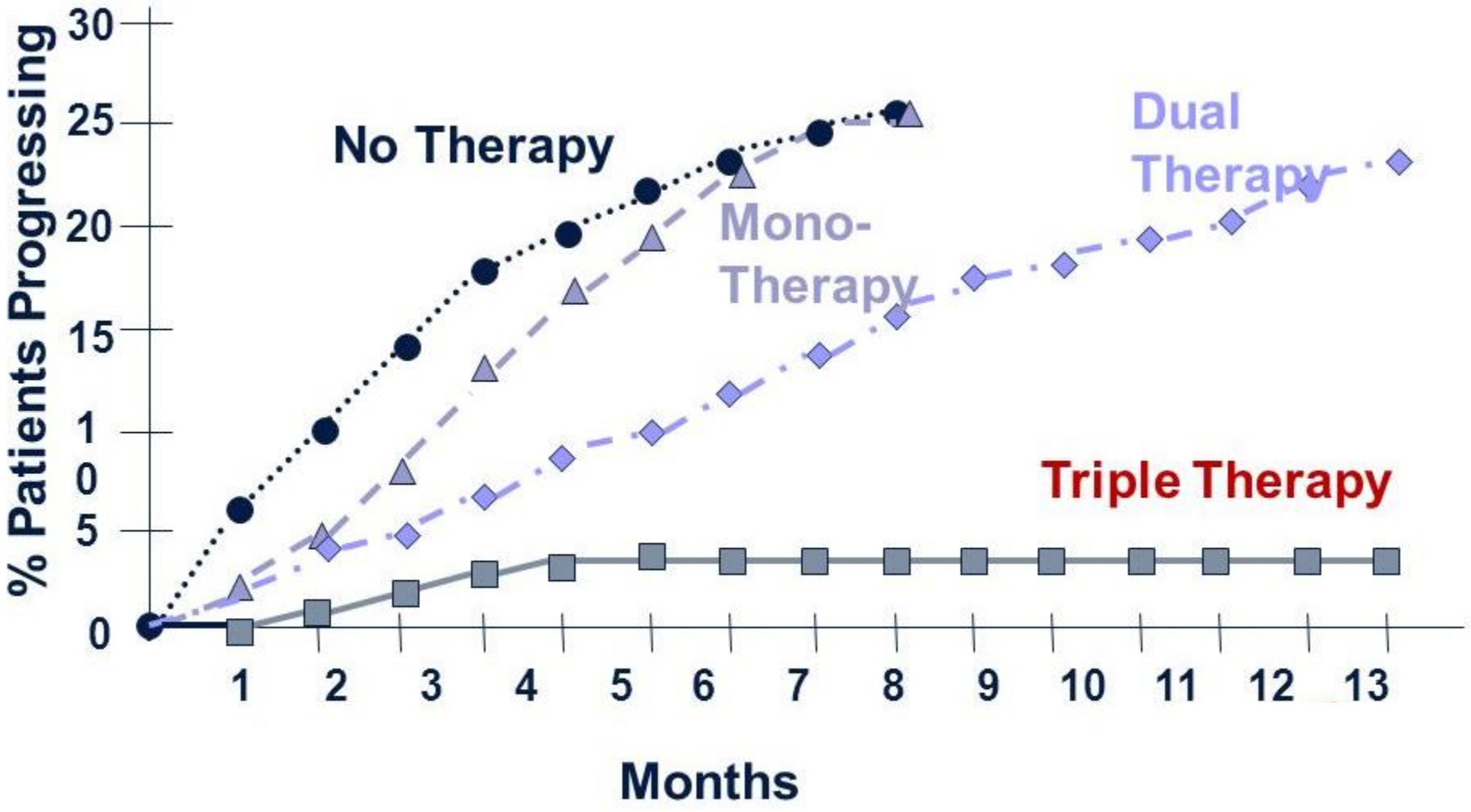
2019
Dovato (FDC)

Drug Class Abbreviations:
CA: CCR5 Antagonist; **FDC:** Fixed-Dose Combination; **FI:** Fusion Inhibitor; **INSTI:** Integrase Inhibitor; **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor; **NRTI:** Nucleoside Reverse Transcriptase Inhibitor; **PE:** Pharmacokinetic Enhancer; **PI:** Protease Inhibitor; **PAI:** Post-Attachment Inhibitor

AIDSinfo

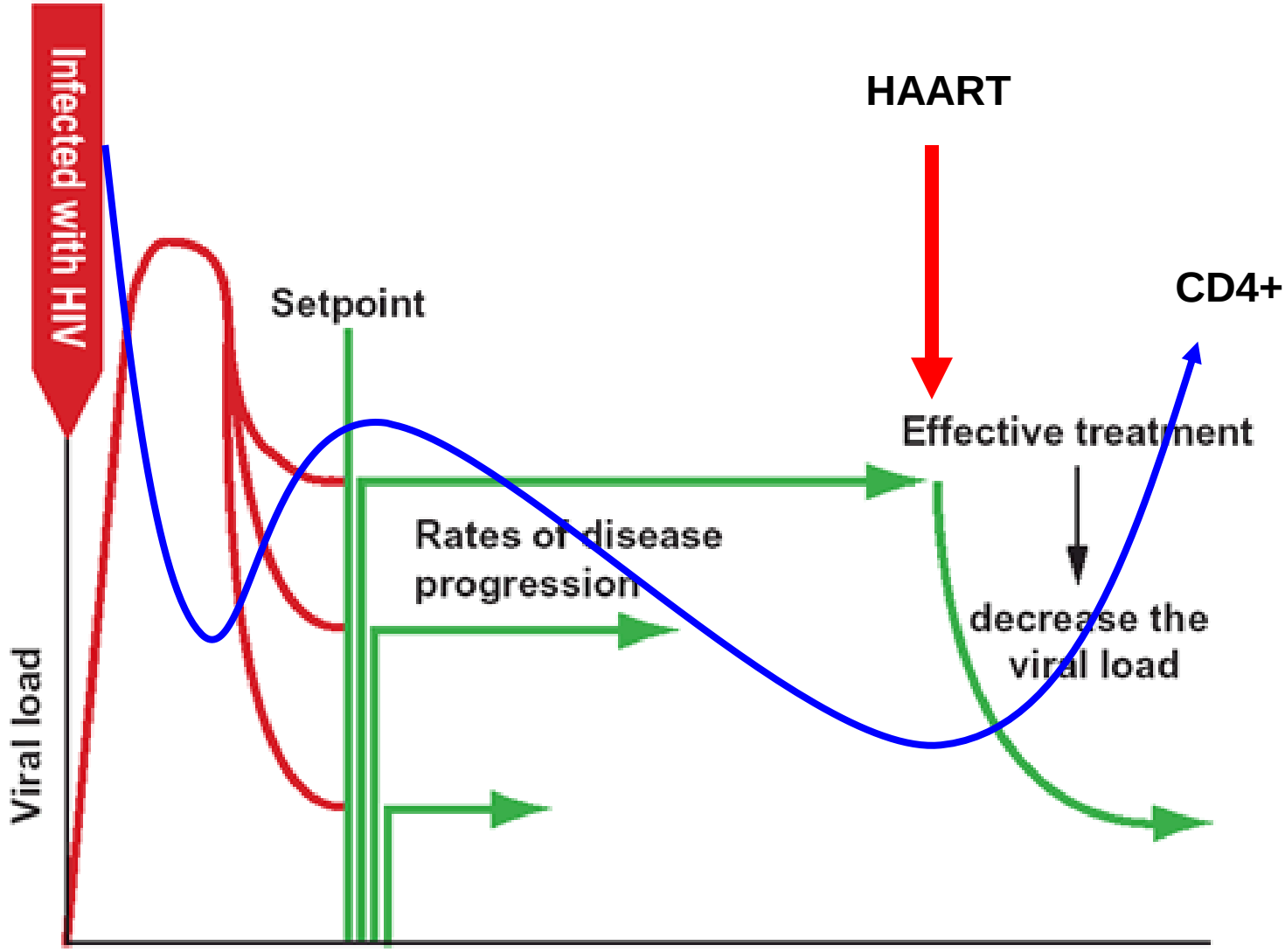
Note: Drugs in gray are no longer available and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations.

HAART Highly active antiretroviral therapy



JAMA 1998

HAART Highly active antiretroviral therapy



HAART Highly active antiretroviral therapy

Terapia combinada:

- três inibidores da transcriptase reversa;
- dois inibidores da transcriptase reversa e um inibidor de protease.

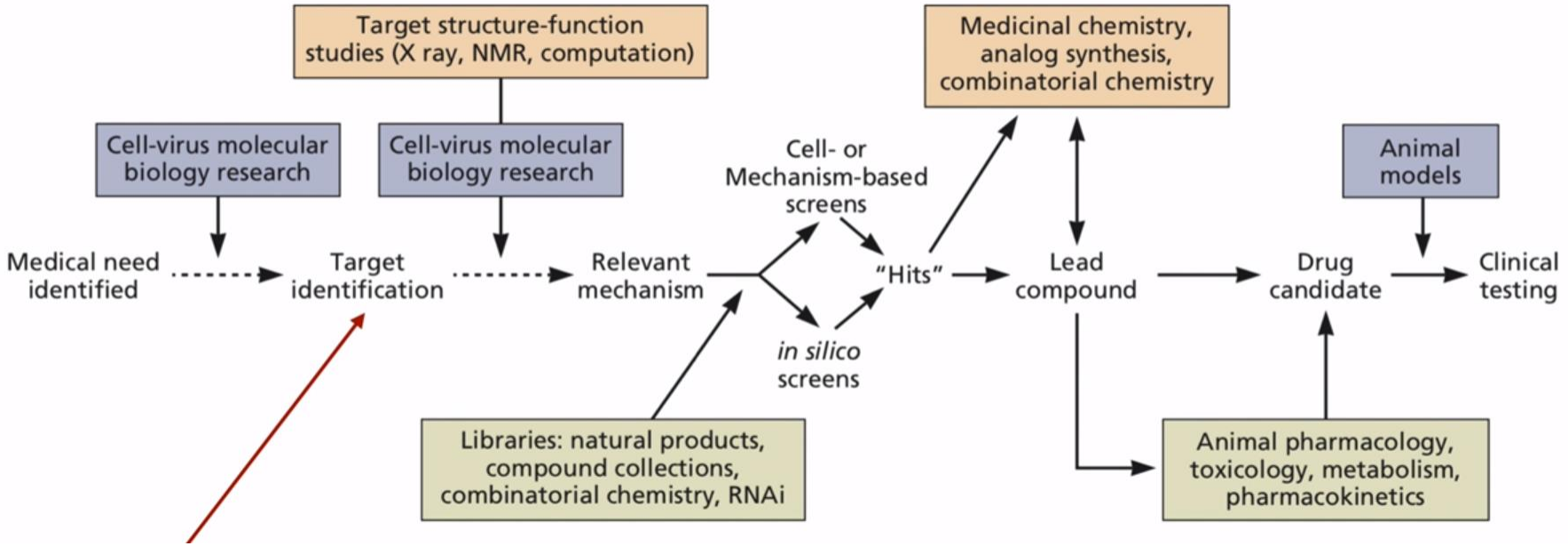
Terapia combinada

PrEP e PEP

Duas Histórias de sucesso...

Por quê apenas duas?

O desenvolvimento de Antivirais é lento e caro

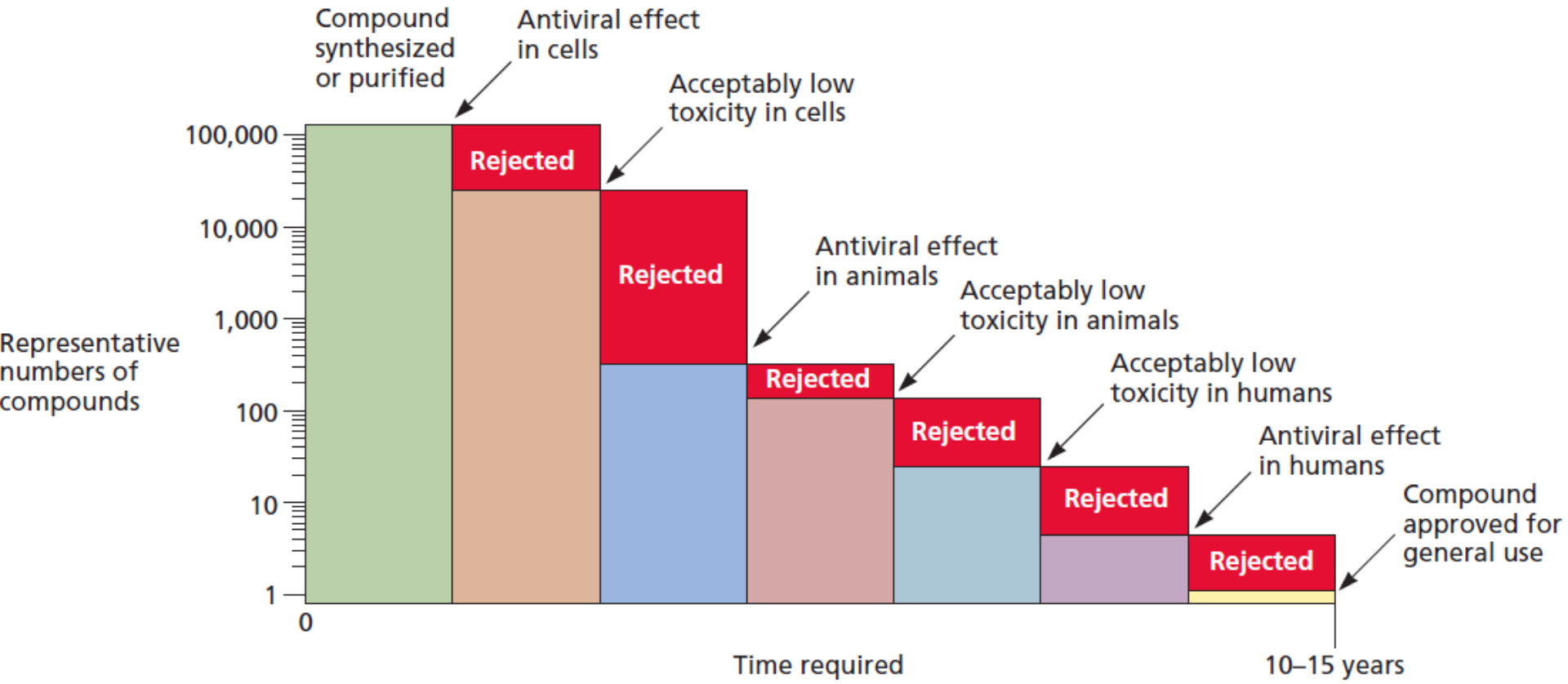


Prova de conceito

- Biodisponibilidade.
- Farmacocinética.
- Segurança.

- Não existem modelos experimentais para alguns vírus.
- Alguns vírus são muito perigosos para trabalhar.
- O antiviral precisa ser potente (atividade parcial não é aceitável).

O desenvolvimento de Antivirais é lento e caro



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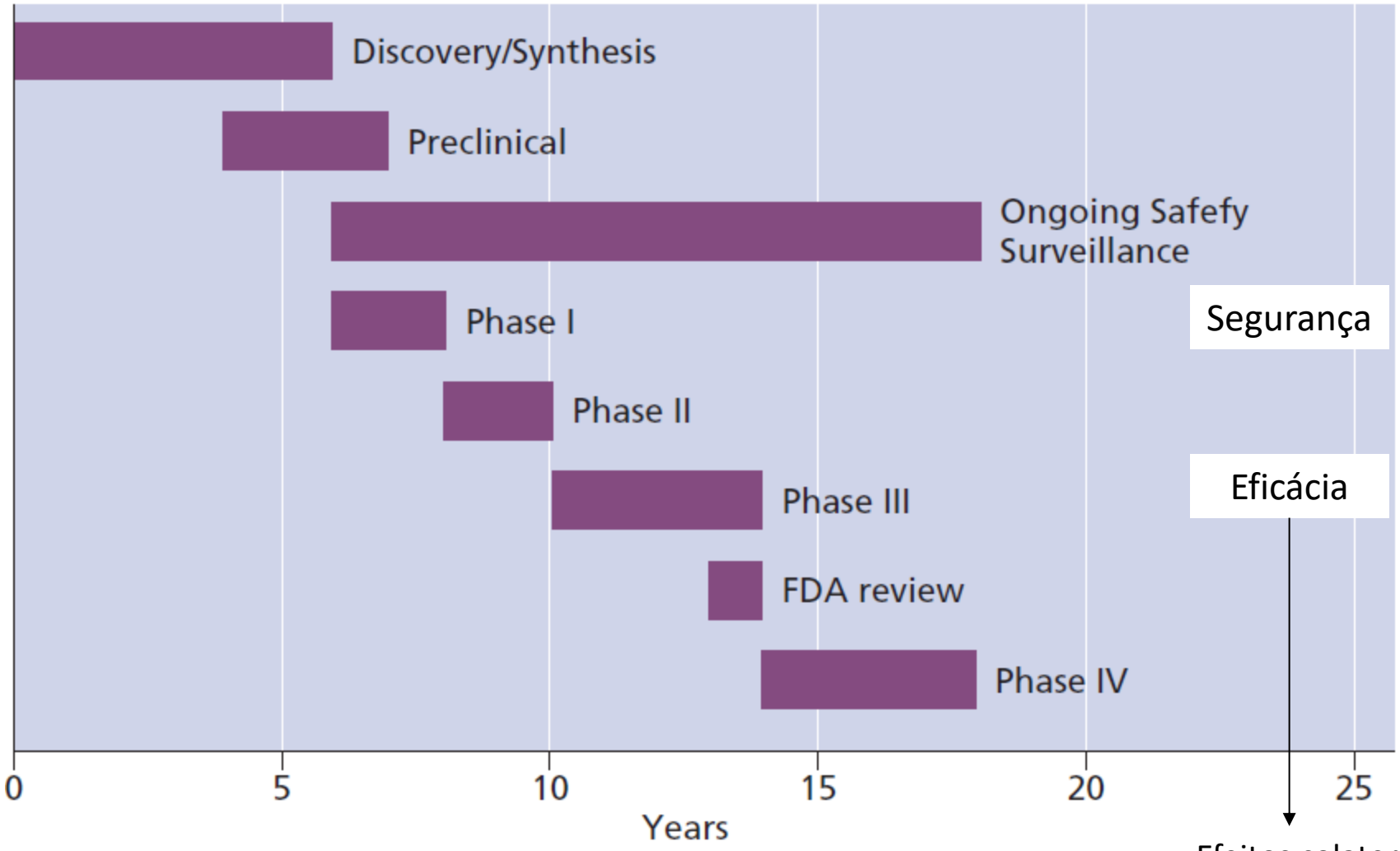
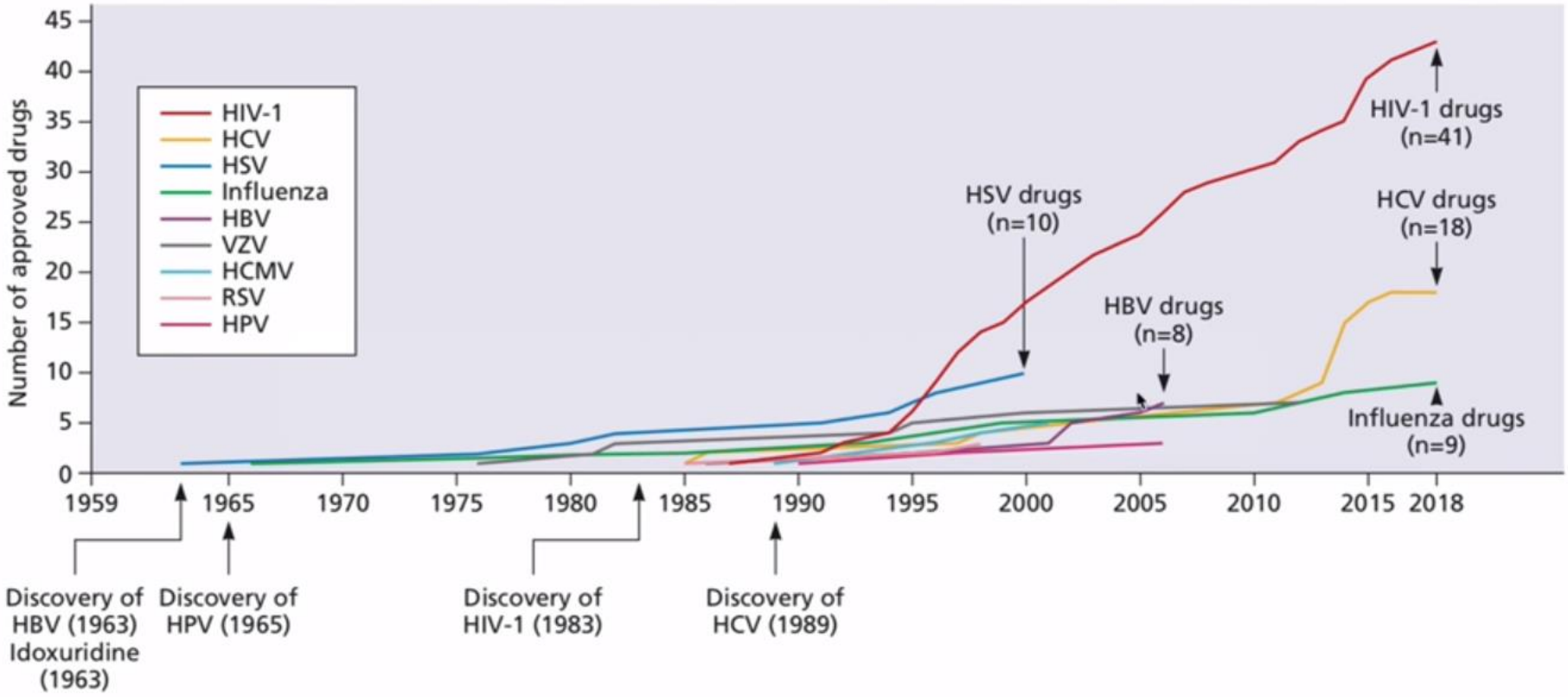


O desenvolvimento de Antivirais é lento e caro

- Poucos fármacos antivirais disponíveis.



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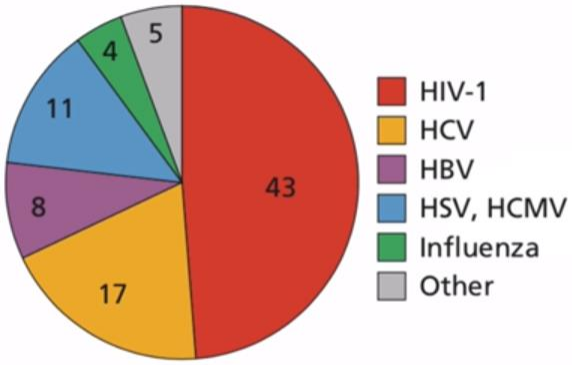
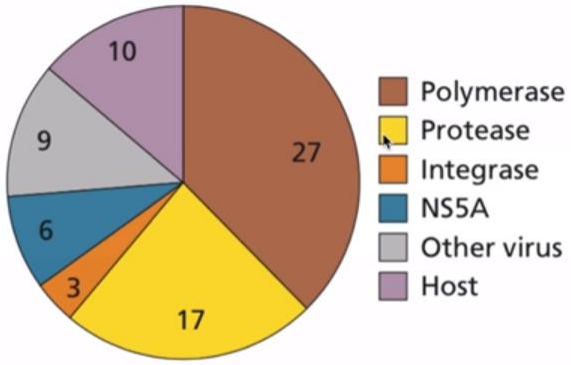
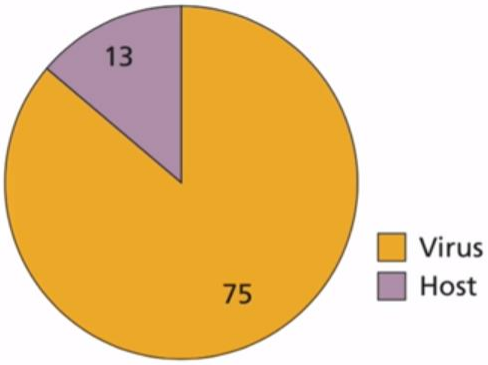




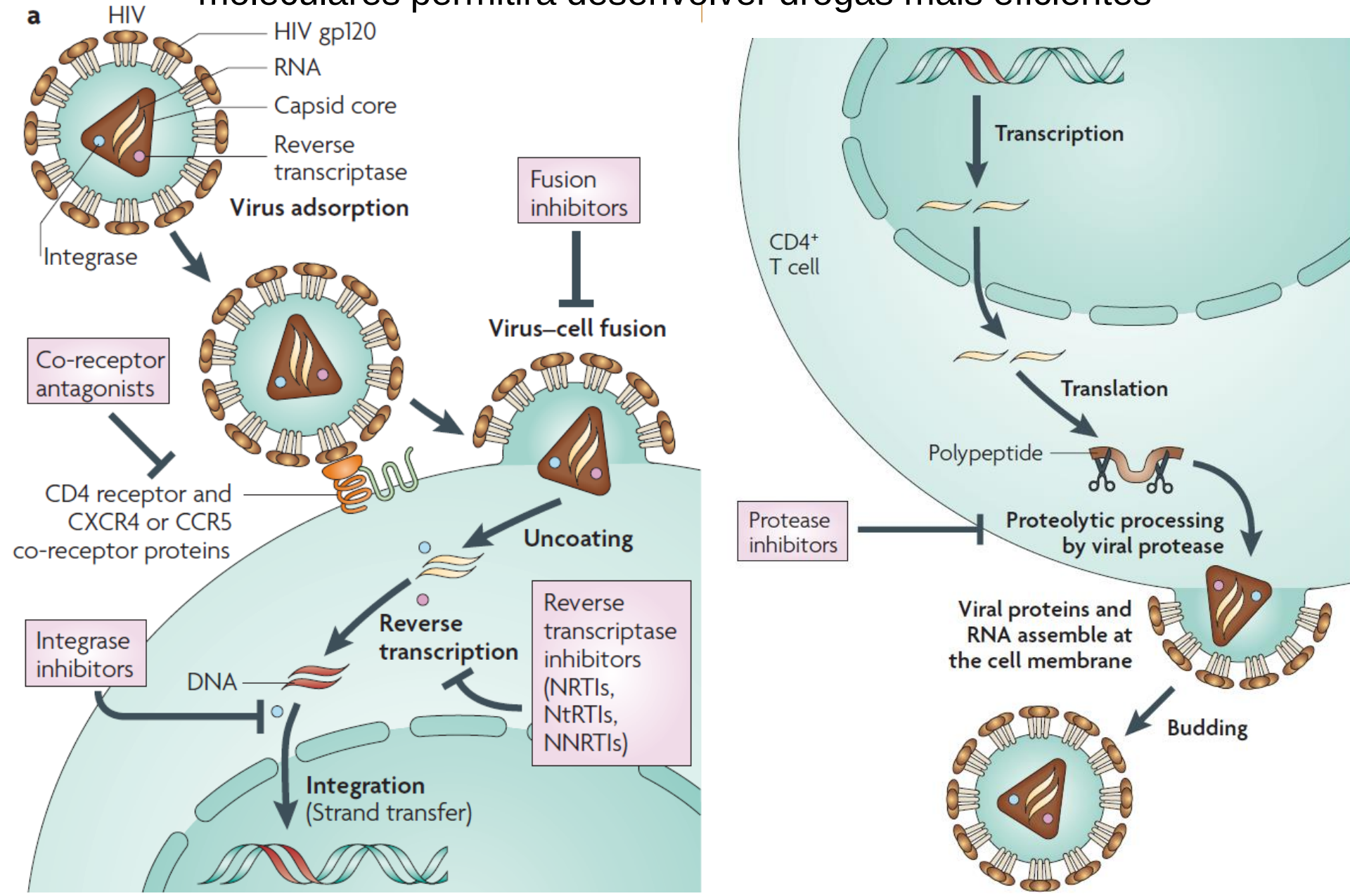


ANTIVIRAIS

- Novas drogas devem ser desenvolvidas.
- Novas estratégias devem ser implementadas.
- Medidas “simples”, porém efetivas podem ser aplicadas.
- Imiquimod, Interferon...

PREVENÇÃO

Entender melhor o ciclo viral e seus componentes em termos moleculares permitirá desenvolver drogas mais eficientes



Obrigado!!!