World Health Organization

HIV/AIDS Updated December 2017

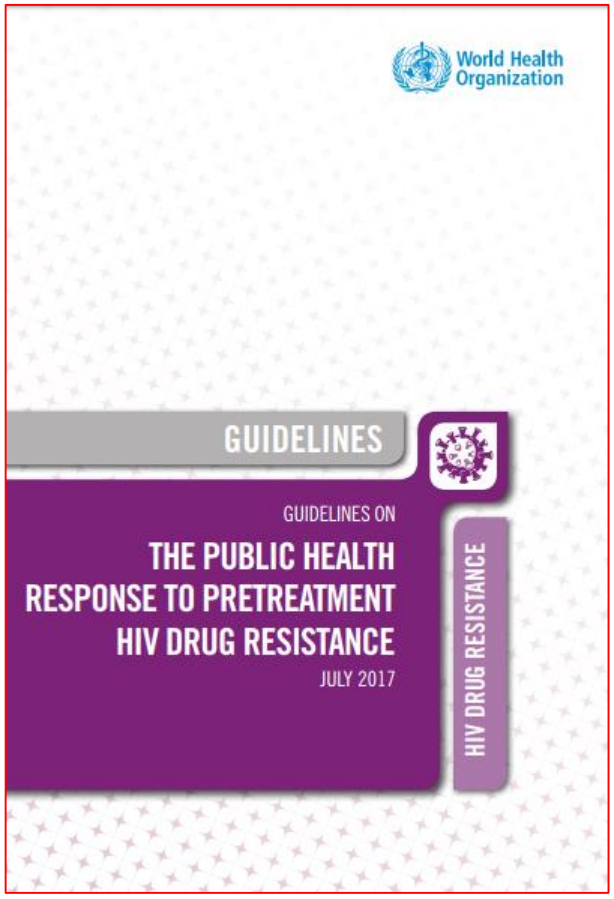
HIV/AIDS remains one of the world's most significant public health challenges, particularly in low- and middle-income countries.
As a result of recent advances in access to antiretroviral therapy (ART), HIV-positive people now live longer and healthier lives. In addition, it has been confirmed that ART prevents onward transmission of HIV.

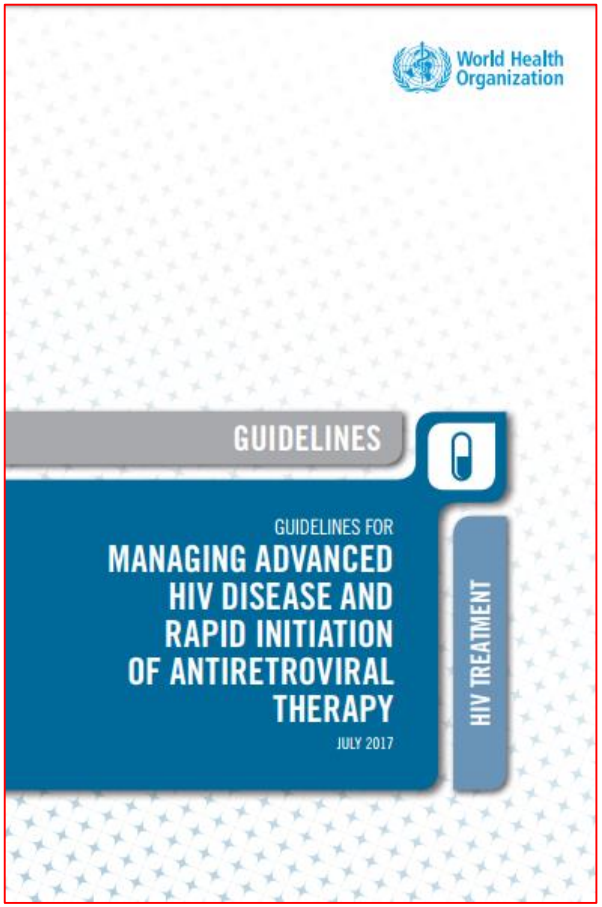
There were approximately 36.7 million people living with HIV at the end of 2016.
20.9 million people living with HIV were receiving ART by mid-2017;
7 out of 10 pregnant women living with HIV received antiretroviral treatment..

Progress has also been made in preventing and eliminating mother-to-child transmission and keeping mothers alive. In 2015, almost 8 out of 10 pregnant women living with HIV, or 1.1 million women, received antiretrovirals (ARVs).

WHO has released a set of normative guidelines and provides support to countries in formulating and implementing policies and programmes to improve and scale up HIV prevention, treatment, care and support services for all people in need.

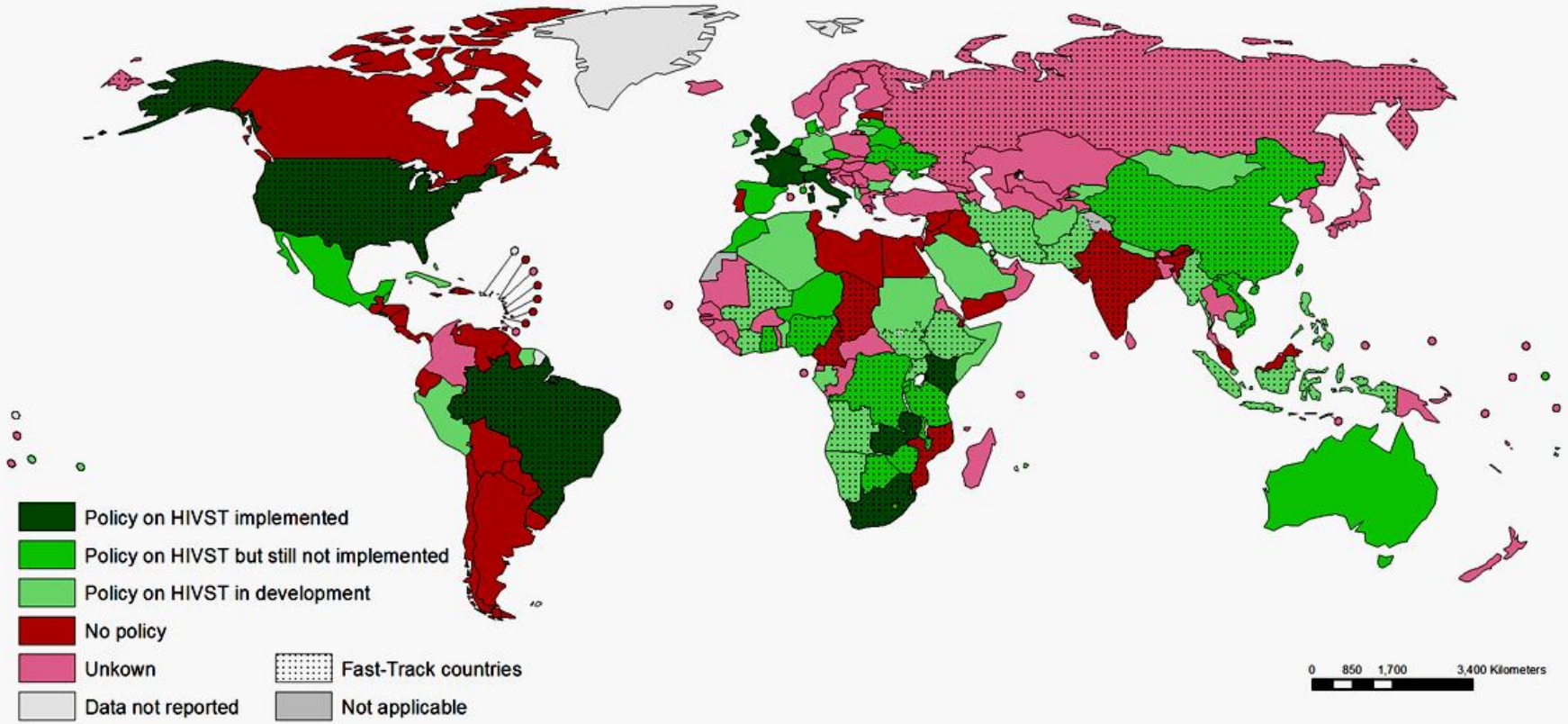
http://www.who.int/mediacentre/factsheets/fs360/en/


World Health Organization
GUIDELINES
GUIDELINES ON
THE PUBLIC HEALTH RESPONSE TO PRETREATMENT HIV DRUG RESISTANCE
JULY 2017
HIV DRUG RESISTANCE


World Health Organization
GUIDELINES
GUIDELINES FOR
MANAGING ADVANCED HIV DISEASE AND RAPID INITIATION OF ANTIRETROVIRAL THERAPY
JULY 2017
HIV TREATMENT


World Health Organization
SUPPLEMENT
GUIDELINES ON
HIV SELF-TESTING AND PARTNER NOTIFICATION
SUPPLEMENT TO CONSOLIDATED GUIDELINES ON HIV TESTING SERVICES
DECEMBER 2016
HIV TESTING SERVICES

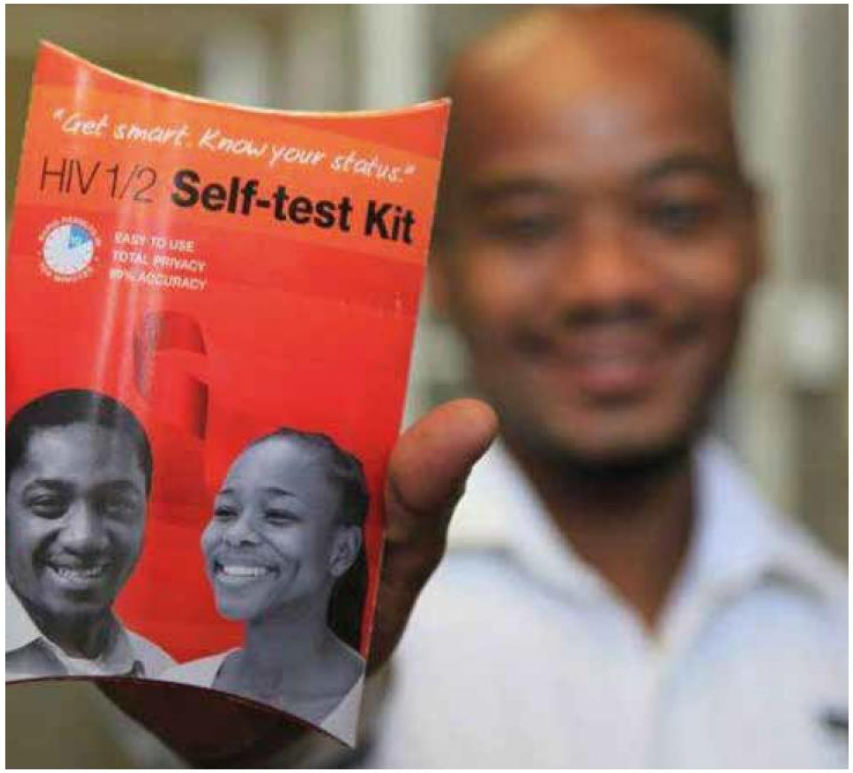
Status of HIV self-testing (HIVST) in national policies (situation as of November 2017)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

World Health Organization



- Between 2010 and 2014, more than 600 million people received HIV testing services in 122 low- and middle-income countries (LMICs);

- In 2015, it was estimated that 55 per cent of PLHIV in Africa were aware of their HIV status [6, 7], an increase from 2005 when only10 per cent of PLHIV in Africa were aware of their status;

- Men continue to have lower testing rates than women in nearly all countries. Nearly 70 per cent of adult HIV tests reported in 76 LMICs in 2014 were among women;

~7500 young women (15-24 years) acquired HIV every week in 2015; the majority of whom were in southern Africa. half of 15-19 year olds testing HIV-positive were first time testers

Brand name (Manufacturer/ Supplier)	Generation	Sensitivity	Specificity	Approval status	Markets	Price in US$ per test
autotest VIH® (AAZ Labs, France)	2nd	100.00%	99.80%	CE marked	Several in Europe[1]	HIC retail: 22-28 Distributor: 8 - 15 (volume dependent)
BioSURE HIV Self-Test (hardcase & softcase)+ (BioSURE, United Kingdom)[2]	2nd	99.70%	99.90%	CE marked	United Kingdom	HIC retail: 42 – 48 HIC public sector: 7.50 – 15 LMIC ex-works: 5
INSTI® HIV Self Test (box) (bioLytical Lab., Canada)	3rd	100.00%	99.80%	CE marked	Several in Europe[3]	HIC retail: 33
OraQuick® In-Home HIV Test* (OraSure Technologies., USA)	2nd	91.70%	99.98%	FDA	USA	HIC retail: 40
OraQuick® HIV Self Test* (OraSure Technologies, USA[4])	2nd	99.02%+	100%+	WHO PQ	Kenya, planning on South Africa	LMIC retail: 9.50 LMIC ex-works: 2 for 50 countries (see Box 5)

GUIDELINES

GUIDELINES FOR

THE DIAGNOSIS, PREVENTION AND MANAGEMENT OF CRYPTOCOCCAL DISEASE IN HIV-INFECTED ADULTS, ADOLESCENTS AND CHILDREN

MARCH 2018

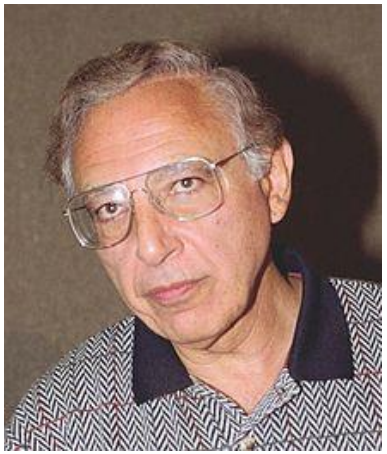
HIV TREATMENT

Sindrome da immunodeficienza acquisita

- HIV: le cellule bersaglio linfociti T di tipo CD4, fondamentali nella risposta adattativa contro svariati tipi di agenti patogeni.
- Indebolimento progressivo del sistema immunitario (immunodepressione), > rischio di infezioni e malattie opportunistiche da parte di virus, batteri, protozoi e funghi, potenzialmente letali;
- I sieropositivi producono anticorpi diretti e possono trasmettere l'infezione anche prima che gli stessi siano dosabili nel sangue (4-6 w, 6m).
- Nella fase conclamata dell'Aids si possono sviluppare diverse forme di tumore, soprattutto linfomi e sarcoma di Kaposi.

Françoise Barré-Sinoussi

Luc Montagnier



Robert Gallo

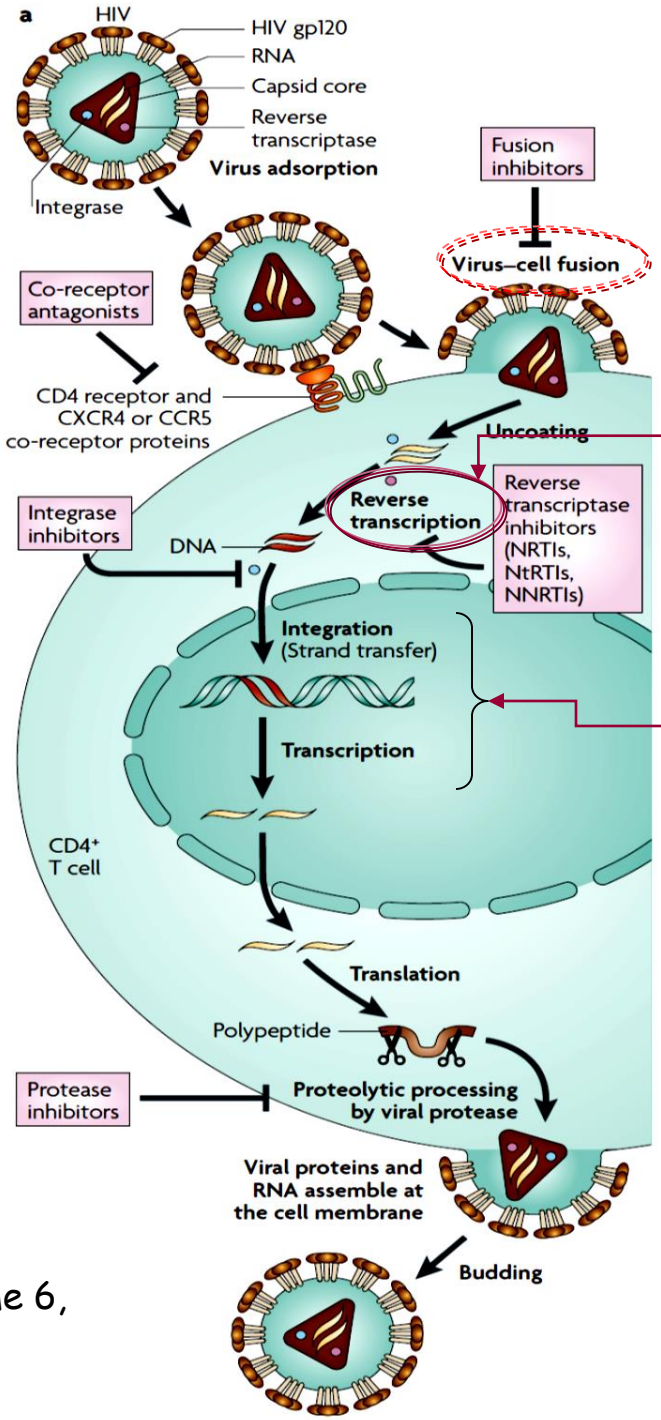
Harald zur Hausen

The early spread and epidemic ignition of HIV-1 in human populations. Science 2014, 346(6205), 56-61.
1970s and 'Patient 0' HIV-1 genomes illuminate early HIV/AIDS history in North America. Nature. 2016, 539(7627), 98–101.

HIV

Retrovirus (RNA) che replica mediante un DNA provirale (doppia elica) intermedio.

HCV invece è un (+) RNA virus che replica tramite un (-) RNA intermedio



Endocitosi per HCV

Fase cruciale nel ciclo replicativo→trascrizione del genoma virale (singola elica) a DNA provirale (doppia elica)

Fase HIV specifica

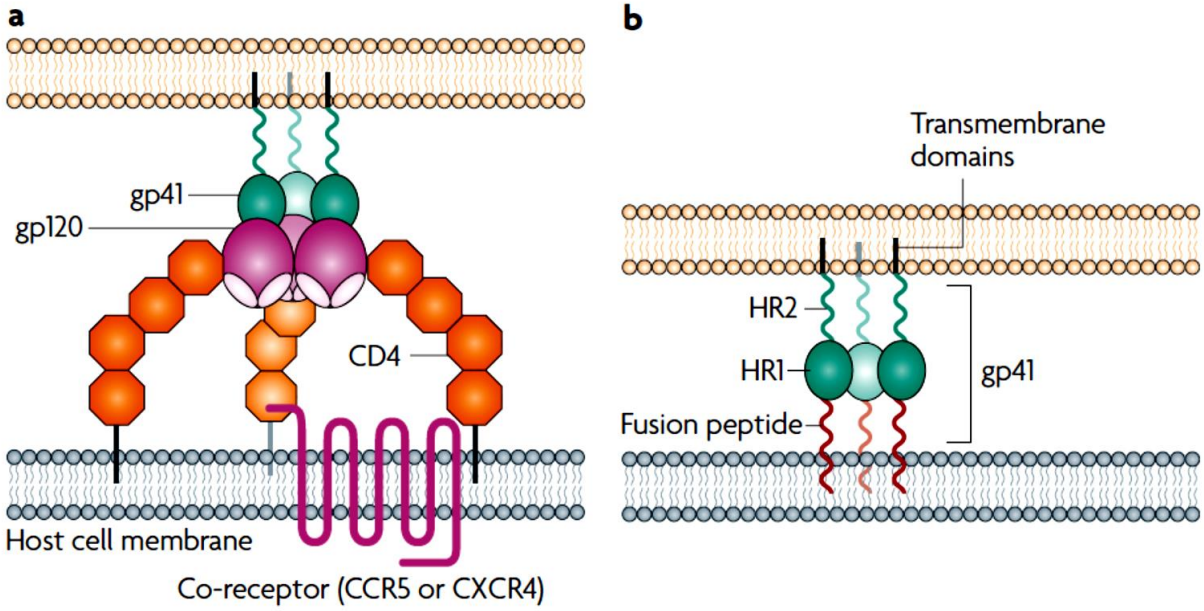
nature reviews drug discovery volume 6, |december, 2007, 10

https://timeline.avert.org/

http://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMoa0708975&aid=NEJMoa0708975_attach_1&area=

https://www.youtube.com/watch?v=odRyv7V8LAE

Viral entry inhibitors



Chemochine umane

Enfuvirtide:
peptide omologo della regione HR2

Infezione di cellule $CD4^+$:

- La glicoproteina virale gp120 interagisce in sequenza con il recettore CD4, co-recettore CCR5 o CXCR4;
- Questa sequenza opera una modificazione conformazionale della proteina gp120 e la conseguente apertura all'interazione dell'estremità del peptide di fusione gp41 (quattro domini funzionali: HR1, HR2, peptidi di fusione) con la membrana della cellula ospite;

Enfuvirtide

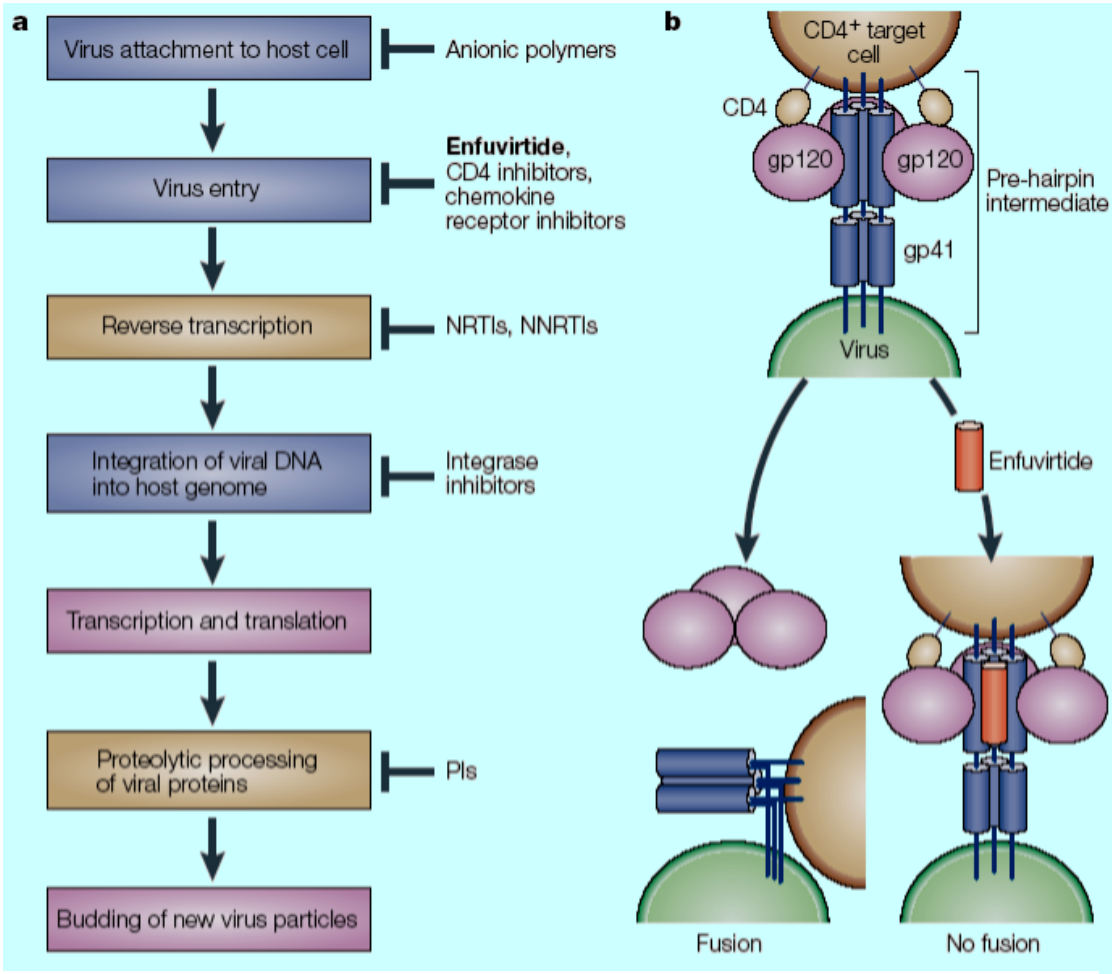
Brand name: Fuzeon
Companies: Trimeris/Roche
Approved: 13 March 2003
Condition treated: HIV-1 infection
Action: inhibits viral entry into host cells
CAS number: 159519-65-0

Capostipite di una nuova classe di farmaci anti-HIV (approvazione accellerata)

E' un polipeptide di 36 AA :

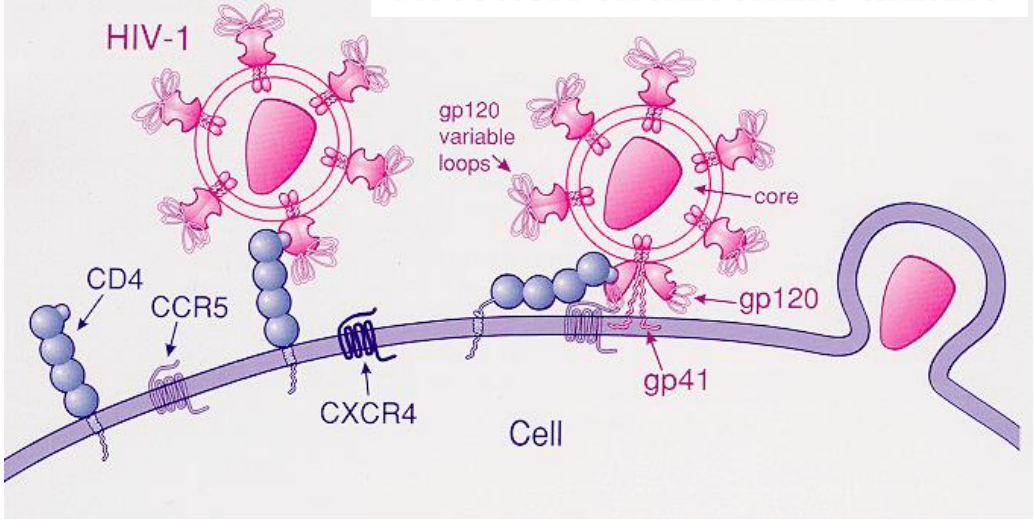
NH_2Phe---------TyrCOMe

- Usato in combinazione con HAARTs;
- Iniez. Sc.
- Resistenza per mutazione HR1 non crociata con altri *entry inhibitors*;
- Sinergia con rapamicina in caso di HIV che usano co-recettori CCR5 (riduzione espressione CCR5).



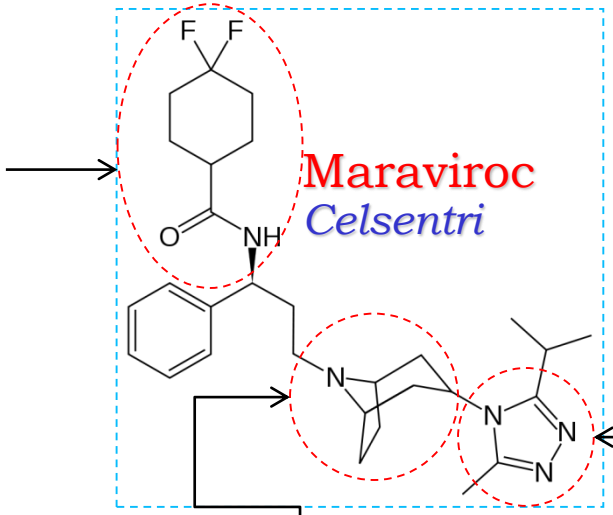
Enfuvirtide si lega ad una regione della gp41 che ne media il cambiamento conformazionale dall'intermedio "pre-forcina" alla struttura di fusione attiva, prevenendo così la fusione e l'ingresso del virus (in basso a destra).

Recettori chemochine umane



Viral entry inhibitors: antagonisti co-recettori

Antagonisti CCR5



Maraviroc
Celsentri

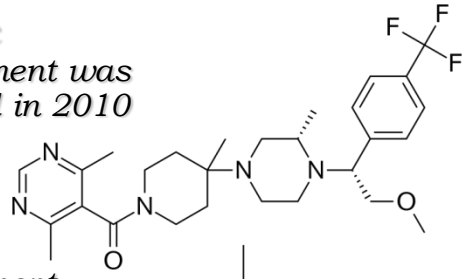
CCR5, recettore attraverso cui il virus entra nella cellula CD4+; maraviroc primo antagonista CCR5, la prima nuova classe di farmaci antiretrovirali di tipo orale scoperta nel corso degli ultimi 10 anni.

Virus CCR5-tropico; virus CXCR4 tropico.

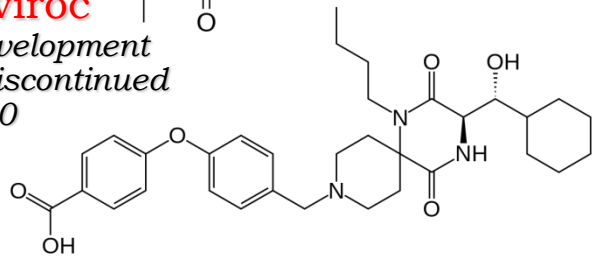
Alcuni ceppi di HIV usano sia i recettori CCR5 che CXCR4 (tropismo duplice, virus R5X4). Alcuni pazienti infine hanno un'infezione mista da virus R5 e X4 (tropismo misto). Il tropismo del virus può variare nel tempo: la comparsa del virus X4 è associata alla progressione della malattia.

una delezione naturale nel gene *CCR5* conferisce resistenza ai virus CCR5-tropic strain tra i più frequentemente trasmessi sessualmente

Vicriviroc
the development was discontinued in 2010



Aplaviroc
the development was discontinued in 2010

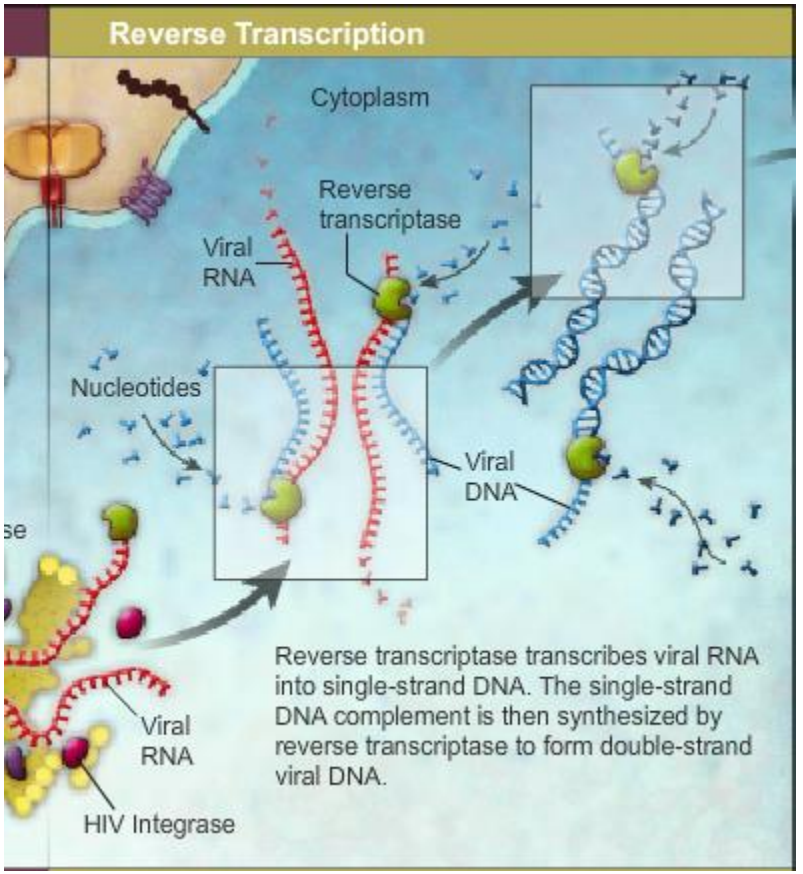


INIBITORI DELLA TRASCRITTASI INVERSA (RTI)

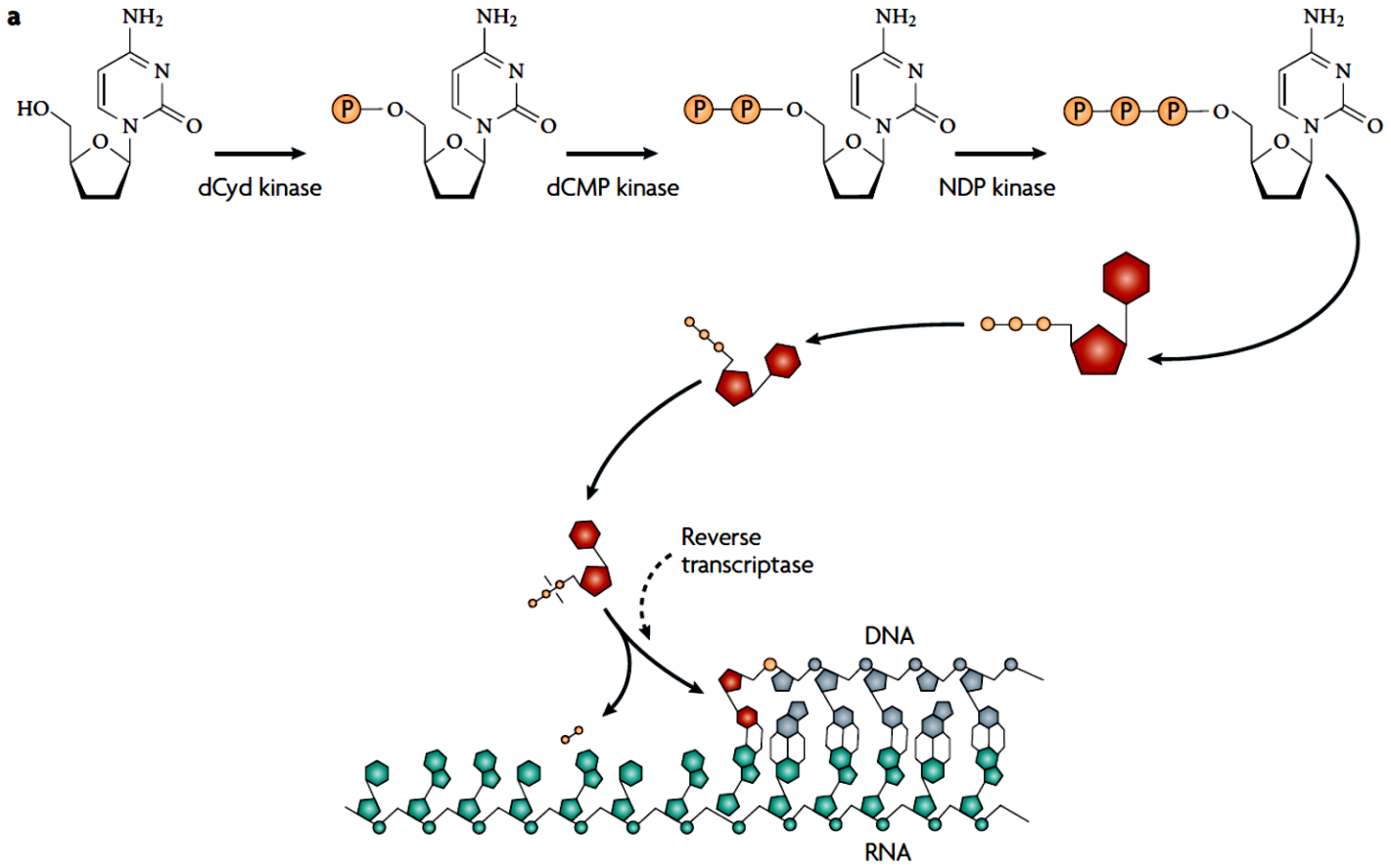
- **RTI** catalizza la trascrizione dell'RNA virale in una doppia catena di DNA lineare

- La RTI agisce in una prima fase come una DNA polimerasi RNA-dipendente, sintetizzando una prima catena di DNA complementare a una catena di RNA virale, mentre nella fase successiva si comporta da DNA polimerasi-DNA-dipendente, sintetizzando una seconda catena di DNA sullo stampo del DNA neoformato.

- Tutti gli inibitori della trascrittasi inversa prevengono l'infezione di nuove cellule, senza peraltro interferire con la replicazione dell'HIV già integrato nel genoma della cellula; bloccano pertanto l'infezione acuta delle cellule, ma solo in misura minima sono in grado di agire sulle cellule infettate cronicamente.

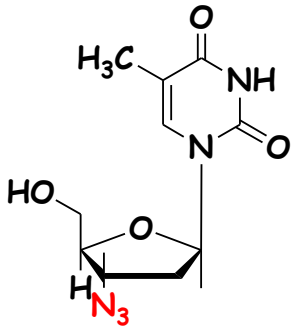


INIBITORI DELLA TRASCRITTASI INVERSA

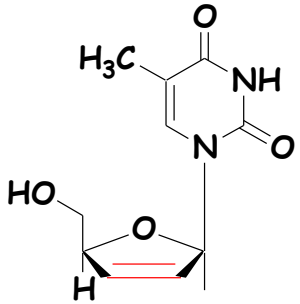


- Meccanismo d'azione semplificato (es. 2',3'-dideossicitidina) di inibitori nucleosidici della trascrittasi inversa (NRTIs);
- Tre stadi di fosforilazione convertono il 2',3'-dideossinucleoside nel suo derivato 5'-trifosfato (inibitore competitivo e/o *chain terminator*)

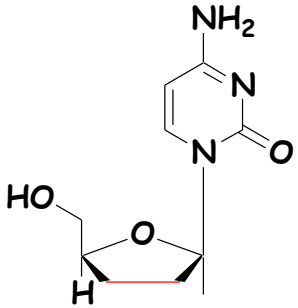
INIBITORI NUCLEOSIDI DELLA TRASCRITTASI INVERSA (NRTIs)



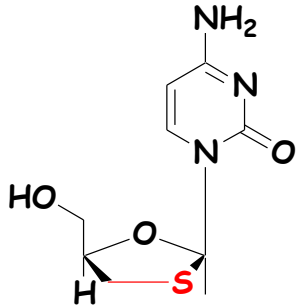
ZIDOVUDINA
(3'-azido-3'-deossi ***timidina****; AZT, 1985)*
(Retrovir)



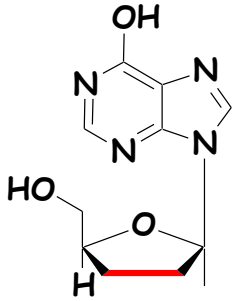
STAVUDINA
(2',3'-deidro-3'-deossi ***timidina****)*
(Zerit)



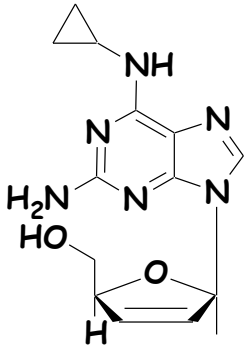
ZALCITABINA
(2',3'-dideossi ***citidina*** *DDC)*
(Hivid)



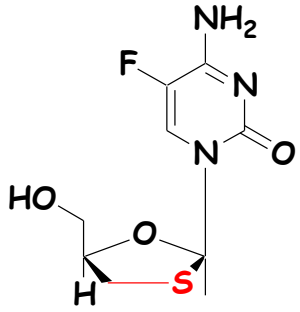
LAMIVUDINA
(2'-deossi-2'- ***tiacitidina****)*
(Epivir)



DIDANOSINA
(2',3'-
*dideossi****inosina****, DDI)*
(Videx)



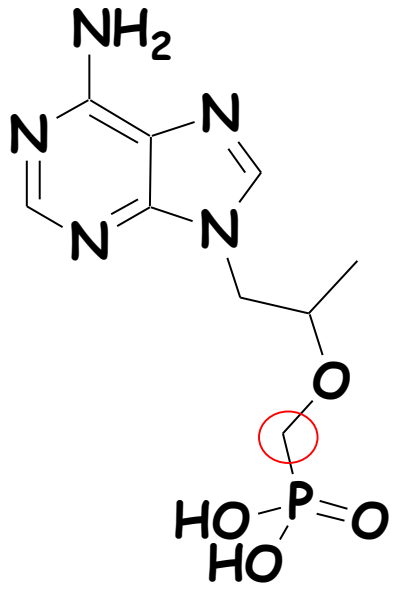
ABACAVIR
(Ziagen)



EMTRICITABINA
(2'-deossi-2'-tia-5-
*fluoro****citidina****)*
(Emtriva)

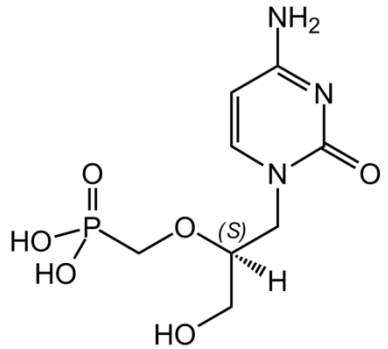
INIBITORI NUCLEOTIDICI DELLA TRASCRITTASI INVERSA (NtRTIs)

Tenofovir
(Viread)



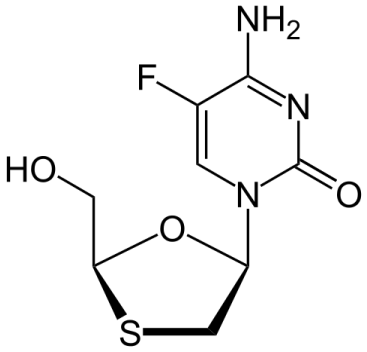
Acido [2-(6-Amino-purin-9-yl)-1-metil-etossimetil]-fosfonico

- Meccanismo d'azione simile ai NRTIs ma la presenza di un gruppo fosfonato (cfr. Cidofovir) abilita queste molecole al by-pass della prima reazione di fosforilazione che può limitare l'attività;
- non idrolizzato da esterasi che normalmente convertono il nucleoside monofosfato a nucleoside;

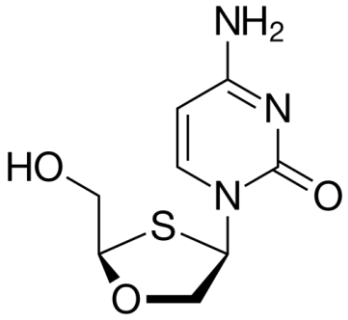


Effetti collaterali importanti: tossicità epatica (epatomegalia) e acidosi lattica (comune a tutta la classe)

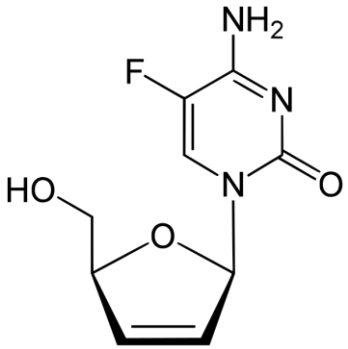
Nuovi NRTIs (Fase IIIa/b)



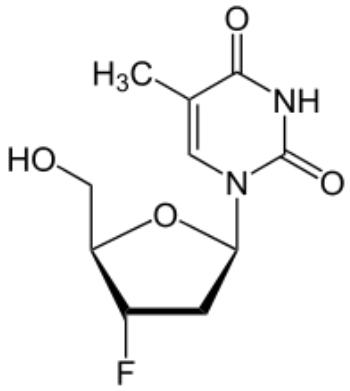
Racivir
(cfr Emcitrabina, enantiomero)



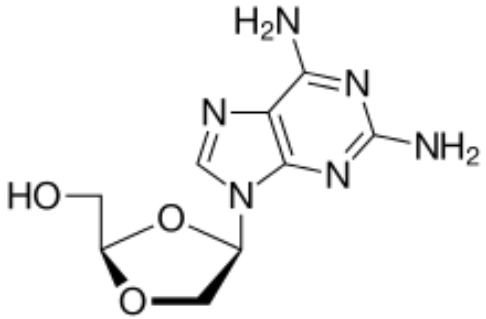
Apricitabina



Dexelvucitabina /elvucitabina



Alovudina

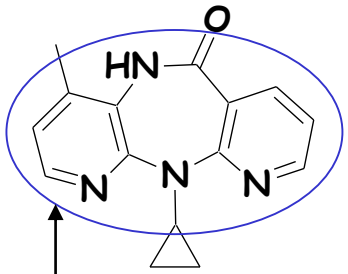


Diaminopurina diossolano (*Amdoxovir*)

INIBITORI NON NUCLEOSIDICI DELLA TRASCRITTASI INVERSA (NNRTIs)

NEVIRAPINA
(Viramune)

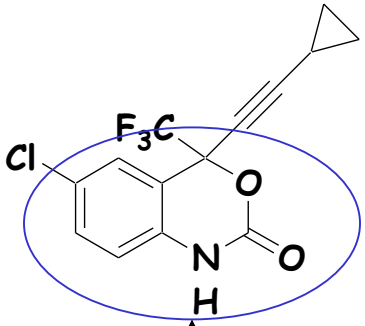
11-cyclopropyl-5,11-dihydro-4-methy-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one



Dipirido diazepinone

EFAVIRENZ
(Sustiva)

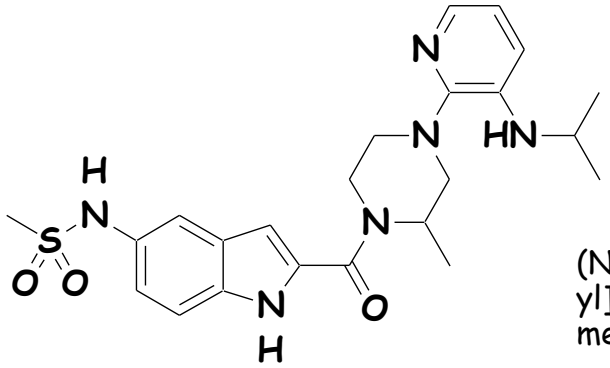
(S) -6- chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one



benzoxazinone

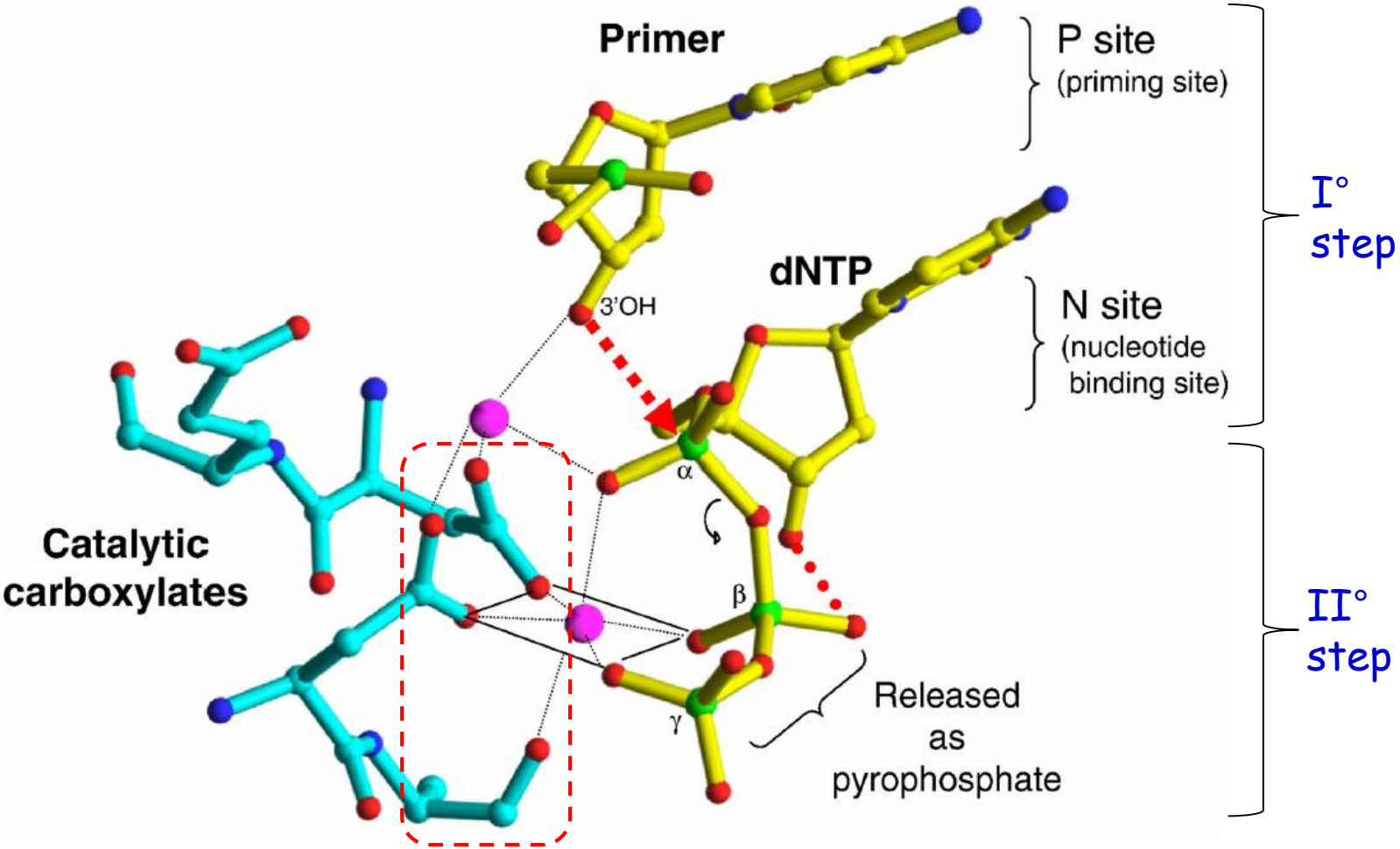
DELAVIRDINA
(Rescriptor)

(N-[2-[4-[3-(1-Methylethylamino)pyridin-2-yl]piperazin-1-yl]carbonyl-1H-indol-5-yl] methanesulfonamide)

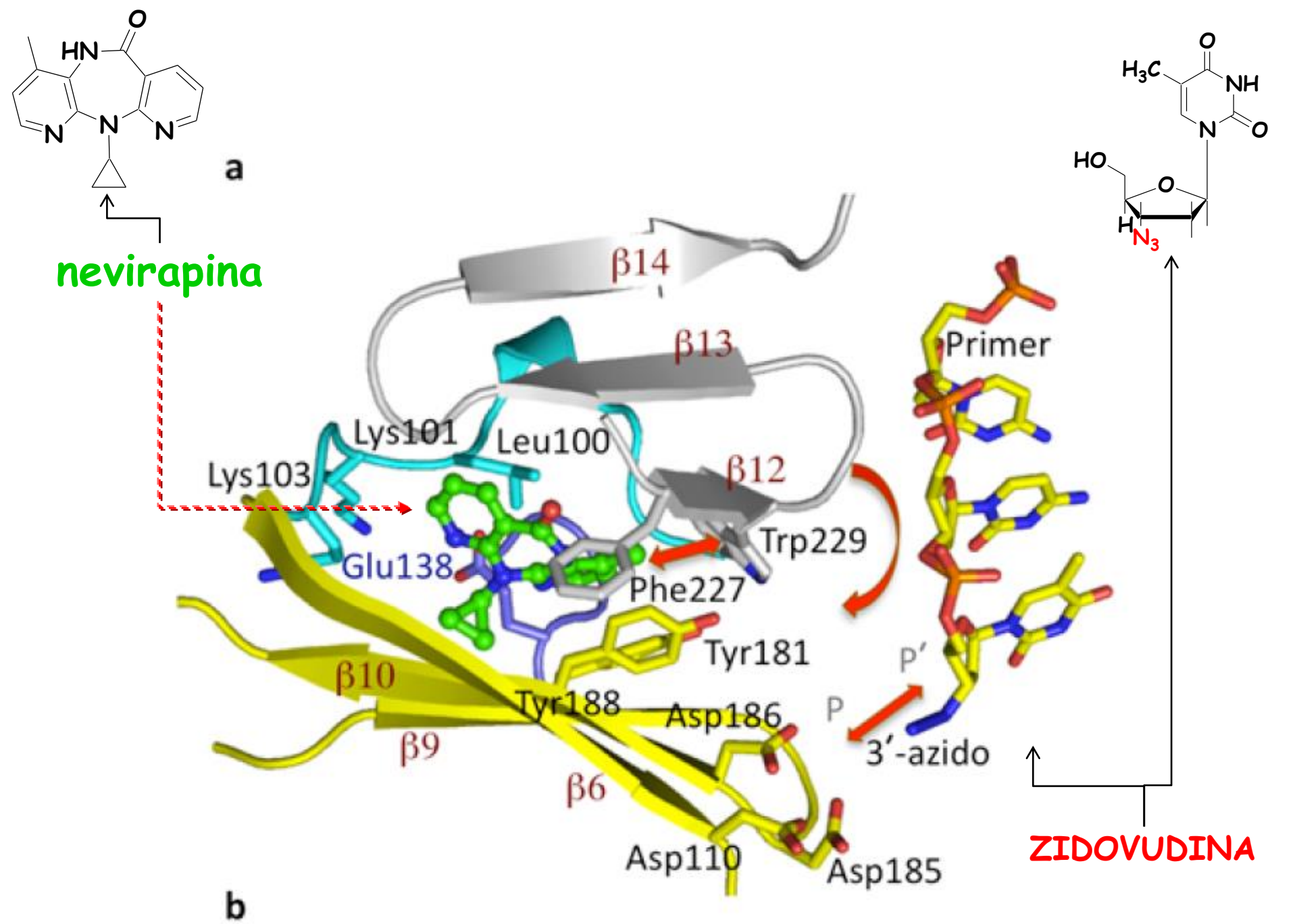


Interferenza con modificazione conformazionale della RT necessaria per la translocazione del primer templato dopo l'incorporazione dei nucleotidi; la formazione di un complesso provoca lo spostamento del primer DNA di ~5.5 Å allontanadolo dalla corretta posizione nel sito attivo della polimerasi.

The rate-limiting step in the polymerization reaction is a conformational change in which a portion of the p66 fingers subdomain closes down on the incoming dNTP, which helps to precisely align the 3'-OH of the primer, the α-phosphate of the dNTP, and the polymerase active site.

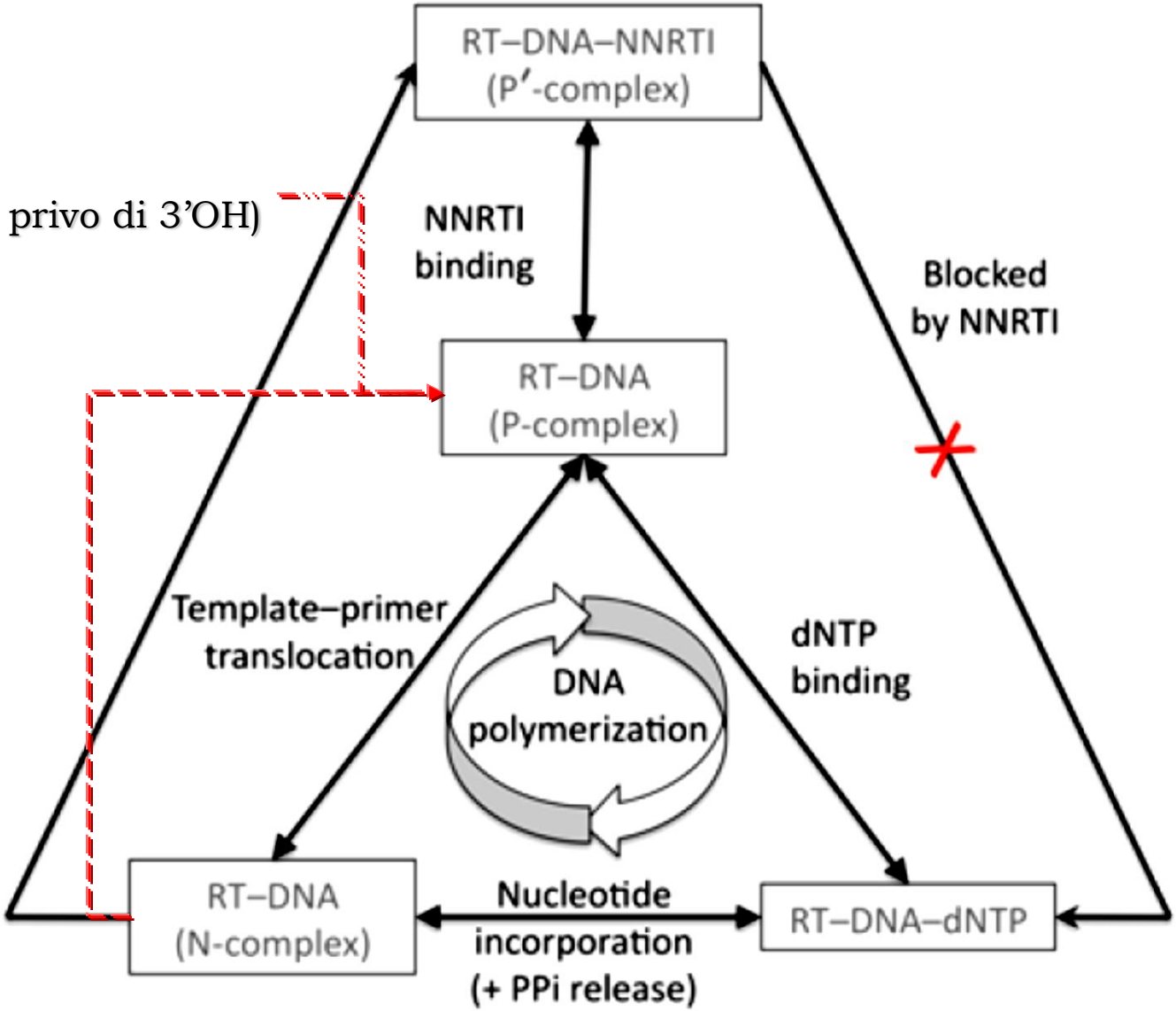


J Mol Biol. 2009 January 23; 385(3): 693–713.



Nature Structural & Molecular Biology 19, 253–259 (2012)

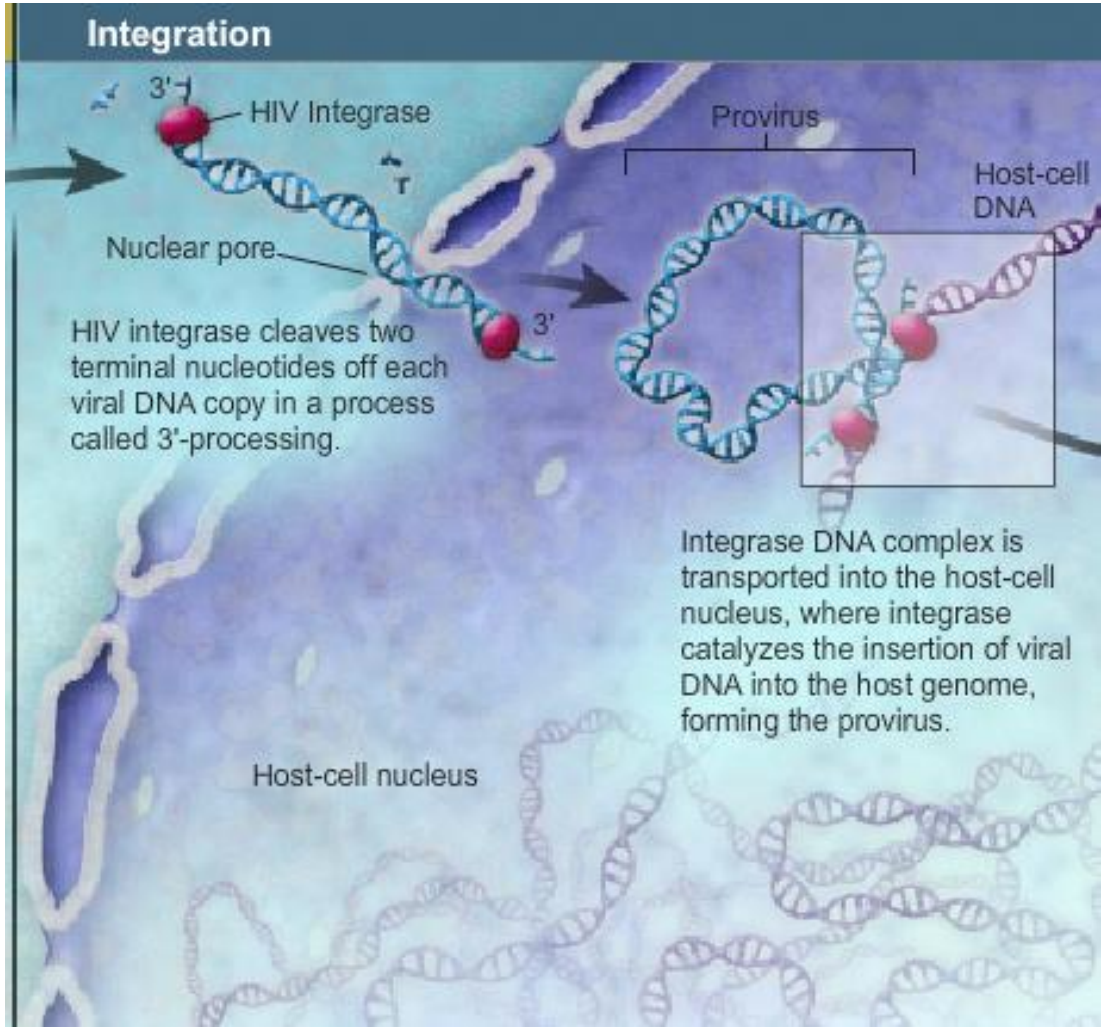
NRTI
(P-complex privo di 3'OH)



NRTI

Nature Structural & Molecular Biology 19, 253–259 (2012)

Trascrizione inversa



Trascrizione

https://www.youtube.com/watch?v=RO8MP3wMvqg

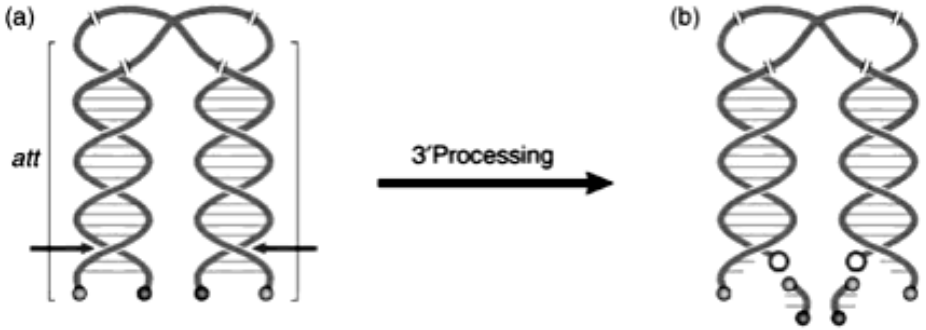
1.50-3,00 min

Successful Drug Discovery-2015

6- Elvitegravir A New HIV-1 Integrase Inhibitor for Antiretroviral

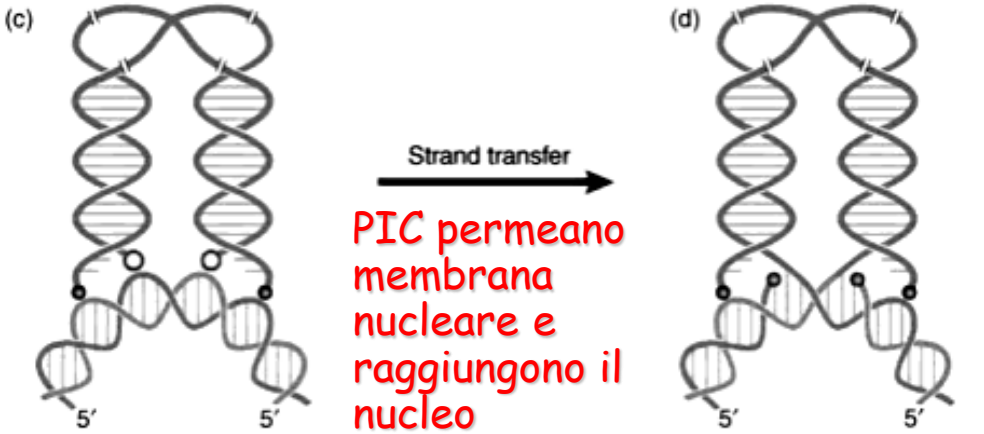
HIV: 40-100 molecole di integrasi

processo 3' integrasi-mediato



cleavage endonucleotidico alle estremità 3' (*CA-3'-OH*)

L'integrasi a questo punto resta legata al DNA provirale come complesso multimerico PICs (complessi di preintegrazione)

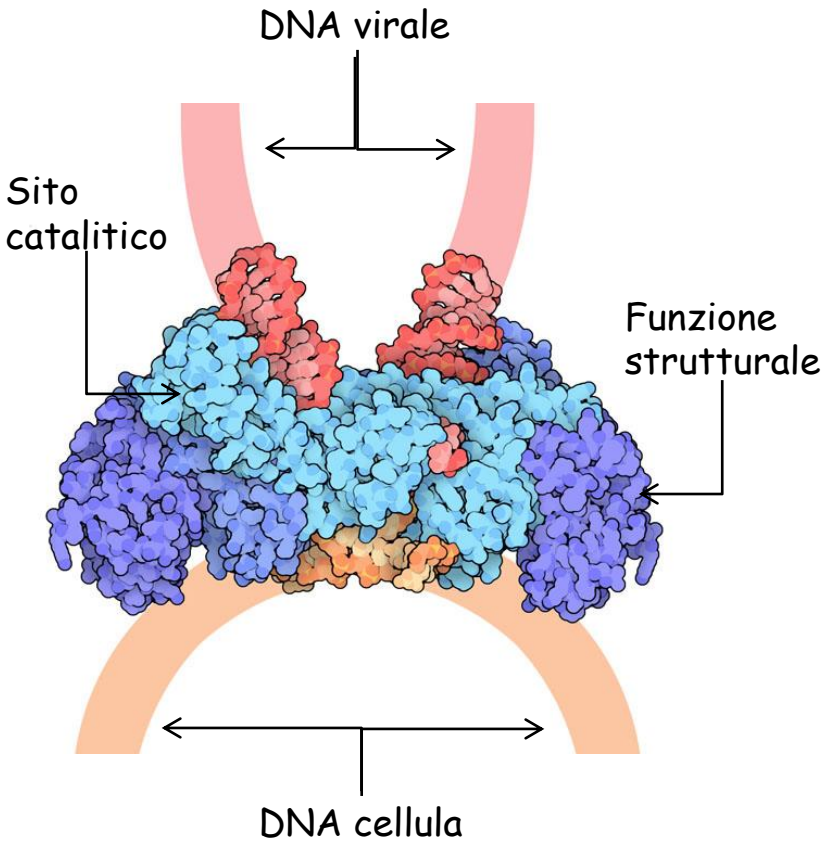


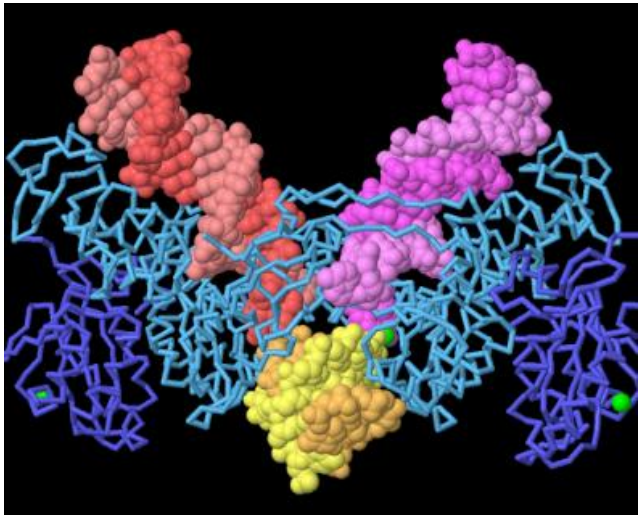
PIC permeano membrana nucleare e raggiungono il nucleo

Unione estremità 3' DNA virale con fosfato 5' cromosoma ospite

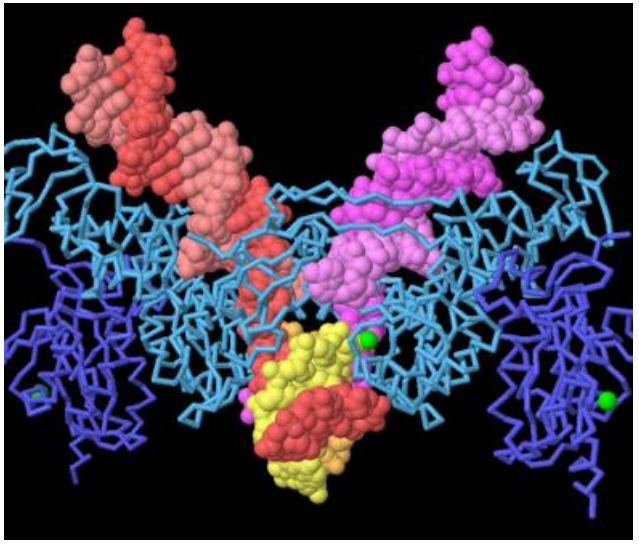
Il processo 3' ha luogo nel citoplasma e segue la fase di trascrizione inversa. Questo processo genera idrossili reattivi (3') ad entrambe le estremità del DNA virale. Multimeri di integrasi restano legati al DNA virale e migrano nel nucleo sotto forma di complessi di preintegrazione. Una reazione successiva, sempre catalizzata da integrasi, trasferisce uno strand (unione 3' terminale) inserendo entrambe le estremità del DNA virale nel cromosoma ospite.

prototype foamy virus (PFV)





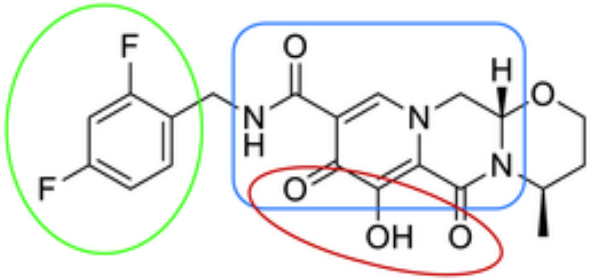
target capture complex



strand transfer complex

Inibitori Integrasi

alo-benzile

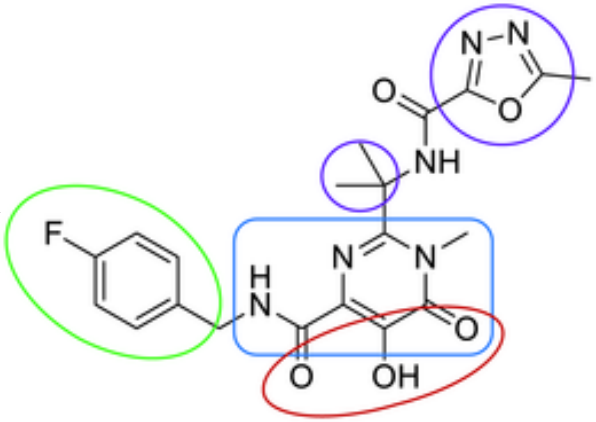


A

Dolutegravir *(Tivicay)*

EMA 2014

(4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5] pyrazino [2,1-b][1,3]oxazine-9-carboxamide

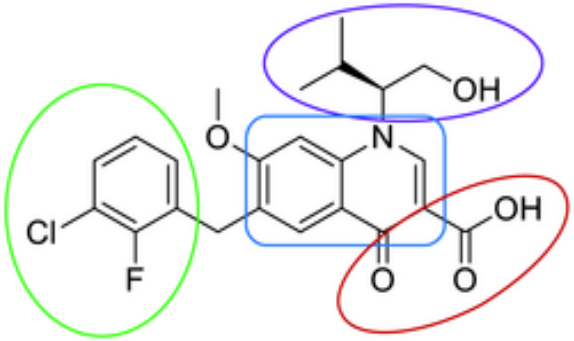


B

Raltegravir (*Isentress*)

EMA 2007

N-(4-fluorobenzyl)-5-hydroxy-1-methyl-2-(2-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}-2-propanyl)-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide



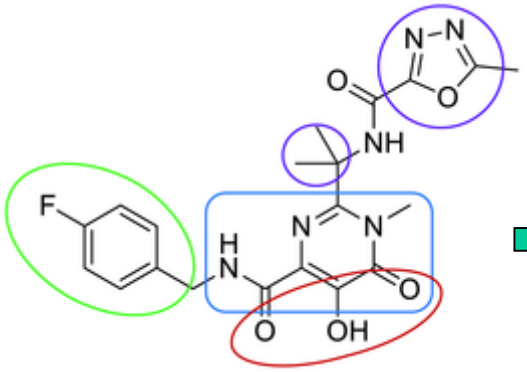
C

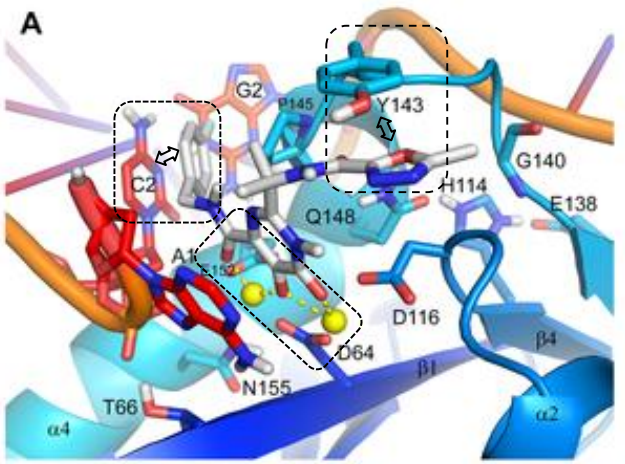
Elvitegravir *(Genvoya[1], Stribild[2])*

6-[(3-chloro-2-fluoro-phenyl)methyl]-1-[(1S)-1-(hydroxymethyl)-2-methyl-propyl]-7-methoxy-4-oxo-quinoline-3-carboxylic acid

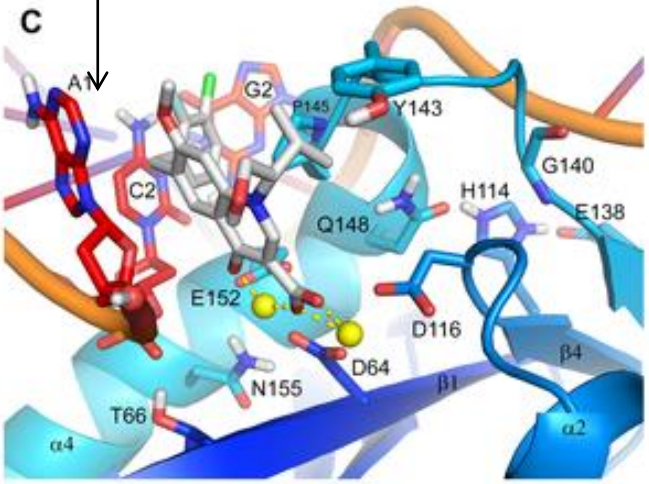
1) +cobicistat / emtricitabine / tenofovir alafenamide EMA 2015; 2) + cobicistat / emtricitabine / tenofovir disoproxil fumarate EMA 2013

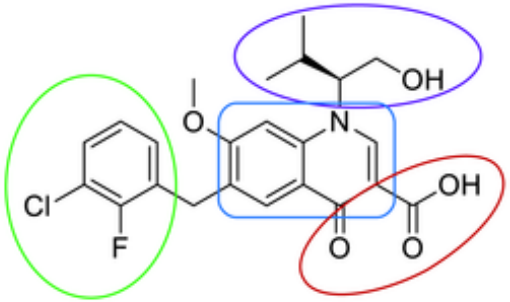
Raltegravir





π–π stacking

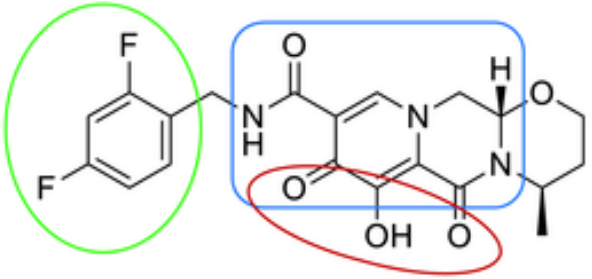


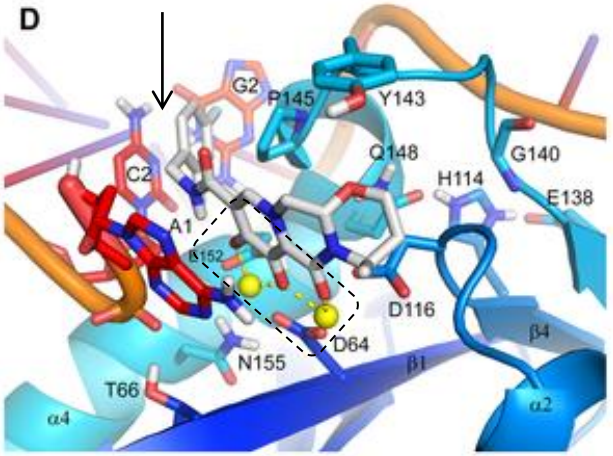


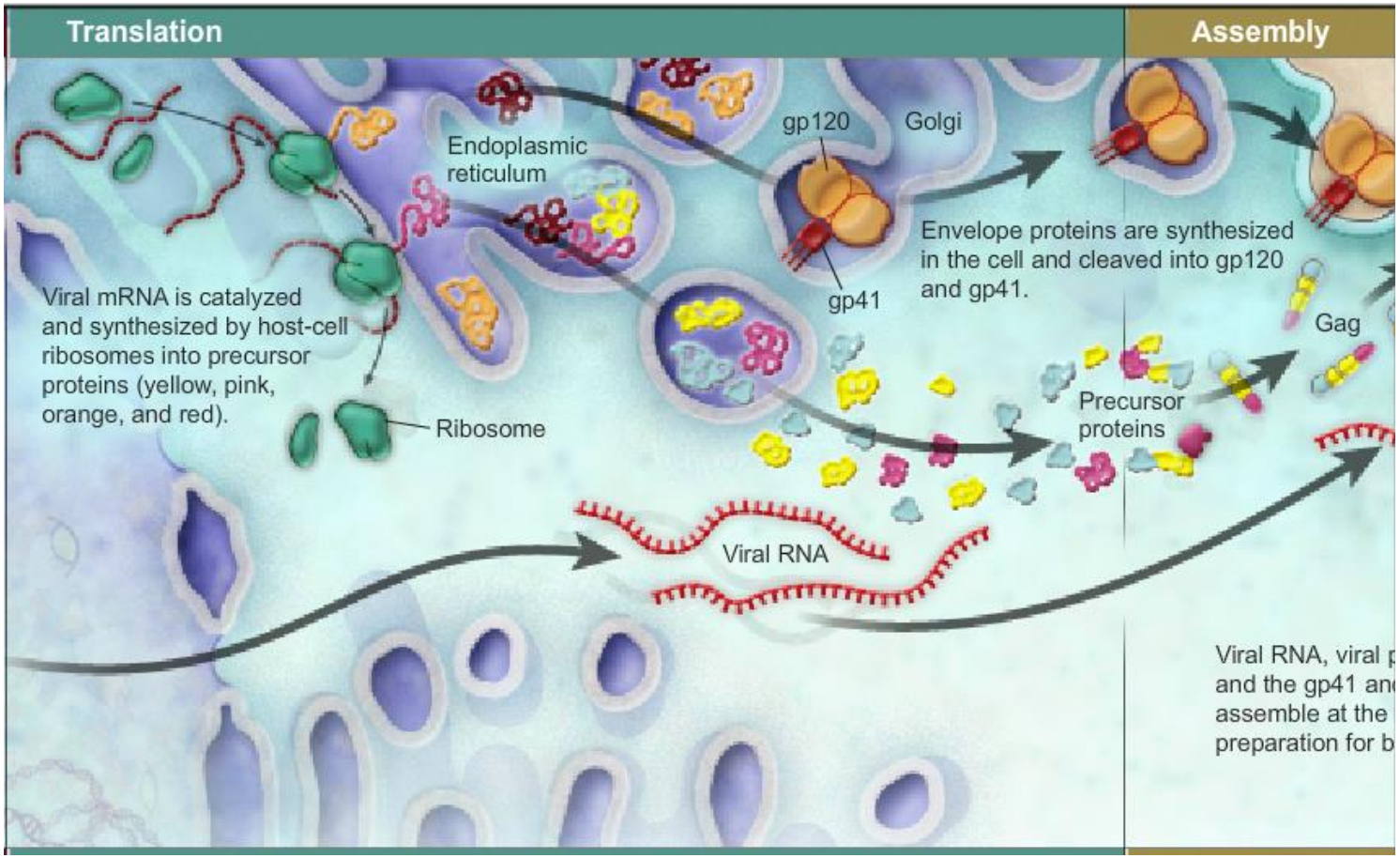
Elvitegravir

π–π stacking

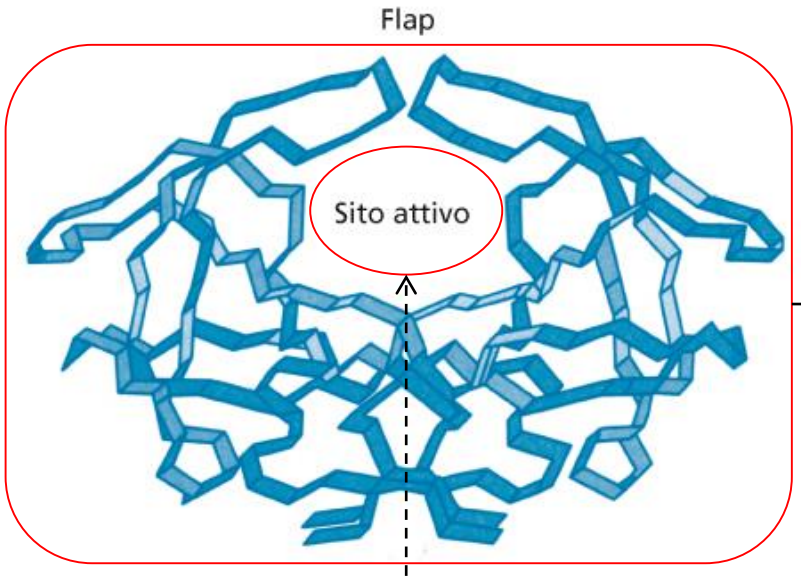
Dolutegravir







https://www.youtube.com/watch?v=odRyv7V8LAE&t=134s



HIV proteasi: enzima proteolitico (aspartil proteasi) responsabile dell'attivazione (idrolisi) di un precursore poliproteico in proteine biologicamente attive. Questo processo si completa durante o subito dopo la fase di gemmazione virale che produce virioni maturi. L'inibizione di questo stadio post-traslazionale arresta la maturazione bloccando l'infettività dei virioni.

Omodimero (asse di simmetria C2) di due subunità identiche (99aa)

asp-thr-gly

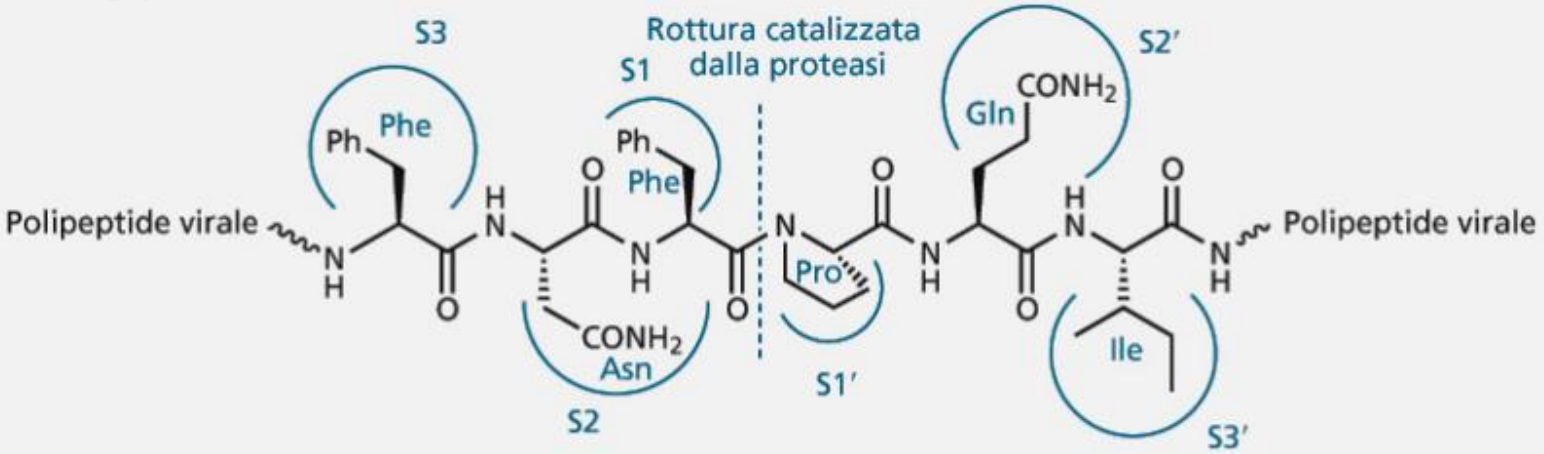


FIGURA 20.16 Il legame peptidico amminoacido aromatico-prolina, che è scisso dalla HIV proteasi (sei degli otto siti di legame sono mostrati nella figura).

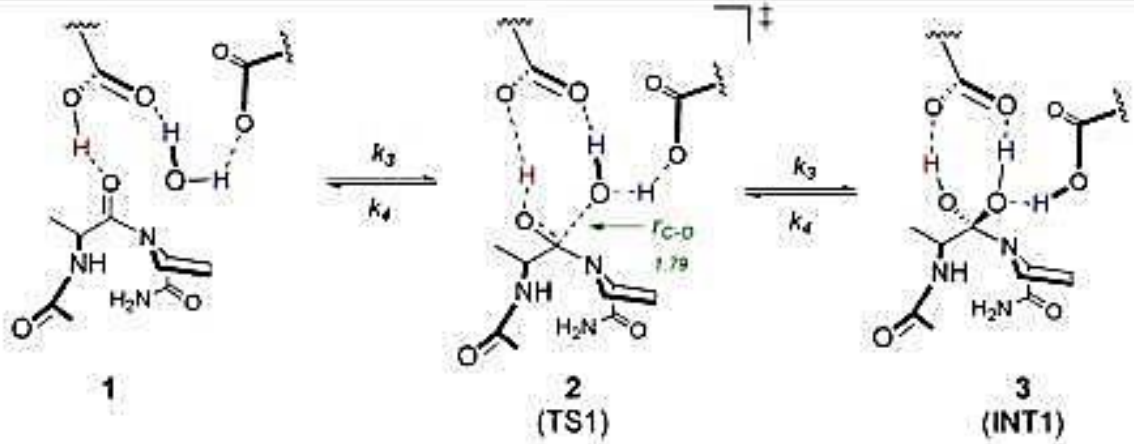
Table 2.1 Examples of aspartic proteases and their biological functions.

Aspartic proteases	Biological functions
Human aspartic proteases	
Pepsin	Protein digestion in the stomach
Gastricsin	Digestion in stomach and seminal plasma
Cathepsin D	Proteolysis in lysosomes
Cathepsin E	Located in subcellular vesicles, function unknown
Napsin	Present in kidney and lung, function unknown
Renin	Regulation of blood pressure
Memapsin 1 (BACE2)	Function unknown
Memapsin 2 (BACE1)	Neuronal development and functions
γ-Secretase (presenilin)	Cellular differentiation, proteolysis of membrane proteins
Signal peptide peptidase	Leader sequence removal of specific proteins
Plant aspartic proteases	
Cardosins (cynarases)	Insect defense for the flowers of cardoon
Barley aspartic protease	Protein digestion during germination of seeds
Microbial and pathogen aspartic proteases	
Plasmepsin 2	Hemoglobin digestion in vacuoles of *P. falciparum*
Rhizopuspepsin	Extracellular protein hydrolysis by *R. chinensis*
Endothiapepsin	Extracellular protein hydrolysis by *E. parasitica*
Penicillopepsin	Extracellular protein hydrolysis by *penicillium* fungi
Candida SAPs	Virulent factors for *Candida* species
Proteinase A	Cellular protein hydrolysis in yeast vacuoles
Barrierpepsin	Cleavage of α-factor for cell cycle regulation of yeast
Retroviral aspartic proteases	
HIV protease	Processing of viral polyproteins for virion assembly
HTLV-1 protease	Processing of viral polyproteins for virion assembly

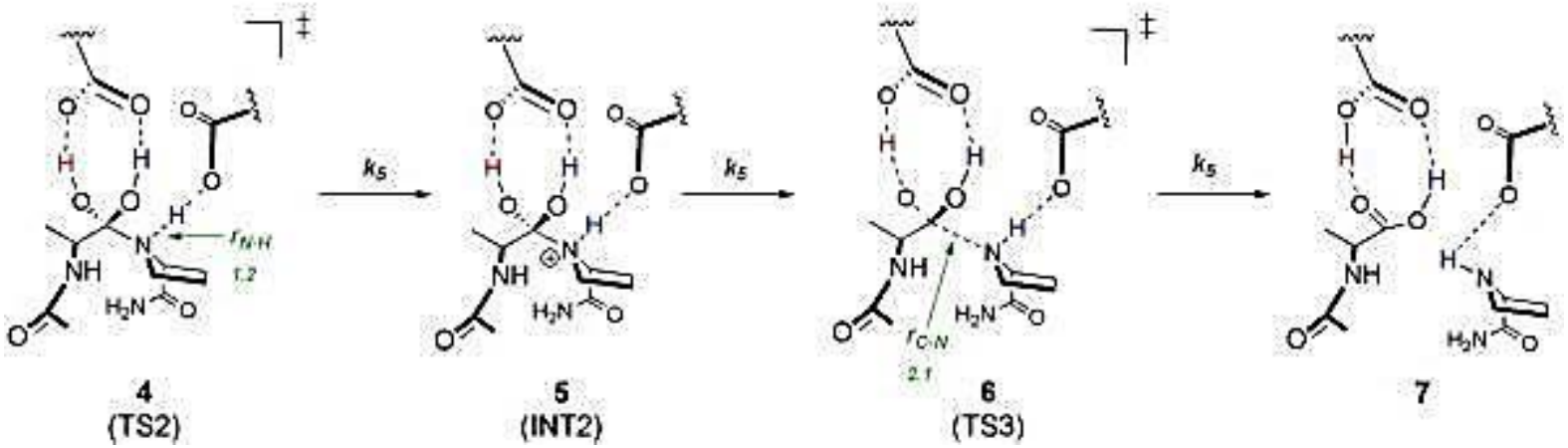
attacco nucleofilo H_2O

phe-pro

complesso enzima-substrato



intermedio tetraedrico gem-diolico



N-protonazione della Pro

intermedio ammidico protonato

scissione legame C-N

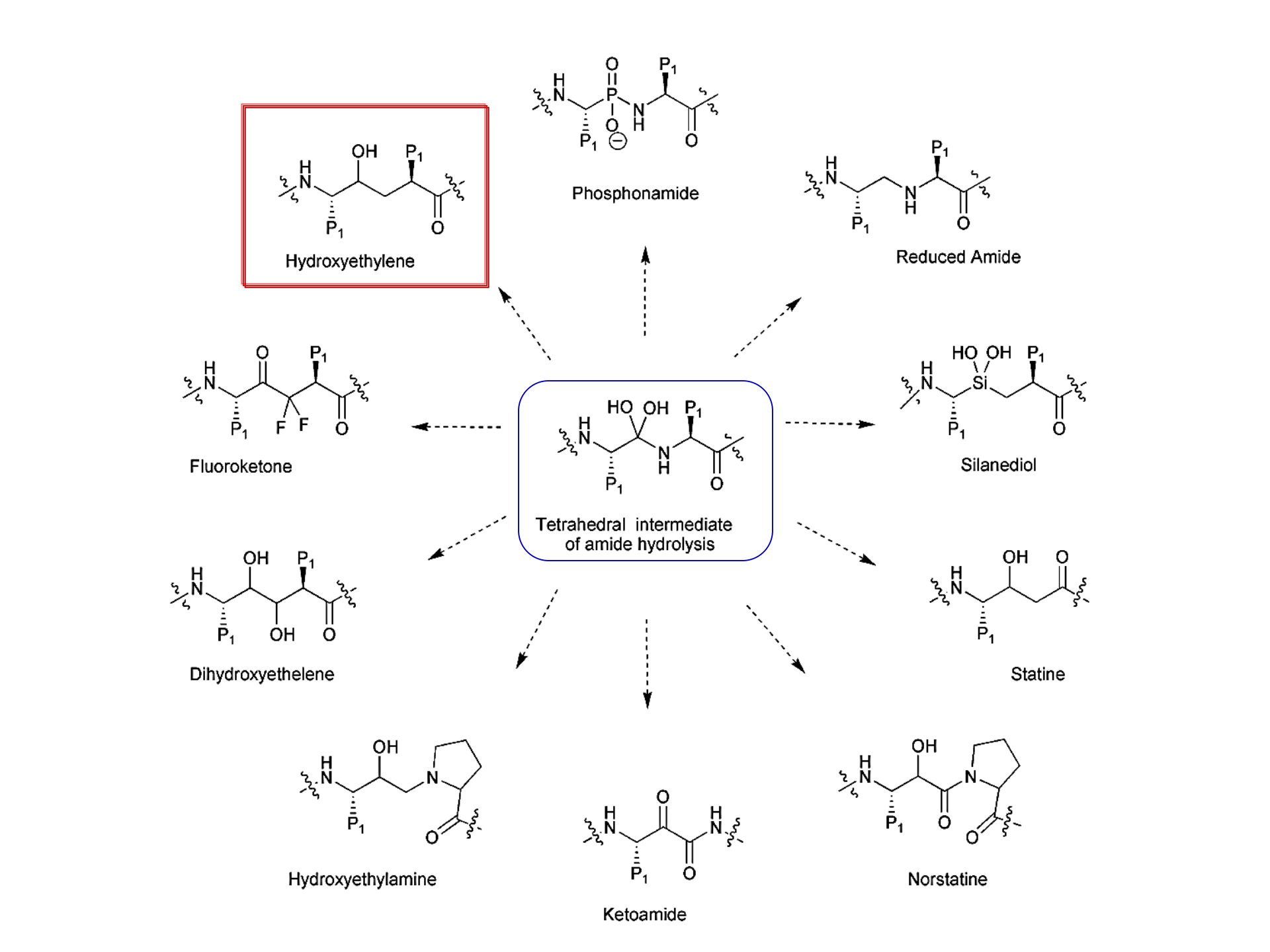
complesso enzima-prodotto

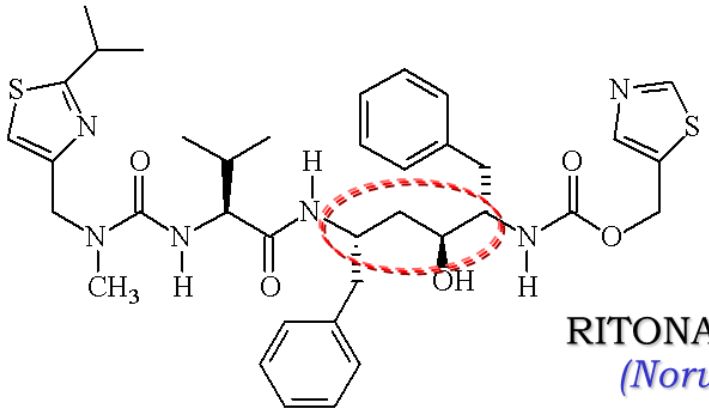
3 principali strategie per la progettazione di inibitori di proteasi:

1. Mimetici dello stato di transizione: inibitori competitivi (peptidi) del substrato naturale nel binding al sito catalitico dell'enzima;
2. Modificazioni che alterano la stereospecificità (assi di simmetria C2) con formazione di specifici HB e interazioni idrofobiche;
3. Sviluppo di inibitori con migliore profilo farmacocinetico (peptidomimetici).

Inibitori HIV proteasi:

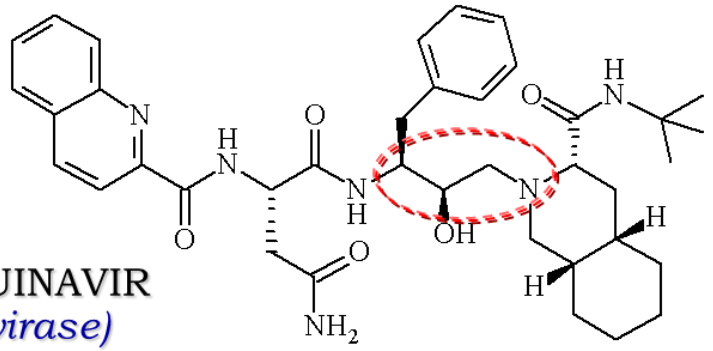
- peptidici I^ generazione;
- non-peptidici II^ generazione;
  - La regione scissile ha una sequenza phe-pro alle posizioni 167 and 168 della proteina substrato;
  - Gli inibitori sono resistenti all'idrolisi per sostituzione del legame scissile con un gruppo non-scissile e ancora capace di legarsi al sito catalitico (es. idrossietilene).


Hydroxyethylene
Phosphonamide
Reduced Amide
Fluoroketone
Tetrahedral intermediate of amide hydrolysis
Silanediol
Dihydroxyethelene
Statine
Hydroxyethylamine
Ketoamide
Norstatine



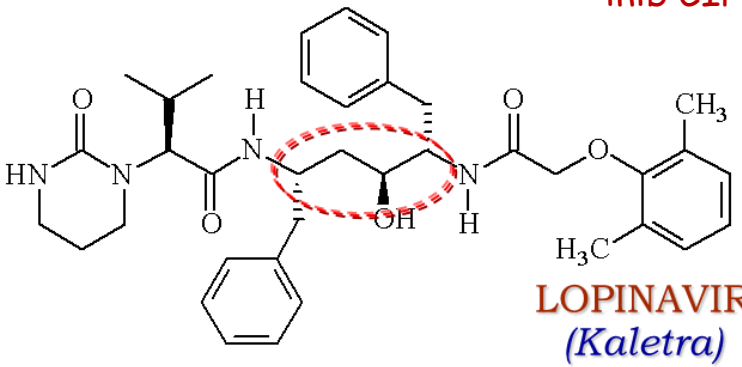
RITONAVIR
(Norvir)

inib CIP3A4

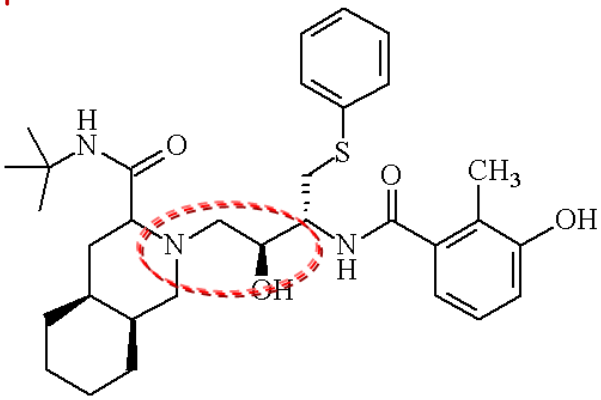


SAQUINAVIR
(Invirase)

inib CIP3A4

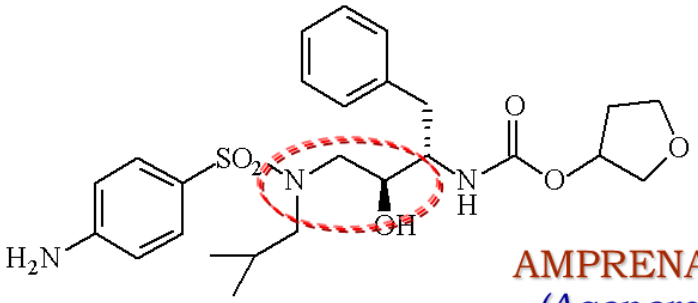


LOPINAVIR
(Kaletra)

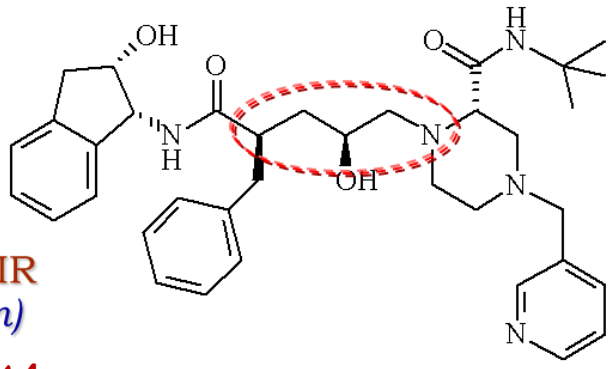


NELFINAVIR
(Viracept)

inib CIP3A4



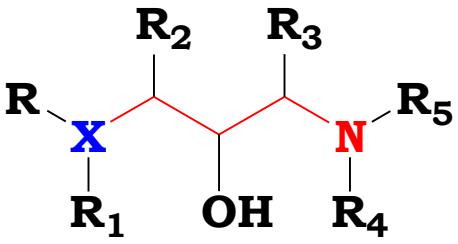
AMPRENAVIR
(Agenerase)



INDINAVIR
(Crixivan)

inib CIP3A4

deriv. 1,3-diammino-2-propanolo



X=N
R_2=H, Bz
R_3=H, Bz, CH_2-S-ph

saquinavir
nelfinavir
amprenavir

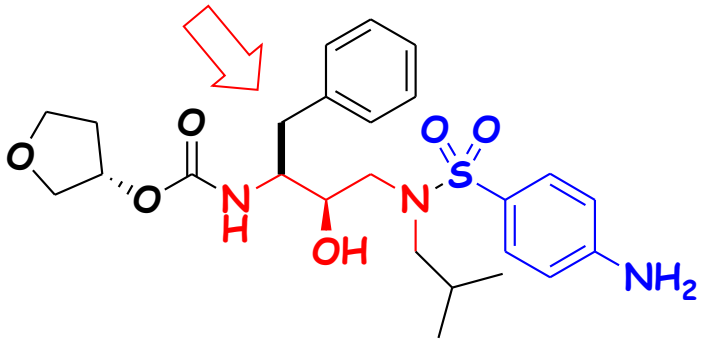
X=C
R_1=Bz
R_2=H
R_3=H, Bz,

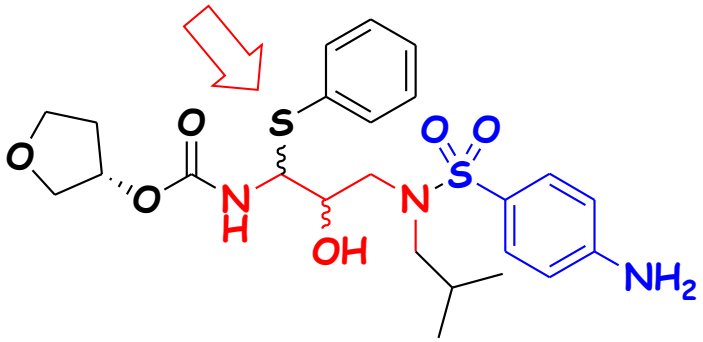
ritonavir
lopinavir
indinavir

deriv. 1-ammino-2-butanolo

Esempio di isosteria nello sviluppo dell'amprenavir.

size, shape, electronic distribution, chemical reactivity, lipophilicity and hydrogen bonding capacity





Amprenavir

S, S, R = IC_{50} = 0,001 µM

emivita *(idrolisi)* ~ *1440min*

S, S, R = IC_{50} = 1,4 µM

S, S, S = IC_{50} = 11,6 µM

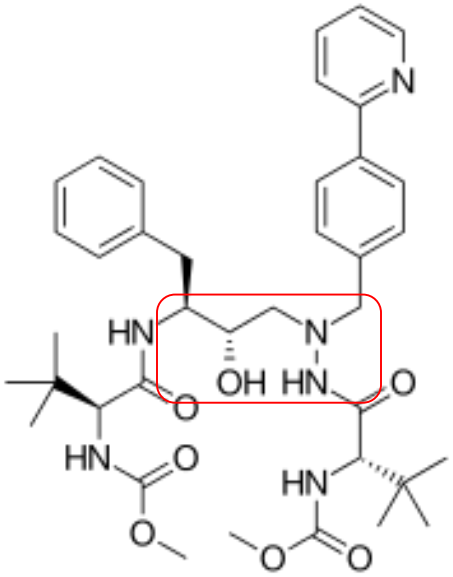
S, R, S = IC_{50} = 12,5 µM

S, R, R = IC_{50} = 16,7 µM

emivita *(idrolisi)* ~ *10min*

Luc Rocheblave et al. J. Med. Chem., 2002, 45 (15), pp 3321–3324

Più recenti inibitori dell' HIV proteasi



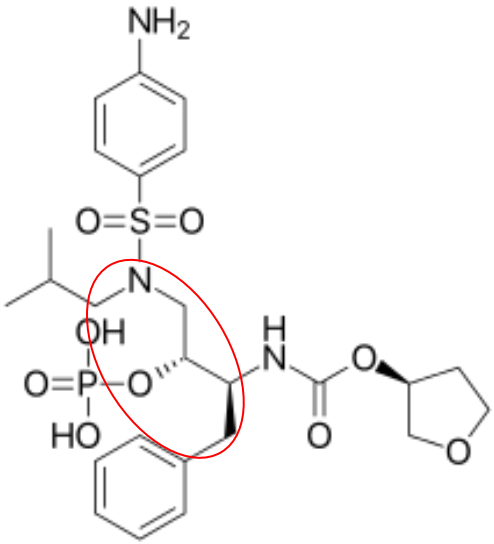
Atazanavir

Reyataz

In associazione con ritonavir a basso dosaggio, pazienti adulti con infezione da HIV–1 e pazienti pediatrici dai 6 anni in su in associazione con altri antiretrovirali. (FDA 2003)

Fosamprenavir

Telzir



In associazione con ritonavir a basso dosaggio, pazienti adulti, adolescenti e bambini dai 6 anni in poi con infezione da (HIV-1) in combinazione con altri farmaci antiretrovirali. (EMEA 2004)

Terapia HAART

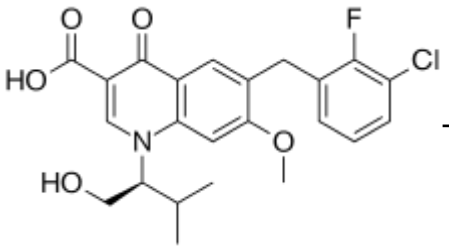
Negli ultimi anni sono stati sviluppati diversi protocolli terapeutici che prevedono l'uso combinato di più farmaci antiretrovirali.

Questo approccio, che va sotto il nome di "highly active antiretroviral therapy" (HAART), ha portato ad un significativo prolungamento della sopravvivenza e ad una marcata riduzione di infezioni opportunistiche e di decessi.

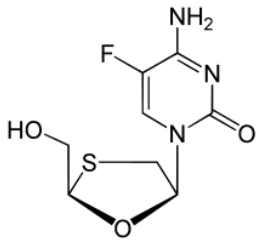
Se la HAART viene iniziata precocemente ed utilizzata costantemente e correttamente, si possono avere alte percentuali di sopravvivenza.

La "highly active antiretroviral therapy" comporta l'associazione di due NRTI con un inibitore NNRTI, oppure con uno o due inibitori di proteasi

AIDSinfo Drug Database
http://aidsinfo.nih.gov/drugs/424/atripla/0/patient#

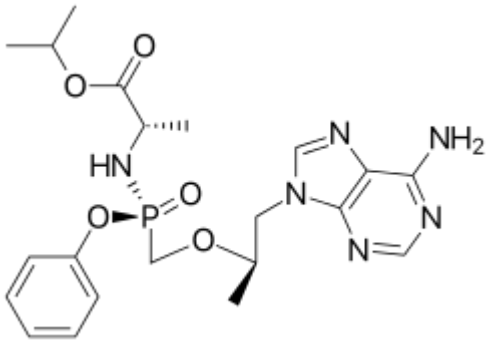


Elvitegravir
inibitore integrasi

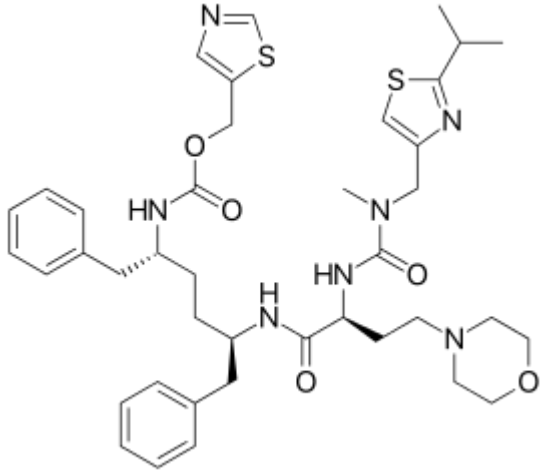


Emricitabina
inibitore transcrittasi inversa

Genvoya
(EMEA 19/11/2015)



Tenofovir alafenamide
inibitore transcrittasi inversa



Cobicistat
inibitore citocromo P4503A

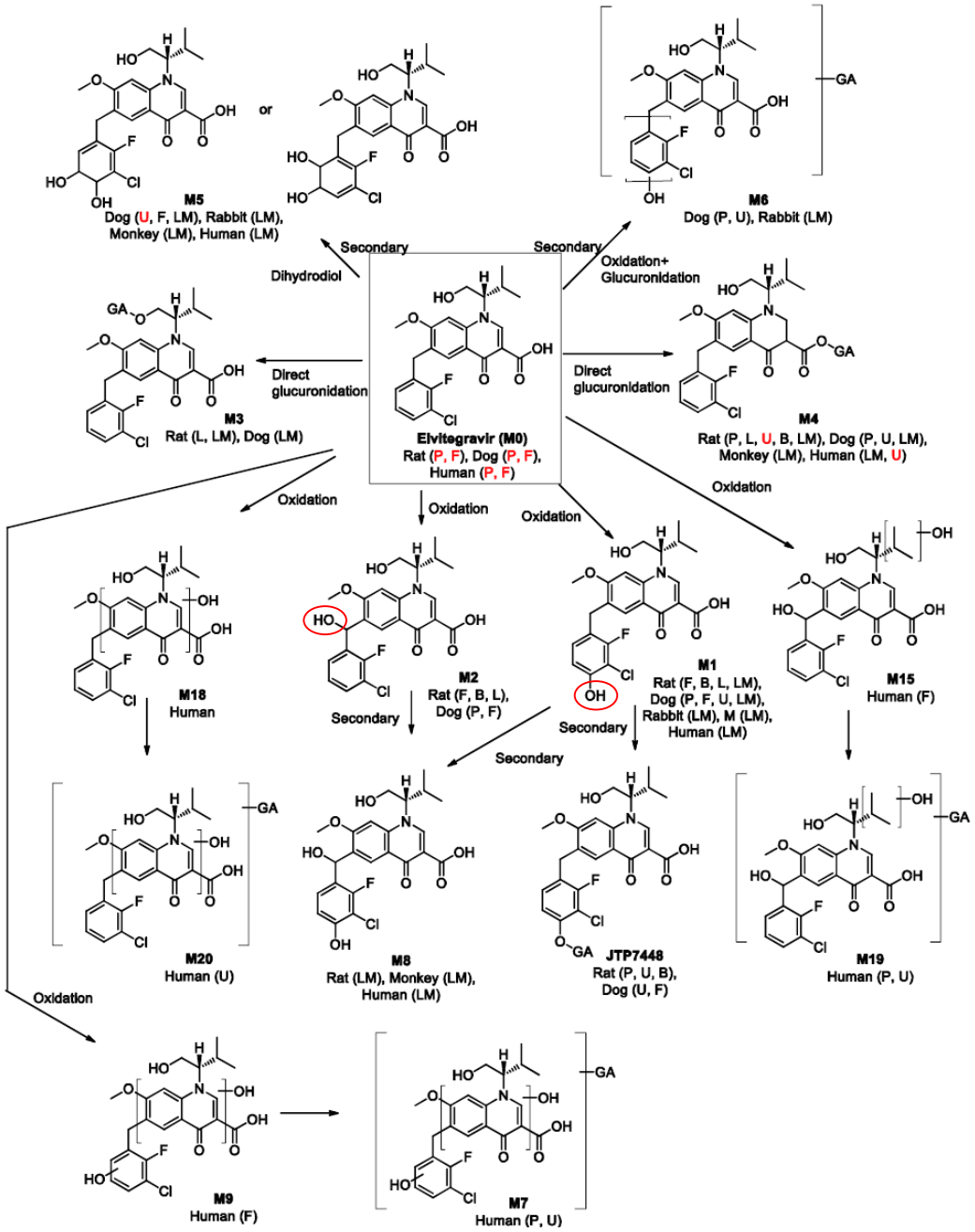
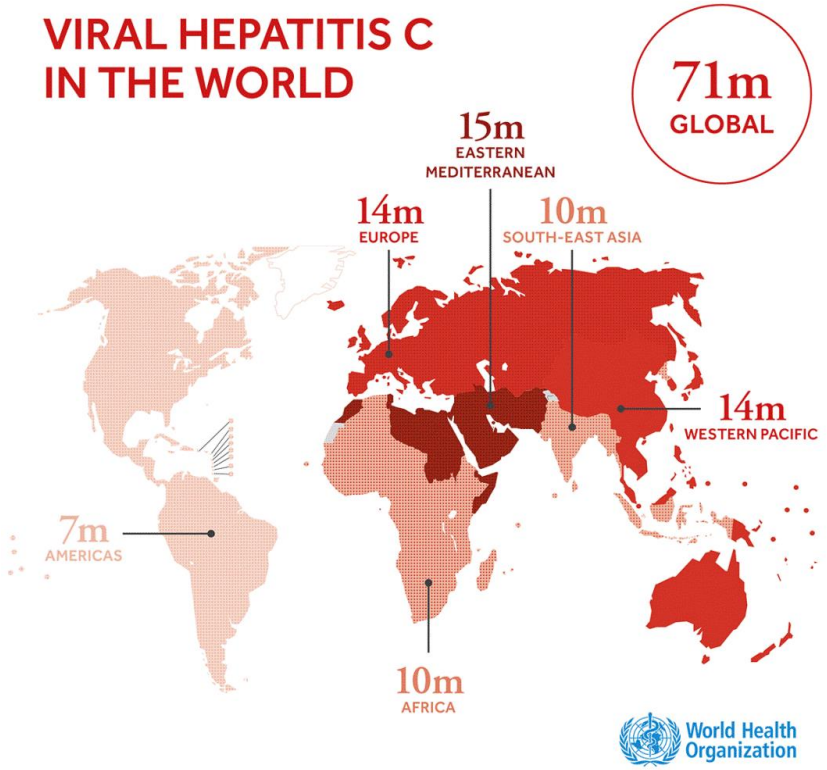


Figure B Proposed Metabolic Pathway of Elvitegravir[21, 22]

The red labels represent the major component in matrices. P = plasma, U = urine, B = bile, F = feces, L = liver, LM = liver microsomes, GA = glucuronide.

World Health Organization

GLOBAL HEPATITIS REPORT, 2017



A goal of eliminating viral hepatitis as a major public health threat by 2030;

- to reduce the incidence of chronic hepatitis infection from the current 6–10 million cases of chronic infection to 0.9 million infections by 2030;
- to reduce the annual deaths from chronic hepatitis from 1.4 million to less than 0.5 million by 2030.

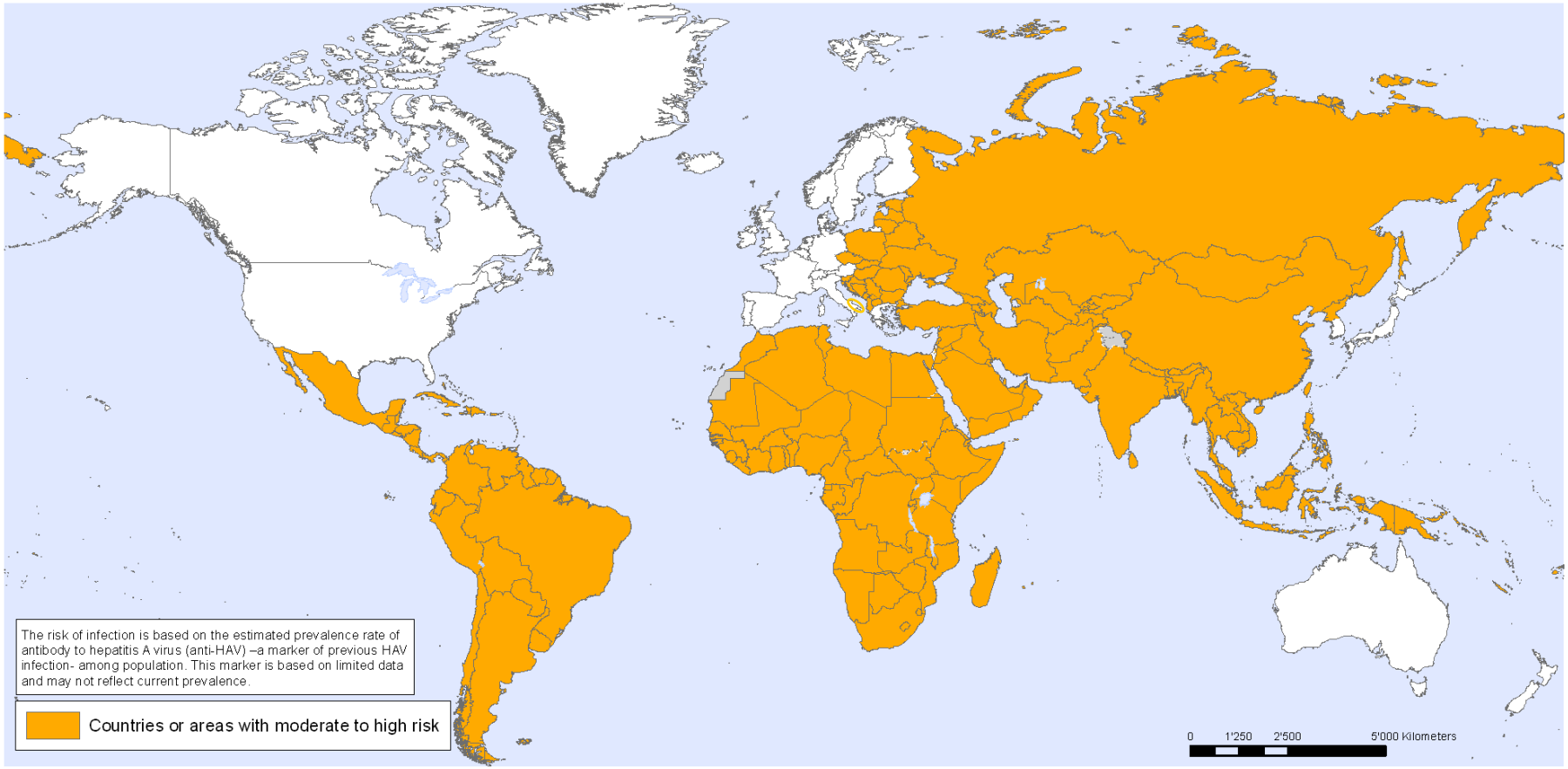
World Health Organization

Hepatitis A Updated July 2016 Key facts

Hepatitis A is a viral liver disease that can cause mild to severe illness.

- 1.4 million cases of hepatitis A every year.
- The hepatitis A virus is transmitted through ingestion of contaminated food and water, or through direct contact with an infectious person (poor personal hygiene).
- Improved sanitation and the hepatitis A vaccine are the most effective ways to combat the disease.
- Unlike hepatitis B and C, hepatitis A infection does not cause chronic liver disease and is rarely fatal.
- The hepatitis A virus is one of the most frequent causes of foodborne infection.
- Hepatitis A viruses persist in the environment and can resist food-production processes routinely used to inactivate and/or control bacterial pathogens.

Hepatitis A, countries or areas at risk



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization.
Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine 2010 Sep;28(41):6653-7
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Chironna et al. BMC Infectious Diseases 2012, 12:271
http://www.biomedcentral.com/1471-2334/12/271

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Hepatitis A in Puglia (South Italy) after 10 years of universal vaccination: need for strict monitoring and catch-up vaccination

Maria Chironna[1,3*], Rosa Prato[2,3], Anna Sallustio[1], Domenico Martinelli[2,3], Silvio Tafuri[1,3], Michele Quarto[1,3] and Cinzia Germinario[1,3]

Abstract

Background: Raw seafood consumption was identified as the major risk factor for hepatitis A during the large epidemic of 1996 and 1997 in Puglia (South Italy). In Puglia, vaccination for toddlers and preadolescents has been recommended since 1998.
The aim of the study was to evaluate the incidence, seroprevalence, molecular epidemiology, and environmental circulation of hepatitis A virus (HAV) in Puglia more than ten years after the introduction of anti-HAV vaccination in the regional immunization program.

Methods: Data on the incidence of acute hepatitis A in Puglia were analyzed. Characteristics and risk factors of 97 acute hepatitis A cases occurring in 2008–2009 were analyzed. Serum samples from 868 individuals aged 0 to 40 years were tested for anti-HAV antibodies. Fecal samples from 49 hepatitis A cases were analyzed by sequence analysis in the VP1/P2A region. In 2008, 203 mussel samples and 202 water samples from artesian wells were tested for HAV-RNA.

Results: Between 1998 and 2009, the incidence of acute hepatitis A declined from 14.8 to 0.8 per 100,000. The most frequent risk factors reported by cases in 2008–2009 were shellfish consumption (85%) and travel outside of Puglia or Italy (26%). Seroepidemiologic survey revealed high susceptibility to HAV in children and adults up to age 30 (65%-70%). None of the mussel or water samples were HAV-positive. Phylogenetic analysis revealed co-circulation of subtypes IA (74%) and IB (26%) and clustering of strains with strains from Germany and France, and those previously circulating in Puglia.

World Health Organization

Hepatitis B Updated July 2016 Key facts

- Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease.
- The virus is transmitted through contact with the blood or other body fluids of an infected person.
- An estimated 240 million people are chronically infected with hepatitis B (defined as hepatitis B surface antigen positive for at least 6 months).
- More than 686000 (780000, 2015) people die every year due to complications of hepatitis B, including cirrhosis and liver cancer
- The hepatitis B virus is 50 to 100 times more infectious than HIV.
- Hepatitis B is an important occupational hazard for health workers.
- A vaccine against hepatitis B has been available since 1982 (Italia 1991). The vaccine is 95% effective in preventing infection and the development of chronic disease and liver cancer due to hepatitis B.

World Health Organization

Hepatitis C Updated July 2016 Key facts

- Hepatitis C is a liver disease caused by the hepatitis C virus (HCV).
- The disease can range in severity from a mild illness lasting a few weeks to a serious, lifelong condition that can lead to cirrhosis of the liver or liver cancer.
- The hepatitis C virus is transmitted through contact with the blood of an infected person.
- About 130-150 million people are chronically infected with hepatitis C virus, and more than 700000 (500000, 2015) people die every year from hepatitis C-related liver diseases. A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer.
- Antiviral medicines can cure approximately 90% of persons with hepatitis C infection, thereby reducing the risk of death from liver cancer and cirrhosis, but access to diagnosis and treatment is low.
- There is currently no vaccine for hepatitis C; however, research in this area is ongoing.

World Health Organization

Hepatitis D Updated July 2016 Key facts

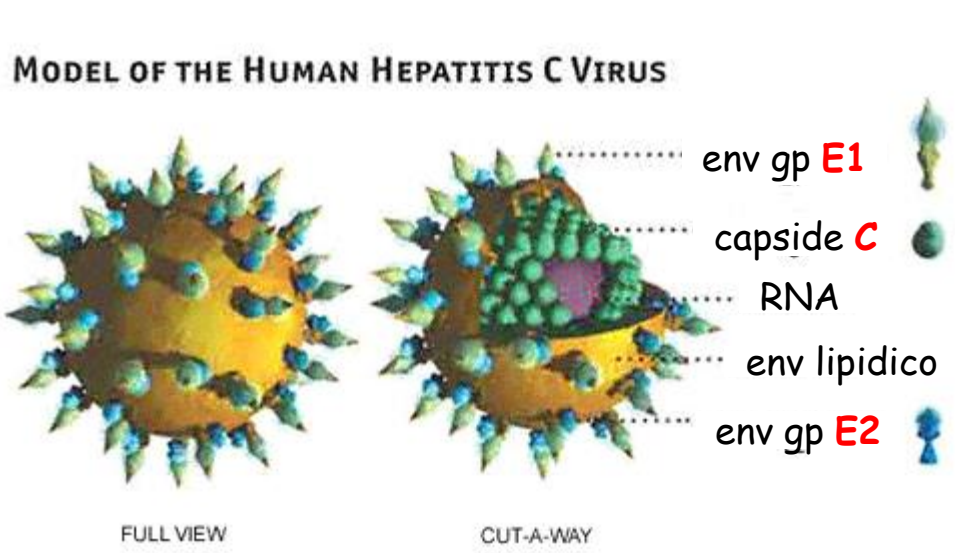
- Hepatitis D virus (HDV) is a ribonucleic acid (RNA) virus that requires hepatitis B virus (HBV) for its replication. HDV infection occurs only simultaneously or as super-infection with HBV.
- The virus is transmitted through contact with the blood or other body fluids of an infected person.
- Vertical transmission from mother to child is rare.
- Approximately 15 million people across the world are chronically coinfected with HDV and HBV 1.
- Currently there is no effective antiviral treatment for hepatitis D.
- Hepatitis D infection can be prevented by hepatitis B immunization.

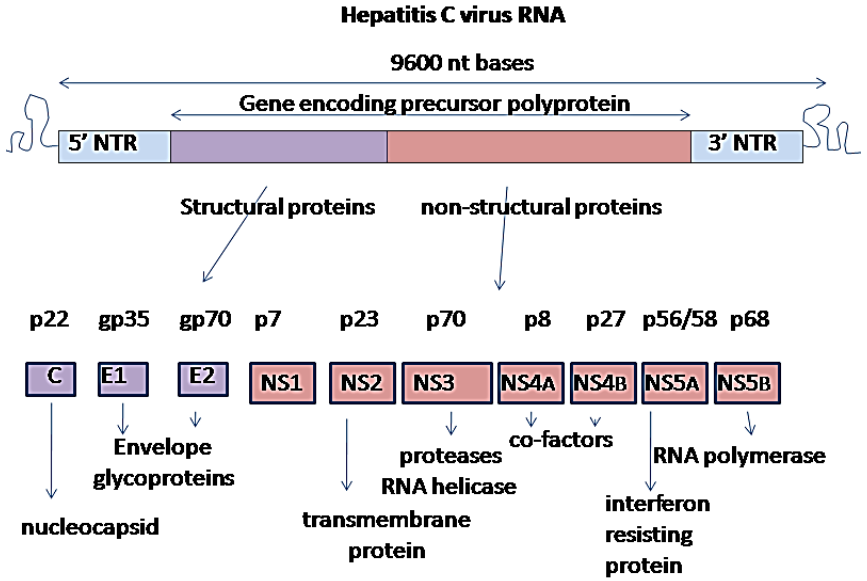
World Health Organization

Hepatitis E Updated July 2016 Key facts

- Hepatitis E is a liver disease caused by the hepatitis E virus: a non-enveloped, positive-sense, single-stranded RNA virus.
- Every year there are an estimated 20 million hepatitis E infections, over 3.3 million (3.0, 2015) symptomatic cases of hepatitis E, and 56600 hepatitis E-related deaths.
- Hepatitis E is usually self-limiting but may develop into fulminant hepatitis (acute liver failure).
- The hepatitis E virus is transmitted via the faecal-oral route, principally via contaminated water.
- Hepatitis E is found worldwide, but the prevalence is highest in East and South Asia.
- China has produced and licensed the first vaccine to prevent hepatitis E virus infection, although it is not yet available globally.

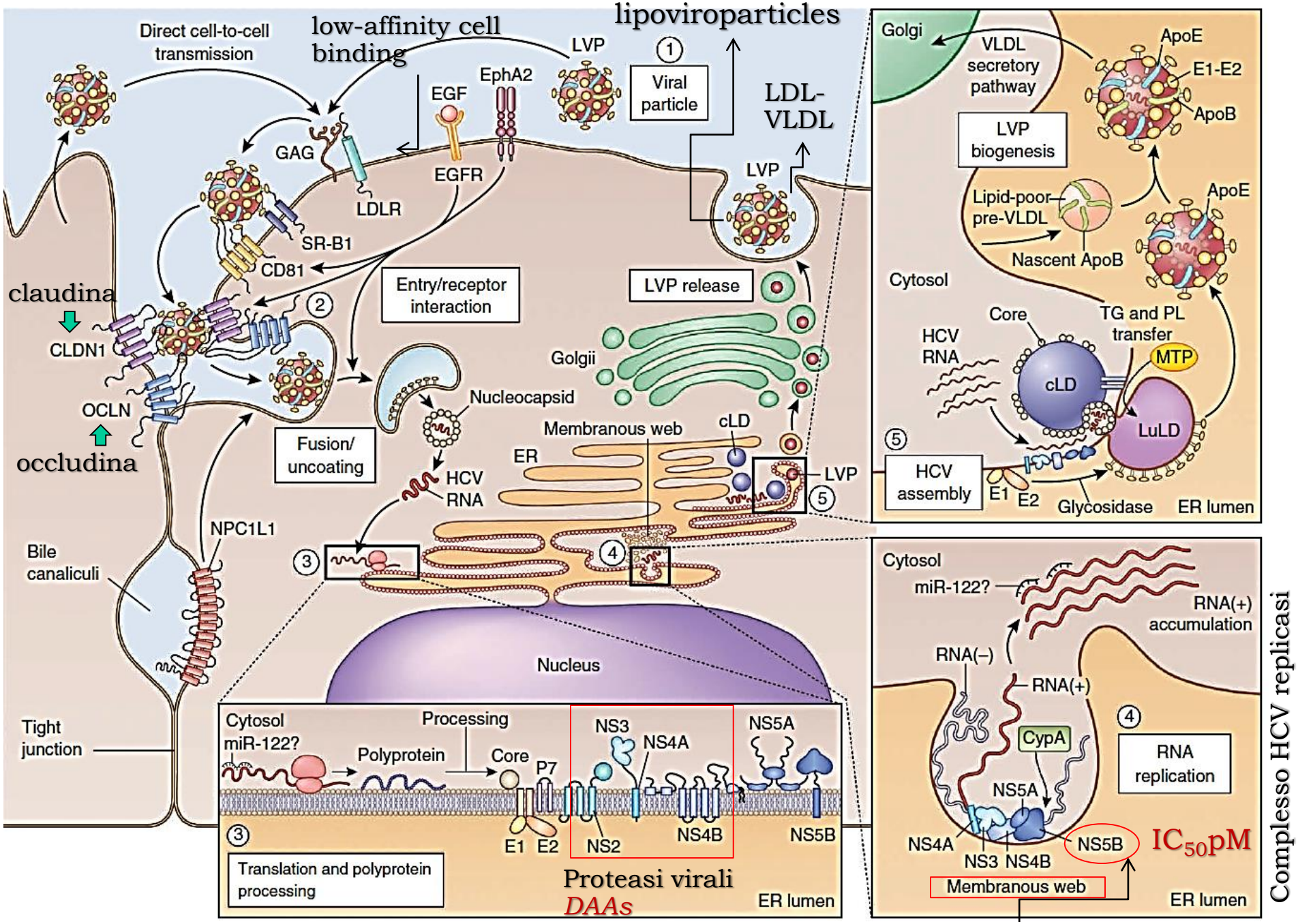
HCV (55–65 nm), enveloped, (+), (SS) RNA virus, *Flaviviridae (famiglia).* Core di materiale genetico circondato da inviluppo proteico protettivo in una matrice lipidica.





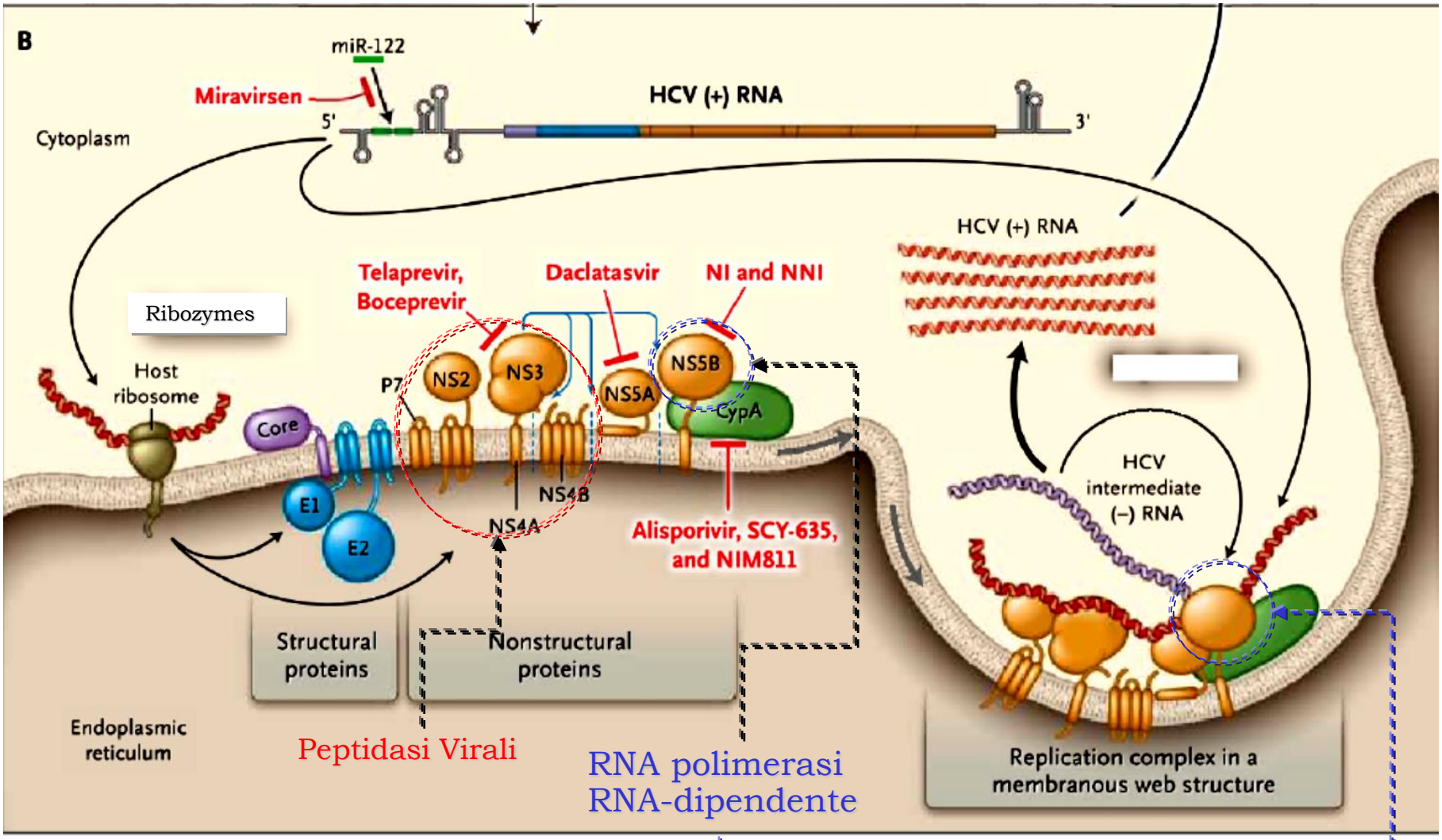
C: 191aa, tre domini, terzo dominio sequenza segnale per la proteina E1;
E1/E2: proteine env., altamente glicosilate, importanti x l'entrata del virus, E1 subunità fusogenica, E2 binding recettoriale;
p7 (NS1): 63aa, proteina di membrana (RE), importante x replicazione genoma e morfogenesi;
NS2: 21-23 kDa, proteina transmembrana, attività proteasica;
NS3: 67 kDa, proteasi serinica (*N* term), NTPasi/elicasi (*C* term), complesso con NS4A (cofattore proteinasi);
NS4A: 27 kDa, membrana RE;
NS5A: fosfoproteina idrofilica, replicazione virale, trasduzione segnale cellulare, risposta interferone;
NS5B: 65 kDa, RNA polimerasi RNA dipendente, replicazione RNA usando filamento RNA virale positivo come templato,.

https://www.youtube.com/watch?v=fV-jhNQs_WE



Nature Medicine 2013, 19 (7)

RNA polimerasi RNA-dipendente



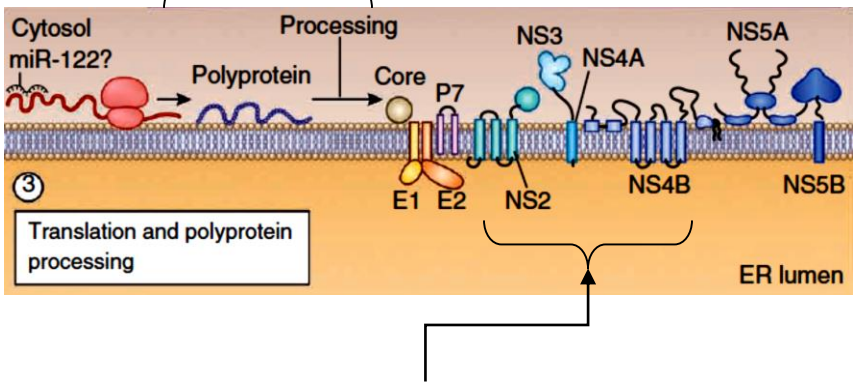
Peptidasi Virali

RNA polimerasi
RNA-dipendente

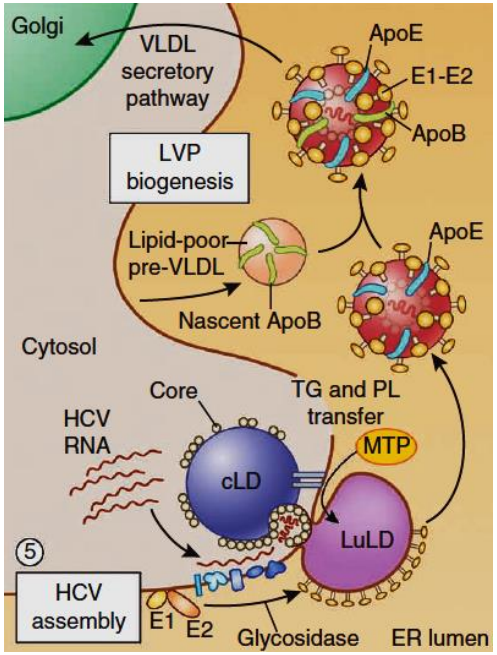
Mirarvirsen

Antagonista nucleotidico del miR-122, con efficacia verso tutti i genotipi;

poliproteina è "*smembrata*", sia durante che dopo la translazione, da proteasi cellulari (signalasi e peptide-segnale peptidasi) e..



..proteasi virali NS2-NS3 e NS3-NS4A→ 10 proteine.
Il cleavage NS2-NS3 è essenziale per la formazione della RNA replicasi.

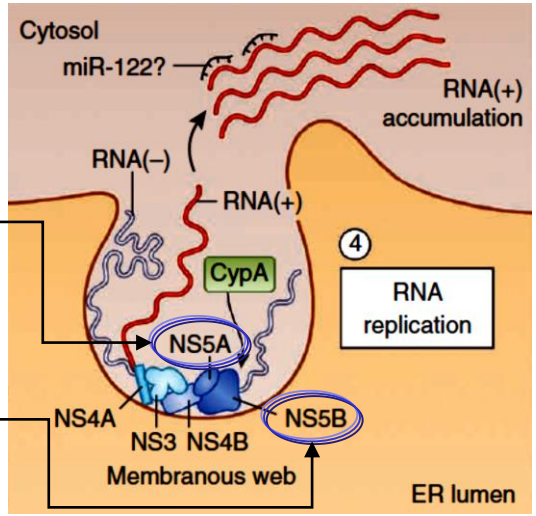


Processo accoppiato con la sintesi lipidica della cellula ospite

telaprevir (2011)
boceprevir (2011)
simprevir (2014)
faldaprevir (sosp)
vaniprevir (JP 2014)
asunaprevir (JP 2014)

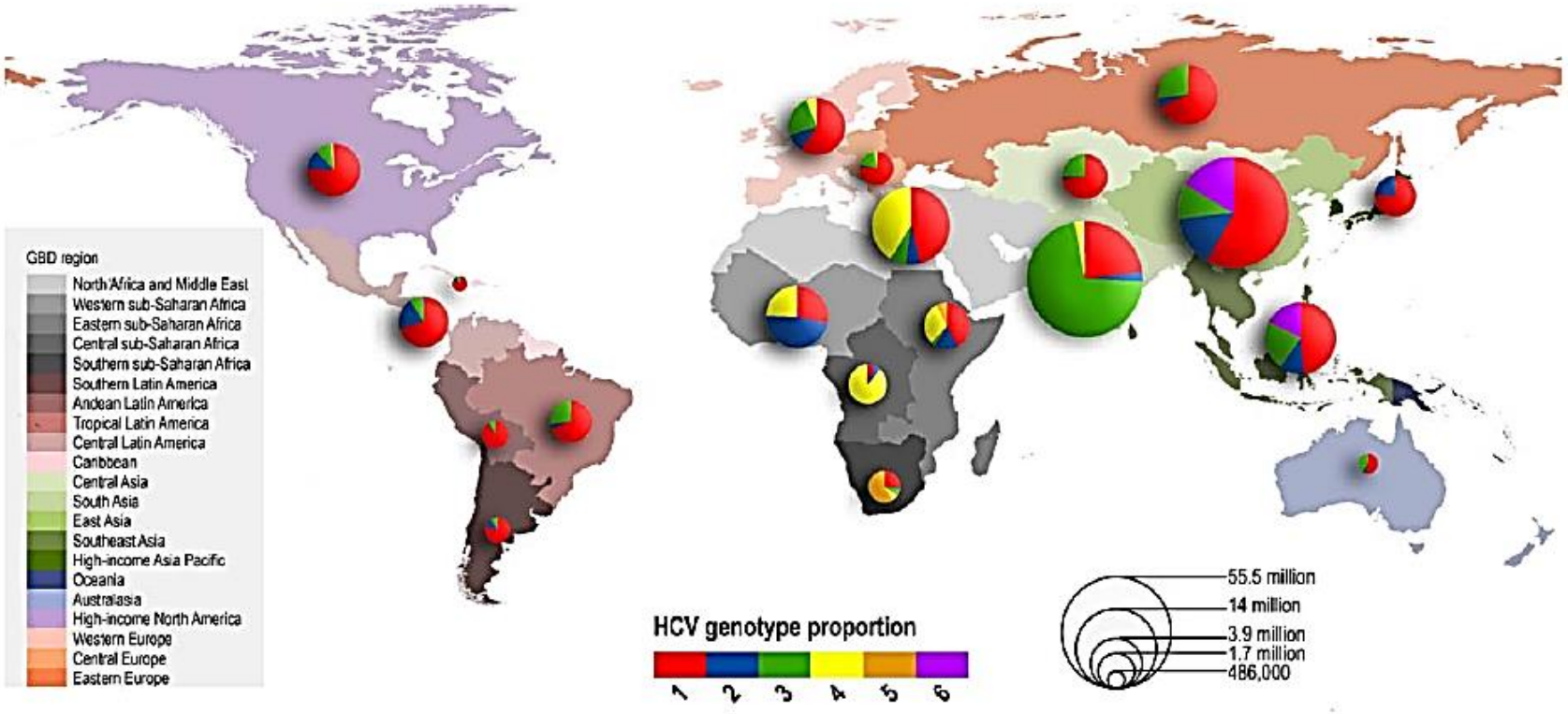
NS5A: fosfoproteina essenziale per la replicazione RNA con struttura a tre domini di cui il primo disponibile in alta risoluzione; inibitori più potenti (IC50<pM).

NS5B (RNA polimerasi RNA dipendente) enzima chiave, target per inibitori NS e NT (chain terminator) e NN; tossicità mitocondriale.

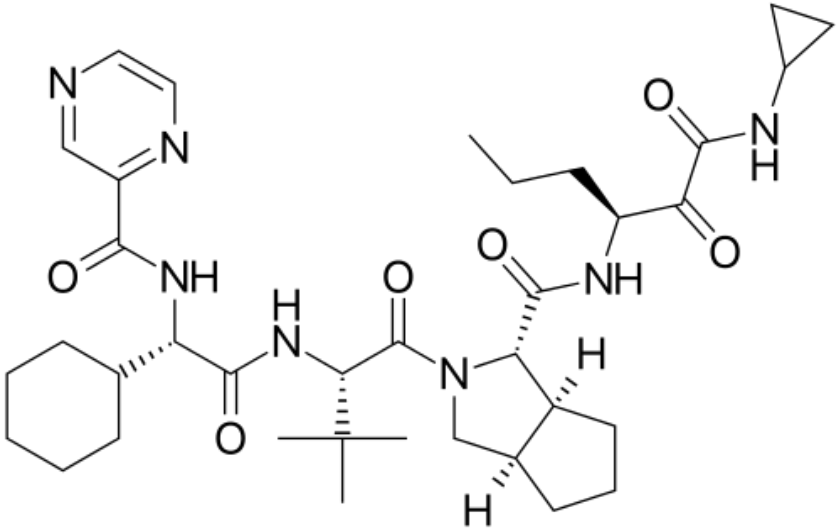


https://www.youtube.com/watch?v=_q1xe_FPqKc

- HCV strains are classified into seven recognized genotypes (1-7) on the basis of phylogenetic and sequence analyses of whole viral genomes.
- HCV strains belonging to different genotypes differ at 30- 35% of nucleotide sites.
- Within each genotype, HCV is further classified into 67 confirmed and 20 provisional subtypes. Strains that belong to the same subtype differ at <15% of nucleotide sites.

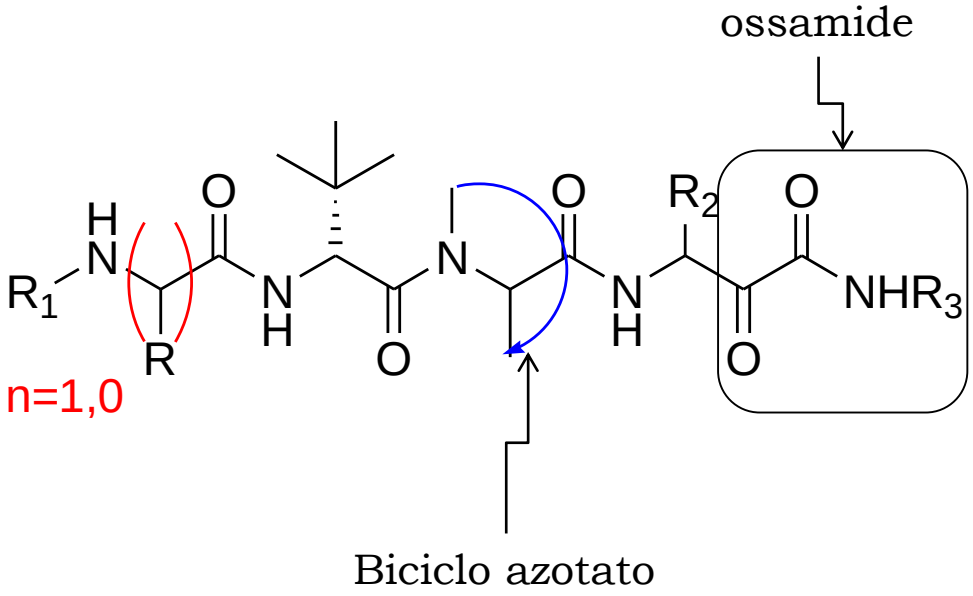


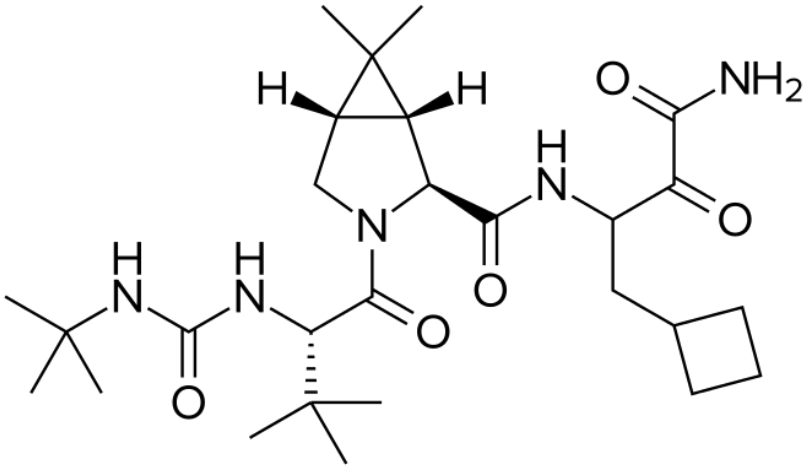
Inibitori NS3-NS4A serin-proteasi. I^ generazione



Telaprevir *(Incivo)*

Primo farmaco attivo in casi di epatite C refrattari ad altre terapie; casi cronici di genotipo 1.





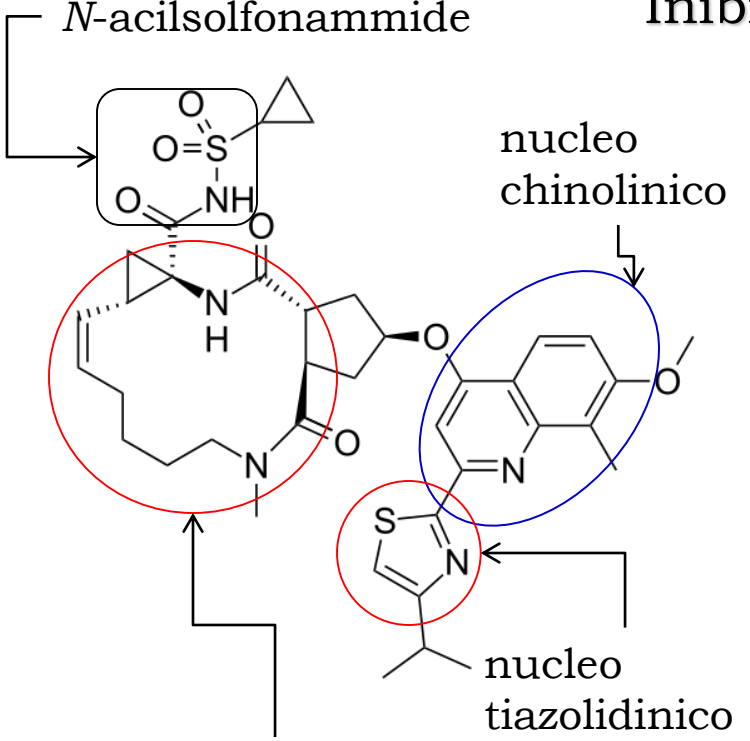
Boceprevir *(Victrelis).*

Inibitore di NS3-4A serin proteasi;

Successful Drug Discovery-2015

10- Discovery and Development of Telaprevir (Incivek™) – A Protease Inhibitor to Treat Hepatitis C Infection

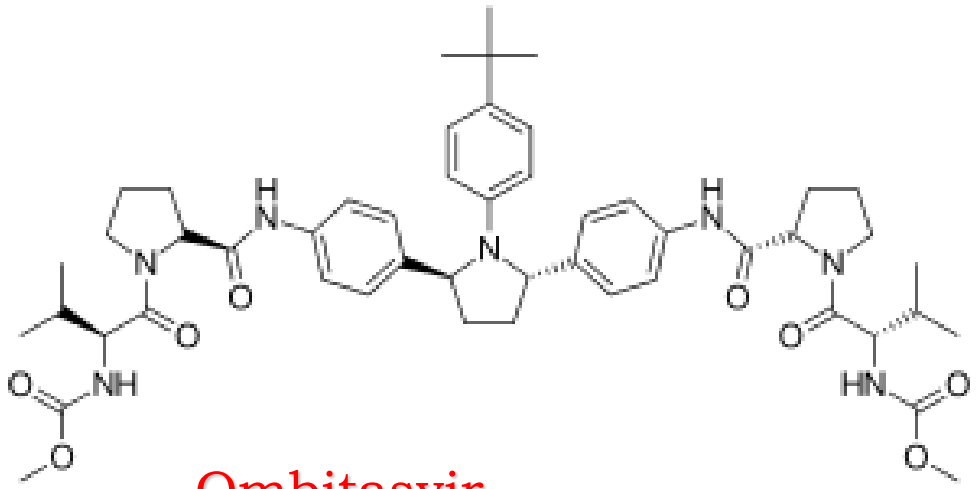
Inibitori NS3-NS4A proteasi. II^ generazione



Simprevir
(Olysio)

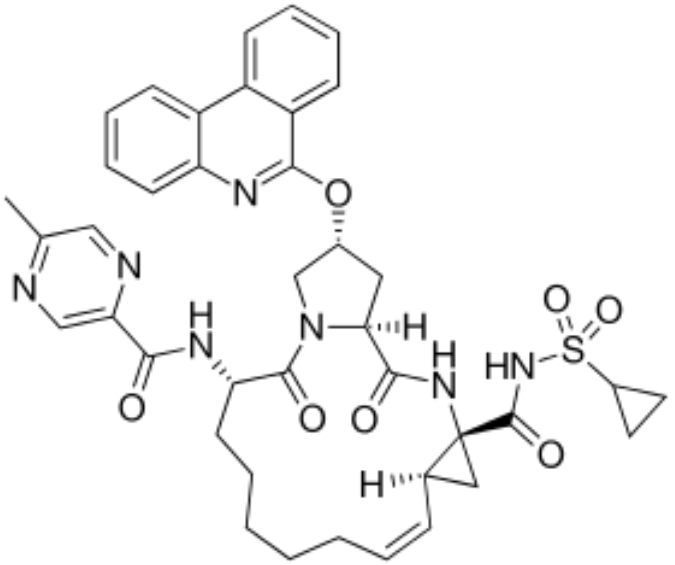
inibitore di proteasi di nuova generazione per il trattamento degli adulti con Epatite C di genotipo 1 e 4 (~60% dei pazienti italiani).

Il trattamento combinato con simeprevir e sofosbuvir rappresenta l'associazione di antivirali orali, senza interferone, con la più alta percentuale di successo, in termini di risposta virologica sostenuta (12 settimane, > 90%). Ribavirina ininfluente



Ombitasvir

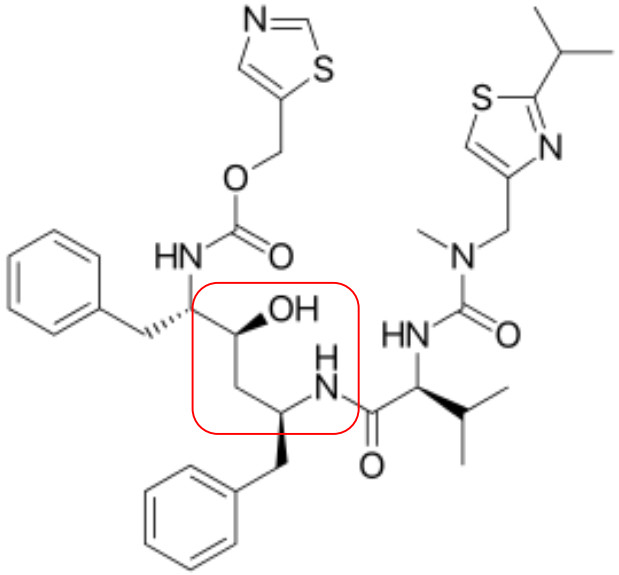
Inibitore NS5A



Paritaprevir

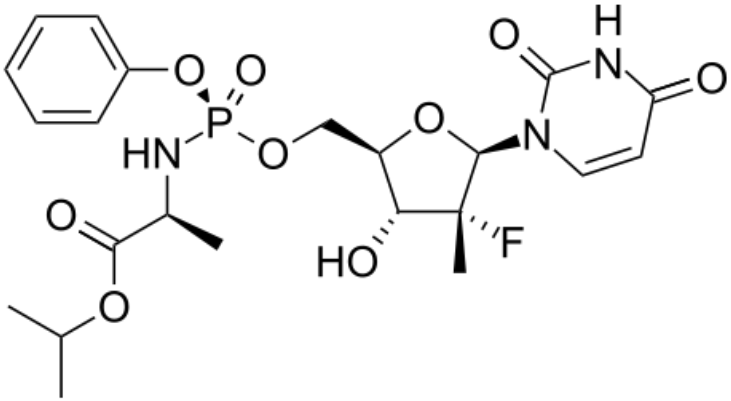
Inibitore NS3-4A
(proteasi serinica)

Viekirax



Ritonavir

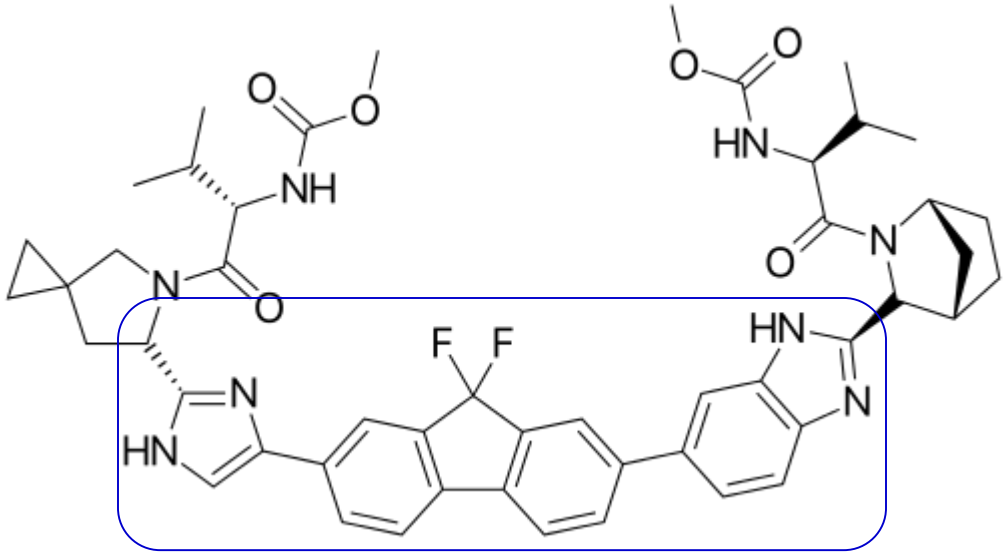
Inibitore aspartil
proteasi
(cfr HIV, HAART)



Sofosbuvir(Sovaldi)

Isopropil (2S)-2-[[[(2R,3R,4R,5R)-5-(2,4-diossopirimidin-1-il)-4-fluoro-3-idrossi-4-metil-tetraidrofuran-2-il]metossi-fenossi-fosforil]amino]propanoato

Analogo uridil nucleotide, inibitore (HCV) polimerasi (NS5B), RNA polimerasi RNA-dipendente.
Totale eradicazione nel 90% dei casi.
Approvazione AIFA dic 2014

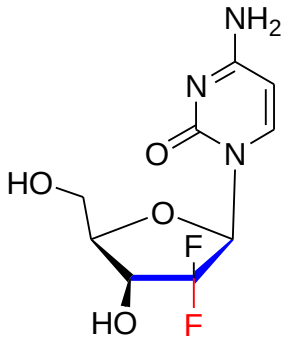


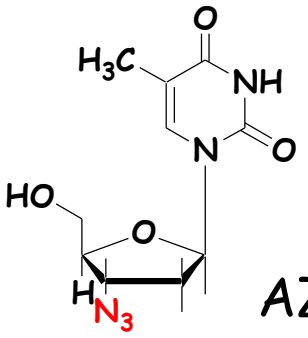
Ledipasvir

(+ sofosbuvir → *Harvoni*)

Inibitore NS5A. Previene l'iperfosforilazione di NS5A. Genotipi 1a, 1b, 4a, 5a meno verso 2a e 3a. AIFA 14/05/2015.

Gemcitabina

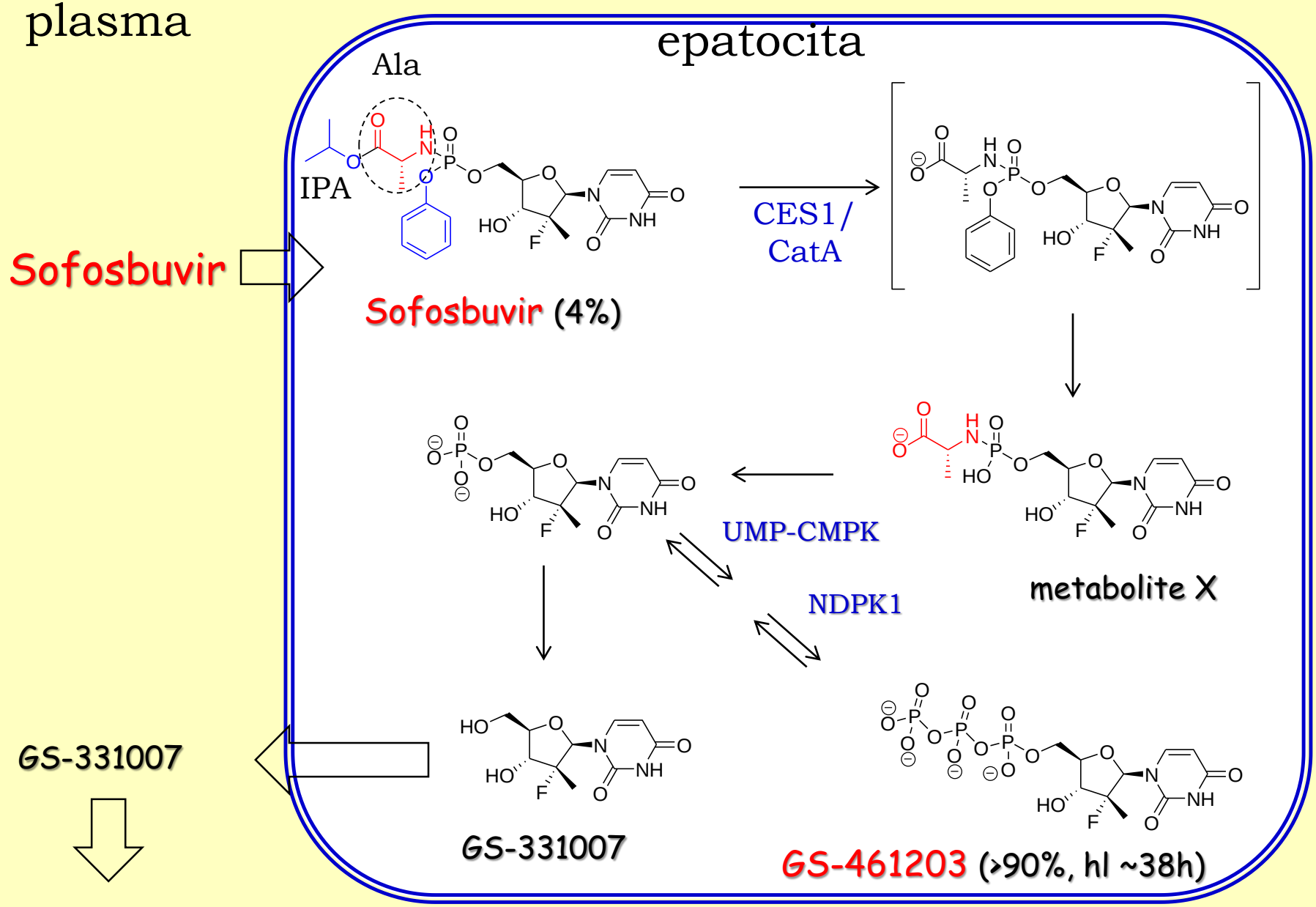




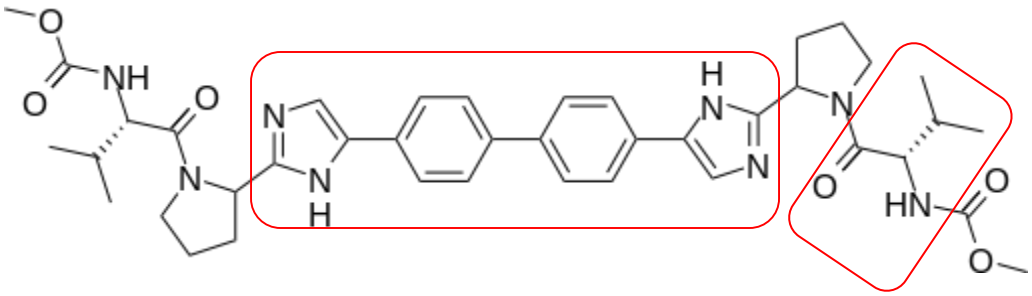
AZT

plasma

epatocita



Bryant B. Summers et al. Sofosbuvir, a novel nucleotide analogue inhibitor used for the treatment of hepatitis C virus. , Journal of Pharmacy and Pharmacology 2014

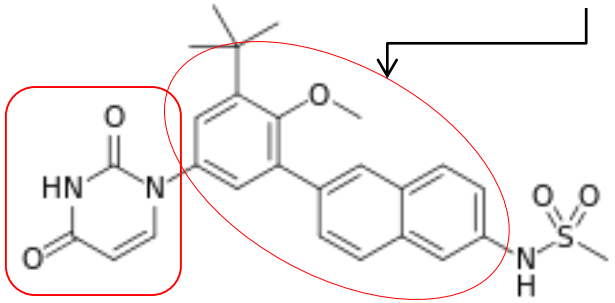


Inibitore NS5A

Daclatasvir
(Daklinza)

FDA Appr 2015 (genot 3),
2016 (genot 1 e 3)

metossifenilnaftalene

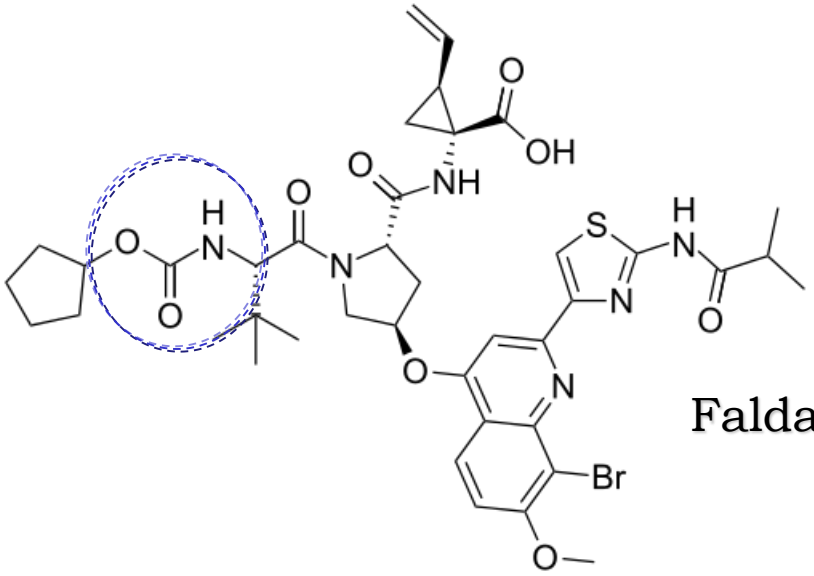


Inibitore NS5B

Dasabuvir
(Exviera)

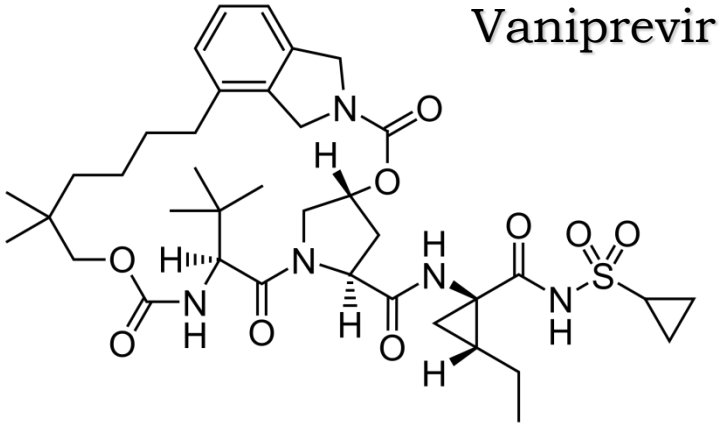
FDA Appr 2014 (genot 1 e sottot),
WHO List of Essential Medicines,

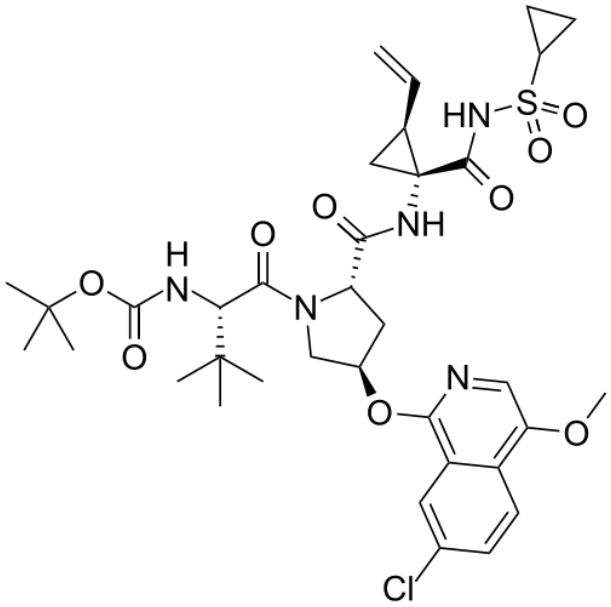
Inibitori NS3-NS4A proteasi. II^ generazione; fase 3



Faldaprevir

Vaniprevir

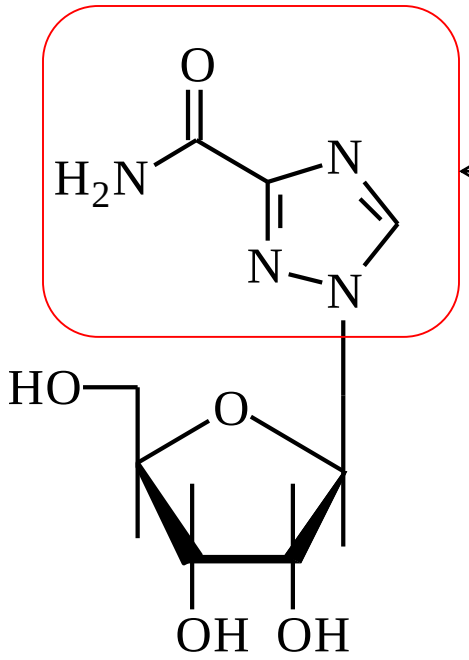




Asunaprevir

FARMACI PER L'EPATITE CRONICA C

- Interferoni alfa-2a, alfa-2b o interferone alfacon-1
- Associazione interferone alfa-2b più ribavirina orale.

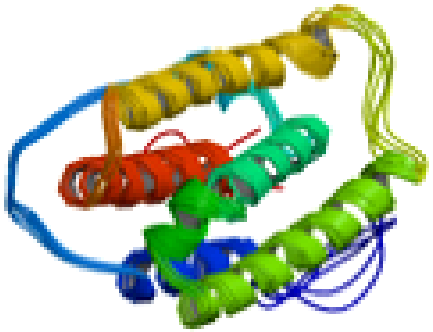


1,2,4-triazol-3-carbossamide

- Nucleoside sintetico;
- Inibisce una vasta gamma di virus a DNA e a RNA.
- Viene fosforilato a derivati mono-, di- e trifosfato
- Inibisce la sintesi dell'RNA messaggero virale.

Ribavirina

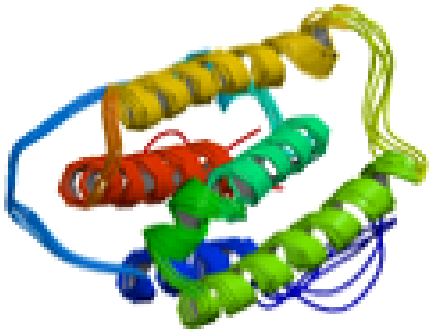
(Moderiba, Rebetol, Virazole, Copegus, equiv)



Interferone α (human leukocyte protein moiety reduced). Interferone A (tipo I) 165 aa con Lys23. Prodotto con tecnologia DNA ricombinante, simile interferone secreto da leucociti.

Usato come agente antivirale o antineoplastico.
Lega i recettori tipo I (IFNAR1 and IFNAR2c) che, dopo dimerizzazione, attivano due Janus kinasi (tirosin kinasi) (Jak1 and Tyk2).
Queste transfosforilano se stesse e i recettori INFAR che legano Stat1 e Stat2 (trasduttori di segnale e attivatori della trascrizione che dimerizzano e attivano molte proteine immunomodulatrici e antivirali.

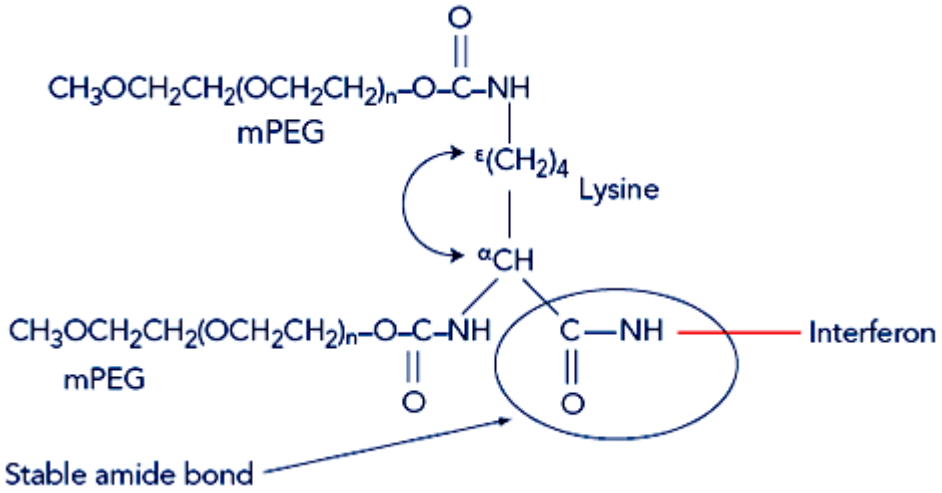
Trattamento dell'epatite cronica C, leucemia a cellule capellute (neoplasia rara), sarcoma di Kaposi AIDS correlato, leucemia mielogenica cronica, verruche orali da infezioni HIV.



Peginterferone alfa-2a

coniugato covalente di interferone ricombinante alfa-2a con una singola catena di PEG (bis-monometossi polietilen glicole).
Il sostituente PEG è legato a un singolo sito dell'interferone alfa via legame amidico stabile con lisina.
Peginterferone alfa-2a ha un peso molecolare approssimativo di 60,000 daltons.
Interferone alfa-2a è prodotto con tecnologia DNA ricombinante (gene interferone leucocitario umano inserito in *Escherichia coli*.
La proteina risultante ha 165 amino acidi.
La struttura PEG protegge la molecola da proteolisi in vivo incrementando l'emivita e riducendo l'immunogenicità.

Medesime indicazioni terapeutiche dell'interferone alfa-2a



http://www.presadiretta.rai.it/dl/portali/site/puntata/ContentItem-729dab2f-5eaa-4c96-8f3f-c9299dfe0cca.html

Boceprevir (*Victrelis*): 84 cps 1061 euro; Telaprevir (*Incivo*) : 24 cps 3102 euro; Simeprevir (*Olysio*) 28 cps 13405 euro; *Viekirax* (Ombitasvir+Paritaprevir+Ritonavir) 56 cpr 21257 euro; Sofosbuvir (*Sovaldi*) 28 cps 24756 euro; *Harvoni* (Sofosbuvir+ Ledipasvir) 28 cpr 27506 euro

La storia di un farmaco eccezionale (Sofosbuvir *(Sovaldi)*), un salvavita, che però è così costoso da mettere in discussione l'accesso alle cure garantito a tutti dalla nostra Costituzione. E allora, come si forma il prezzo di un farmaco?.
La chiamano il "killer silenzioso". E' l'Epatite C. Per anni non mostra sintomi e poi di colpo si sveglia e colpisce con complicazioni anche gravissime per la salute e ogni anno uccide 10mila italiani.
Esiste un farmaco in grado di curarla, ma è costosissimo e il Servizio Sanitario non ce la fa a darlo gratuitamente a tutti quelli che ne hanno bisogno. L'Agenzia Italiana per il farmaco ha chiuso un accordo con la multinazionale americana che lo produce per la fornitura di 50mila trattamenti, solo per i casi più gravi. E tutti gli altri?
Le storie di chi quel farmaco lo ha preso, di chi lo aspetta, di chi se lo procura a modo suo.
E ancora, come si determina il prezzo di un farmaco che può salvare la vita?