Caratteristiche degli antivirali

Il successo della terapia si basa:

1. Interferenza con funzioni specifiche del virus

o

2. Interferenza con funzioni cellulari che impediscono la replicazione del virus

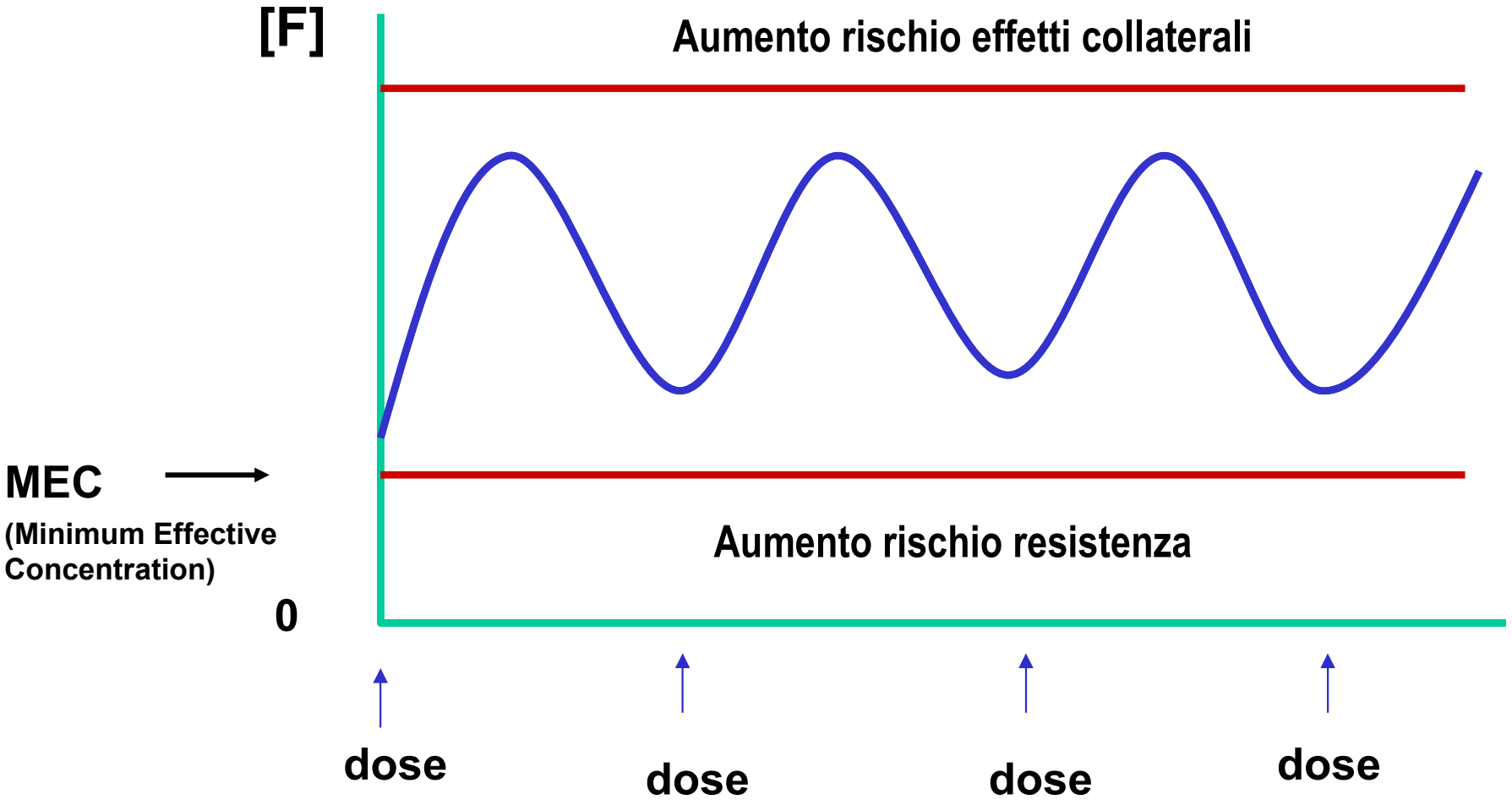
Idealmente, il farmaco deve essere:

1. Idrosolubile
2. Stabile nel circolazione
3. Facilmente assunto dalla cellula

e NON:

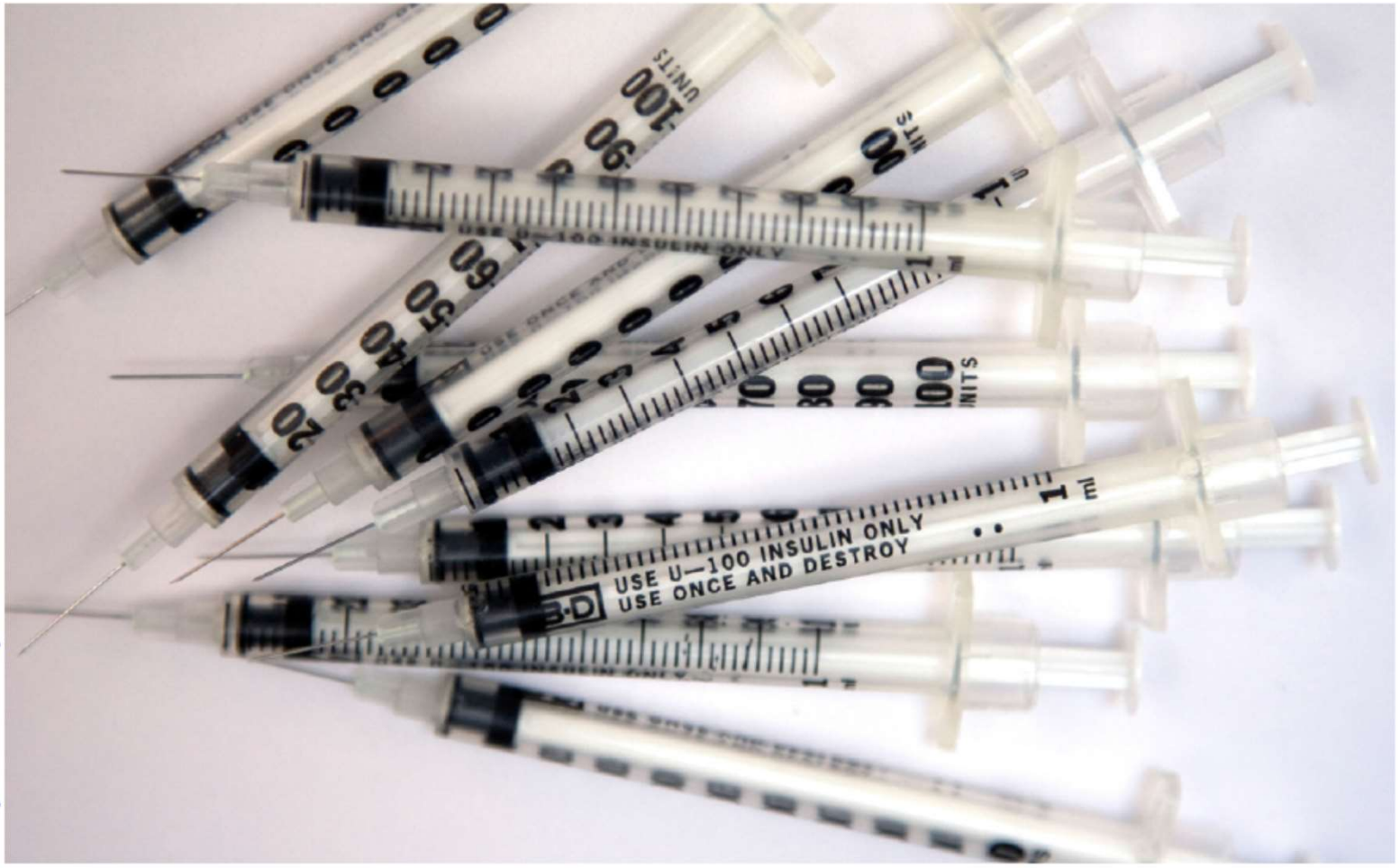
1. Tossico
2. Cangerogenico
3. Allergenico
4. Mutageno
5. Teratogeno

•Rispetto della posologia e resistenza



Long-acting HIV drugs advanced to overcome adherence challenge

APRIL 2014 NATURE MEDICINE

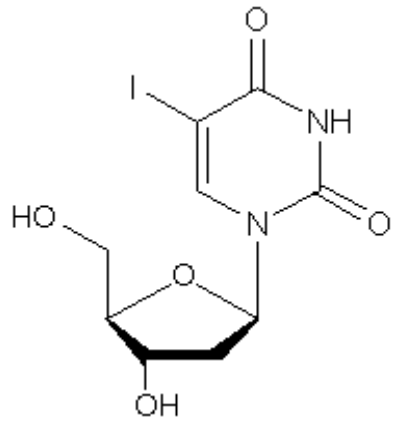


Jeffrey Blackler / Alamy

Sticking it to HIV: Long-acting injections could help promote adherence.

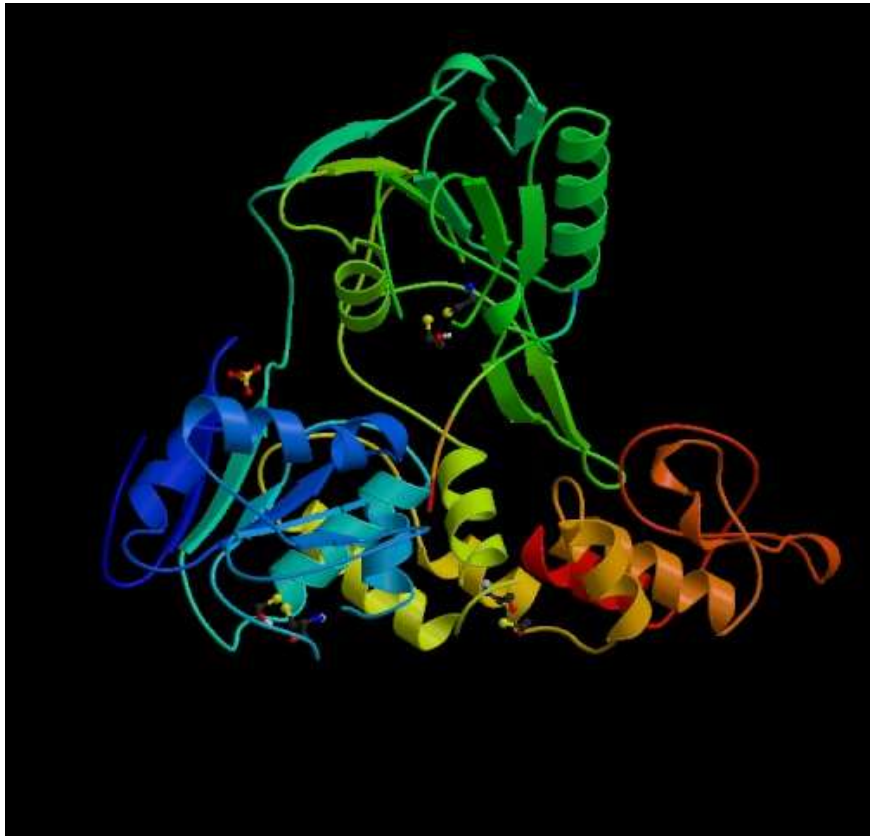
Storia della terapia antivirale

- Immunizzazione passiva
  - Primo metodo di terapia antivirale
- Agenti Selettivi
  - **Idoxuridina** (1963), **analogo** della **pirimidina** azione contro la sintesi del DNA virale.
    - Cheratite erpetica
    - Assenza di specificità



Metodi per lo sviluppo di farmaci antivirali

- Genomica
  - *Microarrays*
  - Determinazione della risposta cellulare all'infezione virale
- Proteomica
  - *Crystal Structures*
  - *Binding Sites*
  - *Protein Data Bank*



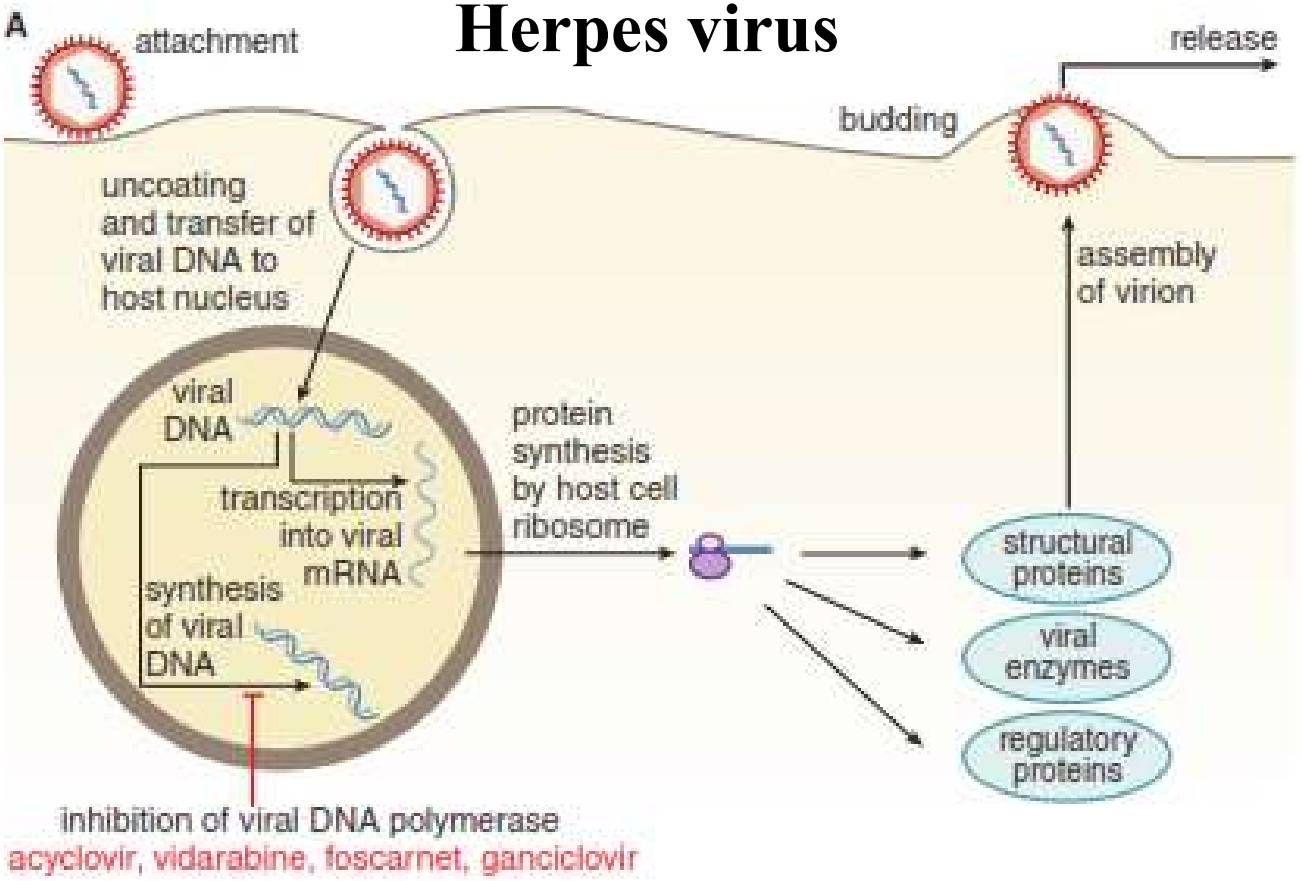
HCV NS3 protein (helicase) bound to DNA

Trials Clinici

- Fase I
  - Primo utilizzo nella specie umana
  - Tollerabilità e sicurezza
  - Tempo: da mesi a un anno
  - Da 20 a 100 volontari sani
- Fase II
  - Efficacia del farmaco
  - Centinaia di volontari
- Fase III
  - Comparazione con trattamento *standard*

Replicazione di un virus a DNA

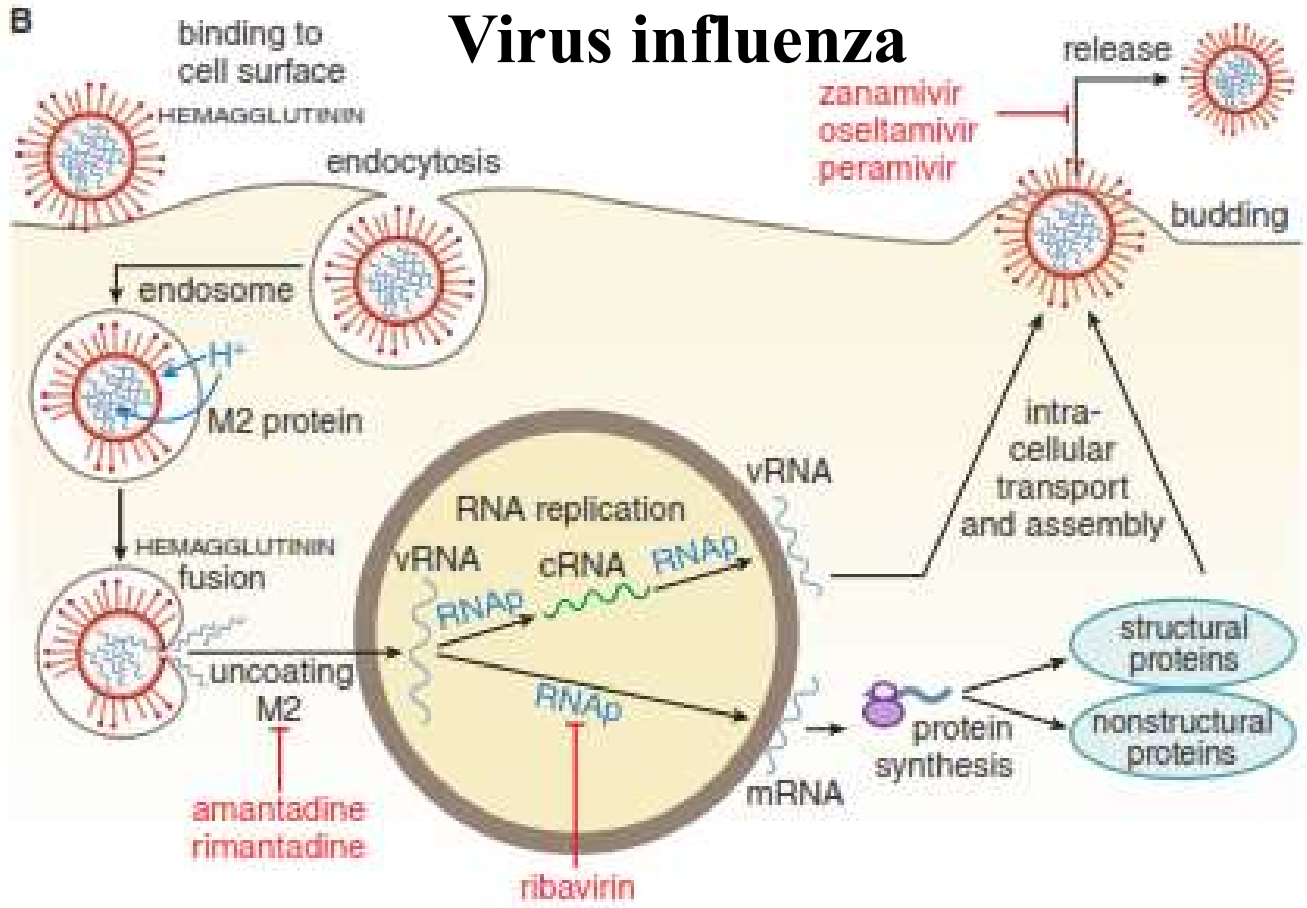
Herpes virus



Dopo l'infezione, viene trascritto un piccolo numero di geni precoci; questi geni codificano per proteine che regolano la propria sintesi e sono responsabili della sintesi dei primi geni coinvolti nella replicazione del genoma, come timidina chinasi (TK), DNA polimerasi. Dopo la replicazione del DNA, la maggior parte dei geni dell'herpes virus (chiamati geni tardivi) sono espressi e codificano proteine che sono incorporate o aiutano nell'assemblaggio dei virioni della progenie.

Replicazione di un virus a RNA

Virus influenza



Penetrazione per endocitosi all'interno di una vescicola membranosa.
Fusione della membrana virale con quella della vescicola → liberazione del virione all'interno della cellula. Il virus contiene l'enzima RNA polimerasi necessario per la duplicazione del proprio genoma a RNA. L'RNA polimerasi utilizza come stampo l'RNA. Il filamento di RNA virale così sintetizzato serve poi sia da mRNA sia da stampo per la sintesi di nuove copie del genoma virale.

Antivirali attivi contro i virus erpetici

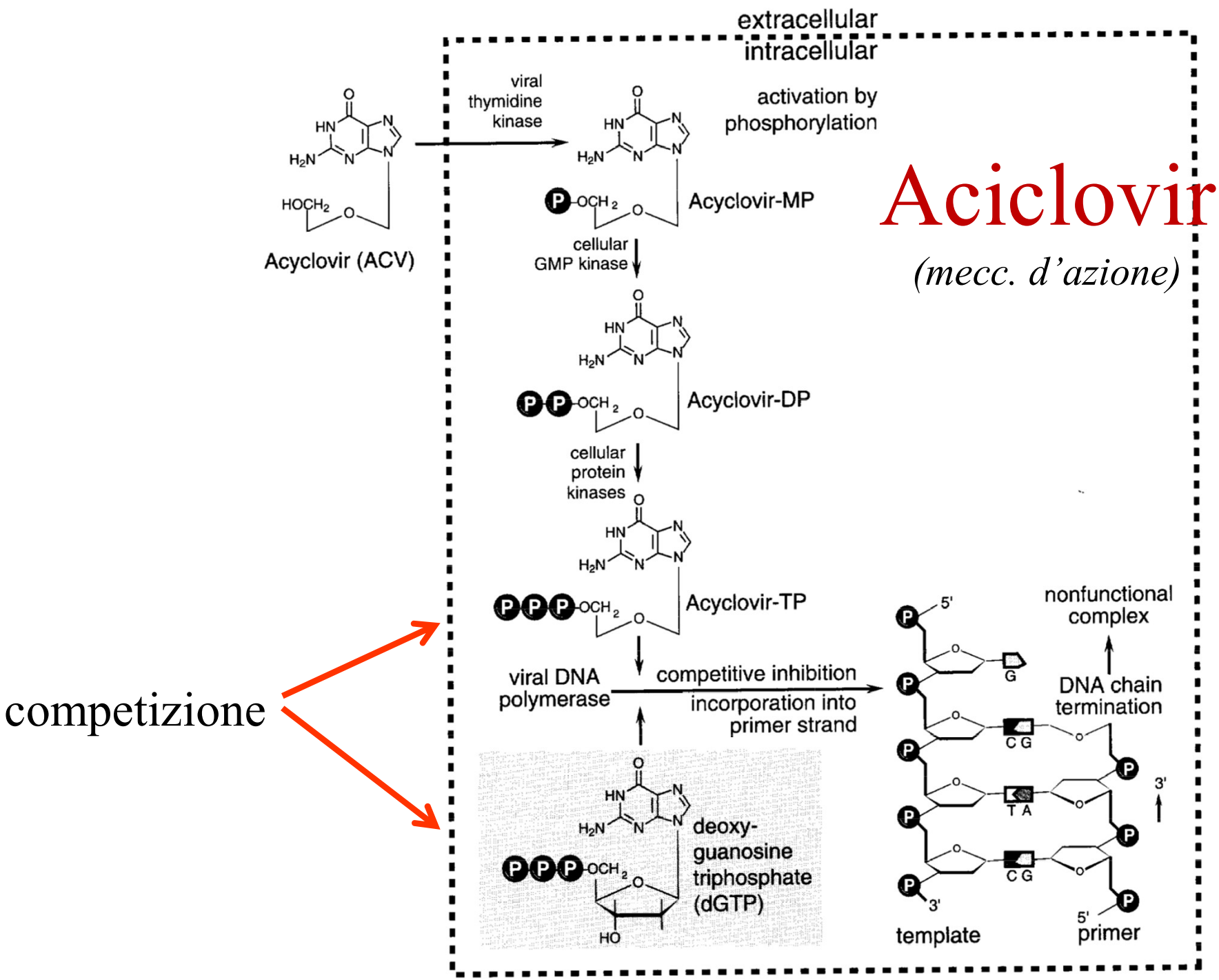
- **Aciclovir**
- Valaciclovir
- Penciclovir
- Famciclovir
- Trifluridina

Aciclovir

- Analogo nucleosidico purinico sintetico con attività inibitoria nei confronti dei virus erpetici umani, come il virus Herpes simplex (HSV) di tipo 1 e 2 e il virus Varicella zoster (VZV).
- **Convertito** dalla **timidina chinasi virale** (**selettività**) da aciclovir monofosfato→trifosfato →inib. DNA polimerasi virale *(vedi dopo)*. Resistenza.
- Somm.: i.v, p.o, topica. t/2= 3 ore. Filtr. ren. (60-90%).
- Scarsi effetti collaterali (eff. gastr., dopo iv: effetti neurologici; letargia, sint. extrapiramidale, tremori).

Aciclovir

(mecc. d'azione)



SPECIFICITÁ E SELETTIVITÁ

La timidina chinasi (TK) è un enzima presente anche nella cellula eucariote. L'aciclovir ha una scarsa o nulla affinità per la TK cellulare ed elevata per la TK virale.

Inoltre, l'infezione da HSV induce la TK virale.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2005, p. 1055–1059 Vol. 49, No. 3
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.3.1055–1059.2005

Sfortunatamente….

Herpes Simplex Virus Thymidine Kinase Mutations Associated with Resistance to Acyclovir: a Site-Directed Mutagenesis Study

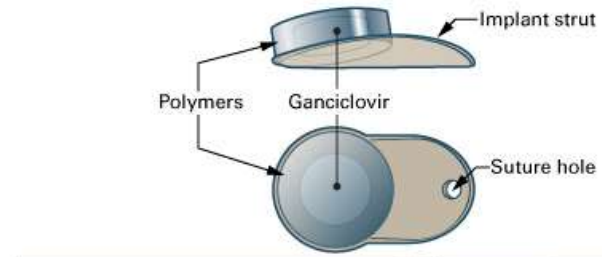
E. Frobert,[1]* T. Ooka,[2] J. C. Cortay,[2] B. Lina,[1] D. Thouvenot,[1] and F. Morfin[1]

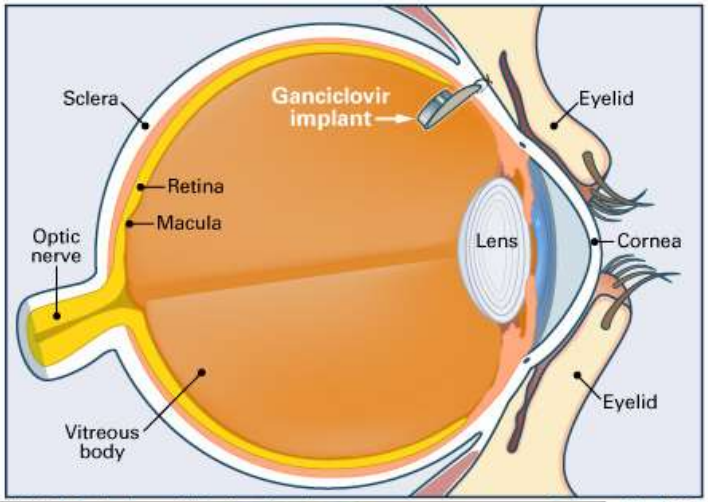
Agenti attivi contro il Citomegalovirus (CMV)

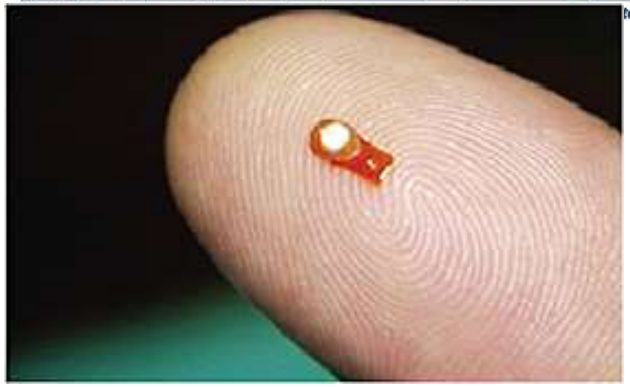
- **Ganciclovir**
- Valganciclovir
- Foscarnet
- Cidofovir
- Formivirsen

•**Ganciclovir**. Attivo contro citomegalovirus. Profarmaco. Inib. DNA polimerasi virale (simile all'aciclovir). Bassa (5-10%) biodisponibilità dopo somm. orale. Via endovenosa. t/2=4 ore. Eliminazione renale.

•**Effetti collaterali**: Mielodepressione. Disturbi gastrointestinali e del SNC. Nefrotossicità. Aumento enzimi epatici. In modelli sperimentali, ha mostrato teratogenicità.

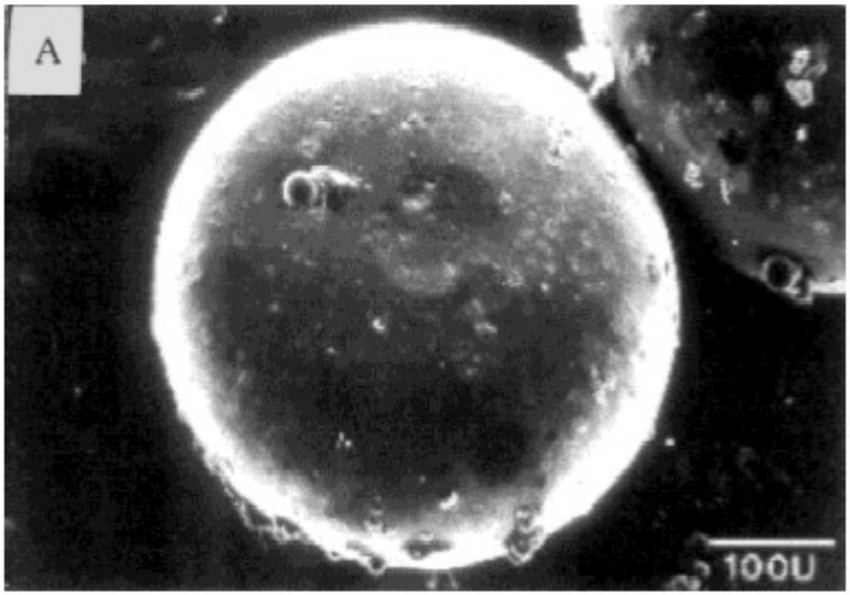






Biodegradable PLGA Microspheres Loaded with Ganciclovir for Intraocular Administration. Encapsulation Technique, *In Vitro* Release Profiles, and Sterilization Process

Rocio Herrero-Vanrell,[1,2,3] Loreto Ramirez,[2] Ana Fernandez-Carballido,[2] and Miguel F. Refojo[1]

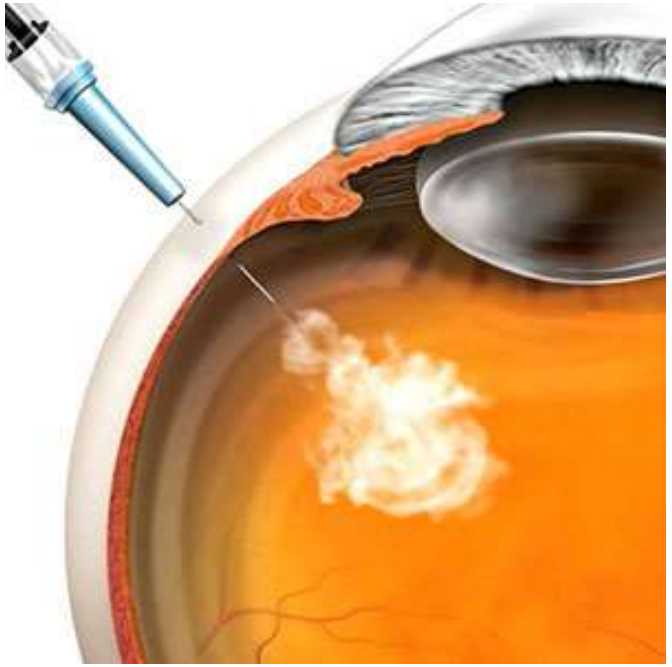


Impiegato (**ritirato**) nel trattamento della retinite da CMV (principale patologia virale oculare opportunistica in pz. HIV+)

Treatment of cytomegalovirus anterior segment infection with intravitreal injection of ganciclovir in adjunction with or without oral valganciclovir: a long-term results

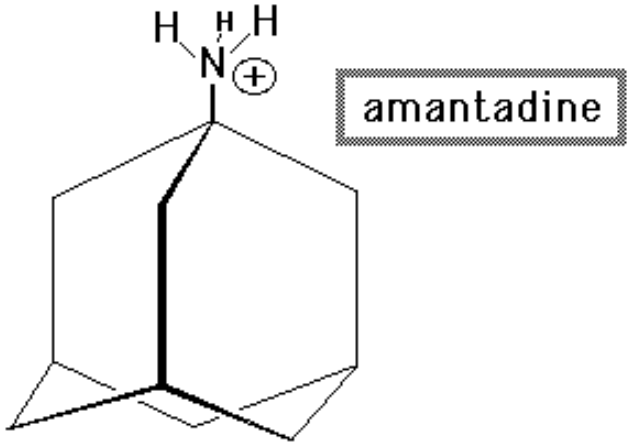
Yu-Chun Cheng[1,3], Eugene Yu-Chuan Kang[1,3], Yih-Shiou Hwang[1,2]✉ & Ching-Hsi Hsiao[1,2]✉

Scientific Reports | (2021) 11:3105



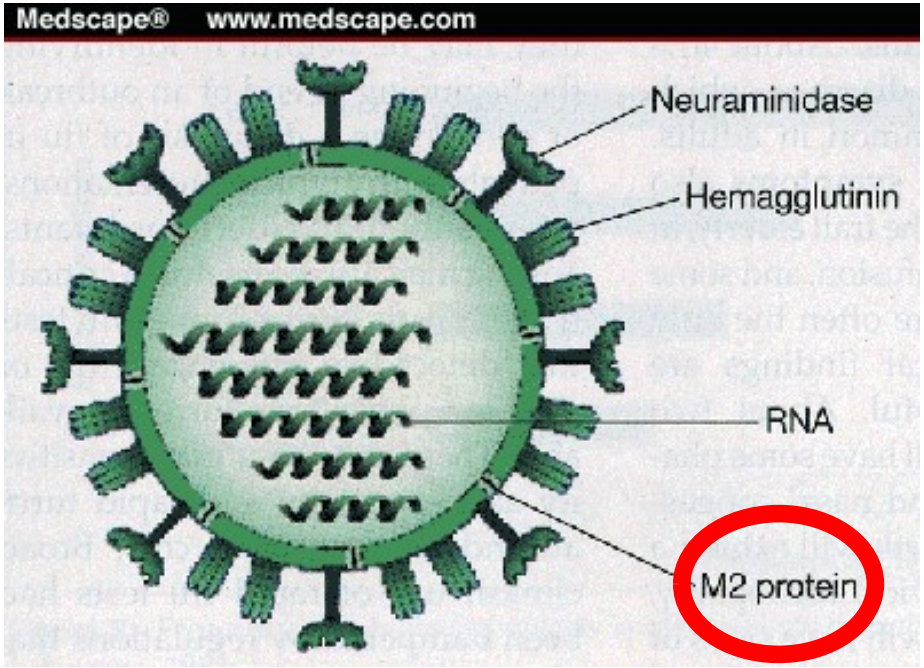
Farmaci attivi contro i virus influenzali

- **Amantadina**
- **Zanamivir**
- **Oseltamivir**



•**<u>Amantadina</u>**. Interagisce con la prot. M2. Inibizione dell'adsorbimento e della penetrazione del virus nella cellula ospite. Virus influenza A. Scarsa efficacia. Uso?

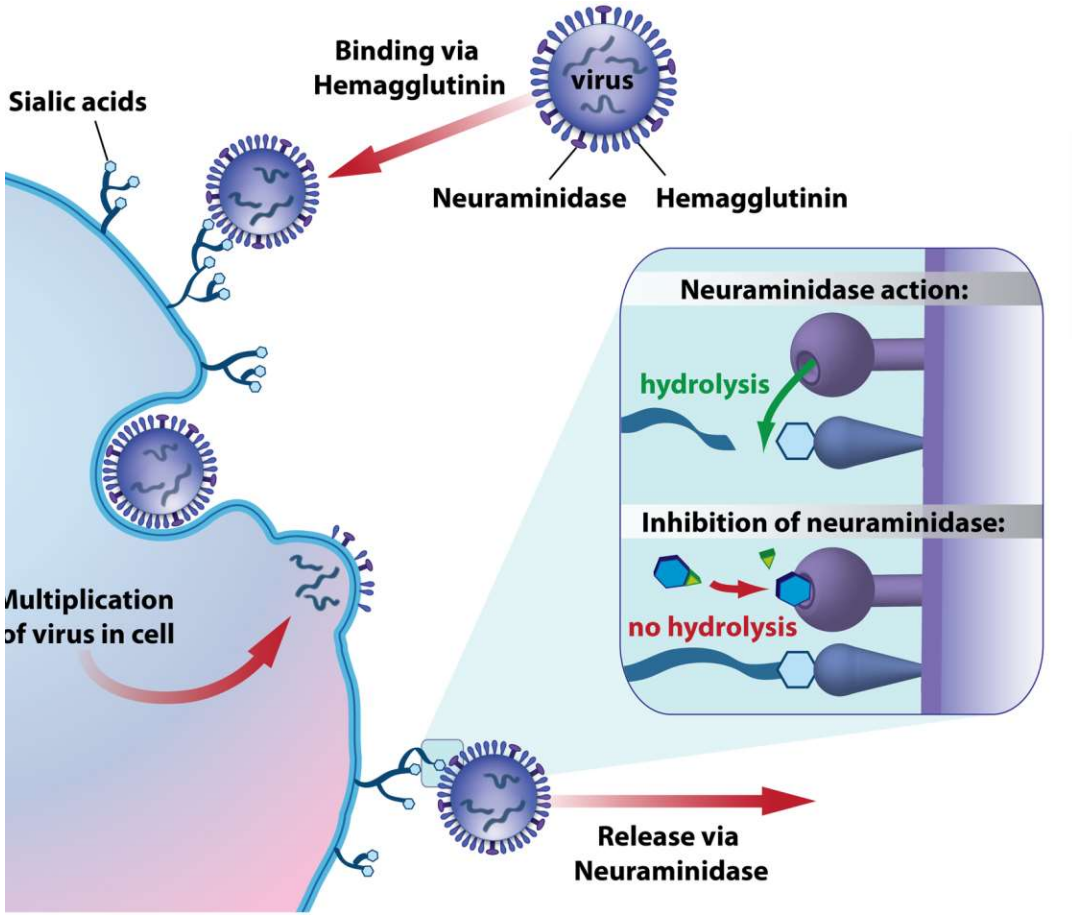
•Scarsi effetti collaterali (insonnia, capogiri, disartria), buona farmacocinetica dopo somm. orale. Attualmente, si utilizza prevalentemente nel Parkinson per inibizione ricaptazione DA e <u>antagonismo GLUr di tipo NMDA (*Mantadan*)</u>.

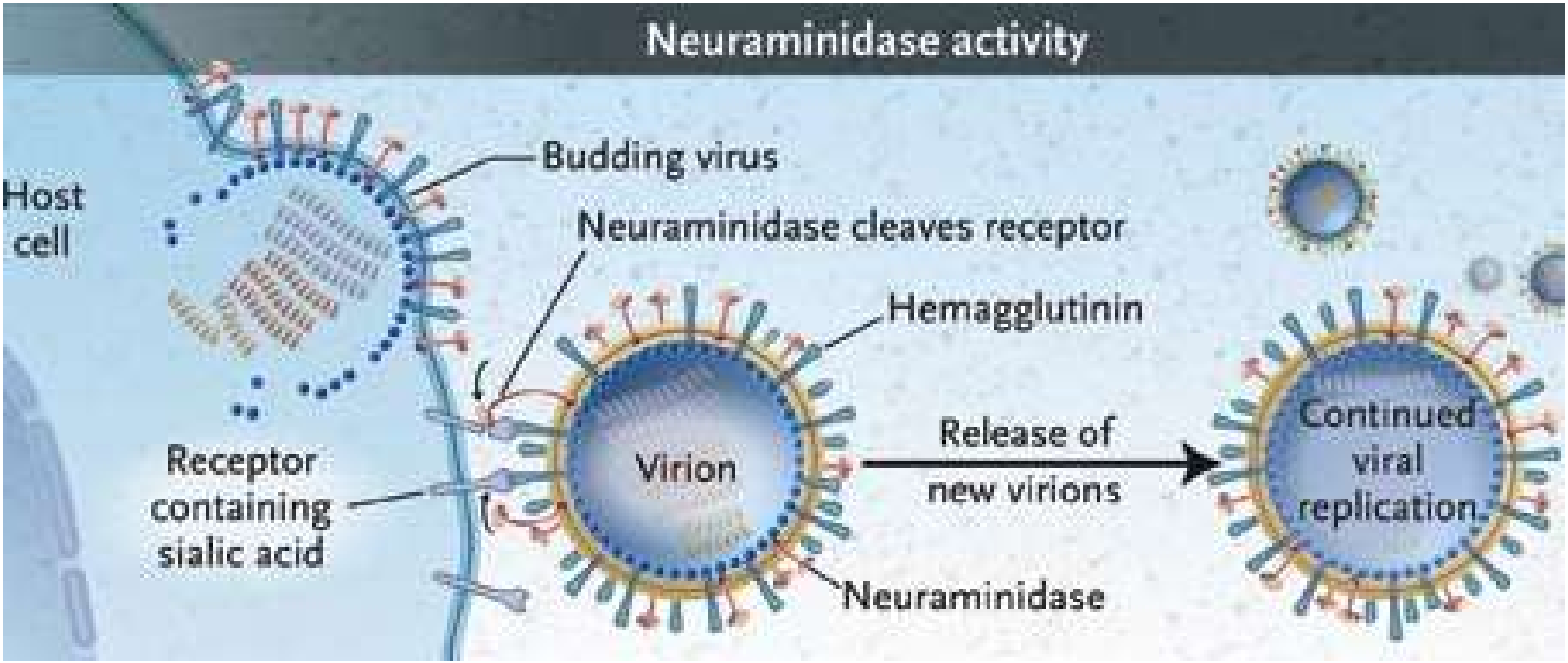


Inibitori delle neuraminidasi

Agiscono inibendo l'enzima virale neuraminidasi che scinde il legame tra emoagglutinina ed acido sialico permettendo la gemmazione. A differenza dell'amantadina e rimantadina, presentano minori effetti indesiderati e sono attivi contro i virus dell'influenza A e B.

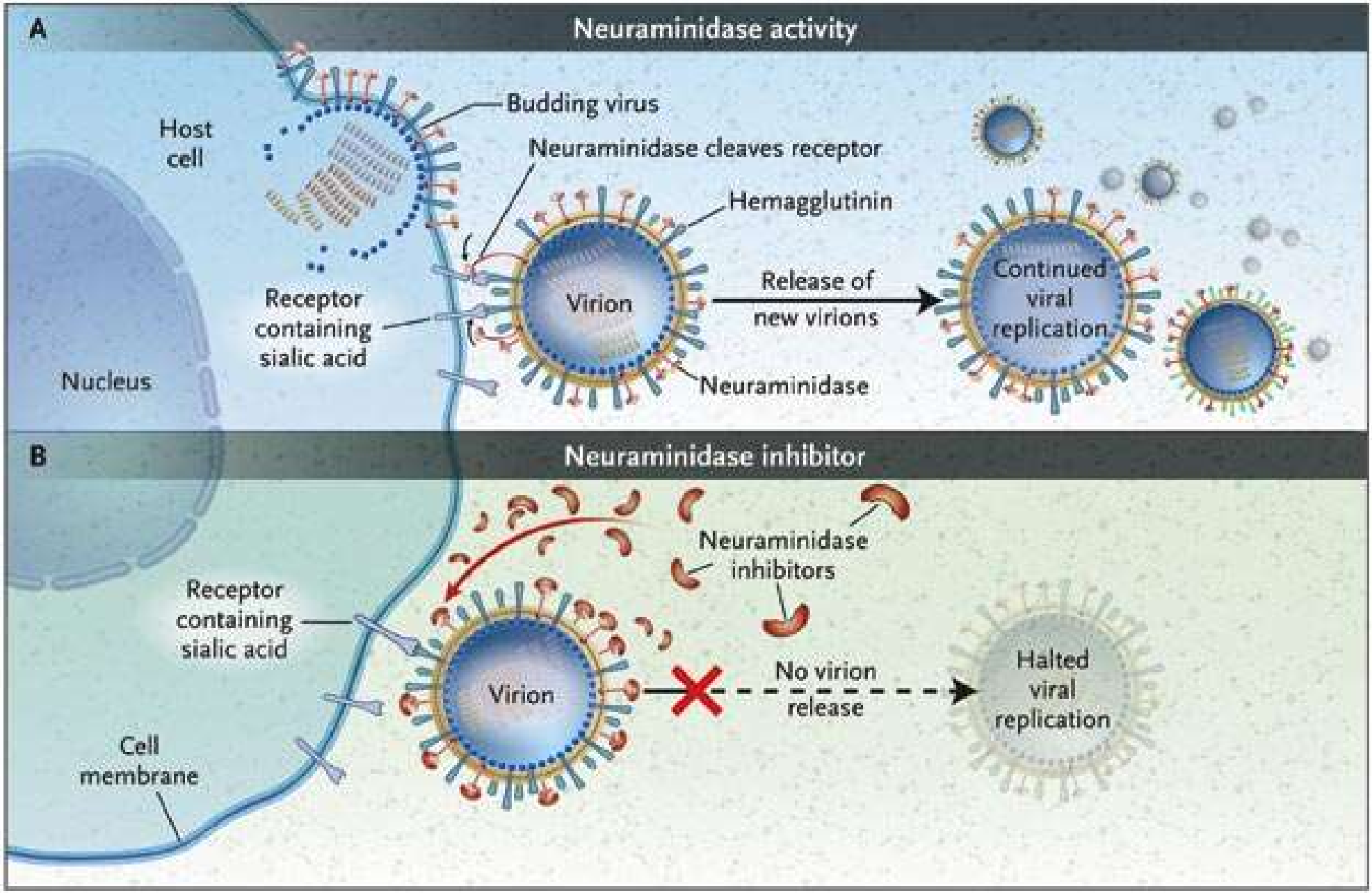
- **Oseltamivir**
- **Zanamivir**





Nei virus influenzali di tipo A, la **neuraminidasi** agisce al termine del ciclo di replicazione virale, consentendo la fuoriuscita delle particelle virali dalla cellula ospite.
Nell'uomo, il deficit di **neuraminidasi** (alfa-D-neuraminidasi) è la causa di malattie caratterizzate da accumulo nelle cellule nervose di gangliosidi (sialidosi).

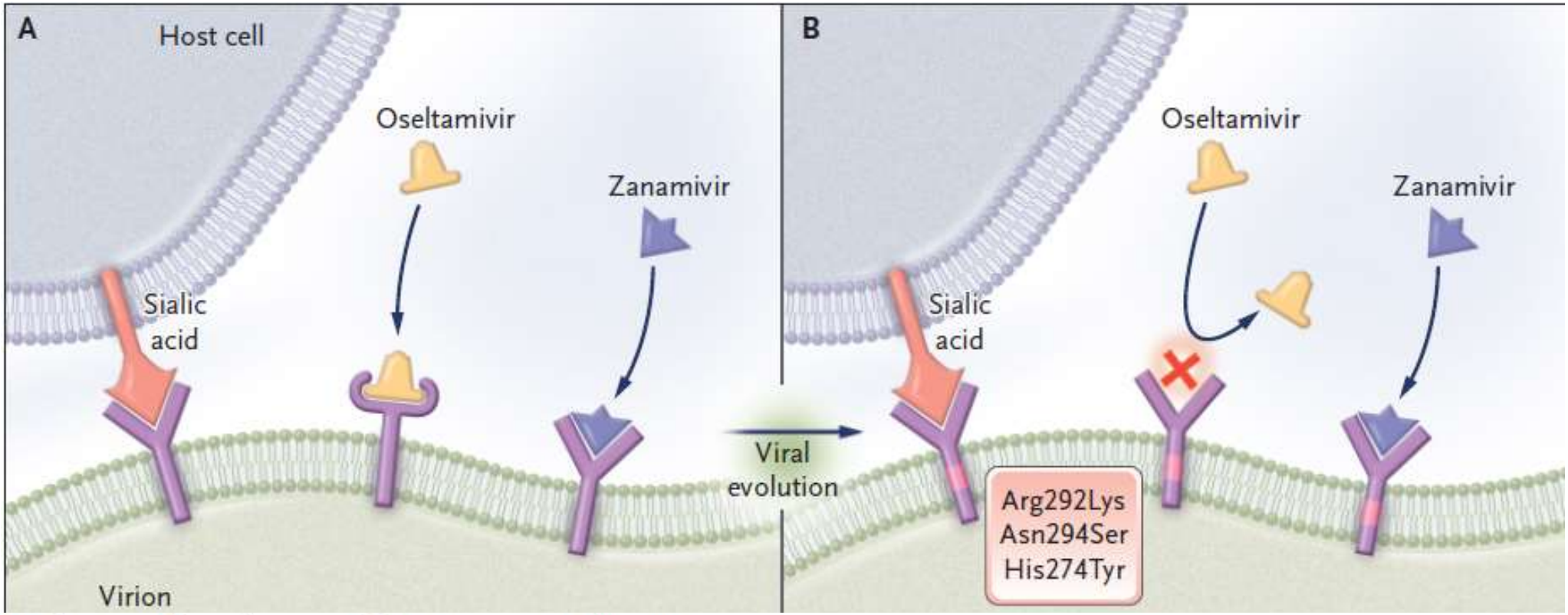
Meccanismo d'azione



Global Transmission of Oseltamivir-Resistant Influenza

Anne Moscona, M.D.

N ENGL J MED 360;10 NEJM.ORG MARCH 5, 2009



Mechanism of Development of Resistance to Oseltamivir.

Binding of oseltamivir, but not zanamivir, to the neuraminidase active site requires a shape change that creates a pocket (Panel A), and mutations that prevent formation of this pocket may prevent binding of oseltamivir but permit binding of zanamivir (Panel B).

The NEW ENGLAND JOURNAL of MEDICINE

Emergence of Oseltamivir-Resistant Pandemic H1N1 Virus during Prophylaxis

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Neuraminidase Inhibitors for Influenza

Anne Moscona, M.D.

Table 1. Dosing Schedule of Neuraminidase Inhibitors for the Treatment and Prevention of Influenza, According to Patient's Age and Coexisting Illnesses.*

Antiviral Drug	Recommended Dose According to Age				Coexisting Illness	
	1–6 yr	7–12 yr	13–64 yr	≥65 yr	Renal Disease	Hepatic Disease
Treatment						
Zanamivir	NA	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	—
Oseltamivir	Weight <15 kg: 30 mg twice daily for 5 days; 15–23 kg: 45 mg twice daily for 5 days; >23–40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	Weight <15 kg: 30 mg twice daily for 5 days; 15–23 kg: 45 mg twice daily for 5 days; >23–40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	75 mg twice daily for 5 days	75 mg twice daily for 5 days	For adults, reduce dose if creatinine clearance is ≤30 ml/min; if creatinine clearance is 10–30 ml/min, 75 mg once daily†	Not evaluated
Prevention						
Oseltamivir	NA	NA	75 mg once daily for >7 days (up to 6 wk)	75 mg once daily for >7 days (up to 6 wk)	If creatinine clearance is 10–30 ml/min, 75 mg every other day†	Not evaluated

* The doses listed are those currently approved in the United States. NA denotes not applicable.
† No regimen is available for patients with end-stage renal disease.

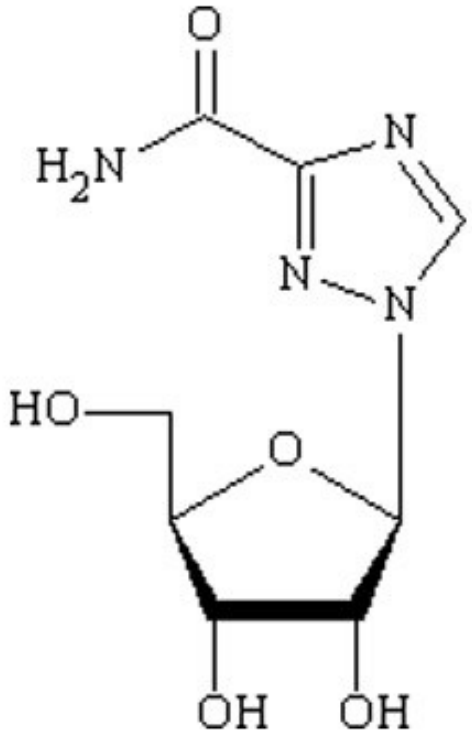
The NEW ENGLAND JOURNAL of MEDICINE
REVIEW ARTICLE
DRUG THERAPY
Neuraminidase Inhibitors for Influenza
Anne Moscona, M.D.

Table 4. Percentage of Patients with Serious or Minor Adverse Effects Associated with the Administration of Neuraminidase Inhibitors.

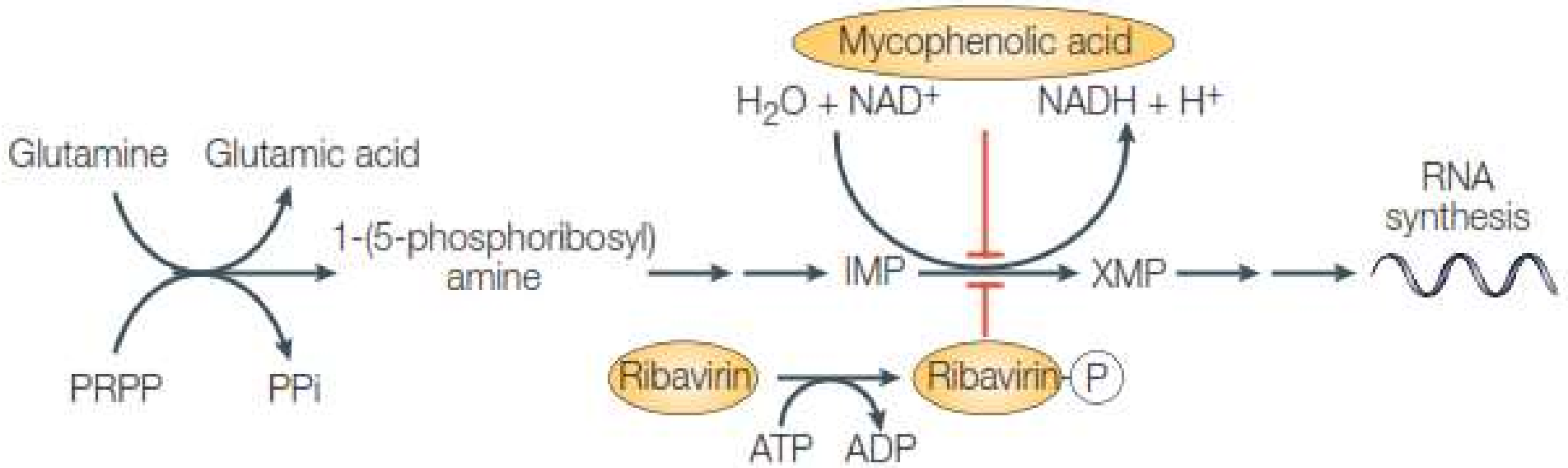
Drug and Use	Adverse Effects
Zanamivir treatment*	Serious or life-threatening: Allergic or allergic-like reaction, arrhythmia, bronchospasm, dyspnea, facial edema, rash, seizure, syncope, urticaria (<1.5%) Minor: Central nervous system: headache (2%), dizziness (2%) Gastrointestinal system: nausea (3%), diarrhea (adults, 3%; children, 2%), vomiting (adults, 1%; children, 2%) Respiratory system: sinusitis (3%), bronchitis (2%), cough (2%), other nasal signs and symptoms (2%), infection (ear, nose, and throat: adults, 2%; children, 5%)
Oseltamivir treatment†	Serious or life-threatening: Aggravation of diabetes, arrhythmia, confusion, hepatitis, pseudomembranous colitis, pyrexia, rash, seizure, swelling of face or tongue, toxic epidermal necrolysis, unstable angina (<1%) Minor: Central nervous system: insomnia (adults, 1%), vertigo (1%) Gastrointestinal system: nausea (10%), vomiting (9%)
Oseltamivir prophylaxis‡	Similar to those reported during treatment, but generally with lower incidence More common with prophylactic use: headache (20%), fatigue (8%), cough (6%), diarrhea (3%)

Agenti attivi contro i virus epatici

- Interferoni
- **Ribavirina**
- Adefovir



Ribavirina: meccanismo d'azione



Analogo della **guanosina**. Blocca la sintesi del RNA **inibendo** l'azione dell'**enzima** inosina 5'-monofosfato (**IMP**) deidrogenasi impedendo la conversione di IMP a XMP (xantosina 5'-monofosfato).
Il blocco enzimatico favorisce **l'aumento** di **IMP**.
Azione simile all'**acido aminofenolico** utilizzato per impedire il rigetto nei trapiantati (es.: rene).

•**Ribavirina.** *Biodisponibilità* 45%. T/2=30-40 ore. Emivita intraeritrocitaria 40 giorni. *Eliminazione:* renale 40%.

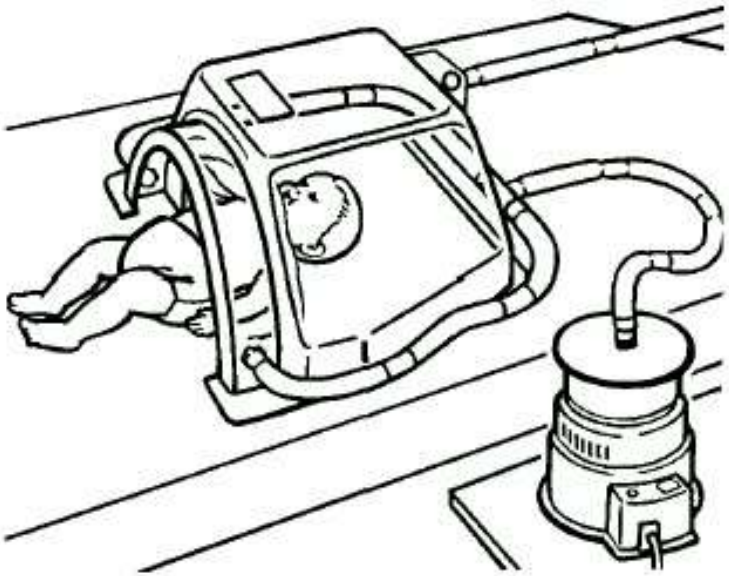
•Induce **errori** nella **replicazione** e nella **trascrizione** del genoma virale, producendo **mutazioni** che **inattivano mRNA** e proteine.

•*Indicazioni*: Nell'epatite cronica (**+ INF alfa-2b**). Nelle affezioni gravi delle vie respiratorie da virus respiratorio sinciziale (bambini) per aerosol. Usato (iv) anche nella febbre emorragica.

•*Reazioni avverse*: anemia emolitica, broncospasmo (per inalazione). **Teratogenico** (attenzione personale medico durante aereosol).

Occupational exposures to aerosolized pharmaceuticals and control strategies

by John A Decker, MS,[1] Teresa A Seitz, MPH,[1] Ruth A Shults, MPH,[1] Scott Deitchman, MD,[1] Samuel P Tucker, PhD,[2] Barry R Belinky, BS,[2] Nancy J Clark, MS[1]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Therapy for Hepatitis C — The Costs of Success

Jay H. Hoofnagle, M.D., and Averell H. Sherker, M.D.

May 22, 2014
N Engl J Med 2014; 370:1993-2001
DOI: 10.1056/NEJMoa1316145

EDITORIAL

Simple, Effective, but Out of Reach? Public Health Implications of HCV Drugs

John W. Ward, M.D., and Jonathan H. Mermin, M.D., M.P.H.

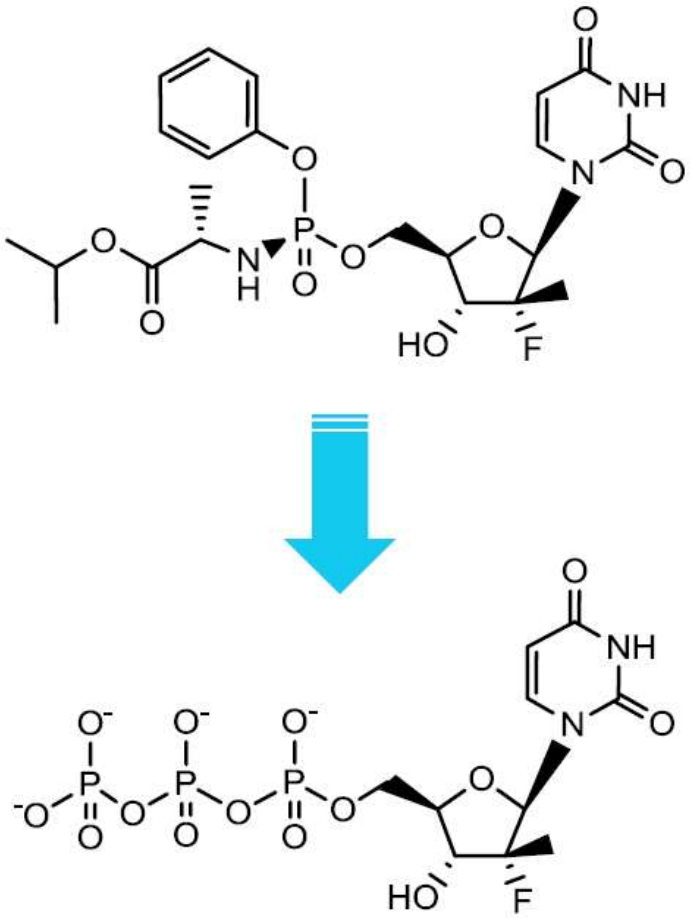
Patients do not benefit from a drug they cannot afford. Although studies by the Centers for Disease Control and Prevention have shown that treating all HCV-infected persons is cost-effective from a societal perspective,[9] the price of current medications is a formidable barrier for many. Despite U.S. recommendations that all HCV-infected persons should receive treatment,[10] health plans and payers have responded to the cost of HCV medications ($83,000 to $153,000 per course of treatment) by instituting restrictive reimbursement policies. In 33 state Medicaid

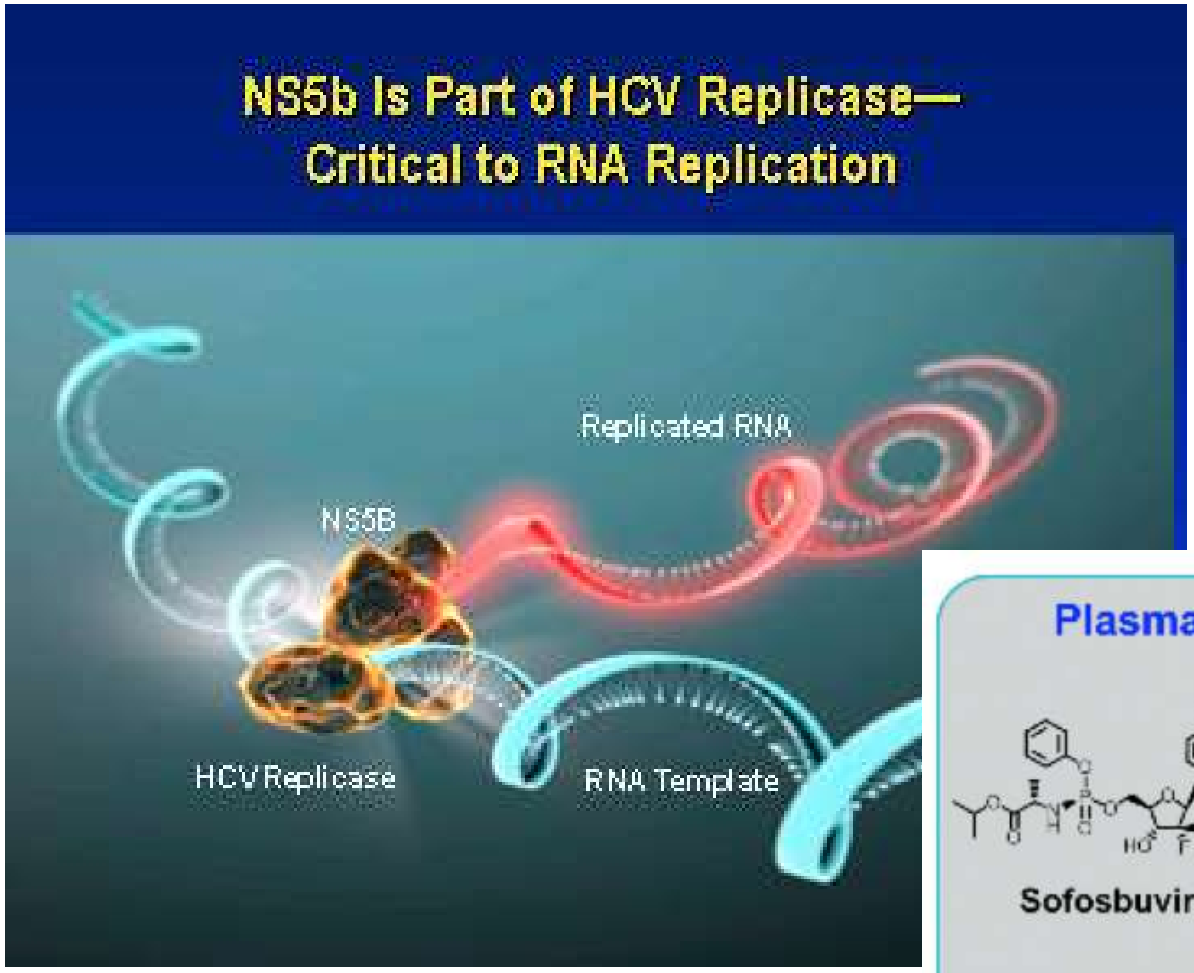
Inibitore pan-genotipico del RNA polimerasi NS5B RNA-dipendente del HCV necessaria per la replicazione virale.

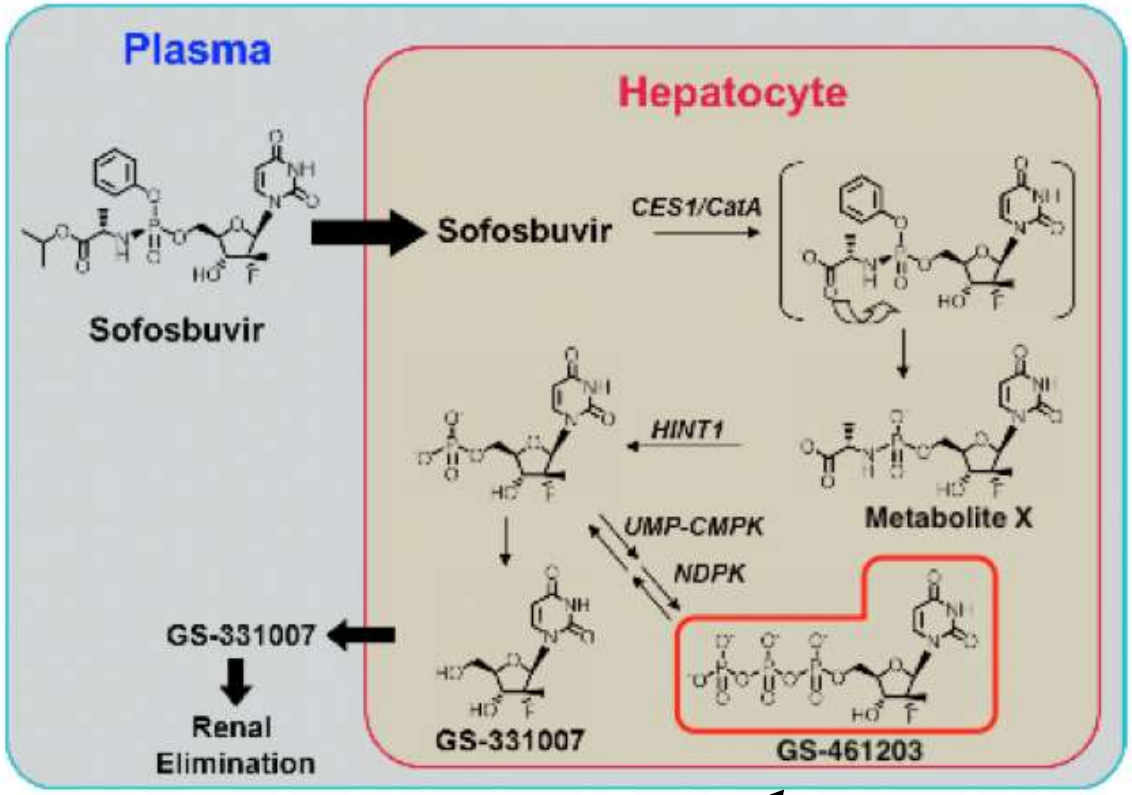
NS5B: proteina non strutturale 5B

Sofosbuvir

- Uridine nucleotide analog HCV NS5B polymerase inhibitor
- Prodrug, efficiently taken up by hepatocytes
- Undergoes intracellular activation to triphosphate form



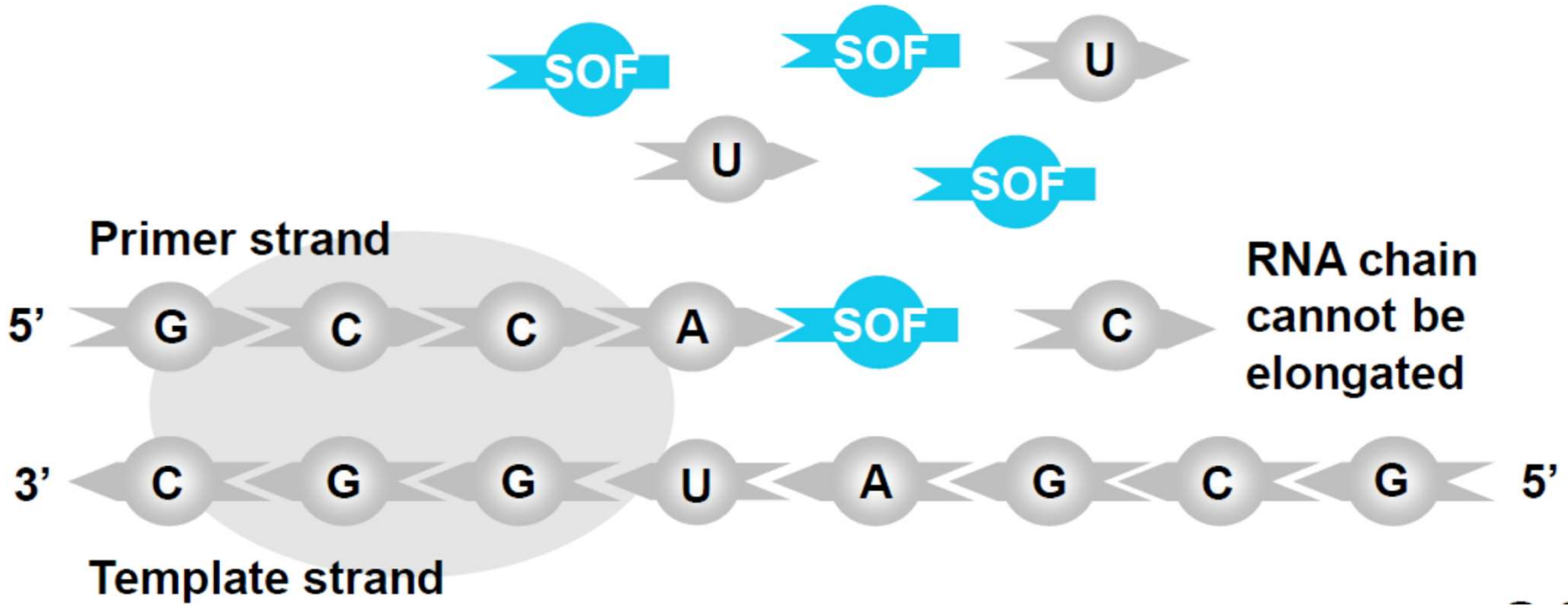




Metabolita attivo

Sofosbuvir Mechanism of Action

- Competes with natural nucleotides
- Chain termination stops replication
- Mechanism applies to all HCV genotypes



Benefits of Sofosbuvir Inhibition of NS5B

- Active site of the NS5B enzyme is relatively well conserved across genotypes
- The S282T mutation causes reduced sensitivity to sofosbuvir in vitro
- The S282T mutation has not been detected in untreated patients
- S282T mutations in sofosbuvir-treated patients are rare

Sofosbuvir Nonclinical Safety

- The active triphosphate metabolite of sofosbuvir is not an inhibitor of host DNA or RNA polymerases, including mitochondrial polymerases
- Sofosbuvir was well tolerated in chronic toxicity studies
- Sofosbuvir is not genotoxic
- Sofosbuvir had no adverse effects on fertility or embryo-fetal development
  - Proposed pregnancy category B

Sofosbuvir: Clinical Pharmacology Profile

- Sofosbuvir is an orally bioavailable nucleotide prodrug
- Sofosbuvir is rapidly taken up by the liver
- Long half-life (~18 h) for active triphosphate

Sofosbuvir: Clinical Pharmacology in Special Populations

- No CYP450 hepatic metabolism
- No dose adjustment in hepatic impairment
- No dose adjustment if creatinine clearance >30 mL/min
- No impact of HCV patient characteristics on exposure
  - No impact of BMI, age, sex, race, or cirrhosis on pharmacokinetics

Sofosbuvir: Drug Interactions Profile

- No clinically significant interactions
  - Methadone
  - Cyclosporine, tacrolimus
  - Antiretrovirals (FTC, TDF, RPV, EFV, DRV/r, RAL)
- Potential interactions
  - Potent P-glycoprotein and/or BCRP inducers
    - Antimycobacterials, anticonvulsants, St. John's wort

BCRP=breast cancer resistance protein; DRV/r=darunavir boosted with ritonavir; EFV=efavirenz; FTC=emtricitabine; RAL=raltegravir; RPV=rilpivirine; TDF=tenofovir disoproxil fumarate.

Most Common AEs (≥15%)

SOF+PEG/RBV vs PEG/RBV (Through Week 12 of Treatment)

Patients	NEUTRINO SOF+PEG/RBV[a] (N=327) %	FISSION PEG/RBV[a] (N=243) %
Fatigue	58	51
Headache	36	43
Nausea	34	26
Insomnia	25	27
Anemia	21	7
Rash	17	12
Decreased appetite	17	17
Pyrexia	17	12
Chills	17	18
Neutropenia	17	10
Pruritus	16	13
Flu-like symptoms	16	17

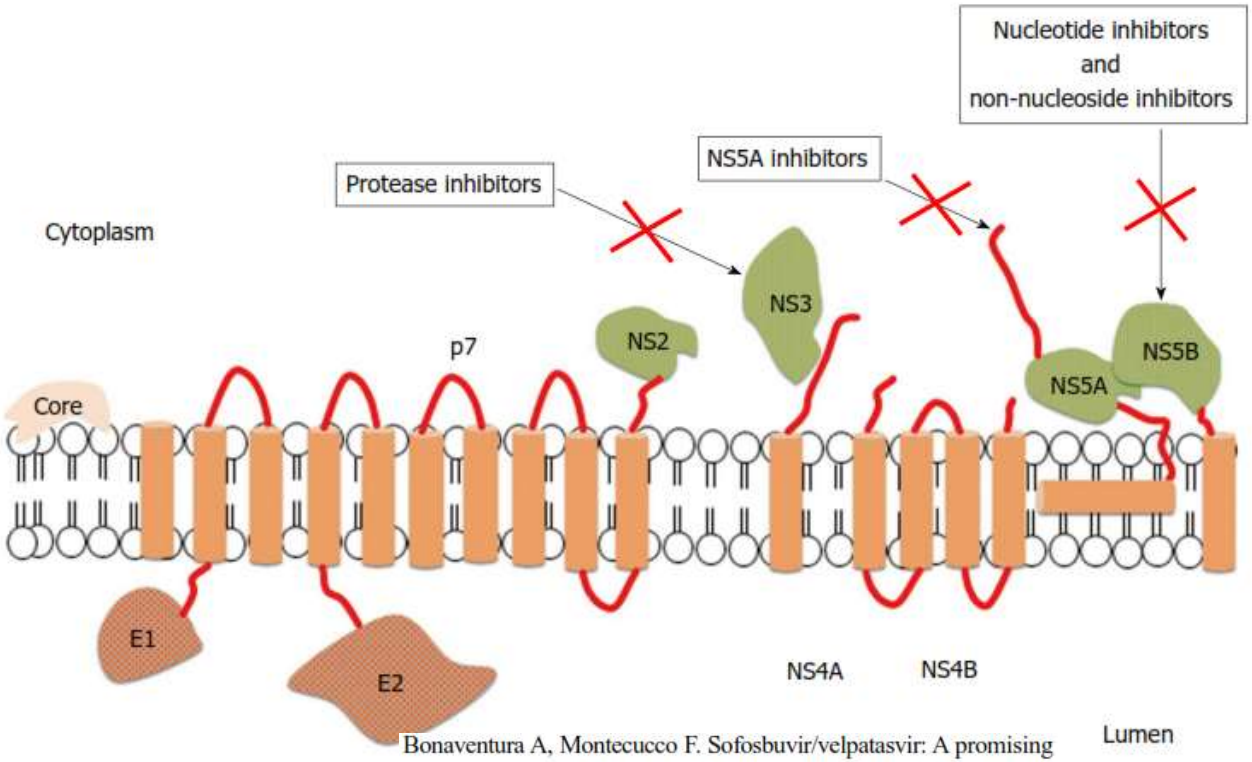
AE: effetti avversi

Sofosbuvir–velpatasvir: A single-tablet treatment for hepatitis C infection of all genotypes

Misty M. Miller, Pharm.D., BCPS, AAHIVP, Department of Pharmacy: Clinical and Administrative Sciences, University of Oklahoma College of Pharmacy, Oklahoma City, OK.

Purpose. The pharmacology, pharmacokinetics, interaction potential, efficacy, and safety of the newest direct-acting antiviral (DAA) medication for the treatment of chronic hepatitis C are reviewed.

Am J Health-Syst Pharm. 2017; 74:1045-52



Bonaventura A, Montecucco F. Sofosbuvir/velpatasvir: A promising combination. *World J Hepatol* 2016; 8(19): 785-789 Available

Velpatasvir: inibitore della proteina virale NS5A del complesso proteico della polimerasi virale

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 31, 2015 VOL. 373 NO. 27

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection

J.J. Feld, I.M. Jacobson, C. Hézode, T. Asselah, P.J. Ruane, N. Gruener, A. Abergel, A. Mangia, C.-L. Lai, H.L.Y. Chan, F. Mazzotta, C. Moreno, E. Yoshida, S.D. Shafran, W.J. Towner, T.T. Tran, J. McNally, A. Osinusi, E. Svarovskaia, Y. Zhu, D.M. Brainard, J.G. McHutchison, K. Agarwal, and S. Zeuzem, for the ASTRAL-1 Investigators*

CONCLUSIONS

Once-daily sofosbuvir–velpatasvir for 12 weeks provided high rates of sustained virologic response among both previously treated and untreated patients infected with HCV genotype 1, 2, 4, 5, or 6, including those with compensated cirrhosis. (Funded by Gilead Sciences; ClinicalTrials.gov number, NCT02201940.)

Table 3. Discontinuations, Adverse Events, and Hematologic Abnormalities.

Event	Placebo (N=116)	Sofosbuvir–Velpatasvir (N=624)
	no. of patients (%)	
Discontinuation of treatment owing to an adverse event	2 (2)	1 (<1)
Serious adverse event*	0	15 (2)
Any adverse event	89 (77)	485 (78)
Common adverse events†		
Headache	33 (28)	182 (29)
Fatigue	23 (20)	126 (20)
Nasopharyngitis	12 (10)	79 (13)
Nausea	13 (11)	75 (12)
Insomnia	11 (9)	50 (8)
Diarrhea	8 (7)	48 (8)
Asthenia	9 (8)	41 (7)
Arthralgia	9 (8)	40 (6)
Cough	4 (3)	39 (6)
Back pain	11 (9)	29 (5)
Myalgia	6 (5)	25 (4)
Hematologic event		
Hemoglobin level <10 g/dl	0	2 (<1)
Lymphocyte count 350 to <500 per mm^3	0	3 (<1)
Neutrophil count 500 to <750 per mm^3	0	4 (1)
Platelet count 25,000 to <50,000 per mm^3	0	1 (<1)

* No single serious adverse event occurred in more than 1 patient. In the safe

Epclusa
Associazione sofosbuvir (400 mg)/velpatasvir (100 mg)

Farmaci **induttori** della **glicoproteina P** (P-gp) o del **citocromo P450** (rifampicina, rifabutina, iperico [Hypericum perforatum], carbamazepina, fenobarbital e fenitoina) possono **ridurre** in misura significativa la **concentrazione plasmatica** di sofosbuvir o velpatasvir determinando una perdita dell'efficacia di Epclusa. Inoltre, **velpatasvir** è un **inibitore** del trasportatore di farmaci **P-gp**, della proteina di resistenza del tumore mammario (**BCRP**). La cosomministrazione di Epclusa con medicinali che sono substrati di tali trasportatori può aumentare l'esposizione a tali medicinali.

Approvata anche una formulazione pediatrica.

L'AIFA è riuscita a contrattare per il **prezzo** dell'Epclusa che partiva da **16.600** euro, cifra questa ridotta prima del 50% e poi ancora del 20% per giungere ad un costo finale di circa **4.000** euro a paziente.

CHRONIC HEPATITIS C TREATMENT EXPANSION
Generic Manufacturing for Developing Countries

GILEAD

Gilead is working to enable access to its medicines for all people who can benefit from them, regardless of where they live or their economic means.

Snapshot

Gilead has agreements with 14 companies to manufacture generic hepatitis C medicines for **105 developing countries**

There are an estimated **71 million** people living with hepatitis C worldwide

Gilead also offers its branded hepatitis C medicines at a single, **significantly reduced price** across these countries

4.2 Posologia e modo di somministrazione

Il trattamento con Epclusa deve essere iniziato e monitorato da un medico esperto nella gestione di pazienti con infezione da HCV.

Posologia

La dose raccomandata di Epclusa è una compressa per via orale una volta al giorno, da assumersi con o senza cibo (vedere paragrafo 5.2).

Tabella 1: Trattamento e durata raccomandati per tutti i genotipi di HCV

Popolazione di pazienti[a]	Trattamento e durata
Pazienti senza cirrosi e pazienti con cirrosi compensata	Epclusa per 12 settimane L'aggiunta di ribavirina può essere presa in considerazione per i pazienti con infezione da HCV di genotipo 3 con cirrosi compensata (vedere paragrafo 5.1).
Pazienti con cirrosi scompensata	Epclusa + ribavirina per 12 settimane

a. Include pazienti con co-infezione da virus dell'immunodeficienza umana (HIV) e pazienti con HCV ricorrente in seguito a trapianto di fegato (vedere paragrafo 4.4).

Co-infezione HCV/HBV (virus dell'epatite B)

Casi di riattivazione del virus dell'epatite B (HBV), alcuni dei quali fatali, sono stati riportati durante o dopo il trattamento con agenti antivirali ad azione diretta. Il test di accertamento dell'HBV deve essere eseguito in tutti i pazienti prima dell'inizio del trattamento. I pazienti con co-infezione HBV/HCV sono a rischio di riattivazione di HBV e devono quindi essere monitorati e gestiti in accordo alle attuali linee guida cliniche.

da: agenzia europea per i medicinali (ema).

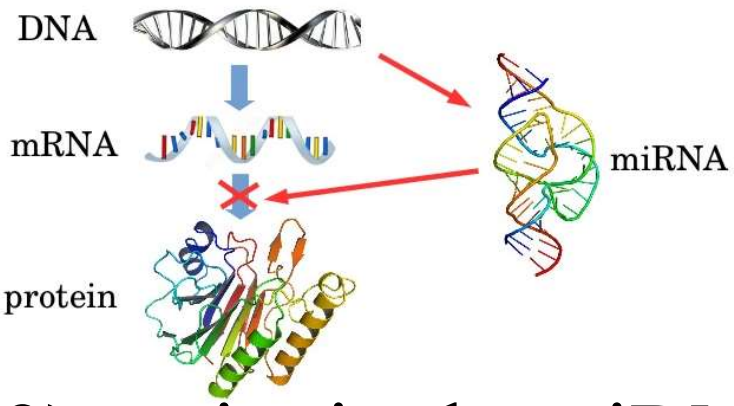
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

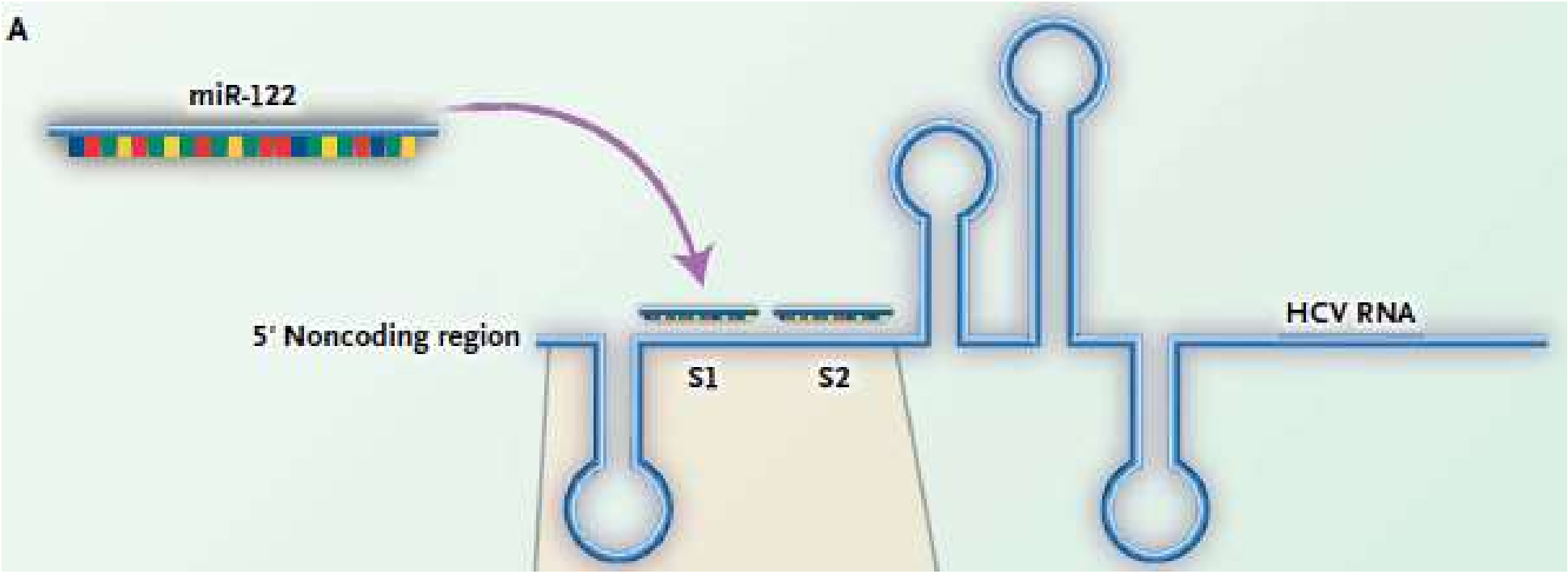
Treatment of HCV Infection by Targeting MicroRNA

Harry L.A. Janssen, M.D., Ph.D., Hendrik W. Reesink, M.D., Ph.D., Eric J. Lawitz, M.D., Stefan Zeuzem, M.D., Maribel Rodriguez-Torres, M.D., Keyur Patel, M.D., Adriaan J. van der Meer, M.D., Amy K. Patick, Ph.D., Alice Chen, B.A., Yi Zhou, Ph.D., Robert Persson, Ph.D., Barney D. King, M.D., Sakari Kauppinen, Ph.D., Arthur A. Levin, Ph.D., and Michael R. Hodges, M.D.

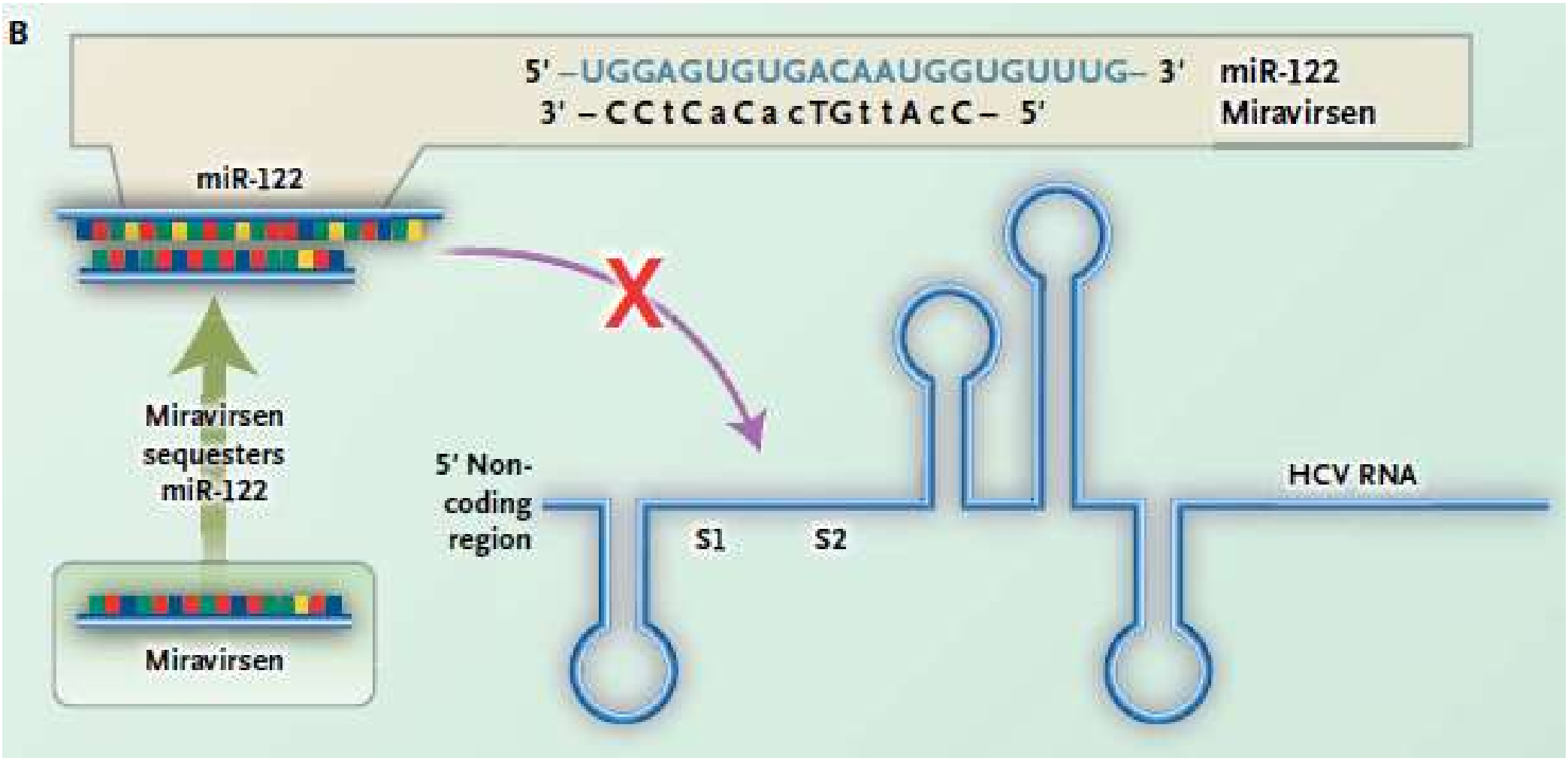
•**microRNA (miRNA**):piccole molecole endogene di RNA non codificante, a singolo filamento, di 20-22 nucleotidi implicate nella regolazione post-trascrizionale tramite l'inibizione della traduzione di determinati mRNA.



•**microRNA-122 (miR-122):** principale miRNA espresso nel fegato. Regolala biosintesi del colesterolo ed il metabolismo lipidico. **È essenziale per stabilità e propagazione del RNA del virus dell'epatite C (HCV).**



microRNA-122 (miR-122) si **lega** a due siti target ravvicinati (S1 e S2) nella regione non codificante del genoma dell'HCV e quindi **promuove** la **propagazione** dell'RNA dell'**HCV**



Miravirsen, un oligonucleotide antisenso modificato, **sequestra** il **miR-122 maturo** provocando **l'inibizione** funzionale di miR-122.

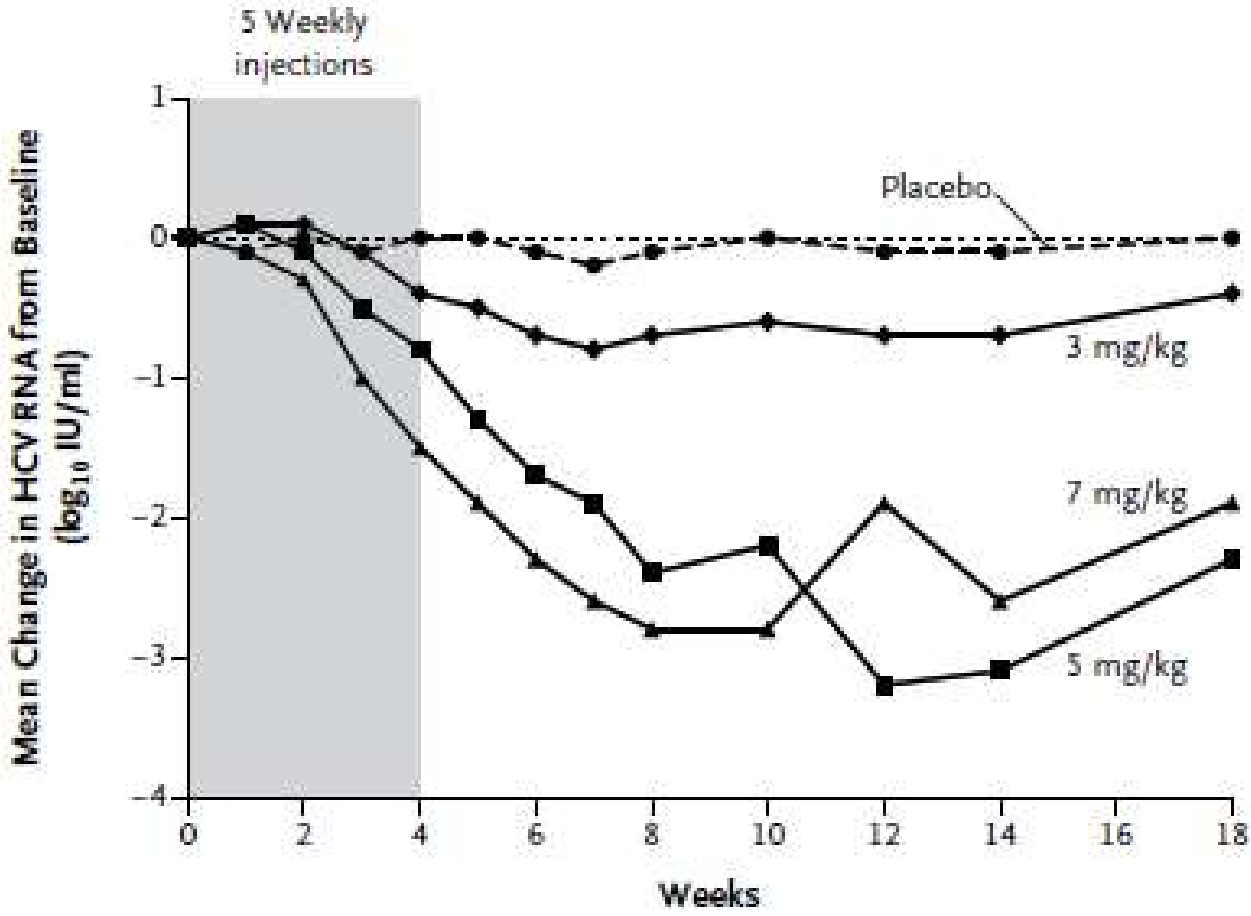


Figure 2. Change from Baseline in HCV RNA Levels.

Shown are the mean changes in HCV RNA levels from baseline for patients receiving 3 mg, 5 mg, or 7 mg of miravirsen per kilogram of body weight, as compared with placebo. Miravirsen was administered in five weekly subcutaneous injections during the first 29 days of the study (gray shading). The dashed line indicates no change from baseline. The HCV RNA levels during the use of pegylated interferon and ribavirin in some patients were not included in this analysis.

U.S. National Library of Medicine

ClinicalTrials.gov

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Modify Search Start Over

6 Studies found for: **miravirsen**

Search Details

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Completed	Drug Interaction Study to Assess the Effect of Co-Administered **Miravirsen** and Telaprevir in Healthy Subjects	• Hepatitis C • Chronic Hepatitis C	• Drug: **Miravirsen** sodium • Drug: Telaprevir
2	☐	Unknown †	**Miravirsen** Study in Null Responder to Pegylated Interferon Alpha Plus Ribavirin Subjects With Chronic Hepatitis C	• Hepatitis C	• Drug: **Miravirsen** sodium
3	☐	Unknown †	**Miravirsen** in Combination With Telaprevir and Ribavirin in Null Responder to Pegylated-Interferon Alpha Plus Ribavirin Subjects With Chronic Hepatitis C Virus Infection	• Hepatitis C, Chronic	• Drug: **Miravirsen** • Drug: Telaprevir • Drug: Ribavirin
4	☐	Completed	Multiple Ascending Dose Study of **Miravirsen** in Treatment-Naïve Chronic Hepatitis C Subjects	• Hepatitis C	• Drug: **miravirsen** • Drug: saline
5	☐	Completed	Long-Term Extension Study of **Miravirsen** Among Participants With Genotype 1 Chronic Hepatitis C (CHC) Who Have Not Responded to Pegylated-Interferon Alpha Plus Ribavirin	• Chronic Hepatitis C	
6	☐	Completed	Long Term Extension Study is Designed to Monitor Long-Term Efficacy and Safety of **Miravirsen** Sodium in Combination With Telaprevir and Ribavirin in Subjects With Chronic Hepatitis C Virus Genotype 1 Infection	• HCV	

miR-122–based therapies select for three distinct resistance mechanisms based on alterations in RNA structure

PNAS 2021 Vol. 118 No. 33 e2103671118

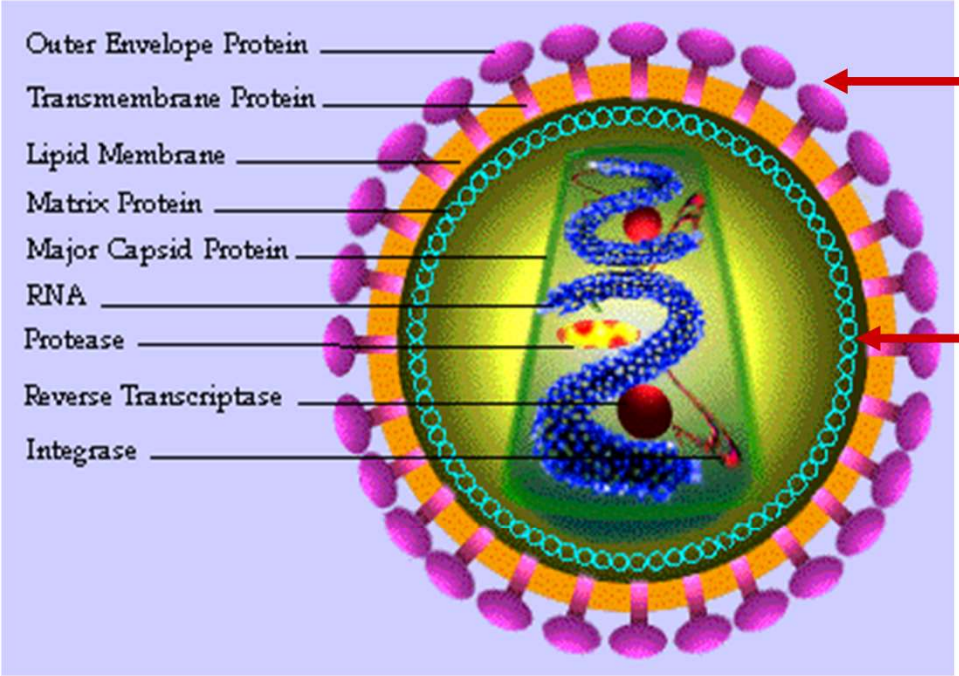
Jasmin Chahal[a], Luca F. R. Gebert[b], Carolina Camargo[a], Ian J. MacRae[b], and Selena M. Sagan[a,c,1]

Taken together, these findings provide insight into the mechanism(s) of miR-122–mediated viral RNA accumulation and provide mechanisms of antiviral resistance mediated by changes in RNA structure.

HIV

- HIV –***H****uman* ***I****mmunodeficiency* ***V****irus* è il **retrovirus** responsabile del AIDS
- HIV appartiene alla gruppo dei **lentivirus (**utilizzati oggi come vettori di geni in terapia genica).
- HIV interagisce con le cellule che esprimono recettori CD4 (cellule T4 e macrofagi).

Caratteristiche dell'HIV

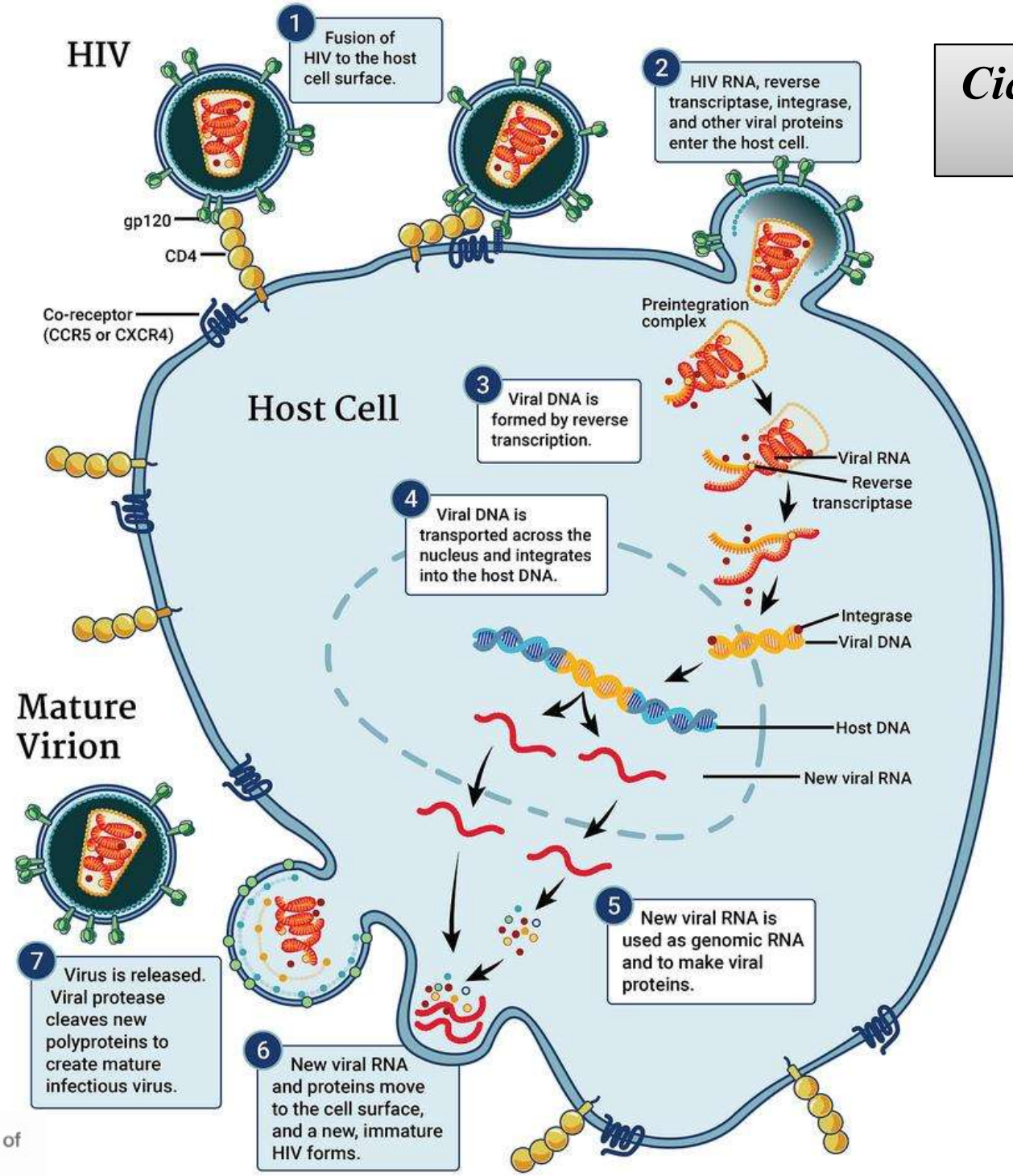


Viral Envelope

Viral Core

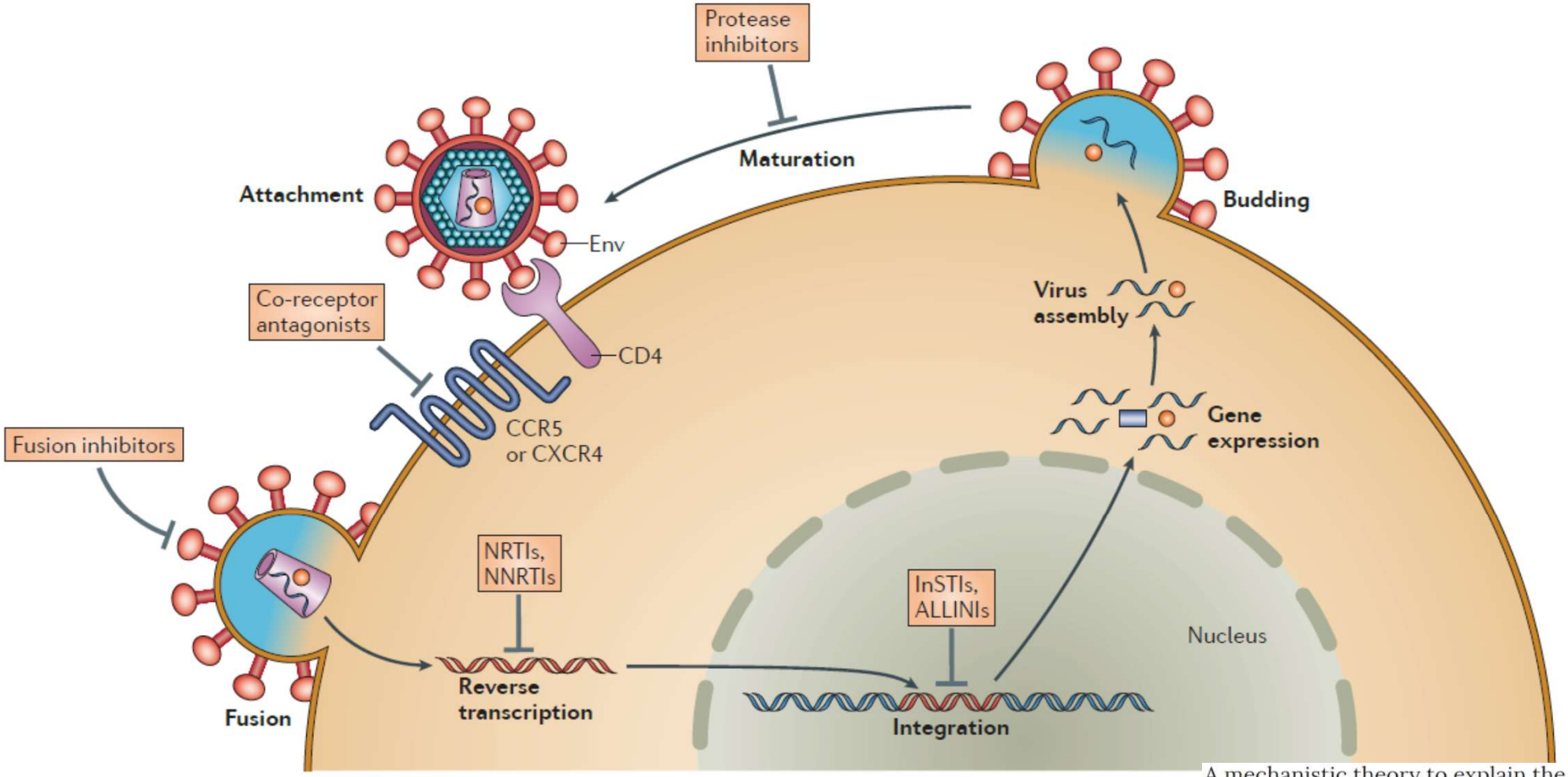
Una volta integrato nella cellula bersaglio come provirus, si serve dell'enzima **trascrittasi inversa** (RT) per copiare il proprio genoma durante la replicazione cellulare, persistendo negli individui infetti per tutta la vita.

Ciclo replicativo dell'HIV



NIH National Institute of Allergy and Infectious Diseases

Bersagli dei farmaci



A mechanistic theory to explain the efficacy of antiretroviral therapy

Sarah B. Laskey & Robert F. Siliciano

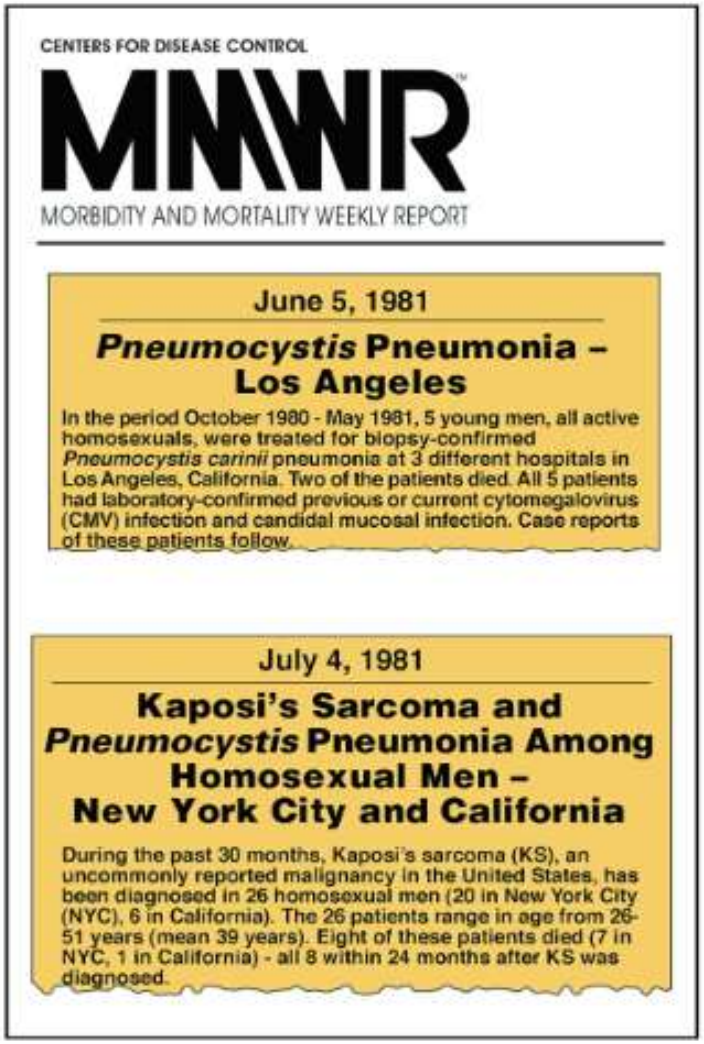
Nature Reviews Microbiology **12**, 772–780 (2014) | Download Citation

NRTI: Inibitori Nucleosidici della Transcrittasi Inversa
NNRTI: Inibitori Non Nucleosidici della Transcrittasi Inversa
INSTIs: Integrase strand transfer inhibitors
ALLINIs: Allosteric integrase inhibitors

Four Decades of HIV/AIDS — Much Accomplished, Much to Do

Anthony S. Fauci, M.D., and H. Clifford Lane, M.D.

N ENGL J MED 383;1 NEJM.ORG JULY 2, 2020



CENTERS FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

June 5, 1981

***Pneumocystis* Pneumonia – Los Angeles**

In the period October 1980 - May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

July 4, 1981

Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men – New York City and California

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City (NYC), 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California) - all 8 within 24 months after KS was diagnosed.

Figure 1
The original MMWR reports of the first recognized AIDS cases in the summer of 1981.

1980s

- **1981:** AIDS epidemic first recognized; cases reported in New York and California; life expectancy, 6–12 mo
- **1984:** HIV definitively established as causal agent of AIDS
- **1985:** First FDA approval of a test that detects antibodies to HIV
- **1986:** IOM establishes the Committee on a National Strategy for AIDS, which publishes *Confronting AIDS: Directions for Public Health, Health Care, and Research*
- **1987:** First FDA approval of a drug to treat HIV (Retrovir [azidothymidine, or AZT; now called zidovudine])

1990s

- **1995:** First FDA approval of a protease inhibitor (Invirase [saquinavir])
- **1996:** First FDA approval of a viral load test for HIV
  First FDA approval of a nonnucleoside reverse-transcriptase inhibitor (Viramune [nevirapine])
  Striking efficacy of combination antiretroviral treatment demonstrated

2000s

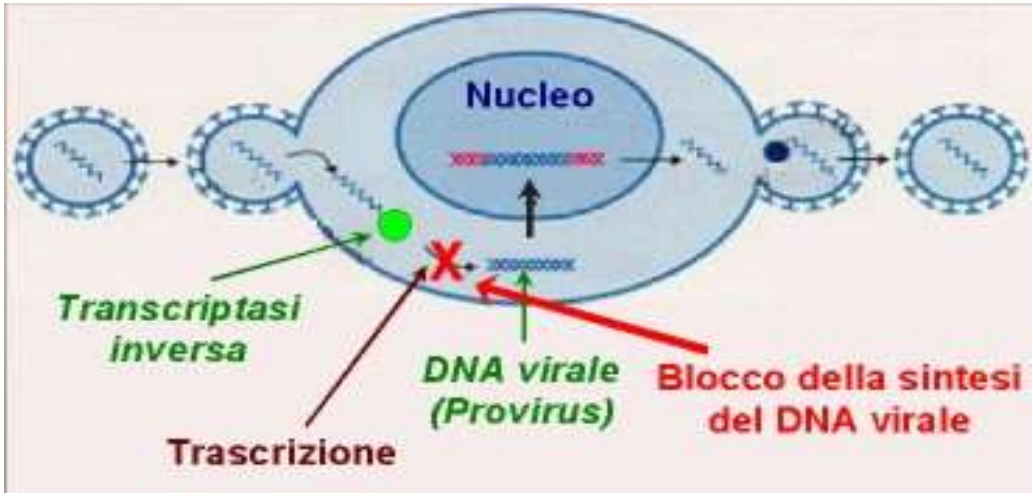
- **2003:** President George W. Bush establishes President's Emergency Plan for AIDS Relief (PEPFAR)
  First FDA approval of an entry inhibitor (Fuzeon [enfuvirtide])
- **2007:** First FDA approval of an integrase inhibitor (Isentress [raltegravir])
- **2009:** Results of the RV 144 vaccine trial published (first HIV vaccine with a signal of efficacy)

2010s

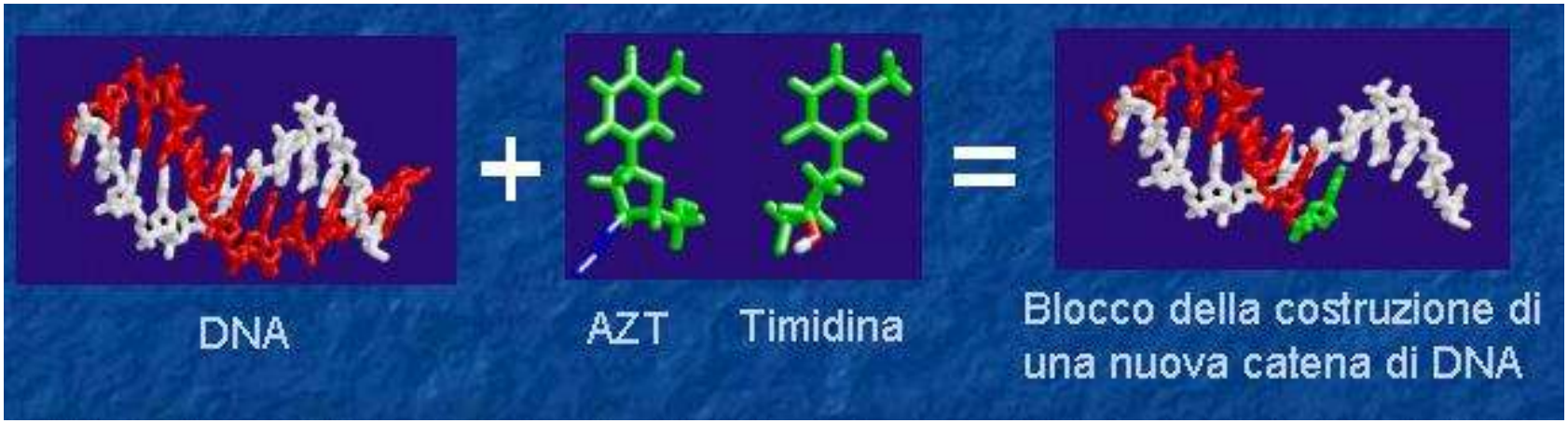
- **2012:** First FDA approval of a treatment for preexposure prophylaxis (Truvada [emtricitabine–tenofovir])
- **2018:** 37.9 million people living with HIV; life expectancy while receiving treatment, close to normal

Inibitori Nucleosidici della Transcrittasi Inversa (nRTI)

- I farmaci appartenenti a questa classe sono stati **i primi** ad essere utilizzati nella terapia dell'infezione da HIV; il capostipite di questi infatti, la **Zidovudina (AZT)**, è stata utilizzata fin dal **1987**. I **risultati** che si ottenevano erano però solo **transitori**, e questo era dovuto al fatto che il suo impiego in **monoterapia** provocava rapidamente l'insorgenza di **resistenze**.



•Questi farmaci inibiscono il processo di replicazione del virus mediante il ***blocco*** della ***trascrizione dell'RNA virale in DNA provirale***; agiscono sostituendosi alle basi azotate durante la trascrizione, in modo che il DNA provirale neoformato sia incompleto e quindi incapace di originare nuove particelle virali.



Zidovudina (AZT)

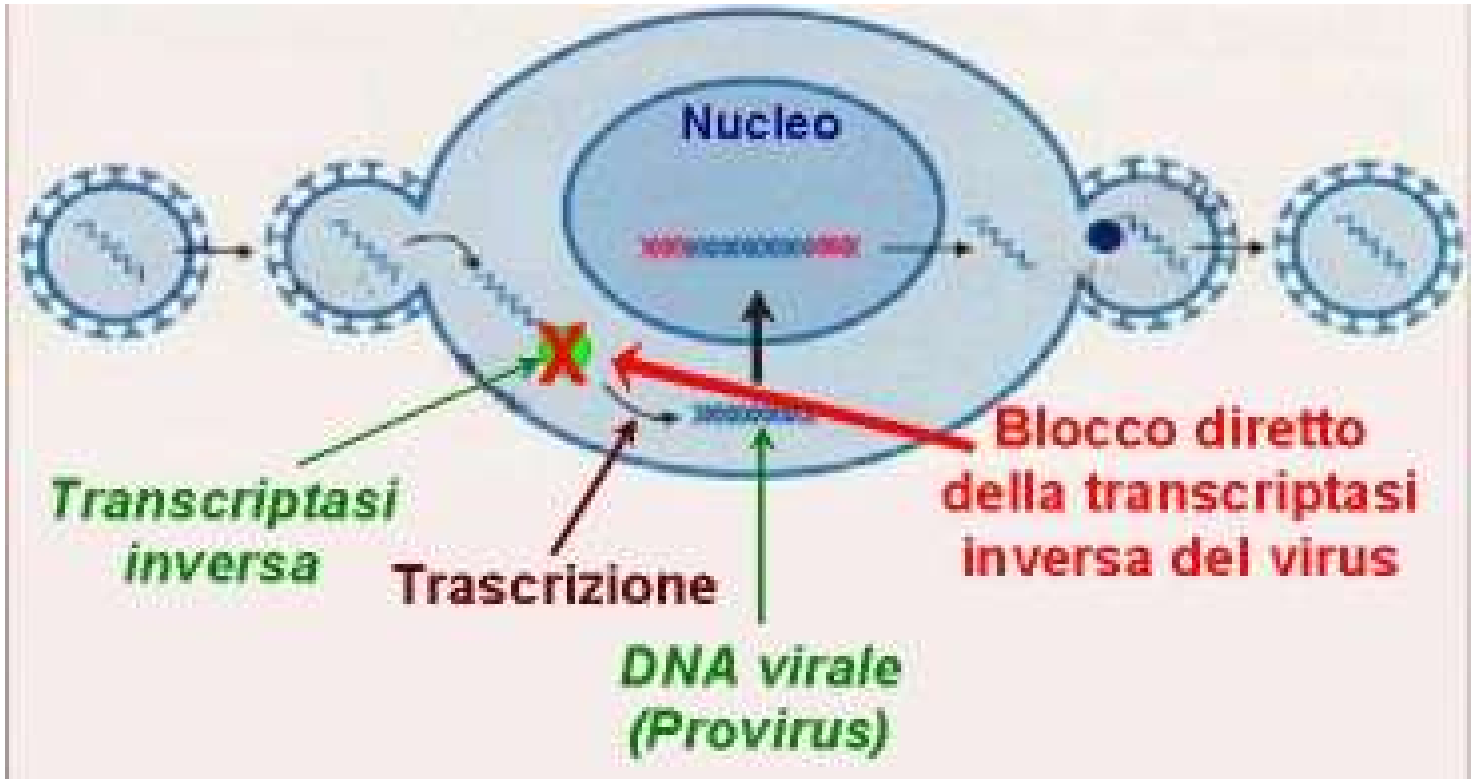
- **Farmacocinetica**: L'AZT viene ben **assorbito** nell'intestino, con una biodisponibilità del 60%. **Emivita** serica: 1,1 ora; emivita intracellulare: 3 ore. **Eliminazione** prevalentemente per via renale. L'AZT **diffonde** nel liquido cerebrospinale, con un rapporto di circa 0,5 rispetto alla concentrazione ematica.
- **Effetti collaterali**: **Effetti ematologici**: anemia e neutropenia. **Tossicità epatica**:controllare periodicamente i valori di transaminasi. **Effetti gastroenterici**: nausea, vomito, dolori addominali, calo dell'appetito, dispepsia. **Altro**: cefalea, astenia, insonnia, esantema. Sono stati descritti casi di sofferenza muscolare acuta (miosite). **Casi di acidosi lattica ed epatomegalia severa con steatosi anche fatale sono stati riportati con l'impiego di tutti gli analoghi nucleosidici, da soli o in combinazione fra loro.**
- **Dosaggio**: 300 mg due volte al giorno.

Inibitori Non Nucleosidici della Transcrittasi Inversa (NNRTI)

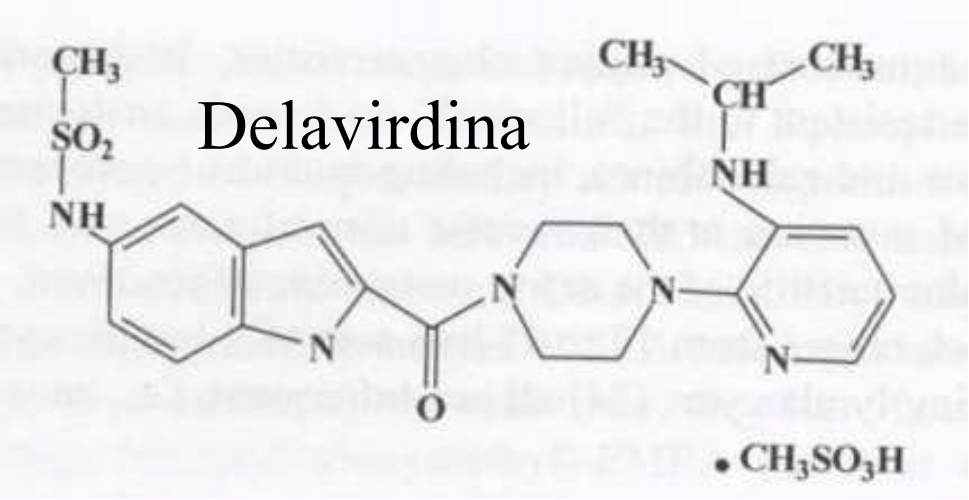
Questa classe di farmaci fu scoperta nel ‘90, ma il loro sviluppo era stato ostacolato dagli **scarsi risultati** ottenuti in seguito all'impiego in **monoterapia** (rapida insorgenza di resistenza).

Sono stati poi rivalutati con successo nell'ambito delle **terapie** di **combinazione.**

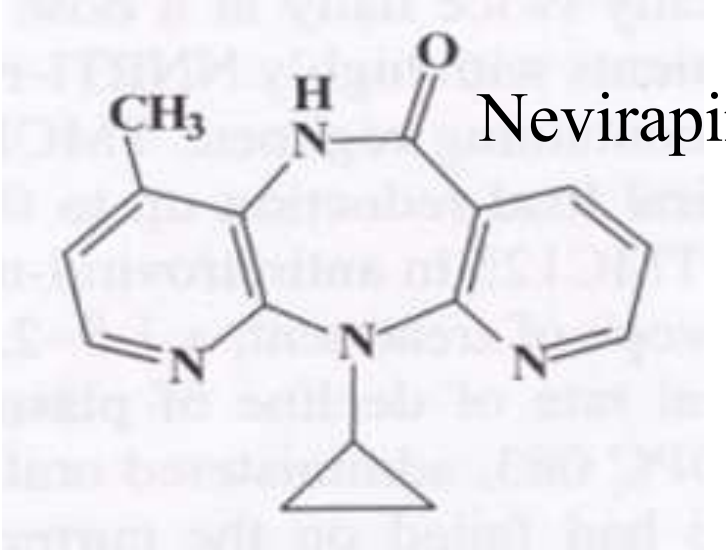
Sono **inibitori della transcriptasi inversa**, ma agiscono con un meccanismo diverso: si **legano direttamente al sito attivo dell'enzima**, bloccandone l'azione ed **impedendo** così che avvenga la **formazione** del **DNA provirale**.



Delavirdina



Nevirapina



Nevirapina (NNRTI)

- **Farmacocinetica**: rapidamente **assorbita** dopo somm. orale. **Biodisponibilità** >90%. t1/2: 25-30 ore. **Eliminazione**: renale 80%, fecale 10%.**Buona diffusione** nel liquido cerebrospinale.

- **Tossicità epatica severa, potenzialmente fatale, compresa epatite colestatica fulminante, necrosi epatica ed insufficienza epatica**. Sono stati segnalati rari casi di epatiti gravi con evoluzione fatale; più frequentemente si possono osservare lievi alterazioni degli indici epatici (transaminasi). **Altro**: nausea, stanchezza, febbre, cefalea, sonnolenza.

  La Nevirapina non deve mai essere ripresa dopo un episodio di epatite severa o di una reazione di ipersensibilità.

- **Induttore p450!**

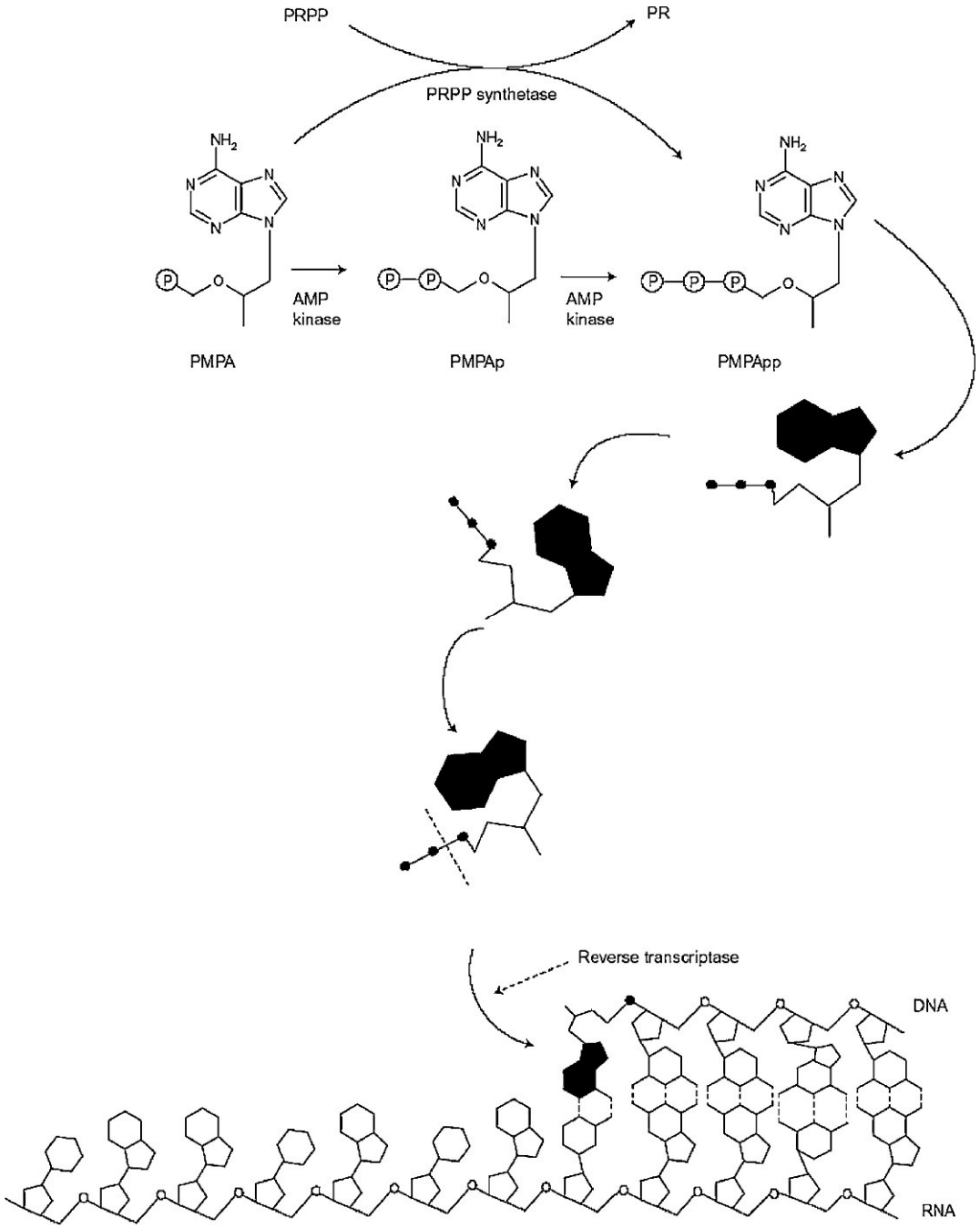
- **Dose:** 400 mg/giorno

Efavirenz Sustiva (NNRTI)

- **Farmacocinetica**: **Biodisponibilità**: > 60%.t1/2: 40-55 ore. **Eliminazione**: renale 14-34%, fecale 16-61%. Buona **diffusione** nel liquido cerebrospinale.
- **Effetti collaterali: disturbi neurologici** (senso di stordimento, difficoltà di concentrazione, amnesie, sonnolenza, comparsa di incubi notturni, insonnia, agitazione, allucinazioni, euforia) prevalentemente nelle prime 2-3 settimane di terapia. **Reazioni allergiche**: febbre e rash; rari casi di Sindrome di Stevens-Johnson
- **Altro**: alterazioni della funzionalità epatica, dislipidemia, disturbi gastro- intestinali**, falsa positività del test per i cannabinoidi.**
- **Induttore p450!**
- **Dose:** 600 mg/giorno

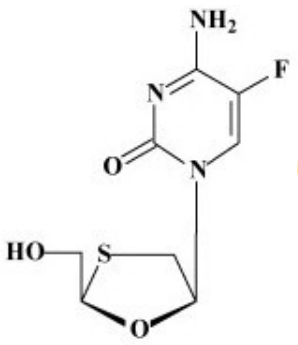
Altri Inibitori Nucleosidici della Transcrittasi Inversa (nRTI)

- **TENOFOVIR** (TDF): deriva dal profarmaco tenofovir disoproxil fumarato (migliore farmacocinetica). Il TDF inibisce l'attività della transcrittasi inversa di HIV entrando in **competizione** con il naturale substrato **deoxyadenosine 5'-trifosfato** e, dopo incorporazione nel DNA, come "**chain terminator".**

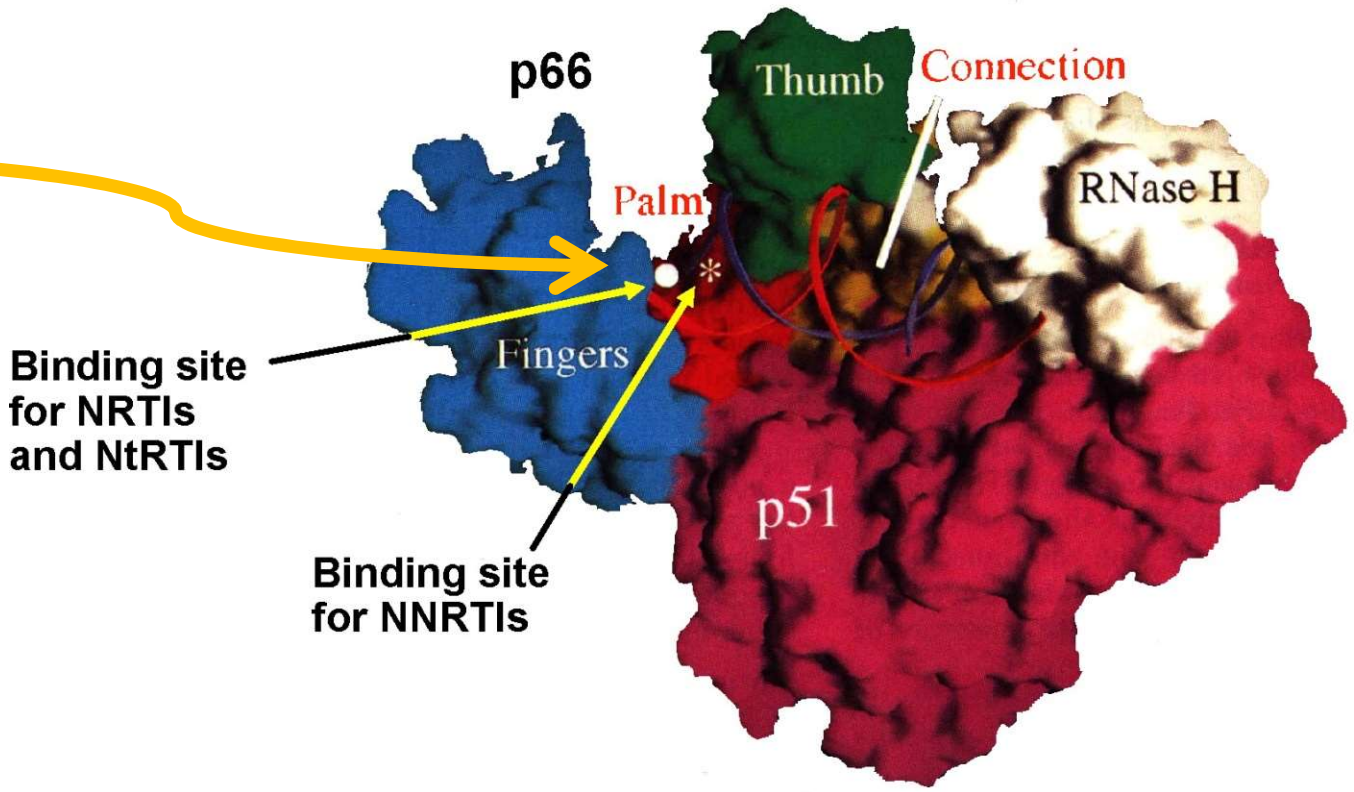


Meccanismo di azione del tenofovir. Dopo fosforilazione a difosfato, agisce come un terminatore di catena obbligatorio nella reazione di trascrittasi inversa.

Emtricitabina (FTC)



(-)FTC
Emtricitabine
(-)-β-L-3'-thia-2',3'-dideoxy-5-fluorocytidine
Emtriva®



Human immunodeficiency virus (HIV) **reverse transcriptase** with the **binding site** for the nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs) and the binding site for the non-nucleoside reverse transcriptase inhibitors (NNRTIs).

TRUVADA: associazione di emtricitabina e tenofovir

Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals (Review)

Okwundu CI, Uthman OA, Okoromah CAN

THE COCHRANE COLLABORATION®

Background

More than 30 years into the global HIV/AIDS epidemic, infection rates remain alarmingly high, with over 2.7 million people becoming infected every year. There is a need for HIV prevention strategies that are more effective. Oral antiretroviral pre-exposure prophylaxis (PrEP) in high-risk individuals may be a reliable tool in preventing the transmission of HIV.

Authors' conclusions

Finding from this review suggests that pre-exposure prophylaxis with TDF alone or TDF-FTC reduces the risk of acquiring HIV in high-risk individuals including people in serodiscordant relationships, men who have sex with men and other high risk men and women.

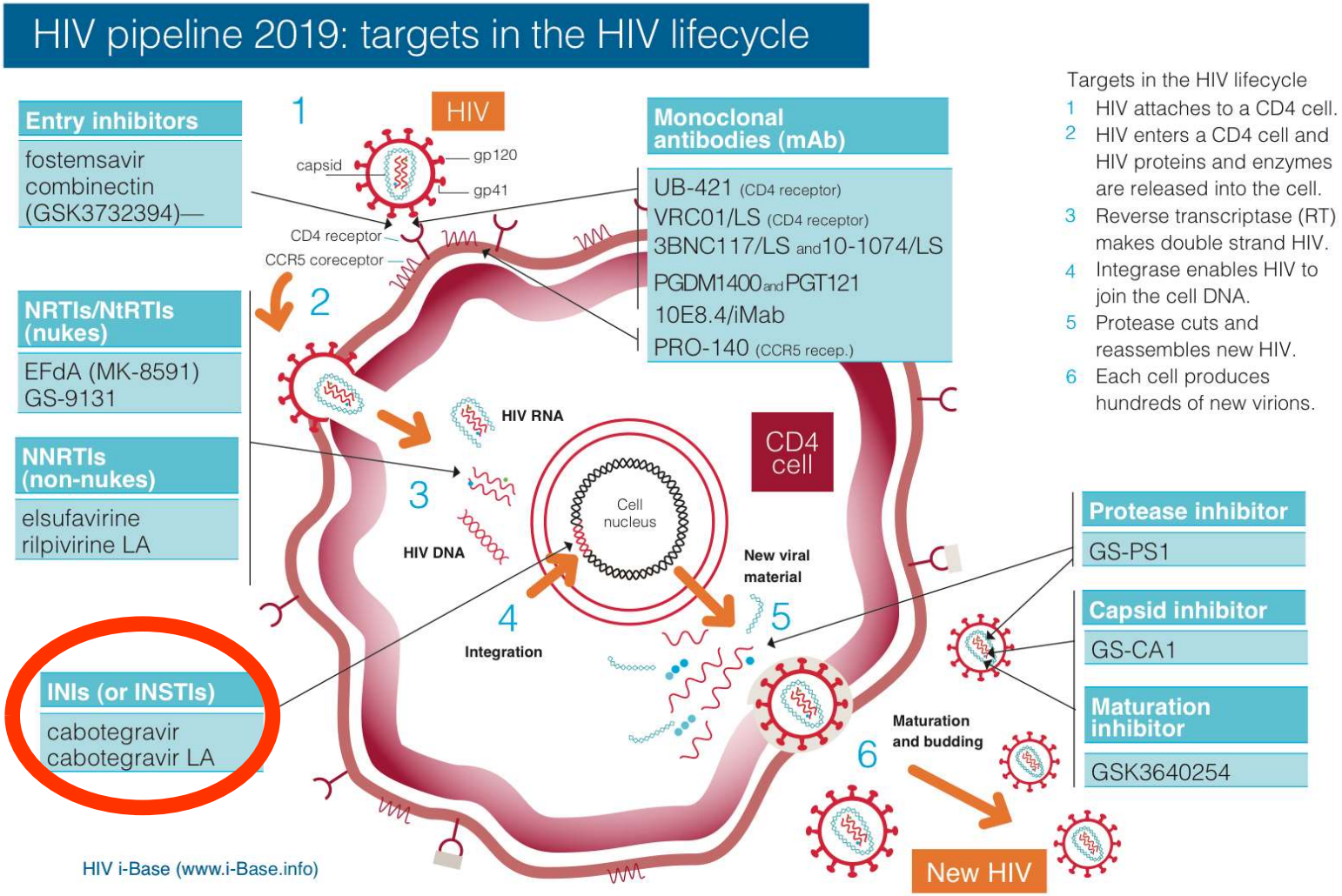
Trial results reveal that long-acting injectable cabotegravir as PrEP is highly effective in preventing HIV acquisition in women

9 November 2020 | Departmental news | Reading time: 5 min (1444 words)

Related

CABOTEGRAVIR

(inibitore dell'integrasi)



NEWS · 09 MARCH 2021 · CORRECTION 09 MARCH 2021 nature

Achilles' heel spotted for promising HIV prevention drug

Bi-monthly injections of cabotegravir kept most people free of HIV, but also hid infections and fueled resistance in rare cases, study finds.

I ricercatori hanno rivisitato una sperimentazione clinica del farmaco su 4.570 persone, esaminando campioni di sangue raccolti durante lo studio e hanno scoperto che quattro persone che hanno contratto l'HIV nonostante ricevessero iniezioni del ***cabotegravir****, erano state infettate per più di un mese prima dei normali test HIV.*
Durante questo periodo, hanno sviluppato resistenza a ***cabotegravir*** *e* ***terapie*** *strettamente* ***correlate*** *che vengono utilizzate per trattare le infezioni da HIV. Sebbene le alternative a questi farmaci comuni possano trattare le infezioni da HIV, possono essere costose o difficili da ottenere in alcuni paesi.*

ELSEVIER

Taking aim at a moving target: designing drugs to inhibit drug-resistant HIV-1 reverse transcriptases

Stefan G Sarafianos[1], Kalyan Das[1], Stephen H Hughes[2] and Eddy Arnold[1]*

HIV undergoes rapid genetic variation; this variation is caused primarily by the enormous number of viruses produced daily in an infected individual. Because of this variation, HIV presents a moving target for drug and vaccine development. The variation within individuals has led to the generation of diverse HIV-1 subtypes, which further complicates the development of effective drugs and vaccines. In general, it is more difficult to hit a moving target than a stationary target. Two broad strategies for hitting a moving target (in this case, HIV replication) are to understand the movement and to aim at the portions that move the least. In the case of anti-HIV drug development, the first option can be addressed by understanding the mechanism(s) of drug resistance and developing drugs that effectively inhibit mutant viruses. The second can be addressed by designing drugs that interact with portions of the viral machinery that are evolutionarily conserved, such as enzyme active sites.

HIVdb Program

Genotypic Resistance Interpretation Algorithm

Sierra version 2.4.2 (last updated on 2019-11-01)
HIVdb version 8.9-1 (last updated on 2019-10-25)

HIVdb accepts user-submitted protease, RT, and integrase sequences or mutations and returns inferred levels of resistance to the most commonly used protease, nucleoside, non-nucleoside, and integrase inhibitors. Its purpose is educational and as such it provides extensive comments and a highly transparent scoring system that is hyperlinked to data in the HIV Drug Resistance Database. A detailed description of the program as well as all updates is in the Release Notes. A web service has been created to allow users to access HIVdb programmatically.

Protease, RT, and integrase mutations can be entered using either the text box or auto-suggestion boxes. To use the text box, type each mutation separated by one or more spaces. The consensus wildtype and separating commas are optional. If there is a mixture of more than one amino acid at a position, write both amino amino acids (an intervening slash is optional). Insertions should be indicated by "Insertion" and deletions by "Deletion".

Drug display options

By default, results will be shown for checked ARVs. Use checkboxes for additional ARVs. (select all ARVs, revert to default)

NRTI: ☑ ABC ☑ AZT ☑ FTC ☑ 3TC ☑ TDF ☐ D4T ☐ DDI

NNRTI: ☑ DOR ☑ EFV ☑ ETR ☑ NVP ☑ RPV

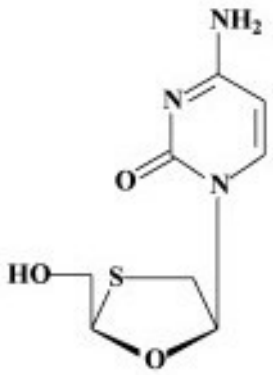
INSTI: ☑ BIC ☑ DTG ☑ EVG ☑ RAL

PI: ☑ ATV/r ☑ DRV/r ☑ LPV/r ☐ FPV/r ☐ IDV/r ☐ NFV ☐ SQV/r ☐ TPV/r

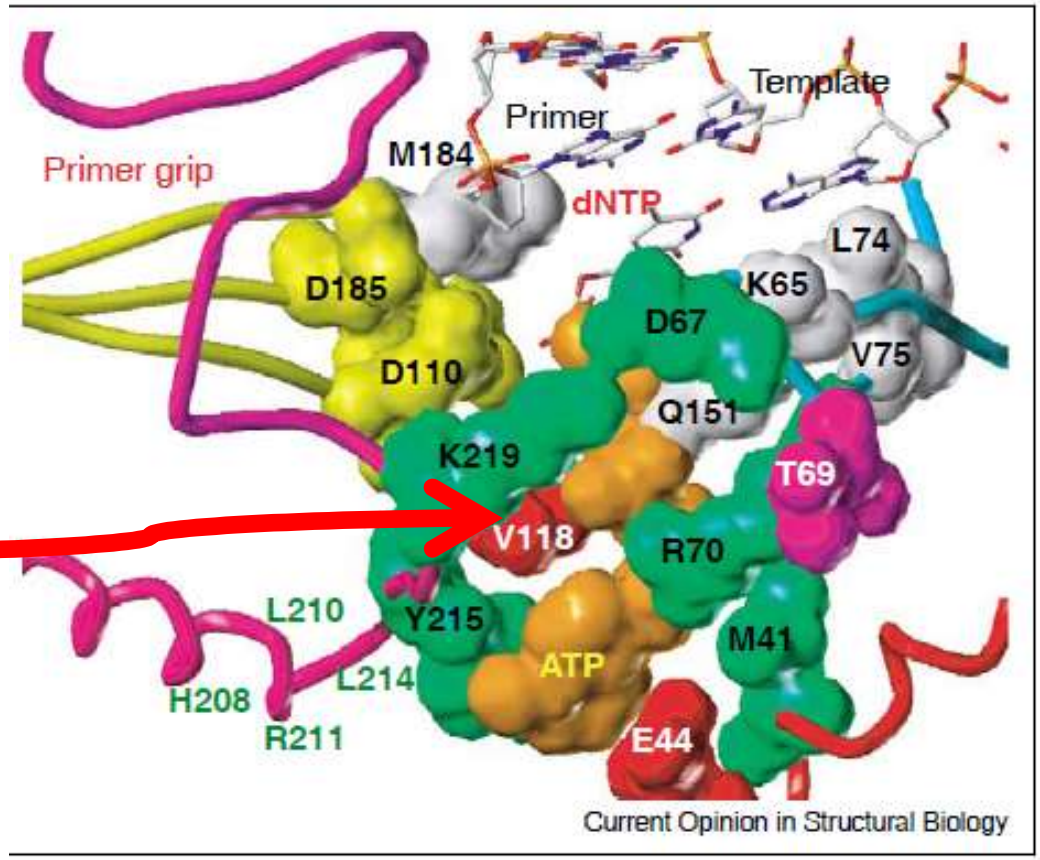
Input mutations | Input sequences

Reverse Transcriptase | Protease | Integrase

Lamivudina-3TC



Lamivudine
2',3'-Dideoxy-3'-thiacytidine
3TC
Epivir®



Epivir: 30 mg/die p.o.

Scarsi effetti collaterali.

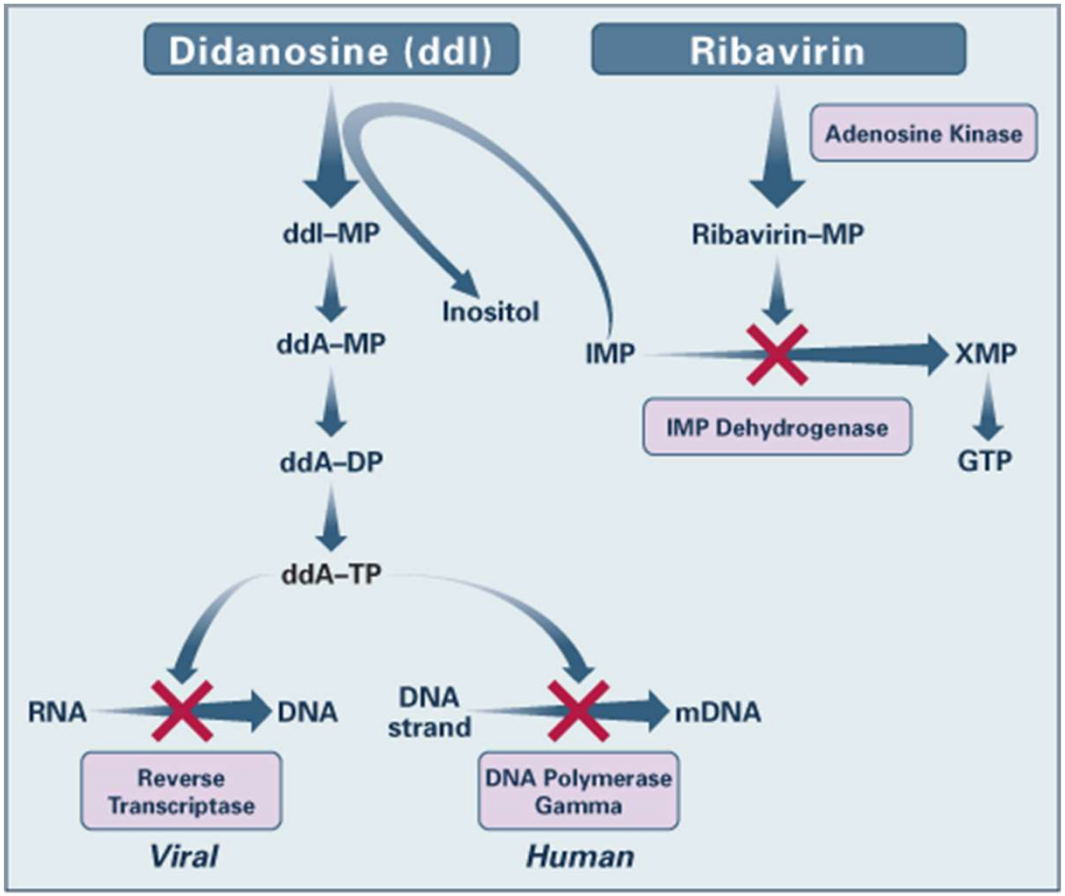
Non raccomandato in monoterapia.

Mutations that affect ATP binding and NRTI excision. The van der Waals surface of ATP is shown in orange. The sidechains of residues that are mutated in AZT-R RTs are shown in green. Residues where mutations alter the ability of the enzyme to excise 3TC (44, 118) are shown in red. Residues where mutations alter the efficiency and specificity of the excision reaction in the presence of AZT-R mutations (69 insertion complex) are shown in pink. The catalytic aspartic acid residues are shown in yellow. Other NRTI-resistance mutations are shown in gray.

Didanosina (ddI)

Meccanismo d'azione e interazione con ribavirina.

<u>Non usare in associazione.</u>



IMP = inosine monophosphate,
AMP = adenosine monophosphate,
ADP = adenosine diphosphate,
ATP = adenosine triphosphate

La ribavirina (*vedi terapia HCV*) inibisce la IMP deidrogenasi portando ad un **aumento** del pool di **IMP** disponibile per agire come donatore di fosfato per la trasformazione finale della didanosina (ddI) ddA-TP, il metabolita attivo trifosforilato di didanosina. Il **ddA-TP inibisce** sia la **trascrittasi inversa** del **HIV** sia la DNA polimerasi-gamma **mitocondriale umana**. L'aumentata concentrazione intracellulare di ddA-TP può portare ad un **aumento della tossicità mitocondriale con manifestazioni cliniche di pancreatite, neuropatia periferica e acidosi lattica.**

Didanosina

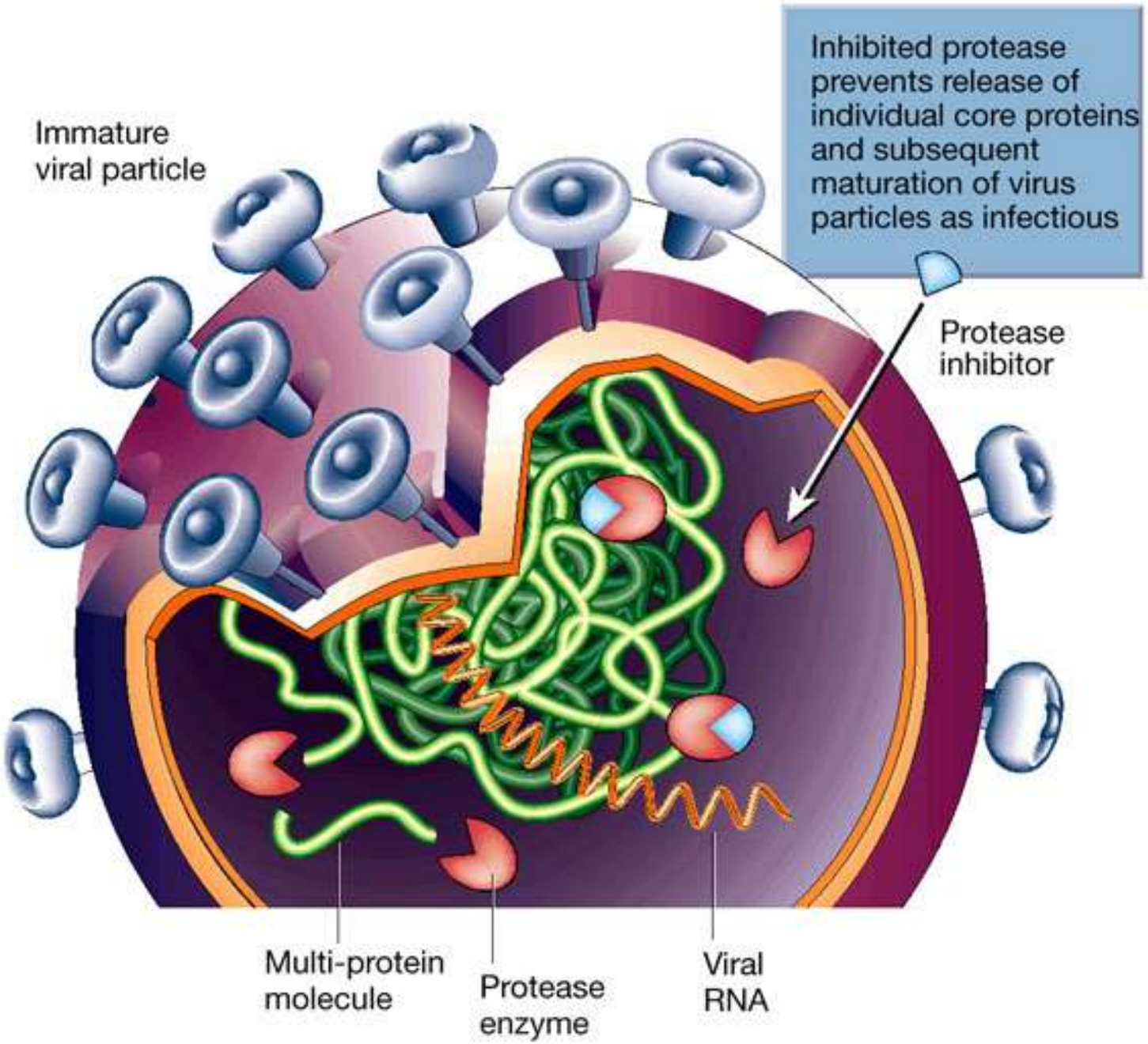
- In associazione solo quando altri antiretrovirali non possono essere utilizzati.
- Dosaggio: per peso corporeo > 60 kg: 400 mg al giorno; per p.c. < di 60 kg: 250 mg al giorno.
- Modificare il dosaggio in base alla clearance della creatinina:

Clearance della creatinina (ml/min)/Peso del paziente	Dose totale giornaliera	
	almeno 60 kg (dose, mg)	meno di 60 kg (dose, mg)
Almeno 60	400 mg	250 mg
30-59	200 mg	150 mg*
10-29	150 mg*	100 mg*
Meno di 10	100 mg*	75 mg*

- A causa dei suoi numerosi eventi avversi potenzialmente gravi, la didanosina è stata ampiamente sostituita da agenti meglio tollerati ed è ora utilizzata raramente.

Inibitori della Proteasi (IP)

Sono i farmaci che hanno radicalmente modificato l'impatto della terapia antiretrovirale, essendo caratterizzati da una potente attività di blocco della replicazione virale. Agiscono nell'ultima fase del ciclo replicativo del HIV, **inibendo** la **proteasi virale**, un **enzima** che **permette** la **maturazione** delle nuove particelle virali rendendole a loro volta infettanti.


Inhibited protease prevents release of individual core proteins and subsequent maturation of virus particles as infectious
Immature viral particle
Protease inhibitor
Multi-protein molecule
Protease enzyme
Viral RNA

Indinavir (IP)

- **Farmacocinetica**:

Biodisponibilità dopo somministrazione orale: 65%.

Emivita: 1,5 - 2 ore.

Eliminazione: prevalentemente per via epatica.

- **Inibizione p450.**
- **Diverse interazioni farmacologiche** (vedi in seguito)
- 800 mg/3 volte al giorno

Table 2
Drug Interactions: Pharmacokinetic Parameters for Indinavir in the Presence of the Coadministered Drug
(See PRECAUTIONS, Table 9 for Recommended Alterations in Dose or Regimen)

Coadministered drug	Dose of Coadministered drug (mg)	Dose of CRIXIVAN (mg)	n	Ratio (with/without coadministered drug) of Indinavir Pharmacokinetic Parameters (90% CI); No Effect =1.00		
				C_{max}	AUC	C_{min}
Cimetidine	600 twice daily, 6 days	400 single dose	12	1.07 (0.77, 1.49)	0.98 (0.81, 1.19)	0.82 (0.69, 0.99)
Clarithromycin	500 q12h, 7 days	800 three times daily, 7 days	10	1.08 (0.85, 1.38)	1.19 (1.00, 1.42)	1.57 (1.16, 2.12)
Delavirdine	400 three times daily	400 three times daily, 7 days	28	0.64[1] (0.48, 0.86)	No significant change[1]	2.18[1] (1.16, 4.12)
Delavirdine	400 three times daily	600 three times daily, 7 days	28	No significant change	1.53[1] (1.07, 2.20)	3.98[1] (2.04, 7.78)
Efavirenz[2]	600 once daily, 10 days	1000 three times daily, 10 days	20			
		After morning dose		No significant change[1]	0.67[1] (0.61, 0.74)	0.61[1] (0.49, 0.76)
		After afternoon dose		No significant change[1]	0.63[1] (0.54, 0.74)	0.48[1] (0.43, 0.53)
		After evening dose		0.71[1] (0.57, 0.89)	0.54[1] (0.46, 0.63)	0.43[1] (0.37, 0.50)
Fluconazole[2]	400 once daily, 8 days	1000 three times daily, 7 days	11	0.87 (0.72, 1.05)	0.76 (0.59, 0.98)	0.90 (0.72, 1.12)
Grapefruit Juice	8 oz.	400 single dose	10	0.65 (0.53, 0.79)	0.73 (0.60, 0.87)	0.90 (0.71, 1.15)
Isoniazid	300 once daily in the morning, 8 days	800 three times daily, 7 days	11	0.95 (0.88, 1.03)	0.99 (0.87, 1.13)	0.89 (0.75, 1.06)
Itraconazole	200 twice daily, 7 days	600 three times daily, 7 days	12	0.78[1] (0.69, 0.88)	0.99[1] (0.91, 1.06)	1.49[1] (1.28, 1.74)
Ketoconazole	400 once daily, 7 days	600 three times daily, 7 days	12	0.69[1] (0.61, 0.78)	0.80[1] (0.74, 0.87)	1.29[1] (1.11, 1.51)
	400 once daily, 7 days	400 three times daily, 7 days	12	0.42[1] (0.37, 0.47)	0.44[1] (0.41, 0.48)	0.73[1] (0.62, 0.85)
Methadone	20-60 once daily in the morning, 8 days	800 three times daily, 8 days	10	See text below for discussion of interaction.		
Quinidine	200 single dose	400 single dose	10	0.96 (0.79, 1.18)	1.07 (0.89, 1.28)	0.93 (0.73, 1.19)
Rifabutin	150 once daily in the morning, 10 days	800 three times daily, 10 days	14	0.80 (0.72, 0.89)	0.68 (0.60, 0.76)	0.60 (0.51, 0.72)
Rifabutin	300 once daily in the morning, 10 days	800 three times daily, 10 days	10	0.75 (0.61, 0.91)	0.66 (0.56, 0.77)	0.61 (0.50, 0.75)
Rifampin	600 once daily in the morning, 8 days	800 three times daily, 7 days	12	0.13 (0.08, 0.22)	0.08 (0.06, 0.11)	Not Done
Ritonavir	100 twice daily, 14 days	800 twice daily, 14 days	10, 16[3]	See text below for discussion of interaction.		
Ritonavir	200 twice daily, 14 days	800 twice daily, 14 days	9, 16[3]	See text below for discussion of interaction.		
Sildenafil	25 single dose	800 three times daily	6	See text below for discussion of interaction.		
St. John's wort (*Hypericum perforatum*, standardized to 0.3 % hypericin)	300 three times daily with meals, 14 days	800 three times daily	8	Not Available	0.46 (0.34, 0.58)[4]	0.19 (0.06, 0.33)[4]
Stavudine (d4T)[2]	40 twice daily, 7 days	800 three times daily, 7 days	11	0.95 (0.80, 1.11)	0.95 (0.80, 1.12)	1.13 (0.83, 1.53)
Trimethoprim/ Sulfamethoxazole	800 Trimethoprim/ 160 Sulfamethoxazole q12h, 7 days	400 four times daily, 7 days	12	1.12 (0.87, 1.46)	0.98 (0.81, 1.18)	0.83 (0.72, 0.95)
Zidovudine[2]	200 three times daily, 7 days	1000 three times daily, 7 days	12	1.06 (0.91, 1.25)	1.05 (0.86, 1.28)	1.02 (0.77, 1.35)
Zidovudine/Lamivudine (3TC)[2]	200/150 three times daily, 7 days	800 three times daily, 7 days	6, 9[5]	1.05 (0.83, 1.33)	1.04 (0.67, 1.61)	0.98 (0.56, 1.73)

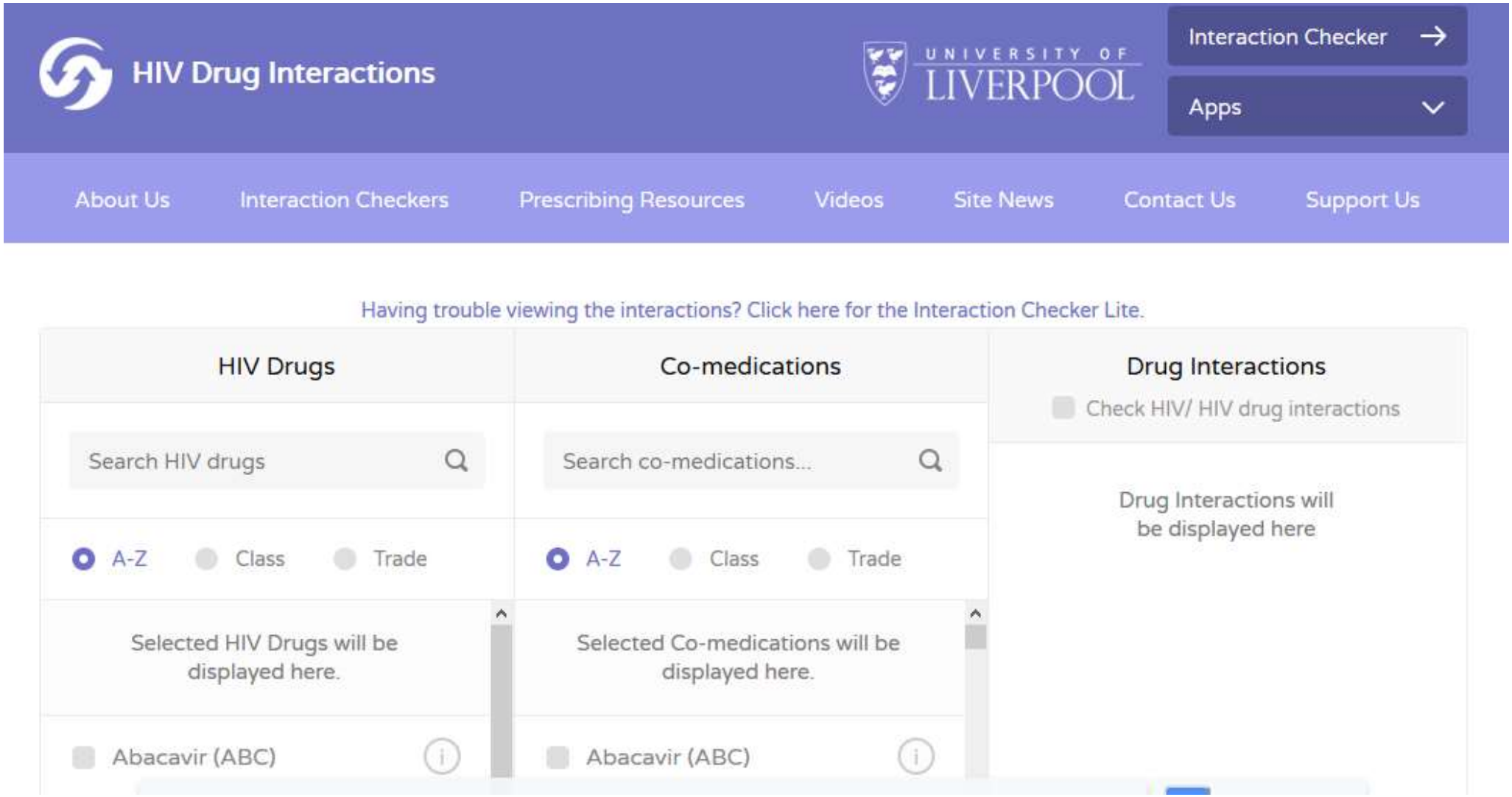
All interaction studies conducted in healthy, HIV-negative adult subjects, unless otherwise indicated.
[1] Relative to indinavir 800 mg three times daily alone.
[2] Study conducted in HIV-positive subjects.
[3] Comparison to historical data on 16 subjects receiving indinavir alone.
[4] 95% CI.
[5] Parallel group design; n for indinavir + coadministered drug, n for indinavir alone.

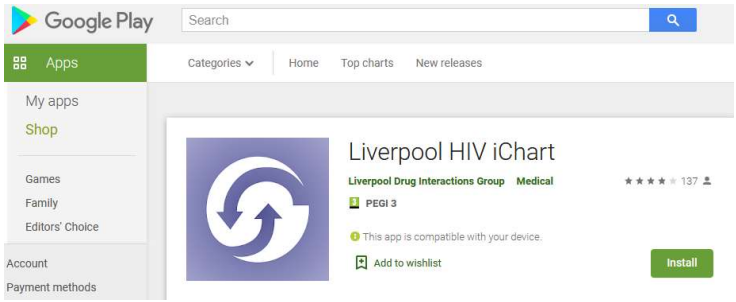
CRIXIVAN® (indinavir sulfate) 9640608

Table 3
Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Indinavir
(See PRECAUTIONS, Table 9 for Recommended Alterations in Dose or Regimen)

Coadministered drug	Dose of Coadministered drug (mg)	Dose of CRIXIVAN (mg)	n	Ratio (with/without CRIXIVAN) of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect =1.00		
				C_{max}	AUC	C_{min}
Clarithromycin	500 twice daily, 7 days	800 three times daily, 7 days	12	1.19 (1.02, 1.39)	1.47 (1.30, 1.65)	1.97 (1.58, 2.46) n=11
Efavirenz	200 once daily, 14 days	800 three times daily, 14 days	20	No significant change	No significant change	–
Ethinyl Estradiol (ORTHO-NOVUM 1/35)[1]	35 mcg, 8 days	800 three times daily, 8 days	18	1.02 (0.96, 1.09)	1.22 (1.15, 1.30)	1.37 (1.24, 1.51)
Isoniazid	300 once daily in the morning, 8 days	800 three times daily, 8 days	11	1.34 (1.12, 1.60)	1.12 (1.03, 1.22)	1.00 (0.92, 1.08)
Methadone[2]	20-60 once daily in the morning, 8 days	800 three times daily, 8 days	12	0.93 (0.84, 1.03)	0.96 (0.86, 1.06)	1.06 (0.94, 1.19)
Norethindrone (ORTHO-NOVUM 1/35)[1]	1 mcg, 8 days	800 three times daily, 8 days	18	1.05 (0.95, 1.16)	1.26 (1.20, 1.31)	1.44 (1.32, 1.57)
Rifabutin *150 mg once daily in the morning, 11 days + indinavir compared to 300 mg once daily in the morning, 11 days alone	150 once daily in the morning, 10 days	800 three times daily, 10 days	14	1.29 (1.05, 1.59)	1.54 (1.33, 1.79)	1.99 (1.71, 2.31) n=13
	300 once daily in the morning, 10 days	800 three times daily, 10 days	10	2.34 (1.64, 3.35)	2.73 (1.99, 3.77)	3.44 (2.65, 4.46) n=9
Ritonavir	100 twice daily, 14 days	800 twice daily, 14 days	10, 4[3]	1.61 (1.13, 2.29)	1.72 (1.20, 2.46)	1.62 (0.93, 2.85)
	200 twice daily, 14 days	800 twice daily, 14 days	9, 5[3]	1.19 (0.85, 1.66)	1.96 (1.39, 2.76)	4.71 (2.66, 8.33) n=9, 4
Saquinavir						
Hard gel formulation	600 single dose	800 three times daily, 2 days	6	4.7 (2.7, 8.1)	6.0 (4.0, 9.1)	2.9 (1.7, 4.7)[4]
Soft gel formulation	800 single dose	800 three times daily, 2 days	6	6.5 (4.7, 9.1)	7.2 (4.3, 11.9)	5.5 (2.2, 14.1)[4]
Soft gel formulation	1200 single dose	800 three times daily, 2 days	6	4.0 (2.7, 5.9)	4.6 (3.2, 6.7)	5.5 (3.7, 8.3)[4]
Sildenafil	25 single dose	800 three times daily	6	See text below for discussion of interaction.		
Stavudine[2]	40 twice daily, 7 days	800 three times daily, 7 days	13	0.86 (0.73, 1.03)	1.21 (1.09, 1.33)	Not Done
Theophylline	250 single dose (on Days 1 and 7)	800 three times daily, 6 days (Days 2 to 7)	12, 4[3]	0.88 (0.76, 1.03)	1.14 (1.04, 1.24)	1.13 (0.86, 1.49) n=7, 3
Trimethoprim/ Sulfamethoxazole						
Trimethoprim	800 Trimethoprim/ 160 Sulfamethoxazole q12h, 7 days	400 q6h, 7 days	12	1.16 (1.05, 1.32)	1.18 (1.05, 1.33)	1.18 (1.00, 1.39)
Trimethoprim/ Sulfamethoxazole						
Sulfamethoxazole	800 Trimethoprim/ 160 Sulfamethoxazole q12h, 7 days	400 q6h, 7 days	12	1.01 (0.95, 1.08)	1.05 (1.01, 1.09)	1.05 (0.97, 1.14)
Vardenafil	10 single dose	800 three times daily	18	See text below for discussion of interaction.		
Zidovudine[2]	200 three times daily, 7 days	1000 three times daily, 7 days	12	0.89 (0.73, 1.09)	1.17 (1.07, 1.29)	1.51 (0.71, 3.20) n=4
Zidovudine/Lamivudine[2]						
Zidovudine	200/150 three times daily, 7 days	800 three times daily, 7 days	6, 7[3]	1.23 (0.74, 2.03)	1.39 (1.02, 1.89)	1.08 (0.77, 1.50) n=5, 5

Risorse on line





https://www.hiv-druginteractions.org/checker

Nelfinavir (IP)

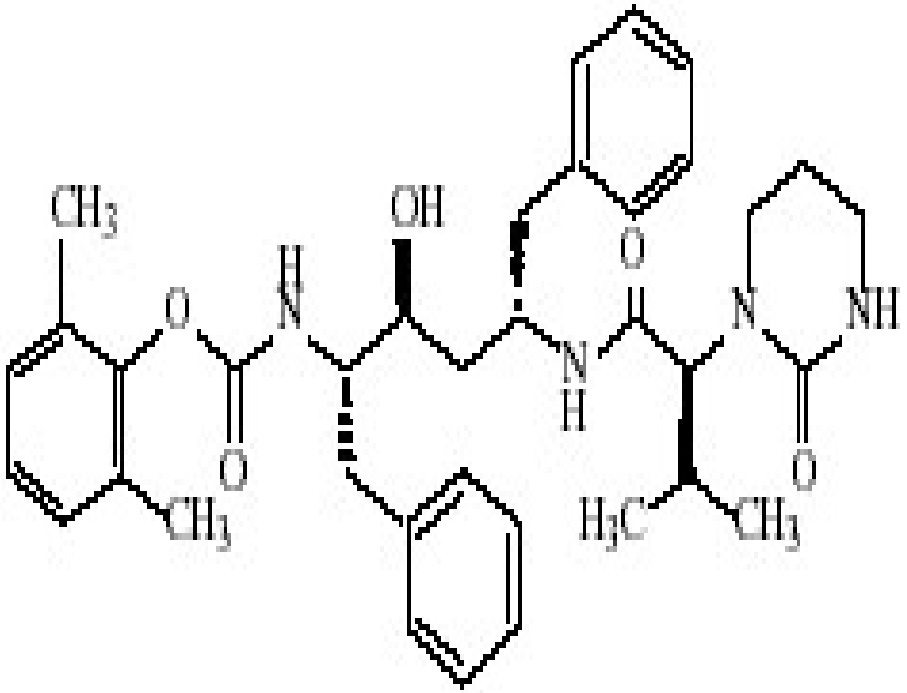
- **Farmacocinetica**:

Biodisponibilità dopo somministrazione orale: 20-80%.

Emivita: **3,5 - 5 ore**. Eliminazione: prevalentemente per via epatica.

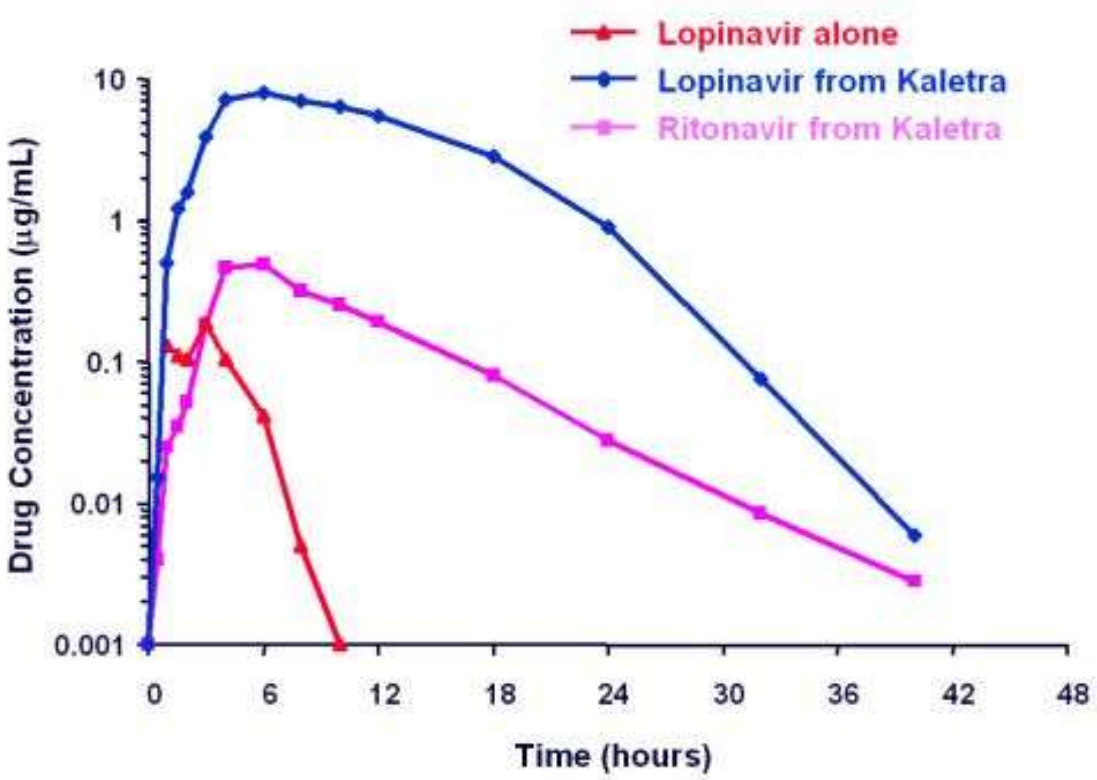
- **Disturbi gastro-intestinali:** Diarrea, meteorismo, nausea, dolori addominali. **Altro:** Rash, incremento delle transaminasi
- **Inibisce il citocromo p450.** **Dosaggio:** 750 mg/3 volte al giorno

Lopinavir (IP)



- Il lopinavir approvato in combinazione con il ritonavir (IP).
- **<u>Il metabolismo del Lopinavir è inibito dal Ritonavir (p450 3A4).</u>**

Lopinavir e Ritonavir (*Kaletra*)



Formulazione di Lopinavir (133,3 mg) associato a Ritonavir (33.3 mg). Finalità: **incrementare** le caratteristiche **farmacocinetiche (t/2)**, rendendo possibile la somministrazione bigiornaliera (il lopinavir ha emivita breve) ed il raggiungimento di concentrazioni minime più elevate. Questi vantaggi in termini farmacocinetici comportano un minor rischio di sviluppare resistenze.

Interazioni Kaletra

Table 2. Drugs that Should Not Be Administered Concomitantly with Lopinavir-Ritonavir[1]

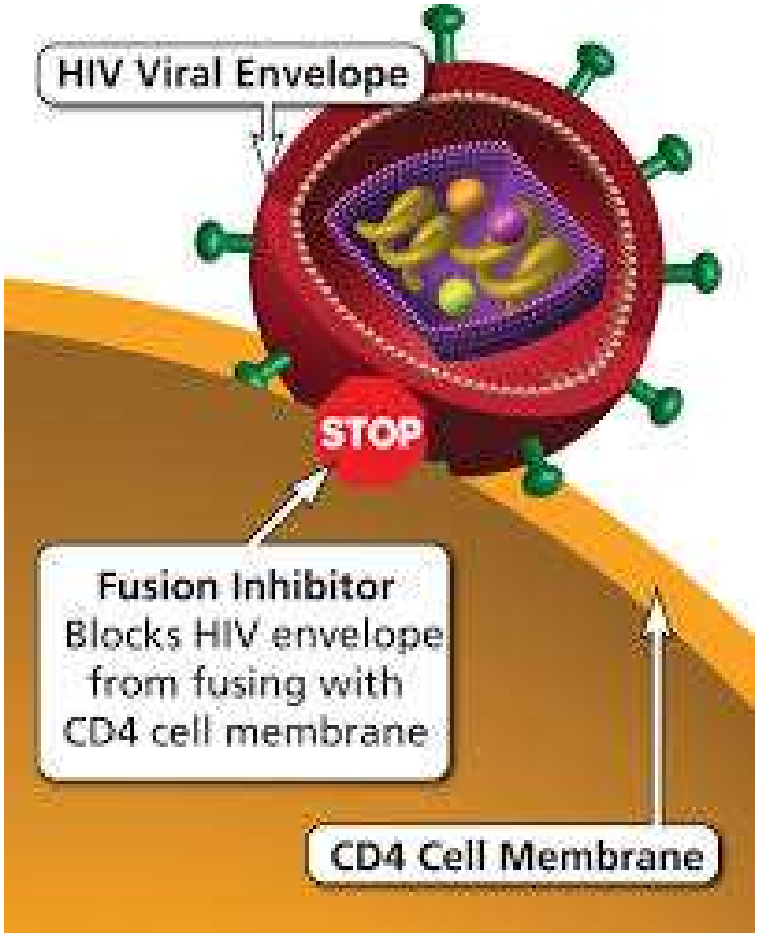
Drug Class, Drug Name	Comments
Antiarrhythmics Flecainide, propafenone	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antihistamines Astemizole,[a] terfenadine[a]	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial agent Rifampin	May lead to loss of virologic response and possible resistance to lopinavir-ritonavir, the class of protease inhibitors, or other coadministered antiretroviral agents.
Ergot derivatives Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues
Gastrointestinal motility agent Cisapride[a]	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal product St. John's Wort (*Hypericum perforatum*)	May lead to loss of virologic response and possible resistance to lopinavir-ritonavir or to the class of protease inhibitors.
HMG-CoA reductase inhibitors Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic Pimozide	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative-hypnotics Midazolam, triazolam	Contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.
[a]No longer available in the United States.

Effetti collaterali comuni degli IP

- **Iperglicemia:** sono stati segnalati casi di **peggioramento** dei valori glicemici in pazienti già diabetici, **e casi di nuova insorgenza di diabete**, compresi casi di chetoacidosi diabetica.
- **Lipodistrofia** (redistribuzione del grasso corporeo) e **dislipidemia:** sono stati riscontrati con aumentata frequenza in corso di terapia con IP. **L'ipertrigliceridemia e l'ipercolesterolemia** devono essere attentamente **valutati** per il rischio di **complicanze cardiovascolari**.
- Possibile aumento di **episodi emorragici** in pazienti con emofilia.

Inibitori della fusione

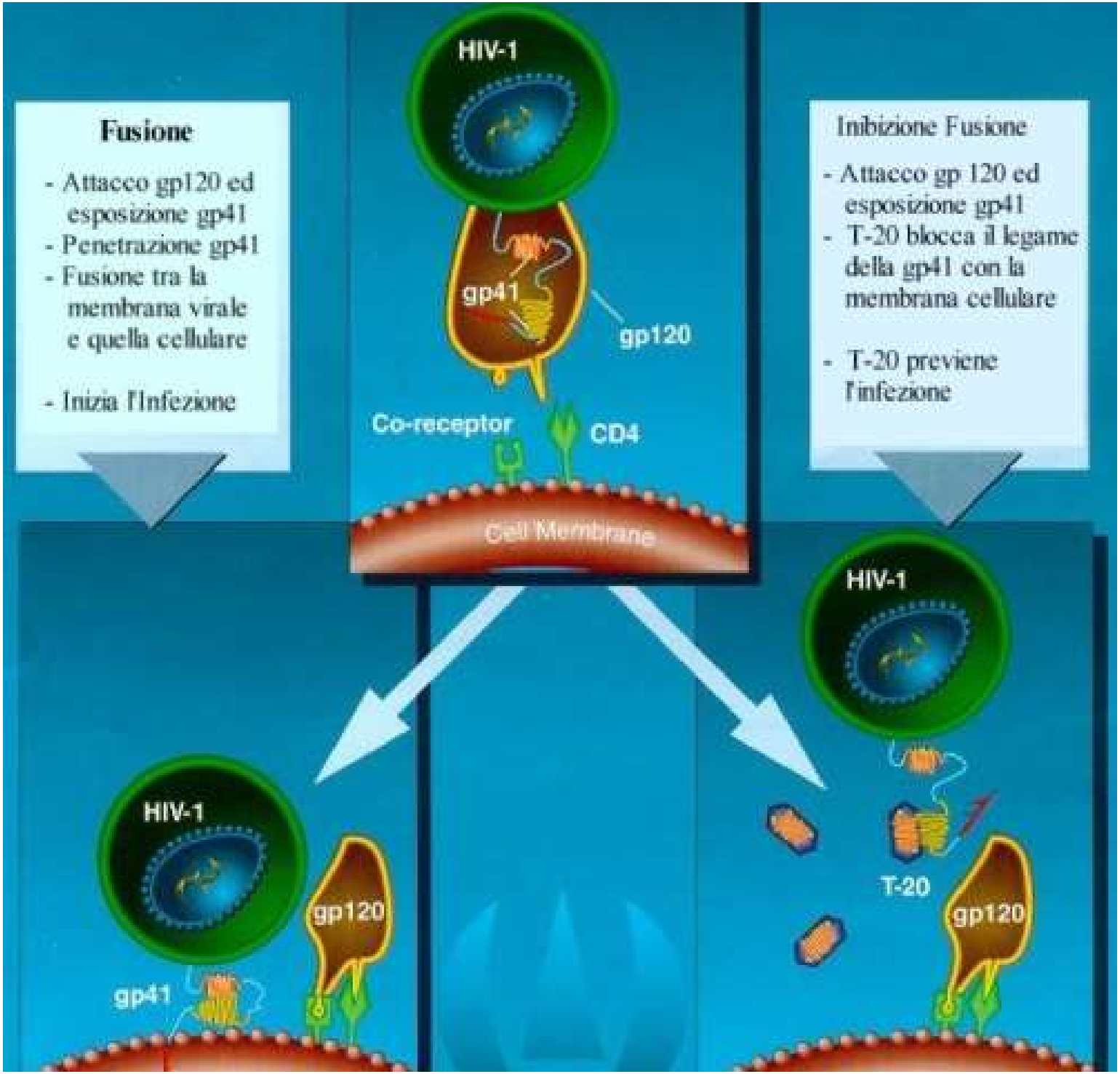


Discussion of the NIH AIDS research plan in the Oval Office of the White House on December 3, 1996. From left to right: Harold Varmus (NIH Director), Vice President Al Gore, Anthony S. Fauci, and President Bill Clinton.

Inibitori della Fusione
Enfuvirtide (T-20)

- Capostipite della classe degli **inibitori della fusione**. E' un peptide biomimetico di sintesi, **derivato dalla proteina transmembrana gp41 del virus HIV**.
  L'enfuvirtide lega la proteina virale gp41, impedendone il legame con la cellula e quindi bloccandone l'ingresso.

Meccanismo d'azione del T-20



Enfuvirtide

- In associazione con altri antiretrovirali in pz. che non hanno risposto positivamente (o intolleranti) a regimi contenenti almeno un antiretrovirale delle seguenti classi: inibitori della proteasi, inibitori nucleosidicidici (e non) della trascrittasi inversa.
- Nell'adulto, 90 mg/giorno s.c.
- Non influenza CYP3A4, CYP2D6, CYP1A2, CYP2C19 e CYP2E1

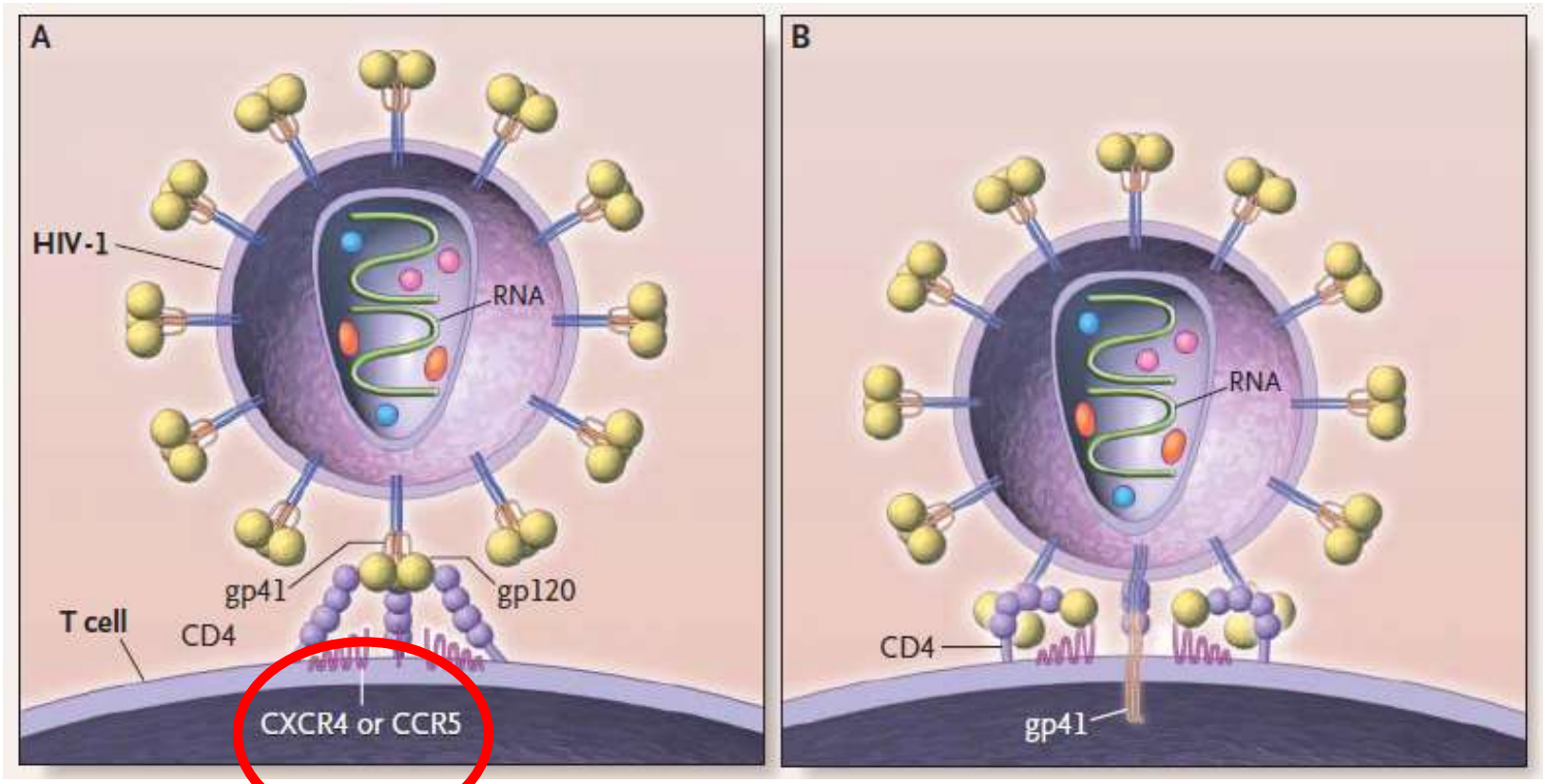
Assessment of drug-drug interaction potential of enfuvirtide in human immunodeficiency virus type 1–infected patients

Xiaoping Zhang, PhD, Jacob P. Lalezari, MD, Andrew D. Badley, MD, Albert Dorr, PhD, Stanley J. Kolis, MS, Tosca Kinchelow, MD, and Indravadan H. Patel, PhD

doi:10.1016/j.clpt.2004.02.003

Enfuvirtide

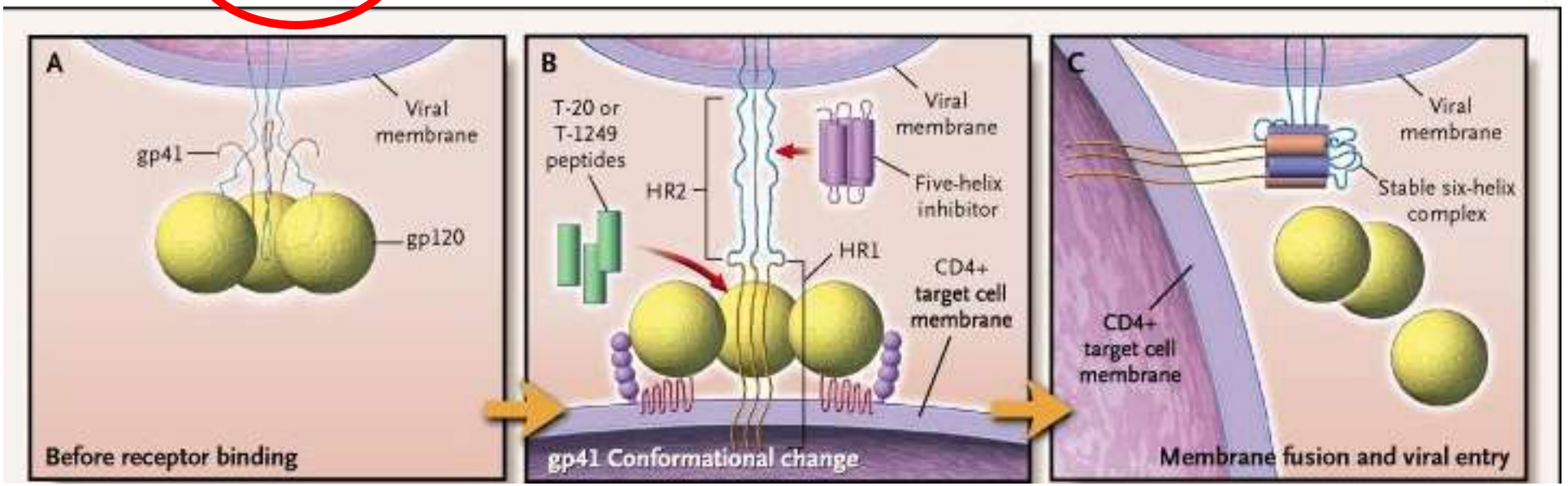
Effetti collaterali: Frequente (98 %) irritazione cutanea lieve-moderata nella sede di iniezione. Segnalate inoltre gravi reazioni allergiche con sintomi quali: febbre, difficoltà di respirazione, rash, presenza di sangue nelle urine.
Negli studi clinici eseguiti è stata notata una maggiore incidenza di polmoniti batteriche nei pazienti in trattamento con T-20.



TARGET:

CXCR4

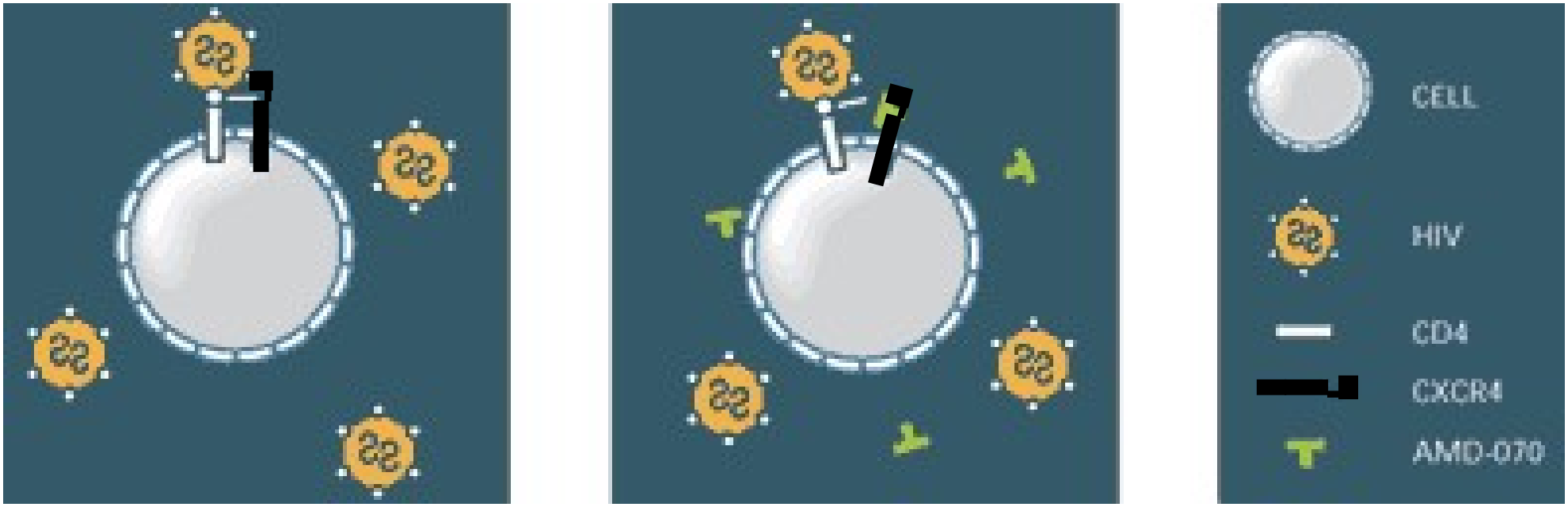
CCR5



Kilby & Eron : N Engl J Med

•CCR5 chemokine receptor 5; CXCR4 chemokine receptor 4.

AMD070 - un inibitore CXCR4



AMD070 previene l'adesione e l'ingresso del HIV nelle cellule CD4+ tramite l'interazione con il co-recettore CXCR-4, **sospeso in fase II.**

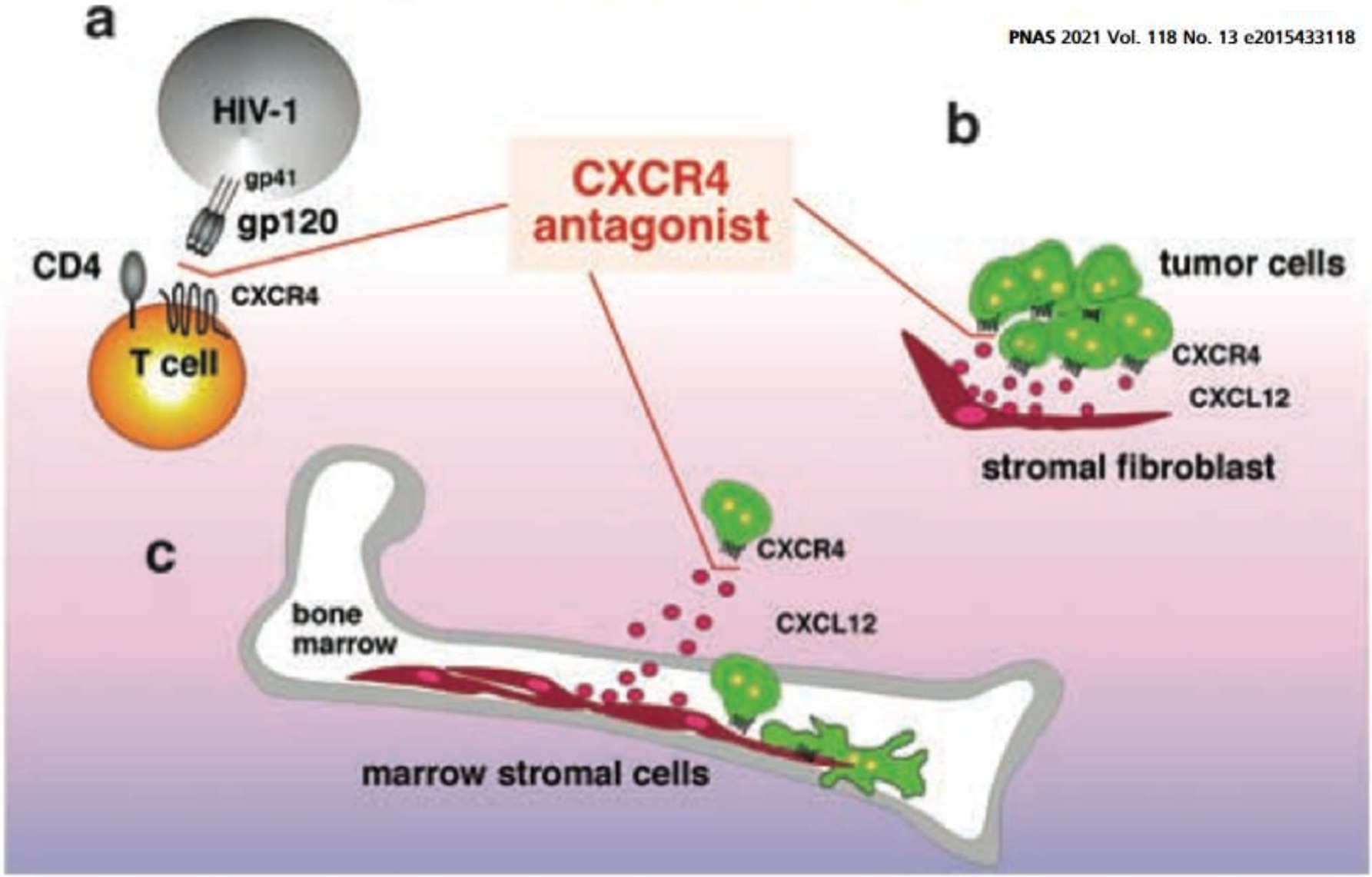
… *however, there is a clear preference for HIV to use CCR5 over CXCR4, rendering CCR5 as the more desirable drug target.* Kim et al., 2016.

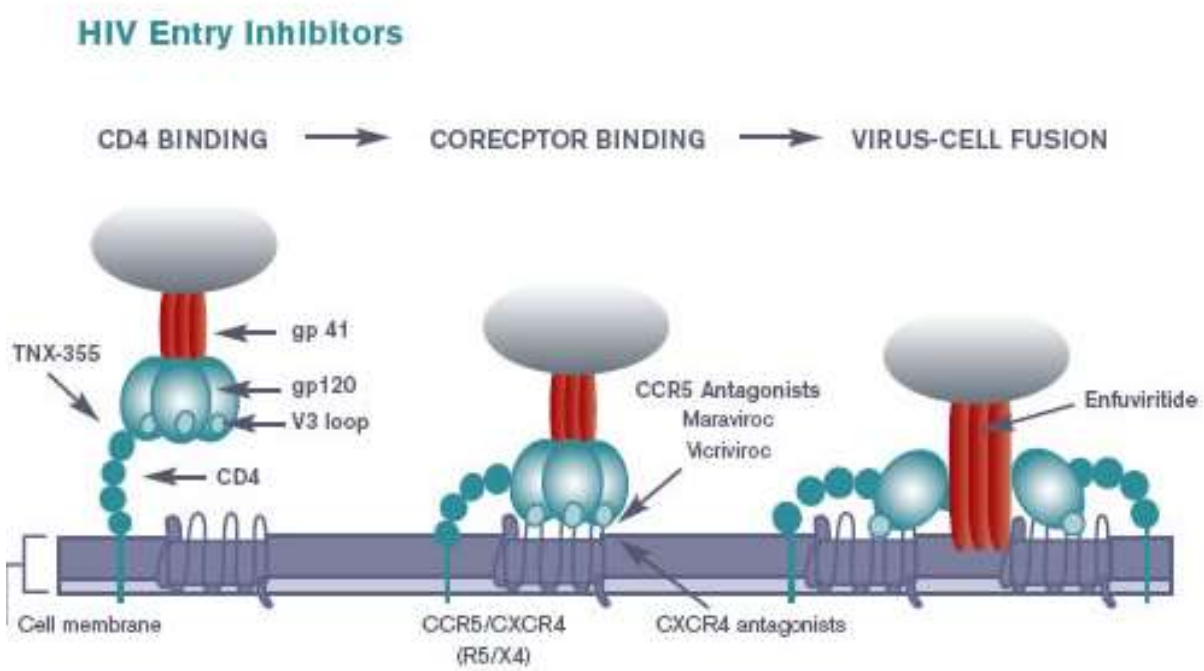
doi: [10.1080/13543784.2016.1254615]

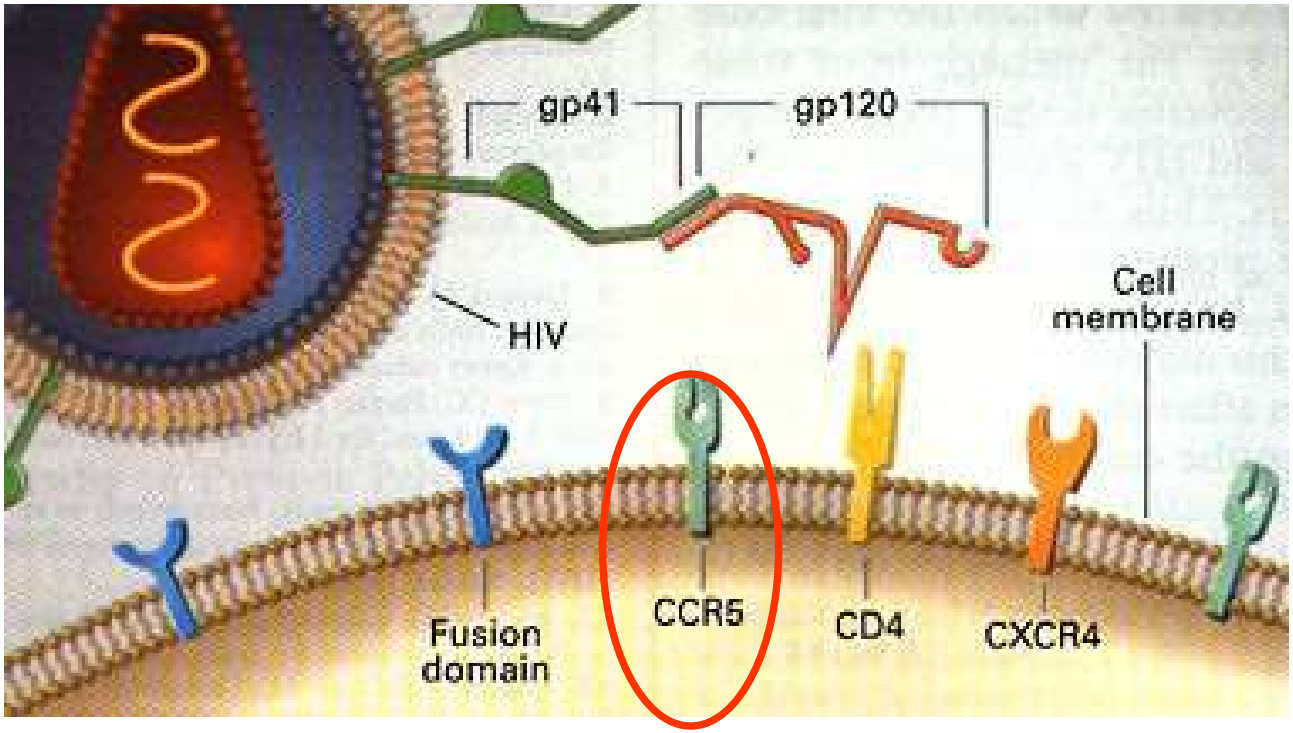
A highly selective and potent CXCR4 antagonist for hepatocellular carcinoma treatment

Jen-Shin Song[a,1], Chih-Chun Chang[b,1], Chien-Huang Wu[a,1], Trinh Kieu Dinh[b], Jiing-Jyh Jan[a], Kuan-Wei Huang[b], Ming-Chen Chou[a], Ting-Yun Shiue[b], Kai-Chia Yeh[a], Yi-Yu Ke[a], Teng-Kuang Yeh[a], Yen-Nhi Ngoc Ta[b], Chia-Jui Lee[a], Jing-Kai Huang[a], Yun-Chieh Sung[b], Kak-Shan Shia[a,2], and Yunching Chen[b,2]

PNAS 2021 Vol. 118 No. 13 e2015433118





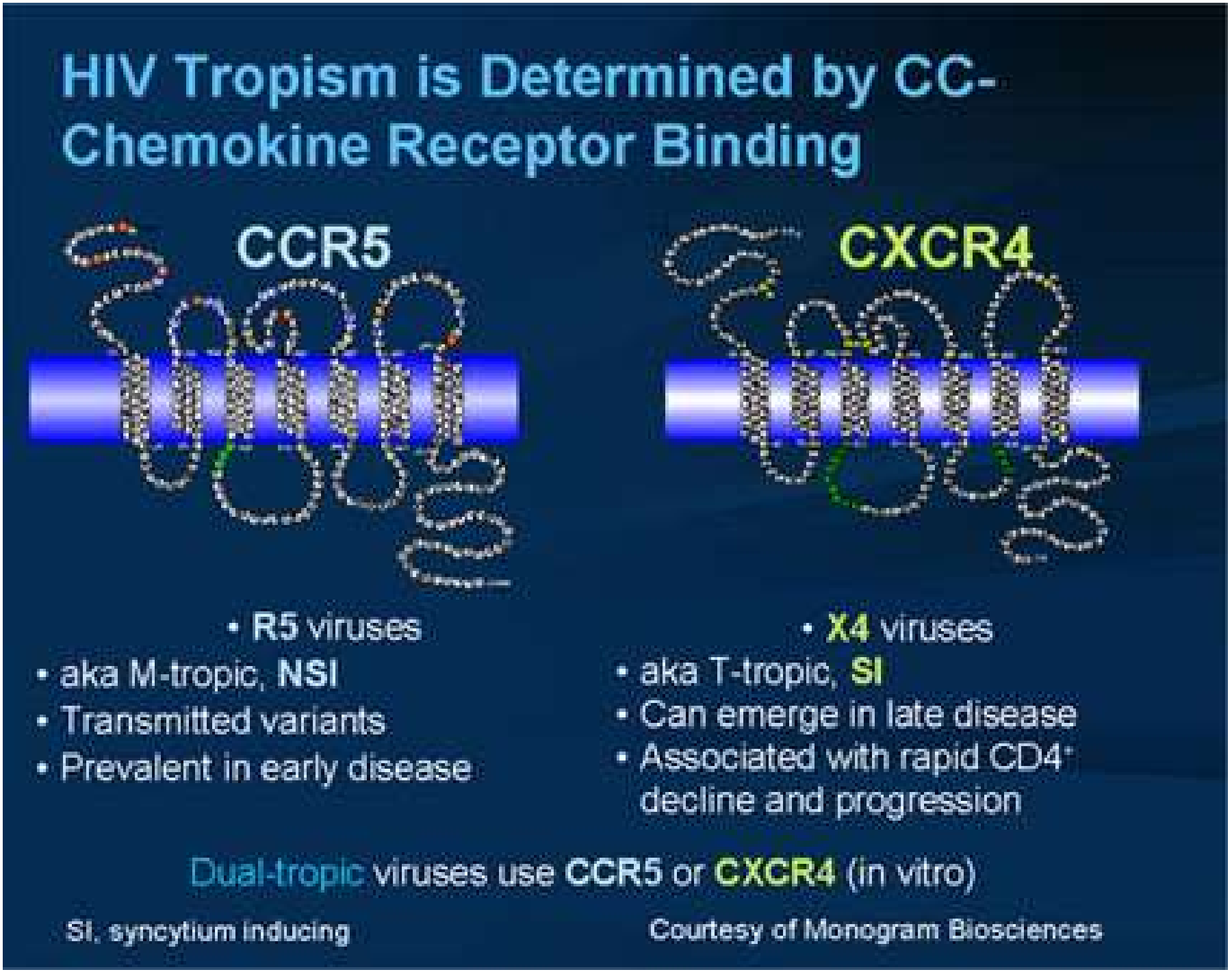


Maraviroc (*Celsentri*) è un antagonista del corecettore CCR5. Agisce interferendo con il processo di "ingresso" nella cellula bloccando il corecettore fondamentale per questo processo.

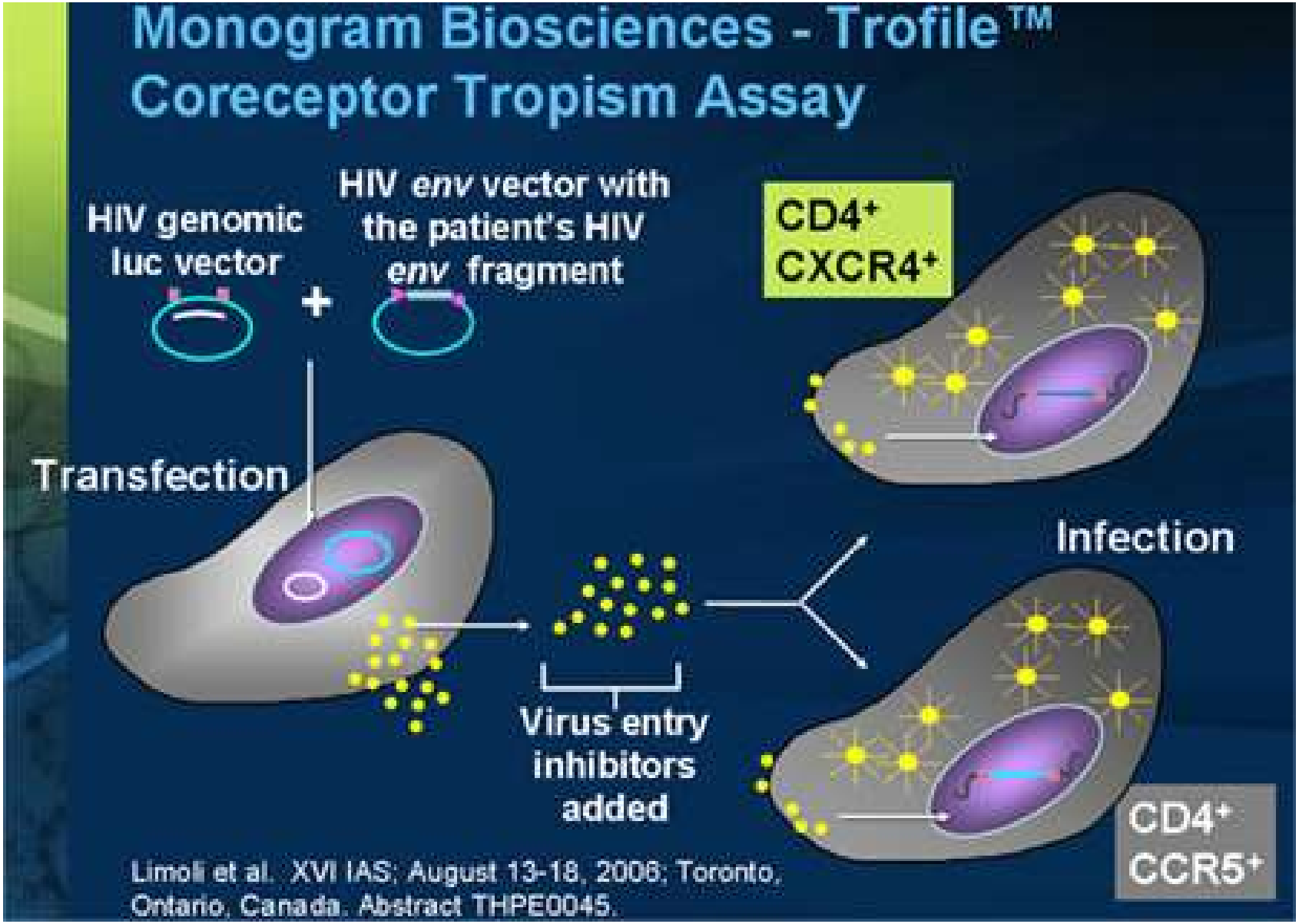
Maraviroc

- Prima di iniziare il trattamento con Maraviroc è necessario confermare che è presente solo un'infezione causata dal virus HIV-1 CCR5-tropico utilizzando un test adeguatamente validato e sensibile su un campione di sangue appena prelevato.

Razionale alla base della scelta dell'inibitore fusione



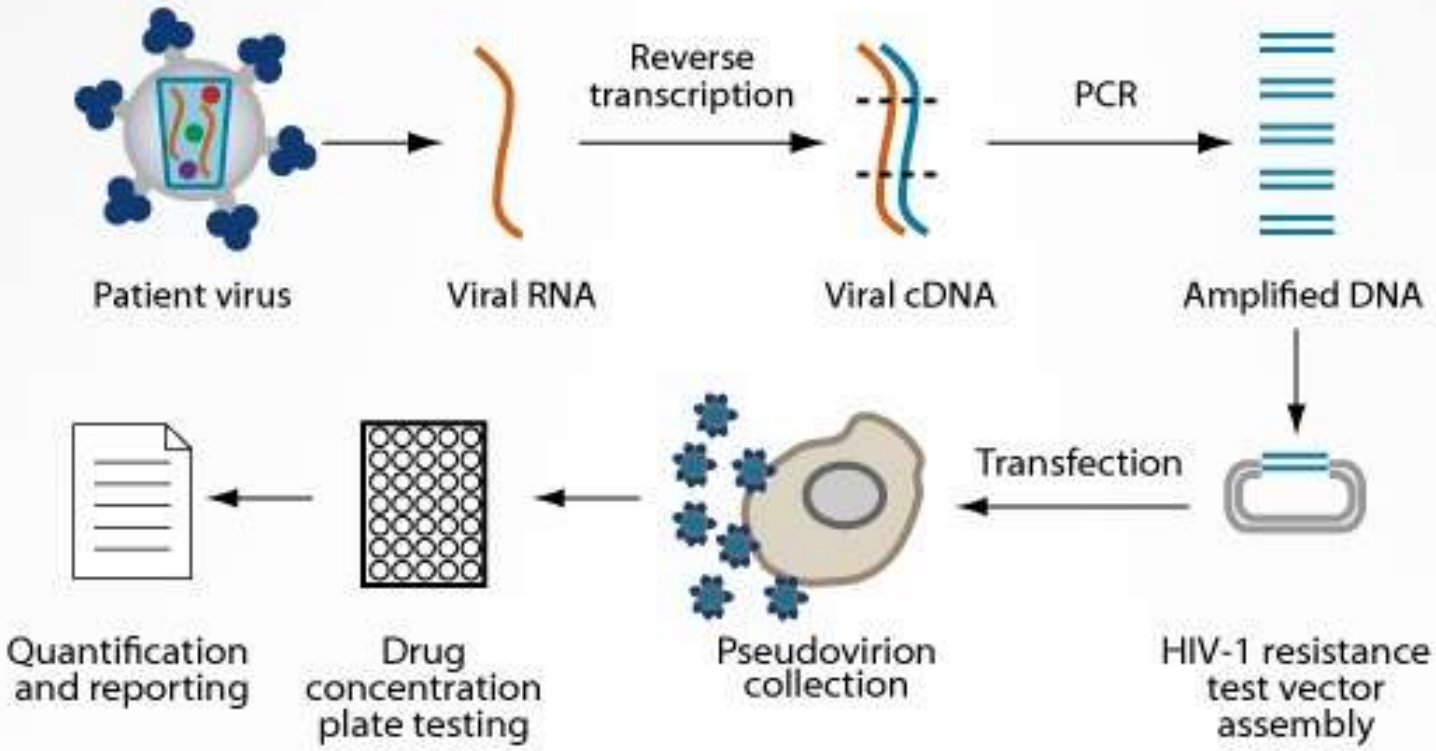
Il virus dell'HIV può essere CCR5-tropico, se utilizza il co-recettore CCR5, X4-tropico se utilizza il co-recettore CXCR4, e duplice/misto (DM-tropico) se utilizza entrambi i co-recettori



Monogram BIOSCIENCES
LabCorp Specialty Testing Group

HIV Phenotypic Testing

Phenotypic testing is one of two types of HIV drug resistance testing. Phenotypic testing is performed by exposing a sample of an individual's HIV to all of the available antiretroviral drugs.



By directly measuring the ability of HIV to grow in the presence of these drugs, scientists can determine which drugs will work, and which viruses are no longer responsive to the current regimen. The activity of a patient's HIV in the presence of the antiretroviral drugs is compared to the activity of a control strain of HIV that is known to be susceptible to a specific drug. This comparison can determine how likely or unlikely a person is to respond to that drug. The results of phenotypic testing can be used by a health care team to select the most active antiretroviral regimen for a particular individual.

Maraviroc

metabolizzato da CYP 3A4 e CYP3A5

Dosaggio (p.o.):

3.3 Recommended Dosage in Adults

Table 1 displays oral dosage of maraviroc based on different concomitant medications [see Drug Interactions (7.1)].

Table 1. Recommended Dosage in Adults

Concomitant Medications	Dosage of SELZENTRY
Potent CYP3A inhibitors (with or without a potent CYP3A inducer) including: • protease inhibitors (except tipranavir/ritonavir) • delavirdine • elvitegravir/ritonavir • ketoconazole, itraconazole, clarithromycin • other potent CYP3A inhibitors (e.g., nefazodone, telithromycin) • boceprevir	150 mg twice daily
Noninteracting concomitant medications, including tipranavir/ritonavir, nevirapine, raltegravir, all nucleoside reverse transcriptase inhibitors (NRTIs), and enfuvirtide[a]	300 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor) including: • efavirenz • rifampin • etravirine • carbamazepine, phenobarbital, and phenytoin	600 mg twice daily

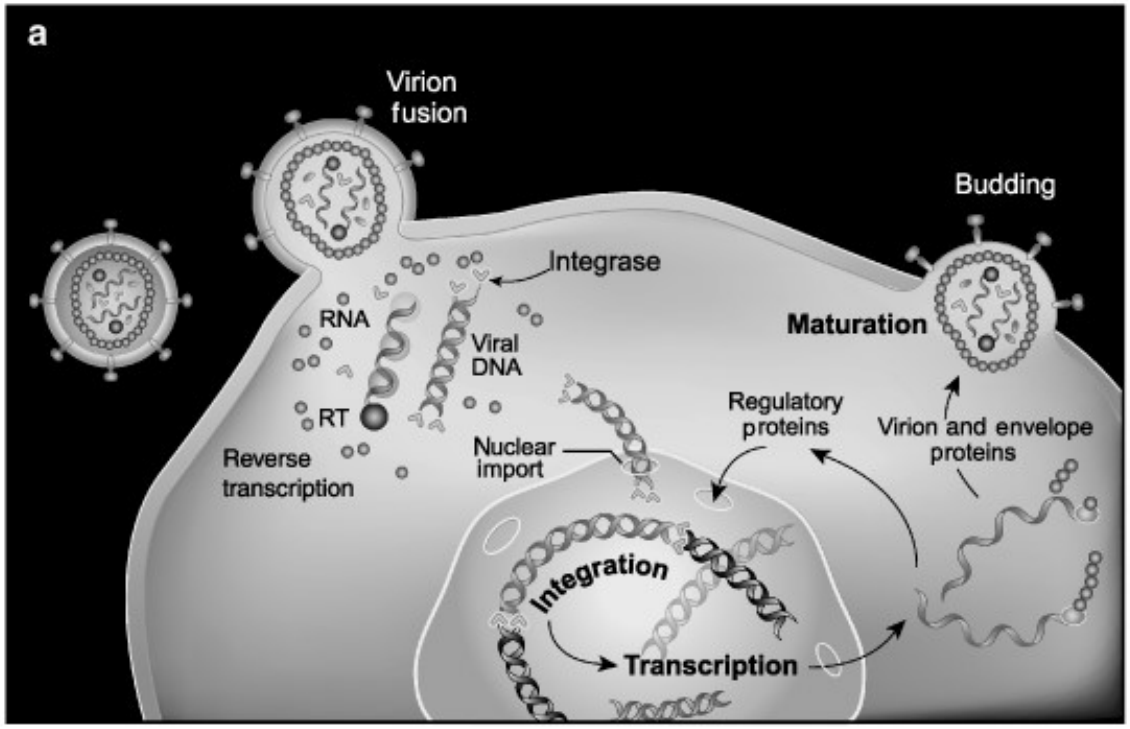
a Noninteracting concomitant medications include all medications that are not potent CYP3A inhibit inducers.

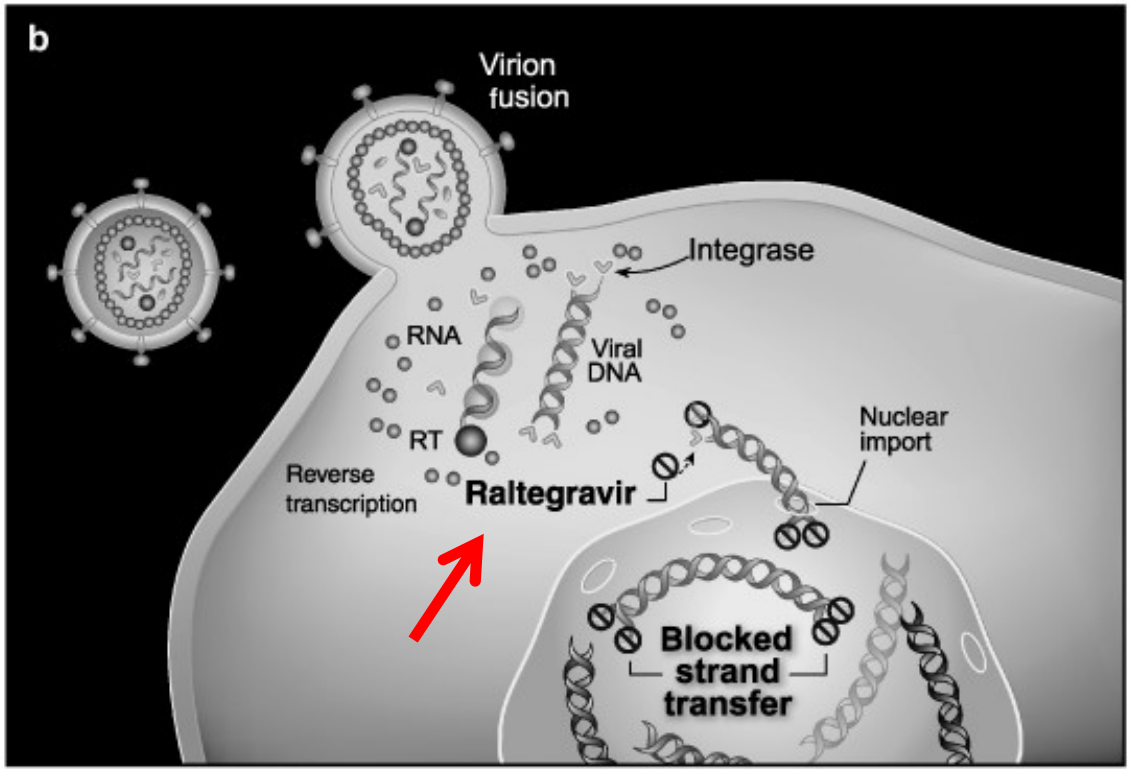
Nei pazienti adulti con **clearance della creatinina <80 mL/min**, che sono anche in trattamento con inibitori potenti del CYP3A4, l'intervallo della dose di maraviroc deve essere aggiustato a 150 mg **una volta al giorno.**

Maraviroc

Principali reazioni avverse:

- Anemia
- Anoressia
- Depressione, insonnia
- Dolore addominale, flatulenza, nausea
- Aumento di alanina aminotransferasi, aumento di aspartato aminotransferasi
- Rash
- Astenia





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 24, 2008 VOL. 359 NO. 4

Raltegravir with Optimized Background Therapy for Resistant HIV-1 Infection

Roy T. Steigbigel, M.D., David A. Cooper, M.D., D.Sc., Princy N. Kumar, M.D., Joseph E. Eron, M.D., Mauro Schechter, M.D., Ph.D., Martin Markowitz, M.D., Mona R. Loutfy, M.D., M.P.H., Jeffrey L. Lennox, M.D.

- Raltegravir (*Isentress*) è il primo farmaco ad essere approvato di una particolare classe di antiretrovirali, gli **inibitori dell'integrasi.**
- Agisce **inibendo l'inserzione** del DNA dell'HIV nel DNA umano, per mezzo dell'enzima integrasi.
- Inibendo l'integrasi da questa funzione essenziale, limita l'abilità del virus di replicare e di infettare nuove cellule.
- La Food and Drug Administration concesse **un'autorizzazione accelerata** alla commercializzazione del Raltegravir per l'impiego nella terapia antiretrovirale **combinata**, solamente in pazienti adulti pre-trattati, con **resistenze ad altri farmaci antiretrovirali (per ostacolare resistenza)**.

Raltegravir

Di norma, in associazione con altre terapie antiretrovirali.

Dosaggio: 400 mg due volte al giorno (p.o.).

Eliminato per glucuronidazione

Scarse (nulle) interazioni farmacometaboliche

Considerevole variabilità farmacocinetica inter- e intra-individuale.

Principali effetti collaterali:

- diminuzione dell'appetito
- insonnia, incubi, comportamento anormale, depressione
- capogiro, cefalea, iperattività psicomotoria
- vertigini
- distensione addominale, dolore addominale, diarrea, flatulenza, nausea, vomito, dispepsia
- eruzione cutanea
- astenia, affaticamento, piressia

SIMIT
Società Italiana
di Malattie Infettive
e Tropicali

In collaborazione con:

Ministero della Salute

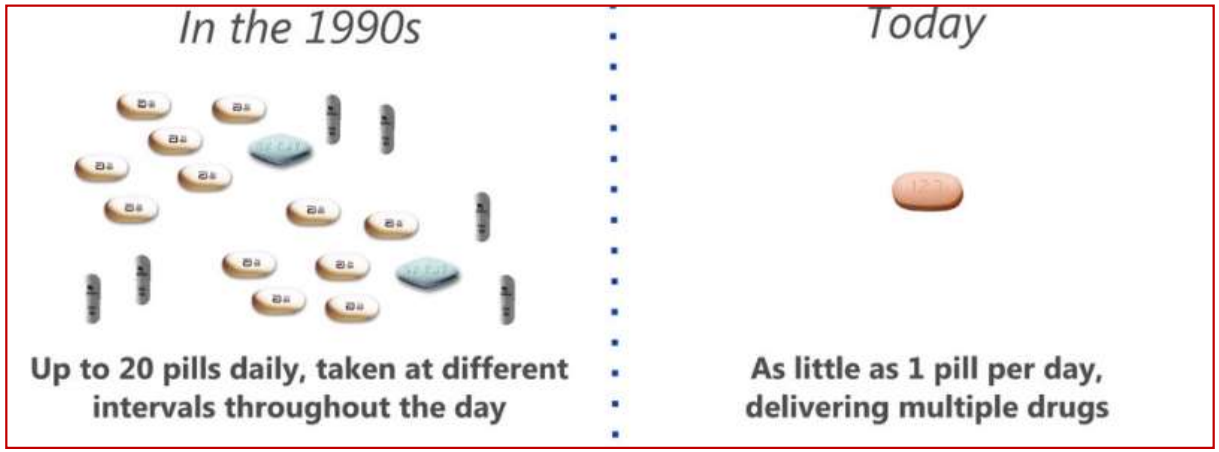
Sezioni L e M del Comitato Tecnico Sanitario

Linee Guida Italiane sull'utilizzo della Terapia Antiretrovirale e la gestione diagnostico-clinica delle persone con infezione da HIV-1

Edizione 2017

Dicembre 2021: nessun aggiornamento.

Razionale:



Fixed Dose Combination Antiretroviral Products

Fixed-dose combination tablets contain two or more medications from one or more drug classes.

These medications may be used as single tablet regimens because they contain multiple antiretroviral drugs that make a full regimen for some patients.

Abacavir/Dolutegravir/ Lamivudine

trade name: TRIUMEQ

600 mg/50 mg/300 mg Triumeq tablet (abacavir/dolutegravir/lamivudine)

Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir DF

trade name: STRIBILD

150 mg/150 mg/200 mg/300 mg Stribild tablet (elvitegravir/cobicistat/ emtricitabine/tenofovir DF)

Emtricitabine/Rilpivirine/ Tenofovir Alafenamide

trade name: ODEFSEY

200 mg/25 mg/25 mg Odefsey tablet (emtricitabine/rilpivirine/tenofovir alafenamide)

Efavirenz/Emtricitabine/ Tenofovir DF

trade name: ATRIPLA

600 mg/200 mg/300 mg Atripla tablet (efavirenz/emtricitabine/tenofovir DF)

Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide

trade name: GENVOYA

150mg/150mg/200mg/10mg Genvoya tablet (elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide)

Emtricitabine/Rilpivirine/ Tenofovir DF

trade name: COMPLERA

200mg/25mg/300mg Complera tablet (emtricitabine/rilpivirine/tenofovir DF)

NRTI Combinations

Abacavir/Lamivudine

trade name: EPZICOM

600 mg/300 mg Epzicom tablet (abacavir/lamivudine)

Abacavir/Lamivudine/ Zidovudine

trade name: TRIZIVIR

300 mg/150 mg/300 mg Trizivir tablet (abacavir/lamivudine/ zidovudine)

Emtricitabine/Tenofovir Alafenamide

trade name: DESCOVY

200 mg/25 mg Descovy tablet (emtricitabine/tenofovir alafenamide)

Emtricitabine/Tenofovir DF

trade name: TRUVADA

200 mg/300 mg Truvada tablet (emtricitabine/tenofovir DF)

100 mg/150 mg Truvada tablet (emtricitabine/tenofovir DF)

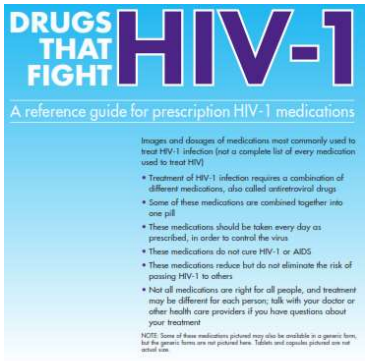
167 mg/250 mg Truvada tablet (emtricitabine/tenofovir DF)

133 mg/200 mg Truvada tablet (emtricitabine/tenofovir DF)

Lamivudine/Zidovudine

trade name: COMBIVIR

150 mg/300 mg Combivir tablet (lamivudine/ zidovudine)



NIH...Turning Discovery into Health®
Published by The U.S. Department of Health and Human Services

NIH National Institute of Allergy and Infectious Diseases

A program of the National Institutes of Health

PK-enhanced PI Formulations

Atazanavir/Cobicistat

trade name: EVOTAZ

300 mg/150 mg Evotaz tablet (atazanavir/cobicistat)

Darunavir/Cobicistat

trade name: PREZCOBIX

800 mg/150 mg Prezcobix tablet (darunavir/cobicistat)

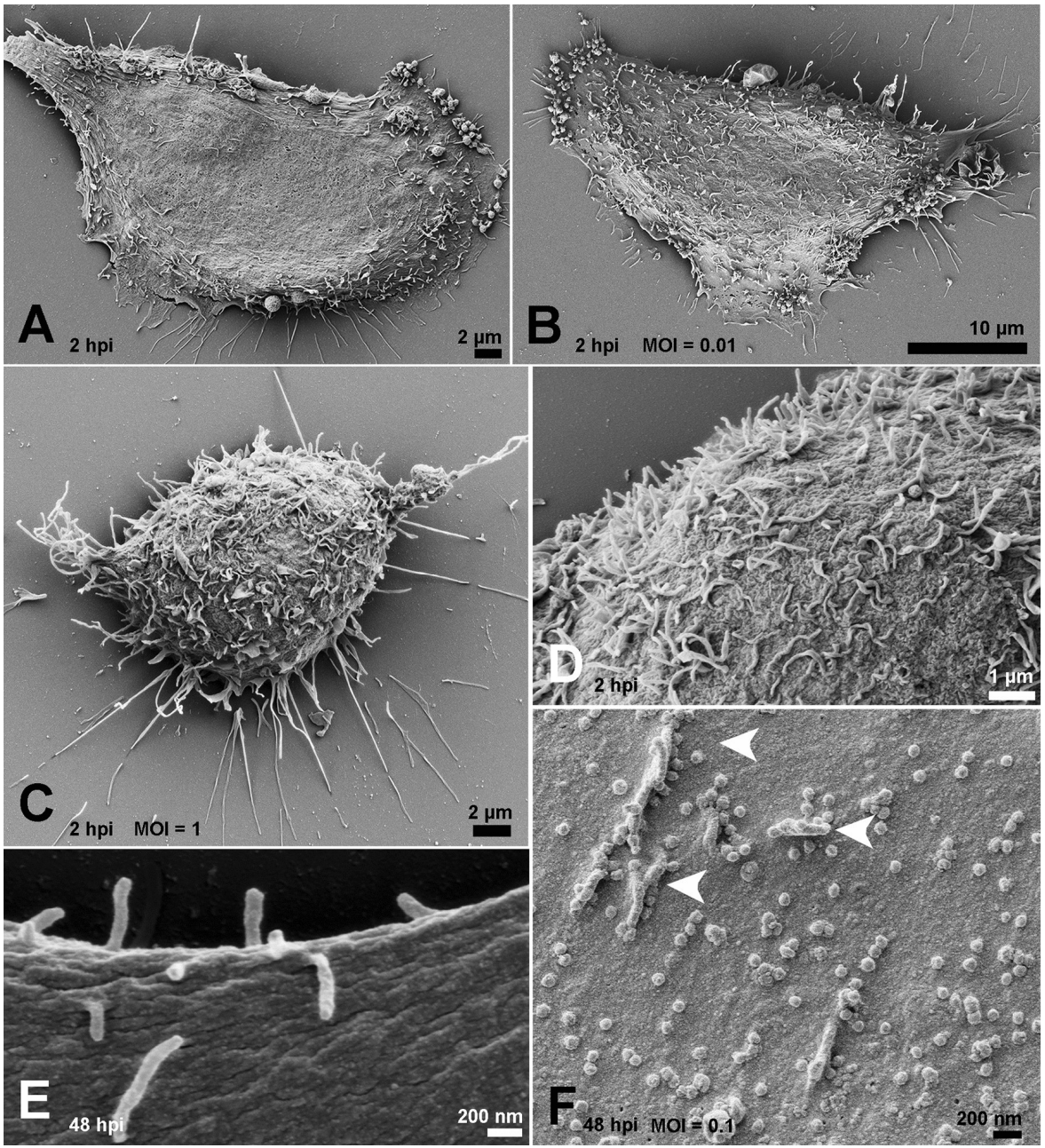
Lopinavir/Ritonavir

trade name: KALETRA

100 mg/25 mg Kaletra tablet (lopinavir/ritonavir)

200 mg/50 mg Kaletra tablet (lopinavir/ritonavir)

80 mg/20 mg/mL Kaletra oral solution (lopinavir/ritonavir)



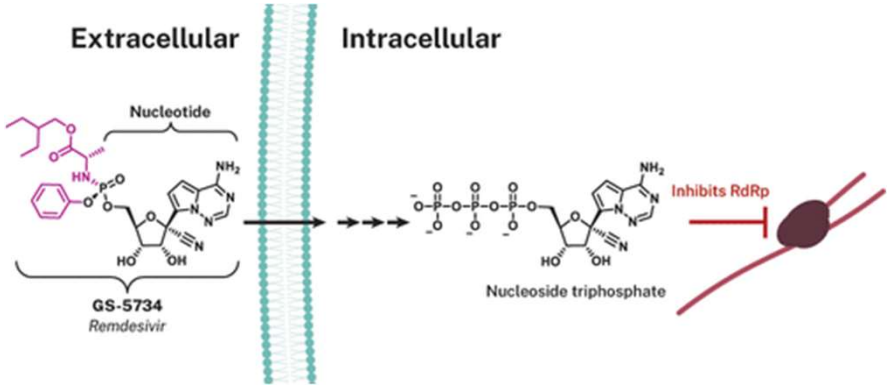
Ultrastructural analysis of SARS-CoV-2 interactions with the host cell via high resolution scanning electron microscopy

Lucio Ayres Caldas[1,5,6✉], Fabiana Avila Carneiro[6], Luiza Mendonça Higa[2], Fábio Luiz Monteiro[2], Gustavo Peixoto da Silva[3], Luciana Jesus da Costa[3], Edison Luiz Durigon[4], Amilcar Tanuri[2] & Wanderley de Souza[1,5]

SCIENTIFIC REPORTS | (2020) 10:16099

Remdesivir

- Remdesivir trifosfato agisce come un analogo dell'ATP e compete con il substrato naturale dell'ATP per l'incorporazione nelle catene di RNA nascente da parte della RNA-polimerasi RNA-dipendente virale (RdRp).
- Sottoposto a test clinici durante l'epidemia del virus Ebola nel periodo 2013-2016.



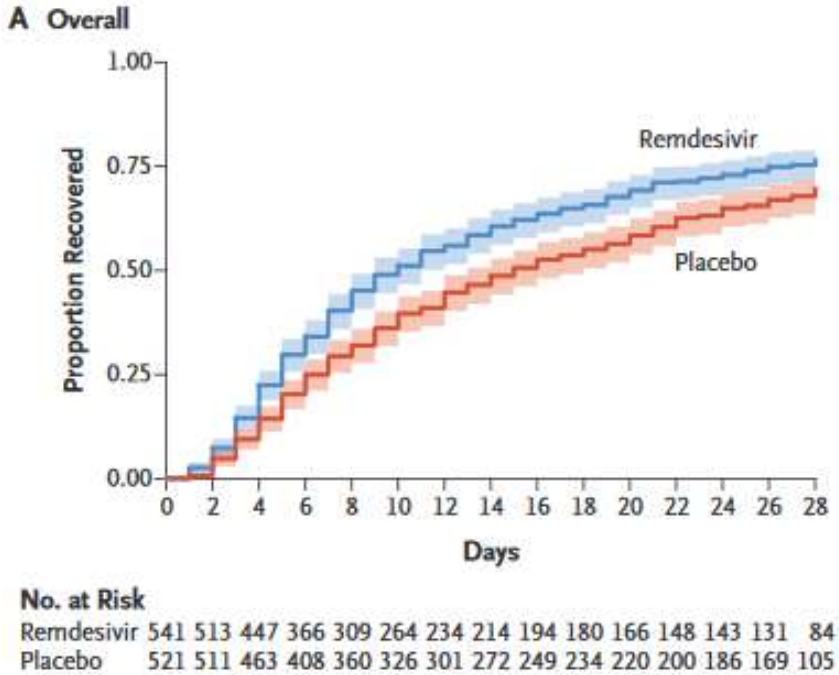
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2020 VOL. 383 NO. 19

Remdesivir for the Treatment of Covid-19 — Final Report

CONCLUSIONS

Our data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

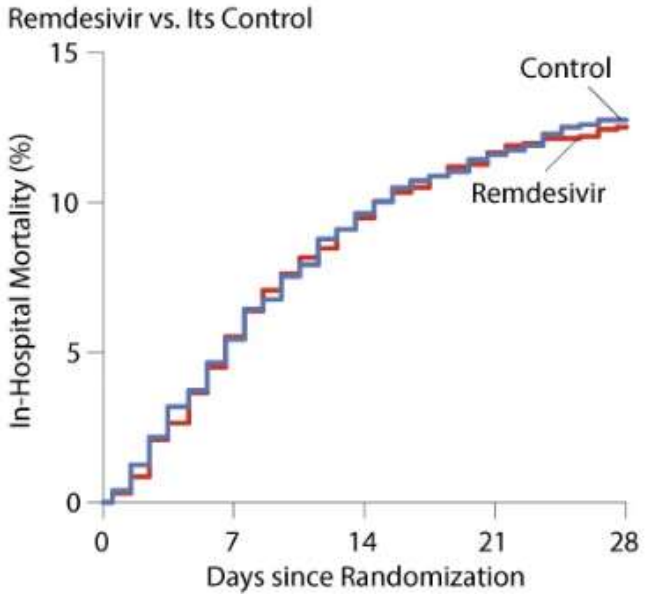
Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

CONCLUSIONS

These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. (Funded by the World Health Organization; ISRCTN Registry number, ISRCTN83971151; ClinicalTrials.gov number, NCT04315948.)

This article was published on December 2, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2023184



?

1 ACTT-1, which examined remdesivir, was placebo-controlled,[9] which avoids any bias in time to discharge. In that trial, however, the proportion of lower-risk patients (i.e., those not already receiving high-flow oxygen or ventilation) happened to be appreciably greater in the remdesivir group than in the placebo group. This chance imbalance might account for some of the differences in time to recovery between ACTT-1 and the Solidarity trial.

December 2, 2020
DOI: 10.1056/NEJMoa2023184

1. In quello studio ***(ACTT-1)***, tuttavia, la proporzione di pazienti a basso rischio (cioè quelli che non ricevevano già ossigeno o ventilazione ad alto flusso) si è rivelata sensibilmente maggiore nel gruppo remdesivir rispetto al gruppo placebo**. Questo squilibrio potrebbe spiegare alcune delle differenze nel tempo di recupero tra ACTT-1 e lo studio Solidarity.**

2 For each of these four repurposed nonspecific antivirals, several thousand patients have now undergone randomization in various trials. The unpromising overall findings from the regimens tested suffice to refute early hopes, based on smaller or nonrandomized studies, that any of these regimens will substantially reduce inpatient mortality, the initiation of mechanical ventilation, or hospitalization duration. Narrower confidence intervals would be helpful (particularly for remdesivir), but the main need is for better treatments. The Solidarity trial has been recruiting approximately 2000 patients per month, and efficient factorial designs may allow it to assess further treatments, such as immune modulators or anti–SARS-Cov-2 monoclonal antibodies.

December 2, 2020
DOI: 10.1056/NEJMoa2023184

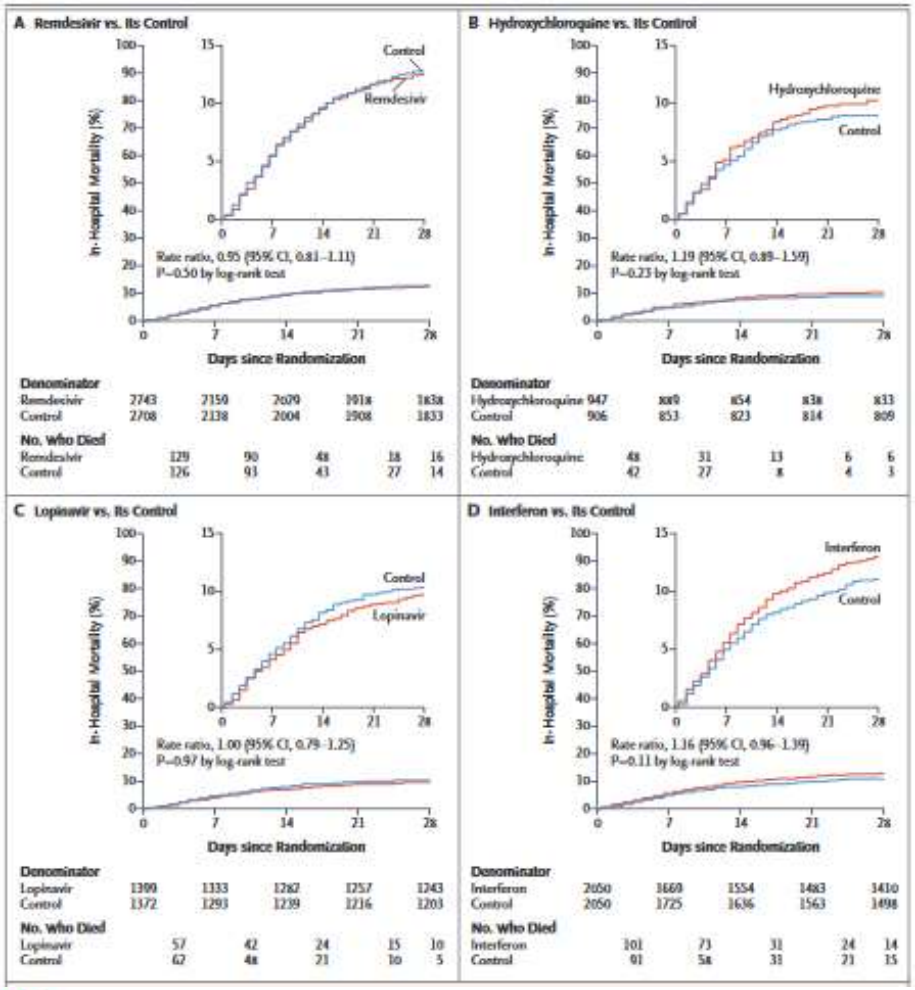
2. Per ciascuno di questi quattro antivirali non specifici riproposti, diverse migliaia di pazienti sono stati ora valutati in vari studi randomizzati**. I risultati complessivi poco promettenti dei regimi testati sono sufficienti a confutare le prime speranze, basate su studi più piccoli o non randomizzati, che uno qualsiasi di questi regimi riduca sostanzialmente la mortalità dei pazienti, l'inizio della ventilazione meccanica o la durata del ricovero.**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 11, 2021 VOL. 384 NO. 6

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*



CONCLUSIONS

These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. (Funded by the World

Remdesivir for severe covid-19: a clinical practice guideline

Bram Rochwerg,[1,2] Arnav Agarwal,[1,3] Linan Zeng,[1,4] Yee-Sin Leo,[5] John Adabie Appiah,[6]

BMJ 2020 ; 371

Population

This recommendation applies only to people with these characteristics:

Disease severity

Mild | Moderate | Severe

Does not apply to:

- ✖ Patients with mild or moderate covid-19
- ✖ Pediatric patients

Applies to people with at least one of:

- ✔ Respiratory rate >30
- ✔ Respiratory distress
- ✔ SpO_2 <94% on room air
- ✔ Requires intensive care admission

⚠ Resource limited settings

Recommendation 1

Usual supportive care
No remdesivir

Strong | Weak

or

Remdesivir
100 mg intravenously daily for 5-10 days

Weak | Strong

> We suggest remdesivir rather than no remdesivir in patients with severe covid-19

Recommendation 2

> Randomised controlled trials examining remdesivir in patients with covid-19 should continue pending further data

Further information is necessary to raise the quality of evidence for all outcomes

Further information is required to identify subgroups of covid-19 patients that are more or less likely to benefit from therapy

Need for further evidence

We place a high value on ensuring that, ultimately, high quality evidence will be available regarding the impact of remdesivir on all critical outcomes. This is necessary to ensure that we will be able to make wise decisions regarding the relative merits of emerging treatments. For example, establishing the magnitude of impact (if any) of remdesivir on mortality will be crucial

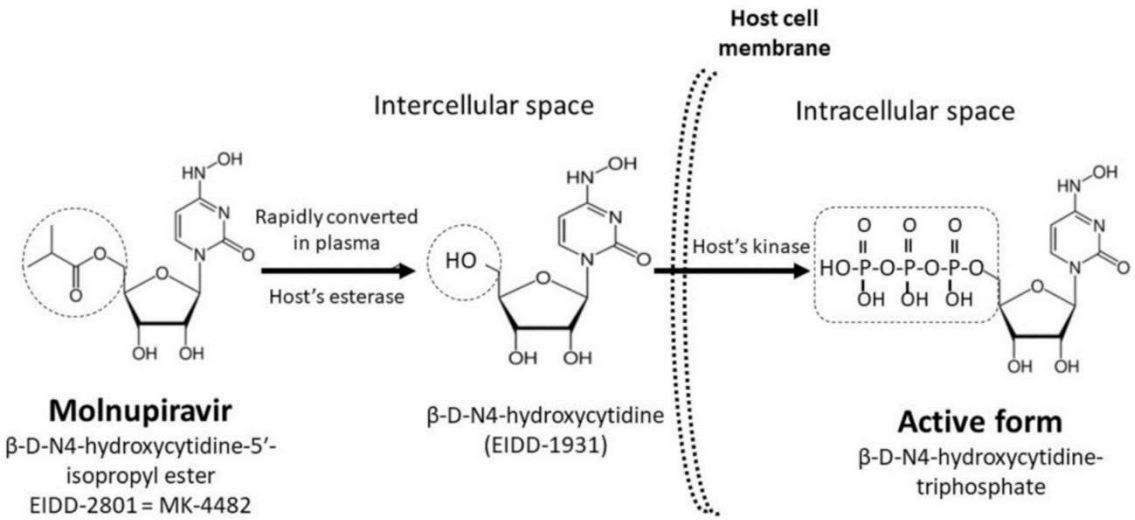
Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis

ARTICLES
https://doi.org/10.1038/s41594-021-00651-0
nature structural & molecular biology

Florian Kabinger[1,5], Carina Stiller[2,5], Jana Schmitzová[1,5], Christian Dienemann[1], Goran Kokic[1], Hauke S. Hillen[3,4], Claudia Höbartner[2]✉ and Patrick Cramer[1]✉

Molnupiravir is an orally available antiviral drug candidate currently in phase III trials for the treatment of patients with COVID-19. Molnupiravir increases the frequency of viral RNA mutations and impairs SARS-CoV-2 replication in animal models and in humans. Here, we establish the molecular mechanisms underlying molnupiravir-induced RNA mutagenesis by the viral RNA-dependent RNA polymerase (RdRp). Biochemical assays show that the RdRp uses the active form of molnupiravir, β-D-N^4-hydroxycytidine (NHC) triphosphate, as a substrate instead of cytidine triphosphate or uridine triphosphate. When the RdRp uses the resulting RNA as a template, NHC directs incorporation of either G or A, leading to mutated RNA products. Structural analysis of RdRp–RNA complexes that contain mutagenesis products shows that NHC can form stable base pairs with either G or A in the RdRp active center, explaining how the polymerase escapes proofreading and synthesizes mutated RNA. This two-step mutagenesis mechanism probably applies to various viral polymerases and can explain the broad-spectrum antiviral activity of molnupiravir.

NATURE STRUCTURAL & MOLECULAR BIOLOGY | VOL 28 | SEPTEMBER 2021 | 740–746 | www.nature.com/nsmb



Inibitore dell'RNA polimerasi virale che interferisce con la produzione dell'RNA virale. Interferendo con la produzione dell'RNA del SARS CoV 2, si ritiene che molnupiravir impedisca la replicazione del virus.

MENU

Agenzia Italiana del Farmaco

Home > Sicurezza dei farmaci > COVID-19: aggiornamento EMA-HMA su molnupiravir

COVID-19: aggiornamento EMA-HMA su molnupiravir

Revisione EMA a sostegno di possibili decisioni nazionali sull'uso precoce

L'Agenzia europea per i medicinali (EMA) e i capi delle agenzie per i medicinali (HMA) hanno convenuto sulla necessità di ulteriori raccomandazioni sui trattamenti contro COVID-19 alla luce dell'aumento dei tassi di infezione e dei decessi dovuti alla malattia in tutta l'UE.

A tal fine, l'EMA ha avviato la revisione dei dati disponibili sull'uso di molnupiravir (anche noto come MK 4482 o Lagevrio) per supportare le autorità nazionali che potrebbero decidere di impiegare il medicinale per il trattamento di COVID-19 prima della sua autorizzazione.

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Covid-19: FDA expert panel recommends authorising molnupiravir but also voices concerns

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Merck's COVID pill loses its lustre: what that means for the pandemic

Molnupiravir was initially heralded by public-health officials as a game-changer for COVID-19, but full clinical-trial data showed lower-than-expected efficacy.

The results, released ahead of the advisory committee meeting, showed that the antiviral, which was developed by the pharmaceutical firm Merck, based in Kenilworth, New Jersey, and the biotechnology company Ridgeback Biotherapeutics in Miami, Florida, decreased the risk of hospitalization from COVID-19 by 30% – down from a 50% reduction observed early in the trial. "That's not all that good," says Katherine Seley-