



ANTIVIRAUX ACTIFS SUR LE VIRUS HIV ET PHARMACOTHERAPIE DU SIDA

Enseignant : F. Van Bambeke

FARM2129 – année 2009-2010

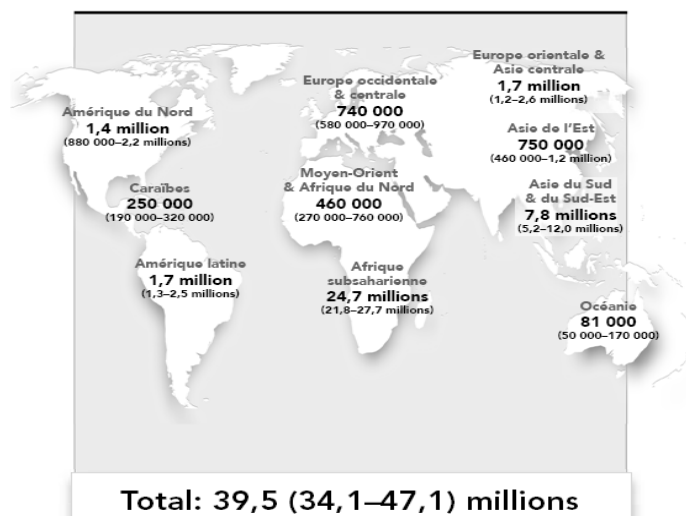
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Le SIDA: données épidémiologiques

ADULTES ET ENFANTS VIVANT AVEC LE VIH
ESTIMATIONS EN 2006



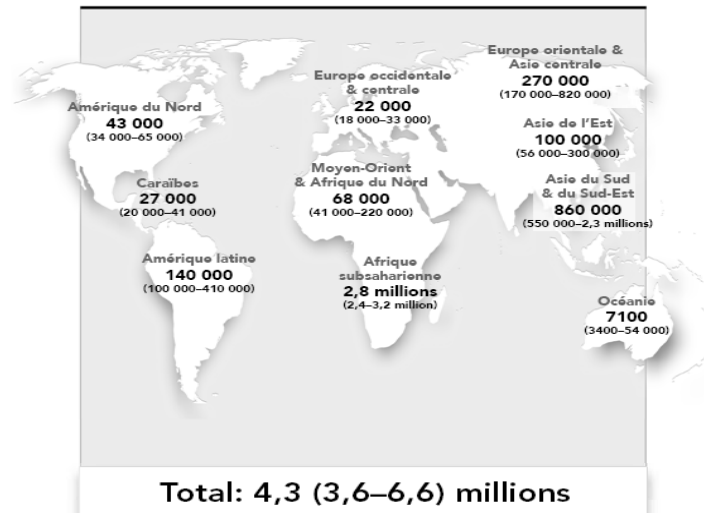
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Le SIDA: données épidémiologiques

NOMBRE ESTIMATIF D'ADULTES ET D'ENFANTS
NOUVELLEMENT INFECTÉS PAR LE VIH EN 2006



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Le SIDA: mortalité en Afrique (2001)

Rank		% of total
• 1	HIV/AIDS	20.6
• 2	Acute lower respiratory infections	10.3
• 3	Malaria	9.1
• 4	Diarrhoeal diseases	7.3
• 5	Perinatal conditions	5.9
• 6	Measles	4.9
• 7	Tuberculosis	3.4
• 8	Cerebrovascular disease	3.2
• 9	Ischaemic heart disease	3.0
• 10	Maternal conditions	2.4

The World Health Report 2000, WHO

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Le SIDA: données épidémiologiques



BELGIUM

I. DEMOGRAPHIC, SOCIAL AND ECONOMIC INDICATORS

Estimated Population	10 419 000
Population Growth Rate	0.2%
Life expectancy at birth	
Women	81
Men	75
Human Development Index	9
Human Poverty Index	
Rank	13 ¹
Value	12.4 ²
Percentage of people with less than US\$ 2 a day	-
Per Capita Gross National Income, ppp, Intl dollar rate	31 360
Per Capita Government Expenditure on Health at Intl dollar rate	1902

II. HIV AND AIDS ESTIMATES

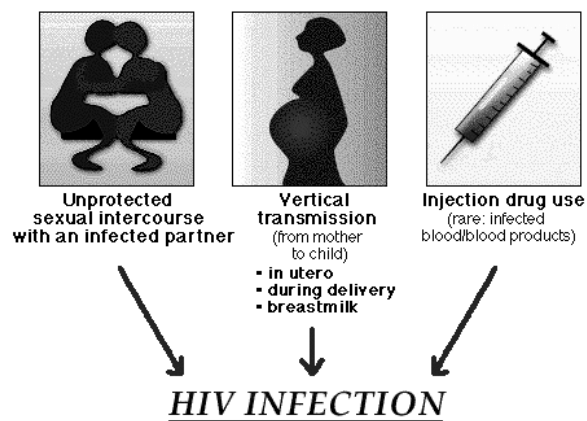
Number of people living with HIV	14 000 [8100 – 22 000]
Adults aged 15 to 49 HIV prevalence rate	0.3 [0.2 – 0.5%]
Adults aged 15 and over living with HIV	14 000 [8100 – 22 000]
Women aged 15 and over living with HIV	5400 [2800 – 9500]
Deaths due to AIDS	<100 [<200]

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Le SIDA: voies de transmission



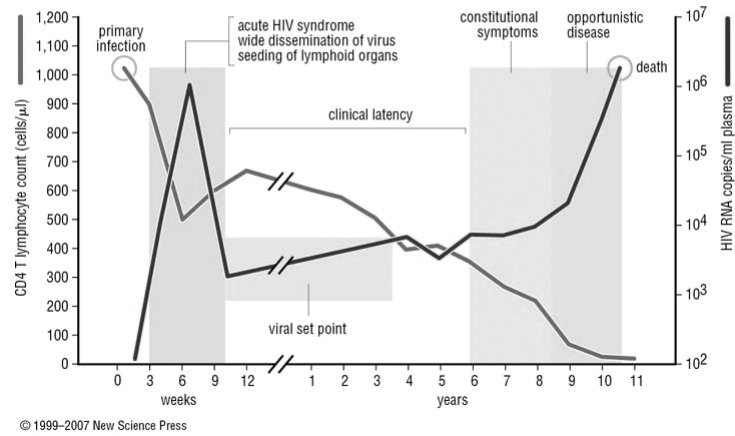
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L'infection à HIV: histoire naturelle

From **Immunity: The Immune Response in Infectious and Inflammatory Disease**
by DeFranco, Locksley and Robertson

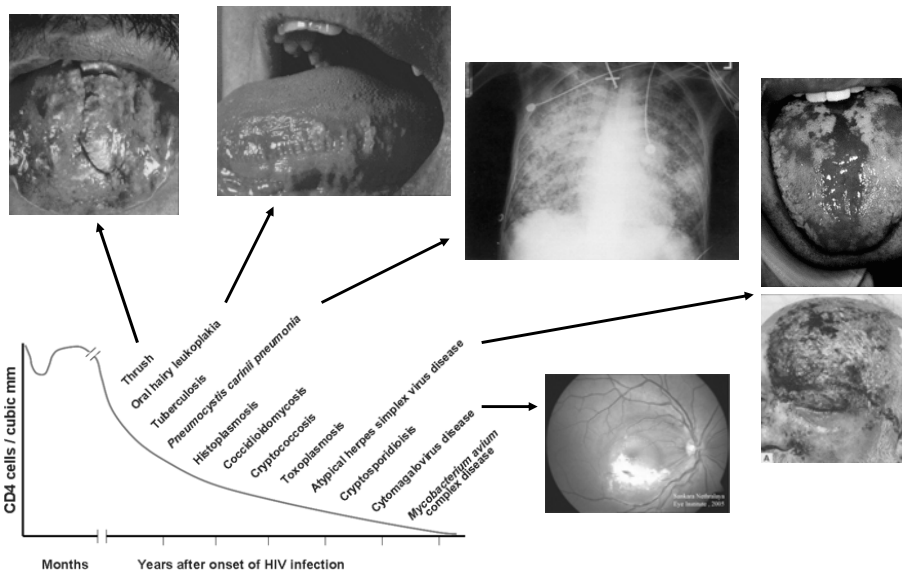


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L'infection à HIV: infections opportunistes

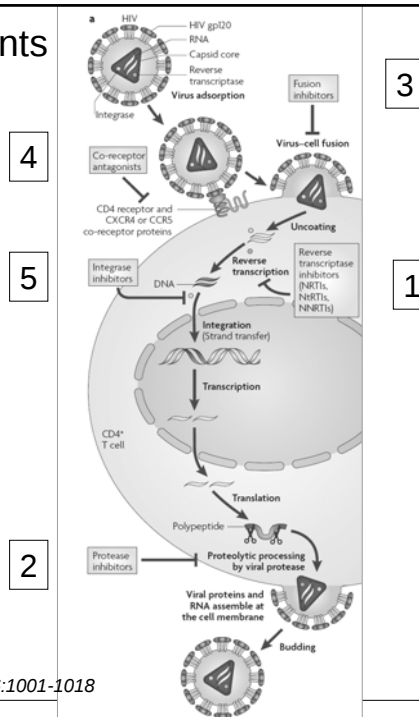


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Cible des médicaments actifs sur le HIV



De Clercq, *Nature Rev. Drug Discov.*(2007) 6:1001-1018

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Historique des médicaments actuels

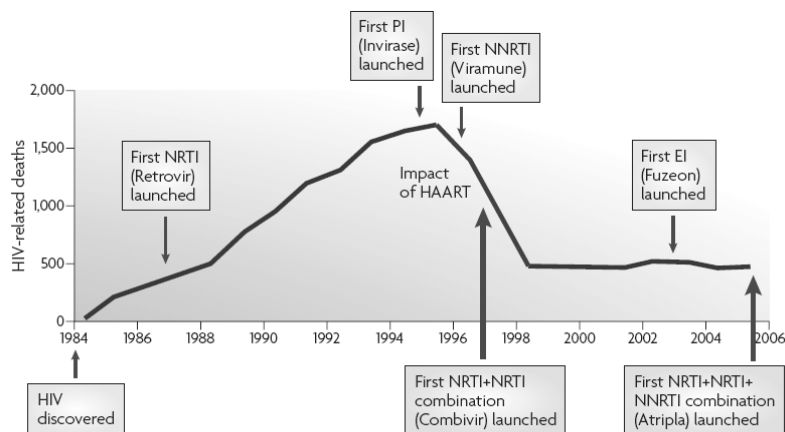


Figure 1 | Timeline of the development of the HIV market (1984–2006) and UK HIV-related deaths (1894–2005)³. EI, entry inhibitors; HAART, highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

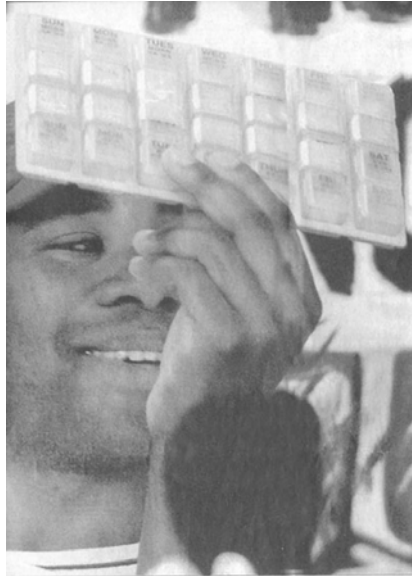
Oversteegen et al, *Nature Rev. Drug Discov.*(2007) 6:951-952

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HAART : Highly Active Anti-Retroviral Therapy



'Aids drugs made me well again'

LYNNE ALTEKOWSKI
and JO-ANNE SMITH/SHAM

DOCTORS gave Matthew Danane just a few years to live after he was diagnosed with HIV, the virus that causes Aids, in 1997.

At that time, life-saving Aids medicines, widely available in the West, were too expensive for poor people in countries like South Africa.

The brand-name medicines, which cost \$1,400 a month, even with discounts offered by drug companies, are still too expensive.

But Danane, 28, from Khayelitsha, has had access to less expensive generic versions, imported from Brazil, and he credits the drugs with restoring his health.

"I am now well," he told a packed news conference in Johannesburg yesterday as he held up a plastic pill box. It has one pill compartment for each day of the week, helping him take his Aids medicines on schedule.

Danane, a nervous smile showing under his blue base-

activist groups announced it had imported the medicines from Brazil in violation of drug-company patent rights but with the full blessing of the Medicines Control Council (MCC).

Citing preliminary results from a pilot project in Khayelitsha, the activists said the Aids drugs had reduced the presence of the virus in people's bloodstreams to undetectable levels after less than one year of treatment. They said patients were getting off their deathbeds and returning to productive work and family lives.

"We literally resuscitated people," said Eric Goemane, who heads the Aids clinic run by Medecine Sans Frontières (MSF) in Khayelitsha.

The preliminary results of the Khayelitsha pilot study - which has reported findings for 80 patients taking the Aids medicines - are the first evidence from a township clinic in South Africa that the Aids drugs can be taken on a long-term basis and can have the same dramatic effect in improving health as they have had in industrialised countries.

ment Action Campaign (TAC), Oxfam and Coats - pointed to the findings yesterday to urge the government to set up pilot projects to provide the drugs to symptomatic Aids patients in each province. They also referred to the results to support their argument that the government should follow Brazil's lead and make its own low-cost generic versions of the drugs.

"It is difficult but it is feasible in developing-country conditions," said Jack Brywood, TAC secretary.

The government did not comment on the activists' demands. It said the MCC would check whether the drugs import was legal.

The drug companies that own the patent rights to the drugs do not have plans to sue the activists. Peter Moore, medical director at GlaxoSmithKline, said the company would wait for the MCC to act.

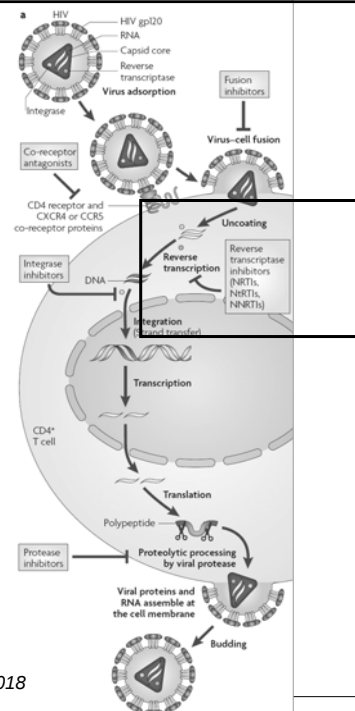
Biohrtel-Ingelheim spokesman Kevin McKenna said he was not surprised at the developments. "I don't think we're falling off our chairs at the moment,"

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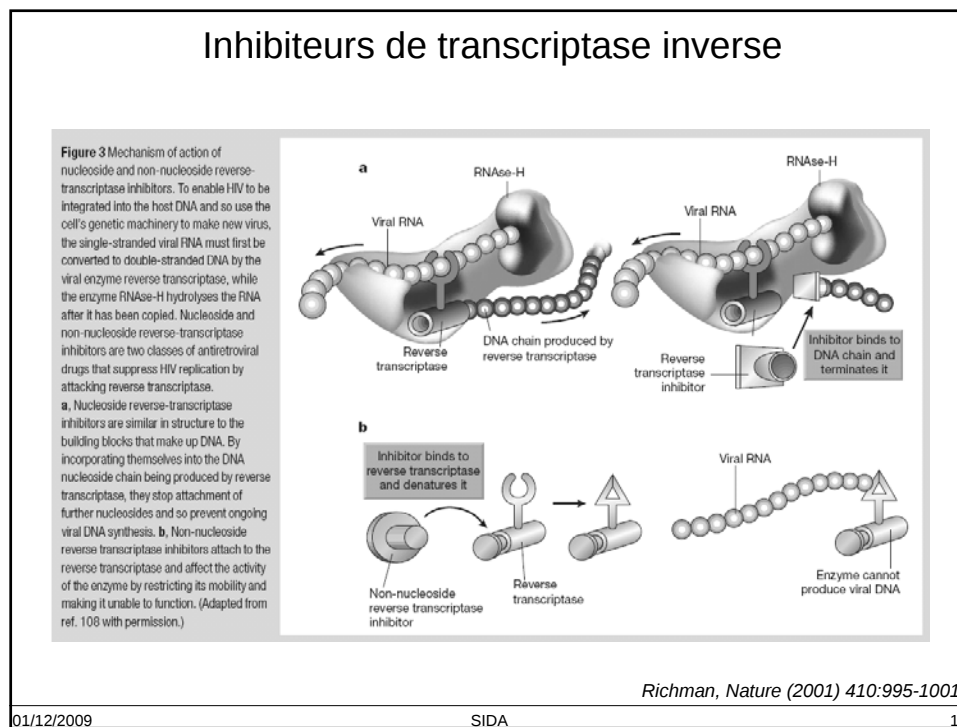
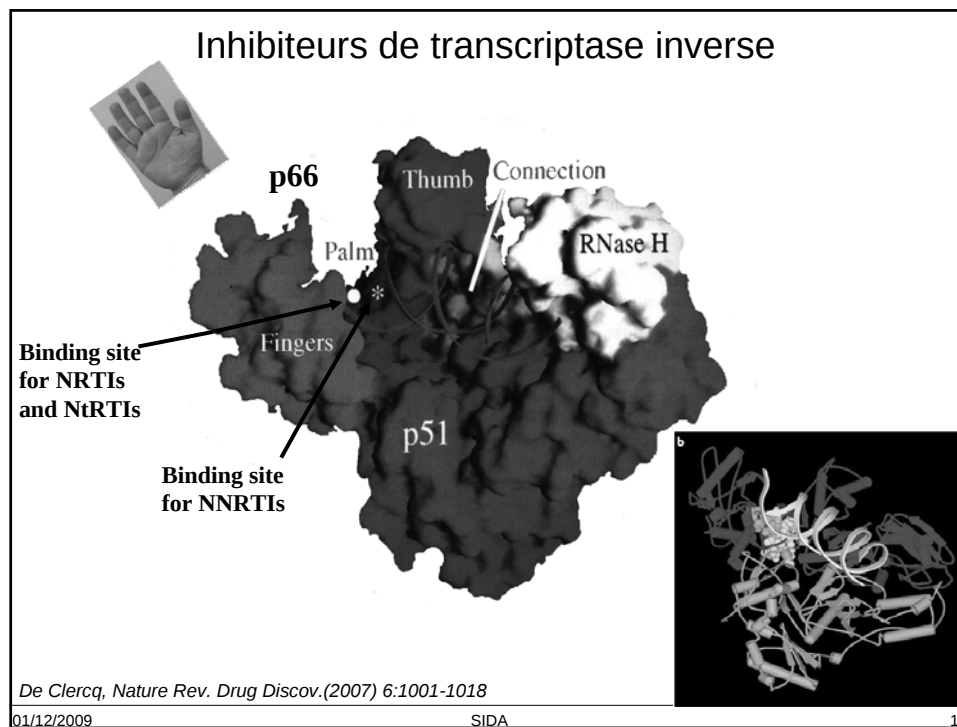
Cible des médicaments actifs sur le HIV



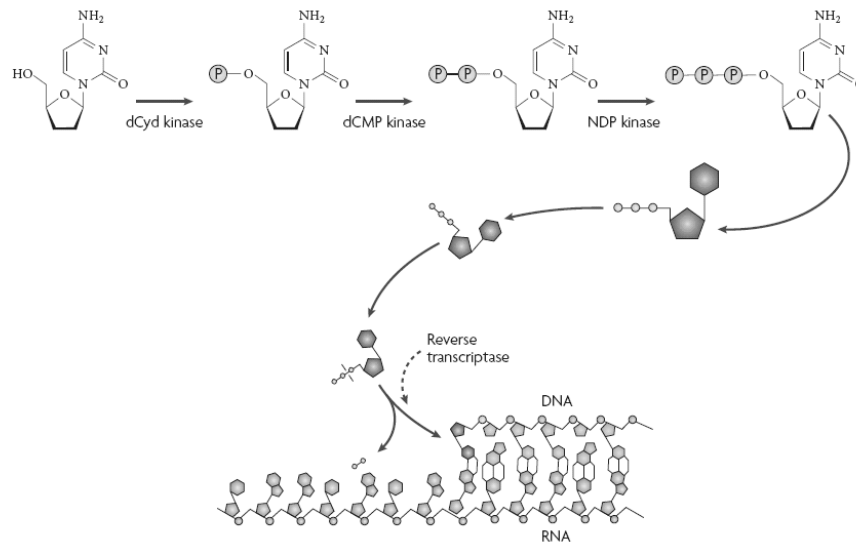
De Clercq, Nature Rev. Drug Discov.(2007) 6:1001-1018

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Mode d'action des inhibiteurs de transcriptase inverse analogues nucléosidiques/nucléotidiques



De Clercq, *Nature Rev. Drug Discov.* (2007) 6:1001-1018

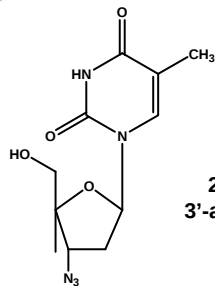
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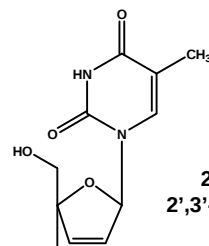
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analogues nucléosidiques

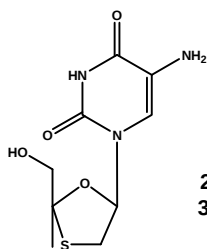
Analogues des bases pyrimidiques



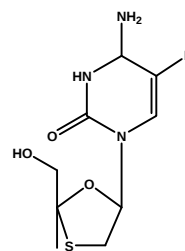
2',3'-Dideoxy-3'-azidothymidine (AZT)
zidovudine



2',3'-Dideohydro-2',3'-dideoxythymidine (D4T)
stavudine



2',3'-Dideoxy-3'-thiacytidine (3TC)
lamivudine



(FTC)
emtricitabine

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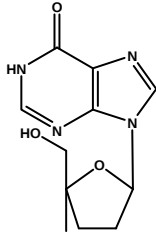
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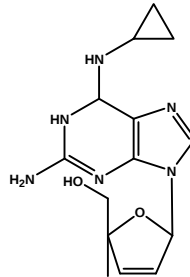


analogues nucléosidiques

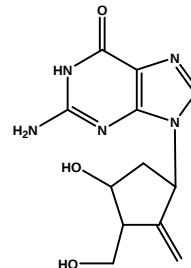
Analogues des bases puriques



**2',3'-Dideoxy-inosine
(DDI)
didanosine**



**2',3'-Dideoxy-inosine
(ABC)
abacavir**



entecavir

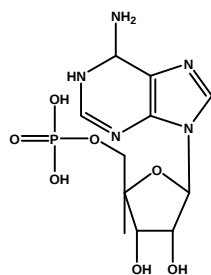
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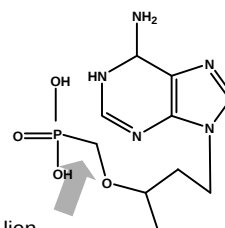
17



analogues nucléotidiques: tenofovir



adenosine-mono-P



lien
phosphonate
stable

tenofovir

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Pharmacocinétique



- bonne biodisponibilité orale
- ⚠ didanosine : résorption réduite par l'acidité gastrique ou la prise de nourriture.
- distribution dans les liquides de l'organisme, y compris le LCR
- $T_{1/2}$ plasmatique courte mais fréquence d'administration dictée par $T_{1/2}$ cellulaire des formes triphosphorylées

Agent	Biodis- ponibilité orale (%)	$t_{1/2}$ sérique (h)	$t_{1/2}$ des formes triphosphate (h)	Voies d'élimination	Principal dosage (adulte)
Zidovudine	63	1.1	3-4	glucurono-conjugaison et élimination rénale	300 mg / 12 h
Didanosine	40 (à jeûn)	1.5	8-24	métabolisme cellulaire	400 mg / 24 h
Stavudine	86	1.1	3	excrétion rénale	40 mg / 12 h
Lamivudine	86	2.5	11-14	excrétion rénale	300 mg / 24 h
Abacavir	83	1.5	3.3	glucurono-conjugaison et carboxylation	300 mg / 24 h
Tenofovir	39 (avec un repas)	12-14	>12 *	excrétion rénale	300 mg / 24 h
Emtricitabine	93	10	>24		200 mg /24 h

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Combinaisons et compliance



Table 1 | Overview of currently launched fixed-dose combination products for the treatment of HIV*

Drug	Class	Pill volume	Total pills per day	Dosing schedule	Combination product	Total pills per day	Dosing schedule	2006 sales [†]
Tenofovir	NRTI	300 mg		Once daily	 		Once daily	1,125
Emtricitabine	NRTI	200 mg		Once daily			Once daily	174
Efavirenz	NNRTI	600 mg		Once daily		-	-	-
Abacavir	NRTI	300 mg		Once daily	 		Once daily	396
Lamivudine	NRTI	300 mg		Once daily			Twice daily	478
Zidovudine	NRTI	300 mg		Twice daily			Twice daily	789

Oversteegen et al, Nature Rev. Drug Discov.(2007) 6:951-952

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Effets secondaires



Communs à la classe

- hyperlactacidémie (menant parfois à une acidose sévère)
- hépatomégalie et stéatose
(inhibition de la DNA-polymérase impliquée dans la réplication du DNA mitochondrial (surtout pour didanosine, stavudine, et zidovudine).

Particuliers à certaines molécules

molécule	Effet secondaire
zidovudine	Anémie neutropénique
didanosine	pancréatite, neuropathie périphérique
stavudine	neuropathie périphérique
abacavir	réactions d'hypersensibilité
tenofovir	toxicité rénale à long terme
emtricitabine	hyperpigmentation des mains et pieds

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Interactions médicamenteuses



- excipient de la didanosine (sels de Mg^{2+} et d' Al^{3+}) :
↓ absorption de nb médicaments:
(kétoconazole, dapsone, tétracyclines, fluoroquinolones) ←
- ganciclovir (et autres médicaments myélotoxiques)
↑ risque de myélosuppression de l'azidothymidine ←
- ranitidine: ↓ faible de l'absorption de la didanosine
- pentamidine : ↑ toxicité pancréatique (didanosine, stavudine et zalcitabine)
- probénécide, pyréméthamine/ sulfadiazine :
↓ glucuronoconjugaison ou élimination rénale de l'azidothymidine
↑ sa toxicité

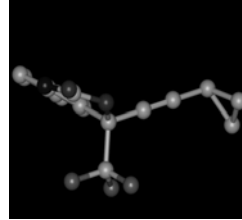
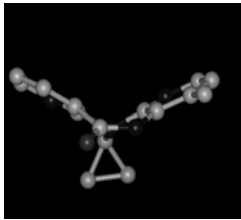
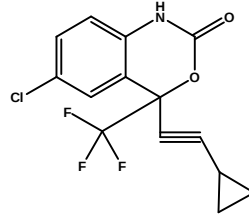
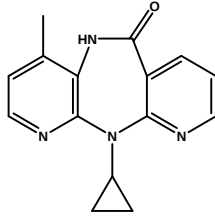
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analogues non nucléosidiques



Inhibiteurs allostériques non compétitifs;
pas de résistance croisée avec les NRTI !

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Pharmacocinétique



névirapine

- bonne résorption orale
- élimination par métabolisation hépatique;
inducteur de son propre métabolisme
 - $t_{1/2}$ = 45 h après une dose unique
 - = 25 h après administration répétée
 - augmentation des posologies après 15 jours de traitement

efavirenz

- forte liaison aux protéines et demi-vie prolongée (40 h)
 - administration 1X/jour
- inducteur et inhibiteur des cytochromes P450 (3A4 et 2B6),
n'entraînant pas de modification importante de son propre métabolisme.

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Effets secondaires



névirapine

- réactions cutanées fréquentes, parfois mortelles (syndrome de Stevens Johnson; nécrolyse cutanée).

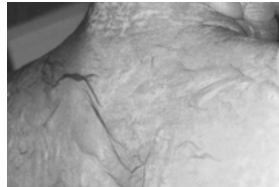


Figure 1. Typical Pattern of Toxic Epidermal Necrolysis. Blisters and wrinkled areas result from full-thickness necrosis of the epidermis.

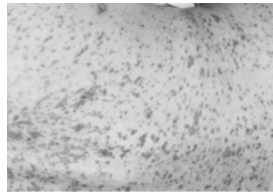


Figure 2. Typical Pattern of Stevens-Johnson Syndrome. Blisters develop on widespread purpuric macules.

→ Interrompre le traitement dès l'apparition de signes précurseurs (rash cutané, fièvre, lésions orales, conjonctivite, douleurs musculaires ou articulaires, malaise généralisé).

- toxicité hépatique (possibilité d'hépatites fulminantes).
- agranulocytose chez les enfants
- nausées, fièvre, maux de tête.

Effets secondaires



Efavirenz

- effets sur le système nerveux :
étourdissements, vertiges, somnolence, maux de tête, dépression
→ administration le soir
- rashs (ne demandent que rarement l'arrêt du traitement).

Interactions médicamenteuses



Inducteurs/inhibiteurs des CYP

Névirapine:

↓ taux sérique de rifabutine, rifampicine
kétokonazole
anticoagulants oraux

Efavirenz:

↓ taux sérique de inhibiteurs de la protéase du virus HIV
méthadone
rifabutine, clarithromycine.
↑ taux sérique de ritonavir

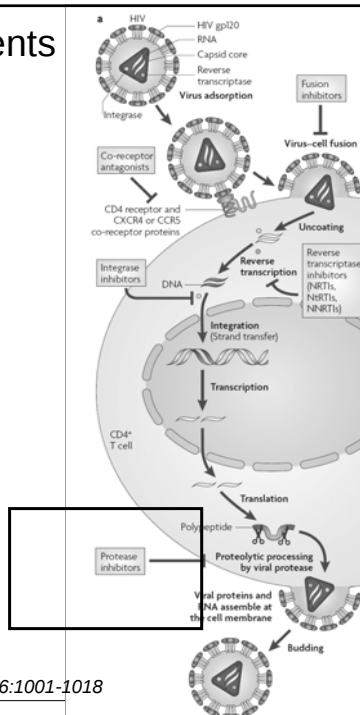
**Patients susceptibles
de développer
des infections
opportunistes !**

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Cible des médicaments actifs sur le HIV



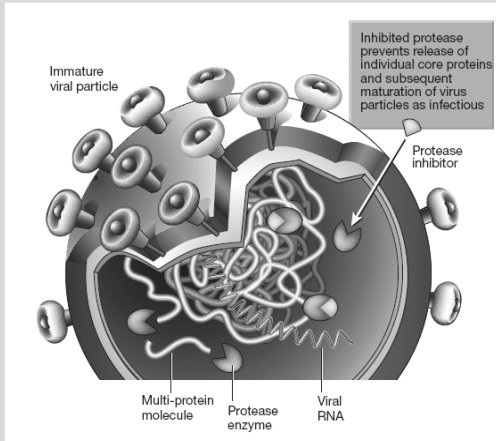
De Clercq, *Nature Rev. Drug Discov.* (2007) 6:1001-1018

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Protéase et inhibiteurs

Figure 4 Mechanism of action of protease inhibitors. After transcription in the nucleus, viral mRNA enters the cytoplasm and uses the host's cellular machinery to manufacture virus proteins. The viral components then gather at the cell membrane and immature viruses bud off the cell. Core proteins are produced as part of long polypeptides, which must be cut into smaller fragments by the enzyme protease in order to form mature, functional proteins. Protease inhibitors bind to the site where protein cutting occurs, and so prevent the enzyme from releasing the individual core proteins. In this way the new viral particles are unable to mature or become infectious. (Adapted from ref. 108 with permission.)



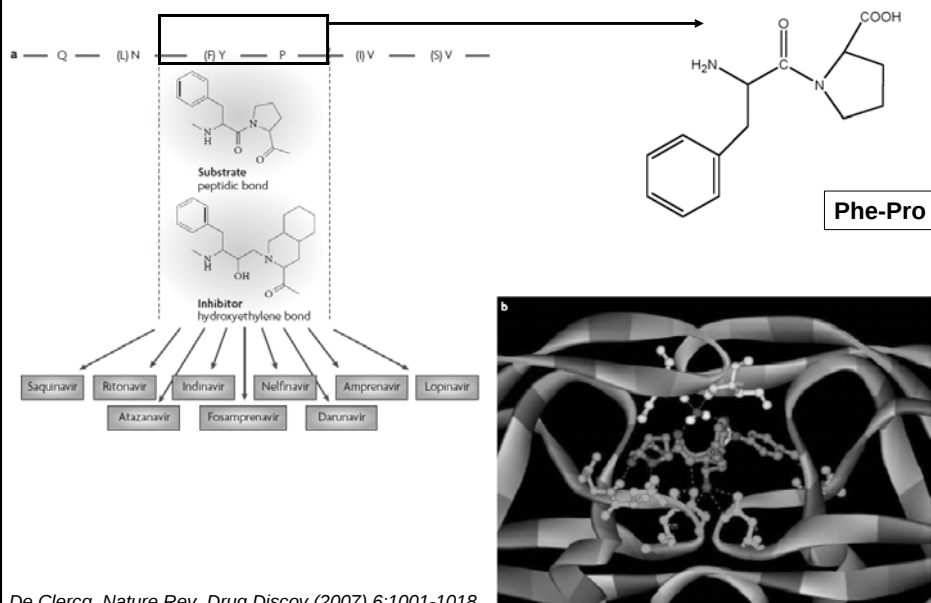
Richman, *Nature* (2001) 410:995-1001

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Inhibiteurs de protéase HIV



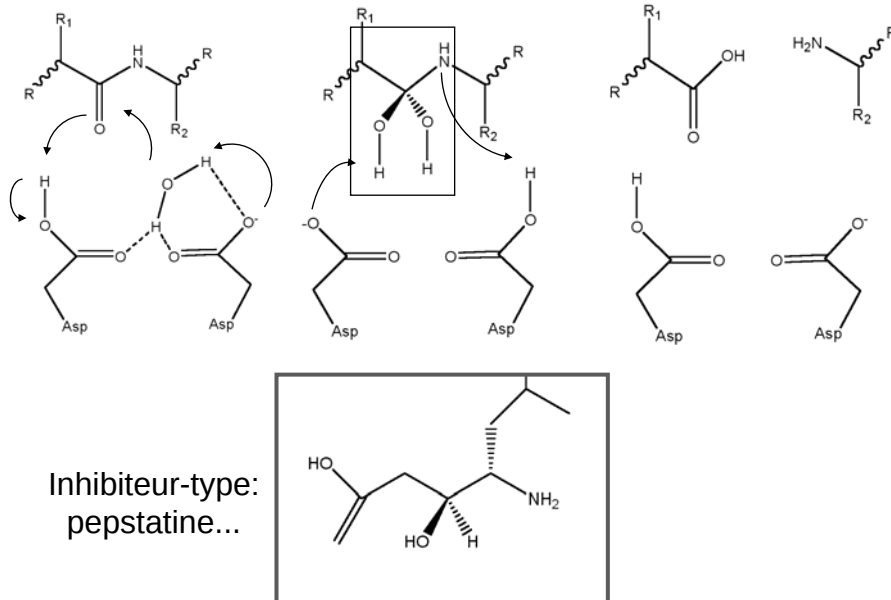
De Clercq, *Nature Rev. Drug Discov.* (2007) 6:1001-1018

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La protéase HIV, une Aspartate- protease

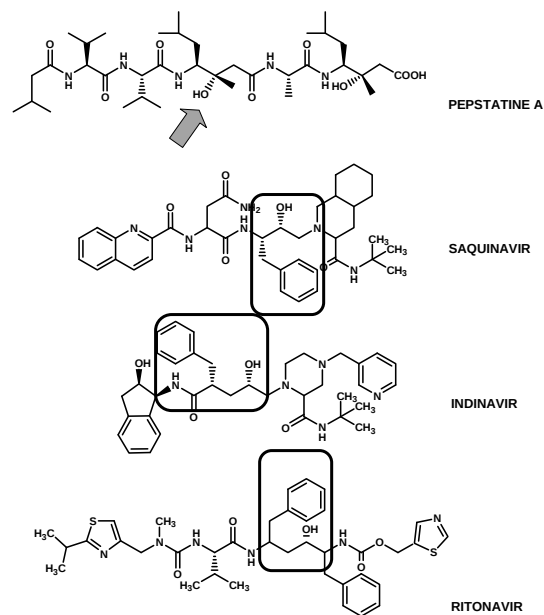


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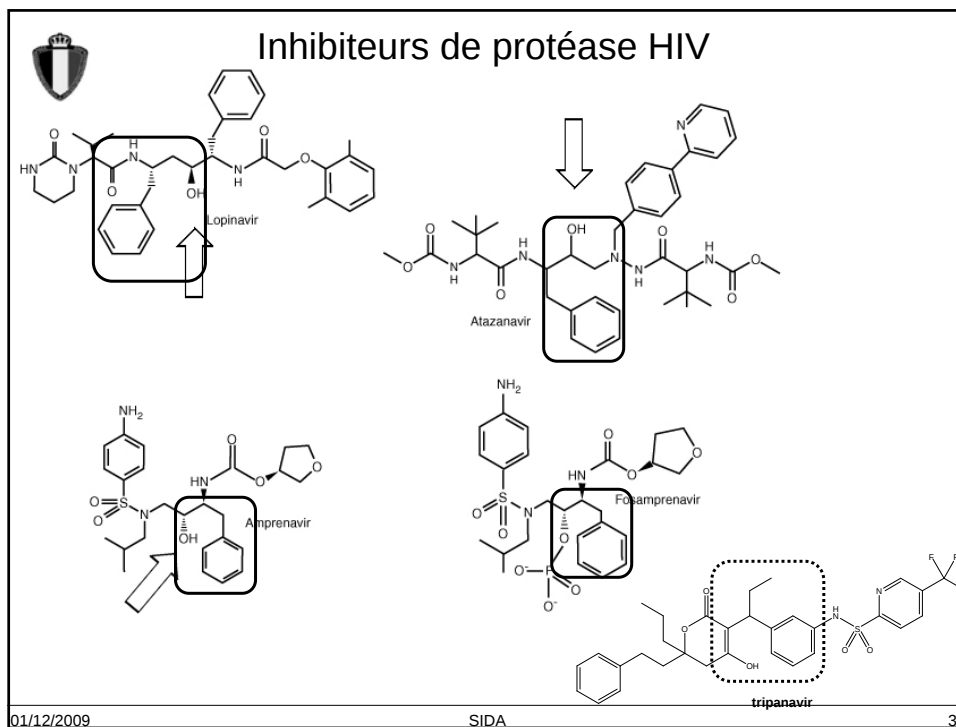
Inhibiteurs de protéase HIV



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Résistance par mutation

MUTATIONS IN THE HIV PROTEASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO PROTEASE INHIBITORS (PIs)

Certaines mutations confèrent des résistances croisées !

	L	10	20	24	32	33	36	46	47	50	53	54	63	71	73	77	82	84	90
Multi-PI Resistance: Accumulation of Mutations	L							M				I					V	I	L
	F							I				V					A	V	M
	R							L				L					T	S	
Indinavir	L	K	L		V		M	M				I		A	G	V	V	I	L
	F							I				V		V	S	A	A	V	M
	R				I		I	L				L		F			T	S	
Ritonavir	L	K			V	L	M	M				I		A	V	V	I	L	
	F							I				V		V	F		I	A	V
	R				I	F	I	L				L		F			T	S	
Saquinavir	L							G				I		A	G	V	V	I	L
	F							V				V		V	S	I	A	V	M
	R											L		F			T	S	
Nelfinavir	L				D		M	M						A	V	V	I	L	
	F				N		I	L				V		V	F		I	A	V
	R							L				L		F			T	S	
Amprenavir	L				V			M	I		I	I					G		L
	F				I			I				V		V		S		V	M
	R							L				L		L			S		
Lopinavir/Ritonavir	L	K	L		V	L		M	I		I	I		A	G	V	V	I	L
	F							I				V		V	S	A	A	V	M
	R				I	F		L				L		F			T	S	
Atazanavir (expanded access)	L				V			M				I		A			V	I	L
	F				I			I				L		V			A	V	M

http://www.iasusa.org/resistance_mutations/index.html

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Pharmacocinétique



- faible biodisponibilité
(poids moléculaire élevé, mauvaise solubilité et instabilité)
- $T_{1/2}$ courte (quelques heures)
→ administrations 2 ou 3 X/jour
- métabolisation par les cytochrome P-450 hépatiques (principalement 3A4).
→ inhibiteurs ou activateurs du métabolisme de nb médicaments.

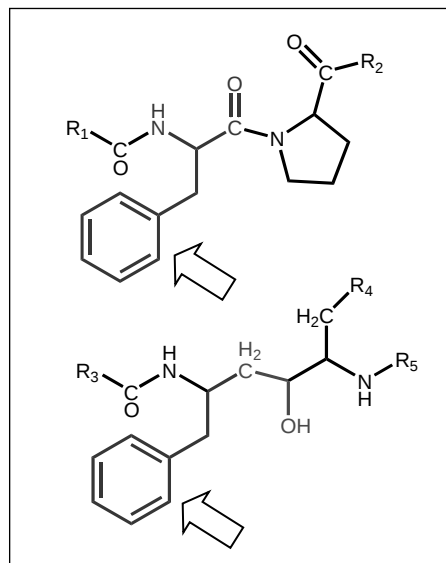
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Inhibiteurs de protéase HIV et cytochromes

- la protéase doit scinder un lien Phe-Pro
- Les inhibiteurs miment donc tous une Phe...



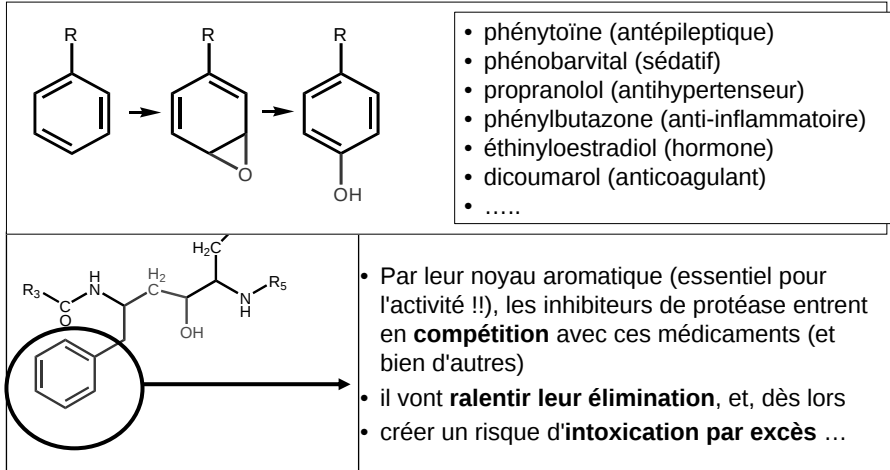
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Inhibiteurs de protéase HIV et cytochromes

- La plupart des médicaments (et autres substances) à noyau aromatique sont métabolisés en dérivés hydroxylés, ce qui est essentiel pour leur élimination



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Pharmacocinétique

- faible biodisponibilité
(poids moléculaire élevé, mauvaise solubilité et instabilité)
- $T_{1/2}$ courte (quelques heures)
→ administrations 2 ou 3 X/Jour
- métabolisation par les cytochrome P-450 hépatiques (principalement 3A4).
→ inhibiteurs ou activateurs du métabolisme de nb médicaments.

Très important pour le ritonavir; utilisé à faible dose comme inhibiteur du métabolisme des autres inhibiteurs de protéase.

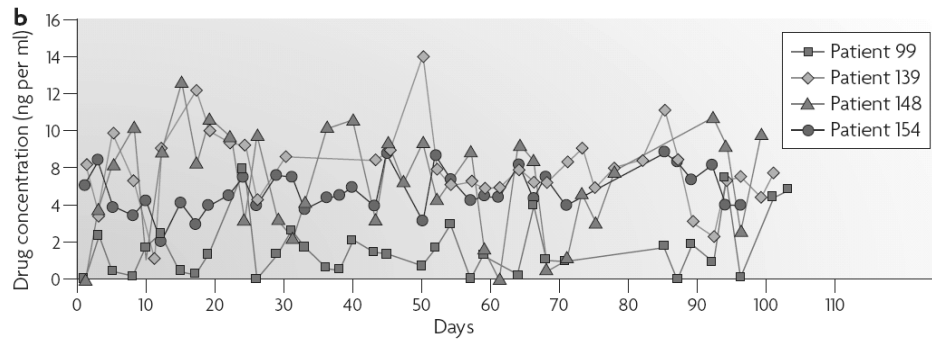
→ 200 mg lopinavir + 50 mg ritonavir (KALETRA®).
[tripranavir + ritonavir]

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Lopinavir: variabilité pharmacocinétique



Measured intra-subject variability in concentrations of lopinavir dosed 400 mg every 12 hours. Participants had undetectable plasma HIV RNA on treatment for at least 3 months, and were seen in the clinic 3 times a week for up to 4 months. Blood for lopinavir concentration analysis was collected at approximately the same time of day at each visit

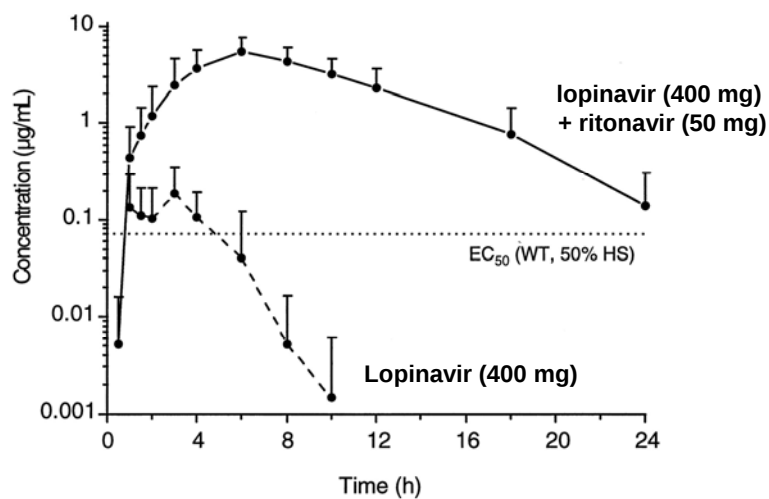
Flexner, *Nature Rev. Drug Discov.*(2007) 6:959-66

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Lopinavir: influence du ritonavir sur le profil PK



Sham et al, *AAC* (1998) 42:3218-24.

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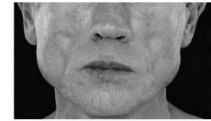
Effets secondaires

"syndrome de lipodystrophie"

- bajoues et dépôts graisseux sur la face
- dépôts de graisse au niveau du cou ["bosse de bison"] et du tronc
- accumulation de graisse derrière les muscles abdominaux
- lipomes disséminés
- hyperplasie graisseuse des seins
- hyperglycémie, hyperinsulinémie
- augmentation des taux lipidiques sériques



risque de diabète non insulino-dépendant et de maladie cardiovasculaire.



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Effets secondaires



Selon la molécule (orientation du choix!)

saquinavir	intolérance gastro-intestinale, diarrhée maux de tête ↗ taux sériques de triglycérides et de cholestérol
ritonavir:	intolérance digestive et diarrhée très importantes paresthésies ↗ transaminases hépatiques disgueusie
indinavir:	intolérance gastro-intestinale, diarrhée hyperbilirubinémie non conjuguée asymptomatique néphrolithiases (peuvent être prévenues par hydratation) ↗ transaminases maux de tête, insomnie
nelfinavir	diarrhée et flatulence fréquentes altération de la formule sanguine ↗ transaminases

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Effets secondaires



Selon la molécule (orientation du choix!)

amprenavir	maux de tête nausée et diarrhée fréquente rash
lopinavir	diarrhée et nausées ↗ importante des taux sériques de triglycérides et de cholestérol
tripanavir	diarrhées et nausées céphalées hépatotoxicité saignements éruptions cutanées
azatanavir	diarrhée et nausées hyperbilirubinémie non conjuguée asymptomatique

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Interactions médicamenteuses



- inhibition des cytochromes : ritonavir > indinavir et nelfinavir > saquinavir
→ nb risques d'interactions à surveiller !
- modification des taux d'IP par d'autres médicaments
 - clarithromycine ↗ taux sérique du ritonavir et de l'indinavir
 - fluconazole ↗ taux sérique du ritonavir
 - kétoconazole ↗ ↗ taux sérique de saquinavir, d'indinavir et de nelfinavir
 - quinidine ↗ taux sérique de l'indinavir
 - rifampicine ↘ le taux sérique de saquinavir (et nelfinavir et ritonavir)
 - névirapine ↘ concentration-pic du saquinavir
- boissons acides ↘ taux sérique de l'indinavir et du nelfinavir
- substrats de P-glycoprotéine et inhibiteurs de MRP2 :
modulation de la pharmacocinétique et interaction avec d'autres médicaments

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Interactions médicamenteuses



Interactions médicamenteuses importantes ou très dangereuses (! = contre indication) des inhibiteurs de protéase anti HIV (à l'exclusion des interactions entre anti-HIV).

Médicaments (classe)	Indavir	Ritonavir	Saquinavir	Nelfinavir	Amprenavir ¹	Lopinavir (assoc. au ritonavir)	Azatanavir	trípanavir (assoc. au ritonavir)
Antibiotiques		clarithromycine rifabutine			clarithromycine metronidazole (!) rifabutine	clarithromycine rifabutine	rifampicine (!)	rifampicine rifabutine clarithromycine
Analgésiques		opiacés mépéridine (!) propoxyphène (!) péroxicam (!)						opiacés et methadone/ mépéridine
Dérivés de l'ergot		tous (!)		tous (!)	tous (!)	tous (!)	tous (!)	
Antiarythmiques		tous (!)	quinidine	amiodarone quinidine		Amiodarone, begrindil, lidocaine (systémique), et quinidine.		
Cardiotoniques		digoxine						
Anticoagulants		coumatriniques				coumatriniques		
Anticonvulsivants	carbamazépine phénytoïne phénobarbital	tous	carbamazépine phénytoïne phénobarbital	carbamazépine phénytoïne phénobarbital		Carbamazépine, phénobarbital, phénytoïne		
Antidépresseur		tous buspérone (!)						millepertuis desipramine
Antihistaminiques	terféndine (!) astémazole (!) autres molécules (!)	terféndine (!) astémazole (!) autres molécules (!)	terféndine (!) astémazole (!) autres molécules (!)	terféndine (!) astémazole (!) autres molécules (!)				
Antifongiques	kétoconazole	kétoconazole itraconazole			kétoconazole	Kétoconazole, itraconazole.		voriconazole (imprédictible)
Anticancéreux		étoposide alcaloïdes vinca tamoxifène					irinotecan	
Autres agents cardiovascul.		la plupart begrindil (!)	antagon. Ca ⁺⁺	antagon. Ca ⁺⁺		antagon. Ca ⁺⁺		

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Interactions médicamenteuses



Voies de transmission

...

Table 135-2. Drug interactions between antiretrovirals and oral contraceptives. Recommended adjustments are listed. Data from CDC.²¹

DRUG INTERACTIONS BETWEEN ANTIRETROVIRALS AND ORAL CONTRACEPTIVES				
Agent	Effect on oral contraceptive	No dose adjustment	Recommendation	
			No data	Use alternative agent or second method
Indinavir	Norethindrone [®] levels ↑26% ethinylestradiol levels ↑24%	X		
Ritonavir [®]	Ethinylestradiol levels ↓40%			X
Saquinavir [®]			X	
Nelfinavir	Norethindrone [®] levels ↓18% ethinylestradiol levels ↓47%			X
Amprenavir [®]	Potential for interaction		X	X
Lopinavir	Ethinylestradiol levels ↓42%			X
Nevirapine [®]	Ethinylestradiol levels ↓20%			X
Delavirdine			X	
Efavirenz [®]	Ethinylestradiol levels ↑37% no data on norethindrone [®] levels			X

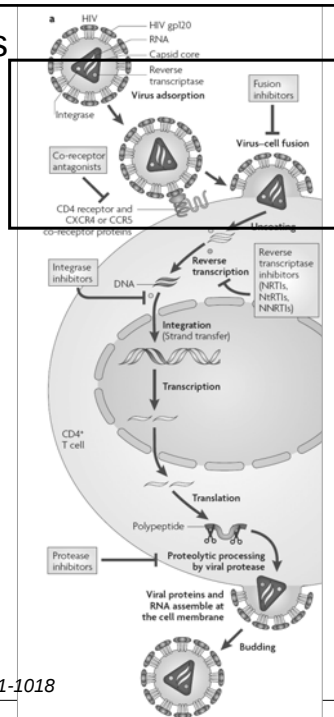
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Cible des médicaments actifs sur le HIV

Inhibiteurs d'entrée



De Clercq, *Nature Rev. Drug Discov.* (2007) 6:1001-1018

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Récepteurs cellulaires au virus HIV

	CD4	CCR5	CXCR4
Structure			
Function	Coreceptor for MHC class II during stimulation of T-helper cells	Receptor for CCL3 (MIP1-α), CCL4 (MIP-β), CCL5 (RANTES). Redundant system	Receptor for CXCL12 (SDF-1). Non-redundant system
Expression	CD4+ T cells, Macrophages, Microglia, Dendritic cells	A subset of memory CD4+ cells, Macrophages	Constitutive in many cell types, including CD4+ T cells and macrophages

Figure 2: Receptors for HIV-1 entry

Este & Telenti, *Lancet* (2007) 370:81-88

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Fusion du virus avec la cellule hôte

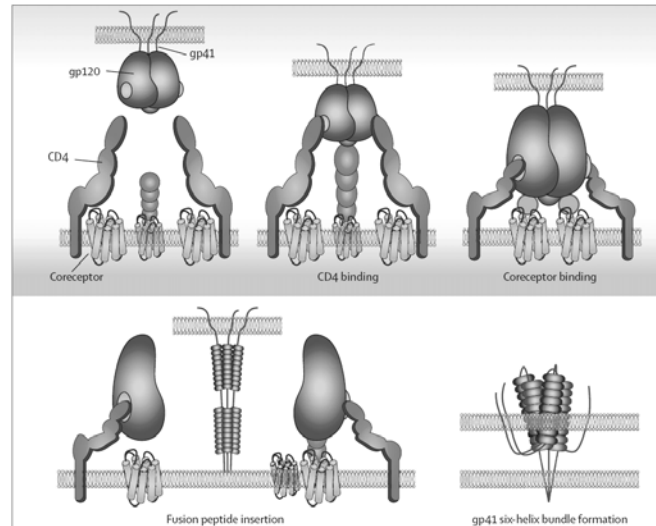


Figure 1: Mechanism of HIV entry
On CD4 binding (binding site for CD4 is shown in yellow), gp120 undergoes conformational changes. CD4-induced epitopes can then bind to chemokine receptors. Thereafter, gp41 is released into a fusogenic conformation and its N-terminal (green) and C-terminal (red) helices form a hairpin structure, leading to the approximation of viral and cellular membranes, which results in membrane fusion.

Este & Telenti, Lancet (2007) 370:81-88

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Inhibiteurs de fusion

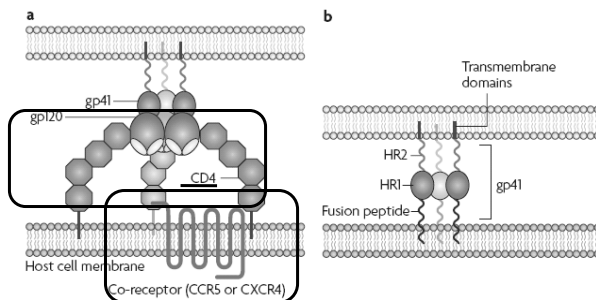


Figure 8 | Inhibiting human immunodeficiency virus (HIV) fusion. When HIV infects a CD4⁺ T cell (a), the viral glycoprotein gp120 first interacts with the CD4 receptor, then with the CCR5 or CXCR4 co-receptor, upon which the viral gp41 will bring the viral envelope in contact with the host cell membrane (b). The gp41 glycoprotein contains four major functional domains: starting from the N terminus towards the C terminus these are the fusion peptide, the heptad repeat 1 (HR1), the heptad repeat 2 (HR2) and the transmembrane domain that anchors gp41 into the viral lipid bilayer. Enfuvirtide is homologous to part of the HR2 region. When the N terminal fusion peptide of gp41 is inserted into the host cell membrane, the three HR2 domains of the gp41 trimer loop back in a triple hairpin and 'zip' themselves into three highly conserved hydrophobic grooves on the outer face of the HR1 trimeric bundle to form a six-helix bundle that pulls the outer membranes of the virus and the cell into close physical proximity, thus enabling the two membranes to fuse¹². This process depends on an interaction of the heptad repeat HR2 with HR1. By being homologous to the HR2 domain, enfuvirtide blocks this interaction³⁰.

La Bonte et al (2003) & De Clercq (2007), Nature Rev. Drug Discov. 2: 345-346 & 6:1001-1018

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Inhibiteurs de fusion

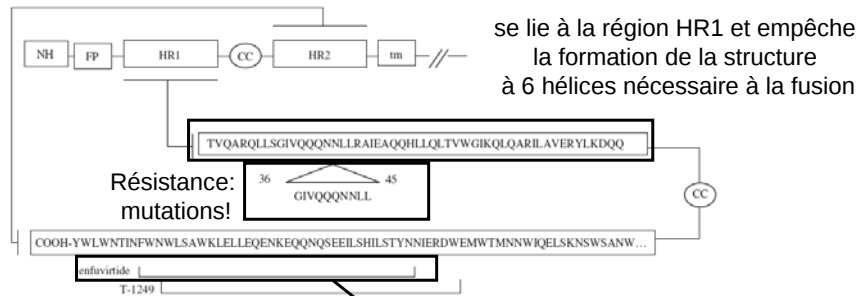


Figure 5. Schematic representation of the gp41 linear structure. Enfuvirtide and T-1249 sequences mimic HR2. FP, fusion peptide; CC, cysteine-cysteine; TM, transmembrane domain.

actif uniquement sur HIV-1

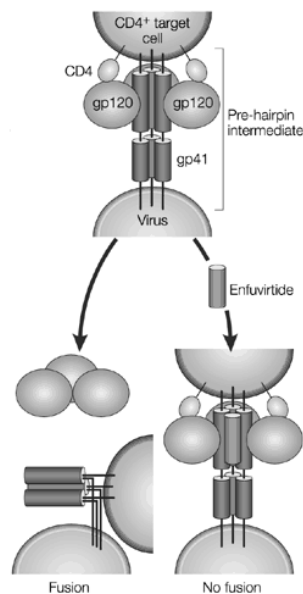
Briz et al, JAC (2006) 2006 57:619-27.

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Inhibiteurs de fusion



The envelope glycoprotein of HIV-1 consists of two non-covalently associated subunits, gp120 and gp41. After attachment of HIV-1 to its target cells carrying the CD4 receptor, gp120 interacts with the CD4 receptor, which initiates a series of conformational changes in gp41 and gp120 that lead to the insertion of a region of gp41 into the membrane of the host cell, and the formation of a 'pre-hairpin intermediate' (top). Further changes in the conformation of gp41 bring the viral and cellular membranes into close enough proximity for membrane fusion (bottom left). Enfuvirtide binds to a region of gp41 that mediates this conformational change from pre-hairpin intermediate to the fusion-active structure, thereby preventing fusion and viral entry

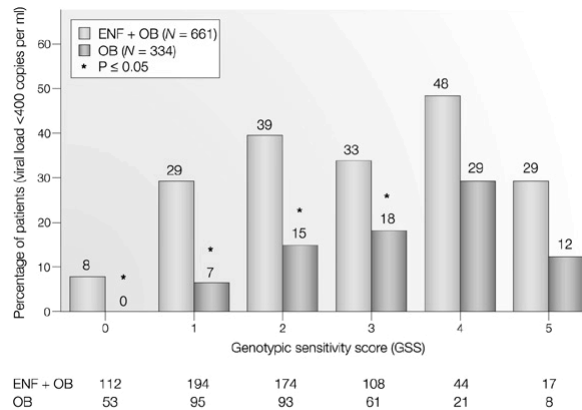
Labonte et al, Nature Reviews Drug Discovery 2, 345-346

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Inhibiteurs de fusion: efficacité clinique



Percent responders with HIV-1 RNA <400 copies per ml, week 48 (intent-to-treat, discontinuation or virological failure = failure).

GSS is the actual number of antiretrovirals that the baseline virus is sensitive to as indicated by standard primary mutations that each virus possesses.

ENF, enfuvirtide; OB, optimized treatment background.

Matthews et al, *Nature Rev. Drug Discov.* (2004) 3:1215-25

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Enfuvirtide: propriétés pharmacologiques



Pharmacocinétique

- médicament peptidique:
 - administration par voie sous-cutanée
 - instable: préparation extemporanée



Risque de transmission par les aiguilles !

$t_{1/2}$: 3-4 heures (hydrolyse); administration 2 X / jour

Effets secondaires:

- réactions cutanées au site d'injection
- réactions d'hypersensibilité pouvant imposer l'arrêt du traitement
- augmentation du risque de pneumonie en début de traitement (raison peu claire)



Patient à risque d'infection opportuniste !

Usage clinique:

- en association avec d'autres antiviraux; patients phase avancée (souches multirésistantes)

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Enfuvirtide: conseils d'auto-administration



2 Injection Sites and Syringe Information

Injection Sites

Changing where you inject FUZEON on your body each time is an important way to lessen how bad your injection site reactions get. For more detailed information about each injection site, see *Your Guide to Taking FUZEON*.



Abdomen



Upper Thighs

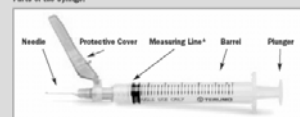


Upper Arms

About the Safety Syringe

- There are two different-sized safety syringes, a 3-cc/mL (large) syringe and a 1-cc/mL (small) syringe.
- Before using the safety syringe, be sure the clear plastic capped needle is tight by pushing it down gently while twisting it clockwise [2A].
- The safety syringes have a colored piece of plastic that is attached to the needle. This piece of plastic is a safety feature that covers the needle after use, lowering the risk of needlestick injuries [2B, 2C].
- Your healthcare provider may recommend other types of syringes for use with FUZEON.
- Never throw your used syringes into the trash. Put them in the sharps container.

Parts of the Syringe:



* The measuring line of the syringe is the edge line of the plunger closest to the needle. Syringe is a registered trademark of Terumo Medical Corporation.



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Enfuvirtide: conseils d'auto-administration



4 Mixing FUZEON

Draw Up Sterile Water

- Gently tap the FUZEON vial to loosen the powder.
- Pick up the 3-cc/mL (large) syringe.
- Using your index finger, pull the colored protection device away from the capped needle.
- To ensure that the needle is secure, hold the clear plastic cap and tighten the needle with a gentle clockwise twist. Do not use too much force as the needle may loosen [2A].
- Pull the clear plastic cap off.
- Pull the plunger back to get 1.1 cc/mL of air [4A].
- Before turning the sterile water vial upside down, slowly inject the air into the vial—and keep the needle in the vial.
- Turn the vial upside down. Make sure the tip of the needle is always below the surface of the water to help keep air bubbles from entering the syringe [4B].
- Slowly pull the plunger back to get 1.1 cc/mL of sterile water into the syringe. Tip! Gently tap or flick the barrel and push and pull the plunger to remove extra air and bubbles. To be sure you end up with 1.1 cc/mL of sterile water in the syringe, you may need to pull the plunger past the 1.1 cc/mL mark. [4C].
- Carefully remove the needle and syringe from the vial.

Inject Sterile Water into FUZEON

- Insert the syringe with sterile water into the FUZEON vial at an angle.
- Inject the sterile water slowly, so that it drips down the side of the vial into the FUZEON powder [4D].



- Remove the needle from the vial. Using one hand, gently press the colored protective cover against a flat surface until you hear a click and the needle is re-secured. *Never use your hand to recover the needle [2B, 2C].*
- Put the used syringe in the sharps container [4E].

Gently Mix FUZEON

- Gently tap the FUZEON vial with your fingertip for 10 seconds to start dissolving the powder. Then gently roll the FUZEON vial between your hands to reduce the mixing time. [4F] Make sure no FUZEON is stuck to the vial wall. After tapping, it could take up to 45 minutes to dissolve. *Important! Never shake the FUZEON vial. Shaking will make the medicine foam and it will take much longer to dissolve.*
- Once the powder starts to dissolve, just set it aside and it will completely dissolve.

Inspect FUZEON

- When completely mixed, the liquid FUZEON should be clear. *Important! Completely dissolved FUZEON should be clear and without foam. [4G] If the FUZEON is foamy [4H] or jelled, allow more time for it to dissolve.*
- If you see bubbles, gently tap the vial until they disappear.
- If you see any particles in the FUZEON once it is completely mixed, do not use that vial. Contact the pharmacy that provided it.
- Mixed FUZEON must be used right away or stored in the vial in the refrigerator and used within 24 hours. Do not store mixed FUZEON in the syringe.



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Enfuvirtide: conseils d'auto-administration



5 Giving the Injection

Choose the Injection Site

- Using your FUZEON Planner to help you, choose a site different from the one you used for your last injection

Important! With the tips of your fingers, feel for any hard bumps. Do not inject in or near bumps or any other types of reactions from past injections. Also, do not inject into moles, scars, bruises, your belly button or areas that could be irritated by a belt or waistband. [5A]

- Clean the injection site with a new alcohol pad. Start in the center, apply pressure and clean in a circular motion, working outward. Allow the site to air-dry [5B]

Draw Up FUZEON

- Clean the FUZEON vial top again, using a new alcohol pad. Allow it to air-dry
- Pick up the 1-cc/mL (small) syringe

Important! Be sure the capped needle is tight by pushing it down slightly while twisting it clockwise. [2A]

- Using your index finger, pull the colored needle-protection device away from the capped needle
- Pull the clear plastic cap off
- Pull back the plunger to get 1 cc/mL of air
- Insert the syringe into the vial of mixed FUZEON
- Before turning the vial upside down, slowly inject the air into the FUZEON, and keep the needle in the vial
- Gently turn the vial upside down [5C]



- Make sure the tip of the needle is always below the surface of the FUZEON to help keep air bubbles from entering the syringe. Slowly pull the plunger to get 1 cc/mL of FUZEON [5D]

Tip! Gently tap or flick the barrel and push and pull the plunger to remove extra air and bubbles. To be sure you end up with 1 cc/mL of FUZEON in the syringe, you may need to pull the plunger past the 1 cc/mL mark. [5E]

- Carefully remove the needle and syringe from the vial

Inject FUZEON

- Pinch and hold a fold of skin around the injection site [5F]

- Pierce the skin at a 45-degree angle. The needle should be inserted most of the way in [5G]

Tip! Your healthcare provider may teach you to inject in a different way.

- Slowly push the plunger all the way to inject FUZEON

- Remove the needle from your skin

- Using one hand, gently press the colored protective cover against a flat surface until you hear a click and the needle is re-covered. **Never use your hand to re-cover the needle [2B, 2C]**

- Put the used syringe in the sharps container [5H]

- Cover the site with a small bandage if you see any blood or medicine



For additional details on FUZEON, please see the accompanying patient package insert.

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Inhibiteurs des co-récepteurs CCR5

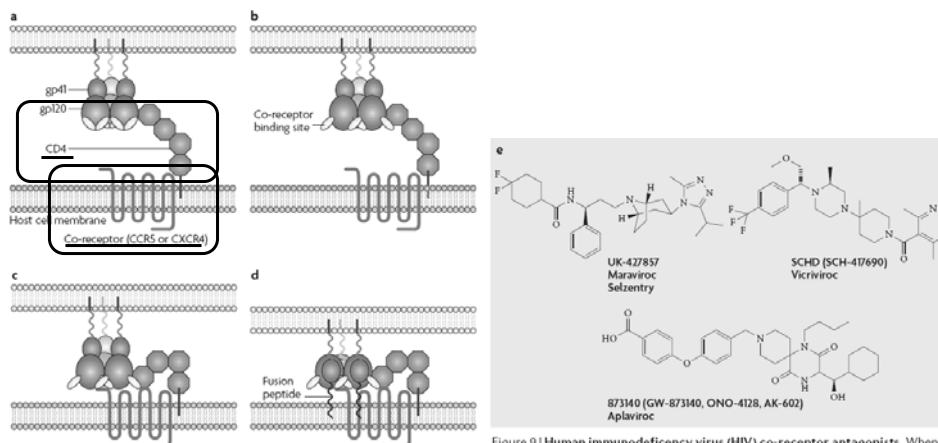


Figure 9 | Human immunodeficiency virus (HIV) co-receptor antagonists. When the HIV glycoprotein gp120 binds to CD4 (a), it induces a conformational change in gp120 that exposes the co-receptor binding site (b); this is a complex domain comprising the V3 loop and specific amino-acid residues in CD4, collectively termed the 'bridging sheet'. Exposure of the co-receptor binding site permits binding of gp120 to the co-receptor (c). Co-receptor antagonists inhibit this step by binding to the co-receptor and changing its shape so that gp120 cannot recognize it. Co-receptor binding induces conformational changes in gp41 and insertion of the fusion peptide into the host cell membrane (d), ultimately resulting in fusion of the viral envelop with the host cell membrane²¹. (e) Structural formulae of selected CCR5 antagonists.

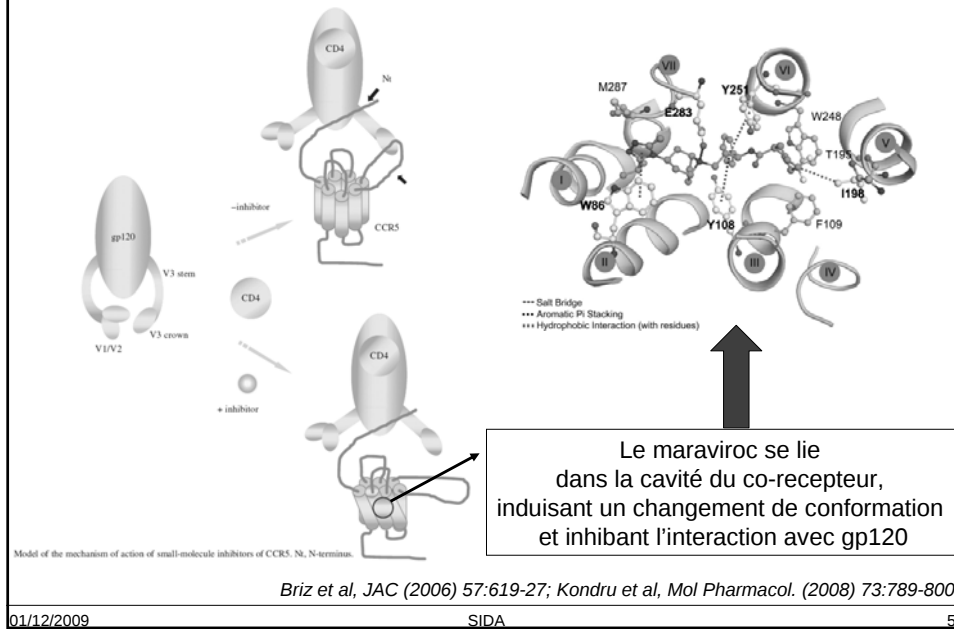
De Clercq, Nature Rev. Drug Discov. (2007) 6:1001-1018

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Antagonistes de CCR5



Maraviroc: propriétés pharmacologiques

Propriétés pharmacocinétiques

- résorption par voie orale
- métabolisme par CYP450, demi-vie ~ 10 h ; administration 2X/jour

Effets secondaires principaux

- troubles gastro-intestinaux
- hépatotoxicité.
- risque accru d'infections possible (réponse immunitaire réduite par blocage de CCR5 ?)

Interactions médicamenteuses

- maraviroc = substrat du CYP450 et de P-glycoprotéine ;
dose à adapter en fonction des traitements reçus par le patient

Concomitant drug effect	Concomitant medication examples	Dosage
No net alteration in metabolism	Tipranavir plus ritonavir, nevirapine, all NRTIs, and enfuvirtide	300 mg BID
CYP3A inhibitors (with or without a CYP3A inducer)	Ritonavir, all boosted protease inhibitors (except tipranavir plus ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazadone, and telithromycin	150 mg BID
CYP3A inducers alone	Efavirenz, etravirine, rifampin, carbamazepine, phenobarbital, and phenytoin	600 mg BID

Usage clinique

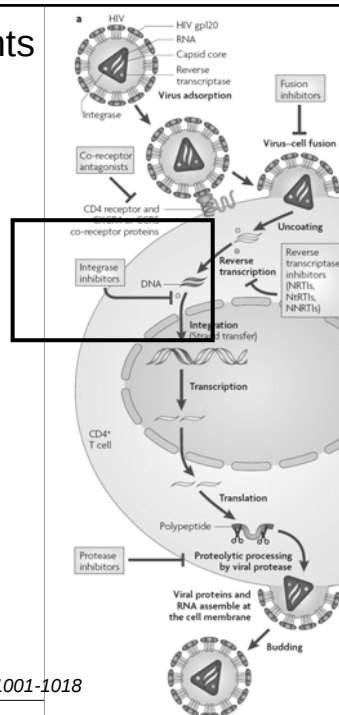
- uniquement dans les infections à HIV-1 ayant un tropisme pour CCR5
- en association avec d'autres antiviraux; patients phase avancée (souches multirésistantes)

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Cible des médicaments actifs sur le HIV

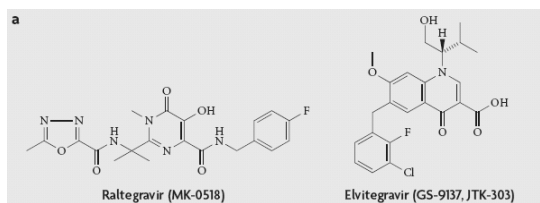
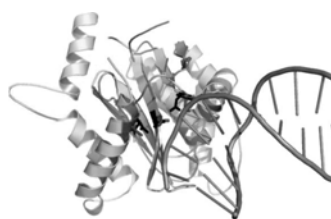
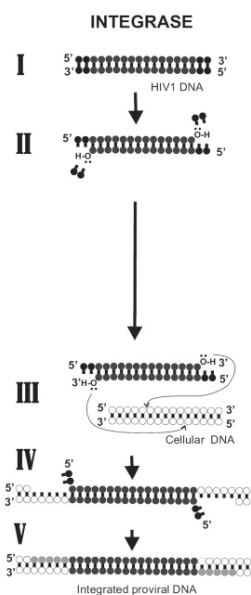


De Clercq, *Nature Rev. Drug Discov.* (2007) 6:1001-1018

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Inhibiteurs d'intégrase



Savarino, *Retrovirology*. (2007) 4:21

01/12/2009

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Raltegravir: propriétés pharmacologiques

Propriétés pharmacocinétiques

- résorption par voie orale (400 mg 2x/jour)
- pas de métabolisme par CYP450 mais par glucurono-conjugaison

Effets secondaires principaux

- maux de tête, vertiges, fatigue, arthralgies
- troubles gastro-intestinaux (nausées, diarrhées)
- éruptions cutanées

Interactions médicamenteuses

- PAS d'interaction ~ CYP
- + rifampicine: ↓ des conc. sanguines de raltégravir par induction de la glucuronoconjugaison
- + inhibiteur de sécrétion d'acide gastrique: ↑ résorption orale

Usage clinique

- en association avec d'autres antviraux; patients phase avancée (souches multirésistantes)

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PHARMACOTHERAPIE DU SIDA



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Buts du traitement

- ↓ charge virale
0.5-0.75 $\log_{10}$ en 4 semaines ou 1 $\log_{10}$ en 8 semaines
- charge virale non détectable à 4-6 mois
(< 50 - 20 copies)
- restaurer ou préserver la fonction immunitaire
- réduire la morbidité et la mortalité



Trithérapie pour éviter la sélection de résistance

01/12/2009

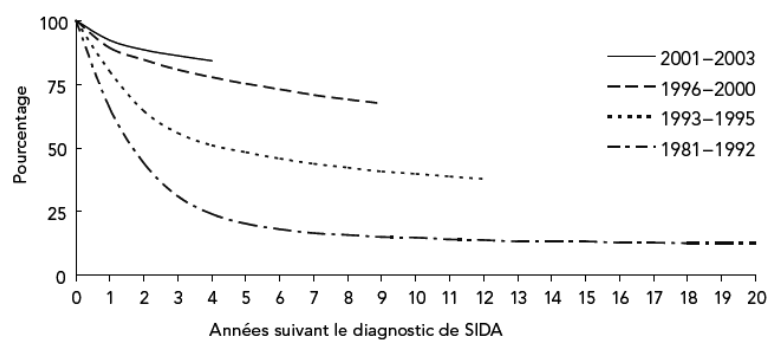
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Grâce au HAART la survie des patients s'améliore



Pourcentage de personnes encore en vie en juin 2006,
par cohortes selon les années suivant le diagnostic de SIDA
entre 1981 et 2003 et par année de diagnostic



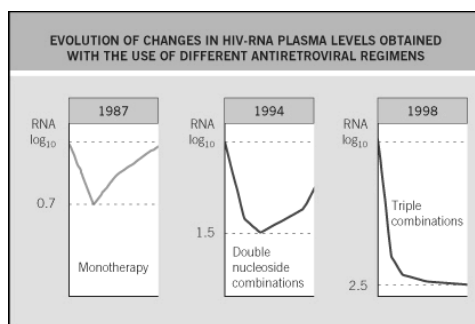
Source : CDC Twenty-five years of HIV/AIDS - Etats-Unis, 1981-2006. MMWR 2006.

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Grâce au HAART la survie des patients s'améliore



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Algorithme de traitement proposé par l'OMS (1/3)

TABLE 6. RECOMMENDATIONS FOR INITIATING ART IN PLHIV		
WHO clinical stage ^a	CD4 cell count	Recommendation
1	<200/mm ³	Treat
	200–350/mm ³	Consider treatment ^b
2	<200/mm ³	Treat
	200–350/mm ³	Consider treatment ^b
3	200–350/mm ³	Treat
4	Regardless of CD4 count	Treat

1. asymptomatique, adénopathie
2. Candidose, infections respiratoire, herpes
3. Candidose récurrente, ulcération de la bouche, infections pulmonaires sévères, diarrhée inexpliquée
4. Infections opportunistes

www.euro.who.int/document/e90840.pdf

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Algorithme de traitement proposé par l'OMS (2/3)

TABLE 7. RECOMMENDED FIRST-LINE HAART	
ARV drug classes	HAART regimens
2 NRTIs + 1 NNRTI	ZDV + 3TC + (EFV ^a or NVP)
	or TDF + FTC + (EFV ^a or NVP)
	or ABC + 3TC + (EFV ^a or NVP)

^a EFV is highlighted as the preferred NNRTI.



TABLE 8. CRITERIA FOR TREATMENT SUCCESS				
	Virological		Immunological	Clinical
Marker	Viral Load		CD4 cell count	Clinical stage
Time ^a	24 weeks	48 weeks	24–48 weeks	By 12 weeks of treatment initiation should be asymptomatic or have few symptoms
Suggested ranges ^a	<400 copies/ml	<50 copies/ml	Increase from baseline by at least 50–100 cells/mm ³	Stage 1 or 2 ^b

www.euro.who.int/document/e90840.pdf

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Algorithme de traitement proposé par l'OMS (3/3)



TABLE 9. RECOMMENDED SECOND-LINE HAART FOR ADULTS AND ADOLESCENTS	
First-line HAART regimens	Second-line HAART regimens after treatment failure
ZDV + 3TC + (EFV or NVP)	LPV/r ^a (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ABC or LPV/r ^a (or ATV/r, SQV/r, FPV/r, IDV/r) + TDF + ABC or LPV/r ^a (or ATV/r, SQV/r, FPV/r, IDV/r) + TDF + (ZDV + 3TC) ^b
TDF + FTC + (EFV or NVP)	LPV/r ^a (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ABC or LPV/r ^a (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ZDV
ABC + 3TC + (EFV or NVP)	LPV/r ^a (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ZDV or LPV/r ^a (or ATV/r, SQV/r, FPV/r, IDV/r) + ZDV + TDF (+ 3TC) ^b

**Adapter le choix en fonction des risques de résistance croisée
et d'interaction médicamenteuse...**

www.euro.who.int/document/e90840.pdf

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Gare aux interactions médicamenteuses

Un outil pour le pharmacien !

The screenshot shows the website www.hiv-druginteractions.org. It features a navigation menu with links to Interaction Charts, News & Archive, About Us, Pharmacy Resources, Links, Meetings, Tools, Feedback, and Home. The main content area lists several categories of drug interactions with corresponding PDF download links:

- Protease Inhibitor Drug Interactions**: Colour Printer Version, Black & White Printer Version
- Non nucleoside RT Inhibitor Drug Interactions**: Colour Printer Version, Black & White Printer Version
- Nucleoside/Nucleotide RT Inhibitor Drug Interactions**: Colour Printer Version, Black & White Printer Version
- Entry/Integrase Inhibitor Drug Interactions**: Colour Printer Version, Black & White Printer Version

At the bottom, there are logos for major sponsors: Abbott Laboratories, Gilead, and other sponsors.

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Suivi des patients



TABLE 10.	FREQUENCY OF LABORATORY TESTING, GENERALLY AND WITH SPECIFIC ARV USE							
	Baseline	Week 2	Week 4	Week 8	Week 16	Week 24	Week 36	Week 48
Viral load	X			X		X	X	X
CD4 count	X			X		X	(X)	X
Complete blood count	X		X	X	X (ZDV)	X	(X)	X
Liver Function Test (LFT)	X	X (NVP)	X	X (NVP, ZDV, PIs)	X (NVP, PIs)	X	(X)	X
Cholesterol triglycerides	X (PIs)				X (PIs)			X (PIs)
Renal function test	X	X (TDF)	X (TDF, IDV)			X	(X)	X

X: laboratory tests to be performed irrespective of the ARVs being administered; X (ARV): laboratory tests to be performed if an ARV in parentheses is being administered; (X): optional test.

www.euro.who.int/document/e90840.pdf

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Prévention de la transmission foeto-maternelle

REVERSE TRANSCRIPTASE INHIBITORS						
FDA approved						
Agent	Transmission to fetus prevented*	Neonates	Children	FDA pregnancy category ^[dagger]	Placental transfer (%)	
Zidovudine ^R	Yes	Yes	Yes	C	85	
Didanosine ^R	No	Yes	Yes	B	50	
Lamivudine ^R	Yes	No	≥3 months	C	100	
Stavudine ^R	No	No	≥1 months	C	76 (rhesus monkeys)	
Zalcitabine ^R	No	No	No	C	30-50 (rhesus monkeys)	
Abacavir	No	No	≥3 months	C	Yes (rats)	
Nevirapine ^R	Yes	No	≥2 months	C	100	
Delavirdine	No	No	No	C	?	
Efavirenz ^R	No	No	≥3 years	C	100 (rhesus monkeys)	
Tenofovir	No	No	No	B	Yes (rat, monkey)	

PROTEASE INHIBITORS						
FDA approved						
Agent	Transmission to fetus prevented*	Neonates	Children	FDA pregnancy category ^[dagger]	Placental transfer	
Nelfinavir	No	No	≥2 years	B	Minimal	
Indinavir	No	No	No	C	Minimal	
Ritonavir ^R	No	No	≥2 years	B	Minimal	
Saquinavir ^R	No	No	No	B	Minimal	
Amprenavir ^R	No	No	≥4 years	C	?	
Lopinavir/ritonavir	No	No	≥6 months	C	?	

Ne passent pas
la barrière placentaire



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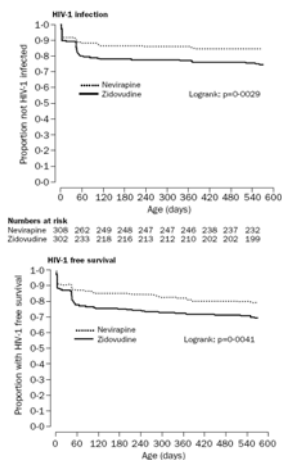
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Prévention de la transmission foeto-maternelle

→ Traitement suggéré:

- AZT or AZT/3TC – pendant la gestation et continuer pendant l'accouchement
- Nevirapine – 1 dose à la mère et à l'enfant (zones défavorisées)



Methods From November, 1997, to April, 1999, HIV-1 infected pregnant women in Kampala, Uganda, were randomly assigned nevirapine (200 mg at labour onset and 2 mg/kg for babies within 72 h of birth; regimen A) or zidovudine (600 mg orally at labour onset and 300 mg every 3 h until delivery, and 4 mg/kg orally twice daily for babies for 7 days, regimen B). Infant HIV-1 testing was done at birth, age 6–8 and 14–16 weeks, and age 12 months by HIV-1 RNA PCR, and by HIV-1 antibody at 18 months.

Traitement court:
la nevirapine
est plus efficace !

Jackson et al, Lancet (2003) 362:859-68.



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Prévention lors d'une exposition accidentelle à un matériel contaminé



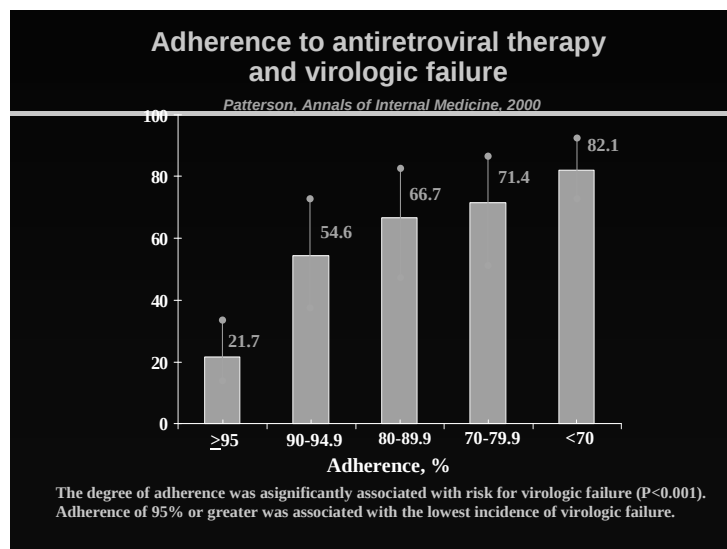
- traitement administré le plus rapidement possible ; 4 semaines
- association puissante : 2 NRTI et 1 IP
(zidovudine-lamivudine-indinavir)
[bonne tolérance et interactions médicamenteuses limitées]
- surveillance clinique et biologique à maintenir plus longtemps.

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Importance de l'adhérence au traitement



J. Nachega, 2006

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Comment améliorer la compliance ?



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Comment améliorer la compliance ?



Simplification des régimes thérapeutiques: comparaison entre 1996 et 2004

1996:

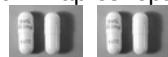
ddl + d4T + SQV

-24 gélules/jour:

-SQV: 6 gel 3 X/jour avec la nourriture



-ddl: 2 gel 2 X jour ½ hr avant
ou 2 h après repas



-d4T: 1 co 2 X /jour



2004:

TDF/FTC or ABC/3TC + EFV

- 1 co 2 X/ jour + 1 co 1X/jour



pas restriction par rapport au repas

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Comment améliorer la compliance ?



Reasons for Missing Doses of Antiretroviral Therapy

US

Chesney

- Simply forgot
- Slept through dose
- Away from home
- Change in routine
- Busy with other things
- Too sick
- Depressed

Africa

Weidle, Orrell, Nachega, Brown,

- Forgot
- Away from home
- Schedule difficulties
- Ran out of pills
- Cost
- Home language
- Fear of stigmatization by sexual partner

J. Nachega, 2006

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.. Un rôle de choix pour le pharmacien !



http://www.ascp.com/public/pubs/tcp/1998/nov/hivaids.shtml

ascp AMERICAN SOCIETY OF CONSULTANT PHARMACISTS

- Membership
- Practice Resources
- Meetings & Education
- Government Affairs
- Publications & Products
- ConsultNet™
- Students & New Practitioners
- ASCP Calendar
- ASCP Foundation
- News

Quick jump to...

Current Concepts in

HIV/AIDS Pharmacotherapy

Pharmacists have assumed an increasingly important role in monitoring and fine-tuning HIV drug therapy for maximal effectiveness....

http://www.fip.org/activities/activities_working_aidsmember.html

The International Pharmaceutical Federation (FIP) and World Health Organisation (WHO) Working Group on AIDS and Drug Addiction

PHARMACISTS AS KEY FOR PREVENTION AND PHARMACEUTICAL CARE PROVIDERS FOR PEOPLE LIVING WITH HIV

COMPOSITION OF THE WORKING GROUP

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Association Chrétienne des Institutions Sociales et de Santé,

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Conseil National de l'Ordre des pharmaciens

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