Pharmacotherapy of HIV Management for Clinicians

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Global Summary of the AIDS Epidemic—December 2008

Number of people living with HIV in 2008		
	Total	33.4 million [31.1 million–35.8 million]
	Adults	31.3 million [29.2 million–33.7 million]
	Women	15.7 million [14.2 million–17.2 million]
	Children under 15 years	2.1 million [1.2 million–2.9 million]
People newly infected with HIV in 2008		
	Total	2.7 million [2.4 million–3.0 million]
	Adults	2.3 million [2.0 million–2.5 million]
	Children under 15 years	430 000 [240 000–610 000]
AIDS-related deaths in 2008		
	Total	2.0 million [1.7 million–2.4 million]
	Adults	1.7 million [1.4 million–2.1 million]
	Children under 15 years	280 000 [150 000–410 000]

2009 AIDS epidemic update. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) 2009.

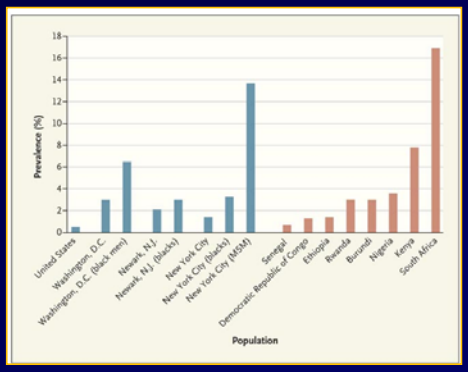
Global Summary of the AIDS Epidemic—December 2008

Region	Adults & children living with HIV/AIDS	Adults & children newly infected	Adult prevalence*	Deaths of adults & children
Sub-Saharan Africa	22.4 million	1.9 million	5.2%	1.4 million
North Africa & Middle East	310,000	35,000	0.2%	20,000
South and South-East Asia	3.8 million	280,000	0.3%	270,000
East Asia	850,000	75,000	<0.1%	59,000
Oceania	59,000	3900	0.3%	2,000
Latin America	2.0 million	170,000	0.6%	77,000
Caribbean	240,000	20,000	1.0%	12,000
Eastern Europe & Central Asia	1.5 million	110,000	0.7%	87,000
North America	1.4 million	55,000	0.4%	25,000
Western & Central Europe	850,000	30,000	0.3%	13,000
Global Total	33.4 million	2.7 million	0.8%	2.0 million

* Proportion of adults aged 15-49 who were living with HIV/AIDS

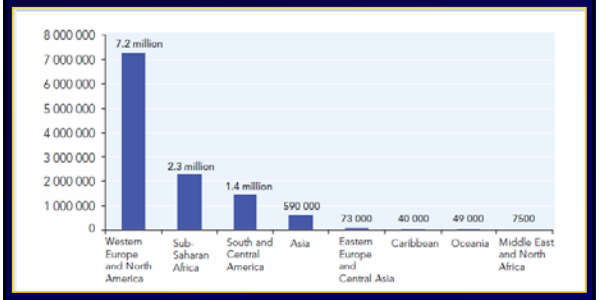
2009 AIDS epidemic update. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) 2009.

HIV Prevalence



El-Sadar W, et al. AIDS in America--Forgotten but not gone. N Engl J Med 2010;(Epub ahead of the print 10.1056/NEJMp1000069).

Estimated Number of Life-Years Added Due to Antiretroviral Therapy



2009 AIDS epidemic update. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) 2009.

WHEN TO START HAART?

Indications for Initiating Antiretroviral Therapy

- History of an AIDS-defining illness or CD4 count < 350 cells/mm^3
- Regardless of CD4 count
  - Pregnancy
  - HIV-associated nephropathy
  - Hepatitis B virus (HBV) coinfection (when HBV treatment is indicated)

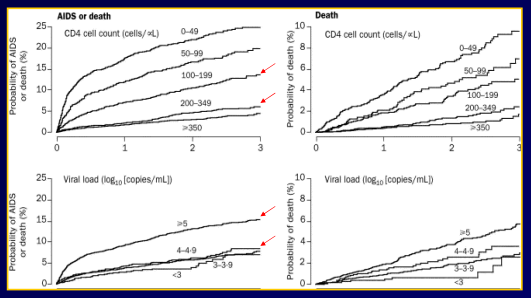
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov.

Indications for Initiating Antiretroviral Therapy

- CD4 counts between 350 and 500 cells/mm^3
  - Panel was divided
    - 55% with AII rating
    - 45% with BII rating
- CD4 counts > 500 cells/mm^3
  - Panel was divided
    - 50% with BIII
    - 50% with CIII

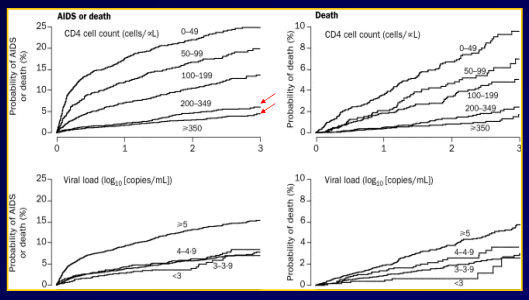
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov.

When to Start HAART?



Reprinted from The Lancet, 360, Egger M. et al, Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies, 119-29, Copyright (2002).

When to Start HAART?



Reprinted from The Lancet, 360, Egger M, et al, Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies, 119-29, Copyright (2002).

When to Start HAART? Determinants of a First-AIDS-defining Malignancy

Variable	Cumulative Exposure	P-value
CD4 cell count, < 200 cells/mm^3 Per additional year of exposure	1.36 (1.21-1.54)	<0.001
Plasma HIV RNA level, > 500 copies/mL Per additional year of exposure	1.27 (1.15-1.40)	<0.001
ARV exposure Per additional year	0.82 (0.74-0.91)	<0.001

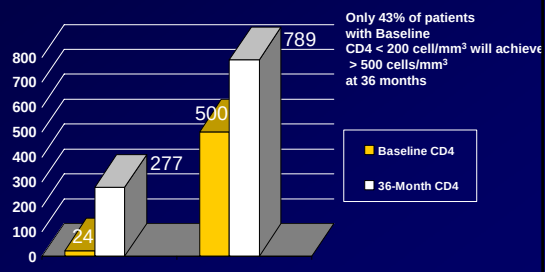
Bruyand M, et al. Clin Infect Dis 2009;49:1109-16.

When to Start HAART? Determinants of a First Non-AIDS-defining Malignancy

Variable	Cumulative Exposure	P-value
CD4 cell count, < 500 cells/mm^3 Per additional year of exposure	1.13 (1.03-1.24)	<0.01
Plasma HIV RNA level, > 500 copies/mL Per additional year of exposure	1.03 (0.94-1.13)	<0.49
ARV exposure Per additional year	0.99 (0.91-1.08)	<0.87

Bruyand M, et al. Clin Infect Dis 2009;49:1109-16.

When to Start HAART?
Impact of CD4 cell count at 36 months



The antiretroviral therapy cohort collaboration (ART-CC). AIDS 2009.

www.googleimages.com

When to Start HAART?

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EDITORIAL

Volume 333:450-451 August 17, 1995 Number 7

Time to Hit HIV, Early and Hard

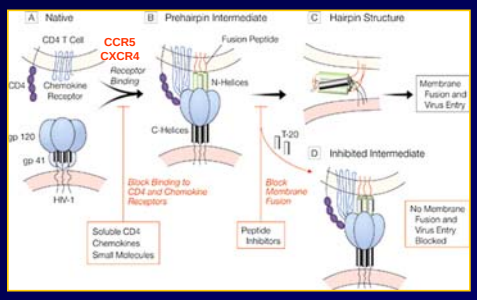
Early treatment of asymptomatic human immunodeficiency virus type 1 (HIV-1) infection remains controversial. In the AIDS Clinical Trials Group 019 study, zidovudine was shown in 1990 to slow the clinical progression to AIDS in infected but asymptomatic subjects.[1] However, a follow-up of those subjects found no evidence of longer survival with the use of zidovudine.[2] Furthermore, the Concorde study found that there was not only no survival benefit from early treatment with zidovudine, but also no effect on the overall progression of disease.[3] Now, in this issue of the Journal, Volberding et al. report the further results of the AIDS Clinical Trials Group study, which show that immediate zidovudine therapy, as compared with deferred treatment, in asymptomatic persons with CD4 lymphocyte counts of 500 or more cells per cubic millimeter does not prolong the disease-free period or confer a survival benefit.[4] At the same time, Ensoli-de Lotz et al. show that the use of zidovudine earlier, during primary HIV-1 infection and six months thereafter, results in a detectable improvement in the clinical course as well as an increase in the CD4 cell count.[5] The seemingly contradictory nature of these new findings, although attributable in part to differences in study design and study subjects, can be explained in the light of recent observations on the pathogenesis of HIV-1.

WHICH HAART TO START?

Pharmacologic Agents

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov.

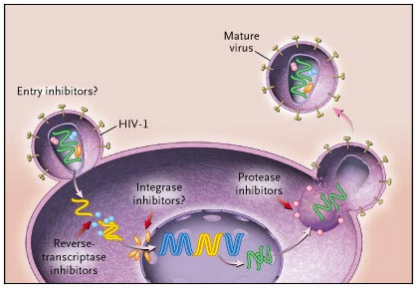
ARV Mechanism of Action



D'Souza et al. JAMA 2000;284:215-22.

Cervia et al. CID 2003;37:1102-6.

ARV Mechanism of Action



Kilby JM et al. N Engl J Med 2003;348:2228-38.

Preferred HAART Regimens

Panel's Recommendations:

- *The Panel recommends initiating antiretroviral therapy in treatment naïve patients with 1 of the following 3 types of regimen:*
  - *NNRTI + 2 NRTI*
  - *PI (preferably boosted with ritonavir) + 2 NRTI*
  - *INSTI + 2 NRTI*
- *The Panel recommends the following as preferred regimens for treatment naïve patients:*
  - *Efavirenz + tenofovir + emtricitabine (AI)*
  - *Ritonavir-boosted atazanavir + tenofovir + emtricitabine (AI)*
  - *Ritonavir-boosted darunavir + tenofovir + emtricitabine (AI)*
  - *Raltegravir + tenofovir + emtricitabine (AI)*
- *A list of Panel recommended alternative and acceptable regimens can be found in Table 8a.*
- *Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.*
- *Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.*

INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov.

ART Components for Treatment Naïve Patients

PI-BASED REGIMENS (RITONAVIR-BOOSTED OR UNBOOSTED PI + 2 NRTIs)

Panel's Recommendations:

Preferred PI (in alphabetical order):

- *atazanavir + ritonavir once daily (AI)*
- *darunavir + ritonavir once daily (AI)*
- *fosamprenavir + ritonavir twice daily (BI)*
- *lopinavir/ritonavir (coformulated) once or twice daily (AI)*

Alternative PI (BI) (in alphabetical order):

- *atazanavir* (unboosted) once daily*
- *fosamprenavir (unboosted) twice daily*
- *fosamprenavir + ritonavir once daily*
- *saquinavir + ritonavir twice daily*

** Ritonavir 100mg per day must be given when tenofovir or efavirenz is used with atazanavir.*

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. November 3, 2008. www.aidsinfo.nih.gov.

ART Components for Treatment Naïve Patients

DUAL-NUCLEOSIDE OPTIONS AS PART OF INITIAL COMBINATION THERAPY

Panel's Recommendations:

Preferred dual-NRTI (AI):

- *tenofovir/emtricitabine*(coformulated)*

Alternative dual-NRTIs (BI) (in alphabetical order):

- *abacavir/lamivudine* (coformulated) in patients tested negative of HLA-B*5701*
- *didanosine + (lamivudine or emtricitabine)*
- *zidovudine/lamivudine*(coformulated)*

** Emtricitabine may be used in place of lamivudine or vice versa.*

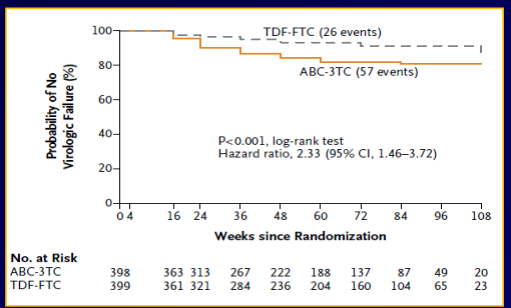
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. November 3, 2008. www.aidsinfo.nih.gov.

Which HAART to Start?

- AIDS Clinical Trials Group A5202
  - Phase 3B, 96-week study
  - Initial once-daily ARV treatment regimens
    - Abacavir 600 mg/lamivudine 300 mg, or
    - Tenofovir 300 mg/emtricitabine 200 mg with
    - Atazanavir 300 mg/ritonavir 100 mg or
    - Efavirenz 600 mg
  - 1858 eligible patients
  - 797 patients with baseline HIV PCR > 100,000 copies/mL

Sax PE, et al. N Engl J Med 2009;361:2230-40.

Which HAART to Start? A5202



Sax PE, et al. N Engl J Med 2009;361:2230-40.

Which HAART to Start? Individual Tailoring

- Comorbid conditions
- Baseline genotypic analysis
  - Ranges between 6-16%
  - Cost-effective
- Pharmacogenomic analysis
- Adherence
- Drug Interactions
- Resistance prediction
- Expected toxicities

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov. Treatment for Adult HIV Infection. JAMA 2006;296:827-43

Measurements of Resistance

- Genotypic test
  - Detection of HIV genetic mutations predominating at the time of sample
  - Significance of mutations not evaluated
  - Difficult to perform if HIV <1000 copies
  - $360-480/test

Guidelines for the Use in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov. Treatment for Adult HIV Infection. JAMA 2006;296:827-43. Topics in HIV Medicine 2006;2006:13:106-17

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Pharmacogenomic Analysis

- Abacavir hypersensitivity reaction
  - Incidence: 5-8% patients
  - Onset: within 6 weeks of therapy
  - Early discontinuation of therapy
- HLA-B*5701 screening
  - 100% Negative Predictive Value
  - 47.9% Positive Predictive Value
  - True hypersensitivity reactions: 2.7%

Mallal S, et al. *N Engl J Med* 2008;358:568-79.

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Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov. Treatment for Adult HIV Infection. JAMA 2006;296:827-43.

Patient Case

- 56 yo AAM presents for initial evaluation
- PMH:
  - HTN
  - Obesity (138kg)
- SH:
  - Tobacco (+)
  - Occasional EtOH
- Medications:
  - Amlodipine/benazapril 10mg/40mg
  - Followed by PCP with poor control

Patient Case

143 | 107 | 21 / 96
3.5 | 24 | 1.13

5.8 / 12.3 / 207
34.7

UA: ptn (-); glucose (-)

HLA-B*5701 Negative

LFTs	AST 22	ALT 21	ALP 111
Cholesterol	HDL 33	LDL 103	TG 101
Surrogate markers	CD_4 261 (9%) cells/mm^3	HIV PCR 155,000 copies/ml	HAV (-) HBV (-) HCV (-)
Baseline Genotype	NRTIs None reported	NNRTIs None reported	PIs L63P

Preferred HAART Regimens

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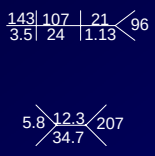
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov. Treatment for Adult HIV Infection. JAMA 2006;296:827-43

Which HAART to Start?

- A. Efavirenz
- B. Atazanavir/ritonavir
- C. Darunavir/ritonavir
- D. Raltegravir

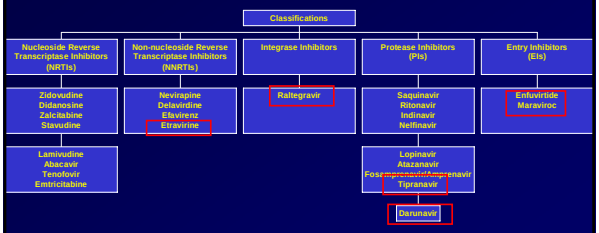
Patient Case



LFTs	AST 17	ALT 17	ALP 123
Cholesterol	HDL 42	LDL 112	TG 180
Surrogate markers	CD_4 392 (14) cells/mm^3	HIV PCR <50 copies/mL	

WHICH HAART TO START FOR THE PATIENT WITH RESISTANCE?

Pharmacologic Agents



Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov.

Goals of Therapy in the Resistant Patient

- Defined Goals
  - To achieve plasma HIV PCR below assay detection

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov. Treatment of Adult HIV Infection. JAMA 2006;296:827-43

Patient Case: Multidrug Resistance

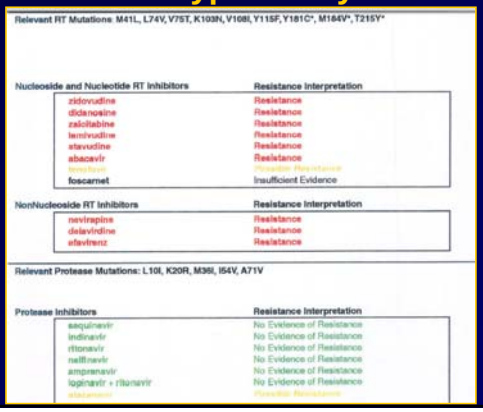
- 46yo WM with HIV diagnosed in 1983
  - PMH:
    - Kaposi's sarcoma
    - COPD
    - Peripheral neuropathy
- Prior HAART includes:
  - All NRTIs with ? HSR to abacavir
  - Efavirenz and Nevirapine
  - Fosamprenavir/ritonavir [(most recent HAART) 2005-2008]
  - Saquinavir
  - Full dose ritonavir in 1996
- HIV PCR= 135,000 copies/mL
- CD_4=120 (10%) cells/mm^3

Which HAART to Start for the Patient with Resistance?

- Comorbid conditions
- Baseline genotypic analysis
  - Ranges between 6-16%
  - Cost-effective
- Pharmacogenomic analysis
- Adherence
- Drug Interactions
- Resistance prediction
- Expected toxicities
- Assessment of treatment failure
  - Adherence issues
  - Medication intolerance
  - Pharmacokinetic issues
    - Food/fasting requirements
    - Drug-drug interactions
  - Suspected drug resistance
    - Genotypic analysis
    - Phenotypic analysis
  - Virologic suppression
  - Immunologic failure

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov.

Genotypic Analysis



Relevant RT Mutations: M41L, L74V, V75T, K103N, V108I, Y115F, Y181C*, M184V*, T215Y*

Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
zidovudine	Resistance
didanosine	Resistance
zalcitabine	Resistance
lamivudine	Resistance
stavudine	Resistance
abacavir	Resistance
tenofovir	Possible Resistance
foscarnet	Insufficient Evidence

NonNucleoside RT Inhibitors	Resistance Interpretation
nevirapine	Resistance
delavirdine	Resistance
efavirenz	Resistance

Relevant Protease Mutations: L10I, K20R, M36I, I54V, A71V

Protease Inhibitors	Resistance Interpretation
saquinavir	No Evidence of Resistance
indinavir	No Evidence of Resistance
ritonavir	No Evidence of Resistance
nelfinavir	No Evidence of Resistance
amprenavir	No Evidence of Resistance
lopinavir + ritonavir	No Evidence of Resistance
atazanavir	Possible Resistance

Measurements of Resistance

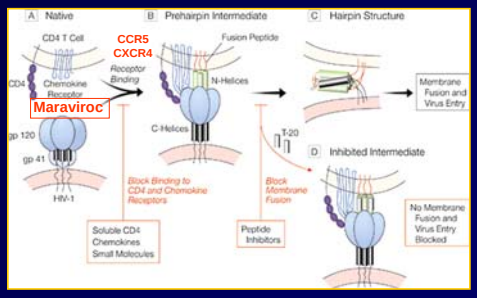
- Phenotypic test
  - Growth properties of HIV in the presence of antiretroviral agents
  - IC 50, 90, 95%
  - Difficult to perform if HIV <1000 copies
  - $900/test

Guidelines for the Use of Antiretroviral Agents. December 1, 2009. www.aidsinfo.nih.gov. JAMA 2006;296:827-43. Gallant JE. Topics in HIV Medicine 2005;2005(5):153-157.

Which HAART to Start for the Patient with Resistance?

- A. Etravirine
- B. Darunavir/ritonavir
- C. Enfuvirtide
- D. Maraviroc
- E. Raltegravir
- F. Tipranavir

ARV Mechanism of Action



D'Souza et al. JAMA 2000;284:215-22.

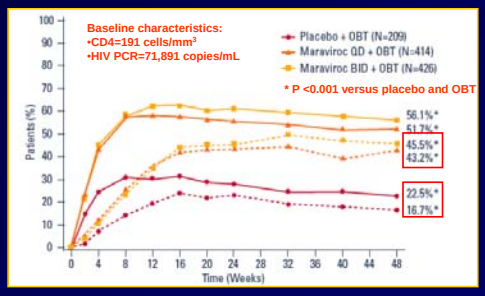
Cervia et al. CID 2003;37:1102-6.

CCR5 Antagonist: Maraviroc (Selzentry)

- CCR5 tropism must be tested prior to initiation
- Maraviroc 150-600 mg bid
- Adverse reactions
  - Cough/Pyrexia
  - URIs
  - Musculoskeletal symptoms
  - Abdominal pain
  - Dizziness
  - Cardiac ischemia
  - Rash
    - Systemic allergic rxn reaction +/- hepatitis
    - Black Box Warning

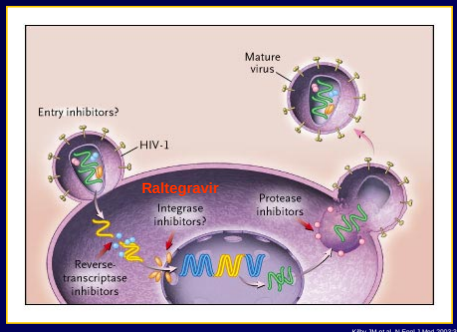
Lalezari J, et al. 14th CROI, Los Angeles, CA. February 27, 2007. Abstract 104bLB. Nelson M, et al. 14th CROI, Los Angeles, CA. February 27, 2007. Abstract 104aLB. Maraviroc Prescribing Information. www.fda.gov

CCR5 Antagonist Maraviroc (Selzentry)



Hardy D, et al. 15th CROI. Boston, USA. February 3-6, 2008. Poster 792. www.natap.org/2008/CROI/croi_43.htm. Gulick RM, et al. N Engl J Med 2008;359:1429-41

ARV Mechanism of Action



Kilby JM et al. N Engl J Med 2003;348:2228-38.

Integrase Inhibitor: Raltegravir (Isentress)

- Novel MOA
- Dosage: 400 mg bid
- Elimination:
  - Metabolism: glucuronidation via UDGT
- Minimal drug interactions
- Adverse events
  - Nausea
  - Headache
  - CPK elevation (6%)

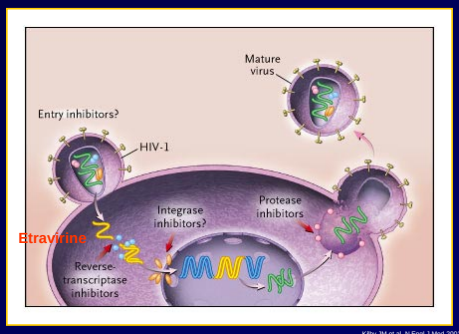
Colquitt AR, Pham PA. The Hopkins HIV Report 2007;19:11-2. Grinsztejn B, et al. Lancet 2007;369:1261-9. Raltegravir Prescribing Information. www.fda.gov.

Raltegravir (Isentress) Phase III Clinical Trial

Benchmark I, II	*Raltegravir 400 mg bid*	*Placebo*
Baseline	(N=462)	(N=237)
Viral Load (copies/mL)	44,668	39,810
CD4 Cell count (cells/mm3)	151	158
Efficacy at Week 48		
< 400 copies/mL	73.1	37.4
< 50 copies/mL	62.8	33.2
CD4 Change (cells/mm3)	109	45

Steigbigel R, et al. N Engl J Med 2008;359:339-54. Steigbigel, R, et al. CID 2010;50:605-12.

ARV Mechanism of Action



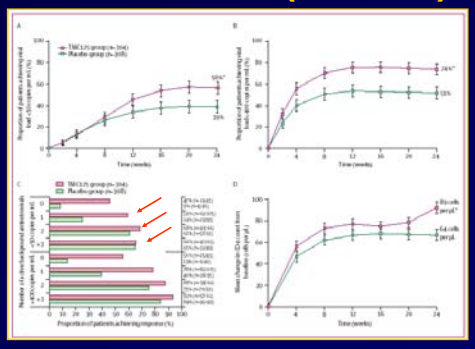
Kilby JM et al. N Engl J Med 2003;348:2228-38.

NNRTI: Etravirine (Intelence)

- Indication: Treatment resistant HIV
- Dosage: 200 mg bid
- Elimination:
  - Metabolism
    - CYP 3A4, 2C9, 2C19
    - Glucuronidation
- Drug Interactions:
  - CYP 3A4 induction
  - CYP 2C9/19 inhibition
- Adverse events:
  - Rash

Colquitt AR, et al. The Hopkins HIV Report 2007;19:8-10. Madruga JV, et al. Lancet 2007;270:29-38. Lazzarin A, et al. Lancet 2007;370:39-48.Etravirine Prescribing Information. www.fda.gov

NNRTI:Etravirine (Intelence)



Reprinted from The Lancet, 370, Madruga JV, et al, Efficacy and safety of TMC 125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results, 29-38, Copyright (2007), AIDS 2009;23:2289-2300

Patient Case: Multidrug Resistance

- 46yo WM with HIV diagnosed in 1983
  - PMH:
    - Kaposi's sarcoma
    - COPD
    - Peripheral neuropathy
- Prior HAART includes:
  - All NRTIs with ? HSR to abacavir
  - Efavirenz and Nevirapine
  - Fosamprenavir/ritonavir [(most recent HAART) 2005-2008]
  - Saquinavir
  - Full dose ritonavir in 1996
- HIV PCR= 135,000 copies/mL
- CD_4=120 (10%) cells/mm^3

Raltegravir-Etravirine Drug-Drug Interactions

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug: No Effect = 1.00			
			n	C_{max}	AUC	C_{min}
atazanavir	400 mg daily	100 mg single dose	10	1.53 (1.11, 2.12)	1.72 (1.47, 2.02)	1.95 (1.30, 2.92)
atazanavir/ritonavir	300 mg/100 mg daily	400 mg twice daily	10	1.24 (0.87, 1.77)	1.41 (1.12, 1.78)	1.77 (1.39, 2.25)
efavirenz	600 mg daily	400 mg single dose	9	0.64 (0.41, 0.98)	0.64 (0.52, 0.80)	0.79 (0.49, 1.28)
etravirine	200 mg twice daily	400 mg twice daily	19	0.89 (0.68, 1.15)	0.90 (0.68, 1.18)	0.66 (0.34, 1.26)
omeprazole	20 mg daily	400 mg single dose	14 (10 for AUC)	4.15 (2.82, 6.10)	3.12 (2.13, 4.56)	1.46 (1.10, 1.93)
rifampin	600 mg daily	400 mg single dose	9	0.62 (0.37, 1.04)	0.60 (0.39, 0.91)	0.39 (0.30, 0.51)
rifampin	600 mg daily	400 mg twice daily when administered alone; 800 mg twice daily when administered with rifampin	14	1.62 (1.12, 2.33)	1.27 (0.94, 1.71)	0.47 (0.36, 0.61)

Raltegravir prescribing information. www.fda.gov.

Patient Case: Multidrug Resistance

- Raltegravir 800 mg AM/400 mg PM
- Etravirine 200 mg twice daily
- Tenofovir 300 mg/Emtricitabine 200 mg once daily

Patient Case: Multidrug Resistance

Follow-up	CD4 count (cells/mm3)	HIV PCR (copies/mL)
Baseline	120 (10%)	135,000
Four weeks	285 (15%)	200
Four months	288 (16%)	< 48
Eight months	272 (17%)	< 48
Eleven months	306 (17%)	59
Fifteen months	324 (18%)	56.1
Nineteen months	240 (15%)	< 48

Patient Case: Multidrug Resistance

	ETV C_{trough} (ng/ml)	RAL C_{trough} (ng/ml)	ARV-associated C_{trough} (ng/ml)
Case 1			
June 2008	–	189	4633 (DRV)
August 2008	Initiation	313	2240 (DRV)
September 2008	1105	10*	3516 (DRV)
October 2008	671	5*	2674 (DRV)
Case 2			
December 2007	NA*	30 (800 mg/day)	90 (TDF)
February 2008	NA*	67 (1200 mg/day)	
Case 3			
June 2008	NA*	12*	4046 (DRV)
September 2008	368	9*	3476 (DRV)
December 2008	274	22	1984 (DRV)
Case 4			
December 2008	564	29	

*Raltegravir C_{trough} lower than the IC 95 (14.6 ng/mL)

Menard A, et al. AIDS 2009;23:869-71.

Raltegravir
Drug-Drug Interactions

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00		
			n	C_{max}	AUC	C_{min}
atazanavir	400 mg daily	100 mg single dose	10	1.53 (1.11, 2.12)	1.72 (1.47, 2.02)	1.95 (1.30, 2.92)
atazanavir/ritonavir	300 mg/100 mg daily	400 mg twice daily	10	1.24 (0.87, 1.77)	1.41 (1.12, 1.78)	1.77 (1.39, 2.25)
efavirenz	600 mg daily	400 mg single dose	9	0.64 (0.41, 0.98)	0.64 (0.52, 0.80)	0.79 (0.49, 1.28)
etravirine	200 mg twice daily	400 mg twice daily	19	0.89 (0.68, 1.15)	0.90 (0.68, 1.18)	0.66 (0.34, 1.26)
omeprazole	20 mg daily	400 mg single dose	14 (10 for AUC)	4.15 (2.82, 6.10)	3.12 (2.13, 4.56)	1.46 (1.10, 1.93)
rifampin	600 mg daily	400 mg single dose	9	0.62 (0.37, 1.04)	0.60 (0.39, 0.91)	0.39 (0.30, 0.51)
rifampin	600 mg daily	400 mg twice daily when administered alone; 800 mg twice daily when administered with rifampin	14	1.62 (1.12, 2.33)	1.27 (0.94, 1.71)	0.47 (0.36, 0.61)

Raltegravir prescribing information. www.fda.gov.

Raltegravir
Drug-Drug Interactions

	No atazanavir substudy		Atazanavir substudy		Combined substudies	
	n	Value	n	Value	n	Value
Change from baseline in HIV-1 RNA (log_{10} copies per mL)						
Raltegravir 200 mg	29	-1·83 (-2·21 to -1·45)	12	-1·73 (-2·29 to -1·16)	41	-1·80 (-2·10 to -1·50)
Raltegravir 400 mg	31	-1·76 (-2·15 to -1·37)	14	-2·11 (-2·51 to -1·72)	45	-1·87 (-2·16 to -1·58)
Raltegravir 600 mg	31	-1·74 (-2·08 to -1·41)	13	-2·07 (-2·51 to -1·63)	44	-1·84 (-2·10 to -1·58)
Placebo	33	-0·26 (-0·52 to 0·01)	12	-0·60 (-1·30 to 0·09)	45	-0·35 (-0·61 to -0·09)
Proportion of patients with HIV-1 RNA <400 copies per mL						
Raltegravir 200 mg	30	70·0% (50·6 to 85·3)	13	69·2% (38·6 to 90·9)	43	69·8% (53·9 to 82·8)
Raltegravir 400 mg	31	64·5% (45·4 to 80·8)	14	85·7% (57·2 to 98·2)	45	71·1% (55·7 to 83·6)
Raltegravir 600 mg	32	62·5% (43·7 to 78·9)	13	92·3% (64·0 to 99·8)	45	71·1% (55·7 to 83·6)
Placebo	33	12·1% (3·4 to 28·2)	12	25·0% (5·5 to 57·2)	45	15·6% (6·5 to 29·5)
Proportion of patients with HIV-1 RNA <50 copies per mL						
Raltegravir 200 mg	30	63·3% (43·9 to 80·1)	13	69·2% (38·6 to 90·9)	43	65·1% (49·1 to 79·0)
Raltegravir 400 mg	31	48·4% (30·2 to 66·9)	14	71·4% (41·9 to 91·6)	45	55·6% (40·0 to 70·4)
Raltegravir 600 mg	32	56·3% (37·7 to 73·6)	13	92·3% (64·0 to 99·8)	45	66·7% (51·1 to 80·0)
Placebo	33	12·1% (3·4 to 28·2)	12	16·7% (2·1 to 48·4)	45	13·3% (5·1 to 26·8)
Change from baseline in CD4 cell count (cells per μL)						
Raltegravir 200 mg	29	60·5 (12·9 to 108·1)	12	68·5 (23·8 to 113·2)	41	62·9 (27·8 to 97·9)
Raltegravir 400 mg	30	102·1 (59·0 to 145·6)	13	137·2 (57·0 to 217·3)	43	112·8 (75·7 to 150·0)
Raltegravir 600 mg	30	93·8 (48·9 to 138·6)	12	94·8 (44·5 to 145·2)	42	94·1 (60·1 to 128·0)
Placebo	32	8·4 (-9·4 to 26·2)	11	-3·3 (-38·5 to 32·0)	43	5·4 (-9·9 to 20·7)

Grinsztejn B, et al. Lancet 2007;369:161-9.

Future Antiretrovirals

- Rilpivirine
  - NNRTI
  - 96-week, Phase II data
  - Dosage=25 mg
  - Drug-drug interaction with acid suppression
- Elvitegravir
  - Integrase inhibitor
  - Significant CYP interactions (CYP 3A4)
  - Pharmacokinetic enhancement with ritonavir

Fulco PP, et al. Pharmacotherapy 2009;29:281-94. Pozniak AL, et al. AIDS 2010;24:55-65. Correll T, et al. Pharmacotherapy 2008;28:90-101. DeJesus E, et al. J Acquir Immune Defic Syndr 2006;43:1-5.

HAART AND ADVERSE EVENTS

HAART and Adverse Events

Side-effect	New learning points	Most promising therapies*
Lipoatrophy	Largely preventable by avoidance of stavudine and zidovudine Contribution of protease inhibitors less certain Consider annual DEXA in those receiving stavudine, zidovudine, or protease inhibitor	Stavudine and zidovudine cessation helpful but improvement very gradual Pioglitazone (in those not receiving stavudine) Uridine Pravastatin
Central fat accumulation	Treatment directions limited by uncertainty about whether central fat accumulation is direct drug effect or secondary to lipoatrophy	Growth hormone Growth-hormone releasing hormone analogue Metformin
Dyslipidaemia	No proven benefit for diet or exercise	Protease inhibitor and/or NRTI cessation Pravastatin, low-dose atorvastatin, or rosuvastatin
Insulin resistance/ diabetes	Fasting glucose is poor tool for diagnosis of diabetes Consider oral glucose tolerance testing in higher-risk patients	Follow standard diabetic treatment guidelines
Cardiovascular disease	Withdrawal of ART increases risk, perhaps because of declines in HDL-cholesterol Traditional risk factors affect risk more than ART	Address all risk factors, such as smoking, hypertension and diabetes, not just raised total cholesterol
Hepatotoxicity	Nevirapine be initiated only in ART-naive men and women with CD4+ lymphocyte counts <400 and 250 cells per μL, respectively Didanosine associated rarely with hepatic fibrosis, nodular regenerative hyperplasia, and portal hypertension	Nil
Hypersensitivity	Abacavir hypersensitivity strongly linked to HLAB*5701 ancestral haplotype	Molecular testing for HLAB*5701 may prevent most abacavir hypersensitivity
Osteoporosis	Tenofovir associated with small increased risk of osteopenia over 3 years, but not with increased fracture rate Role of routine screening (bone mineral densitometry) unknown	Alendronate
Nephrotoxicity	Tenofovir associated with small increased risk of grade 3–4 nephrotoxicity	Nil
Enfuvirtide injection-site reactions	Occurs in 98% of patients and does not abate over time Has substantially affected use of enfuvirtide	Maybe less severe with use of needle-free injection device

Reprinted from The Lancet. Calmy A, et al. Lancet 2007;370:12-4. Copyright (2007).

Hypersensitivity: Rash

IMPORTANT DRUG WARNING

August 2009

Dear Healthcare Professional:

Tibotec Therapeutics, in cooperation with the U.S. Food and Drug Administration, would like to inform you of an important safety update to the Severe Skin Reactions WARNINGS AND PRECAUTIONS section (5.1) of the INTELENCE™ (etravirine) tablets prescribing information.

Specifically, the existing Warning and Precaution regarding Severe Skin Reactions has been strengthened to reflect that there have been postmarketing reports of:

- fatality due to toxic epidermal necrolysis
- hypersensitivity reactions, sometimes accompanied by hepatic failure

Additionally, Guidance has been added that INTELENCE should be immediately discontinued when signs and symptoms of severe skin or hypersensitivity reactions develop. Given the clini relevance of these adverse reactions, the following information regarding severe skin and hypersensitivity reactions has been included in the INTELENCE Prescribing Information:

5 WARNINGS AND PRECAUTIONS

5.1 Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized

www.fda.gov

Hypersensitivity: Rash

- Etravirine
  - Clinical trial data: 14-20%
  - Higher incidence in females
  - Onset: 11-14 days
  - Duration: 12-16 days
  - Discontinuation rate: 2%

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. Madruga JV, et al. Lancet 2007;270:29-38. Lazzarin A, et al. Lancet 2007;370:39-48.Etravirine Prescribing Information. www.fda.gov

Hypersensitivity: Rash

- Protease Inhibitors
  - Atazanavir* (20%)
  - Darunavir* (7%, clinical trials 16%)
  - Fosamprenavir* (19%)
  - Lopinavir/ritonavir (clinical trials 7%)
  - Tipranavir* (10% adults; 21% pediatrics)

*Sulfonamides

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. December 1, 2009. www.aidsinfo.nih.gov.Prescribing Information www.fda.gov

HAART and Adverse Events

Side-effect	New learning points	Most promising therapies*
Lipoatrophy	Largely preventable by avoidance of stavudine and zidovudine Contribution of protease inhibitors less certain Consider annual DEXA in those receiving stavudine, zidovudine, or protease inhibitor	Stavudine and zidovudine cessation helpful but improvement very gradual Pioglitazone (in those not receiving stavudine) Uridine Pravastatin
Central fat accumulation	Treatment directions limited by uncertainty about whether central fat accumulation is direct drug effect or secondary to lipoatrophy	Growth hormone Growth-hormone releasing-hormone analogue Metformin
Dyslipidaemia	No proven benefit for diet or exercise	Protease inhibitor and/or UNRTI-sparing Pravastatin, low-dose atorvastatin, or rosuvastatin
Insulin resistance/ diabetes	Fasting glucose is poor tool for diagnosis of diabetes Consider oral glucose tolerance testing in higher-risk patients	Follow standard diabetic treatment guidelines
Cardiovascular disease	Withdrawal of ART increases risk, perhaps because of declines in HDL-cholesterol Traditional risk factors affect risk more than ART	Address all risk factors, such as smoking, hypertension and diabetes, not just raised total cholesterol
Hepatotoxicity	Nevirapine be initiated only in ART-naive men and women with CD4+ lymphocyte counts <400 and 250 cells per μL, respectively Didanosine associated only with hepatic fibrosis, nodular regenerative hyperplasia, and portal hypertension	Nil
Hypersensitivity	Abacavir hypersensitivity strongly linked to HLA-B*5701 ancestral haplotype	Molecular testing for HLA-B*5701 may prevent most abacavir hypersensitivity
Osteoporosis	Tenofovir associated with small increased risk of osteopenia over 3 years, but not with increased fracture rate Role of routine screening (bone mineral densitometry) unknown	Alendronate
Nephrotoxicity	Tenofovir associated with small increased risk of grade 3–4 nephrotoxicity	Nil
Enfuvirtide injection-site reactions	Occurs in 98% of patients and does not abate over time Has substantially affected use of enfuvirtide	Maybe less severe with use of needle-free injection device

Reprinted from The Lancet. Calmy A, et al. Lancet 2007;370:12-4. Copyright (2007).

Nephrotoxicity

- Nephrolithiasis
  - Indinavir
  - Atazanavir
- Acute interstitial nephritis
  - Atazanavir

HAART and Adverse Events

Side-effect	New learning points	Most promising therapies*
Lipoatrophy	Largely preventable by avoidance of stavudine and zidovudine Contribution of protease inhibitors less certain Consider annual DEXA in those receiving stavudine, zidovudine, or protease inhibitor	Stavudine and zidovudine cessation helpful but improvement very gradual Pioglitazone (in those not receiving stavudine) Uridine Pravastatin
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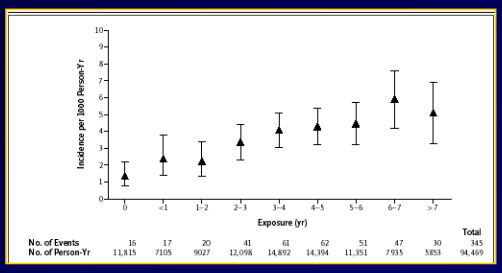
Reprinted from The Lancet. Calmy A, et al. Lancet 2007;370:12-4. Copyright (2007).

HAART and Adverse Events

- Veterans Affairs Database
  - Retrospective data
  - Cardiovascular mortality
- Myocardial infarction (D:A:D study group)
  - Prospective study
  - 11 international cohorts
  - N=23,437 patients

Bozette SA, et al. N Engl J Med 2003;348:702-10.
The D:A:D Study Group. N Engl J Med 2003;349:1993-2003.
The D:A:D Study Group. N Engl J Med 2007;356:1723-35.
Bozzette SA, et al. J Acquir Immune Defic Syndr 2008;47:338-41.
Bedimo R, et al. 5th IAS Conference on HIV Pathogenesis. 2009. (Abstract).

HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy



HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

Variable	Unadjusted Model		Adjusted Model 1†		Adjusted Model 2‡	
	Relative Rate (95% CI)	P Value	Relative Rate (95% CI)	P Value	Relative Rate (95% CI)	P Value
Exposure to protease inhibitors (per additional year)	1.17 (1.12–1.23)	<0.001	1.16 (1.10–1.23)	<0.001	1.10 (1.04–1.18)	0.002
Exposure to nonnucleoside reverse-transcriptase inhibitors (per additional year)	1.07 (1.00–1.14)	0.04	1.05 (0.98–1.13)	0.17	1.00 (0.93–1.09)	0.92

+ Adjusted model:
- **Gender**
- **Cohort**
- **HIV transmission group**
- **Race/ethnic group**
- **Age**
- **BMI**
- **Family history**
- **Smoking status**
- **CV history**
- **Calendar year**

++ Adjusted model:
- **Diabetes mellitus**
- **Hypertension**
- **Dyslipidemia**

HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

Risk of MI associated with adjusted cumulative or recent exposure to 13 drugs from 3 drug classes

	NRTI							PI				NNRTI	
Drug	**ZDV**	**ddI**	**ddC**	**d4T**	**3TC**	**ABC**	**TDF**	**IDV +/-r**	**NFV**	**LPV/r**	**SAQ +/-r**	**NVP**	**EFV**
# PYFU	138108	74407	29676	95320	152009	53300	39157	68469	56529	37136	44657	61855	58946
RR (95% CI) recent use	**0.99** (0.78-1.26)	***1.41*** *(1.09-1.82)*	**1.01** (0.42-2.43)	**1.02** (0.78-1.32)	**1.21** (0.95-1.55)	***1.68*** *(1.33-2.13)*	**1.14** (0.85-1.52)	-	-	-	-	-	-
RR (95% CI) /year	**1.04** (0.99-1.08)	***1.00*** *(0.94-1.06)*	**1.03** (0.93-1.14)	**1.03** (0.98-1.09)	**0.99** (0.94-1.05)	***1.07*** *(1.01-1.14)*	**1.05** (0.92-1.19)	***1.12*** *(1.07-1.18)*	**1.04** (0.98-1.11)	***1.13*** *(1.05-1.21)*	**1.05** (0.98-1.11)	**0.97** (0.92-1.03)	**1.02** (0.98-1.08)

Lundgren J. et al. CROI 2009;Abstract 44LB. Worm SW, et al. JID 2010;201: (epub ahead of the print).

HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

November 2009

Dear Healthcare Professional:

LEXIVA® (fosamprenavir calcium) Tablets and Oral Suspension:
Myocardial Infarction and Dyslipidemia

GlaxoSmithKline would like to inform you of data presented at the 16th Conference on Retroviruses and Opportunistic Infections (CROI 2009) relating to a potential association between LEXIVA Tablets and Oral Suspension and myocardial infarction in HIV infected adults.

Action Being Taken by GSK

GSK has added myocardial infarction and hypercholesterolemia to the Adverse Reactions section of the LEXIVA Tablets and Oral Suspension prescribing information (Section 6.2 Postmarketing Experience). Elevations in triglyceride levels are already described in the Adverse Reactions section of the LEXIVA Tablets and Oral Suspension prescribing information (Section 5.8 Warnings and Precautions, Section 6.1 Clinical Trials).

GSK has modified the existing Warnings and Precautions statement (Section 5.8 Lipid Elevations) in the prescribing information for LEXIVA Tablets and Oral Suspension to highlight that increases in cholesterol have occurred with treatment. This statement highlights the importance of lipids management by including a recommendation that triglyceride and cholesterol testing should be performed prior to initiating therapy with LEXIVA Tablets and Oral Suspension and at periodic intervals during therapy.

www.fda.gov

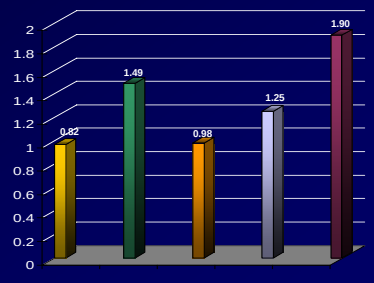
HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

- NRTI risk
  - Zidovudine
  - Didanosine
  - Stavudine
  - Lamivudine
  - Abacavir

D:A:D Study Group. Lancet 2008;371:1417-26.

HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

- NRTI risk
  - Zidovudine
  - Didanosine
  - Stavudine
  - Lamivudine
  - Abacavir



D:A:D Study Group. Lancet 2008;371:1417-26. Bedimo R, et al. 5th IAS Conference on HIV Pathogenesis. 2009; (Abstract).

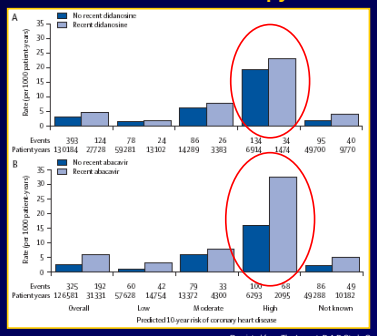
HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

Risk of MI associated with adjusted cumulative or recent exposure to 13 drugs from 3 drug classes

	NRTI							PI				NNRTI	
Drug	**ZDV**	**ddI**	**ddC**	**d4T**	**3TC**	**ABC**	**TDF**	**IDV +/-r**	**NFV**	**LPV/r**	**SAQ +/-r**	**NVP**	**EFV**
# PYFU	138108	74407	29676	95320	152009	53300	39157	68469	56529	37136	44657	61855	58946
RR (95% CI) recent use	**0.99** (0.78-1.26)	***1.41*** *(1.09-1.82)*	**1.01** (0.42-2.43)	**1.02** (0.78-1.32)	**1.21** (0.95-1.55)	***1.68*** *(1.33-2.13)*	**1.14** (0.85-1.52)	-	-	-	-	-	-
RR (95% CI) /year	**1.04** (0.99-1.08)	***1.00*** *(0.94-1.06)*	**1.03** (0.93-1.14)	**1.03** (0.98-1.08)	**0.99** (0.94-1.05)	***1.07*** *(1.01-1.14)*	**1.05** (0.92-1.19)	***1.12*** *(1.07-1.18)*	**1.04** (0.98-1.11)	***1.13*** *(1.05-1.21)*	**1.05** (0.98-1.11)	**0.97** (0.92-1.03)	**1.02** (0.96-1.08)

Lundgren J, et al. CROI 2009;Abstract 44LB. Worm SW, et al. JID 2010;201: (epub ahead of the print).

HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy



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HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

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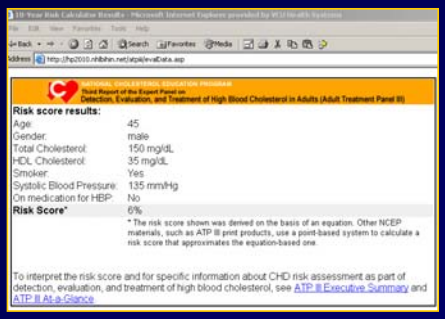
HAART and Adverse Events

Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy



10-Year Risk Calculation Results - Microsoft Internet Explorer provided by [illegible]

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Address http://hp2010.nhlbihin.net/atpiii/calc/calcData.asp

NATIONAL CHOLESTEROL EDUCATION PROGRAM

Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk score results:

Age:	45
Gender:	male
Total Cholesterol:	150 mg/dL
HDL Cholesterol:	35 mg/dL
Smoker:	Yes
Systolic Blood Pressure:	135 mm/Hg
On medication for HBP:	No
Risk Score*	6%

* The risk score shown was derived on the basis of an equation. Other NCEP materials, such as ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.

To interpret the risk score and for specific information about CHD risk assessment as part of detection, evaluation, and treatment of high blood cholesterol, see ATP III Executive Summary and ATP III At-a-Glance

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Questions