

**Current Issues in
Antiretroviral Therapy:
A Case-Based Panel
Discussion**

Jeffrey L. Lennox, MD
Professor of Medicine
Emory University School of Medicine

The International AIDS Society–USA

Case 1

Slide 2

- 24 yo Black man
- Newly diagnosed
- PMHx remarkable for asthma, syphilis, and shigella
- No medications
- Full-time job, no insurance
- High school graduate, dropped out after first semester of college.

Slide #3: This slide will be available during Dr Lennox's presentation.

Accumulating Data that ART Therapy Reduces HIV Transmission

Slide 4

- Evaluate effect of ART on HIV transmission among HIV serodiscordant, heterosexual couples (2993)
- ARV only if clinically indicated, negative partner tested q3 mo.
 - ▶ Not on ARV: 171 linked infections (3.4/100 CY)
 - ▶ On ARV: 4 linked infections (0.7/100 CY)
 - ▶ Sexual risk behavior lower in those on ARV (19% vs 25%; $p < 0.05$)

Sullivan P, et al. Abstr# 52bLb

DHHS Guidelines: Initiation of ART

Slide 5

- History of AIDS-defining illness (AI)
- CD4 count <350 cells/mm³ (AI). Also for CD4 count 350-500 cells/mm³ (A/BI)
- Pregnant women* (AI)
- Persons with HIV-associated nephropathy (AII)
- Persons coinfectd with hepatitis B virus (HBV), when HBV treatment is indicated (treatment with fully suppressive antiviral drugs active against both HIV and HBV is recommended.) (AIII)
- Rapidly declining CD4 counts (>100 cells/mm³ decrease per year) (AIII)

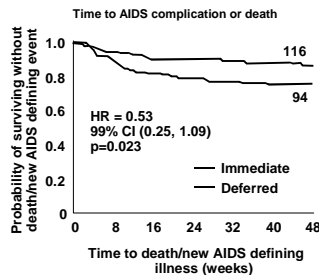
www.aidsinfo.org 12/09

* For women who do not require antiretroviral therapy for their own health, consideration can be given to discontinuing antiretroviral drugs postpartum.

ACTG A5164: Immediate vs delayed ARVs in setting of acute OIs

Slide 6

- Most common OIs: PCP (63%), *Cryptococcus* (12%), BI (12%); *TB excluded*
- No difference in primary endpoint between groups
- Immediate treatment had reduced rate of AIDS progression or death (14.2%) vs deferred treatment (24.1%)
- No differences in IRIS (10 immediate vs 13 deferred)
 - However, 70% of patients with PCP received corticosteroids



Zolopa A, 15th CROI 2008, #142

DHHS Guidelines: ART and OI's

Slide 7

- In patients with OI for which there is no effective therapy (cryptosporidiosis, microsporidiosis, PML), but for which antiretroviral therapy may improve outcomes by improving immune responses, treatment should be started **as soon as possible (AIII)**.
- In the setting of cryptococcal meningitis or non-tuberculous mycobacterial infections, for which immediate therapy may increase the risk of immune reconstitution inflammatory syndrome (IRIS), a short delay may be warranted **(CIII)**.
- In the setting of other OIs, such as PCP, early initiation of antiretroviral therapy is associated with increased survival, and therapy should not be delayed **(AI)**.

www.aidsinfo.org 12/09

The Sapit Trial- When to start ART in the context of TB treatment?

Slide 8

- Open-label trial in HIV patients with active TB (n = 642)
- Randomized to one of 3 arms
 - Arm 1: ART initiated during intensive phase of TB treatment
 - Arm 2: ART initiated after intensive phase of TB treatment
 - Arm 1 & 2: integrated arm
 - Arm 3: ART initiated after TB treatment completed
 - sequential arm

	Integrated Arm (n = 429)	Sequential Arm (n = 213)
Number of deaths (%)	25 (5%)	27 (13%)
Person-years of f/u	466	222
Mortality rate/100 p-y	5.4	12.1
IRIS	12.1%	3.8%

Abdool Karim S, CROI 2009 Abst# 36a

The PART Trial- Is ART useful in the context of CD4 >350 and TB treatment?

Slide 9

- Open-label trial in Ugandan HIV patients with active TB (n = 232)
 - Randomized to one of 2 arms
 - Arm 1: 24 weeks of ART initiated during intensive phase of TB treatment
 - Arm 2: ART initiated if CD4 declined to <350
- Primary outcome CD4 <250, AIDS, Death

	Immediate (n = 109)	Deferred (n = 114)
8Wk culture negative (%)	92	88
Primary Outcome (%)	16	23
# AIDS/Death @ 12 months	0	7

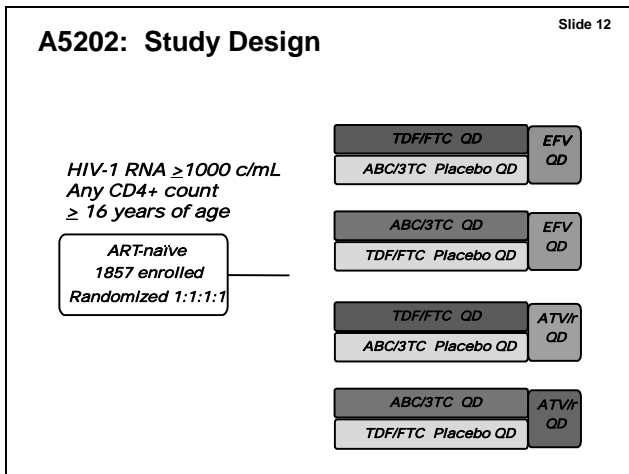
Walusimbi M, CROI 2010 Abst# 105

Slide #10: This slide will be available during Dr Lennox's presentation.

Slide 11

DHHS Initial Treatment: 12/09

Preferred Regimens for Initial Therapy				
	Class			Daily Pill Burden
TDF + FTC QD plus one from the next column	NNRTI	Efavirenz	QD	1
	PI	Atazanavir/rit	QD	3
		Darunavir/rit	QD	4
INI	Raltegravir	BID	3	



Slide 13

A5202- Results in those with HIV RNA <10⁵ at Baseline

Endpoint	ABC/ 3TC+ EFV	TDF/ FTC+ EFV	p	ABC/ 3TC+ ATVr	TDF/ FTC+ ATVr	p
% No VF at 96Wk	87	89		88	90	
# Safety Endpoint	98	83	.03	80	70	
# Tolerability Endpoint	117	87	.005	100	78	.018

Switches for presumed ABC HSR were greater, but not statistically so, for the ABC/3TC arms

Cohen CROI 2010

Slide 14

A5202- ATV/r vs EFV Results for Entire Study

Endpoint	ABC/ 3TC+ EFV	ABC/ 3TC+ ATVr	TDF/ FTC+ EFV	TDF/ FTC+ ATVr
% No VF at 96Wk	85	83	90	89
# Safety Endpoint	187	170	147	141
# Tolerability Endpoint	186	142	142	126

More NRTI resistance occurred in the EFV arms

No differences in CVD endpoints, renal endpoints

Cohen CROI 2010

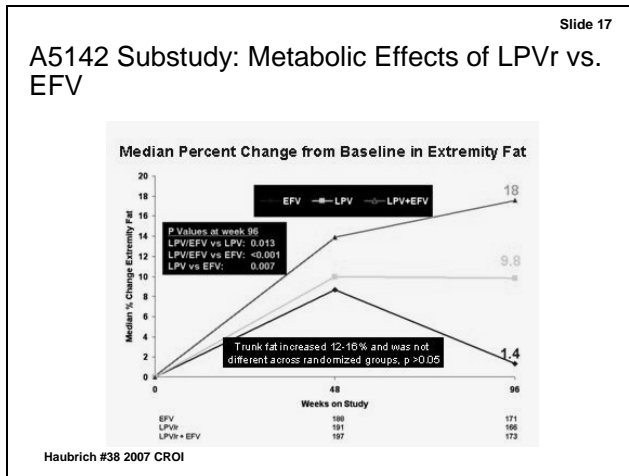
Slide 15

A5202 – Lipid Changes

- T Chol EFV > ATV/r
- LDL Chol EFV > ATV/r
- HDL Chol EFV > ATV/r
- TG EFV=ATV/r, except for ABC/3TC +
ATV where TG were the highest

McComsey CROI 2010

Slide #16: This slide will be available during Dr Lennox's presentation.



Slide 18

A5224 - A5202 Metabolic Substudy

- 65–70 patients from each arm of A5202
- DEXA at 0,24,48 & 96 weeks; Abdominal C.T. at 0 & 96 weeks
- At 96 weeks lumbar BMD 2% lower in TDF/FTC arm (p=0.04), and 1.5 % lower in ATV/r arm (p=0.05)
- ATV/r arms gained ~1kg more in limb fat than EFV arms, but also ~1kg more in trunk fat
- No difference in percent limb fat changes between the two NRTI backbones

McComsey CROI 2010

EuroSIDA – ARV effects on CrCL

- Analyzed all patients who had ≥ 3 serum creatinine measurements
- CKD defined as eGFR < 60 or 25% decrease
- 6843 patients: 43% MSM, 85% white, 25% HCV+
- 3.3 % (1.1/100 py) developed CRD

	TDF	IDV	ATV	LPV
IRR/yr	1.16	1.12	1.21	1.08

Increasing age, HTN, HCV and low CD4 count all increased the risk of CKD for those receiving TDF.

Slide #20: This slide will be available during Dr Lennox’s presentation.

Can Initial Regimens be Simplified Once Sustained Virologic Suppression Achieved?

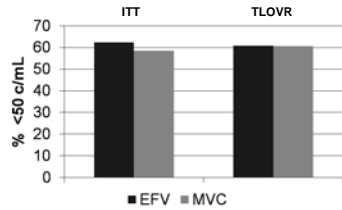
- ARIES Study: PI boosting lead in followed by unboosting**
- 515 naive patients, HLAB*5701 neg, given 36 wks of ABC/3TC+ ATV 300mg + RTV 100mg
 - If HIV RNA<50c/ml @ 36 Wks: randomized to continue or stop the RTV
 - Endpoint at 48 Wks post-randomization

	% HIV RNA<50c/mL at 48 Weeks	
	ATV (n=210)	ATV/RTV (n=209)
BL VL<100,000	85	79
BL VL>100,000	87	82

Total cholesterol and triglycerides slightly improved in the ATV alone arm.

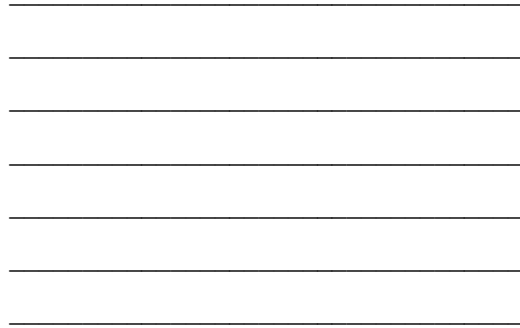
Reanalysis of Week 96 Virologic Efficacy in MERIT With Enhanced Tropism Assay

- Enhanced tropism assay reclassified 15% of patients from R5 to D/M at screening



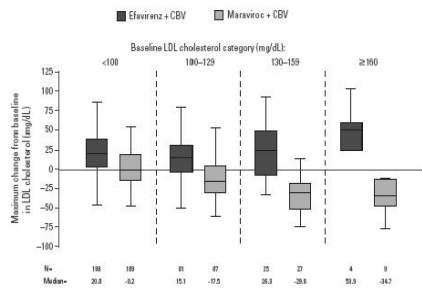
- CD4+ change greater with MVC vs EFV (+212 vs +171 cells/mm³)
- EFV more likely D/C AEs (15.5% vs 6.1%), while MVC more likely D/C for lack of response (12.5% vs 5.9%).

Heera J, et al. IAS 2009. Abstract TUAB103



MERIT Study: Lipid Profile of MVC vs EFV

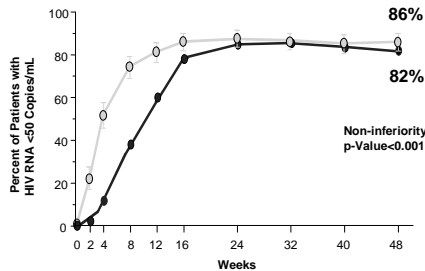
Figure 2. Median maximum change from baseline in LDL cholesterol levels by baseline NCEP LDL cholesterol category



De Jesus E. 15th CROI 2008, 929



STARTMRK – RAL vs EFV both with TDF/FTC

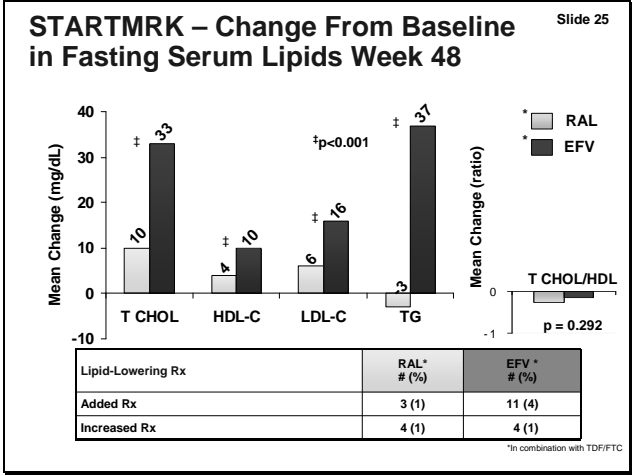


Number of Contributing Patients

○ Raltegravir 400 mg b.i.d.*	281	279	281	279	281	279	278	280	280
● Efavirenz 600 mg q.h.s.*	282	282	282	281	282	280	280	281	281

*In combination with TDF/FTC





Elvitegravir Quad Slide 26

- GS 9350 is a drug with similar boosting activity to RTV, with no antiviral activity. Developed to boost the Gilead integrase inhibitor Elvitegravir (ELV)
- In tissue culture models no effect on fat metabolism
- In a 14-day monotherapy study in healthy volunteers 100mg and 200mg doses demonstrated similar cytochrome blocking activity as ritonavir 100mg.
- In a small study in HIV- volunteers a single pill of TDF/FTC/ELV150mg/GS9350 produced ELV levels similar to TDF/FTC + ELV + RTV 100mg.
- ATV300mg + GS9350 study also in progress

Kearney B, CROI 2009, 121

Gilead Quad-Phase II Study in Treatment Naïve Patients Slide 27

	Quad (50)	TDF/FTC/EFV (25)
HIV RNA \geq 50 @ 24 wk	90%	85%
Grade 3/4 A/E	0%	9%
Abnl dreams	10%	39%
Cr Change	0.14	0.04
eGFR Change	-18 mL/min	-7mL/min

- In healthy volunteers GS9350 inhibited tubular secretion of creatinine

Cohen CROI 2010

Slide 28

Case 2

- 44 year old patient has been on TDF/FTC/EFV for 3 years.
- Nadir CD4 was 4 cells/mm³
- Current CD4 is 175 cells/mm³
- His HIV RNA is consistently <50 copies/mL.
- He wants to “add a new drug” to see if his T-cells can be made to increase.

Slide 29

RAL Intensification – Effect on Immunologic Parameters

- 30 pts with HIV RNA < 50 & CD7 < 350 randomized 1:1 to RAL or placebo. 21 patients got serial rectal biopsies
- At week 12 the change in HIV RNA was -2.5 copies in placebo arm and -1.9 copies in RAL arm
- No effect on:
 - CD4 numbers
 - proviral DNA
 - CD8 or CD4 activation
 - Gut CD4 or CD8 activation
 - gag specific T cell responses

Hatano CROI 2010

Slide 30

Case 2 Continued

- 44 year old patient has been on TDF/FTC/EFV for 3 years.
- Nadir CD4 was 4 cells/mm³
- Current CD4 is 175 cells/mm³
- His HIV RNA is now >1000
- A phenotype and genotype are performed

DRUG		SUSCEPTIBILITY				Evidence of Susceptibility		Net Assessment	
Generic Name	Cutoffs (Lower - Upper)	Fold Change	Increasing Drug Susceptibility	Decreasing Drug Susceptibility	Pheno Sense	Gene Seq			
NRTI	Abacavir	(4.5 - 6.5)	8.25			N	N	Resistant	
	Didanosine	(1.3 - 2.2)	3.34			N	N	Resistant	
	Emtricitabine	(3.5)	>MAX			N	N	Resistant	
	Lamivudine	(3.5)	>MAX			N	N	Resistant	
	Stavudine	(1.7)	1.36			Y	Y	Sensitive	3
	Zidovudine	(1.9)	0.80			Y	Y	Sensitive	3,20
	Tenofovir	(1.4 - 4)	2.19			P	N	Partially Sensitive	3
NRTI Mutations		K65R, M184V							
NNRTI	Delavirdine	(6.2)	8.44			N	N	Resistant	4
	Efavirenz	(3)	108			N	N	Resistant	
	Nevirapine	(4.5)	109			N	N	Resistant	
NNRTI Mutations		K103N, P225H							
PI	Atazanavir	(2.2)	1.04			Y	Y	Sensitive	
		(5.2)	1.04			Y	Y	Sensitive	
	Fosamprenavir	(2)	1.78			Y	Y	Sensitive	
		(4 - 11)	1.78			Y	Y	Sensitive	
	Indinavir	(2.1)	1.30			Y	Y	Sensitive	
		(10)	1.30			Y	Y	Sensitive	
	Lopinavir	(9 - 55)	1.27			Y	Y	Sensitive	
	Nelfinavir	(3.6)	1.47			Y	Y	Sensitive	
	Ritonavir	(2.5)	1.51			Y	Y	Sensitive	
	Saquinavir	(1.7)	1.04			Y	Y	Sensitive	
	(2.3 - 12)	1.04			Y	Y	Sensitive		
Tipranavir	(2 - 8)	1.07			Y	Y	Sensitive		
PI Mutations		L63A							

Lower Clinical Cutoff (in bold)
 Upper Clinical Cutoff (in bold)
 Biological Cutoff
 Hypersusceptibility Cutoff
 Sensitive
 Partially Sensitive
 Resistant
 Y Evidence of Drug Sensitivity
 P Evidence of Partial Drug Sensitivity
 N Evidence of Drug Resistance

Slide #32: This slide will be available during Dr Lennox's presentation.

Slide 33

ODIN Study - Once vs Twice Daily DRV in treatment experienced patients

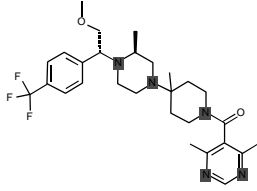
- Randomized, double-blind study in patients failing ART without primary DRV mutations
- 46 % were PI naïve

	DRV/r 800/100 QD (219)	DRV/r 600/100 BID (238)
≥ 2 Active OBR	70%	65%
HIV RNA < 50 c/mL at 48 weeks	72.1%	70.9%
Viral Failure	22.1%	18.2%
DRV Resistance	#1	#0

Cahn CROI 2010

Slide #34: This slide will be available during Dr Lennox's presentation.

Vicriviroc



- Oral CCR5 receptor antagonist
- Plasma concentrations increased markedly by CYP3A4 inhibitors¹
- Plasma half-life >24 hours
- Once-daily dosing²
- No food effect³
- Potent and durable antiretroviral activity in CCR5-tropic ART-experienced subjects⁴

1. Sansone A, et al. CROI 2006 [abstr. 582].
2. Seiberling M, et al. IWC/PHI 2005 [poster 6.4].
3. Sansone A, et al. ICAAC 2005 [abstr. A-1200].
4. Gulick R, et al. *JID* 2007;196:304-12.

Vicriviroc in Treatment Experienced Patients – Victor E3 & E4

- Placebo controlled phase 3 study. CCR5 using HIV confirmed by tropism testing (ES). Patients with documented resistance to ≥ 2 classes
- VCV 30mg daily + OBR vs. Placebo + OBR
35% given RAV and 40% DRV

	VCV	Control
% HIV RNA < 50	64	62
% HIV RNA < 400	72	71
% Active OBR ≥ 3	61	65
% C5 \rightarrow X4	14	3
# Deaths	7	0

Gathe CROI 2010

S/GSK1349572 – 2nd Generation INI

- Protein adjusted IC₉₀ 64 ng/mL
- Tested sensitivity of various mutants to RAL and S/GSK

Mutation	S/GSK Mean Fold Change	RAL Mean Fold Change
143R	>2	16
148H	>2	13
148K	>2	83
148R	>2	47
155H	>2	11

Seki 2010 CROI

Slide #38: This slide will be available during Dr Lennox's presentation.

Persistent CNS HIV and cognitive impairment is associated with worse ART penetration Slide 39

- 300 participants from 6 centers (USA CHARTER cohort), with <50 copies/mL HIV RNA in plasma and CSF.
- HIV RNA testing with 2 copies/mL assay
- Results
 - 122/300 (41%) had CSF HIV RNA >2 copies/mL
 - More likely to be on meds with lower CNS-penetration effectiveness (CPE) ranks, specifically
 - Tenofovir < abacavir
 - Efavirenz < nevirapine
 - Emtricitabine < lamivudine

Letendre, 2009 CROI

CNS Penetration Effectiveness – Data from 2010 CROI Slide 40

Abst # 417 – 136 pts, 51% with C.I. C.I. measured by 8 tests. No correlation was found between C.P.E. and C.I.

Abst # 416 – C.P.E. did not predict C.I.

Abst # 433 – Increased C.P.E. correlated with better performance in 3/6 neuro-psych tests

Abst # 432 – C.P.E. did not predict HIV RNA levels in CSF

Slide #41: This slide will be available during Dr Lennox's presentation.

Slide 42

Vitamin D Insufficiency – New data from CROI

Risk Factors

Cohort	# p/s	% Insufficient	Non White	BMI	HTN	NNRTI	Time on ART
SUN-US	672	71.6	√	√	√	√	
Ancona-Italy	852	54	√	√		√	√
Swiss	211	62	√			√	

- The SUN and Ancona cohorts found age to be a risk, the Swiss did not
- In Swiss cohort Vit D lower in Spring than in Fall
- 116 pts followed prospectively in Ancona, Vit D levels fell after HAART

Slide 43

Mom was right, drink your milk!
