

Anti-retroviral therapy

When to start, when to start

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Session objectives

- Goals of therapy
- When to start:
 - Comparison of guidelines
 - Rationale behind guidelines
- What to start

Goals of ARVs

- Main goal: improve QOL
- Clinical goal: decrease AIDS and non-AIDS morbidity/mortality
- Surrogate goal: decrease VL and increase CD4
- ?public health goal: decrease onward transmission

When to start?



When to start?



When to start

CD4 Count (cells/mm ³)	BHIVA 2008	EACS 2009	DHHS Jan 2011	IAS Jul 2010
< 350	ART recommended	ART recommended	ART recommended	ART recommended
>350 - <500	ART may be considered if: <ul style="list-style-type: none"> •ADI; any HIV-related co-morbidity •Low CD4% (eg: < 14%) •High risk of CV disease •Hepatitis B or C co-infection 	ART may be offered if: <ul style="list-style-type: none"> •Viral load > 100,000 cp/mL •Symptomatic •Age > 55 •Hepatitis C co-infection 	ART recommended* <ul style="list-style-type: none"> •Pregnancy •HIVAN •HBV co-infection •Symptomatic <small>*55% panel strong recommendation; 45% moderate recommendation</small>	ART recommended
CD4 > 500	Defer	Defer but consider	Offer but not mandatory* <small>*50% panel in favour; 50% optional</small>	Consider -unless elite controller or stable CD4/low VL

Where do treatment guidelines (advocating earlier Rx?) come from?

- Treatment reduces
 - Risk of progression to AIDS/death
 - Non-AIDS related complications
- Availability of newer regimens with improved efficacy, convenience and tolerability
- Randomised controlled trials
 - Naïve sub-study of SMART
 - CIPRA HT001
- Cohort studies showing benefit
- Growing evidence that treatment reduces HIV transmission

Adverse Events Leading to Study Drug Discontinuation Through Week 96

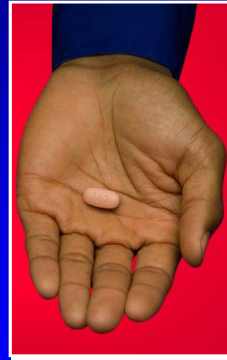
Safety Population	TDF+FTC+EFV (n = 257)	CBV+EFV (n = 254)
No. w/ any Adverse Event ^a	12 (5%)	28 (11%) ^b
Adverse Event		
Anemia/ ↓ Hgb	0	14 (6%) ^c
Fatigue	0	5 (2%)
Nausea	1 (< 1%)	4 (2%)
Rash	4 (2%)	1 (< 1%)
Drug Eruption	2 (< 1%)	0
Vomiting	0	2 (< 1%)
Neutropenia	0	2 (< 1%)

- a. Occurring in more than 1 patient in either arm; patients may have > 1 event
 b. p = 0.023
 c. p < 0.001

Gallant JE, et al. XVI International AIDS Conference, 2006; #TUPE0064.

Significant Advances in Simplifying Regimens

Daily Pill Burden...from the early days of combination therapies in the 1990s to where we are today...



Single Tablet Regimen

Evidence favouring start <350

- 2 Randomised Controlled Trials
 - Naïve sub-study of SMART
 - CIPRA HT001

SMART Study Design

CD4+ cell count >350 cells/mm³

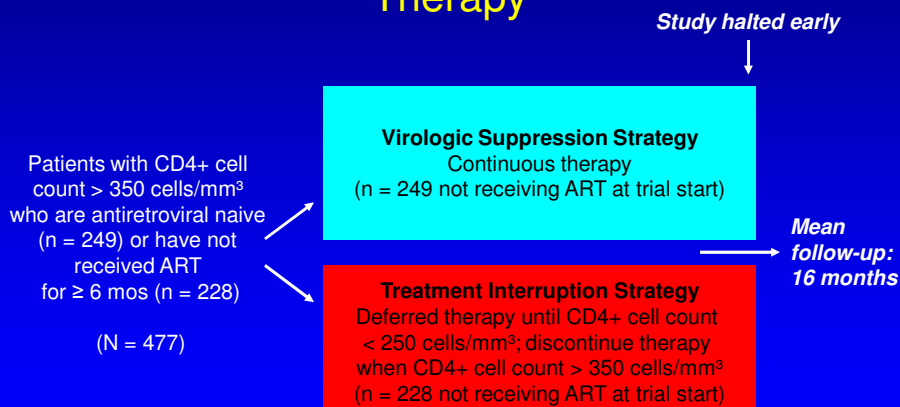
n = 2752

Virologic Suppression (VS) Strategy
[Use of ART to maintain viral load as low as possible throughout follow-up]

n = 2720

Drug Conservation (DC) Strategy
[Stop or defer ART until CD4+ < 250; then *episodic* ART based on CD4+ cell count to increase counts to > 350]

SMART Substudy: Analysis in Patients not receiving ART at study entry of impact of Immediate vs Deferred Therapy



Emery S, et al. JID 2008.

SMART Substudy: Immediate therapy reduces risk of OI/death/serious non-AIDS events

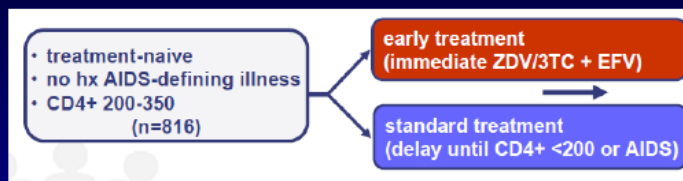
- Patients who initiated and remained on antiretroviral therapy at higher CD4+ cell counts (> 350 cells/mm³) had better outcomes vs those who deferred and interrupted HAART
- Caveat: small number of patients analyzed and not all treatment naive

Event, n (Rate per 100 Person-Years)				
	Interrupted HAART	Continuous HAART	HR	P Value
OI/death				
• Overall	15 (4.8)	4 (1.1)	4.4	.009
OI				
• Overall	11 (3.5)	3 (0.8)	4.4	.02
Serious non-AIDS				
• Overall	12 (3.9)	2 (0.5)	7.1	.01
Composite*				
• Overall	21 (7.0)	5 (1.3)	5.1	.001

*Includes OI and serious non-AIDS events.
Emery S, et al. JID 2008.

CIPRA HT001

- Randomized controlled trial in Haiti of early vs. deferred therapy in HIV-infected patients with CD4 count 200-350



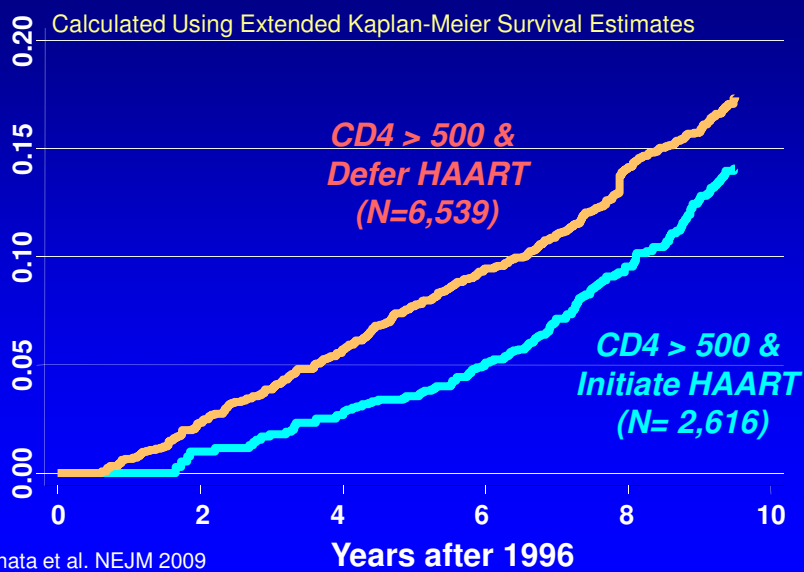
- DSMB stopped trial after median follow-up of 21 months because of excess mortality in the standard of care arm

	Early	Standard	HR (p-value)
Death	6	23	4.0 (0.0011)
Incident TB	18	36	2.0 (0.0125)

Fitzgerald D, NEJM, 2010

Cohort data

NA-Accord: supports initiating ART at CD4 threshold of 500



ART-CC: supports initiating ART at CD4 threshold of 350

CD4 cell count comparison, cells/mm ³	Adjusted Hazard Ratio for AIDS or Death (95% CI)
0-100 vs 100-200	3.35 (2.99-3.75)
226-325 vs 326-425	1.21 (1.01-1.46)
251-350 vs 351-450	1.28 (1.04-1.57)
276-375 vs 376-475	1.19 (0.96-1.47)
351-450 vs 451-550	0.99 (0.76-1.29)

- Clear benefit of starting at CD4 > 350 compared with waiting (and high risk of progression at lower CD4 counts supported)
- No clear benefit of starting treatment above ~ 400 or 500
- Absolute rates of death became relatively low at higher CD4 thresholds

Sterne J et al. Lancet 2009

Interpretation?

- One cohort suggests no advantage above 350
- The other suggests about 1% survival advantage of treating above 350
- Results may be affected by unmeasured confounding factors
- Data is supportive of a theoretical advantage, but this magnitude of advantage could easily be explained by errors inherent in the analyses
- Toxicity and resistance not included as end-points

CASCADE: Risk of AIDS and Death by CD4+ Cell Count Strata at Start of ART

- CASCADE collaboration: observational cohort of HIV seroconverters from 23 clinical cohorts in Europe, Australia, Canada similar to NA-ACCORD and ART-CC
 - Current analysis included 9455 patients ≥ 6 mos after estimated seroconversion in CD4+ cell count strata up to 799 cells/mm³
 - Study period: January 1, 1996 - May 31, 2009
- Endpoints
 - AIDS or death
 - Death
 - Non-AIDS outcomes not included

Funk MJ, et al. AIDS 2010. Abstract THLB201.

Effect of Tx Initiation on AIDS and Death

CD4+ Cell Count, cells/mm ³	Adjusted HR (95% CI)
0-49	0.32 (0.17- 0.59)
50-199	0.48 (0.31-0.74)
200-349	0.59 (0.43-0.81)
350-499	0.75 (0.49-1.14)
500-799	1.10 (0.67-1.79)

Effect of Tx Initiation on Death

CD4+ Cell Count, cells/mm ³	Adjusted HR (95% CI)
0-49	0.37 (0.14-0.95)
50-199	0.55 (0.28-1.07)
200-349	0.71 (0.44-1.15)
350-499	0.51 (0.33-0.80)
500-799	1.02 (0.49-2.12)

CASCADE: Absolute Risk Difference and Number Needed to Treat 3 Yrs From BL

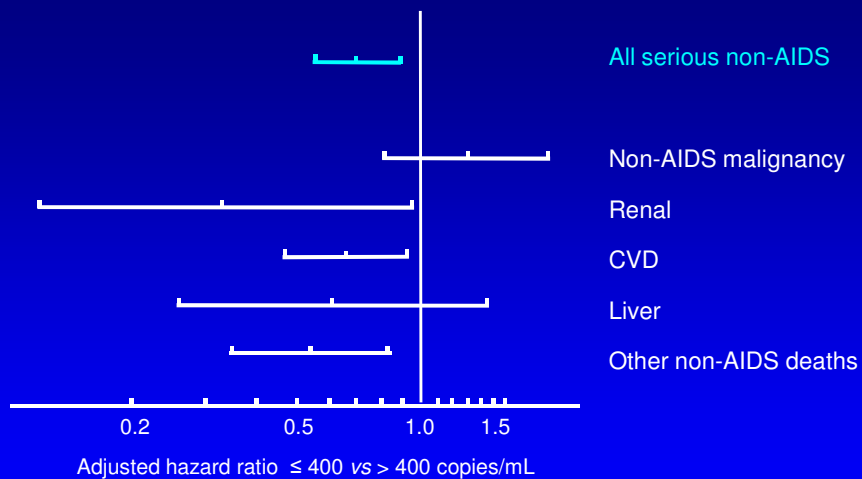
CD4+ Cell Count, cells/mm ³	Cumulative Risk for AIDS/Death, %		Cumulative Risk Diff at 3 Yrs (95% CI)	Number Needed to Treat at 3 Yrs to Prevent 1 AIDS Event or Death (95% CI)
	Defer	Initiate		
0-49	46.6	16.6	-30.0 (-45.1 to -15.0)	3 (2-7)
50-199	20.7	5.7	-15.0 (-19.7 to -10.3)	7 (5-10)
200-349	10.3	5.5	-4.8 (-7.0 to -2.6)	21 (14-38)
350-499	6.3	3.4	-2.9 (-5.0 to -0.9)	34 (20-115)
500-799	4.9	5.2	0.3 (-3.7 to 4.2)	∞
CD4+ Cell Count	Cumulative Risk for Death Alone, %		Cumulative Risk Diff at 3 Yrs (95% CI)	NNT at 3 Yrs to Prevent 1 Death
0-49	26.8	8.6	-18.2 (-32.0 to -4.4)	6 (3-23)
50-199	9.1	1.9	-7.2 (-10.1 to -4.4)	14 (10-23)
200-349	4.1	2.7	-1.4 (-3.0 to 0.3)	74 (33- ∞)
350-499	2.1	0.7	-1.4 (-2.2 to -0.6)	71 (45-165)
500-799	1.7	1.2	-0.4 (-2.0 to 1.2)	239 (49- ∞)

Funk, MJ, et al. AIDS 2010. Abstract THLB201.

Potential Benefits of earlier initiation of ART

- Reduced risks of
 - Certain cancers
 - Cardiovascular disease
 - Liver disease
 - Renal disease

HIV RNA and Risk of Serious Non-AIDS Events: SMART



Adjusted for age, gender, prior AIDS, hep B/C, smoking, latest CD4 count

Philips A CROI 2008

SMART, unpublished

Association Between Current CD4+ Cell Count & Non-AIDS Complications

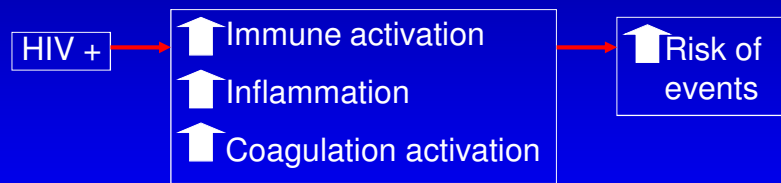
Study	Lower Current CD4+ Cell Count Significantly Associated With Increased Risk?			
	Non-AIDS malignancies	Renal disease/death	CVD events/death	Liver disease/death
FIRST	Yes	Yes	Trend, NS	No
D:A:D	Yes	Yes	Trend, NS	Yes
CASCADE	Yes	NA	Yes	Yes
SMART	Trend, NS	Trend, NS	Trend, NS	Yes

Phillips A, et al. CROI 2008. Abstract 8.

CD4 and morbidity/mortality

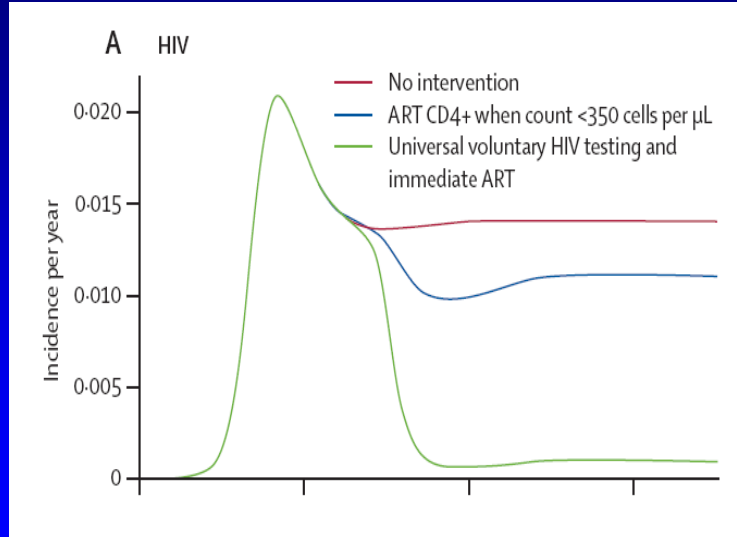
- Decreasing CD4 is associated with an increase in risk of AIDS, serious non-AIDS deaths, and all-cause mortality
- Consistent across many cohorts of HIV-infected people

How does HIV increase non-AIDS disease risk?



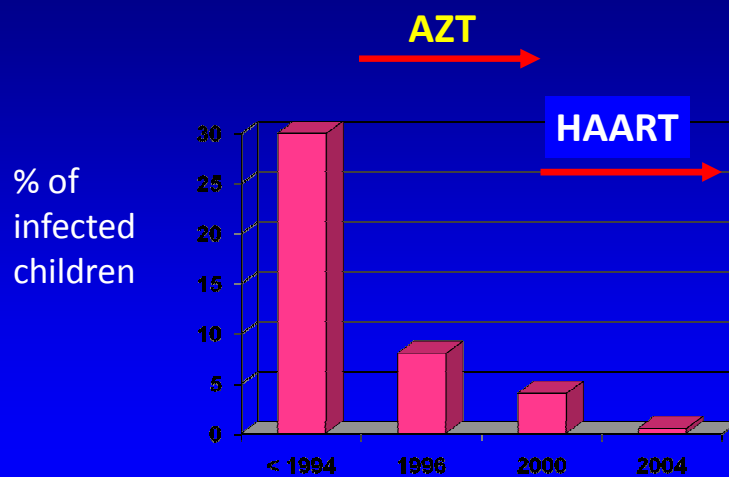
Transmission

'Test and Treat concept'

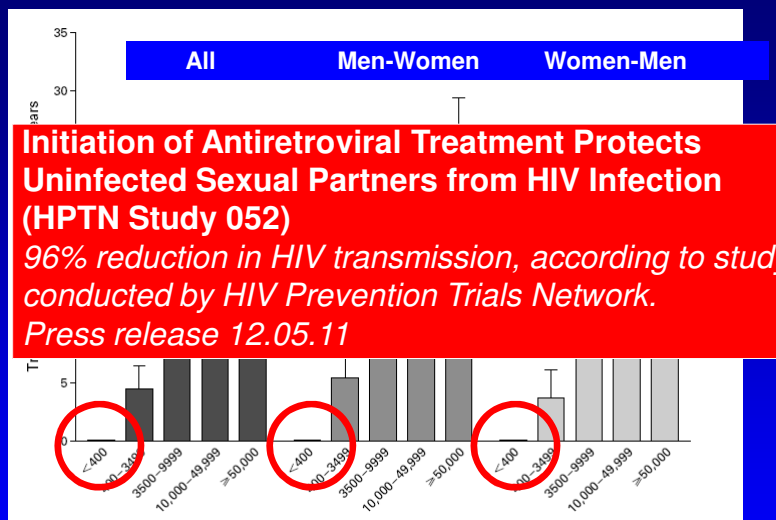


Granich et al 2009 Lancet

Mother to Child Transmission



Adapted from Coovadia and Lallemand, NEJM 2004 28



« Rakai » Study: Transmission risk as a function of viral load

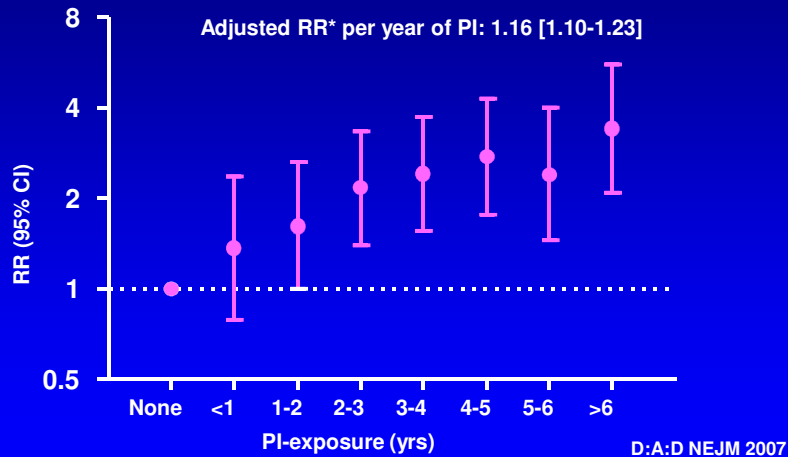
Quinn et al. N Engl J Med 2000;342:921-9

What studies are planned to test the strategy?

- Botswana Cohort Pilot (*Essex*)
- HPTN 065 in US-NYC, DC (*El-Sadr, Mayer*)
- PopART Uganda, Tanzania, Malawi, Zambia (*Fidler, Hayes, Kamali, Kapiga, Ayles*)
- HPTN Africa (*Mastro, Hodder*)
- Kenya (*Little*)
- ANRS TasP S Africa (*Hirschel and Dabis*)

However, there are complications...

Relative rate of MI according to PI exposure



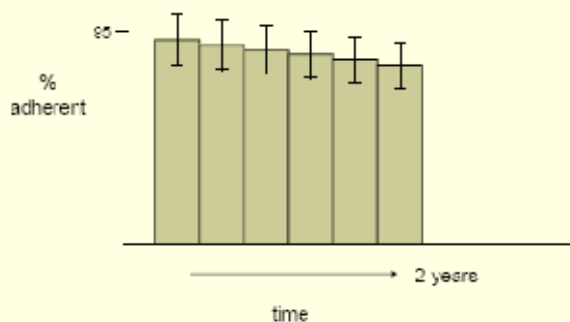
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Many organ systems are affected by ART

- cardiovascular system
- kidneys
- liver
- bone
- peripheral nervous tissue
- muco-cutaneous membranes

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CPCRA - adherence with time



Resistance & loss of drug options are also potential problems

	Years from start of ART (≥ 3 drugs)				
	2	4	6	8	10
Risk of extensive triple class failure	0%	1%	3%	5%	8%

Extensive Failure Definition. Nucleoside class: virologic failure of ≥ 1 drug from (i) zidovudine, stavudine, (ii) 3TC, FTC and (iii) ddI, tenofovir, abacavir. NNRTI class: virologic failure of efavirenz or nevirapine. PI class: virologic failure of at least one ritonavir-boosted PI

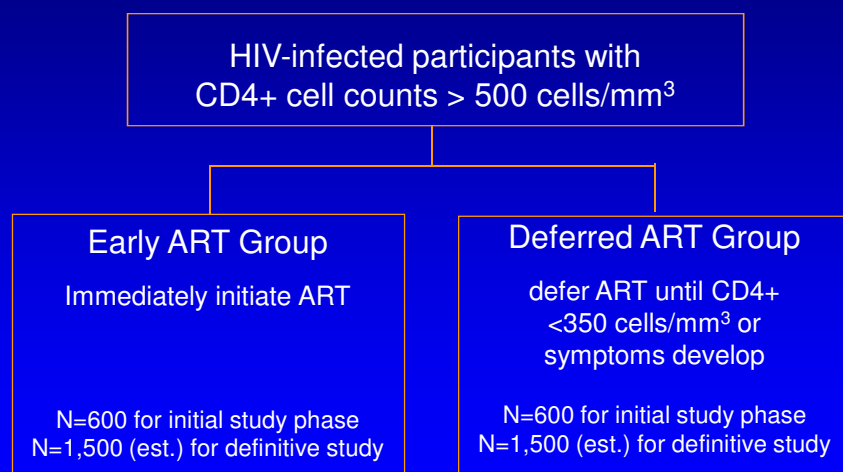
UK CHIC – CROI 2007

When should antiretroviral therapy be initiated?

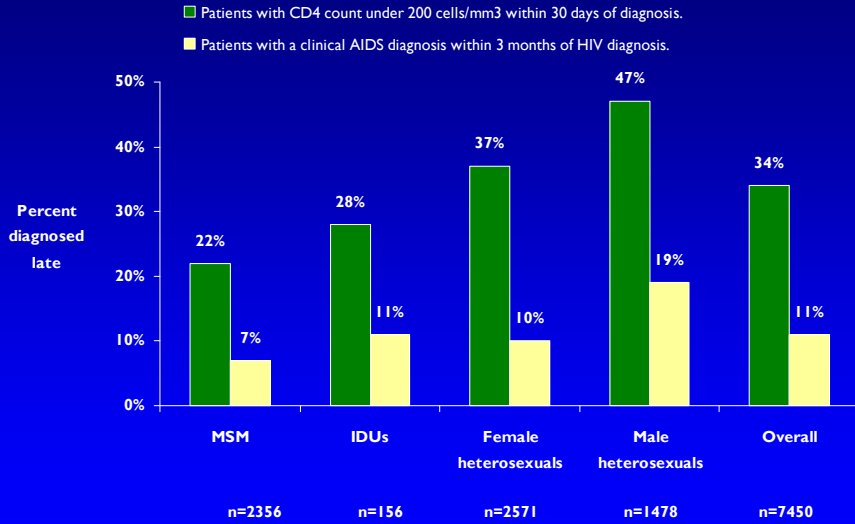
	Early ART	Deferred ART
PROS	<p>Reduce risk of death/AIDS/serious non-AIDS</p> <p><i>Reduce HIV transmission</i></p>	<p>Preserve drugs for use when needed</p> <p><i>Reduce costs</i></p>
CONS	<p>Increased side effects</p> <p>Limit future options</p> <p><i>Increased costs</i></p>	<p>Higher risk of AIDS/non-AIDS events/death</p> <p><i>Increased HIV transmission</i></p>

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INSIGHT: the START trial Strategic Timing of Antiretroviral Treatment

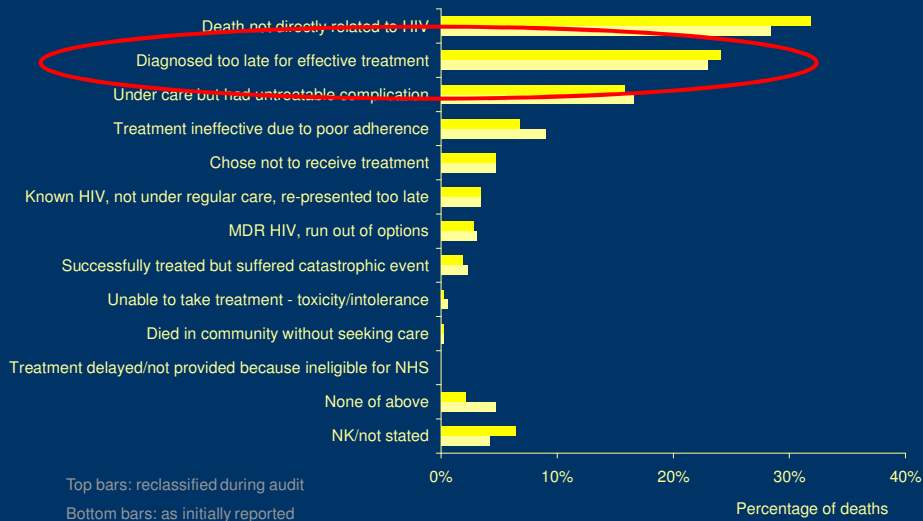


Late diagnosis of HIV infection



Reports of HIV/AIDS diagnosis and CD4 Surveillance

BHIVA Audit 2006: Scenario leading to death



Mortality audit BHIVA audit and Standards Sub-Committee 2006; accessible at www.bhiva.org

Summary – when to start

- All guidelines shifting towards earlier treatment
- Increased recognition of non-AIDS morbidity/mortality
- RCT currently underway
- Patient choice remains essential
- Earlier treatment initiation requires earlier diagnosis

What to Start?

What to start – preferred regimens

Agent	BHIVA 2008	EACS 2009	DHHS Jan 2011	IAS Jul 2010
NRTI	TDF/FTC or ABC/3TC	TDF/FTC or ABC/3TC	TDF/FTC (CBV if pregnant)	TDF/FTC
NNRTI	Efavirenz	Efavirenz or NVP	Efavirenz	Efavirenz
PI		ATV/r DRV/r LPV/r SQV/r	ATV/r DRV/r od (LOP/r if pregnant)	ATV/r DRV/r od
other			Raltegravir	Raltegravir

BHIVA GUIDELINES 2008

What to start with – preferred regimens

Regimen	A	B	C
Preferred regimen	Efavirenz*	Tenofovir*#	Lamivudine#§
		Abacavir§	Emtricitabine**
Alternative	Lopinavir/r	Didanosine	
	Fosamprenavir/r	Zidovudine [¶]	
	Atazanavir/r		
	Saquinavir/r		
Specific groups	Nevirapine		
	Atazanavir**		

Chose one drug from columns A,B and C. Licensing based on EMEA.

* Co-formulated as Atripla (licensed for virologically suppressed patients only).

Co-formulated as Truvada. [¶] Co-formulated as Combivir. [§] Co-formulated as Kivexa.

^{||} Only when CD4 <250 cells/μL in female patients and <400 cells/μL in male patients.

** Where there are established CVD risk factors and a PI is required

What to start with

- **Efavirenz should be considered first line in all patients**
 - Nevirapine should be reserved for women wishing to become pregnant & patients with mental health problems (within set CD4 count criteria)
- **Boosted PIs should be reserved for specific groups of patients:**
 - NRTI/NNRTI resistance, women wishing to become pregnant and some patients with psychiatric problems
- **Truvada & Kivexa recommended as the nucleoside backbones of choice**
 - Kivexa should be reserved for patients who are HLA-B*5701 negative and should be used in caution in patients with a baseline VL >100,000 copies/mL, or where there is a significant risk of CVD

Differences between guidelines

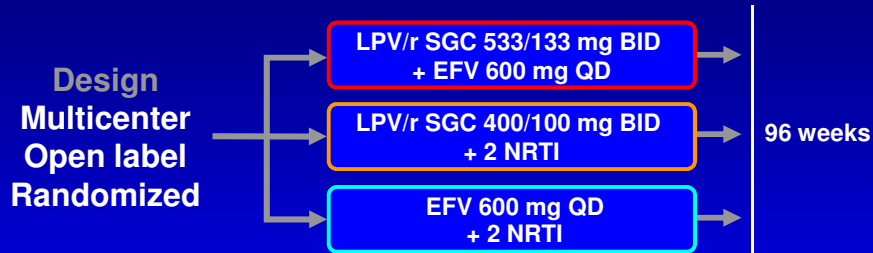
- ABC in backbone still a recommended agent in BHIVA and EACS guidelines while it is an alternative choice in US guidelines
- Lopinavir/r based regimen moved to alternative choice in US guidelines unless in pregnant women where it remains the preferred agent as LPV/r (twice daily) + ZDV/3TC (LPV/r once daily is contraindicated in pregnant women)
- Raltegravir placed as a preferred agent as part of the initial HAART combination regimen in US guidelines, while it was positioned as an alternative choice in initiation of therapy in EACS guidelines, and not (?yet) in BHIVA guidelines

EFV vs PIs in BHIVA Guidelines

- EFV preferred over boosted PIs by BHIVA due to
 - Efficacy and durability (virologic efficacy superior to LPV/RTV in ACTG 5142)
 - Safety profile
 - Dosing convenience and cost
- Boosted PIs considered alternative in special settings
 - Primary NRTI/NNRTI resistance
 - Psychiatric illness
 - Pregnancy

Gazzard BG, et al. HIV Med. 2008;9:563-608.

A5142 Study Design



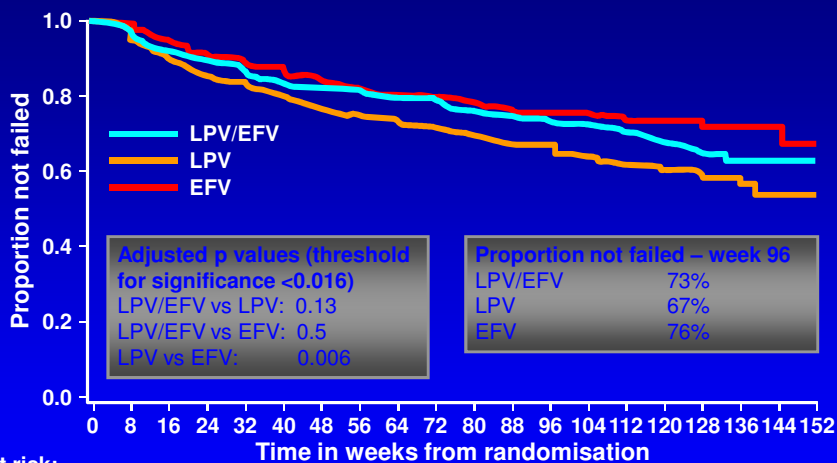
Population:
ARV-naïve
HIV RNA >2,000 c/mL
Any CD4 count

2 NRTI = 3TC
+ Investigator Selection of
AZT or d4T XR or TDF

Stratification:
HIV RNA > 100,000 c/ml
Hepatitis infection
Selection of NRTI

Riddler SA, et al. NEJM 2008

Time to virologic failure

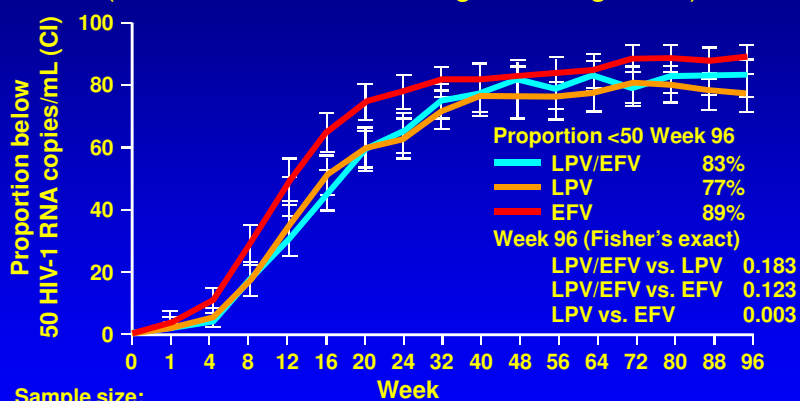


No at risk:

	0	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	
LPV/EFV	250	208	187	171	131	58	10														
LPV	253	206	180	164	116	62	3														
EFV	250	204	183	170	121	60	8														

Proportion with HIV RNA <50 copies/mL

(Intention to treat, missing values ignored)

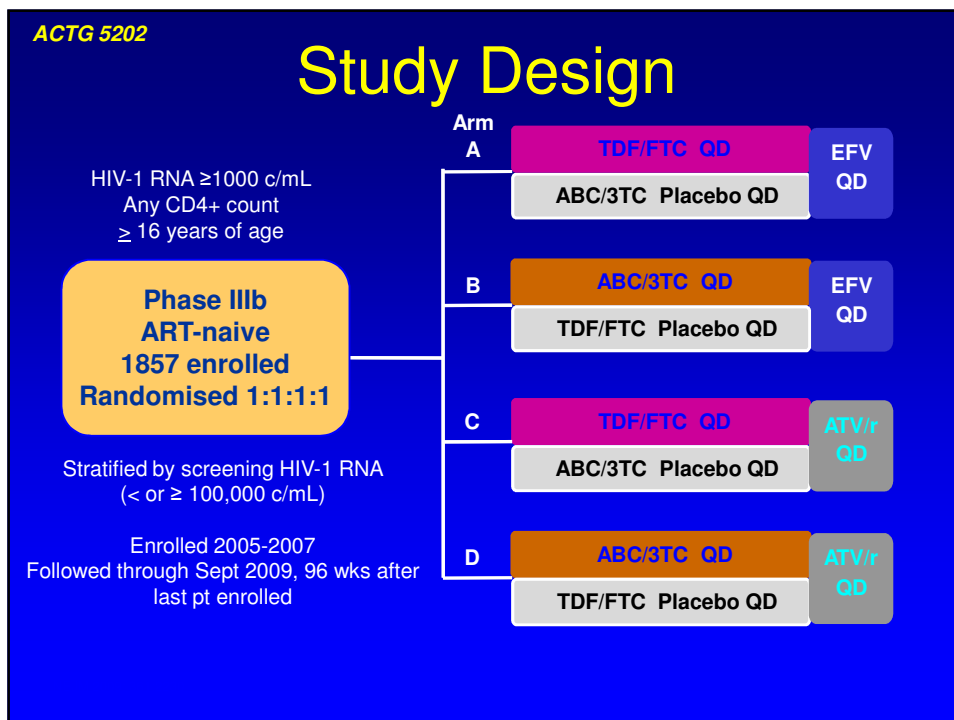


Sample size:

	0	4	8	12	16	20	24	32	40	48	56	64	72	80	88	96
LPV/EFV	250	229	224	212	201	178										
LPV	253	231	226	217	201	177										
EFV	250	235	228	217	206	180										

BUT in boosted LPV arm

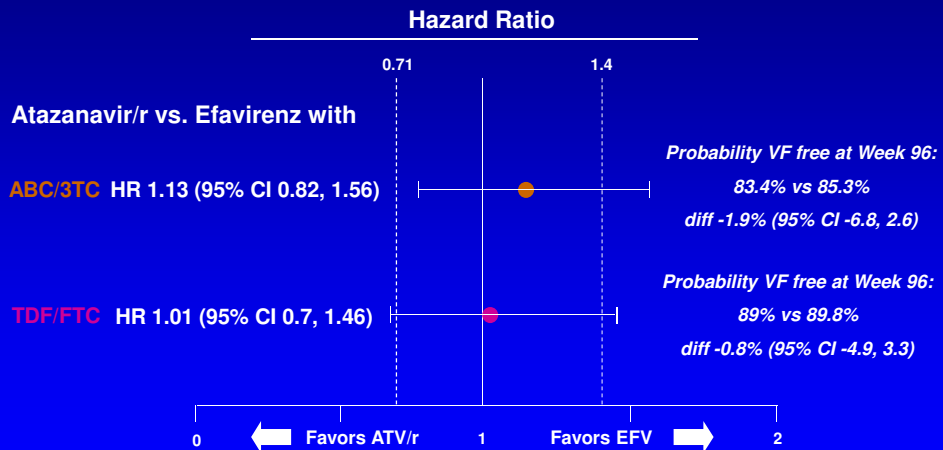
- Improved immunological response
- Less class-emergent resistance
- Less fat loss
- (no significant differences in treatment-limiting toxicity or grade 3/4 adverse events)



ACTG 5202 Atazanavir/r vs Efavirenz – overall population

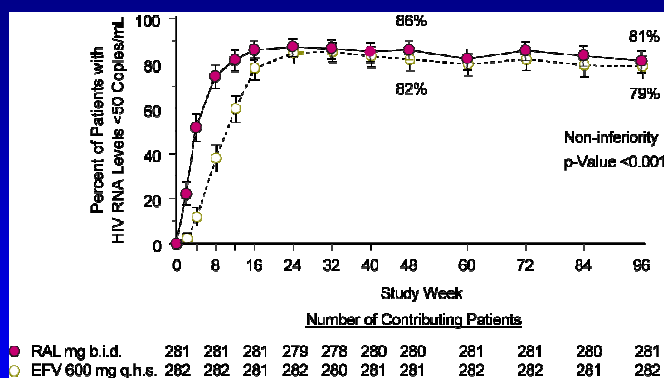
Primary Efficacy Endpoint – Time to Virologic Failure (ITT)

Atazanavir/r vs Efavirenz – overall population



Darr, E. et al. 17th CROI, San Francisco, CA, 2010, presentation 59LB.

RAL vs EFV for first-line HAART - STARTMRK



- Proportion (%) of Patients With HIV RNA <400 c/mL At 96 Weeks (Non-Completer = Failure)
 - RAL group 85% vs. EFV group 81%
 - Non-inferiority p<0.001

Lennox et al. Lancet 2009

Choice of NNRTI

NNRTI-based regimens

2NN: grade 3 or 4 laboratory toxicities

%	NVP-qd n=220	NVP-bd n=387	EFV n=40 0	NVP+EFV V n=209	p
hepatobiliary lab. toxicity *	13.2	7.8	4.5	8.6	0.002
non-hepatobiliary lab. toxicity	8.2	12.9	8.8	9.6	0.161
neutropenia	2.3	3.9	1.8	5.3	
amylase	1.8	3.1	3.5	1.4	
triglycerides	1.4	1.3	1.3	0.5	
alkaline phosphatase	0.5	1.3	0.8	1.9	

* elevated AST and/or ALT

hepatobiliary: only significant difference: NVP-qd vs EFV, $p < 0.001$

Which boosted PI?

Which boosted PI?

- BHIVA guidelines 2008 recommend LPV/r or ATV/r or FOS/r or SQV/r
- Clinical trials show non-inferiority between these agents at 48 weeks
 - KLEAN¹
 - GEMINI²
 - CASTLE³
 - ARTEMIS⁴

¹Eron J *et al.* Lancet 2006. ²Walmsley S *et al.* EACS 2007. ³Molina JM *et al.* Lancet 2008

⁴Ortiz A *et al.* AIDS 2008.

ARTEMIS: phase III study design

- 689 ARV-naïve patients
- VL > 5000
- No CD4 entry

DRV/r 800/100 mg qd + TDF 300 mg and FTC 200 mg (n = 343)

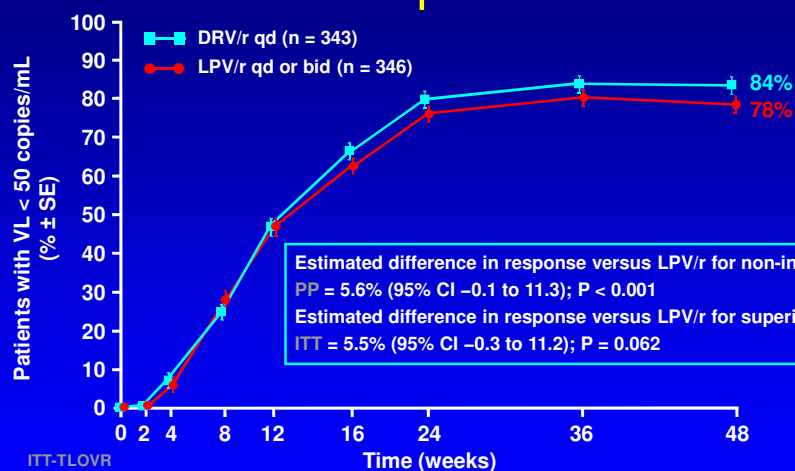
LPV/r 400/100 mg bid or 800/200 mg qd + TDF 300 mg and FTC 200 mg (n = 346)

LPV dosing		LPV formulation	
qd =	15%	Capsule only =	15%
bid =	77%	Tablet only =	2%
bid/qd =	7%	Capsule/tablet switch =	83%

Dosing was based on regulatory approval; switch to LPV/r tablet was made according to local regulatory approval and drug availability.

DeJesus E, et al. 47th ICAAC, 2007. Poster H-718b.

Virological response up to week 48 < 50 copies/mL



Estimated difference in response versus LPV/r for non-inferiority:
 PP = 5.6% (95% CI -0.1 to 11.3); P < 0.001
 Estimated difference in response versus LPV/r for superiority:
 ITT = 5.5% (95% CI -0.3 to 11.2); P = 0.062

ITT-TLOVR
 The PP population comprised all patients in the ITT group who completed the first 48 weeks of the study without major protocol violation. TLOVR = time to loss of virological response.

DeJesus E, et al. 47th ICAAC, 2007. Poster H-718b.

Efficacy and Safety of Boosted Once-Daily Atazanavir and Twice-Daily Lopinavir Regimens in Treatment-Naïve HIV-1 Infected Subjects

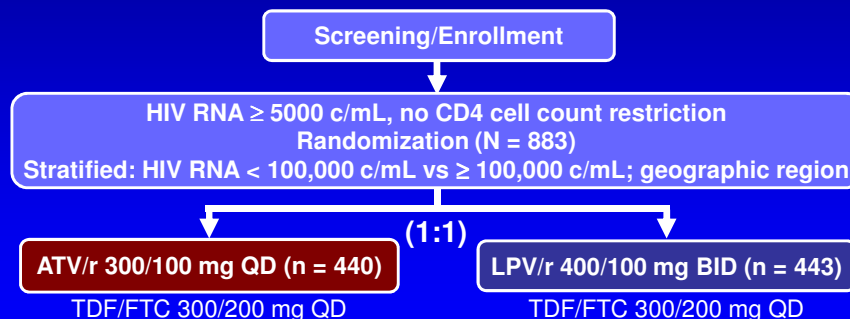
CASTLE: 48-Week Results

J. M. Molina,¹ J. Andrade-Villanueva,² J. Echevarria,³ P. Chetchotisakd,⁴ J. Corral,⁵ N. David,⁶ M. Mancini,⁷ L. Percival,⁷ A. Thiry,⁷ D. McGrath⁷

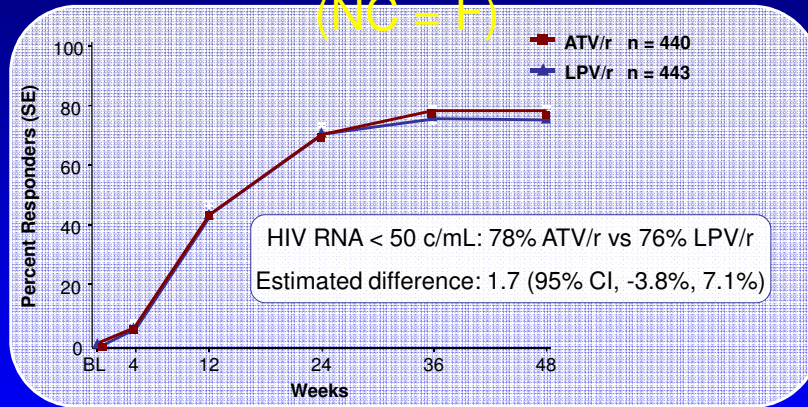
¹Hopital Saint-Louis, Paris, France; ²Hospital Civil De Guadalajara, Guadalajara, Mexico; ³Hospital Nacional Cayetano Heredia, Lima, Peru; ⁴Khonkaen University, Khonkaen, Thailand; ⁵Hospital Interzonal Gral. De Agudos Oscar Alende, Buenos Aires, Argentina; ⁶Brooklyn Medical Centre, Western Cape, South Africa; ⁷Bristol-Myers Squibb, Wallingford, CT, USA

Study Design

International, multicenter, open-label, randomized, 96-week study to determine the comparative clinical efficacy and safety of ATV/r and LPV/r in treatment-naïve HIV-1 infected subjects



Primary Efficacy End Point ITT-Confirmed Virologic Response (NC = F)



ATV/r has non-inferior antiviral efficacy compared with LPV/r

Supporting Analyses:

ITT-TLOVR: HIV RNA < 50 c/mL: ATV/r 78%, LPV/r 76%; 1.9 (-3.6, 7.4)
OT-VROC: HIV RNA < 50 c/mL: ATV/r 84%, LPV/r 87%; -3.5 (-8.7, 1.8)

Which NRTI backbone?

Which NRTI backbone?

Recommendations

- Truvada or Kivexa should be the first choice for nucleoside backbone to be used with efavirenz. However, Kivexa should be reserved for patients who are HLA-B*5701 negative and used in caution in those with viral loads over 100,000 copies/ml or where there is significant risk for CVD
- Combivir remains the coformulation of choice in patients using ART to prevent mother-to-child transmission

CROI 2008 D:A:D Study

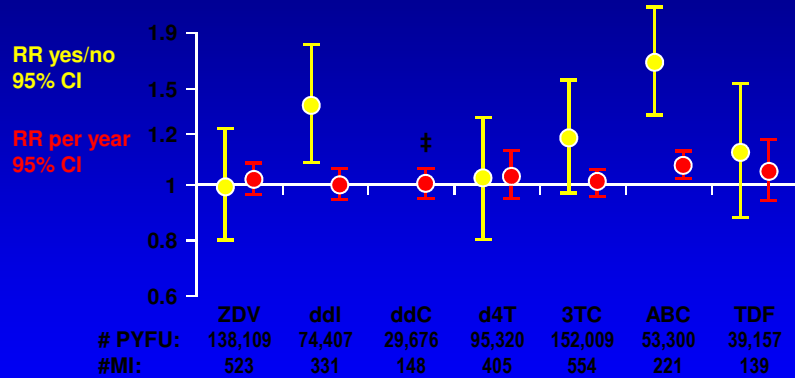
Recent Use of ABC and ddI Associated with Increased Risk of MI

Rates of MI		
NRTIs	Cum., recent ¹ + past ² use Rel. rate [95% CI]; p-value	
Abacavir	Cumulative use (per year)	1.00 [0.92, 1.08]; p = 0.91
	Any recent ¹ use	1.94 [1.48, 2.55]; p = 0.0001
	Any past ² use	1.29 [0.94, 1.77]; p = 0.12
Didanosine	Cumulative use (per year)	1.00 [0.93, 1.07]; p = 0.91
	Any recent ¹ use	1.53 [1.10, 2.13]; p = 0.01
	Any past ² use	1.08 [0.84, 1.39]; p = 0.54

¹Recent = still using or stopped within last 6 months; ²Past = last used more than 6 months ago

Sabin C et al., CROI 2008; #957c.

D:A:D study: NRTIs and risk of MI – recent* and cumulative** exposure

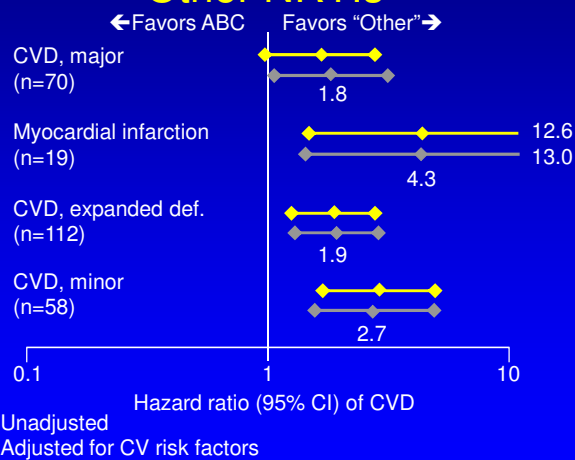


* Recent = current or within the last 6 months.
 ** Cumulative = From time of first exposure until end of follow-up (intention-to-treat)
 ‡ Not shown (low number of patient currently on ddC)

Adapted from Lundgren JD, et al. 16th CROI, Montreal, Canada Feb 2009; Abstr LB44

SMART

Hazard Ratios for Four Types of CVD while Receiving “ABC (no DDI)” vs. Using “Other NRTIs”



Lundgren et al, 17th International AIDS Conference, México City, México, 2008; Oral THAB0305.

Study design

Study	Association?	
D:A:D	✓	Cohort collaboration (prospective)
Danish HIV Cohort	✓	Cohort (linked with registries)
Montreal study	✓	Nested case-control study
SMART	✓	<i>Post-hoc</i> subgroup analysis of RCT (use of ABC not randomised)
STEAL	✓	Pre-planned secondary analysis of RCT (use of ABC randomised)
Brighton study	✓	Nested case-control study
VA Clinical Case Registry	✓	Cohort (retrospective)
FHDH ANRS CO4	?	Nested case-control study
Boston Cohort	✗	Cohort (retrospective)
GSK studies	✗	<i>Post-hoc</i> meta-analysis of RCTs
ACTG A5001/ALLRT	✗	<i>Post-hoc</i> meta-analysis of RCTs
FDA meta-analysis	✗	<i>Post-hoc</i> meta-analysis of RCTs

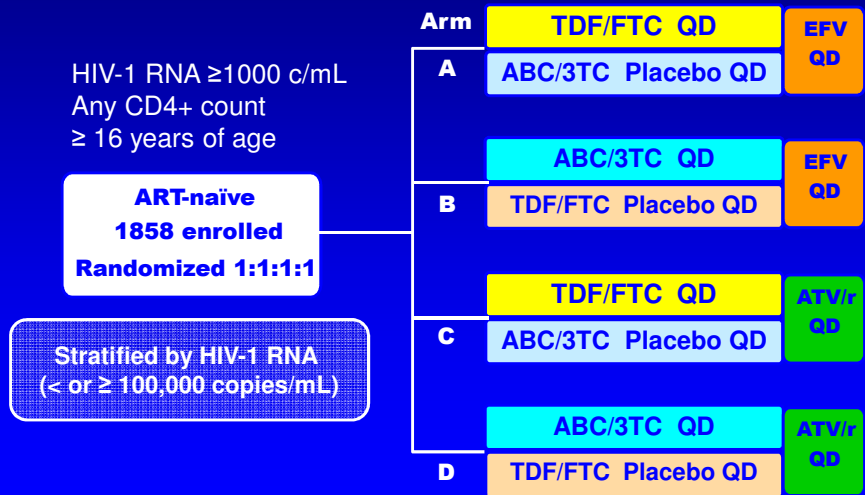
Abacavir and CV risk

Study	N	Design	Effect	Effect Size (95% CI)
D:A:D	33,347	Observational cohort	Yes	RR: 1.90 (1.47-2.45)
SMART	2752	Observational RCT	Yes	HR: 4.25 (1.39-13.0)
GSK	14,174	Pooled RCTs	No	RR: 0.81 (0.38-1.75)
STEAL	357	RCT	Yes	HR (tenofovir): 0.12 (0.02-0.98)
Danish	2952	Prospective cohort	Yes	RR: 2.00 (1.10-3.64)
FHDH	1151	Nested case control	No	OR: 1.27 (0.64-2.49)
ALLRT	3207	ACTG RCT	No	HR: 1.00 (0.4-2.9)
VA	19,424	Observational	No	HR: 1.18 (0.92-1.50)
QPHID	1209	Nested case control	Yes	HR: 1.69 (1.17-2.44)
Italian	5051	16 RCTs	No	OR: 1.10 (0.56-2.10)
MGH	6517	Observational cohort	No	OR: 1.42 (0.85-2.34)

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk.

ACTG 5202

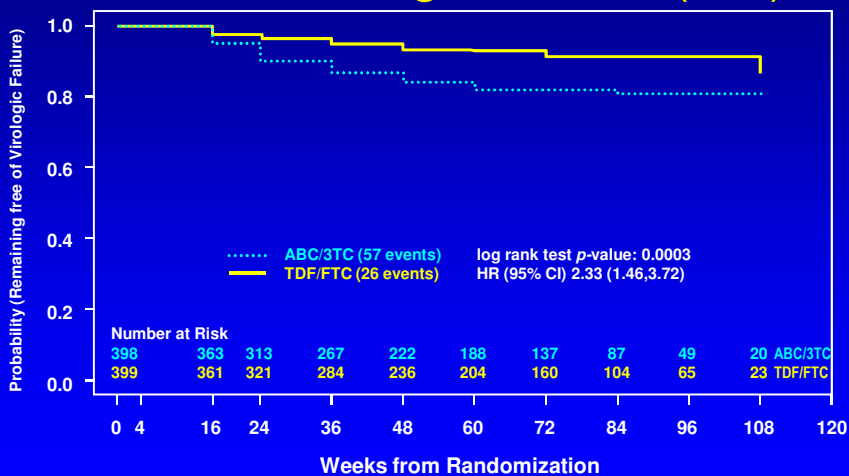
Study Design



Sax PE, et al., 17th International AIDS Conference, México City, México, 2008; Oral #THAB0303.

ACTG 5202

Primary Efficacy Endpoint Time to Virologic Failure (ITT)



Sax PE, et al., 17th International AIDS Conference, México City, México, 2008; Oral #THAB0303.

Other strategies

- Newer agents
 - Etravirine (TMC-125): switch study
 - Rilpivirine (TMC-278): ECHO and THRIVE
 - Maraviroc: MERIT study
- NRTI-sparing
 - SPARTAN: RAL/ATV (unboosted) vs ATV/r/Truvada
 - PROGRESS: RAL/LPV/r vs LPV/r/Truvada
 - MVC/ATV/r od vs ATV/r/Truvada
 - NEAT study: on-going

Summary of what to start

- British guidelines currently recommend EFV-based regimen for initial therapy
- Truvada and Kivexa are the nucleoside backbones of choice - however, Kivexa should be reserved for patients who are HLA-B*5701 negative and used with caution if baseline VL > 100000 copies/ml or significant risk of CVD

Choosing HAART

- Need to be individualised for the patient
- Screen for HBV/HCV, DM, renal disease; perform a CVS risk assessment; take a psychosocial history; consider plans for pregnancy and/or contraception in women
- Other considerations include cost, availability, clinical trials

Summary

- All guidelines are shifting towards earlier treatment
- Continued need for earlier diagnosis*
- Choice of initial regimen should be individualised

*HIV Testing Guidelines 2008; www.bhiva.org