14th Annual Conference of the
National HIV Nurses Association (NHIVNA)

National HIV Nurses Association

Dr Andy Ustianowski

North Manchester General Hospital

14-15 June 2012, Manchester Conference Centre

Antiretroviral Update…

Andy Ustianowski
North Manchester General Hospital

Outline

- I will concentrate on naïve patients…
  - BHIVA guidance 2008-2012
    - Studies that informed the changes
    - Agents that are not there (and why)
- New drugs that are coming through in next 1-2 years
- Only briefly mention experienced patients at end

BHIVA Guidance 2008

	Backbone (NRTIs)	3rd Agent
Preferred:	Tenofovir & Emtricitabine Abacavir & Lamivudine	Efavirenz
Alternative:		Lopinavir/ritonavir Fosamprenavir/ritonavir Atazanavir/ritonavir Saquinavir/ritonavir
Other possibilities:	Zidovudine (AZT) Didanosine (ddI)	Nevirapine

HIV Medicine 2008;9:563-608

BHIVA Guidance 2008-2012

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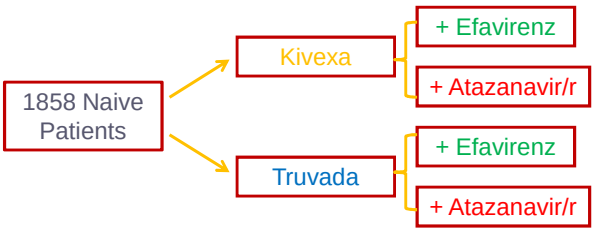
HIV Medicine 2008;9:563-608; www.bhiva.org/documents/Guidelines/Treatment/2012/120430TreatmentGuidelines.pdf

ACTG 5202: (Kivexa vs Truvada)



Interim analysis:

Those with high initial viral loads (797 patients had VL>100,000):

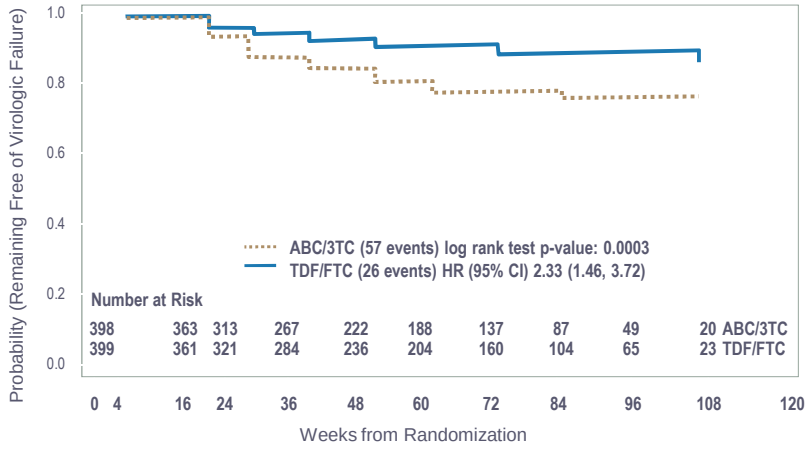
Virologic failure rates Kivexa 14%
Truvada 7%

Hazard ratio 2.33 (95% Confidence Interval 1.46-3.72, p=0.0003)

Therefore those on Kivexa offered switch.....

Sax et al. 17th International AIDS Conference; 2008; Mexico. Abstract THAB0303

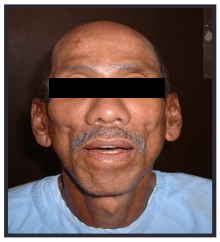
ACTG 5202: (Kivexa vs Truvada)

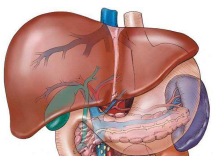


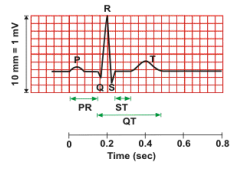
Sax et al, IAC 2008, Oral THAB00303

AZT/ddI/Saquinavir

- 'Dropped' due to toxicity/lack of advantages







P wave (0.08 - 0.10 s) QRS (0.06 - 0.10 s)
P-R interval (0.12 - 0.20 s) Q-T_C interval (≤ 0.44 s)*
*$QT_C = QT/\sqrt{RR}$

BHIVA Guidance 2008-2012

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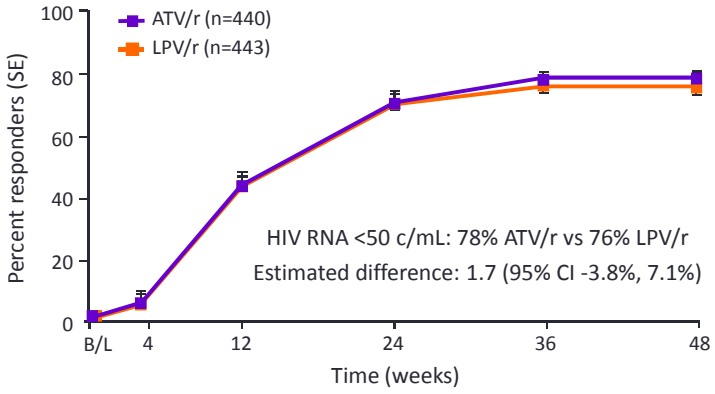
Other possibilities:		Nevirapine

HIV Medicine 2008;9:563-608; www.bhiva.org/documents/Guidelines/Treatment/2012/120430TreatmentGuidelines.pdf

CASTLE: Atazanavir/r vs Lopinavir/r

Primary efficacy end point ITT - confirmed virologic response (NC = F)



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

Supporting analyses:

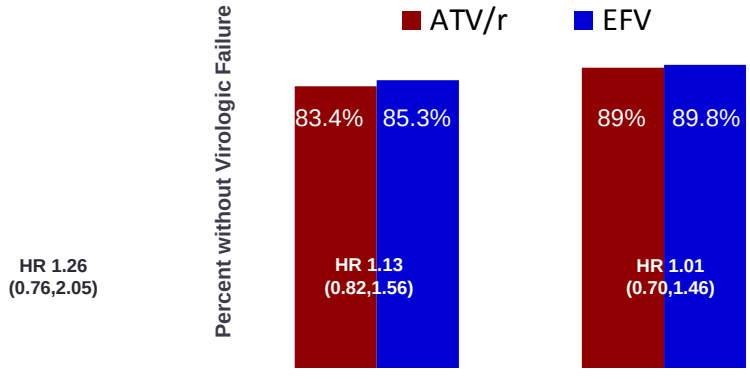
ITT-TLOVR: HIV RNA <50 c/mL: ATV/r 78%, LPV/r 76%; 1.9 (-3.6, 7.4)

OT-VROC: HIV RNA <50 c/mL: ATV/r 84%, LPV/r 87%; -3.5 (-8.7, 1.8)

Molina J-M et al. CROI 2008; Presentation 37

ACTG 5202: ATV/r vs. EFV

Week 96 % with Virologic Suppression



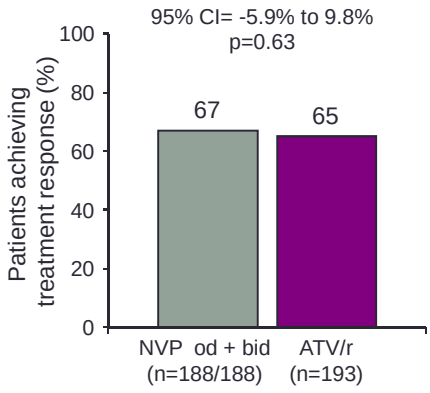
	ABC/3TC	TDF/FTC
CD4 Change (cells/mm^3)	250 251	252 221
P=	0.89	0.002

Daar E, et al. 17th CROI; San Francisco, CA; February 16-19, 2010. Abst. 59LB.

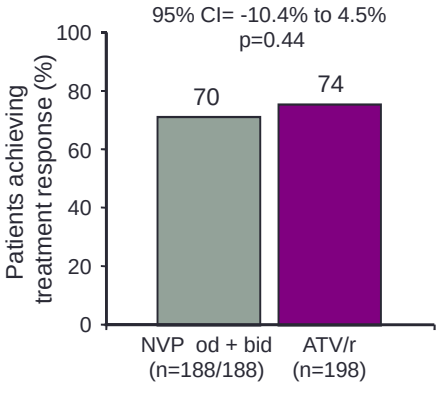
ARTEN: Nevirapine vs Atazanavir/r

HIV-1 RNA <50 copies/ml (Wk 48)

Treatment response by primary endpoint (ITT) (two visits prior Wk 48)



Treatment response by sensitivity analysis: TLOVR algorithm (ITT)



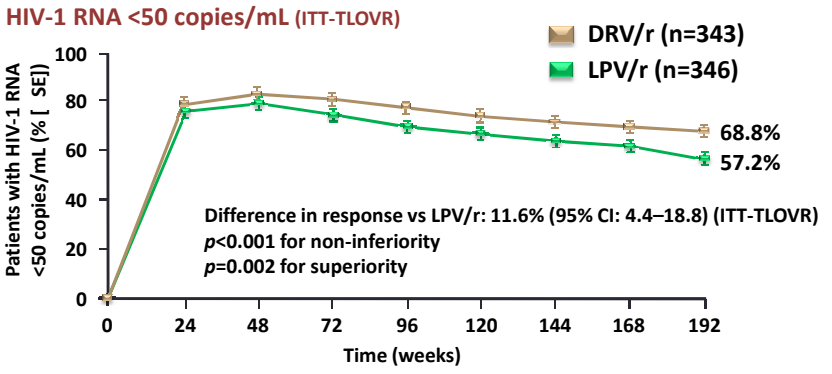
Soriano et al. IAS 2009, Cape Town, South Africa, poster LBPE07

BHIVA Guidance 2008-2012

	Backbone (NRTIs)	3rd Agent
Preferred:	Tenofovir & Emtricitabine	Efavirenz Atazanavir/ritonavir Darunavir/ritonavir Raltegravir
Alternative:	Abacavir & Lamivudine	Lopinavir/ritonavir Fosamprenavir/ritonavir Nevirapine Rilpivirine
Other possibilities:		

HIV Medicine 2008;9:563-608; www.bhiva.org/documents/Guidelines/Treatment/2012/120430TreatmentGuidelines.pdf

ARTEMIS: Darunavir/r vs Lopinavir/r



	DRV/r (n=343)	LPV/r (n=346)
<50 copies at 96 wks	79%	71%
<50 copies at 192 wks	68.8%	57.2%
Mean increase in CD4 at 192 weeks from BL	+266 cells/mm^3	+269 cells/mm^3

Orkin C *et al*. HIV10 2010. Abst P3

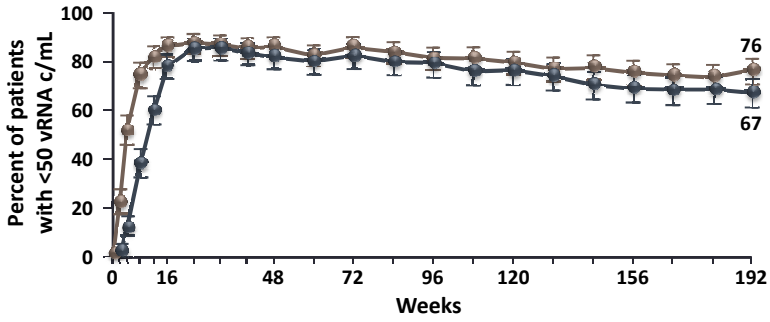
STARTMRK: RAL vs. EFV at 192 weeks

Randomized (1:1), double blind

ART-naïve subjects (N=561)

- RAL (400 mg BID) + TDF/FTC QD + EFV Placebo n=245
- EFV (600 mg QHS) + TDF/FTC QD + RAL Placebo n=232

Proportion of patients with <50 RNA c/mL over time (Primary NC=F approach)



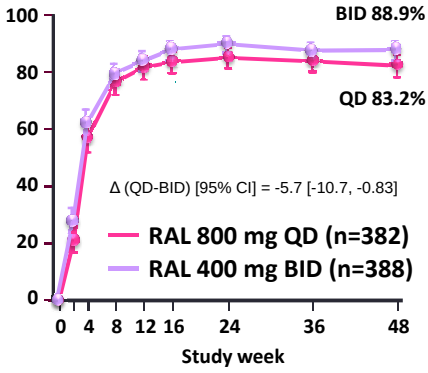
No differences by age, gender, region, race, hepatitis co-infection, baseline plasma RNA level >100,000 copies/mL, CD4 count ≤200 cells/mm³, viral subtypes

Rockstroh J. 11TH EACS. Abstract #11. PS1/1

QDMRK: RAL (800 QD) vs RAL (400 BID)

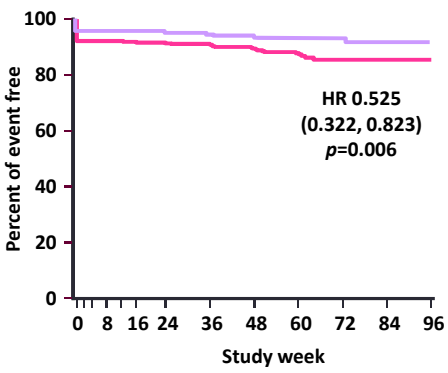
Primary endpoint Week 48

% Patients HIV RNA <50 c/ml (NC=F†)



Secondary endpoint Week 96

Time to Loss of Virologic Response (TLOVR) All patients



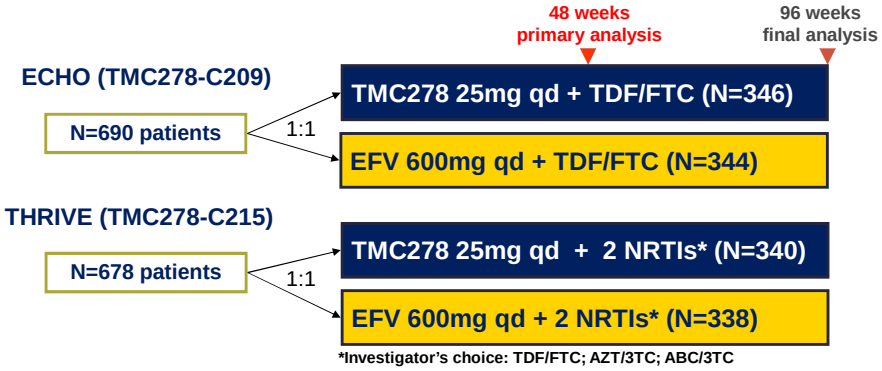
*All patients received TDF/FTC FDC

† Non-completer equals failure (NC=F) approach treats all discontinuations as failures

Time to Loss of Virologic Response is equal to zero if discontinued due to lack of efficacy; Loss of Virologic Response: Confirmed rebound (2 consecutive vRNA above 50 cp/mL) after confirmed suppression (2 consecutive vRNA <50 cp/mL)

Eron J *et al*. CROI 2011. Abst 150LB

ECHO and THRIVE: Rilpivirine vs EFV



- **Main inclusion criteria: viral load (VL) ≥ 5000 c/mL; no NNRTI RAMs†; sensitivity to the NRTIs‡**
- **Primary objective: demonstrate non-inferiority (12% margin) vs. EFV in confirmed virologic response (VL <50 c/mL, ITT-TLOVR) at Week 48**
- **Stratification factors: screening VL and NRTI background (THRIVE only)**

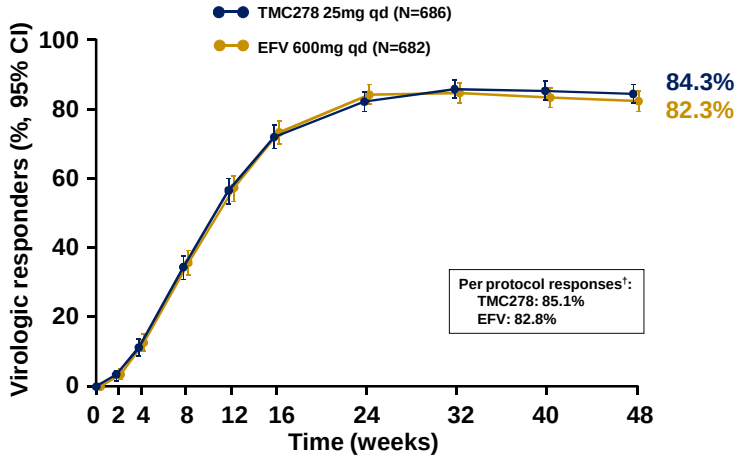
†From 39 NNRTI RAMs based on list of 44[1]
‡Determined using virco®TYPE HIV-1 test
ITT = intent-to-treat; TLOVR = time-to-loss of virologic response
Pooled analyses were preplanned

[1]Tambuyzer L et al. Antivir Ther 2009;14:103–9

Cohen et al. AIDS 2010, Vienna, Abstract THLBB206

Pooled ECHO and THRIVE:

VL <50 copies/mL over 48 weeks (ITT-TLOVR)



- **Mean change in CD4 cell count from baseline at Week 48 (NC=F‡): TMC278: +192 vs. EFV: +176 cells/mm³**

CI = confidence interval; †Excluding major protocol violators; ‡missing values after discontinuation imputed with change = 0; LOCF otherwise

Cohen et al. AIDS 2010, Vienna, Abstract THLBB206

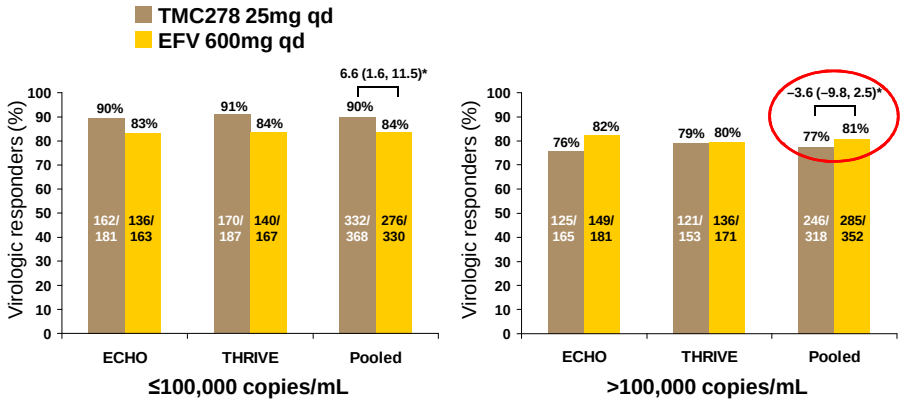
ECHO and THRIVE:
ITT-TLOVR outcome at Week 48

Outcome at Week 48†, %	Pooled TMC278 N=686	Pooled EFV N=682	ECHO TMC278 N=346	ECHO EFV N=344	THRIVE TMC278 N=340	THRIVE EFV N=338
VL <50 copies/mL	84.3	82.3	82.9	82.8	85.6	81.7
Virologic failure‡	9.0	4.8	11.0	4.4	7.1	5.3
– Rebounder	3.5	2.2	4.6	2.3	2.4	2.1
– Never suppressed	5.5	2.6	6.4	2.0	4.7	3.3
Discontinued due to AE	2.0	6.7	1.7	7.3	2.4	6.2
Discontinued for other reasons§	4.5	5.7	4.3	5.5	4.7	5.9
Death	0.1	0.4	0	0	0.3	0.9

†Analysis performed up to Week 48; ‡Determined by TLOVR in the ITT population: confirmed response before Week 48 and confirmed rebound (rebounders) at or before Week 48, or no confirmed response before Week 48 (never suppressed); §Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, sponsor's decision; AE = adverse event

Cohen et al. AIDS 2010, Vienna, Abstract THLBB206

ECHO and THRIVE:
VL <50 copies/mL by baseline VL (ITT-TLOVR)



- NRTI background had no effect on virologic response
- No differences between treatment groups in virologic response by gender, region or race

*Difference in response rates (95% CI)

Eron J, et al. 50th ICAAC, Boston 2010

BHIVA Guidance 2012

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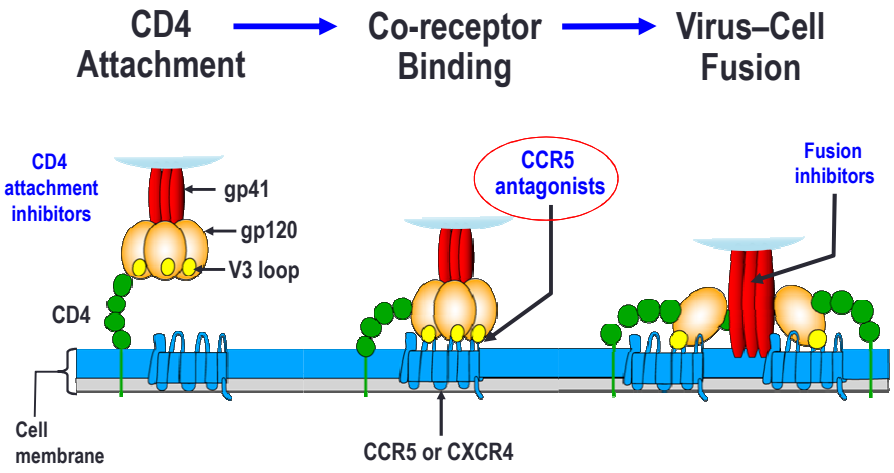
www.bhiva.org/documents/Guidelines/Treatment/2012/120430TreatmentGuidelines.pdf

What isn't there….

Maraviroc

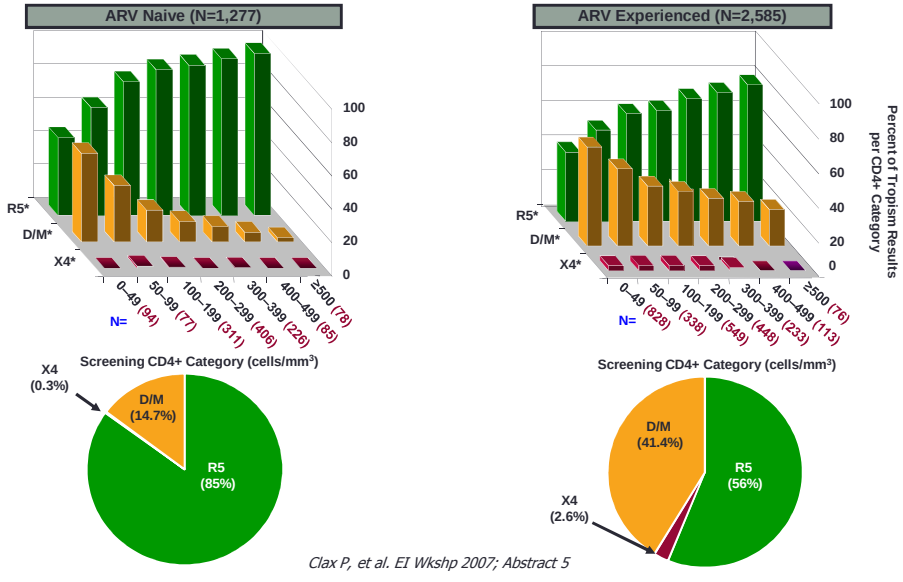
Etravirine

HIV Attachment, Co-receptor Binding, and Fusion



Adapted from Moore JP, *et al. Proc Natl Acad Sci USA* 2003;100:10598–602

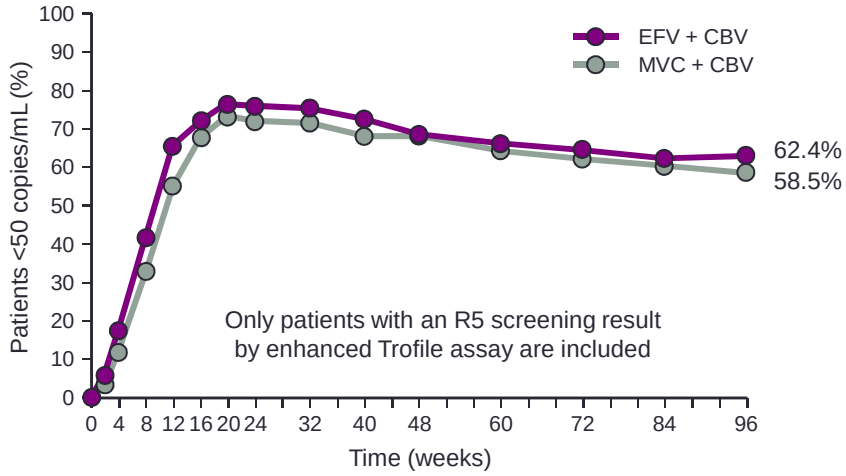
CD4+ Cell Counts and Treatment Experience Are Important Clinical Predictors of Tropism



Clax P, et al. EI Wkshp 2007; Abstract 5

MERIT-ES re-analysis: MVC vs EFV

Patients with HIV-1 RNA <50 copies/mL by visit through week 96



A4001026 Study – MERIT-ES 96 weeks

Heera J et al. IAS 2009

Etravirine

The number of mutations required to substantially decrease the efficacy of an antiviral drug

First-generation NNRTI

One mutation correlates with reduced virological response

Next-generation NNRTI (ETR)

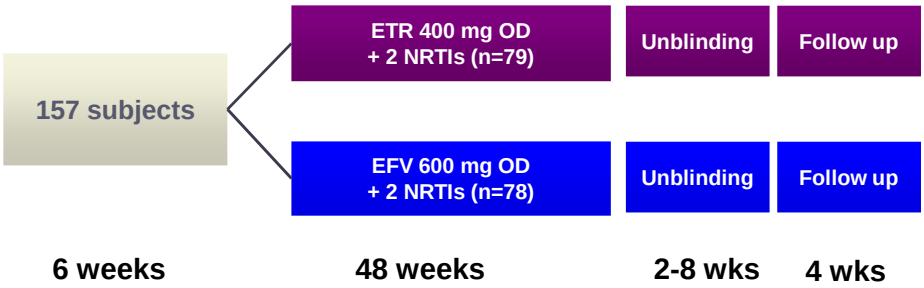
The presence of multiple NNRTI mutations at baseline is usually required to confer a reduced response

Increasing number of mutations at baseline

1. Antinori A, et al. AIDS Res Hum Retroviruses. 2002;18:835–8.
2. Lecossier D, et al. J Acquir Immune Defic Syndr. 2005;38:37–42.
3. Vingerhoets J, et al. 17th IDHRW 2008 [Poster 32].
4. De Béthune MP, et al. 4th EHDRW 2006 [Poster 51].
5. de Mendoza C, et al. HIV Clin Trials. 2006;7:163–71.

SENSE: ETR vs EFV

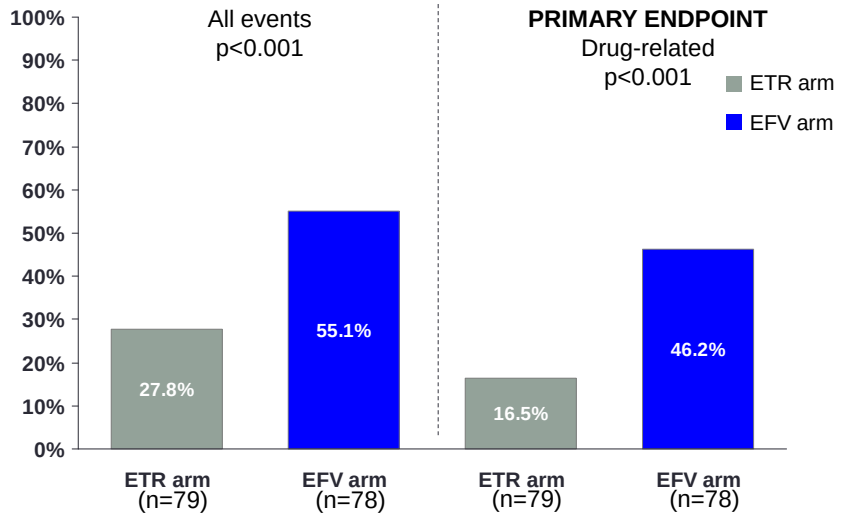
Inclusion: Treatment naïve, HIV RNA >5,000 copies/mL
No evidence of primary resistance to NRTIs or NNRTIs by Genotype or Virtual Phenotype



Double-blinded, placebo controlled to Week 48
Two investigator-selected NRTIs (AZT+3TC; ABC+3TC; TDF+FTC)

Gazzard et al. AIDS 2010, Vienna, Abstract LBPE19

SENSE: Grade 1 – 4 Treatment Emergent Neuropsychiatric adverse events (ITT)



Gazzard et al. AIDS 2010, Vienna, Abstract LBPE19

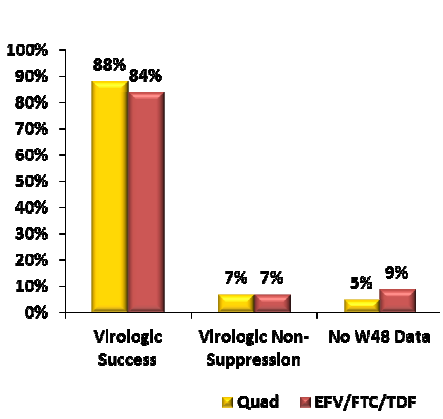
Next ARVs on the way

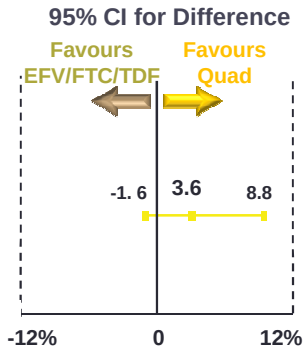
- QUAD
  - Cobicistat, Elvitegravir, TRV
  - And separate components…
- Dolutegravir
- GS-7340
- Lersivirine

QUAD vs Atripla (236-0102)

Primary endpoint (HIV-1 RNA < 50 copies/ml)

Quad was non-inferior to EFV/FTC/TDF at Week 48

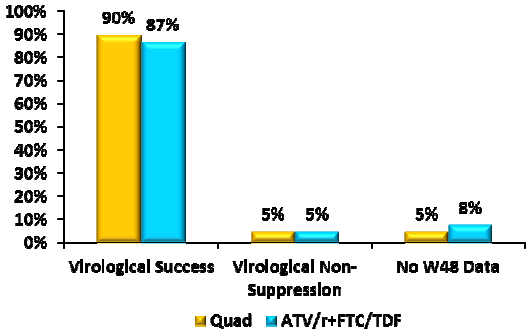


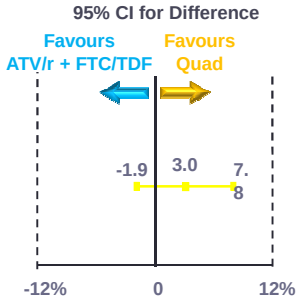


Sax P et al. CROI 2012; Seattle. #101.

QUAD vs ATV/r (236-0103)

Primary endpoint (HIV-1 RNA < 50 copies/ml)





DeJesus E et al. CROI 2012; Seattle. Poster 627.

QUAD – Adverse events

QUAD vs. *Atripla*

- QUAD associated with more:
  - Nausea (21 vs.14%)*
- Atripla associated with more:
  - Abnormal dreams (15 vs.27%)^
  - Insomnia (9 vs.14%)*
  - Dizziness (7 vs.24%)^
  - Rash (6 vs.12%)#
- Discontinuations due to AE
  - QUAD = 4%
  - Atripla = 5%

QUAD vs. *ATV/r*

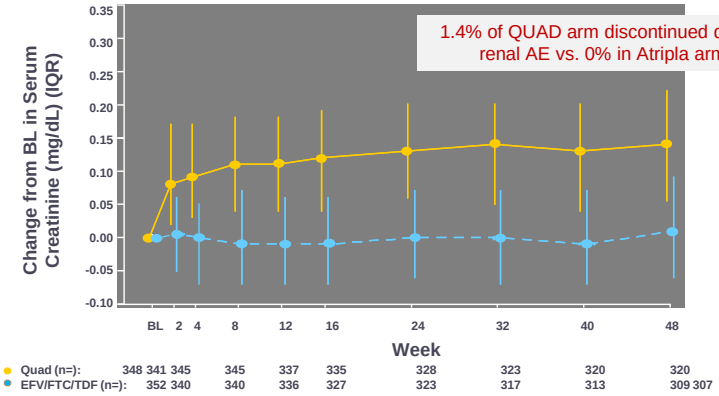
- ATV/r associated with more:
  - Scleral icterus (14 vs.1%)
- Otherwise similar:
  - Diarrhoea (22 vs.27%)
  - Nausea (20 vs.19%)
- Discontinuations due to AE
  - QUAD = 4%
  - ATV/r = 5%

* $p < 0.05$; ^ $p < 0.001$; # $p=0.009$

Sax P et al. CROI 2012; Seattle. #101; DeJesus E et al. CROI 2012; Seattle. Poster 627.

But it interferes with eGFR…

QUAD vs. Atripla – Study 236-0102

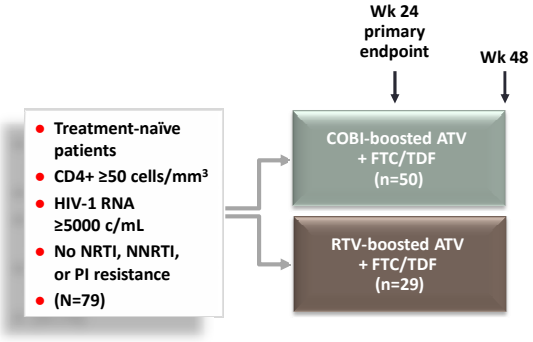


Median change at Week 48: 0.14 mg/dL vs. 0.01 mg/dL (Quad vs. EFV/FTC/TDF group, $p<0.001$)

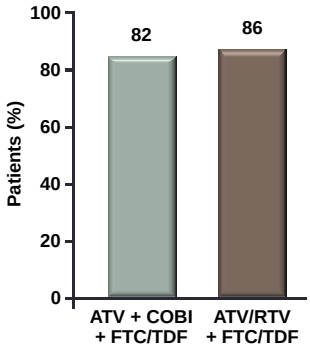
Sax P et al. CROI 2012; Seattle. #101.

COBI-boosted ATV vs ATV/r

Phase II study comparing COBI (GS-9350) vs RTV as boosting agent for ATV

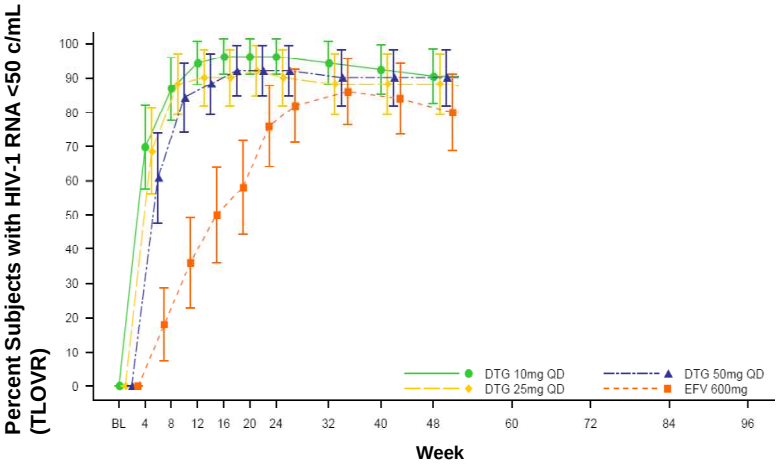


HIV-1 RNA <50 c/mL at Wk 48



Elion R et al. ICAAC 2010. Abstract H-938b.

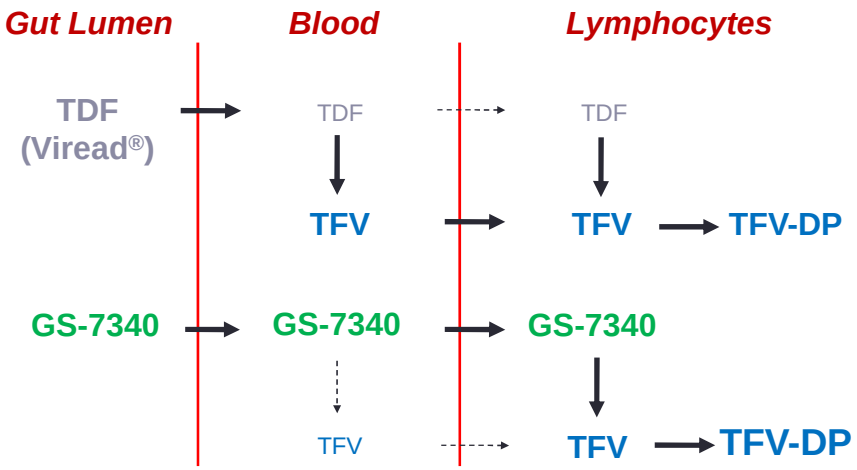
Dolutegravir vs EFV



95% confidence intervals are derived using the normal approximation.

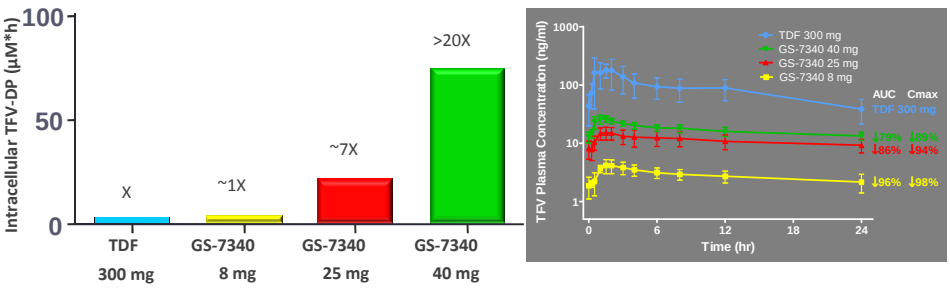
Stellbrink HJ et al. CROI 2012; Seattle. #102LB.

GS-7340: Novel Prodrug of Tenofovir (TFV)



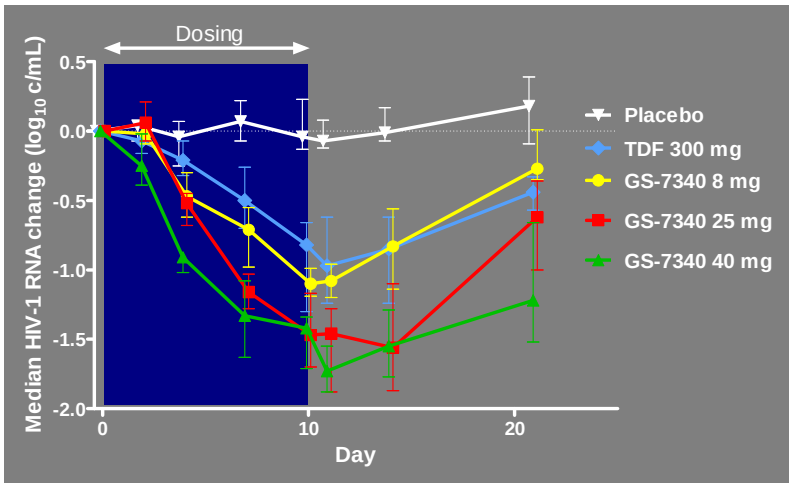
Ruane P et al. CROI 2012; Seattle. #103

GS-7340: Lower plasma TFV but higher intracellular levels



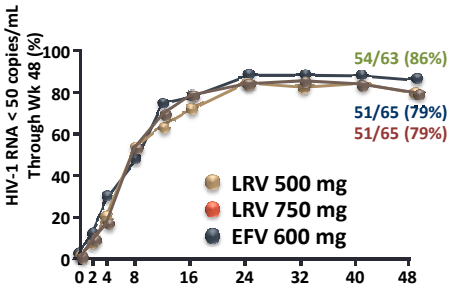
Ruane P et al. CROI 2012; Seattle. #103

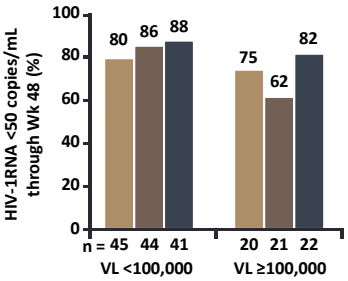
GS-7340 & viral dynamics



Ruane P et al. CROI 2012; Seattle. #103

Lersivirine vs Efavirenz





But there seems to be a high incidence of nausea……

Vernazza P *et al.* IAS 2011. Abstract TUAB0101.

Summary

- There have been changes in our positioning of ARVs
  - New data/studies
  - New BHIVA guidance
- Also a few new drugs coming through
  - Some may well shake things up….
- I have concentrated on naïve patients
  - Could extrapolate to 'early' patients
- For experienced patients there is also promise for the newer agents…..
  - However we have lesser data than we used to have
  - And be wary of PK issues in switch