17TH ANNUAL CONFERENCE OF THE BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association BHIVA

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St Thomas' Hospital, London

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Guy's and St Thomas' NHS
NHS Foundation Trust

HIV / ARV switch
The itch to switch: opinion and options

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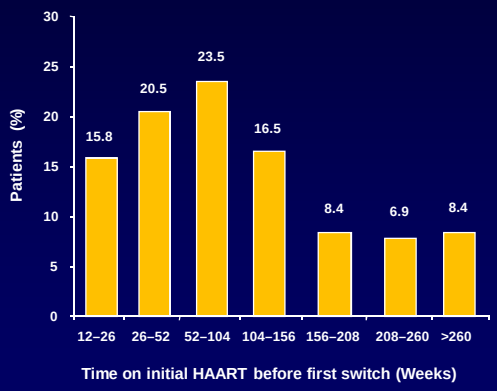
7/3/2011

Typical clinical trial exclusion criteria

- Lifestyle (drug user, alcohol, chaotic etc)
- Co-morbidity
- Age extremity
- Acute illness, CD4 ,VL
- pregnancy, breast feeding
- Polypharmacy
- Laboratory abnormalities
- investigational drugs
- active treatment of other HIV-related conditions

Changing initial therapy: When and why?

Time to first HAART switch (2004–2005)



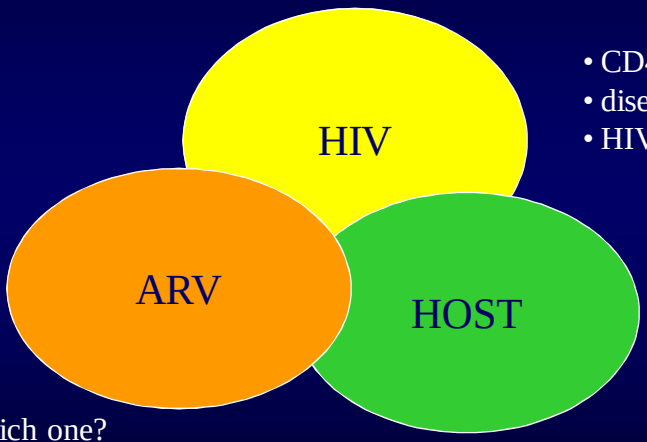
n = 430 patients from 169 HIV-treatment centres in the UK and Ireland

Hart et al. HIV Med 2007;8:186–191

Reasons for changing initial therapy

	Patients %
Toxicity	
Total	51.0
Metabolic	16.2
Virological failure	30.2
Adherence difficulties	14.4
Patient choice	9.8
Treatment simplification	9.6
Poor CD4 response	4.8
Comorbidity and/or potential for drug interaction	5.0
Planning pregnancy or pregnant	4.3
Therapy not conforming to current recommendations	3.4
Trial endpoint	0.7

Aetiology



- CD4 count
- disease stage
- HIV *per se*?

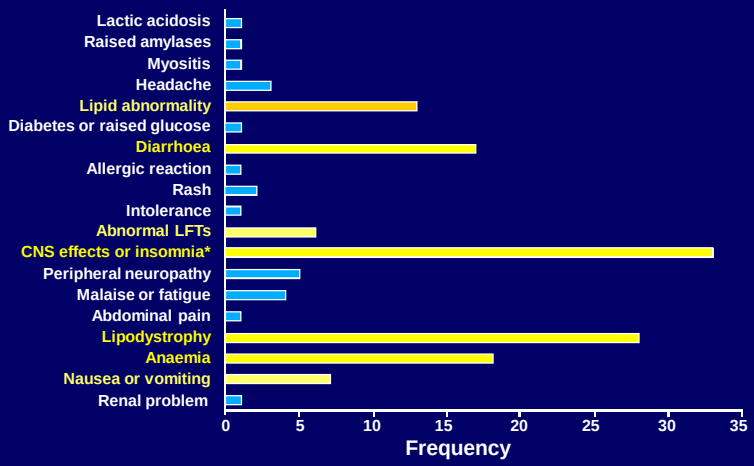
- age
- sex
- race
- genetics
- co-morbidity

- which one?
- class or drug specific?

- "immune reconstitution"

Toxicities as a reason for treatment changes

Specific toxicities associated with treatment changes in virologically-suppressed patients (n=508)

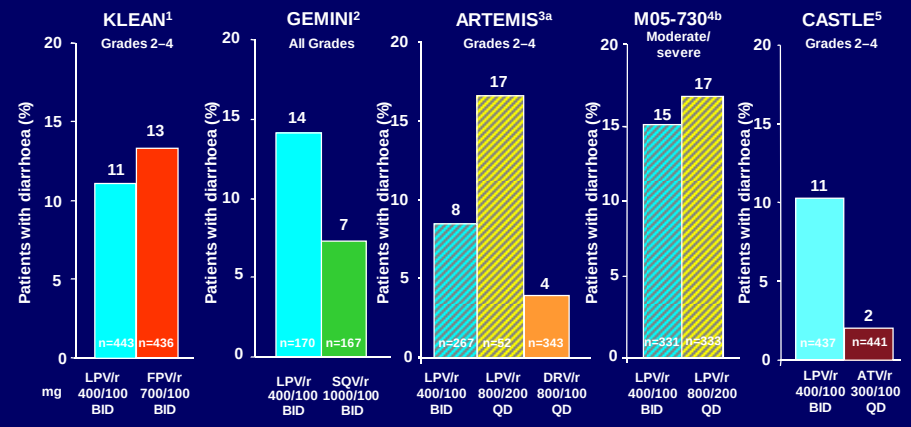


*CNS effects comprised 23% of the total toxicities and all reports were in patients taking EFV

Modified from Lodwick R et al. AIDS 2008;22:1039–1046; data from Royal Free, London

177/UKM/08-01/CM/063

Drug-related Diarrhoea in Treatment-Naïve Patients at 48 Weeks



Bars with hatching represent studies in which patients received meltrex formulation

Neither FPV/r nor LPV/r QD are licensed in the EU. Unboosted ATV is not licensed in the EU. The EU licensed dose of DRV/r is 600/100 mg BID
Data in figures are from different studies and cannot be compared directly
[a]83% of patients switched from SGC to tabs during study[6]
[b]For first 8 weeks, patients were randomised to SGC or tabs within dosing groups. After this, all patients received tabs[4]

Adapted from: 1. Eron J, et al. Lancet 2006;368:476–482; 2. Walmsley S, et al. EACS 2007, Abstract PS1/4
3. Clumeck N, et al. EACS 2007, Abstract LBPS 7/5; 4. Gathe J, et al. CROI 2008, Abstract 775; 5. Molina JM, et al. CROI 2008, Abstract 37;
6. De Jesus E, et al. ICAAC 2007, Abstract LBA H-718b

177/UKM/08-01/CM/063

Atazanavir and hyperbilirubinaemia

Hyperbilirubinaemia:
- incidence: 83%

Jaundice:
- incidence: 5%
- discontinuation: <1%

Mechanism:
- glucuronidation
- dose-related (RTV)

Management:
- cosmetic
- ? role of genomics

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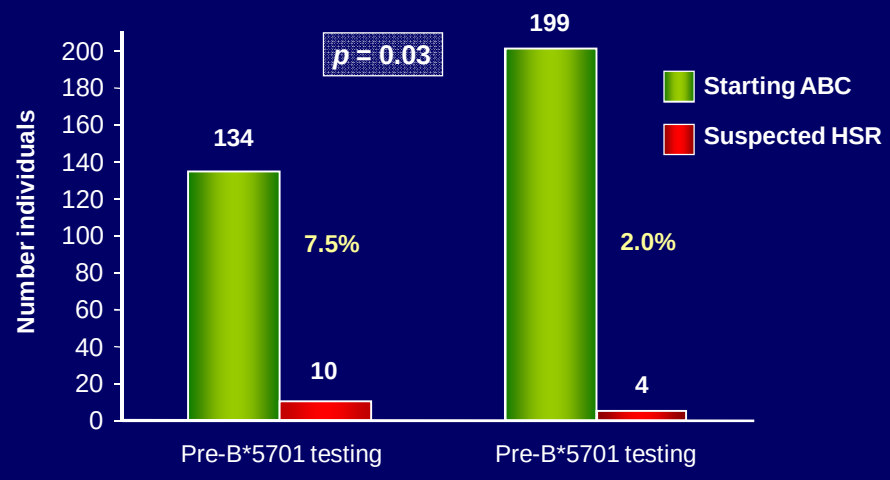
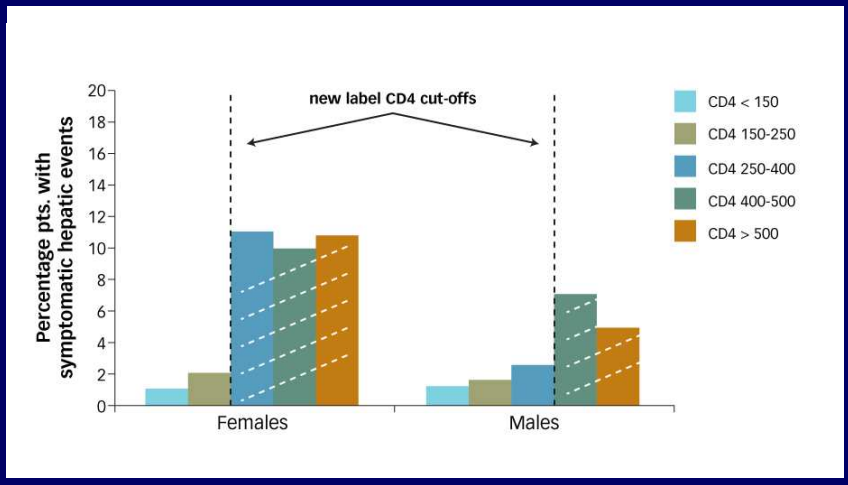
Suspected HSR pre- & post- prospective B*5701 testing



Adapted from Waters, et al. *HIV8*. 2006 Glasgow, UK. Session PL9.2

177/UKM/08-01/CM/063

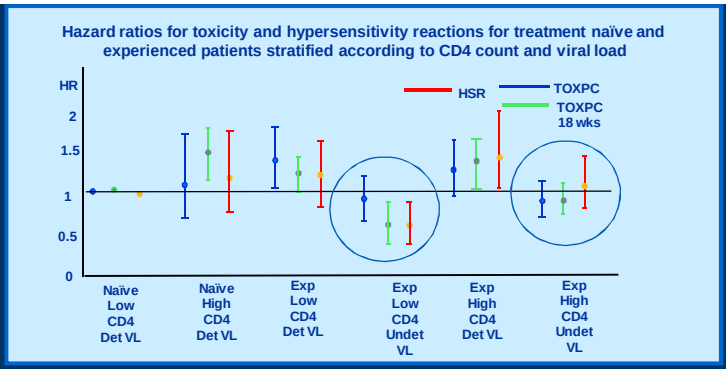
Background to CD4 cut-offs for Nevirapine



Adapted from Leith J, Summary Addendum to VIRAMUNE Expanded Hepatic Analysis, January 2005, U02-3364.

177/UKM/08-01/CM/063

Results

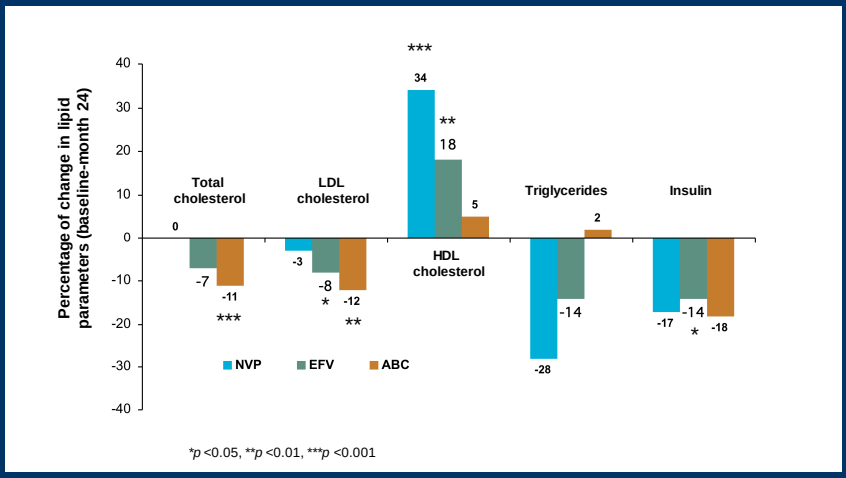


- Experienced pts with high CD4 and VL >400 had higher risk for TOXPC HR 1.4 (p=0.0001) and HSR HR 1.8 (p=0.002)
- ARV-experienced patients with high CD4 cell counts and VL <400 copies/mL had no increased risk for TOXPC (HR 0.89, CI 0.70-1.14); TOXPC within 18 weeks (HR 0.94, CI 0.78-1.13); or HSR (HR 1.10, CI 0.82-1.46)

Boehringer Ingelheim

Kesselring, A et al, AIDS 2009, 23:1689-1699

NEFA study: Metabolic changes in patients switching from PI to abacavir (ABC), efavirenz (EFV) or nevirapine (NVP): Changes in lipid profile and insulin by treatment group



Boehringer Ingelheim

Fisac et al. *AIDS* 2005;19:917–925.

Liver Safety of Two Nucleoside Analogs Plus Efavirenz, Nevirapine or a Ritonavir-Boosted Protease Inhibitor in HIV/HCV-Coinfected Drug-Naive Patients

Macías J, Mallolas J, López-Cortés LF, et al
HIV10
Poster P091

HIV/HCV-coinfected treatment-naive patients with an initial regimen including two NRTI plus EFV, NVP or a PI/r

Retrospective, multicenter cohort

Study included 745 patients treated in 26 hospitals in Spain, 1 January 2000–30 June 2006

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Characteristics of the Study Population

Macías J, et al
Poster P091

Characteristic	Treatment group			*p*
	NVP *n*=126	EFV *n*=323	PI/r *n*=296	
Male gender, *n* (%)	96 (76)	251 (78)	221 (75)	0.67
Age*, years	41 (37-46)	42 (36-46)	41 (37-45)	1.0
Intravenous drug use *n* (%)	94 (85)	239 (79)	242 (85)	0.1
Daily alcohol intake > 50 g/day†	11 (13)	35 (15)	44 (20)	0.2
CDC clinical category C, *n* (%)	25 (23)	93 (31)	85 (32)	0.19
CD4 cell counts*, cells/mL	255 (150-412)	210 (107-291)	158 (73-275)	0.001
Log plasma HIV RNA*, copies/mL	4.7 (4.2-5.1)	4.9 (4.3-5.4)	5.0 (4.3-5.5)	0.004
HCV genotype‡, *n* (%) 1 2 3 4	 50 (65) 1 (1.3) 14 (18) 12 (16)	 141 (61) 5 (2.2) 56 (24) 30 (13)	 110 (59) 2 (1.1) 41 (22) 35 (19)	0.63
ALT*, IU/mL	42 (29-63)	51 (32-87)	49 (30-72)	0.015
AST*, IU/M	38 (28-54)	46 (32-81)	46 (32-70)	0.002
Total bilirubin*, mg/dL	0.6 (0.4-0.83)	0.5 (0.4-0.8)	0.53 (0.4-0.76)	0.71
Significant liver fibrosis§, *n* (%)	81 (77)	29 (81)	57 (74)	0.74
Cirrhosis, *n* (%)	22 (7)	5 (4)	41 (6)	0.37

*Median (Q1-Q3). † Available in 530 patients. ‡ Available in 497 patients. § Available in 218 patients

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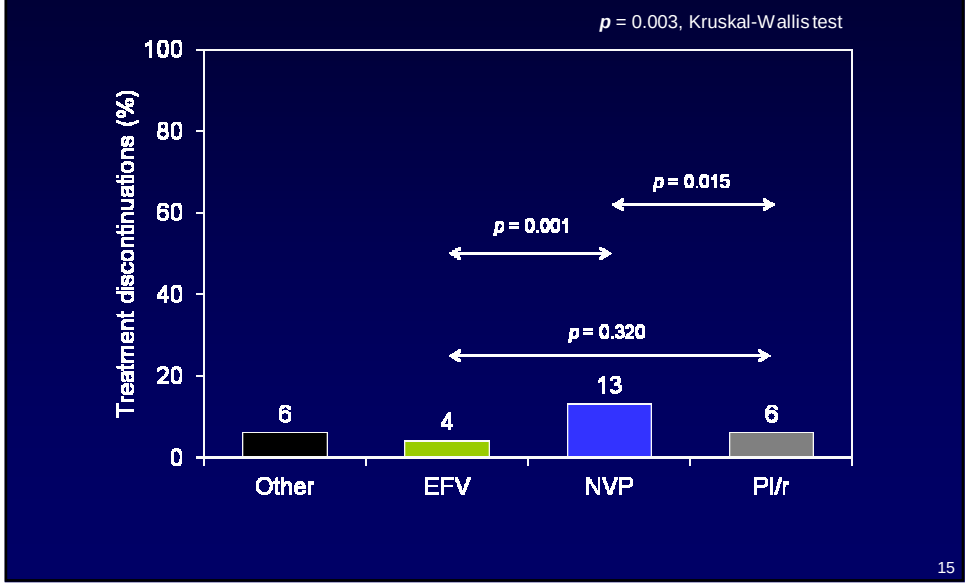
Treatment Discontinuations Due to Hepatic Events

Macías J, et al
Poster P091



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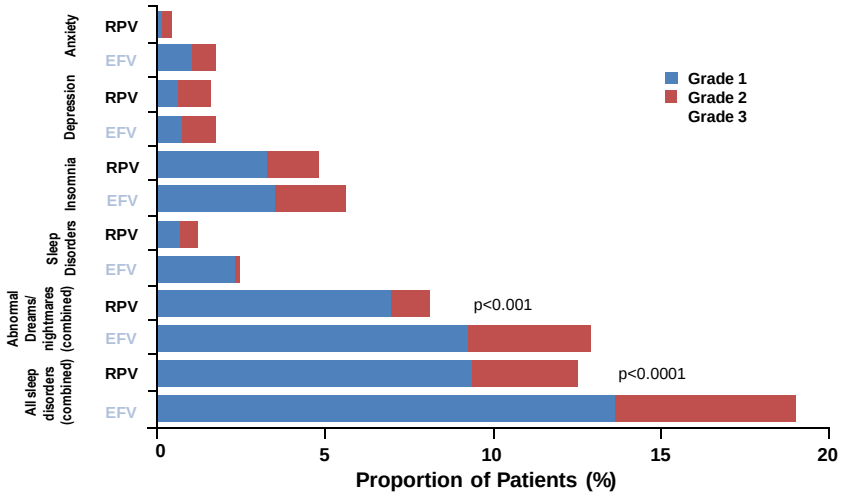
ECHO/THRIVE: Grade of Psychiatric AEs by Randomized Group



New tabs…expected Aug 2011

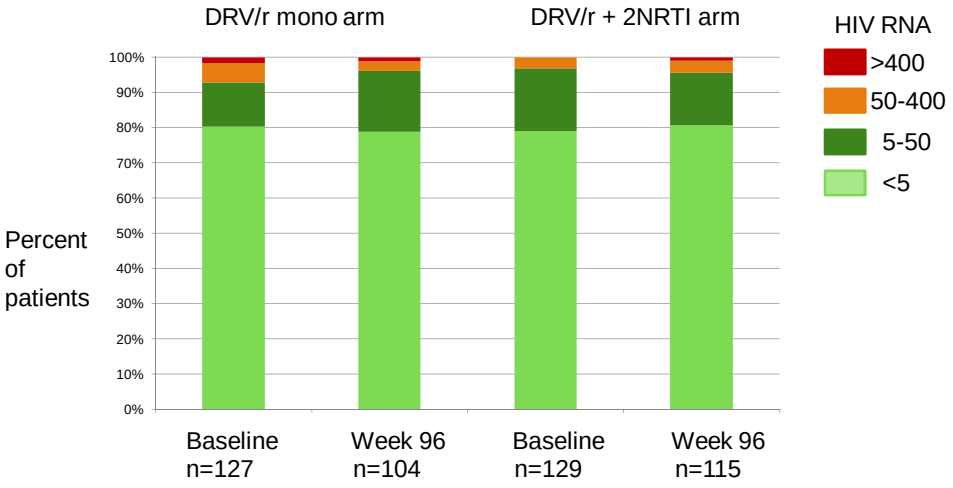
Please note that like the 100 mg tablet, the 200mg uncoated tablet can also be dispersed in water

Monotherapy Trial Results: Per Protocol and Impact of NRTI Intensification

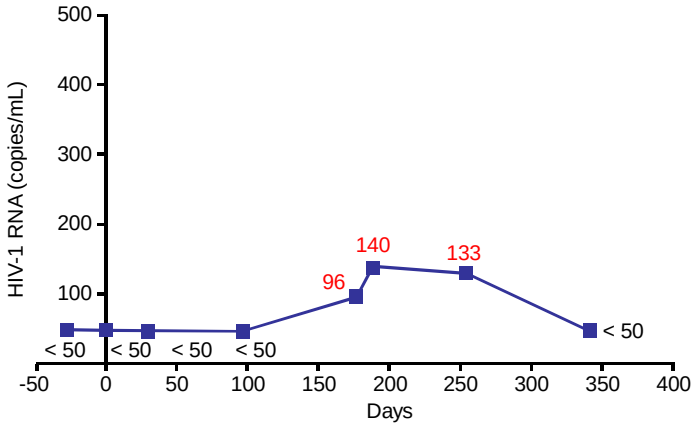
Study	Outcomes
MONET[1]	▪ Monotherapy NOT noninferior in PP, S = F analysis at Wk 96 (Δ = -5.2%; 95% CI: -14.3% to +5.8%) ▪ If resuppression with intensification included as success, then mono noninferior (Δ = +2.4%; 95% CI: -4.0% to +8.8%) ▪ 7/8 viremic pts resuppressed with reintensification
MONOI[2]	▪ Monotherapy noninferior in PP, S = F analysis at Wk 48 (Δ = -4.9%: 90% CI: -9.1% to -0.8%) ▪ 3/3 viremic pts in monotherapy arm resuppressed with intensification
OK04[3,4]	▪ Monotherapy noninferior in PP (intensification allowed) analysis at Wk 96 (Δ = -9%; 95% CI: -20% to +1.2% for triple therapy vs monotherapy) ▪ 3/4 viremic pts on monotherapy resuppressed with intensification at 48 wks; 10/12 viremic pts on monotherapy resuppressed with intensification at 96 wks

1. Rieger A, et al. AIDS 2010. Abstract THLBB209. 2. Katlama C, et al. AIDS. 2010;24:2365-2374.
3. Arribas J, et al. J Acquir Immune Defic Syndr. 2005;40:280-287. 4. Arribas JR, et al. J Acquir Immune Defic Syndr. 2009;51:147-152.

MONET trial: HIV RNA at baseline and Week 96 (observed data analysis)

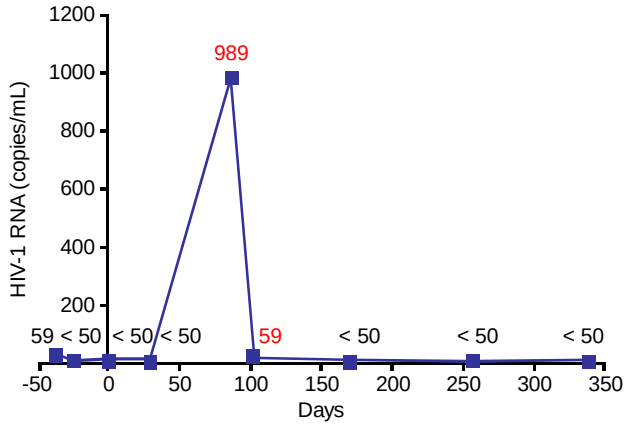


Success or Failure?



Patient in MONET trial on DRV/RTV monotherapy and confirmed 3 consecutive "double blips" meeting the definition of failure. He was kept on monotherapy arm with viral resuppression. Resistance tests failed to show any genotypic mutations.

Success or Failure?



Patient in MONET trial on triple regimen and confirmed consecutive "double blips" meeting the definition of failure. He was kept on the same randomized triple arm with subsequent viral resuppression.

HIV Replication in Sanctuary Sites

- 96% of patients with undetectable plasma HIV-1 RNA on triple regimen have suppressed CNS viral load[1]
- Questions:
  - Do we really need 3 drugs to control HIV replication in sanctuary sites when plasma HIV-1 RNA is fully suppressed?
  - Do boosted PIs sufficiently penetrate into CNS for long-term control?
  - Can boosted PI monotherapy control HIV-1 RNA in the genital tract?

1. Letendre S, et al. CROI 2010. Abstract 172.

MONOI: Drug resistance in VFs

- **Virologic failure in 3 pts (2.7%) on monotherapy vs 0 on standard therapy**
  - Low DRV drug levels noted in 1 pt
  - No DRV RAMs in any pt with virologic failure
  - All 3 pts regained HIV-1 RNA < 50 c/mL on reintroduction of 2 NRTIs

*Virologic failure defined as consecutive HIV-1 RNA > 400 c/mL or treatment modification or discontinuation.

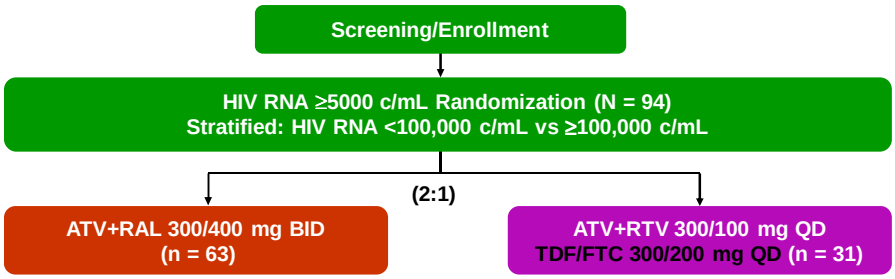
- **Viremia detected in CSF in 2 of 3 pts with serious CNS disorders on monotherapy arm**
  - Each pt had HIV-1 RNA < 200 c/mL in CSF following reintroduction of NRTIs

Katlama C, et al. IAS 2009. Abstract WELBB102.

IAC 2010

Study Design

Kozal M, et al
Presentation THLBB204



- **Primary endpoint:**
  - Determine the proportion of patients with HIV RNA <50 c/mL at Week 24
- **Secondary endpoints:**
  - Change from baseline in CD4 cell counts at Weeks 24, 48, and 96
  - Safety through Weeks 24, 48, and 96
  - Assess pharmacokinetics of ATV+RAL experimental regimen

Please note that Atazanavir 300 mg BID is an experimental dose not approved for treatment of HIV-infected naïve patients.

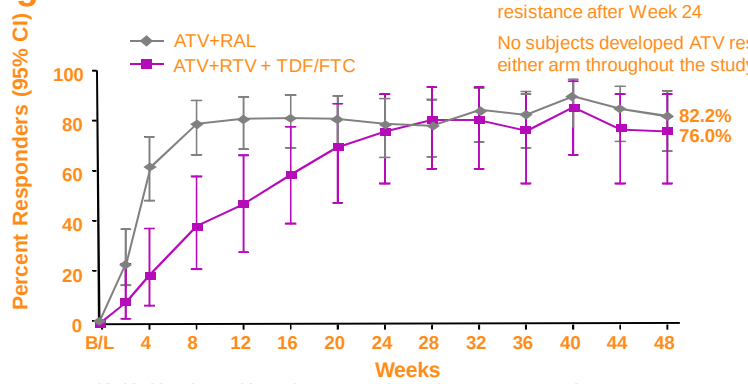
IAC 2010

Response Rate (HIV RNA <50 c/mL) Through Week 48 VR-OC

Kozal M, et al
Presentation THLBB204

No additional subjects developed RAL resistance after Week 24

No subjects developed ATV resistance in either arm throughout the study



ATV+RAL: N=63	62	62	61	62	59	57	52	56	51	51	48	47	45
ATV+RTV+TDF/FTC: N=30	29	28	29	28	27	23	25	26	26	25	27	25	25

Week 48 CD4+ mean change from baseline: ATV+RAL: 235 cells/cm^3 ; ATV/RTV+TDF/FTC: 197 cells/cm^3

VR-OC is an on-treatment method. It classifies subjects as responders according to a single on-treatment HIV RNA measurement <50 c/mL closest to the planned visit and within a pre-defined visit window. The denominator is based on subjects with an on-treatment HIV RNA measurement in that visit window.

Please note that Atazanavir 300 mg BID is an experimental dose not approved for treatment of HIV-infected naïve patients.

54 YR MSM

- HIV1 antibody positive 1989, PCP 1995 & 2005
- PN
- Pneumothorax 1998
- Chronic hepatitis-C

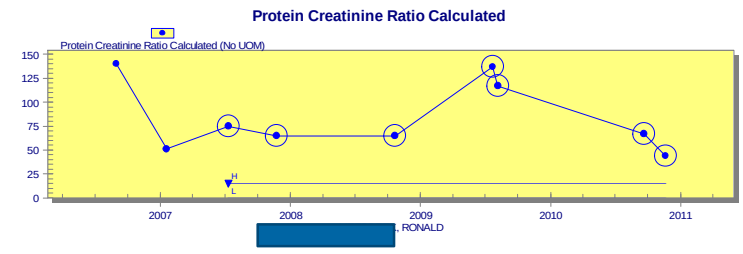
- ARV since 1997
- AZT,ddI,d4T, 3TC, TDF, ATV/r, Fos APV/r
- Not keen on NNRTI - EFV,NVP,ETV
- K65R, M184V
- G2P

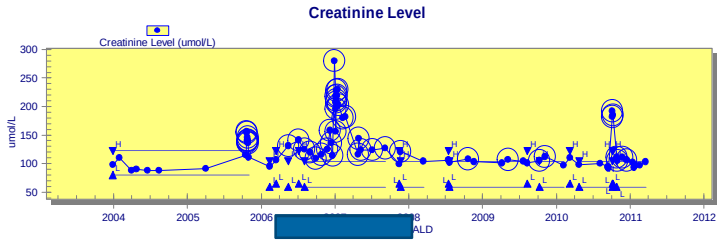
- HIV – diagnosed 1989
- Type 2 diabetes – diagnosed 2006
- Chronic hepatitis C with previous interferon therapy
- Hypertension
- Emphysema / Chronic infection with M Kansasii
- Ischemic heart disease
- Acute kidney injury – creatinine 185umol/l
- Obstruction to right kidney secondary to calculi with stenting 2005 (18% function of right kidney on MAG3)

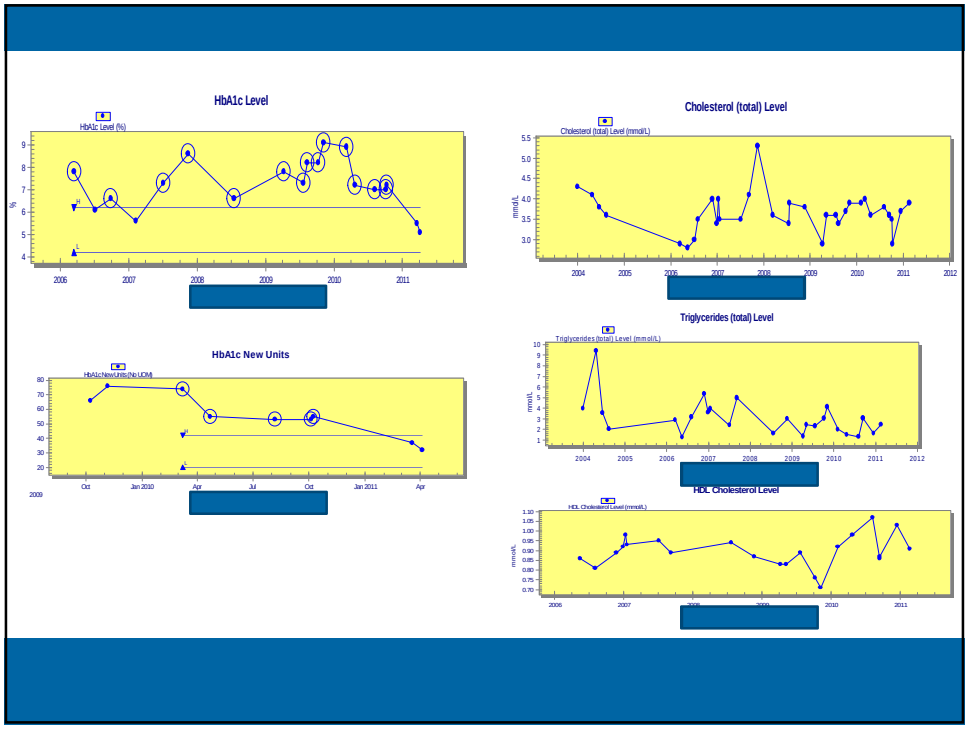
• atazanavir	400mg to 300mg bd to 200mg bd	
• raltegrevir	400mg	bd
• candesartan	32mg	od- on hold
• ramipril	5mg	od-on hold
• amlodipine	5mg	od-started
• fenofibrate	1 capsule	od
• omacor	1g	od
• repaglinide	2tabs	tds
• asprin	75mg	od
• dihydrocodeine	2tabs	am
• inhalers		

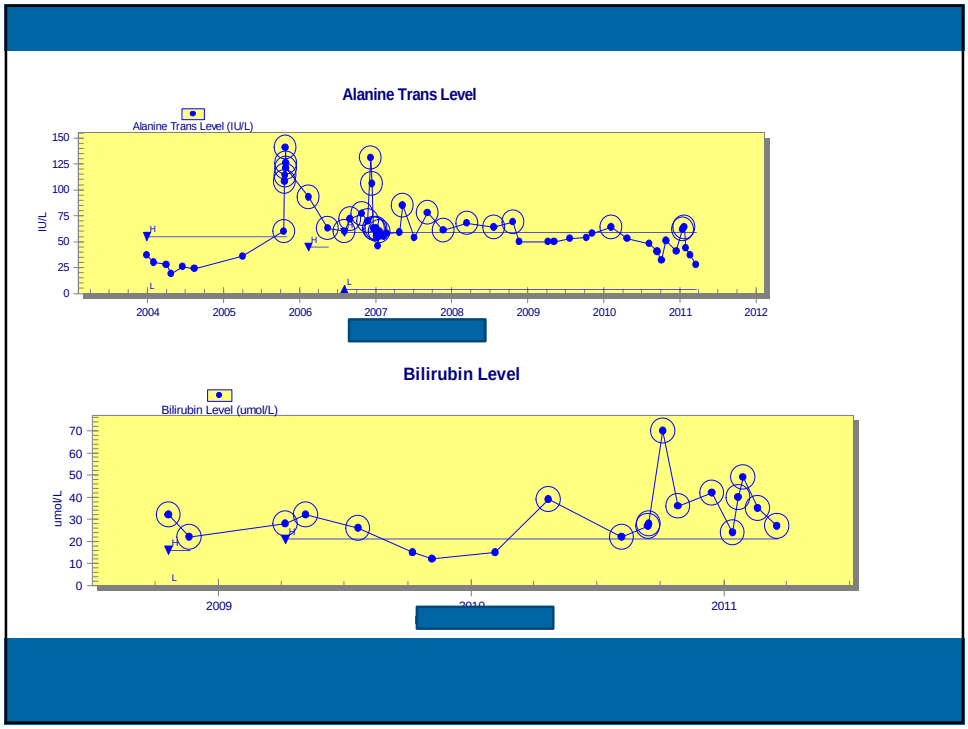
- l **Atazanavir** and **Raltegravir**: Coadministration of atazanavir/ritonavir increased raltegravir AUC (41%), Cmax (24%) and Cmin (77%). However, concomitant use of raltegravir and atazanavir/ritonavir did not result in a unique safety signal in clinical studies, therefore, no dose adjustment of raltegravir is required.
- The effect on atazanavir was not studied. Based on the changes in raltegravir pharmacokinetics, we would advise monitoring.

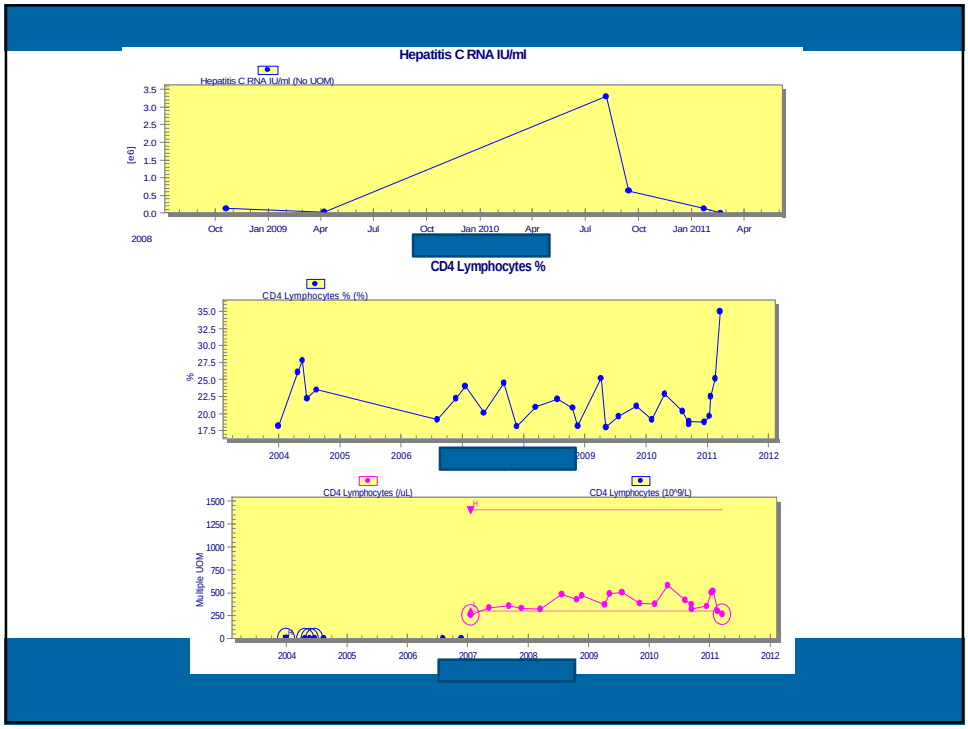
- **Atazanavir** and **Repaglinide**: Caution should be used when unboosted atazanavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (eg, repaglinide) as concentrations may increase. No clinically significant interactions are expected when administered with atazanavir/ritonavir.

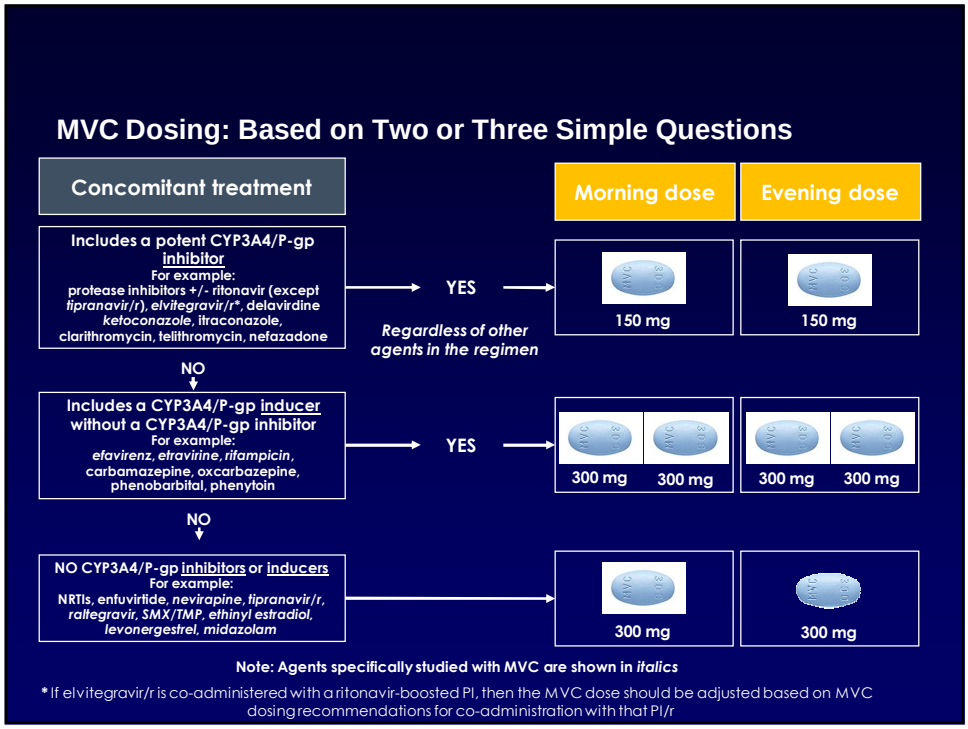





HbA1c Level
HbA1c Level (%)
Cholesterol (total) Level
Cholesterol (total) Level (mmol/L)
HbA1c New Units
Triglycerides (total) Level
Triglycerides (total) Level (mmol/L)
HDL Cholesterol Level
HDL Cholesterol Level (mmol/L)


Alanine Trans Level
Alanine Trans Level (IU/L)
IU/L
Bilirubin Level
Bilirubin Level (umol/L)
umol/L


Hepatitis C RNA IU/ml
Hepatitis C RNA IU/ml (No UOM)
[e6]
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Oct
Jan 2009
Apr
Jul
Oct
Jan 2010
Apr
Jul
Oct
Jan 2011
Apr
2008
CD4 Lymphocytes %
CD4 Lymphocytes % (%)
%
35.0
32.5
30.0
27.5
25.0
22.5
20.0
17.5
2004
2005
2006
2009
2010
2011
2012
CD4 Lymphocytes (/uL)
CD4 Lymphocytes (10^9/L)
Multiple UOM
1500
1250
1000
750
500
250
0
2004
2005
2006
2007
2008
2009
2010
2011
2012


MVC Dosing: Based on Two or Three Simple Questions
Concomitant treatment
Morning dose
Evening dose
Includes a potent CYP3A4/P-gp inhibitor
For example:
protease inhibitors +/- ritonavir (except tipranavir/r), elvitegravir/r*, delavirdine
ketoconazole, itraconazole, clarithromycin, telithromycin, nefazadone
YES
Regardless of other agents in the regimen
150 mg
150 mg
NO
Includes a CYP3A4/P-gp inducer without a CYP3A4/P-gp inhibitor
For example:
efavirenz, etravirine, rifampicin, carbamazepine, oxcarbazepine, phenobarbital, phenytoin
YES
300 mg
300 mg
300 mg
300 mg
NO
NO CYP3A4/P-gp inhibitors or inducers
For example:
NRTIs, enfuvirtide, nevirapine, tipranavir/r, raltegravir, SMX/TMP, ethinyl estradiol, levonergestrel, midazolam
300 mg
300 mg
Note: Agents specifically studied with MVC are shown in italics
* If elvitegravir/r is co-administered with a ritonavir-boosted PI, then the MVC dose should be adjusted based on MVC dosing recommendations for co-administration with that PI/r

Thank you

The itch to switch: opinion and options