

BHIVA 'BEST OF CROI' FEEDBACK MEETINGS
London | Manchester | Edinburgh



Complications of Disease and Treatment

February 2008

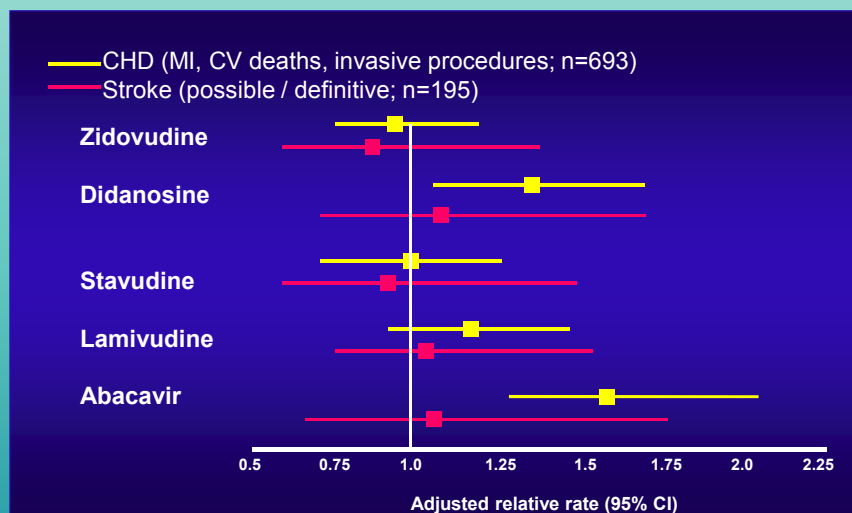
- Association between NRTIs and risk of myocardial infarction
- Relationship between inflammatory and activation markers, HIV infection and clinical disease.
- Association between HIV viraemia and cancer risk
- Risk factors for reduction in BMD: HIV or non HIV

DAD Study

- Prospective cohort initiated in 1999
- To study Adverse Events related to HIV therapy
- 33,347 patients globally
- Analysis to 1st Feb 2007
- 517 (1.5%) myocardial infarctions (MI) in 157,912 prospective observational patient-years

Sabin C et al DAD study group. 15th CROI Boston, 2008, Po:957C

Relationship between recent use of NRTIs and risk of CHD and stroke



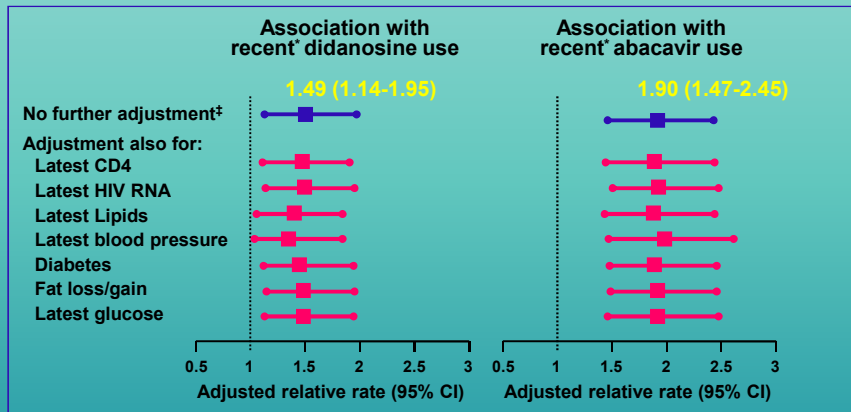
Recent* = still using or stopped within last 6 months

Risk reversed on stopping Abacavir or DDI:

Abacavir past use (> 6 months ago) RR: 1.29 (0.94-1.77)

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

**Association with recent ddl and ABC use and risk of MI:
Additional adjustment for factors that may be influenced by CART**



* Recent = still using or stopped within last 6 months
 ‡ All data depicted are also adjusted for age, sex, ethnicity HIV risk, calendar year, cohort, and CV risk factors (eg smoking, family history) that are unlikely to be modified strongly by cART use and cumulative exposure to other antiretroviral drugs.

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

**Rate of MI for recent Abacavir use by predicted
10 yr CHD risk**

| Framingham risk group (10 yr CHD risk) | Rate of MI / 1000 pyrs by abacavir use | | Risk rate (compared to low CHD risk group) |
|---|---|---------------|--|
| | Recent use | No recent use | |
| Overall | 6.1 | 2.6 | |
| Low (<10%) | 3.3 | 1.2 | 1.0 |
| Moderate (10-20%) | 9.8 | 7.1 | 2.19 (1.64-2.92) |
| High (>20%) | 31.3 | 11.2 | 3.22 (2.27-4.57) |

- Recent use : still using or stopped within 6 months
- There was a significant interaction between the predicted 10 yr CHD risk and recent use of Abacavir (p=0.04)

Sabin et al Ab 957c CROI 2008

Patients in GSK Clinical Trials had comparable myocardial events, regardless of abacavir use

Overall exposure to ABC

| Exposure to ABC | Person years | Number of MIs | Rate (/1000 Person Years) | Relative rate (95% CI; p-value) |
|-----------------|--------------|---------------|---------------------------|-----------------------------------|
| None | 4,653 | 11 | 2.363 | |
| ABC | 7,848 | 16 | 2.039 | 0.863 (0.40, 1.86; p=0.706) |

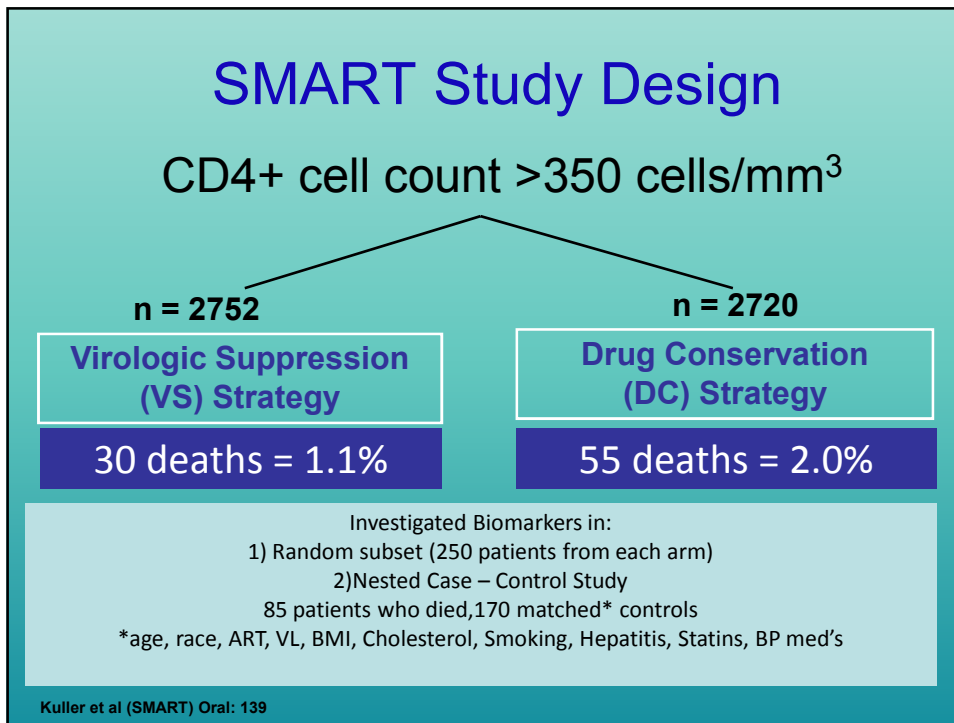
A trend towards a protective effect of abacavir-containing therapy and the development of Ischaemic Coronary Artery and Coronary Artery Disorders, compared to non-ABC containing was observed (p=0.055).

Relationship between inflammatory and activation markers, HIV infection and clinical disease (death and CVD)

- Kuller et al SMART study group Abs 139
- Calmy et al STACCATO trial Abs 140
- Ross et al Abs 954
- Ross et al Abs 949
- Kristoffersen et al Abs 953

General conclusion:

- HIV infection is associated with increased levels of Inflammatory and endothelial activation markers compared to HIV negative population
- Elevated inflammatory and activation markers correlate with risk of clinical disease
- Treatment with ART reduces levels of these biomarkers



Baseline Biomarkers and All Cause Mortality

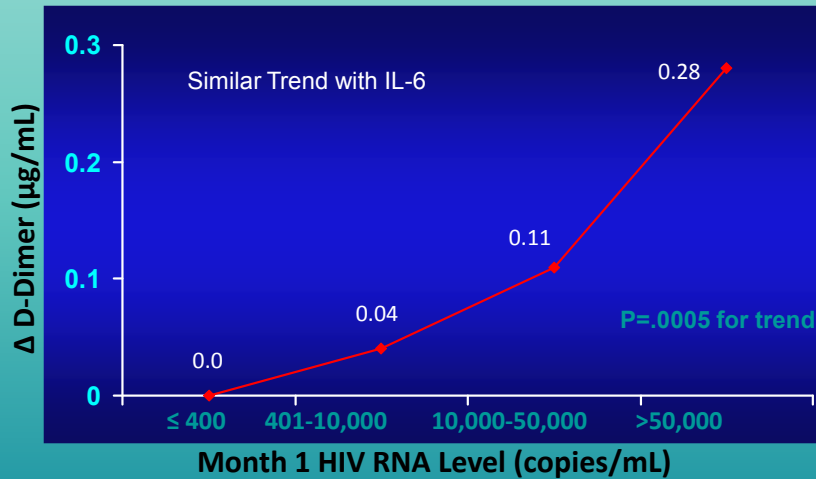
| Marker | Un-adjusted | | Adjusted | |
|-----------|--|---------|--|---------|
| | OR (4 th /1 st) | P-Value | OR (4 th /1 st) | P-Value |
| Hs-CRP | 2.0 | 0.05 | 2.8 | 0.03 |
| Amyloid A | 2.2 | 0.07 | 2.6 | 0.09 |
| Amyloid P | 0.7 | 0.39 | 1.1 | 0.84 |
| IL-6 | 8.3 | <0.0001 | 11.8 | <0.0001 |
| D-Dimer | 12.4 | <0.0001 | 26.5 | <0.0001 |
| F1.2 | 1.0 | 0.92 | 1.2 | 0.66 |

*Adjusted for age, race, ART, VL, BMI, Cholesterol, Smoking, Hepatitis, Statins, BP med's

- Highest levels of D-Dimer at baseline associated with greatest risk of mortality
- Stopping therapy in the DC arm resulted in increased levels of D-dimer and IL-6 after 1 month

Kuller et al (SMART) Oral: 139

Change in D-Dimer* ($\mu\text{g/mL}$) from Baseline to 1 Month



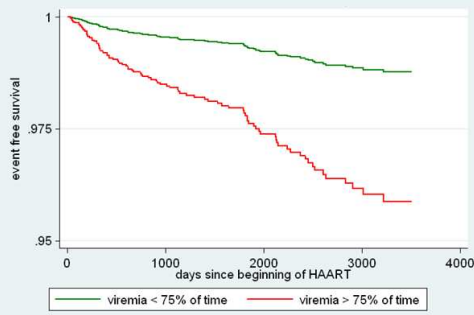
* DC patients on ART at baseline with HIV RNA ≤ 400 copies/mL
Kuller et al (SMART) Oral: 139

Association between HIV viraemia and malignancy risk

- Zoufaly et al; Insufficient virus suppression during HAART is a strong predictor for the development of AIDS related lymphoma: German CLINSURV cohort. Abs 16
- Bruyand et al; Immune deficiency and risk of AIDS defining and Non-AIDS defining cancers: ANRS CO3 Aquitaine cohort 1998-2006. Abs 15

Insufficient virus suppression during HAART is a strong predictor for the development of AIDS related lymphoma: results of the German ClinSurv cohort

Probability of lymphoma diagnosis



N: 6458; lymphomas : 94
Viraemia: 75% or more of VL
Measurements >500 copies/ml

Strong Predictors

- Age
- Latest CD4 count < 350
- Cumulative detectable viraemia
- Viraemia is the only directly modifiable factor
- Higher impact of viraemia for Burkitt's lymphoma

Zoufaly A et al. Oral: 16

Malignancy: Immunodeficiency and Risk of AIDS defining and Non-AIDS defining Cancers: ANRS CO3 Aquitaine Cohort, 1998-2006.

Methods

- ANRS CO3 cohort (1998-2006)

Results

- 4194 patients included: 251 incident cancers : 109 AIDS defining (NHL and KS), 142 non-AIDS defining (lung, skin, HD, HCC, Anal Ca).
- New findings:
 - There was a higher incidence of AIDS cancers in patients with longstanding uncontrolled viral load whatever the CD4 count
 - Higher incidence of non-AIDS cancers related to low CD4 counts but not to HIV RNA.
 - Therefore both CD4 counts and viral load should be considered risks of cancer

Bruyand M et al, Oral:15

Reduction in bone mineral density:

? role of HIV and non HIV related factors

- Brown T et al Abs 966
- Guillemi et al Abs 969
- Duvivier et al Abs 967
- Cazanave et al Abs 970

General conclusion:

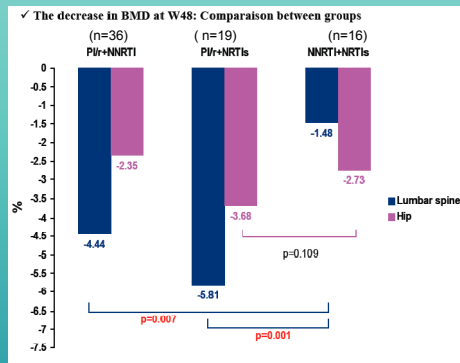
- Reduced BMD common in HIV +ve patients
- Multiple risk factors involved include: immunodeficiency, HIV viraemia, non HIV related factors and potentially ART regimen.

Changes in Bone Mineral Density

| Abstract | n | ARV Regime | Results |
|---|-----|---|--|
| Poster 969 Cross sectional study | 299 | NNRTI/NRTI and PI based | On DEXA scan 54% had osteopenia and 13% osteoporosis Associations with ↓BMD: older age, low BMI, ethnicity, and low CD4 count and in men - ↓physical activity and ↑alcohol intake. TDF, but not PIs or total ART exposure associated with ↓BMD |
| Poster 966 RCT | 155 | ART naïve subjects randomised to EFV/ZDV/3TC or LPVr/ZDV/3TC. | At 96 weeks F/U: RF for >5% decrease BMD from baseline - low baseline CD4, non black race. No association with ARV regimen used. |

PI Regimens Reduce Bone Mineral Density Greater than NNRTI Regimens: A Substudy of the HIPPOCAMPE-ANRS 121 Trial (Poster 967)

- BMD impaired in 31% of patients before starting any ARV suggesting a causative role of HIV.
- At 1 year, decrease in lumbar spine BMD more pronounced in either PI-containing regimens compared to NNRTI/2NRTI.



Swiss Cohort study

- Increased Serum Alkaline phosphatase may reflect increased bone resorption and compensatory osteoblastic activity
- Prospective study in pts either initiating (698), reinitiating (380) or discontinuing (127) ART with or without Tenofovir
- Strong significant association between increased Alk Phos and TDF use
- Increase in Alk Phos not associated with ALT or Hep C.

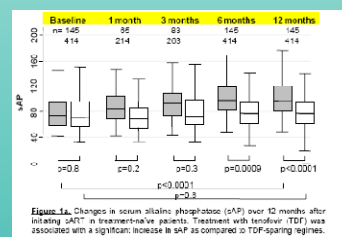


Figure 1a. Changes in serum alkaline phosphatase (sAP) over 12 months after initiating sART¹ in treatment-naïve patients. Treatment with tenofovir (TDF) was associated with a significant increase in sAP as compared to TDF-sparing regimens.

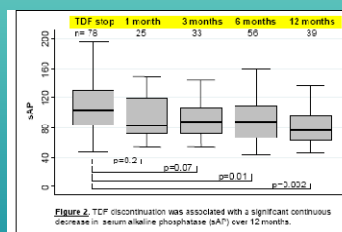


Figure 2. TDF discontinuation was associated with a significant continuous decrease in serum alkaline phosphatase (sAP) over 12 months.

Fux et al Abs 968 CROI 2008

Summary

- Increasing evidence that uncontrolled HIV viraemia associated with increased risk of clinical disease irrespective of CD4 count
- Exploring the relationship between ART, individual drugs, clinical disease and toxicity remains very important in the long term.