British HIV Association
BHIVA

BHIVA 'Best of CROI' Feedback Meetings

London | Birmingham
Haydock | Wakefield | Newcastle
Edinburgh | Cardiff

British HIV Association
BHIVA

Complications of Disease and Treatment

British HIV Association
BHIVA

Topic

- Cardiovascular Disease
- ART, Vitamin-D and Bone
- Renal
- Neurocognitive Disorder

British HIV Association BHIVA

CVD

- What was our understanding already?:
  - CVD is more common in HIV population
    - ?effect of HIV (particularly uncontrolled), ?early ageing, or ?just confounding
  - Some association with ARVs
- What about from CROI?
  - It is more common…
    - Relative risk 1.81 (1.49-2.20) [#59]
      - Large Veterans cohort in US (~30,000 HIV+ case-matched to ~60,000 HIV-)
    - But mean age similar – i.e. not 'early ageing' [#59, #61]

British HIV Association BHIVA

IHD in HIV

- Pathogenesis of MI (Coronary CT studies)
  - Difference from non-HIV population is excessive non-calcified plaques [#62, #63, #185]
    - Inherently more unstable/vulnerable (rupture → symptoms)
  - (But note that overall coronary calcium score still a good and useful marker for IHD risk)

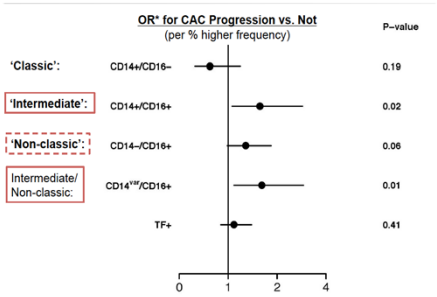
- Treatment of MI:
  - DAD: Improved short-term mortality post-MI [#748]
    - Seems to be because there is better access/use of standard peri/post-MI interventions utilised in general population
  - US: Similar door-to-balloon times for STEMIs than HIV-negatives [#751]

- And we are now seeing more heart failure [Large Veterans cohort - #750]
  - ?not dying of their MI & living longer so more chance of HF

British HIV Association BHIVA

Cardiovascular Risk: Immune Activation

- **What was our understanding already?:**
  - HIV-positive individuals have an increased risk of CVD.
  - Immune activation is believed to contribute to CVD but mechanism is unclear
- **Setting**
  - SUN investigators, observational study (n=436), FU for 2 years
  - Identify markers of immune activation associated with coronary artery calcium (CAC) score
- **Conclusion**
  - Markers of CD16+ activated monocytes, but not 'classic' monocytes or activated T-cells correlate with progression of CAC score



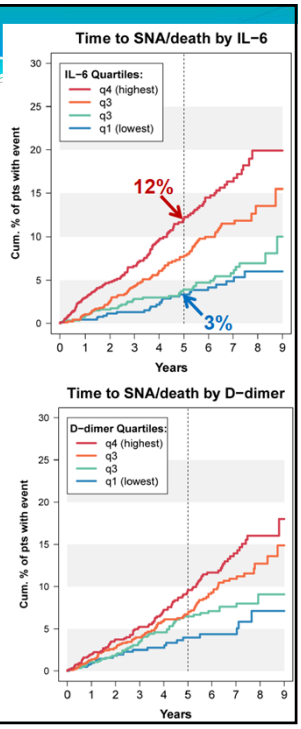
Baker J. et al 66LB

British HIV Association BHIVA

Non-AIDS events, Death and Inflammation

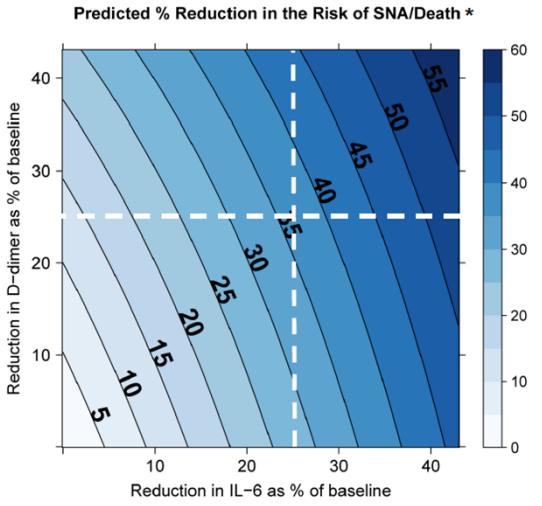
- **What was our understanding already?:**
  - HIV-positive individuals have an increased risk of non-AIDS related death.
  - Markers of inflammation and coagulation may predict risk
- **Setting**
  - INSIGHT investigators, observational study (n=3766), FU 4.9 years
  - On ART with VL<500 copies/ml
  - 262 patients with serious non-AIDS event/death
- **Conclusion**
  - Both IL-6 and D-dimer predict risk of serious non-AIDS events and death in patients with suppressed VL and high CD4 count

Grund B et al. et al 60



Cardiovascular risk

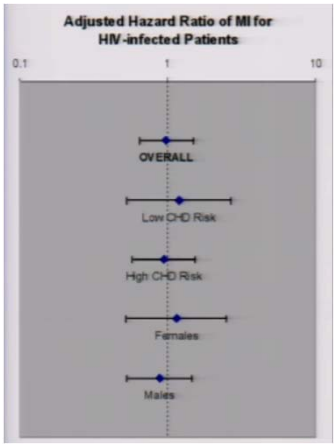
- **Impact:**
  - 25% reduction in composite IL-6/D-dimer provides 37% reduction in SNA/death
  - HR0.67
- **Use**
  - Suggestion to use composite score in assessing efficacy of therapeutic intreventions that modify risk of serious non-AIDS events e.g METRIC Trial



Grund B et al. et al 60

Cardiovascular Prevention: Aspirin (ASA) Use

- **What was our understanding already?:**
  - ASA reduces risk of MI in HIV-
  - Little data in HIV+
- **Setting**
  - Cohort study
  - Partners Healthcare n= 3,698 with 33, 348 controls
  - Record ASA use (prescriptions) and MI incidence 2000-2009
- **Conclusion**
  - ASA use lower in HIV+ particularly men and those with high CHD risk.
  - ASA use had no obvious effect on reducing MI (in contrast to HIV-)



Suchindran Set al. et al 65

British HIV Association BHIVA

Statin Therapy on Mortality and Incident Diabetes

British HIV Association BHIVA

Impact of Statin Use on Mortality

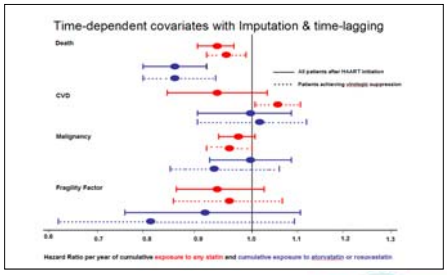
Danish Cohort Study (Abs:766)

- 1738 individuals on HAART /suppressed VL
- Satin therapy associated with non-significant reduced death rate
- Prior use of statin may reduce mortality in individuals after diagnosis of co-morbidities

STATIN USE (time-updated variable)	MRR (95% CI) Unadjusted	MRR (95% CI) Adjusted
	BEFORE COMORBIDITY	
Time before initiation of a statin	Ref (1)	Ref (1)
Time after initiation of a statin	1.39 (0.44-4.69)	1.12 (0.34-3.62)
	AFTER COMORBIDITY	
Time before initiation of a statin	Ref (1)	Ref (1)
Time after initiation of a statin	0.36 (0.12-1.07)	0.34 (0.11-1.04)

Veterans Data (Abs: 767)

- Cumulative exposure of statins (n=25 884) including effect of atorvastatin and rosuvastatin
- Statin therapy associated with a trend towards lower non-AIDS complications and mortality and
- Impact was higher with atorvastatin and rosuvastatin (p=non-significant)

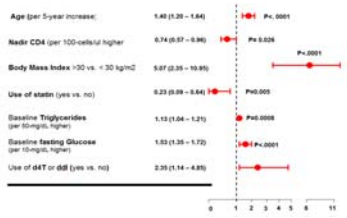


Comment: Statin therapy may reduce mortality in individuals with co-morbidities particularly CVD

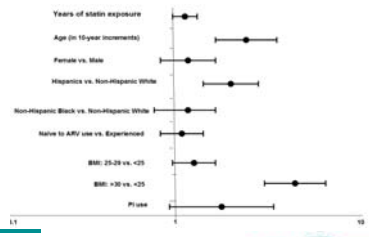
British HIV Association BHIVA

Statin Use and Incident Diabetes

- European Study (Abs: 764)
  - 5380 patients followed for 9.8 years
  - BMI>30, raised TG, baseline Glucose, use of d4T, ddI had association
  - Statin associated with 77% reduction of risk of DM



- American Study (HOPS) Abs: 765
  - 4847 patients followed for 49 months
  - Cumulative statin use associated with incident DM with increased risk in Hispanics and BMI >30.



Comment: Statin use should be considered where necessary
Risk modification of DM should get priority

British HIV Association BHIVA

ART, Vitamin-D and Bone

British HIV Association BHIVA

Vitamin D

- What was our understanding already?:
  - Significant proportions of HIV cohorts are low in vitamin D
    - But may not always be clinically relevant
  - There is perhaps an association with EFV
  - What we usually measure (25-OH D) is not the biologically active form (1,25-OH D)
- What about from CROI?
  - An association of low 25-OH D with ARVs overall [#827]
    - SMART substudy – higher levels in drug interruption arm
  - But no association of EFV with 1,25-OH D [#807]
    - Have we need looking at the wrong assay previously?

British HIV Association BHIVA

ART and Bone

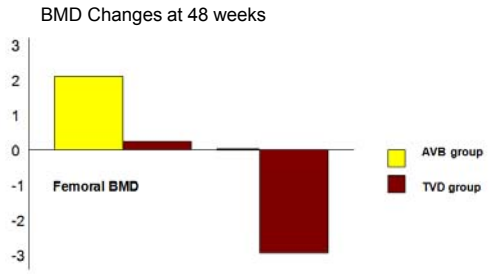
- Prevalence of mild to moderate fractures more common in HIV patients without any clinical fracture (Abs: 822)
  - 175 HIV+ve compared with 120 HIV negative
  - DEXA, Vitamin-D, PTH, phosphate and other risk factors for fracture compared
  - Median age 51 years, mostly male
  - Osteopenia and osteoporosis more common in HIV+ve groups.
  - Vertebral fractures, predominantly multiple, more common 30% vs. 4% in HIV+ve groups

- HIV is an independent predictor of low BMD (Abs:817)
  - Case control observational study (n=474)
  - Fractures not considered.

British HIV Association BHIVA

Switch from Tenofovir to Abacavir and BMD Change: Multicenter RCT (Abs:824)

- 54 patients on TDF regimen for at leats12 months suppressed VL
- Patients have loss of BMD (DEXA)
- Switched to ABC (n=26) and continued with TDF (n=28)
- Significant improvement in BMD particularly at femur in ABC arm



British HIV Association BHIVA

Low CD-4 and Lean Body Mass (LBM) and BMD

ACTG A5224 sub-study [Abs:825]

- 269 patients
- 96 weeks FU
- Gain in LBM but not fat attenuated with loss of hip BMD but not spine and independent of ART regimen

Pooled analysis from three ACTG data [Abs:823]

- 796 patients
- 96 weeks FU
- Low pre-treatment CD-4 strongly associated with BMD loss

British HIV Association BHIVA

Renal

British HIV Association BHIVA

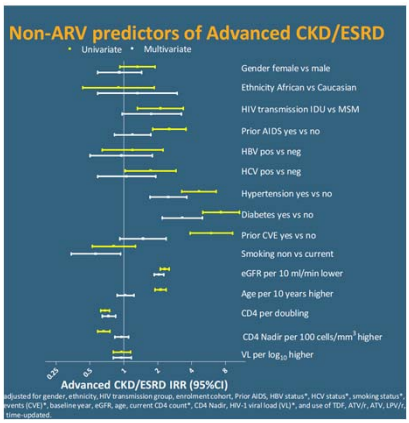
Predictors of Advanced Chronic Kidney Disease and End-Stage Renal Disease (ACKD/ESRD) in HIV-Positive Persons in the D:A:D study.

- 35,192 Patients
- Median follow-up of 6.2 years,
- 0.4% developed ACKD/ESRD

- No association with TDF and other PIs

- An association between ACKD/ESRD and ATV/r exposure in patients with eGFR <60 mL/min at baseline.

- Factors associated with ACKD/ESRD were diabetes, hypertension, lower baseline eGFR, never vs. current smoking and higher current CD4 count.



(Abs: 810)

British HIV Association BHIVA

Reversibility of tenofovir-associated renal dysfunction

- How common is decline in renal function on tenofovir and how reversible is this after treatment discontinuation?

- Setting: UK CHIC study 742 patients
  - HIV-1 infected adults who had discontinued TDF after at least 6 months exposure
  - At least 6 months TDF-free follow-up before and after TDF exposure

- Results
  - 316 (42.6%) experienced rapid eGFR decline and 67 (9.0%) developed CKD on TDF
  - Only 80 (10.8%) of 742 patients had incomplete eGFR recovery.
  - In 28 (35%) of these, eGFR remained well within the normal range.

  - Factors associated with incomplete recovery were a higher
    - eGFR at TDF start,
    - lower eGFR at discontinuation,
    - longer time exposed to TDF,
    - rapid eGFR decline and
    - older age.

Abs: 813

British HIV Association BHIVA

Renal insufficiency on Tenofovir and PIs

- **Background**
  - Tenofovir (TDF) has been associated with development of renal insufficiency. Ritonavir-boosted PIs may contribute.
- **Setting**
  - 741 HIV+ African women (with CrCl ≥60mL/min) were randomised to TDF/FTC/LPV/r or TDF/FTC/NVP
- **Results:**
  - 24 (3%) had Renal events

4.9% of LPV/r arm vs 1.6% of NVP arm.

  - 16 TDF discontinuations

2.7% in LPV/r arm vs 1.6% in NVP arm

  - In the multivariate analysis, randomization to the LPV/r arm was associated with renal events (OR = 3.12, 95%CI [1.21, 8.05], p = 0.019) as were higher baseline HIV-1 RNA and lower baseline CrCl.

Paper 152, Mwafongo et al

Renal insufficiency-miscellaneous

- Does tenofovir based pre-exposure prophylaxis have deleterious efffects on renal function in HIV-ve MSM? (iPrEx study: TDF/FTC vs placebo)
  - Small, statistically significant decrease in CrCl from baseline in TDF/FTC arm (–2.4 mL/min) when compared to placebo (–1.1 mL/min) that was first observed at week 4, persisted throughout treatment and resolved after stopping PrEP. **(Paper 998)**
- Is there increased tenofovir toxicity in different ethnic populations?
  - Long term renal safety of TDF was similar to that of ZDV in HIV+ve patients in Thailand but there was a significantly higher risk of CrCl decline with TDF among patients with low body weight (<60kg). (**Paper 815)**

Neurocognitive Disorders

British HIV Association BHIVA

Neurocognitive disorders

- **What was our understanding already?:**
  - HIV-associated neurocognitive disorders (HAND) are common.
  - Whether the the CNS penetration of anti-retrovirals influences neurocognitive performance is unknown
- **Setting**
  - Randomised trial at five sites for people initiating or switching ART, n=59 (designed for n=120)
  - CNS Targeted (CNS-T) vs. non-Targeted treatment and measured global deficit score at 16 wk
- **Conclusion**
  - Non-significant benefit of CNS-T treatment +7 (95%CI -31 to 62%)
  - Confounded by differences in groups (lower CD4 count, more HCV+ in CNS targeted group).
  - Underpowered but terminated by DMSB

Ellis R. et al 20

British HIV Association BHIVA

Predictors of clinically relevant depression in HIV-infected patients

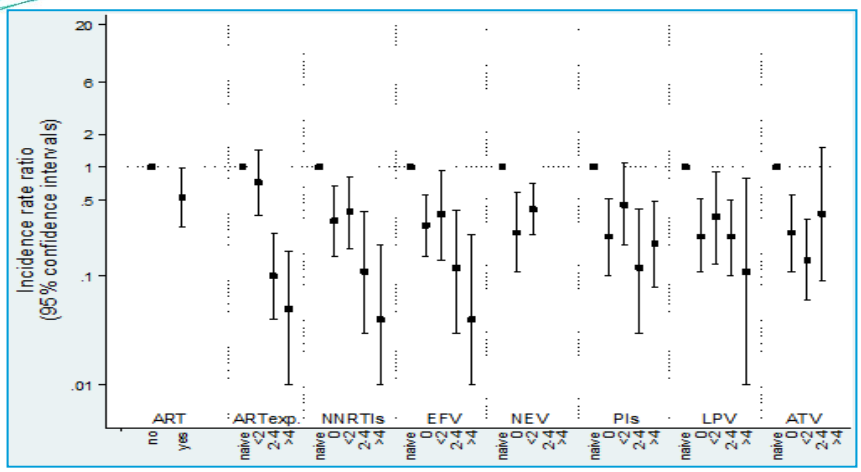
- Multicenter Spanish study (n=5185)
- Investigated for development of clinically significant depression;
- 85% starting therapy during follow-up
- Compared EFV Vs. non-EFV

- 115 developed clinically relevant depression.

Paper 413 Gutierrez, et al

British HIV Association BHIVA

Predictors of clinically relevant depression in HIV patients



- Longer exposure to ART associated with decreased risk of clinical depression (54% decrease in risk of depression per additional year on ART).
- Protective effect on depression also observed when NNRTIs and EFV analysed separately.
- The likelihood significantly increased with age > 50 years.

British HIV Association BHIVA

Screening tools for detection of NCI

Background

- HAND remains prevalent despite of HAART.
- There is still need for improvement in tools for detection of NCI and HAND.

Settings

- 146 examined studied. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and correct classification rate (CCR) of self-reported 3 questions, international HIV Dementia Scale (IHDS), Mini mental Status Examination (MMSE) was determined

Findings .

- Combinations of easy to administer NP tests with the IHDS resulted in increased sensitivity, NPV and CCR.
- Combining IHDS with one or two simple and easy to administer NP test may represent an improvement in the screening approach to the detection of both NCI and HAND.

Paper 455, Antinori, et al

British HIV Association BHIVA

Neurocognition and ageing

- What do we know
- Complex interface between HIV and ageing manifests as longer time to memorise and reduced executive functioning. Ageing effect may be due to HIV itself or associated co morbidities e.g. vascular, Alzheimer's (reduced clearance of amyloid with ritonavir) or Parkinson's.
- Frailty phenotype: diagnosed by a reduction in walking speed, grip strength, body weight and activity level plus more physical exhaustion is more common in HIV

- Lessons from CROI
- Neurocognition worse with a lower performance score such as the Veterans Ageing cohort study (VACS) index (440), Age & HIV disease (439) but only when adjusted for duration of HIV.
- Neurofilament light chain protein associated with axonal damage have higher levels in neuro-asymptomatic patients (443) and predict development of HAND (441)
- CSF Alzheimer's disease profiles using biomarkers present in 11.4% of 44 patients tested (442) . This is over 10x risk in normal population. Increased risk of positive profile with lower CD4 nadir, longer HIV duration and greater neuropsychological impairment. No amyloid imaging done. Unclear what prognosis in future is.
- Patients with HAND (OR 2.3) and symptomatic HAND (OR2.67) are more likely to be frail (444).

British HIV Association BHIVA

Neurocognition

- What do we know
- ARV medications penetrate blood-brain barrier at different efficiencies and theoretically better penetrating drugs may perform better with neuro-cognitive dysfunction.
- Neuro psychological testing is expensive and time consuming limiting its usefulness in routine practice. Simplified screening to detect HAND would be useful if predictive.
- Several studies show a high prevalence of HAND with rates up to 47%

- Lessons from CROI
- RCT of CNS targeted vs non CNS targeted therapy to detect difference in global deficit score at 16 weeks. (20) showed no overall difference. However trial stopped early due to inability to recruit so only data on 59 out of 326 screened patients.
- Combining the International HIV Dementia scale with a neuropsychological test such as the Trails making test A improves the sensitivity, specificity, PPV and NPV for detection of HIV associated neurocognitive Disorder significantly and may save time and costs. (451, 455)
- The rates of HAND in UK HIV pos MSM was better than in HIV negative male general population in 4 out of 7 domains in a study that did not control for education, drug or alcohol use but may imply that HAND may be overestimated (453).

British HIV Association BHIVA

CPE score and its potential impact on clinical outcome

- **Background**
- Whether ARVs with high CNS penetration protect against cognitive deterioration remained unanswered.
- No current evidence to support initiation with better CNS-penetrating HAART.
- **Settings**
- 259 pts randomly selected to undergo NP test and 96 followed for changes on NP test results.
- **Findings** .
- 6 Pts showed clinical improvement, 31 had worsened and 59 remained stable, resulting in 43 pts presenting with HAND (43%).
- Pts with clinical deterioration had a lower CPE both at inclusion (6.9 vs. 8.1, p = 0.005) and at the end of follow-up (7.2 vs. 7.8, p = 0.07) than those with improved or stable performance. This was confirmed by multivariable analysis.

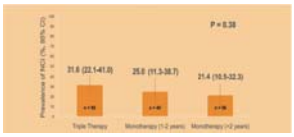
Paper 449 Vasallo, et al

British HIV Association BHIVA

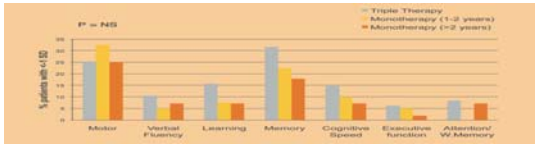
Protease Inhibitor Mono-therapy and rate of Neurocognitive impairment

- **Background**
  - Due to the low CNS Penetration Effectiveness (CPE) of PIs, there are concerns about the use of PI monotherapy and a higher risk for CNS virological failure and neurocognitive impairments.
  - **Settings**
  - CNS viral escape, biomarkers of NCI and evolution of NCI over 48 weeks compared between 95 pts on DRV/r or LPV/r-containing therapy (TT) and 96 on DRV/r or LPV/r monotherapy (MT).
  - **Findings**

No difference in prevalence of NCI by treatment group



No significance difference in the impaired cognitive domains



- No significance difference in % of patients with detectable HIV RNA in CSF between TT and MT (71 *vs*. 50%, p = 0.28); No differences in CSF white blood cells, total proteins, inflammatory or brain injury markers.

Paper 406, Perez-Valero et al

British HIV Association BHIVA

Summary

- Statin therapy may improve mortality when used with co-morbidities and association with Incident Diabetes is debatable
- Improvement in immediate mortality from MI in HIV patients.
- Aspirin use is lower in HIV patients
- Non-calcified coronary plaques are common and more vulnerable for MI events
- Switching TDF to ABC may improve BMD in hip
- Renal: Tenofovir induced renal impairment is reversible
- Neuro: Longer exposure to HAART associated with decreased clinically significant depression

British HIV Association BHIVA

BHIVA 'Best of CROI' Working Party 2013

- **Dr A Apoola**, *Royal Derby Hospital*
- **Dr D Asboe,** *Chelsea and Westminster Hospital, London*
- **Dr S Bhagani,** *Royal Free Hospital, London*
- **Dr D Chadwick,** *James cook University Hospital, Middlesbrough*
- **Dr D Churchill,** *Royal Sussex County Hospital, Brighton*
- **Dr P Collini,** *Sheffield Teaching Hospitals NHS Trust*
- **Dr S Das,** *Coventry and Warwickshire Hospital*
- **Dr D Dockrell,** *Royal Hallamshire Hospital, Sheffield*
- **Dr MJ Fisher,** *Royal Sussex County Hospital, Brighton*
- **Dr A Freeman,** *Cardiff University School of Medicine*
- **Dr A Garcia-Diaz,** *Royal Free Hospital, London*
- **Dr M Gompels,** *North Bristol NHS Trust*
- **Dr J Greig,** *Royal Hallamshire Hospital, Sheffield*
- **Dr R Gupta,** *University College London*
- **Prof S Khoo,** *University of Liverpool*
- **Prof C Leen,** *Western General Hospital, Edinburgh*
- **Dr R O'Connell,** *Royal London Hospital*
- **Dr EC Ong,** *Royal Victoria Infirmary, Newcastle*
- **Dr C Orkin,** *Royal London Hospital*
- **Dr A Palfreeman,** *Leicester Royal Infirmary*
- **Dr M Phillips,** *Manchester Royal Infirmary*
- **Dr K Rogstad,** *Royal Hallamshire Hospital, Sheffield*
- **Prof C Sabin,** *Royal Free and University College London Medical School*
- **Miss K Seden,** *University of Liverpool*
- **Dr J Thornhill,** *Bart's and The London NHS Trust*
- **Dr A Ustianowski,** *North Manchester General Hospital*
- **Miss R Weston,** *Imperial College London*

British HIV Association
BHIVA