ABSTRACTS

7th ANNUAL CONFERENCE OF THE BRITISH HIV ASSOCIATION [BHIVA]

27–29 April 2001

THE HOVE CENTRE BRIGHTON

BHIVA Organising Secretariat
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Abstract selection

The number of high-quality abstracts submitted for presentation at the Annual Conference of the British HIV Association continues to grow, making the task of selection ever harder. Thanks are due to the Scientific Committee (see below) for all the time and effort they put in to overseeing this selection. Unfortunately, due to time and space constraints, it has been necessary to disappoint some potential presenters. The Scientific Committee hope this will not deter anyone from submitting abstracts for future meetings.

Prizes

Bristol-Myers Squibb Travelling Scholarships will be awarded to the five best oral and poster presentations as determined by the Judging Panel. These prizes are worth up to £1000 each and are intended to enable attendance at international meetings.

Two additional prizes will be awarded by BHIVA.

The prizes will be presented on Saturday evening at the Gala Dinner.

In addition, BHIVA will be offering a number of scholarships to scientists wishing to attend the 8th BHIVA Annual Conference in 2002. Awards will be based on acceptance of an abstract for oral presentation at that conference. Those eligible should be studying for a PhD and must apply in writing when submitting their abstracts. Further details will be published in due course.

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Friday 27 April 2001

1440–1540 Research Presentations: Session 1

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Beliefs about HIV and HAART and the decision to accept or reject HAART
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J Elford, Royal Free and University College Medical School, London

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M Hennessy, St James' Hospital, Dublin

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L Sarner, The Greenway Centre, Newham General Hospital, London

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J Morlese, Chelsea & Westminster Hospital, London

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C Mazhude, King's College Hospital, London

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T Powles, Chelsea & Westminster Hospital, London

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J Gill, Chelsea & Westminster Hospital, London

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F Gotch, Chelsea & Westminster Hospital, London

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N Imami, Chelsea & Westminster Hospital, London

1710–1720 Abstract O35
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C Burton, Chelsea & Westminster Hospital, London

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AK Sullivan, Chelsea & Westminster Hospital, London

1730–1800 Selected Poster Presentations

Chair: **Dr James Bingham** Guy's & St Thomas' Hospitals, London

Six posters will be selected and their authors invited to present them orally.

O1

CD4 cell response following HAART initiated at different times from HIV seroconversion

K Porter, on behalf of CASCADE collaboration
MRC Clinical Trials Unit, London, UK

Objective: To examine whether an increase of 100 CD4 cells/µl following the initiation of highly active antiretroviral therapy (HAART) is influenced by the time interval since HIV seroconversion.
Methods: We used logistic regression models, with a CD4 cell rise of at least 100 cells/µl in the 6-month period following HAART initiation as the outcome variable, on pooled data from 19 cohorts from Europe and Australia. All subjects had known or well-estimated times of HIV seroconversion. We examined the association of this CD4 cell response with the time interval since seroconversion to HAART initiation, adjusting for age at seroconversion; sex; exposure category; use of previous therapy; and CD4 cell count at HAART initiation.
Results: Of 585 seroconverters starting HAART, 248 (42%) had an increase of at least 100 cells/µl within 6 months of initiation (overall median increase 88 cells/µl). In this cohort, 108, 150, 182 and 145 persons initiated HAART within 2 years, 2–5, 5–9 and over 9 years following seroconversion, respectively. Of these, 62, 66, 71 and 49 respectively, had a CD4 count rise of at least 100 cells/µl. We found no evidence to suggest that a CD4 rise of 100 cells/µl within 6 months of starting HAART was influenced by the duration of HIV infection. We also found that, compared with those who had been treatment-naive at HAART initiation, prior use of therapy was significantly independently associated with a lower probability of the CD4 cell rise (odds ratio and 95% confidence intervals 0.37, 0.23–0.61; 0.46, 0.29–0.75 for prior use of mono- and dual therapy, respectively).
Conclusions: Our results suggest that a CD4 rise of at least 100 cells/µl can be achieved within 6 months of starting potent antiretroviral therapy regardless of how long after infection it is initiated. Long-term follow-up is required to assess more durable response.

O2

Beliefs about HIV and HAART and the decision to accept or reject HAART

R Horne[1], V Cooper[1], M Fisher[2], D Buick[1]
[1]*Center for Health Care Research, University of Brighton, and* [2]*Royal Sussex County Hospital, Brighton, UK*

Objective: To identify perceptions of HIV and highly active antiretroviral therapy (HAART) that influence the decision to accept or decline HAART.
Methods: Consecutive patients offered HAART were invited to complete validated questionnaires assessing their perceptions of HIV (symptoms, timeline, personal consequences, amenability to control and emotional impact) and beliefs about HAART (perceptions of necessity for HAART and concerns about potential adverse effects). All treatment offers were made within BHIVA guidelines.
Results: Twenty-three (66%) patients accepted HAART and 12 (34%) refused. The decision to accept or decline HAART was influenced by personal beliefs about HIV and HAART. Declining HAART was associated with doubts about its personal necessity (t=–3.12; P<0.005) and to a range of concerns about potential adverse effects (t=2.58; P<0.05). Individuals were significantly more likely to accept HAART if their perceptions of personal necessity outweighed their concerns about adverse effects of HAART (t=–4.18; P<0.001) and if they had experienced more HIV-related symptoms (t=–2.10; P<0.05), especially if these fluctuated over time (t=–2.55; P<0.05). People who accepted HAART were also more likely to believe that the illness would improve with time (t=–3.37; P<0.005). Patients with a higher CD4 count were more likely to doubt the personal necessity for HAART (r=–0.35; P<0.05) and were more likely to decline it (t=2.87; P<0.01). Viral load was not related to perceptions of HIV, beliefs about HAART or to treatment decisions.
Conclusion: This study has identified the types of beliefs that influence the decision to decline or accept HAART. The study is ongoing, but these preliminary findings have implications for the type of support offered to people who are faced with decisions about HAART.

O3

Comparison of first-line antiretroviral therapy success in a cohort analysis of over 1000 patients (protease inhibitor vs non-nucleoside reverse transcriptase inhibitor)

GV Matthews[1], CA Sabin[2], S Mandalia[1], AN Phillips[2], MR Nelson[1], M Bower[1], F Lampe[2], MA Johnson[2], BG Gazzard[1]
[1]*Chelsea and Westminster Hospital and* [2]*Royal Free and University College Medical School, London, UK*

Object: To determine whether the likelihood of achieving viral load (VL) suppression at 6 months is related to the choice of therapy.
Methods: Databases were used to identify all treatment-naive patients starting highly active antiretroviral therapy with a protease inhibitor (PI)-/two PIs- or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen). Proportional hazards analysis and logistic regression were used to determine the likelihood of VL <500 HIV-1 RNA copies/ml by 6 months and to identify variables associated with virological success/failure. Patients excluded were on hard-gel saquinavir (SQV) or had no VL available after commencing therapy.
Results: A total of 1109 patients were included (726 Chelsea and Westminster, 383 Royal Free Hospitals); 60% received a PI (40% indinavir, 41% nelfinavir); 40% received an NNRTI [40% efavirenz (EFV), 60% nevirapine (NVP)]. Adjusting for starting therapy year and centre gave no differences between PI regimens. A comparison of NVP vs EFV suggested a treatment benefit for EFV [relative hazard (RH) 0.81 for NVP]. The final analysis compared PI vs EFV vs NVP. 83% of all patients achieved VL<500 copies/ml by 6 months. In multivariate analysis EFV was associated with increased likelihood of success over both PIs and NVP (RH 0.71 for PI, P=0.007; RH 0.78 for NVP, P=0.04) after controlling for all variables including start year and centre. No effect was seen for baseline CD4, age, sex, ethnicity or prior ADI. Baseline VL was also significantly associated with VL<500 copies/ml.
Conclusion: This large treatment-naive cohort analysis suggests that EFV may be associated with a better initial virological response at 6 months than either PIs or NVP, both of which had similar responses.

O4

Short-course HAART in primary HIV infection (PHI)

S Fidler, M Brady, A Oxenius, D Price, R Phillips, JN Weber
Jefferiss Trust Laboratories, Wright-Fleming Institute, Imperial College School of Medicine, St Mary's Hospital, London, UK

Study design: PHI is defined by: positive polymerase chain reaction (PCR), p24 antigen, HIV-specific immunoglobulin M, positive Western blot Abbott De-tuned assay evolving seropositivity and symptoms of acute seroconversion illness. Patients are offered a choice of short-course highly active antiretroviral therapy (HAART), consisting of Combivir/nevirapine, or no therapy and are followed up monthly.
Clinical endpoints: HIV-specific immune functional studies of both CD4 and CD8 responses measured with an enzyme-linked immuno-sorbent assay (ELISA), proliferation assays and tetramer staining technology. Secondary endpoints are viral load and time to fall in CD4 count to <350 cells/µl.
Results: Of 23 PHI subjects identified, 20 were recruited to the study. Mean age was 26.3 years, and average time from infection to recruitment was 12 weeks with a range of 3–24 weeks. At recruitment, the mean baseline CD4 count was 448 cells/µl (range 90–710) and the mean baseline viral load was 166,966 HIV-1 RNA copies/ml (range 179 to >500,000). Eighteen patients chose to start therapy, and there were two untreated 'controls'. Complete virological control was achieved in all subjects irrespective of pretherapy levels, indicating that this is a potent combination. Follow-up to 56 weeks post recruitment and 32 weeks off therapy shows good viral control with levels remaining <5000 copies/ml off therapy, and the preservation of broad HIV-specific CD4 and CD8 T-cell responses in contrast to untreated control PHIs, in whom initial vigorous early responses are subsequently lost.
Conclusion: Short-course HAART at PHI preserves HIV-specific CD4 T-cell responses and is associated with good long-term virological control.

O5

Response to amprenavir in antiretroviral therapy-experienced patients

D Pillay[1], CA Sabin[2], *on behalf of the Amprenavir Expanded Access Programme*
[1]*Public Health Laboratory Service and University of Birmingham,* [2]*Royal Free and University College Medical School, London, UK*

Objective: To assess response rates to regimens including amprenavir (APV) in heavily pretreated patients.

Methods: A retrospective case-note review and resistance substudy of all patients receiving APV from 17 clinical centres in the UK.

Results: We studied 84 patients (91% male, 68% homo/bisexual, median age 37.5 years). The patients had a median CD4 count and RNA level at baseline of 109 (range 2–580) cells/µl and 5.05 (1.70–6.22) $\log_{10}$ HIV-1 RNA copies/ml, respectively. This was a highly drug-experienced population (median number of drugs exposed to: nine; 94% exposed to protease inhibitors, 81% to non-nucleoside reverse transcriptase inhibitors). The patients had first started antiretroviral therapy 4.0 (0-11.2) years before starting APV. Adherence was good in only 49% of patients, and at baseline the patients had a median of five (0-12) reverse transcriptase mutations and five (1-7) protease mutations. By 6 months after starting APV, viral loads had dropped in 60%, increased in 37% and remained stable in 3%. The median drop in viral load was 0.37 (3.83 to –1.01) $\log_{10}$ copies/ml. CD4 counts had increased in 65%, decreased in 30% and remained stable in 5%, with a median CD4 increase of 10 (–370 to 245) cells/µl. The patients remained on their first course of APV for a median of 8.2 (0.1–38.8) months; 56% of patients stopped their first course of APV, the main reasons being adverse reactions to at least one drug in the regimen, and treatment failure. Clinical and virological predictors of response will be presented.

Discussion: In a highly drug-experienced population with multiple drug resistance, APV-containing regimens can lead to short-term virological benefit in the majority of patients.

O6

The efficacy of lopinavir (ABT378) in individuals experiencing protease inhibitor (PI) failure

MR Nelson, Y Gilleece, NA Qazi, JM Morlese, S Mandalia, BG Gazzard, A Pozniak
Chelsea and Westminster Hospital, London, UK

Aim: To assess the efficacy and toxicity of ABT-378/ritonavir (ABT-378/r) in PI-experienced patients.

Methods: On-going review of ABT378/r-treated patients as part of the Abbott-sponsored compassionate-release programme.

Results: Eighty-three patients received ABT378/r; 74 were male and 49 had a previous AIDS diagnosis. In 63 patients, the new regimen was based on a resistance test. The median number of PI mutations was four (range 0-8). The median number of active drugs (excluding ABT378/r) based on virtual phenotype was two. Eleven patients had not been treated with a non-nucleoside reverse transcriptase inhibitor. The median time on PI was 1280 days and on a nucleoside reverse transcriptase inhibitor, 2907 days.

Month	*n*	CD4	Viral load (HIV-1 RNA copies/ml)				%TG	%Chol
			Median	1 log	<500	<50	>10	>6.7
0	83	70	95298	-	-	-	3.6	4.9
1	79	171	702	89.2%	45%	4%	3.9	12.8
3	71	203	65	86.8%	74%	57%	4.6	20.0
6	52	225	<50	90.3%	76%	67%	5.0	25.0

TG, triglycerides; Chol, cholesterol (in mmol/l). CD4 count as cells/µl.

The response to ABT378 was associated with a higher CD4 count and lower viral load, number of active drugs in regimen and number of PI mutations. Fourteen patients ceased therapy, three due to disease progression, seven lost to follow-up, three due to virological failure and one due to toxicity.

Conclusions: Despite extensive PI experience, patients treated with a regimen containing ABT378/r had very high levels of response, with 76% of individuals on treatment at 6 months experiencing a viral load <500 HIV-1 RNA copies/ml and 67% <50 copies/ml.

O7

The impact of baseline polymorphisms in reverse transcriptase and protease on the outcome of HAART in HIV-1 infected African patients

AJ Frater[1], A Beardall[1], K Ariyoshi[2], D Churchill[1], S Galpin[1], JR Clarke[1], MO McClure,[1] JN Weber[1]
[1]*Jefferiss Trust Laboratories, Wright-Fleming Institute, Imperial College School of Medicine, St Mary's Hospital, London, UK, and* [2]*AIDS Research Centre, National Institute of Infectious Diseases, Tokyo, Japan*

Background: The clinical response to highly active antiretroviral therapy (HAART) of patients infected with African HIV-1 subtypes is poorly documented. We studied a cohort of African patients to assess therapeutic response and investigate the significance of polymorphic codons.

Methods: African patients on HAART were identified from the St Mary's Hospital HIV database. Clinical outcome was assessed using viral load and CD4 counts. Pre- and post-therapy sequences of reverse transcriptase (RT) and protease were obtained using the ABI Viroseq genotyping kit. The impact of subtype and polymorphisms on outcome was assessed statistically, phylogenetically and by d_s/d_n ratios.

Results: 79 treatment-naive African patients commenced HAART; 60/79 had an undetectable viral load for 1 year, with no differences according to regimen; 133 polymorphisms were identified in *pol* (37 in protease and 96 in RT), with a mean of 9.0 in protease and 22.3 in RT per patient. There was no significant difference in the overall numbers of polymorphisms per patient and no single polymorphism affected the clinical outcome. Sequences from patients experiencing viral rebound produced a non-significant change in the d_s/d_n ratios from baseline, suggesting only weak drug pressure.

Conclusions: The response of patients infected with African subtypes of HIV-1 to HAART appears to be independent of regimen, clade and baseline polymorphisms. Non-B subtypes are fully sensitive to HAART, and accordingly, therapy should not be withheld from African patients for reasons of viral diversity.

O8

Resistance-associated mutations in subtype C HIV-1 protease from protease inhibitor (PI)-experienced and -naive patients in UK

P Cane[1], A de Ruiter[2], L Navaratne[2], P Rice[3], M Wiselka[4], R Fox[5], D Pillay[1]
[1]*PHLS ASRU, Birmingham;* [2]*Guy's and St Thomas' Hospital,* [3]*St George's Hospital, London;* [4]*Leicester Royal Infirmary;* [5]*Gartnavel Hospital, Glasgow, UK*

Background: Practically all data on the selection of mutations in HIV-1 associated with the development of resistance to antiretroviral drugs have been derived from studies on subtype B virus. However, subtype C virus is the most prevalent world-wide, and there is increasing evidence of transmission of non-B virus in the developed world, particularly by the heterosexual route. This report describes the variability of HIV-1 protease from PI-experienced and -naive patients infected with HIV-1 subtype C in the UK.

Methods: Plasma samples were submitted for routine HIV-1 genotypic resistance testing. Protease gene sequences were analysed for the presence of drug-resistance associated mutations. Subtype designation was based on *pol* gene sequences and confirmed by analysis of *gag* and *env* genes in some cases.

Results: Samples from 51 patients infected with subtype C HIV-1 were analysed. Therapy information was available for 44 patients, including 26 PI-treated and 18 PI-naive patients. The most common primary mutation observed in the treated patients was L90M (10/26 treated patients compared with 0/18 untreated). G73S, V82A/F and I84V were each observed in two treated patients but only in association with L90M. Although 12 patients had been treated with nelfinavir, D30N was not observed. M36I and I93L have been described as accessory mutations in subtype B HIV-1. These codon changes were observed in most samples from both treated and untreated patients and cannot be considered as resistance-associated mutations in this subtype.

Conclusions: The spectrum and prevalence of PI-associated resistance mutations differed between subtype B and C viruses. Genotypic resistance data from non-B viruses should be interpreted carefully.

O9

Transmission of HIV-1 infection in the UK: the use of phylogenetic analysis to demonstrate relatedness between viruses from source and index individuals

S Taylor[1,5] J Workman[1], P Cane[1] D Ratcliff,[1] R Hextall[2], J Clarke[3], R Nandwani[4], S Drake[5] and D Pillay[1]
[1]*PHLS Antiviral Susceptibility Reference Unit, University of Birmingham, and Departments of Genitourinary Medicine at* [2]*Leeds,* [3]*Wakefield,* [4]*Glasgow and* [5]*Birmingham, UK*

Objective: We undertook a detailed molecular analysis of HIV from five subjects at first diagnosis, whose potential sources of virus were identified.

Methods: Plasma virus was extracted and amplified from these 10 subjects and compared to 25 control patients from around the UK. A 1014 bp region of the *pol* gene, C_2V_3 portion of the *env* gene and the p17 region of the *gag* gene were amplified by nested RT-PCR and the products sequenced. Phylogenetic analysis was performed using CLUSTAL W and DNADIST from the PHYLIP package.

Results: Three of the five index cases had drug-resistant virus at first diagnosis. Two showed the reverse transcriptase (RT) mutations T215D and T215S. One patient seroconverted with virus containing the mutations M41L, K43E, K103N, Y188L, T215Y, D218E, in RT and L10I, L63P, V77I and V82C in protease. *pol* gene phylogenetic analysis revealed a genetic distance of <1% in four out of five sexual partners, supported by bootstrap values >95%. The couple with multidrug resistance mutations demonstrated a genetic distance of 2.5% in the *pol* but a surprisingly high degree of nucleotide sequence divergence in the *env* and *gag* genes of >13% and >7% respectively, suggesting a more complex linkage between these individuals. The possible reasons for these disparities will be discussed.

Conclusions: Molecular epidemiological techniques provide a powerful tool to explore the HIV epidemic, and demonstrates the complexity in determining transmission events between individuals.

O10

Patterns of non-nucleoside reverse transcriptase inhibitor (NNRTI) genotypic and phenotypic resistance in patients infected with either B or non-B HIV-1 subtypes and failing therapy with two nucleoside reverse transcriptase inhibitors (NRTIs) and nevirapine (NVP)

AM Geretti[1,2], M Smith[2], N Osner[2], BA Larder[3], M Zuckerman[2], PJ Easterbrook[1]
[1]*Academic Department of HIV Medicine and* [2]*Department of Virology, GKT School of Medicine, King's College, London, and* [3]*Virco, Cambridge, UK*

Objective: To determine the prevalence and patterns of NNRTI resistance in patients failing therapy with NVP and two NRTIs.

Methods: Eligibility: plasma viral load >1000 copies/ml after >3 months of two NRTIs plus NVP; naive to other NNRTIs. Genotypes were determined by TrueGene (Visible Genetics) or VircoGEN (Virco). Phenotypes were determined by the Antivirogram (Virco) recombinant virus assay.

Results: Genotypes were obtained in 51/60 patients, including 25 B and 26 non-B subtypes, equally distributed between treatment arms; 37 patients (19 B and 18 non-B) had NNRTI resistance mutations and 32 of these also had NRTI resistance mutations. The most common NNRTI mutations were Y181C (51%) and K103N (43%). Of the 19 B subtypes with NNRTI mutations, 58% had K103N and 37% Y181C. Of the 18 non-B subtypes with NNRTI mutations, 17% had K103N and 67% Y181C. No significant differences in the prevalence of K103N and Y181C were detected between treatment arms. In particular, of the patients on ZDV, 25% had K103N and 42% Y181C. Of the patients not receiving ZDV, 46% had K103N and 50% Y181C. Other NNRTI mutations were G190A/S (22%), V108I and K101E/Q (14%), A98G and V106A (8%), V179D and Y188C/L (5%). Phenotypes from 17 patients correlated with genotypes; thus, the large majority of NNRTI resistance mutation patterns confer high-level resistance to all available NNRTIs.

Conclusions: Y181C was more prevalent than K103N for non-B. ZDV+NVP did not favour the emergence of K103N over Y181C.

O11

Genotypic drug-resistance testing after zidovudine (ZDV) monotherapy to reduce mother-to-child transmission (MCT)

N Larbalestier, J Mullen, S. O'Shea, F Cottam, I Chrystie, A de Ruiter
Guy's and St Thomas' Hospital, London, UK

Objective: To determine the prevalence of ZDV resistance mutations following monotherapy in pregnancy.

Methods: All pregnant women on ZDV monotherapy at four treatment centres between Nov 1995 and Dec 2000 were identified. Data were abstracted from the medical notes. Stored plasma was genotyped using the Visible Genetics Trugene™ HIV-1 assay and viral subtyping determined by peptide based enzyme immunoassay.

Results: Of 225 pregnancies, 92 received ZDV monotherapy and suitable delivery samples were available on 62 of these. Preliminary data (one centre) on 16/62: mean baseline CD4 390 cells/µl, median viral load (VL) 5510 HIV-2 RNA copies/ml; 12/16 had non-B subtypes. Mean ZDV exposure at delivery was 11 weeks (range 4–21). A single primary mutation was evident in one woman only at codon 215. Full data will be presented (four centres).

Conclusions: The development of drug resistance in this cohort appears uncommon. The only primary mutation evident occurred in a woman whose baseline VL was high and who, with current guidelines, would now receive highly active antiretroviral therapy. Monotherapy is an attractive intervention to reduce MCT as it limits fetal drug exposure and is well tolerated. In this cohort of asymptomatic women with low VL, future treatment options seem preserved.

O12

Missed opportunities: late presentation or delayed recognition of HIV infection

N Baxter[2], B Moran[2], J Welsh[2], DR Churchill[2], M Fisher[2]
[2]*Royal Sussex County Hospital, Brighton, and* [2]*The Sussex Beacon, Brighton, UK*

Introduction: In the UK over a third of patients are diagnosed HIV-positive with a CD4 count of <200 cells/µl and, as a result, may not benefit optimally from highly active antiretroviral therapy (HAART). We investigated whether opportunities for earlier diagnosis had been missed in those patients diagnosed HIV-positive simultaneously with AIDS.

Methods: The notes of all 70 patients with a new diagnosis of AIDS from 1997 to 2000 were reviewed. Illness prior to AIDS was recorded if it was potentially HIV-related.

Results: Forty-nine patients were eligible for inclusion. Twenty-one were excluded because they had lived or had the HIV diagnosis made outside our health region. Twenty-five had attended hospital before the AIDS diagnosis, and five had been inpatients. Referrals to gastroenterology, dermatology and ear/nose/throat departments predominated. The mean time between first hospital visit and HIV diagnosis was 995 days, median 520 days. Thirteen of the 17 HIV deaths in patients diagnosed HIV-positive during 1997–2000 were from this group. The mean time between HIV diagnosis and death was 202 days, median 69 days. The mean CD4 count at presentation was 76 cells/µl (median 50 cells/µl).

Conclusion: A high proportion of avoidable deaths were due to late recognition of HIV infection. There is clearly a role for increased education of non-HIV specialists about HIV infection.

O13

Changing demographics of new HIV diagnoses at the Royal Free Hospital from 1994 to 2000

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Objectives: To document the changes in ethnicity of new HIV diagnoses and correlate these findings with HIV viral load, CD4 count, reason for testing and stage of illness.

Methods: A retrospective case-note review was performed of all patients newly diagnosed HIV-positive at the Royal Free, or diagnosed elsewhere and referred to the Royal Free for initial HIV care in 1994, 1997 and 2000. Data extracted from the notes included ethnicity, risk for HIV infection, clinical stage of disease, reason for test, CD4 count and HIV viral load.

Results: 144 patients were identified for 1994, 135 for 1994 and 110 for 2000. Over this period, the number of black Africans and black Caribbeans not born in the UK increased from 34 to 54, and the number of white patients from all countries decreased from 124 to 53. Over the same period, the median CD4 count remained similar in the black group, but declined significantly in whites. By 2000, when numbers of black and white patients were equal, the clinical stage of disease, median CD4, HIV viral load and reason for HIV testing was remarkably similar between these groups.

Conclusions: There has been a substantial drop in new HIV diagnoses among white patients (mainly gay men) and a rise in the number of black Africans at this institution from 1994 to 2000. By 2000, white patients were presenting later than blacks with a similar disease stage.

O14

HIV antibody testing

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Introduction: We decided to pilot universal testing on an opt-out basis on the same lines as the antenatal clinic to see if this was acceptable to patients.

Method: We amended all the clinic literature, including notices in reception, clinic leaflets and sheets given to patients when they fill in their personal details, to include information that blood is taken routinely in clinic for testing for HIV. Patients identified as high-risk, and who would have been sent to the health advisor previously, were all referred for a further discussion. We then compared the number of HIV tests done before and after the introduction of the change in policy for the 6 months up to April 2000 and the 6 months afterwards

Results: The total number of new patients seen between October 1999 and March 2000 was 937 patients, and 296 HIV tests were performed on these patients, 31% of the total. The total number of new patients seen between April 2000 and September 2000 was 1052, and 967 HIV tests were performed, 92% of the total.

Conclusion: HIV is now a treatable condition and this study has shown that uptake of the test can be significantly raised in a way that is acceptable to patients and staff.

O15

Incidence of HIV infection among gay men seeking a repeat HIV test

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Objective: To estimate the incidence of HIV infection among gay men seeking a repeat HIV test.

Methods: Of 470 gay men (75% response rate) surveyed in this London NHS same-day HIV-testing clinic between September 1997 and July 1998, 337 (72%) had previously tested negative for HIV and were returning for another test (repeat testers). HIV incidence was estimated by dividing the number of newly diagnosed cases of HIV among repeat testers by the person-years (py) of exposure since the last negative test.

Results: Among the 275 repeat testers who provided information on date of last test, 12 tested HIV-positive; the overall HIV incidence was 1.8 per 100 person-years (12/655.2) (95% confidence interval 0.8, 2.9). HIV incidence was higher among men reporting three or more previous HIV tests (n=151) than men with one or two previous tests (*n*=124) (3.3 vs 1.1 per 100 py, *P*=0.04). Elevated levels of high-risk sexual behaviour were also reported by gay men who had three or more previous HIV tests (42.2% vs 25.3%, *P*=0.002).

Conclusion: In this London HIV-testing clinic, gay men with a history of three or more previous HIV tests reported an increased incidence of HIV infection. For some gay men, repeatedly receiving a negative HIV test result may produce a disinhibiting effect and reinforce high-risk sexual behaviour.

O16

The role of the multidrug transporter P glycoprotein (P-gp) in HIV disease

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Introduction: P-gp is a transmembrane efflux pump for antiretroviral agents, in addition, HIV virus production is decreased in multidrug resistant cell lines *in vitro*. We explored the effect of HIV disease on P-gp expression and function in peripheral blood lymphocytes (PBLs) of HIV infected patients (*n*=71) and healthy controls (*n*=24). PBLs were isolated, fixed, permeabilised, stained (P-gp specific antibody) and quantified by flow cytometry. The MDR1 gene product was confirmed by reverse transcriptase polymerase chain reaction P-gp function was determined by rhodamine efflux and expressed as a ratio. Ritonavir was used to assess inhibition of P-gp function.

Results: P-gp expression was reduced (P<0.05) in the PBLs of treatment-naive HIV-infected patients (3.5±0.53 MFI) compared with controls (6.3±0.43 MFI). Expression was similar in patients successfully treated with highly active antiretroviral therapy (HAART) (7.97±0.58 MFI) compared with controls, but remained reduced (*P*<0.05) in patients unsuppressed despite HAART (2.96±0.86 MFI). P-gp expression correlated with viral load (*P*<0.05) independently of disease stage or CD4 count. P-gp-mediated rhodamine efflux was reduced (*P*<0.05) in untreated (0.41±0.15) and treated unsuppressed patients (0.37±0.07) compared with controls (0.17±0.04). Ritonavir inhibited P–gp function in PBLs from untreated (81.2±7.3%) and treated suppressed (61.7±6.6%) and treated unsuppressed (57.3±10%) patients.

Conclusion: P-gp expression in HIV patients is inversely related to viral load independently of disease stage or treatment. P-gp was functional in all groups and inhibited by ritonavir. I*n vivo*, P-gp appears important for immune reconstitution associated with adequate viral suppression.

O17

Clinical implications of intracellular protease inhibitor concentrations

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Objective: Highly active antiretroviral therapy (HAART) still lacks sufficient potency and durability. As viral replication takes place intracellularly, treatment success may depend upon intracellular (IC) PI concentrations. We examined the relationship between plasma and IC PI concentrations in peripheral blood lymphocytes (PBLs) of HIV patients.
Results: Patients receiving indinavir (IDV; *n*=11) and nelfinavir (NFV; *n*=14) were studied. PBLs were isolated by density centrifugation, stained and counted. Plasma and IC PI concentrations were assayed by LC/MS. AUC, time to peak (T_{max}) and half-life ($t½$) were derived. Data were correlated with HIV plasma RNA levels. IC IDV AUC was lower than plasma (*P*<0.05; 9470±2239 vs 31788±6392) while NFV underwent a ninefold IC accumulation (*P*<0.05; 283251±6687 vs 31034±6911). Two patients receiving IDV had IC levels below the MEC despite acceptable plasma levels and were unsuppressed. In contrast, two patients with subtherapeutic plasma IDV levels had IC concentrations above the MEC and remained suppressed (VL<50cpm). IC IDV T_{max} was delayed compared with plasma. IC $t½$ was longer, thus the mean residence time of IDV within the cell was prolonged (*P*<0.05) this may contribute to efficacy despite poor IC accumulation.
Discussion: For discordant patients, IC IDV concentrations may provide better correlation with virological response than plasma levels. All patients on NFV remained suppressed. This highlights marked differences between PIs with respect to IC accumulation and pharmacokinetic behaviour and has important implications for drug penetration into sanctuary sites and therapeutic drug monitoring. The correlation between plasma and IC AUC was r^2= 0.6 (*P*<0.05), in contrast to NRTIs.

O18

Penetration of efavirenz into the male genital tract: drug concentrations and antiviral activity in semen and blood plasma of HIV-1 infected men (the Triple S study)

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Objective: A prospective study to determine efavirenz (EFV) concentrations and antiviral activity in blood plasma (BP) and seminal plasma (SP) in HIV-1 positive men over the 24 hour dosing period.
Methods: Nineteen HIV-1 positive men on EFV-containing regimens were enrolled to donate matched semen and blood samples at baseline (week 0) and at 24 weeks of EFV therapy for viral load determination. BP and SP samples were assayed for EFV drug concentrations at 12 and 24 hours after EFV administration. When SP and BP samples were collected within 1 hour of each other, a time-specific SP:BP ratio was calculated. SPVL was measured using NABSA. EFV drug concentrations were measured using a sensitive HPLC.
Results: A total of 70 BP and 69 SP samples were analysed. The median EFV concentrations in BP and SP 12 hours post-dose were 2184 ng/ml (843–14,356) and 215 ng/ml (62–622), respectively. At 24 hours post-dose, median values were 1785 ng/ml (694–8096) and 238 ng/ml (49–1256), respectively. The median SP:BP ratio was 0.08 (0.04–0.16) at 12 hours and 0.09 (0.03–0.43) at 24 hours. Absolute median trough SP EFV concentrations exceeded an estimated BP protein-corrected 90% effective concentration (EC_{90}) of 92.8 ng/ml for wild-type HIV-1 by over twofold. Viral load at 24 weeks was reduced below the limit of detection in 18/18 patients in SP and 16 /18 patients in BP.
Conclusions: Standard EFV doses give greater than expected SP concentrations according to protein-binding considerations alone. These data suggest that EFV has antiviral activity in the male genital tract.

O19

The serum level of soluble uPAR is a strong predictor for development of AIDS and death in HIV infected individuals

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Objective: To determine the prognostic value of soluble urokinase receptor (suPAR) and urokinase plasminogen activator (uPA) in a Danish cohort of HIV-infected individuals.
Methods: suPAR and uPA were measured on frozen serum samples from 133 HIV positive patients enrolled in the Copenhagen AIDS Cohort (CAC). The patients were followed from time of serum sampling (median 1986, range 1984–1994) until May 1996 when the first patient received highly active antiretroviral therapy. Serum suPAR and uPA concentrations were measured by enzyme-linked immunosorbent assay.
Results: All patients had measurable uPA and suPAR. The median suPAR level was 1.75 ng/ml (range 0.5–10.9). Grouped by median suPAR level, the high suPAR patients progressed significantly faster to AIDS (median 4.2 years) and death (median 6.6 years) compared to the low suPAR group (median 8.0 and 8.5 years, respectively, *P*< 0.05). By Cox regression analysis, both suPAR and CD4 predicted progression to AIDS (*P*=0.011, HR per ng suPAR increase =1.64 and $\log_{10}$ transformed CD4 counts, *P*=0.014, HR per log decrease=1.72) and to death (*P*<0.001, HR=1.42, and *P*=0.009, HR=1.64, respectively). There was no significant difference in CD4 T cell counts between the high and low suPAR groups (*P*=0.9, *t*-test). No significant association between uPA and HIV progression was found.
Conclusions: suPAR is a strong and independent prognostic factor for HIV disease progression. It is easy to measure and has the potential to be an important tool for determining when to initiate therapy in HIV infected individuals.

O20

Lactic acidosis and hypoglycaemia in three neonates exposed to HAART in utero

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Introduction: Nucleoside reverse transcriptase inhibitors (NRTIs) are administered perinatally to reduce the vertical transmission of HIV-1. Previous concerns regarding possible mitochondrial dysfunction in children exposed *in utero* to zidovudine (ZDV) alone or in combination with lamivudine (3TC) have been reported. We present three cases of unexplained neonatal lactic acidosis and/or hypoglycaemia in non-HIV-infected infants exposed perinatally to ZDV, 3TC and nevirapine.
Case 1: 38/40-week infant delivered by caesarian section with poor CTG: APGAR 4/5/7; hepatosplenomegaly and anaemia; haemoglobin 4.4 g/dl, retics 1, DCT, TORCH screen and parvovirus-negative. Metabolic acidosis from birth to 72 hours, pH 7.06, pCO_2 5.2, HCO_3 10.1, BE 18.6 and lactate 2.8 mmol/l. Recurrent hypoglycaemia, glucose 1.6 mmol/l.
Case 2: 36/40-week infant emergency caesarian section for maternal *Pneumocystis carinii* pneumonia (PCP) and premature labour. APGAR 8/9/10, initial gas pH 7.32. BE –4, glucose <1.0 mmol/l. Persistent severe hypoglycaemia for 96 hours.
Case 3: 31/40-week infant emergency caesarian section for maternal pre-eclamptic toxaemia. APGAR 7/8/9. Lactic acidosis, pH 7.03, BE –22.6, lactate 6.5 and glucose 3.5 mmol/l. Macrocytosis MCV 140, coagulopathy, encephalopathy, liver and renal dysfunction.
Results: All three infants responded to standard neonatal supportive care and are asymptomatic at 19, 26 and 4 months, respectively.
Summary: Although we fully condone the use of antiretroviral therapy in pregnancy, these infants appeared to show acute mitochondrial toxicity, exacerbating neonatal stress. We suggest that all infants perinatally exposed to this therapy require early metabolic assessment.

O21

Serum markers of bone turnover and screening for abnormal bone mineral density (BMD) in an HIV-positive population

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Objective: Abnormal BMD is increasingly reported in HIV positive patients although the aetiology, clinical significance and treatment of this condition are not yet known. It is therefore currently difficult to rationalise screening for abnormal BMD other than as part of research protocols. We aimed to assess the value of serum markers of bone turnover as a screening tool for abnormal (BMD) in HIV-positive subjects.

Methods: Serum levels of a marker of bone formation (PICP) and bone resorption (ICTP) were compared against standard dual-energy X-ray absorptiometry (DEXA) scans. Marker values were designated abnormal if above the mean population value for PICP and if above the median for ICTP, with DEXA scans categorised according to T score (>1 SD below the general population mean being classified as 'abnormal' and >2.5 SD below the mean as osteoporotic).

Results: A total of 95 patients had both DEXA scan and serum markers available, 69 (73%) having 'abnormal' DEXA scans and 13 (19%) of these being osteoporotic. The sensitivity of the bone marker test for abnormal BMD was 68%, specificity 50%, positive predictive value 78% and negative predictive value 37%. In assessing the test for benefit in screening for osteoporosis, sensitivity was 69%, specificity 38%, positive predictive value 15% and negative predictive value 89%.

Conclusions: The predictive value of the combined marker test is such that we cannot accurately identify those at risk of abnormal BMD as determined by DEXA scan. These markers are more likely to be useful when used in conjunction with DEXA scans in longitudinal monitoring of bone turnover.

O22

Immunological changes during treatment interruptions (TI): risk factors and clinical sequelae

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Introduction: Although the possible beneficial effects of HIV TIs remain unproven, many patients are stopping therapy. Studies have shown that there is a risk of significant falls in CD4 count when therapy is interrupted. Identification of risk factors for CD4 drops may inform treatment decisions.

Methods: Patients who had interruptions of highly active antiretroviral therapy (HAART) lasting 2 months or more were identified. Data were collected on reason for stopping therapy, CD4 count and HIV RNA histories, drug therapy and clinical events.

Results: Thirty-eight patients were identified. TI occurred a median of 2.7 (0.5–10.5) years after starting antiretroviral therapy and 1.5 (0.5–3.2) years after starting HAART. The duration of TI was a median of 289 (77–1036) days. Baseline TI RNA levels were undetectable in 18 (47%) patients. During TI there was a significant drop in CD4 count from 348 to 231 (P=0.0001) and CD4 percentage from 17.5 to 14% (P=0.0001) and a significant increase in viral load from 2.78 to 5.17 log (P=0.0001). Those with higher baseline CD4 counts (P=0.0001), but lower nadir CD4 counts (P=0.04) prior to the TI had the largest drops. For patients with sufficient data (n=24) the median rate of CD4 loss prior to HAART was 62.8 cells/µl per year. This was significantly correlated with the change in CD4 count over the TI (r=0.56, P=0.005). Twenty-nine patients had at least one clinical event during TI; in four this was an AIDS defining illness. No factors predicted the development of a clinical event.

Conclusions: Treatment interruptions are accompanied by significant CD4 cell loss and associated disease progression. Individuals with lower nadir CD4 counts and more rapid CD4 cell loss prior to HAART are more at risk and should be fully informed of the potential risks of TIs.

O23

Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy as a result of antiretroviral medication.

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Introduction: Mitochondrial toxicity is now well recognised as a result of nucleoside analogue therapy. We present two cases of acute lactic acidosis in the third trimester of pregnancy.

Case 1: A 30-year-old woman (CD4 count 450 cells/µl, viral load <50 HIV-1 RNA copies/ml) taking didanosine, stavudine and nevirapine for 3 years, presented in the 37th week of pregnancy with an acute onset of severe lactic acidosis (lactate 22.5 mmol/l), resulting in maternal and foetal death.

Case 2: A 31-year-old woman (CD4 count 650 cells/µl, viral load <50 HIV-1 RNA copies/ml) taking didanosine, stavudine and nevirapine for 2 years presented in the 33rd week of pregnancy with acute-onset lactic acidosis (lactate 6.8 mmol/l) and pancreatitis (amylase 1990 IU/l).

Treatment: Both cases were managed supportively and given riboflavin, resulting in a full recovery and delivery of a live infant in the second case.

Discussion: Studies show that late pregnancy may be associated with low riboflavin levels. This, in combination with mitochondrial toxicity, may precipitate sudden-onset severe lactic acidosis. Heightened awareness and further evaluation of risk factors and screening tools is required.

O24

Differences in postprandial lipid metabolism in patients with protease inhibitor (PI)-associated and nucleoside reverse transcriptase inhibitor (NRTI)-associated lipodystrophy

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Objective: To use labelled fatty acids to describe the postprandial metabolism of dietary lipid in HIV-positive men on dual NRTI therapy with self-reported lipodsytrophy who had never received a PI (NRTI-L: n=7).

Methods: [1-^{13}C]Palmitic acid was given as part of a test meal following an overnight fast. Total plasma triacylglycerol (TAG), non-esterified fatty acid (NEFA), ^{13}C-TAG and ^{13}C-NEFA were measured before and for 7 hours after the meal by GC-C-IRMS. The results were then compared with those in a PI-associated lipodystrophy group of HIV-positive men (PI-L: n=6) using the same study design.

Results: NRTI-L patients had lower plasma TAG and NEFA concentrations at baseline with smaller changes in TAG and NEFA throughout the postprandial period than PI-L patients (all P<0.05). NRTI-L patients had lower and less prolonged increases in ^{13}C-TAG than those in PI-L patients [threefold smaller area under the curve (AUC); P<0.05] but greater and more prolonged increases in ^{13}C-NEFA concentrations (1.5-fold greater AUC; P<0.05).

Conclusions: While the PI-treated lipodystrophy group showed an increased retention time of dietary lipid within the circulation as lipoprotein TAG, the NRTI-treated lipodystrophy group showed an increased retention time of dietary lipid within the circulation as NEFA. These results suggest that there may be different effects of these two drug classes on lipid metabolism *in vivo* which may influence the development of the changes in body composition.

O25

Ethnic and gender differences in non-nucleoside reverse transcriptase inhibitor (NNRTI)-induced rash

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Objective: To determine the association of ethnic group and sex with the development of NNRTI-induced rash in a multiethnic cohort of HIV-infected patients.
Methods: Retrospective record analysis of all patients starting nevirapine (NVP)/efavirenz (EFV) between Jan 1997 and Jan 2000. Sex, ethnic group and stage of disease were analysed as potential risk factors for the development of the rash.
Results: A total of 337 records were analysed, including 285 patients on NVP and 52 on EFV. Of the 285 on NVP, 130 (46%) were white males, 93 (33%) black females, 48 (17%) black males and 9 (3%) white females. There was no significant difference in disease stage between the various ethnic groups (24% black females had prior AIDS-defining events vs. 19% of white males). Of the 285 on NVP, 21 (7%) developed a rash, and two-thirds of these discontinued as a result. Of those that developed a rash, 13 (62%) were black females, two (10%) white females, five (24%) white males and one (5%) black male. Female sex was associated with the highest incident risk of 15% (black women 14%, white women 22%) vs. 2–4% for males. Only two patients with a rash had prior AIDS-defining events. Two-thirds were on 400 mg NVP when the rash occurred. The median time to rash was 15 days (range 2–39). Three patients developed a Steven–Johnson type syndrome (two black females, one white male). Of nine developing a rash on NVP and switching to EFV, none had a recurrence. Of the 52 started on EFV, only one white male developed a rash and the drug was stopped.
Conclusions: The 7% incidence of rash in those starting NVP falls within ranges described previously. Female sex is strongly associated with a higher risk of NVP-induced rash. These data do not suggest a difference in the risk of NVP rash on the basis of black/white ethnicity.

O26

HIV-1 specific lymphoproliferative responses and viral blips in patients on HAART receiving interleukin-2 therapy with or without Remune

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Objective: To assess the acute effects of interleukin (IL)-2 therapy on CD4 cell count and viral load, and subsequent effect on the lympho-proliferative responses (LPR) to HIV-1 specific antigens in HIV-1 infected patients on virologically successful, highly active antiretroviral therapy (HAART) with or without a therapeutic vaccine (Remune).
Methods: Patients received IL-2 (5 MU subcutaneously twice a day, for 5 days, three 4-weekly cycles) ± Remune (100 µg intramuscularly, weeks 0 and 12). Samples were taken on days 1 and 5 of each cycle and weeks 12 and 24 for CD4 cell count, viral load (VL) and HIV-1 specific LPR.
Results: Fifteen patients received 41 cycles of IL-2 therapy; six patients also received Remune; 10/15 patients had at least one IL-2 associated viral blip (total 14 blips); four patients had no blips detected (three taking Remune). One patient had baseline VL=100 copies/ml. The median CD4 cell count rose from 377 to 922 cells/µl (P=0.002), but fell acutely on day 5 from 489 to 421 cells/µl (NS). Overall, the median VL remained below detection (BLD). For all IL-2 cycles, the VL rose acutely on day 5 from BLD to 122 copies/ml (P=0.002, range <50–355 copies/ml). Mean HIV-1 specific responses increased: stimulation index (SI) at baseline and week 24 for nef: 2 to 15 (P=0.036), gp120: 2 to 7 (p=0.047) and p24: 4 to 22 (P=0.057) (SI >5 is significant). Of 10 patients with IL-2 associated blips, seven had significant p24 responses, and five maintained them to 24 weeks.
Conclusion: IL-2 therapy was associated with controlled viral blips and an increase in HIV-1 specific LPR in patients receiving HAART with or without Remune. There was a significant CD4 cell count rise but the VL remained BLD at 24 weeks.

O27

Semen mitochondrial DNA damage as a marker of nucleoside analogue toxicity: the effect of HAART on semen quality of HIV-1 infected men

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Background: Nucleoside reverse transcriptase inhibitors may cause side effects due to generation of abnormal mitochondrial (mt)DNA in selected tissues. Spermatogenesis may be particularly susceptible to mtDNA damage from cytoplasmic condensation. We used a novel technique to detect mtDNA deletions in sperm. We also examined semen quality in men on different antiviral regimens.
Methods: 10 HIV-1 positive men on various highly active antiretroviral therapy (HAART) regimens produced semen samples for quality and mtDNA analysis. One patient was followed intensively for 14 months. Sperm counts and motility analyses were by Hamilton Thorn Analyser. Semen mtDNA was isolated from frozen samples by Puregene DNA Isolation Kit and weighed by mass spectrophotometry. MtDNA deletions were detected by long-chain polymerase chain reaction. Testosterone and FSH levels were measured to exclude other possible causes of male infertility.
Results: Significantly more patients treated for >12 months had mtDNA deletions than those treated for <12 months (4/4 vs 1/3 P<0.05, Fisher's exact test). These patients also had poor semen quality and three had clinically evident lipodystrophy; 4/5 treatment-naive patients showed no mtDNA deletions. The intensively followed patient had no mtDNA deletions and good semen quality at baseline but increasing multiple mtDNA deletions at 6 and 14 months. Semen quality changed as therapy altered. Testosterone and FSH were normal.
Conclusions: Changes in semen quality can occur in patients commencing HAART and may be drug-specific. Semen mtDNA damage may be a marker of HAART-related toxicity such as lipodystrophy.

O28

Taxol chemotherapy for anthracycline-refractory AIDS related Kaposi's sarcoma

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Aim: As part of a multicentre open-label treatment protocol, 11 patients (10 males) were recruited who had AIDS-related Kaposi's sarcoma (KS) refractory to liposomal anthracyclines. They had either not responded to anthracycline (n=8) or had progressed within 6 months of completion of the anthracycline (n=3).
Methods: Paelitaxel (Taxol) at 100 mg/m^2 was given over 3 hours every 2 weeks until maximum response or disease progression. Three patients had visceral disease (two gastric, one gastric and pulmonary), five had tumour-associated oedema and 10 were receiving concomitant highly active antiretroviral therapy. A median of 12 cycles (range 2–21+) were administered. The best responses according to the ACTG criteria were nine partial remissions and two stable diseases (response rate 82% (95% confidence interval 58–100%)). The median time to response was 6 weeks (range 4–18). Three responders have progressed. Three grade 3 and one grade 4 episodes of neutropenia were recorded in 122 treatment cycles. Three patients developed grade 2 and one grade 1 peripheral neuropathy. One patient developed grade 2 and seven grade 1 alopecia. The median CD4 cell count at entry was 286 cells/µl (range 62–549) and rose to 352/ml at completion of the study (P>0.05). Similarly, there was no significant change in the HIV viral load, CD8 cells, B cells or natural killer cells during the study. The study has now closed to recruitment due to slow patient accrual; 14 patients were enrolled in total. Paelitaxel is an effective and tolerable therapy for anthracycline-refractory AIDS-KS which does not have adverse short-term effects upon immune parameters.
Sponsorship: The study was supported by Bristol-Myers Squibb Europe.

O29

A prospective study of the effects of HAART on Kaposi's sarcoma (KS) and human herpesvirus 8 (HHV8)

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Background: There have been many reports of AIDS-KS resolving with highly active antiretroviral therapy (HAART). HHV8 is thought to be the causative agent of KS. The effects of HAART on plasma HHV8 were prospectively studied in HIV-positive subjects with and without KS.
Methods: Twenty-one subjects with AIDS-KS and 15 HIV-positive patients without KS were assessed before and during treatment with HAART. Serial samples were taken for HHV8 serology and quantitative real-time polymerase chain reaction (PCR; TaqMan).
Results: All but one of the subjects are homosexual men; 71.4% of KS subjects were seropositive for HHV8 and 76.2% had detectable plasma HHV8 by PCR before starting HAART. In contrast, 53.3% of subjects without KS were HHV8-seropositive and 33.3% were PCR-positive. The subjects were followed for a median of 36 weeks, and 47.6% of subjects with AIDS-KS demonstrated a clinical response to HAART alone. Of the subjects with HHV8 viraemia before treatment, 52.4% achieved an undetectable HHV8 viral load with HAART.
Conclusion: HIV/HHV8 co-infected individuals have a fall in HHV8 viral load following HAART.

O30

Three-year prospective study: discontinuation of maintenance therapy for cytomegalovirus retinitis in AIDS patients on HAART

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Objective: To determine the long-term effects of discontinuation of anti-cytomegalovirus maintenance therapy in patients with cytomegalovirus retinitis (CMVR) receiving highly active antiretroviral therapy (HAART).
Methods: In a prospective 3-year study, 44 patients with AIDS on HAART, with CD4 counts >50 cells/µl and quiescent CMVR for ≥3 months elected to discontinue anti-CMV maintenance therapy.
Results: The median follow-up was 119 weeks (range 12–152). No patient showed reactivation of CMVR or an extraocular CMV infection. Median CD4 and CD8 counts and viral load at entry were 295 cells/µl (range 63–853), 998 cells/µl (range 284–3611) and <1.70 $\log_{10}$ HIV-1 RNA copies/ml (range <1.70–5.38), respectively. The CMV viral load was positive in only one patient shortly before death. Ocular complications secondary to CMVR occurred in 68% of patients.
Conclusions: To our knowledge, this is the longest and largest study of discontinuation of anti-CMV maintenance therapy and supports previous reports suggesting that therapy can be safely stopped in selected patients responding to HAART. However, ophthalmic intervention remains important in view of the vision-threatening complications of previous CMVR

O31

The impact of HIV infection on the hepatitis B (HBV)-specific CD8 response in HIV/HBV coinfected patients

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Objective: To investigate the effect of HIV-related immunodepletion on the specific immune response against a common co-infection. The HBV-specific CD8 response has a critical role in controlling HBV infection, but there are no data on how this is affected by the presence of HIV infection.
Methods: We are using four human leucocyte antigen (HLA)-A2-peptide tetramers to quantify HBV-specific CD8 responses in HIV/HBV co-infected patients. The functional capacity of HBV-specific cells is being analysed with intracellular staining for interferon (IFN)γ following specific stimulation with 10 HLA-A2-restricted peptides. This allows direct *ex-vivo* evaluation of the HBV-specific CD8 response.
Results: We studied 16 patients with natural immunity following HBV infection (nine HIV-negative and seven HIV co-infected). The HIV-infected subjects have a median CD4 count of 400 cells/µl and are antiretroviral therapy-naive. Persistent multispecific HBV-specific CD8 responses are detectable both by tetramer and intracellular cytokine staining in the HBV-immune HIV-negative group but they have not been detected in the HIV-infected group. Similarly, HBV-specific CD8 responses were not detected in a group of HIV-positive HBV co-infected carriers of low infectivity (e-antigen negative).
Conclusion: These data suggest impairment of the size, multispecificity and function of the HBV-specific CD8 response in HIV-infected patients. This impairment of the CD8 response to HBV could be due to impaired CD4 help. The impact of highly active antiretroviral therapy on HBV-specific immune responses will be analysed prospectively.

O32

Immune responses and reconstitution in HIV-1 infected individuals: impact of antiretroviral therapy, cytokines and therapeutic vaccines

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Objective: To assess the reconstitution of cellular immune responses after novel therapeutic immunomodulation.
Methods: HIV-1 specific CD4 and CD8 T-cell responses have been quantified *in vitro* in HIV-positive persons following the administration of cytokines, therapeutic vaccines and following structured treatment interruption or drug therapy change.
Results: Administration of cytokines (±therapeutic vaccines), in highly active antiretroviral therapy (HAART)-treated patients improves both CD4+ and CD8+ HIV-1 specific T-cell responses even in late-stage disease. Virus-specific T-cell responses are also seen during autoimmunisation (occurring during transient viraemia or during structured treatment interruptions), and following therapy change from a protease inhibitor- to a non-nucleoside reverse transcriptase inhibitor-based HAART regimen. However, reconstitution of the HIV-1 specific immune response is mostly transient and reversal to the previous anergic state is rapid.
Conclusions: Viral reservoirs in the latently infected resting CD4+ T cells, on follicular dendritic cells or infected thymic epithelium might be involved in clonal suppression/anergy, which present major obstacles to the maintenance of HIV-1 specific responses and to the eventual eradication of HIV-1.

O33

Immunotherapy in the HAART era: T-cell responses and reconstitution in chronic HIV-1 infection

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Objective: We sought to enhance antiviral CD4 helper (HTL) and CD8 cytotoxic T lymphocyte (CTL) responses in a randomised, phase I immunotherapy study.

Methods: Forty patients are being treated for 16 weeks with highly active antiretroviral therapy (HAART) before randomisation to: (1) HAART alone; (2) HAART + Interleukin-2 (IL-2); (3) HAART + IL-2 + therapeutic vaccination (Remune); (4) HAART + Remune.

Results: We confirm that HAART is insufficient to allow regeneration of HIV-1 specific responses. Despite a mean baseline CD4 T-cell count of 286 cells/µl, Remune was able to induce transient HIV-1 specific T-cell responses. IL-2 substantially increased the CD4 T-cell counts, despite inducing transient viraemia. Three patients in this study received tetanus toxoid vaccination in addition to IL-2. Vaccination with this recall antigen was found to induce responses, the duration of which could be enhanced by IL-2. However, the addition of IL-2 to Remune appears to have limited *in vitro* benefits, suggesting that some HIV specific T-cell anergy may continue. Despite this, virological breakthrough, even without immunotherapy, induced transient CD4 HTL and CD8 CTL responses to HIV-1.

Conclusion: HIV-1 specific CD8 and CD4 T-cell responses are inducible in HAART-treated chronic HIV-1 infection by therapeutic vaccination and IL-2 therapy, or by interruption of HAART.

O34

HIV-1 Gag p24-specific T-helper cell responses associated with control of viraemia are not affected by differential production of interleukin-4 (IL-4)

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Objective: To measure HIV-1 gag p24-specific CD4 helper T-lymphocyte (HTL) responses, which have been shown to correlate inversely with viral load in HIV-1 infected individuals.

Methods: Peripheral blood mononuclear cells from chronically HIV-1 infected individuals with progressive HIV-1 infection (CP), clinical non-progressors (CNP) and discordant progressors (DP) were assessed for HTL proliferation and cytokine production.

Results: CNP were found to respond to a wide range of HIV-1 antigens, across clades with both type-1 and type-2 cytokine profiles. In contrast, DP only responded to clade-B gag p24 with a type-1 cytokine profile. Both patient categories responded broadly to gag p24 overlapping peptides. Detailed analysis of the anti-p24 responses revealed that interferon (IFN)γ and IL-2 were induced early in culture and persisted. IL-2 production always preceded proliferation. IL-10 was produced within 24 hours in culture, after which it declined and was undetectable both at the level of protein and message. Generally, no IL-4 was detected for the DP in contrast to CNP. However, one DP showed signs of clinical progression. At this time IL-4 became predominant in cultures for both HTL and CTL virus-specific responses. IL-4 production in response to recombinant p24 observed in CNP was due to the ability of cells to secrete IL-4 in response to a number of p24 peptides tested.

Conclusions: These findings suggest that strong type-1 virus-specific HTL and CTL responses, not affected by type 2 responses, are present in HIV-1 infected individuals whose viraemia is successfully controlled.

O35

Duration of HIV-1 specific proliferative and interferon (IFN)γ producing T-cell responses during treatment interruption

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Objective: To measure the duration of HIV-1 specific proliferative and IFNγ-producing T-cell responses during the interruption of highly active antiretroviral therapy (HAART).

Methods: Fifteen patients (mean CD4 T-cell count of 432 cells/µl and undetectable viral load) stopped HAART temporarily, due to adverse side effects caused by one or more components, adherence problems or drug toxicity. Response to a wide range of recall and HIV-1 antigens was measured by lymphocyte proliferation assay (LPA). The production of IFNγ in response to several HIV-1 antigens was assessed using spot enzyme-linked immunosorbent (ELISpot) assays.

Results: In eight patients, the viral load returned to pretreatment levels (mean 15,1753 HIV-1 RNA copies/ml) within 2 months of treatment interruption (TI). At baseline (on HAART) there were no proliferative or IFN-γ producing CD4 T-cell responses to HIV-1 antigens. One month after TI, an increase in the response to p24, gp160 and gp120 was detected by both IFN-γ ELISpot and LPA, and this coincided with viral rebound. These responses were reduced by month 2, when the viral load had returned to pre-HAART levels and the CD4 T-cell level had fallen dramatically.

Conclusion: Patients may opt for structured TI, in an attempt to allow re-stimulation of immune responses to HIV-1 in the absence of drug toxicity. Our data suggest that longer cessation of HAART results in loss of regained HIV-1 specific responses.

O36

Effect of interleukin-2 therapy on T-cell phenotypes in HIV-1 infected patients receiving no antiretroviral therapy

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Objective: To determine the effect of interleukin (IL)-2 therapy on T-cell phenotypes in HIV-1 infected patients on no antiretroviral therapy.

Methods: Antiretroviral therapy-naive HIV-1 infected patients with CD4 counts>350cells/µl were enrolled in a multicentre, randomised, open-label, controlled trial of IL-2 therapy (Vanguard), administered at 4.5 or 7.5 MU subcutaneously twice a day for 5 days at 8 weekly intervals for three cycles. Samples for viral load and T-cell subsets were obtained on days 1, 5 and 29 of each IL-2 cycle.

Results: Five patients received 12 cycles of IL-2 (four at 9 MU and one at 15 MU daily). One patient was lost to follow-up after one cycle and one patient did not receive his third cycle due to IL-2 associated pancreatitis complicating cycles 1 (15 MU) and 2 (9 MU). The median CD4 count rose from 407 to 558 cells/µl. The median viral load did not change acutely or at follow-up. For all IL-2 cycles, comparing day 1 to day 5, the percentages of CD4+HLADR+, CD8+HLADR+, CD8+38+, CD4+25+ and CD8+25+ T cells all increased, but all returned to baseline by day 29 following each cycle. A fall was seen in CD8+45RA+ cells on day 5, returning to baseline by day 29. The mean receptor expression rose on day 5 for CD38 receptors on CD4 and CD8 cells and CD25 on the CD4 subset, returning to baseline by 8 weeks.

Conclusions: CD4 and CD8 activation markers rose acutely and transiently following IL-2 therapy in HIV-1 infected patients not receiving highly active antiretroviral therapy, returning to baseline within 4 weeks. CD25 also rose transiently in response to IL-2 therapy in the absence of HAART. No adverse effect on viral load was seen in this subset or in the Vanguard study population.

P1

Meta-analyses: magic and run of the mill

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Objective: To describe practical issues involved in the pooling of data from a number of HIV cohorts to produce a data set for individual patient data meta-analysis using CASCADE data as an illustration.
Methods: CASCADE is a collaboration between the investigators of 19 cohorts in Europe and Australia of persons with known or well-estimated times of HIV seroconversion. Cohort investigators sent data electronically to the co-ordinating centre, where they were imported into Oracle tables, and log files of possible errors and inconsistencies generated. After these were checked and corrected with the relevant cohort investigators, all data were combined and a set of ASCII files of combined standardised data were generated for statistical analyses.
Results: Data were available from 19 cohorts in 10 European countries and Australia. In spite of agreed file specifications, data were received in a wide variety of formats: Access (two cohorts); Excel (two cohorts); SPSS (six cohorts); Stata (one cohort); and ASCII (seven cohorts). Data included; baseline characteristics and follow-up information on AIDS and death (8729 records); CD4 cell counts (88012 records); anti-retroviral therapy (12,568 records); HIV RNA measurements (40,265 records); and all AIDS-defining diseases (3250 records). Information on antiretroviral therapy was the most difficult to standardise, because data from clinics were often recorded longitudinally as regimens rather than as individual drugs. Missing stop dates for some drugs led to an artificial 'accumulation' of the number of drugs in a regimen over time. This was partially resolved by setting the stop date as the midpoint between the date known to have been on therapy and the date known to have stopped therapy and creating an approximation indicator flag.
Conclusions: A balance between imposing excessively complicated and more simple file specifications, which may lead to queries, is difficult. The time and effort required to combine individual studies into a high-quality data set for analysis should not be underestimated.

P2

Familial HIV: a uniquely Irish phenomenon?

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Background: We identified a large number of families in the Dublin cohort that include adult siblings who have been infected with HIV and a small number of families in which a second generation has been infected.
Methods: A retrospective analysis was performed of the HIV cohort attending the unit at St James Hospital Dublin between 1984 and 2000. We identified families with more than one HIV-infected member. Vertical transmission, infection with blood products and sexual transmission between normal partnerships within the family were excluded. Only first-degree relatives were included in the analysis.
Results: In 53 families, more than one family member was infected with HIV, comprising a total of 129 cases of HIV infection; 33 families had two infected members and 20 families had three or more infected members. In one family, five siblings were infected, all by injecting drug use (IDU). In four families, parents and children were infected (non-vertical transmission). A total of 119 of these cases were infected by IDU. We have noted a trend towards a similar morbidity and progression within these family groups.
Discussion: This study suggests that diffusion of HIV needs to be looked at not only in the geographical context but also in the family context and that there is a need for qualitative work to profile at-risk families and devise appropriate interventions.

P3

HIV tests in children attending a genitourinary medicine (GUM) clinic

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Aims: Review of characteristics of children having an HIV pre-test counselling session at the Coventry GUM clinic
Patients and methods: Retrospective review of Coventry GUM clinic attendances between the years 1990 and 2000 for HIV pre-test counselling by persons under the age of 16 years.
Results: We identified 95 children in the period from our records as having been counselled for an HIV test. Of this number, 81 (85.3%) went on to have an HIV test following counselling. Girls made up 75.8% of those receiving HIV pre-test counselling. The median age of those counselled was 14 years (range 4–15), with the highest number of tests carried out in the year 1996. Three of the children had been prostitutes. None of the children tested were HIV-positive. The most common complaint in the attendees was a rape /assault in 23 (24.2%), a discharge in 14 (14.7%) and a needlestick injury in 10 (10.5%). Boys were more likely to present with a needlestick injury (P=0.012). In this cohort, there was no sex difference between those claiming to have been raped/assaulted. Also, there was no statistically significant difference between those claiming rape/assault and those who did not have an HIV test after counselling.
Discussion: A large proportion of those counselled for HIV testing in this age group went on to have an HIV test. Rape/assault is the commonest recorded complaint in children receiving an HIV pre-test counselling session. There is a need for more sex education and risk-reduction education programmes targeted at adolescents.

P4

Sexually transmitted diseases and HIV/AIDS concerns of 15-year-old students in Middlesbrough

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Objectives: To find out what 15-year-old students in Middlesbrough schools want to know about sexual matters.
Design: Written student questions and discussions.
Settings: Eight secondary schools in Middlesbrough, England
Methods: As part of Personal and Social Education (PSE), some secondary schools in Middlesbrough have invited Genito-Urinary Medicine (GUM) staff members to these classes, which contained students of both sexes. Following self introduction, students are given sheets of paper to write down questions anonymously. This is followed by a short talk on confidentiality and GUM clinic protocol. As many questions as possible in the allotted time are answered and discussed. The students also take part in role play.
Results: Accumulated questions can be divided into three main groups: (1) STD/HIV/AIDS (40%); (2) general (35%); (3) pregnancy (25%).

- HIV/AIDS: Can you get AIDS of the bumhole? Can you get HIV from taking drugs? If a girl has her period, can a boy get AIDS?
- Pregnancy: Can a boy get pregnant if two boys have sex? How does one have an abortion? Can you get pregnant if you have sex in water?
- General: What is masturbation? Does it hurt to swallow sperm?

Discussion: These questions serve as framework for discussions and role play for the students. Staff from the GUM/HIV clinic are able to address what the students want rather than follow a set plan. It is hoped that these sessions will educate and inform students and teachers alike. Since we started, more schools have requested our input into their PSE sessions.

P5

The HIV epidemic: is this a turning point?

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Introduction: Worldwide it is estimated that 5.3 million people were infected with HIV in the year 2000, and 30,000 of these infections occurred in Western Europe. It is believed that HIV prevention efforts in the developed world are stalled. This clinic has witnessed a rapid rise in new HIV attendees in the period from January to December 2000. In this study, we sought to examine the characteristics of new HIV diagnoses at this clinic.
Methods: A detailed examination of the new cases of HIV infection at this clinic in 1999 and 2000 was performed. Comparisons were made with previous years using data available from the total HIV cohort.
Results: A total of 1069 people are currently registered for HIV care at this clinic. Of these, 112 first registered in 1999 and there was a 70% increase to 191 in the year 2000. All risk groups have been affected by this increase. The total cohort for 2000 comprises 45% injecting drug users (IDUs), 28% men who have sex with men (MSM), 22% heterosexuals and 3.5% others. In 1989, the total cohort comprised 80% IDUs, 16% MSM, 3.5% heterosexuals and 0.5% others. The new attendees for 1999 and 2000 comprise 33% IVDUs, 29% MSM, 36% heterosexuals and 2% others. There is a shift in the sex distribution of the new attendees for 2000, comprising 117 (61%) males and 74 (39%) females. The current total cohort is 747 (70%) males and 322 (30%) females. The total cohort in 1989 was 266 (73%) males and 99 (26%) females. The heterosexual group has witnessed the most dramatic rise in females (23 in 1999 to 52 in 2000)
Discussion: This clinic has seen a rapid rise in the numbers of new HIV cases in the 12-month period from January to December 2000. Many explanations exist that will be explored in detail. A regrouping of efforts aimed at minimising further increases is mandatory to curb this trend.

P6

HIV and non-HIV associated mortality in the Tayside HIV cohort, 1990–1998

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Objective: To ascertain: the causes of death; the stage of HIV infection at death; and the interval between diagnosis and death, in the Tayside HIV cohort, 1990-1998.
Methods: All known HIV-positive deaths in Tayside, 1990–1998, were included. Data were ascertained by retrospectively analysing case records, death summaries, post-mortem reports and death certificates.
Results: Of 184 patients, the case notes of 159 (86%) were obtainable. Of these, 79% had progressed to AIDS. Of the HIV-related deaths (66%), bacterial pneumonia was present in 47%, AIDS dementia in 38%, *Mycobacterium avium intracellulare* in 25%, lymphoma in 13% and *Pneumocystis carinii* pneumonia in 11%. Of the non-HIV deaths, overdose (51%), alcohol or hepatitis C liver disease (31%) and accident/suicide (10%) were identified as significant factors. Death by transmission category [68% intravenous drug use (IVDU)] was representative of the Tayside cohort as a whole. Death unrelated to HIV, however, was significantly higher in the IVDU group (40% versus 13%, P=0.001). A high proportion (89.5%) of the non-AIDS group died of non-HIV causes. Those exposed to antiretroviral therapy were more likely to die of non-HIV causes (65.5%, P=0.003). The median time from diagnosis to death was significantly shorter in hetero- and homosexuals than in IVDUs (P=0.01).
Conclusion: IVDUs have a higher risk of potentially preventable, non-HIV related death. Hetero- and homosexuals in Tayside, however, appear to present later in the course of their illness.

P7

The impact of non-EU nationals on a genitourinary medicine and infectious disease clinic

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Background: The number of non-EU nationals entering Ireland has increased significantly in recent years from 234 in 1994 to 8000 to the end of August 2000. These figures are reflected in the numbers attending the sexually transmitted infection (STI) services: four in 1994 to 352 in 2000 (Africans 65%, Eastern Europeans 25%, others 10%).
Methods: A retrospective review was undertaken of the non-national cohort attending the GUIDE clinic from 1994 to 2000 to identify demographic and epidemiological factors influencing attendance, diagnosis, subsequent management and follow-up.
Results: Non-EU nationals now constitute 11% of the active cohort of regularly attending HIV patients. To date, 84% are African and 16% are others (Eastern European, Middle East, Caribbean). In 1994, these patients constituted 7% of new diagnoses, with a steady increase in numbers annually to 21% of new diagnoses in 2000. Of this cohort, 68% are female, a figure reflected in those of the pregnancy cohort (49% of the total), and 75% of those diagnosed since the introduction of routine antenatal screening have been non-nationals (only diagnosed opportunistically).
Discussion: The growing needs of an immigrant population are continually highlighted as we experience their differing requirements from medical, cultural and socioeconomic view points. The impact of differing demographics and spectrum of disease presentation on a standardised, established service must be acknowledged if we are to identify the areas where resources need to be improved and intensified in order to ensure the delivery of an appropriate service.

P8

Gender differences in rate of hospital admission and disease progression in the era of HAART

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Objective: To establish whether there is a gender difference in clinical response to highly active antiretroviral therapy (HAART).
Methods: In a clinic cohort of HIV-positive individuals, outcomes assessed were: hospital admission and disease progression (new AIDS diagnosis or death) after starting HAART. Hazard ratios (HR), derived using Cox regression methods, compared female with male rates, adjusting for other factors independently associated with outcome.
Results: A total of 509 males and 151 females were followed over a median of 13 months after starting HAART; 81% of males were Caucasian and 75% homosexual; 58% of females were black African and 85% in the heterosexual risk category. The baseline CD4 count was greater in males than females (192 vs 151x10^6 cells/µl, P=0.01) but viral loads were similar (P=0.13); 56% of males and females were treatment-naive; 17% of males and females were admitted during follow-up, 10% of male and 12% of female admissions being due to an AIDS-defining illness. Main differences in reasons for admission were chest-related (8% of males, 15% of females), GI-related (2% of males, 11% of females) and psychiatric (8% of males, no females). HR for admission was 0.73 [95% confidence interval (CI) 0.43-1.24]; 11% of female admissions were related to gynaecological or obstetric cause. Excluding these from the analysis gave HR=0.64 (95% CI 0.37–1.11); 11% of the males and 7% of the females progressed; 88% of progressions were due to a new AIDS diagnosis (46 in males, 11 in females), and eight males died. HR for progression was 0.70 (95% CI 0.34–1.38).
Conclusions: Our results suggest a possible benefit in females over males in clinical response to HAART but provide no concrete evidence as confidence intervals are wide. Further analysis with longer follow-up or with greater numbers would allow a more powerful analysis.

P9

Impact of deprivation in the Edinburgh HIV cohort

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Objective: Is deprivation as assessed via post-code associated with clinical outcome?
Method: A retrospective analysis of prospectively collected outcome data in the Edinburgh HIV cohort.
Results: The Edinburgh HIV cohort was more deprived than the general Scottish or Lothian population (P<0.001). The more deprived categories contained a greater proportion of drug users (P<0.02), and the less deprived a greater proportion of homosexuals (P<0.001). Less deprived groups had a greater probability of AIDS development (P<0.05) and death (P=0.030). Five-year survival rates from AIDS diagnosis were greater in the less deprived (0.2947 vs. O.1430) (P=0.014) with deprivation linked to a higher bed-day usage after AIDS diagnosis (P<0.001). Type of AIDS-defining illness or use of antiretroviral therapy did not vary significantly across the deprivation spectrum.
Conclusions: In Edinburgh, deprivation is associated (but not necessarily causally) with mode of acquisition of HIV and survival from AIDS but not with access to antiviral therapy or overall survival from the time of infection.

P10

Improved detection of seroconversion by targeted surveillance

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Introduction: Identification of seroconversion is essential for the effective management of early HIV disease, partner notification and for monitoring primary resistance patterns and local epidemiology. In routine clinical practice, seroconversion may be overlooked.
Objective: To determine whether increased vigilance by the multidisciplinary team and the use of newer diagnostic techniques have increased the detection of seroconversion.
Methods: Patients were eligible if they had had a negative HIV test within 18 months of the positive test or had been clinically diagnosed with acute HIV infection confirmed by an evolving serological or Western blot pattern.
Results: From 1994 to 2000, we identified 50 seroconverters (all men, 98% men who have sex with men, median age 35 years); 50% had symptoms suggesting acute HIV infection. There was a significant increase in the number of seroconverters identified in 2000 (P=0.004).

	94	95	96	97	98	99	00
No. newly diagnosed Brighton	52	38	66	57	40	45	68
No. seroconverters	1	4	7	7	8	4	18
% of new patients	2	10	11	12	20	9	27
Negative (–ve) test in Brighton	1	2	7	5	3	4	3
–ve test confirmed elsewhere		1			2		3
Serial IgM/evolving serology*		1		2	2		8
Detuned assay*							2
Western blot					1		2

*Further detuned assay results will be presented. Ig, immunoglobulin.
Conclusion: By increasing awareness within the clinic and instituting active case-finding with supplementary laboratory investigations we substantially increased the pick-up rate in 2000. It is likely that the detuned assay will play an increasingly important role in case confirmation and monitoring of seroincidence.

P11

Teenagers and HIV: what's the problem?

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Introduction: In the UK, 1043 teenagers have been diagnosed HIV-1 antibody positive. There are few data on teenagers infected through sex or intravenous drug use (IVDU).
Objectives: To describe the demographics, presentation and follow-up of such teenagers in six HIV centres in southeast England.
Methods: Retrospective case-note review (Jan 1985 to Dec 2000).
Results: Seventy-nine patients were identified, including 36 newly diagnosed, 25 transferred from other centres and 18 re-accessing care after a median of 4 years. The median age at diagnosis was 18 years (range 16–19); 63% were white (39 males, 11 females); 24% were black African (four males, 16 females). Risk factors recorded were homosexual sex (57%), heterosexual sex (38%), IVDU (11%). Thirty-seven of the 79 acquired HIV in the UK, the majority diagnosed at routine Genitourinary Medicine (GUM) assessment. Of those newly diagnosed, the median CD4 count at presentation was 490 cells/µl (n=32), median viral load 4.14 $\log_{10}$ HIV-1 RNA copies/ml (n=21), and 86% were Centers for Disease Control and Prevention stage A. Almost half (17/36; 47%) were lost to follow-up, 11 within 4 months of diagnosis. Nine of 36 had an STI at the time of diagnosis, with 41% (12/29) of developing a new STI during follow-up. Eleven of the 79 had a mental health history at diagnosis, increasing to 35/49 at follow-up, with 37% with suicidal ideation.
Conclusions: Despite most teenagers being diagnosed in GUM clinics and 25% having a co-existing STI, further STIs were common. Psychiatric morbidity is common and the loss to follow-up high. These data suggest that current approaches to the care of newly diagnosed teenagers are inadequate and a more focused approach is required.

P12

Ethnic differences in stage of presentation of adults newly diagnosed with HIV-1 infection in south London

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Objectives: South London has the UK's highest rate of new HIV infections, and approximately 40% of cases have previously been reported in persons from sub-Saharan Africa. Our main objective was to examine ethnic differences in the clinical and laboratory stage of disease at HIV diagnosis.
Methods: Adult patients attending King's College Hospital with a first positive HIV-1 test result between 1 Jan 1998 and 31 Oct 2000, with data on clinical stage, CD4 count and viral load (VL) were identified. The patients were categorised according to ethnic group, White (Wh), black African (BA), black Caribbean (BC) and other, and comparisons were made between groups using χ^2-tests.
Results: Of 265 new HIV diagnoses, 29.2% were Wh, 56.8% BA and 10.2% BC; 53.3% of patients were born in sub-Saharan Africa and 29.0% in the UK. The distribution of HIV risk group differed significantly according to sex and ethnic group; among Wh men, 76.2% were men who had sex with other men (MSM), 1.6% intravenous drug users (IDUs) and 17.5% heterosexual (Hs), compared with 5.9%, 0% and 92.2% among BA men. BA men were more likely than Wh men to test because of symptoms (44.2% vs. 23.8%, P=0.065), to have a lower median CD4 cell count at diagnosis (204 vs. 356 cells $\times 10^6$/l, P=0.001) and to present with an AIDS diagnosis (25.0% vs. 11.1%, P=0.128). We found no significant differences across ethnic group in age, VL or year of diagnosis.
Conclusions: Despite the widespread availability of HIV services, BA patients in south London continue to present with more advanced HIV disease compared with Wh patients, and to present for HIV testing at the onset of suggestive symptoms. There is an urgent need to address the continuing barriers to the uptake of HIV testing in the African communities.

P13

Biochemical abnormalities associated with hyperlactataemia in HIV-1 positive patients

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Objective: To determine whether hyperlactataemia in HIV-positive patients is associated with other biochemical abnormalities in blood.
Methods: A cross-sectional study of all HIV-1 patients attending the Kobler Clinic for follow-up was undertaken. Venous blood was drawn randomly for lactate measurements as well as routine clinic blood. Treatment histories and current therapy were obtained from the database. Only patients with a lactate measurement after at least 4 months of the current antiretroviral regimen were analysed. Univariate analysis with Cox's proportional hazards model was used to determine the likelihood of detecting lactate >2.5 mmol/l in the cohort.
Results: Of the 1152 patients included, 9% had raised lactate. No statistically significant association was found between age, sex, duration of HIV infection and plasma lactate concentration.

Blood results	Relative hazard	95% Confidence interval
Low chloride <104	1.6	1.0–2.6
Low bicarbonate <29	1.6	1.0–2.5
Low phosphate <1.0	1.5	0.8–2.7
High glucose ≥5.2	1.79	1.16–2.70
ALT ≥26	1.69	1.10–2.56
Cholesterol ≥5.3	1.54	1.00–2.27

Conclusions: Although it has been suggested that routine measurement of lactate may be unhelpful, hyperlactataemia in HIV-positive patients on antiretroviral medication was significantly associated with a number of other biochemical abnormalities, including high alanine aminotransferase (ALT), glucose and cholesterol levels. Hyperlactataemia was also significantly associated with low chloride, bicarbonate and phosphate levels. No association was found between hyperlactataemia and amylase levels.

P14

Effects of efavirenz on lipid metabolism in antiretroviral-naive and -experienced HIV-positive patients with morphologic and metabolic alterations

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Objectives: To evaluate levels of triglycerides (Tg) and cholesterol (Chol) in antiretroviral-naive patients starting efavirenz (EFV)-containing highly active antiretroviral therapy (HAART) and in treated patients with morphological and metabolic alterations (MMA) switching from a protease inhibitor (PI)- to EFV-containing HAART.
Methods: Evaluation of Tg and Chol plasma levels at fixed time-points (baseline, 3, 6, and 9 months) in EFV-treated patients.
Results: We studied 32 antiretroviral-naive patients (28 males) who began EFV-based HAART. Mean plasma Tg levels showed a slight but not significant increase from baseline to month 9 (baseline 140±95 mg/dl; month 3 168±80; month 6 171±89; month 9 155±108). Chol values remained stable from baseline to month 9 (baseline 170±42 mg/dl; month 3 183±49; month 6 192±39; month 9 175±85). We evaluated 45 PI-experienced patients (30 males) who switched to EFV because of MMA (eight type Ib; 23 type III; 14 type IV). In antiretroviral-experienced patients, Tg levels fell significantly from baseline to month 9 (baseline 357±264 mg/dl; month 3 275±134; month 6 254±141; month 9 258±123). The Chol level at month 9 did not differ significantly from baseline (baseline 231±63 mg/dl; month 9 236±52). Type IV MMA resolved in four of 14 patients after switching.
Conclusions: Treatment with EFV was not associated with metabolic alterations (type IV) during a 9-month follow-up in antiretroviral-naive patients. In PI-experienced patients switched to EFV because of MMA, a significant reduction in Tg levels was observed with resolution of type IV MMA in some cases.

P15

Psychological assessment of patients referred to a multidisciplinary lipodystrophy/metabolic clinic

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Objective: To assess the incidence of psychological problems in patients with fat redistribution and/or metabolic disorders associated with highly active antiretroviral therapy (HAART) and close follow-up by a multidisciplinary team.
Methods: DASS scores for depression, anxiety and stress were calculated in 60 patients at 3-monthly intervals. Concerns about body image and general health were also graded. Patients with abnormal scores in any of these categories were followed much more closely. Patients were seen by a psychologist, specialist nurse, dietician and clinician, providing opportunity for continuing education and discussion of presenting issues.
Results: We found that 53% of patients had abnormal scores for depression: 47% severe, 25% mild and 28% moderate, while 37% had abnormal levels for anxiety and 45% abnormal levels of stress; 53% of the patients had body image and 30% had general health concerns. Over subsequent visits, 65% with depression showed an improvement. Similar trends were seen in patients with anxiety and stress, and 54% with body image and 90% with general health concerns improved. In a pilot survey of 100 patients on HAART not attending the clinic and 50 not on treatment showed a 50 and 23% incidence of depression, respectively.
Conclusions: A high degree of psychological symptoms and concerns over body image and general health are present in these patients. Close follow-up by a multidisciplinary team is associated with improvements in all these areas.

P16

Short-term increases in ABT-378/r dose does not affect postprandial lipaemia in HIV-1 seropositive patients

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Objective: To determine whether increasing the dose of ABT-378/ritonavir (ABT-378/r) would exacerbate postprandial lipaemia in HIV-1seropositive patients previously treated with protease inhibitors.
Methods: A prospective study of postprandial lipid handling in eight HIV-1 seropositive patients (seven males) treated with ABT-378/r was undertaken. Each subject was studied after a 10 hour overnight fast and received a test meal containing 45 g fat and had blood drawn before the meal and after 2 and 4 hours. The dose of ABT-378/r was then increased from 400/100 mg to 533/133 mg twice a day and the study was repeated 1 week later.
Results. The mean age, CD4 count and viral load were 45±4 years, 179±60 cells/μl and 5448±5271 HIV-1 RNA copies/ml, respectively.

	Triglyceride concentration (mmol/l)		
	0 hour	2 hour	4 hour
Study 1	4.0±0.6	5.3±0.9*	5.9±0.9*
Study 2	4.2±0.7	4.6±0.5*	5.8±0.5*

*P<0.001 significantly different from 0 hour (analysis of variance with repeated measures). Mean±SEM.
Conclusions: Although the pattern of the postprandial rise in plasma triglyceride concentrations after 2-h and 4-h was the same after increasing the dose of ABT-378/r, there was no significant difference between the two studies. Therefore, this evidence suggests that increasing the dose of ABT-378/r does not alter postprandial lipaemia in the short term.

P17

Interferon-α therapy increases plasma triglyceride concentrations in HIV-1 positive patients

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Objective: To determine whether exogenous interferon-α therapy altered plasma triglyceride concentrations (Tg) in HIV-positive patients.
Methods: A retrospective study of all HIV-1 positive patients treated with subcutaneous interferon-α therapy at the Kobler Centre in whom serial plasma Tg concentrations were available. Each patient received interferon-α at a dose of at least 3 mU three times per week for a minimum of 3 weeks. Ten patients (nine males) were studied, eight of whom were hepatitis C co-infected. The mean age was 37.6 years and the mean CD4 count was 338.5 cells/μl; 60% of the patients had a viral load less than 50 HIV-1 RNA copies/ml.
Results:

	Pretherapy	1 month	2 month
Tg (mmol/l)	3.03±1.09	3.80±1.71	6.20±4.81*
Chol (mmol/l)	5.90±1.91	5.81±2.01	6.80±2.00

*P<0.001 significantly different from pretherapy (analysis of variance with repeated measures). Mean±SD. Chol, cholesterol.
Conclusions: Plasma Tg concentrations are increased in HIV-1 seropositive patients treated with exogenous interferon-α therapy. This evidence supports the hypothesis that increased cytokine concentrations may play a role in the development of dyslipidaemia and lipodystrophy in HIV-infected patients treated with highly active antiretroviral therapy.

P18

Hepatotoxicity in non-nucleoside reverse transcriptase inhibitor-containing regimens

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Objective: To investigate the incidence of biochemical liver abnormalities in patients on non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy.
Methods: In a retrospective analysis of a prospective database, 216 HIV-1 infected patients who had received NNRTI therapy were identified. Alanine aminotransferase (ALT) results from each clinic visit were collected and banded (band 1: standard reference range; band 2: 1.26–2.5× upper level of normal (ULN); band 3: 2.6–5.0× ULN; to band 5: >10× ULN. The initial and maximum band for each patient's therapy combination was recorded. Patients who received less than 4 weeks of therapy were excluded from analysis. The incidence of grade 3/4 toxicity reactions were examined for patients taking nevirapine (NVP) and efavirenz (EFV). Results were compared using the χ^2-test; statistical significance was defined as P<0.05.
Results: Of the 216 patients, 41% were anti-hepatitis C (HCV)-positive; 58% in the EFV group and 50% in NVP group had normal ALT results at the start and during therapy; 8% (DMP) and 11% (NVP) had a rise in ALT level to grade 3/4 toxicity reactions (band 4/5). Of patients who started therapy with abnormal ALT results (25% and 28%, respectively), 13% in the EFV group and 27% in the NVP group deteriorated with therapy. By χ^2 analysis, there was no statistical difference in the incidence of ALT deterioration between patients taking EFV or NVP.
Conclusion: In this retrospective analysis of a cohort of patients with a high incidence of co-infection with HCV, there was no statistical difference between NVP- and EFV-containing regimens and the incidence of abnormal ALT results.

P19

The natural history of lipodystrophy in HIV

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Background: Attention has focused on the mechanisms of lipodystrophy (LPD) in HIV. The natural history, particularly fat redistribution (FR), is relatively neglected, despite being the basis of many of the patients' questions and anxieties.
Method: All visits (n=257) of all patients (n=89) who attended the HIV LPD clinic from Dec 1998 to Jan 2000 were included in the study. Histories, anthropometry, dual-energy X-ray absorptiometry (DEXA) scans, serum lipid and metabolic profiles were taken every 3–6 months.
Results: Of the 89 patients, 91% were male, 9% female, 80% white and 12% black African. The median time from starting highly active antiretroviral therapy (HAART) to noticing body changes among the 73 subjects with FR was 11.8 months, and for each region: face 12.8 months (n=44), arms and legs 11.8 months (n=42), buttocks 16.7 months (n=25), abdomen 15.7 months (n=47), neck 14.7 months (n=8), breasts 10.8 months (n=9). FR stabilised in all regions for at least 6 months in 38 (55%), although most did not change HAART. Over 80% reported stabilisation in at least one region; from first noticing, FR was stable for a median of: face 8.9 months (n=33), arms and legs 9.8 months (n=35), buttocks 9.8 months (n=13), abdomen 9.3 months (n=34). All patients with features of LPD had taken protease inhibitors or stavudine.
Conclusions: A change in HAART is not always required to avoid progressive FR. With adequate counselling and monitoring at regular intervals, patients can make a more informed choice of whether to switch therapy or wait.

P20

A comparative study of dietary advice with and without pravastatin for the treatment of antiretroviral therapy-associated hyperlipidaemia

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Objective: To evaluate the efficacy of pravastatin in antiretroviral-related hyperlipidaemia.
Methods: Thirty-one HIV-positive men on protease inhibitor-based antiretroviral therapy were randomised to receive dietary advice (DA) or pravastatin (PS) plus dietary advice in an open-label trial [viral load(VL)<500 HIV-1 RNA copies/ml and cholesterol >6.5 mmol/l] Pravastatin was given at 20 mg once a day for the first 2 weeks and at 40 mg once a day thereafter. Sampling was performed fasting at day 0 and weeks 12 and 24.
Results: Baseline demographics were well matched, with no significant differences in age, CD4 count, weight, body mass index and lipids. Four patients in the DA arm and two in the PS arm withdrew before week 24. No patient discontinued due to adverse events. All patients have remained with VL <500 copies/ml. Total cholesterol at week 24 fell significantly in the pravastatin (1.2 mmol/l, 17.3%) but not DA (0.3 mmol/l, 4%) arm. The fall in total cholesterol in each group was accounted for entirely by a reduction in low-density lipoprotein (LDL) as high-density lipoprotein (HDL) rose non-significantly by 0.6 mmol/l in both groups. The change in LDL at week 24 was 1.24 mmol/l (19%) with pravastatin and 5.5% with dietary advice alone. Weight, fasting glucose or triglycerides did not significantly change in either group.
Conclusions: Both dietary advice and pravastatin reduce total and increase HDL cholesterol. Pravastatin + DA has significantly greater effects on total and LDL cholesterol than DA alone. No adverse events occurred. Virological control was maintained despite the addition of pravastatin.

P21

Reduction in lactic acidaemia with dichloroacetate in HIV-1 infected patients

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Background: Dichloroacetate (DCA) has been used successfully to treat lactic acidosis (LA) in severe burns and sepsis. We therefore introduced DCA into our treatment protocol for antiretroviral therapy (ART)-associated LA and have reviewed its use to date.
Objective: To assess the effectiveness of DCA in reducing lactic acidaemia in HIV-1 infected patients.
Method: A review of all patients with ART-associated LA treated with DCA at the Chelsea and Westminster Hospital.
Results: Four patients with symptomatic LA received oral DCA therapy in two 50 mg/kg doses 2 hours apart and ART was stopped.

	Subject 1	Subject 2	Subject 3	Subject 4
CD4 (cells/µl)	1092	208	762	516
VL (copies/ml)	<50	<50	<50	<50
ART	d4T/ddI/RTV/ IDV	ZDV/3TC/ NVP	d4T/ddI/RTV/ IDV	d4T/3TC/ EFV
Cumulative time on NRTIs (months)	40	36	35	22.5
Lactate (mmol/l)	5.9	8.7	7.5	10.6
Bicarbonate (mmol/l)	25	17	25	20
No. of DCA treatments	2	5	3	3

d4T, stavudine; ddI, didanosine; EFV, efavirenz; IDV, indinavir; NVP, nevirapine; NRTIs, nucleoside reverse transcriptase inhibitors; RTV, ritonavir; 3TC, lamivudine; VL, viral load; ZDV, zidovudine. The mean lactate concentration fell significantly from 7.3±2.4 to 3.5±1.8 mmol/l 24 hours after each DCA treatment (Student's *t*-test, $P<0.001$). The mean lactate fall was 51.5±20.0%. However, the lactate later rose in all cases, requiring at least one further DCA treatment. Three patients were discharged with normal lactate and complete resolution of symptoms. Two developed acute pancreatitis and one died.

P22

High incidence of sexual dysfunction in patients referred to a multidisciplinary lipodystrophy/metabolic clinic

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Objective: To assess the incidence of sexual dysfunction in 60 patients presenting with fat redistribution and/or metabolic problems referred to a specialist clinic and correlate this with testosterone and oestradiol levels.
Method: In 60 patients, sexual history was taken as part of a general assessment by a multidisciplinary team. Total testosterone and oestradiol levels were also measured.
Results: Thirty-eight of 60 patients complained of sexual difficulties (63%). Ten patients complained of erectile dysfunction, four of loss of libido and nine had combined erectile dysfunction and loss of libido. Five males were not sexually active and three complained of premature ejaculation and orgasmic dysfunction. Half the women complained of sexual problems, including loss of libido, orgasmic dysfunction, vaginismus and dyspareunia. Only three males had low testosterone levels but 17 had elevated oestradiol levels; 13 of these patients had associated sexual dysfunction and four had no complaints. In patients with sexual dysfunction, 17/38 were depressed and 15/32 depressed patients had sexual dysfunction. A pilot study to assess sexual dysfunction in similar patients on highly active antiretroviral therapy and not on treatment is being carried out to compare the incidence of problems in a general clinic.
Conclusions: There is a high incidence of sexual dysfunction in both males and females referred to this clinic. A moderate number of males have associated high oestradiol levels, but not abnormal testosterone levels.

P23

The safety, tolerability and efficacy of switching from nevirapine to efavirenz

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Aim: To assess, retrospectively, the safety, tolerability and viral suppression efficacy of switching from nevirapine (NVP) to efavirenz (EFV) in patients with an undetectable HIV viral load (VL).
Method: Retrospective case-note analysis.
Results: Twenty patients who switched from NVP to EFV were identified. The reason for the switch was hepatitis in eight patients (mean duration 4.8 months, CD4 327 cells/µl), skin rash in five patients mean duration 1 month, CD4 207 cells/µl) and either NVP intolerance, or patient/physician choice in six patients (mean duration 5.2 months, CD4 405 cells/µl). Eleven of these 20 patients had at least one previous non-NVP based antiretroviral regimen. The 'backbone' nucleoside reverse transcriptase inhibitor therapy was changed in eight patients. Three patients developed virological failure at 8, 15 and 24 months, respectively, on the EFV-based regimen. Three further patients stopped or changed the EFV regimen due to intolerance at 2, 3, and 4 months. Two patients had non-EFV related adverse reactions (didanosine-related pancreatitis in one and progressive clinical lipodystropy in one). No patients developed hepatitis or biochemical hyperlipidaemia on the EFV-based regimen.
Conclusions: In patients with an undetectable viral load, switching from NVP to EFV is safe, generally well tolerated and maintains viral suppression efficacy.

P24

Efavirenz versus protease inhibitors in treatment-naive patients

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Objectives: To compare the antiviral efficacy and safety of efavirenz (EFV) and protease inhibitors [PI; nelfinavir (NFV) or indinavir (IDV)] with two nucleoside reverse transcriptase inhibitors (NRTIs) in antiretroviral-naive HIV-positive patients.
Methods: Open, retrospective study on patients who started highly active antiretroviral therapy (HAART) between November 1999 and November 2000 and who continued therapy for at least 12 weeks.
Results: Of 46 patients included, 19 patients started HAART with EFV and 27 patients with PI (18 NFV and 9 IDV). Preliminary results of OD analysis are presented below.

EFV group	Baseline	Week 12	Week 24	Week 36	Week 48
Number of patients	19	19	15	9	3
Median viral load	94,931				
<50 copies/ml		57%	93%	89%	100%
Median CD4 cells/µl	297	414	418	476	424
PI group					
Number of patients	27	27	18	15	4
Median viral load	190,892				
<50 copies/ml	44%	94%	93%	75%	
Median CD4 cells/µl	225	426	440	453	556

Two patients in the EFV group and two in the PI group were lost to follow-up. Overall tolerability was good: three patients presented mild sleep disorders or dizziness under EFV, and spontaneously resolved; in PI group, two patients switched from IDV to NFV due to a rapid increase of bilirubin and one from IDV to EFV due to poor adherence.
Conclusions: These preliminary results suggest that a first-line PI-sparing regimen using NRTIs and EFV is highly effective, safe and appropriate for treatment-naive patients and seems to be superior in terms of virological efficacy with a quicker viral load fall than PIs.

P25

Is it safe to switch from a non-failing antiretroviral regimen to lopinavir?

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Aim: To assess the safety of changing to ABT-378/ritonavir (ABT-378/r) in patients with a negative viral load.
Methods: Ongoing review of patients receiving ABT378/r as part of the Abbott-sponsored compassionate-release programme.
Results: Sixteen patients with a negative viral load were switched to ABT-378/r, 13 previously on a dual protease inhibitor (PI) combination. Reasons for change included PI toxicity, stavudine toxicity and patient request (data to be included). Fourteen patients maintained a negative viral load, and the mean time on ABT-378/r was 4 months (range 1–10). One patient stopped taking antiretroviral therapy with a predictable increase in the viral load, which returned to <50 HIV-1 RNA copies/ml when ABT-378/r was restarted. One patient failed therapy despite adherence. The mean change in cholesterol 3 months after switching to ABT-378 was +10.6% (range –22.2 to +66.7). The mean change in triglycerides was +29.53% (range –42.2 to +225.0)
Conclusion: In this study, 93.7% of patients who switched to ABT-378 for reasons other than virological failure maintained a negative viral load.

P26

Changing use and cost of HIV service provision in NPMS-HHC sites, 1996-1999

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Objective: To describe the use and cost of service provision by stage of HIV infection in English NPMS-HHC clinics.
Method: Data were collected from three London and four non-London sites. Weighted mean per patient-year (wPPY) indices of service use and cost were calculated by stage of HIV infection (Communicable Diseases Surveillance Centre classification) per semester from 1 January 1996 to 31 December 1999.
Results: 9931 patients were seen (84% men and 14% women). Use and cost of services was greatest for AIDS patients. Mean inpatient days for AIDS patients decreased over this period from 11.8 [95% confidence interval (CI) 10.3–13.3] to 5.8 (95% CI 5.1–6.4) wPPY, outpatient visits from 10.7 (95% CI 9.0–12.5) to 8.9 (95% CI 7.8–10.0) and day-ward visits from 3.3 (95% CI 2.3–4.2) to 1.2–2.0 wPPY. Estimated costs of treating AIDS patients with two nucleoside reverse transcriptase inhibitors (NRTIs) + one non-nucleoside reverse transcriptase inhibitor decreased from £25,170 (£19,981–£32,285) to £22,303 (£17,114–£29,418) wPPY, from £26,518 (£21,329–£33,633) to £23,651 (£17,114–£27,391) wPPY for two NRTIs + one protease inhibitor (PI) and from £30,669 (£25,480–£37,784) to £27,802 (£22,613–£34,917) wPPY for two NRTIs + two PIs.
Conclusions: The mean use of services decreased, especially for people with AIDS, less so for people with asymptomatic HIV infection or symptomatic non-AIDS. Estimated costs for treatment with various antiretroviral drugs also decreased over this period.

P27

An audit of first-line antiretroviral prescribing

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Objective: To assess first-line treatment for HIV using highly active antiretroviral therapy (HAART) at the outpatient clinic of a London teaching hospital, and compare it with BHIVA national guidelines.
Methods: Clinical case notes of 172 treatment-naive patients registered from April 1999 were reviewed. Data collected included patient demographic information, Centers for Disease Control and Prevention HIV status at first visit, initial viral load and CD4 counts, treatment eligibility, treatment uptake, regimen prescribed and viral load at 24 weeks. An additional 100 notes are to be reviewed.
Results: Of the 172 patients, 102 were eligible for first-line treatment according to BHIVA guidelines; 83% of these were offered treatment and 21% of patients offered treatment decided not to take it up. There was no significant difference by ethnic group or sex in the uptake of treatment. Reasons for declining treatment included patient feeling unready or reluctant to start and fear of HAART. Of those patients who continued therapy to week 24 (n=37), 78% had a viral load <50 HIV-1 RNA copies/ml and a further 11% had experienced a 1 $\log_{10}$ drop in viral load. Of the 69 patients on first-line HAART, 39% started with one non-nucleoside reverse transcriptase inhibitor and two nucleoside reverse transcriptase inhibitors.
Conclusions: Results from this on-going study indicate that prescribing of first-line HAART in the study clinic meets BHIVA guidelines. The BHIVA guideline recommendations offer a broad scope for variations in prescribing practice. Further data on variations in practice and a discussion of the applications and limitations of the BHIVA guidelines will be presented.

P28

Sequencing to nucleoside reverse transcriptase inhibitor/non-nucleoside reverse transcriptase inhibitor combinations following virological failure of protease inhibitor-containing antiretroviral therapy

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Objective: To describe the outcomes at 12 months of persons changing to nucleoside reverse transcriptase inhibitor (NRTI)/non-nucleoside reverse transcriptase inhibitor (NNRTI) combinations following virological failure of protease inhibitor (PI)-containing antiretroviral combinations.
Methods: Patients on a PI and at least two NRTIs for >1 month and with evidence of virological failure (two consecutive measures >200 HIV-1 RNA copies/ml or a single value >1000 copies/ml) were included. Patients were NNRTI-naive and had been started on combinations of at least two NRTIs and either nevirapine (NVP) or efavirenz (EFV). The primary endpoint was undetectable viral load (UVL; <50 copies/ml) at 12 months. Analysis was performed by the intention to treat method. Univariate logistic regression was used to test for likelihood of success, and multivariate analysis was used to determine significant independent predictors of success after allowing for variability between confounding variables.
Results: Median CD4 count and VL at baseline were 225 cells/µl and 24,000 copies/ml. Overall, 37% had an UVL at 12 months; 51% on three NRTIs had an UVL compared with 33% on two NRTIs [RR 2.6, 95% confidence interval (CI) 1.3–5.3]; 43% of patients on a combination including EFV had an UVL compared with 20% on NVP (RR 0.3, 95% CI 0.2–0.7). Virological failure was considered the principal cause of failure of the new combination in 73%. NNRTI-attributed toxicity was a cause of failure in 25% of EFV and 5% of NVP failures.
Conclusions: Virological success was low at 12 months in patients changing to NRTIs/NNRTI. EFV-containing combinations were significantly better. The use of three NTRIs warrants further study.

P29

Abacavir as salvage therapy in antiretroviral-experienced patients

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Objective: To assess the virological response to the nucleoside reverse transcriptase inhibitor (NRTI) abacavir (ABC) in combination with either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) when used in salvage therapy.

Methods: Retrospective analysis was performed of data extracted from an observational database on HIV-positive patients naive to ABC who received an ABC-containing regimen as salvage therapy. We included all patients receiving ABC for at least 9 months and with a viral load of >500 HIV-1 RNA copies/ml at baseline.

Results: The sample comprised 195 patients with a median of four regimens (IQR: 2–5). At 9 months, 153 (79%) patients had a viral load reduction of >1 $\log_{10}$ copies/ml, 118 (61%) of whom reached <50 copies/ml. Analysis of salvage regimens demonstrated different response rates depending on new drug classes used: 65% of 121 patients who received an NNRTI as a new drug class and 69% of 13 patients who received a PI as a new drug class achieved a viral load of <50 copies/ml within 9 months. The number of previous regimens and CD4 cell count at start of salvage therapy did not influence virological success.

Conclusion: Abacavir is efficacious as salvage therapy in heavily pretreated HIV-positive patients in combination with either PIs or NNRTIs.

P30

A study to evaluate the effects of recycling nucleoside reverse transcriptase inhibitors (NRTIs) in heavily antiretroviral therapy-exposed HIV-1 infected patients with detectable viral loads

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Objective: To determine whether stavudine (d4T)/didanosine (ddI)± hydroxyurea (HU) would benefit patients with virological failure and few treatment options.

Methods: Twenty HIV-positive patients, heavily pretreated with at least four NRTIs + one non-nucleoside reverse transcriptase inhibitor (NNRTI) + one protease inhibitor were included. The first 11 were given d4T/ddI and HU and the remaining 10 were given d4T/ddI alone. Sampling was performed at baseline and at weeks 12–18 for surrogate markers, resistance tests and biochemistry and haematology.

Results: There were no serious adverse drug reactions. In the HU group there were 11 males with a median age of 39 years (range 30–45). In the d4T/ddI group there were nine males and one female with a median age of 44 years (range 31–58).

	d4T/ddI/HU	d4T/ddI
Baseline CD4 (cells/µl)	79 [5–237]	63 (39–249)
Δ CD4	6 (–92–158)	82 (–21–211)
Baseline VL ($\log_{10}$)	4.7 [3.2–5.4]	5.0 [3.9–5.0]
Δ VL	–0.7(–3.7–2.36)	–0.59(–1.9–0.1)

Data analysed using the Kruskal-Wallis test. All values are expressed as a median and a range.

Conclusions: The fall in viral load at 12 weeks was greater in the d4T/ddI group although this did not reach statistical significance. No significant differences were found in the CD4 count in either group. Additional patients are being recruited to the study. Resistance tests at both time points are pending.

P31

Effects of highly active antiretroviral therapy in primary/acute HIV-1 infection

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Objective: To assess the effects of initiating highly active antiretroviral therapy (HAART) in primary/acute HIV-1 infection and determine how it affects HIV-1 specific T-cell responses.

Methods: Four patients presenting with symptomatic acute HIV-1 infection and one with recent infection (<90 days) were assessed for: lymphoproliferation using ^{3}H-TdR incorporation, antigen-induced intracellular interferon (IFN)γ and interleukin-2 (IL-2) production by flow cytometry and detailed phenotypic analysis at baseline and weeks 4, 8, 12 and 24 after initiation of HAART. Correlation with CD4+ T-cell counts and viral load was also carried out.

Results: Lack of proliferation was seen in four of five patients early in HIV-1 infection. However, two of four patients showed detectable HIV-1 induced intracellular IFNγ staining. Phenotypic analysis revealed hyperactivation, seen by an increase in human leucocyte antigen (HLA)-DR and CD38 on both CD4+ and CD8+ T cells. HAART arrested viral replication within 8 weeks, reflected in a reversal of anergy with reappearance of both lymphoproliferative responses and intracellular IFNγ production. Surface expression of HLA-DR and CD38 on both CD4 and CD8 T lymphocytes decreased during treatment.

Conclusions: The CD4+ HTL dysfunction in HIV-1 infection, which occurs early during infection even before the decline in absolute numbers of CD4+ T cells, and which is marked by an early loss of HIV-1 specific responses in terms of both proliferation and IL-2 production, appears distinct from the antigen-induced intracellular IFNγ production. Up-regulation of HLA-DR in immune hyperactivation is suggestive of T:T presentation which is associated with anergy. Early treatment with HAART reverses the anergic state; however, whether these virus-specific responses are sustained, and their long-term effect on the immune control of HIV-1 disease, remains to be elucidated.

P32

Factors predicting outcome of therapy in the Edinburgh injecting drug user population: a retrospective study

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Objective: To determine any factors which might be predictive of a good/poor response to antiretroviral therapy (ART).

Methods: Patients were classified as treated and untreated, responders and non-responders to treatment and sustained responders if the viral load remained below 400 HIV-1 RNA copies/ml for 6 months or more. A variety of patient factors were considered and compared with results from a similar retrospective study carried out 24 months previously.

Results: Of 485 patients, 71% had been treated with ART between March 1997 and Nov 2000. Maximum viral load (VL) and minimum CD4 counts were related to access to treatment. Previously, fewer injecting drug users (IDUs) had access to therapy. By Nov 2000, this difference was no longer evident, with access having risen from 59% to 68%. Responders: 69% of the total achieved a VL of <400 copies/ml (BLD). There was, however, now a difference in transmission category for those who achieved a VL BLD. In 1999, 48% had achieved VL BLD and now there are 62%, but the homo- and heterosexual groups had increased further. Sustained response: There was no significant difference between transmission categories for the sustained responders; IDUs were 64% vs. 63% for the homo- and heterosexual groups.

Conclusions: The fact that IDUs have 'caught up' with other groups may be because of doctor and/or patient confidence in treatment. It may be that the IDUs under treatment more recently are those who are more chaotic and that concerns about their ability to adhere were justified. It is encouraging that 62% of the IDU population treated have attained a very low viral load

P33

Observational protease inhibitor salvage study, using efavirenz plus two new nucleoside reverse transcriptase inhibitors

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Background: The optimum salvage treatment for failed triple therapy with protease inhibitors (PIs) has not yet been defined, although salvage therapy appears to be more effective when families of drugs are used. We conducted a salvage study using efavirenz (EFV) and two new nucleoside reverse transcriptase inhibitors (NRTIs).

Methods: Observational, prospective study in 43 non-nucleoside reverse transcriptase inhibitor (NNRTI)-naive patients, on triple therapy with PI, who had virological failure defined as a viral load (VL) of >50 copies/ml determined on two occasions; 54% were injecting drug users (IDUs) and 67% had AIDS. The mean number of salvage therapies was 2.2±0.2. The patients were treated with EFV+two new NRTIs (n=25) or EFV/stavudine (d4t)/didanosine (ddI)/abacavir (ABC) (n=18). EFV levels were measured 9 hours after the last dose. Previous adherence was poor in 39% of patients, 16% were relapsed drug addicts and 42% had prior lipodystrophy.

Results at 13 months: The patients showed a VL reduction of –1.89 $\log_{10}$ HIV-1 RNA copies/ml, and CD4 increase of 41 cells/µl. An undetectable VL (VLU; <50 copies/ml) was reached by 66% of patients (no difference between groups). The following increases were observed: cholesterol 27 mg/dl; triglycerides 121 mg/dl; low-density lipoprotein 85 mg/dl. Baseline genotypic resistance was studied in 33 patients, 27 of whom did not show K103N. All four patients with K103N had virological failure (P=0.01). In a multivariate study using the Weibull and Cox model, K103N resistance had a relative hazard of 6.4 for virological failure (95% confidence interval 1.6-25.6; P=0.009).

Conclusions: Salvage therapy with EFV plus two new NRTIs or EFV/d4T/ddI/ABC gave VLU in 66% of patients at 13 months, depending on treatment adherence and the presence or absence of baseline K103N.

P34

Once daily highly active antiretroviral therapy in treatment-experienced patients in Edinburgh

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Objective: To examine the feasibility of delivering once-daily highly active antiretroviral therapy (HAART) in a population with adherence difficulties

Method: Patients who had difficulties with adhering to a twice-daily HAART regimen were offered once-daily HAART with appropriate support. The regimen included a combination of once-daily lamivudine (3TC), didanosine (ddI), stavudine (d4T), nevirapine (NVP), efavirenz (EFV), or Fortovase/ritonavir (FTV/RTV). The reduction in HIV RNA viral load, duration of therapy and change in methadone requirements were assessed.

Results: Fourteen patients (seven males) with a mean age of 37 years were recruited. Risk groups: 10 injecting drug users (IDUs), two heterosexuals, two homosexuals. Two females and four males were current drug users on opiate maintenance. Twelve patients were treatment-experienced and two were naive. In addition to their nucleoside reverse transcriptase inhibitor backbone, eight patients (five EFV, three NVP) were on non-nucleoside reverse transcriptase inhibitors, four on FTV/RTV, one NVP with FTV/RTV and one on EFV with FTV/RTV. The mean duration of therapy was 6 months (range 1–16). Five patients on NVP or EFV required an increase in methadone maintenance. Three patients discontinued after 4 weeks of treatment initiation. Ten of 11 patients who had HAART for >4 weeks achieved a viral load <400 HIV-1 RNA copies/ml. Details of the level of support provided to these patients will be described in detail.

Conclusions: Once-daily HAART was successful in 90% of a small cohort of mostly treatment-experienced patients with adherence problems. Once-daily therapy may be a useful option for certain patients with adherence problems.

P35

Why do some patients have a low CD4 count in the era of highly active antiretroviral therapy (HAART)?

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Objective: To audit patients with CD4 counts <50 cells/µl to assess why patients had such advanced immunosuppression in the highly active antiretroviral therapy (HAART) era.

Methods: All patients seen at the Royal Free Hospital between 1 July 1999 and 30 June 2000 with a CD4 count <50 cells/µl were included.

Results: Ninety-four patients (7.6%) had at least one CD4 count <50 cells/µl. These patients were more likely to be heterosexual (P=0.001) and black African (P=0.001) than those with higher CD4 counts, but were of similar age and sex and had been diagnosed with HIV for a similar length of time. Eighteen of the 94 (19.1%) had been diagnosed with HIV within the last 6 months. Only four of these patients had started HAART by the time of the low CD4 count, although a further nine started therapy subsequently. The remaining 76 patients had been diagnosed between 1.05 and 16.9 years before the low count; of these, six had never received antiretroviral treatment (three had only recently attended the clinic and three had chosen not to start therapy), 30 had started treatment but were not on it at the time and 40 patients were on antiretroviral therapy. Those who stopped therapy did so because of choice (36.7%), adverse events (26.7%), virological failure (16.7%), poor compliance (10.0%) or other reasons (10.0%); 17 of these patients subsequently restarted therapy. Of the 40 patients who were on therapy at the time of the low CD4 count, only five were perceived by clinicians to have good adherence to therapy.

Discussion: There are a number of reasons why some patients have low CD4 counts, despite free access to HAART. At our centre, many of these CD4 counts can be explained by poor compliance and treatment interruptions following virological failure or adverse events.

P36

Pharmacokinetic study of indinavir at 600 mg twice a day and ritonavir at 200 mg twice a day in plasma and semen of HIV-1 infected men

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Objective: The aims of this study were (1) to describe the pharmacokinetics of a twice daily regimen of indinavir (IDV)/ritonavir (RTV) at 600/200 mg twice a day; and (2) to describe IDV and RTV concentrations in semen (SP) when administered together.

Methods: Seven steady-state HIV-positive men gave plasma (BP) samples 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours post drug (taken with food), and sequential daily semen samples at different times post drug. IDV and RTV were analysed by liquid chromatography-mass spectrometry (MS)/MS. Viral loads (VL) and CD4 counts were measured at baseline and 12 and 24 weeks post treatment. Two patients changed from IDV 800 mg three times a day; five began RTV2 IDV6 as part of salvage; all took two nucleoside reverse transcriptase inhibitors.

Blood plasma	IDV median (range)	RTV median (range)
C12 hours (ng/ml)	410 (166–693)	450 (260–526)
Cmax (ng/ml)	7734 (3288–9557)	3540 (2360–10,873)
AUC 0-12h (ng/ml.h)	32,521 (18,917-49,870)	26,540 (14,148–40,893)
Tmax (h)	1 (1-4)	2 (1–4)
T1/2 (h)	2.5 (2-4.2)	2.6 (2.1–3)
Semen plasma		
C2 hours (ng/ml)	6230 (3794-9964)	240 (0-750)
C10 hours (ng/ml)	1,215 (435-2,004)	40 (0-290)

Conclusions: IDV was well above the median effective concentration (MEC) of 100 ng/ml at all times. RTV was above the MEC of 2100 ng/ml for approximately 1/2 of the dosing period. Four of six patients had BPVL <50 copies/ml and all six had SPVL<400 copies/ml at 24 weeks.

P37

The role of nurse triage in facilitating non-routine medical care of patients in an HIV clinic

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Introduction: The increased prevalence of HIV along with the current complexity of its management raises the question of how we can continue to meet non-routine HIV medical needs as well as associated health care needs that may not be related to HIV.
Aim: To identify routes of access, outcomes and definitive diagnoses of patients who request medical advice outside their routine clinic appointments and to evaluate the effectiveness of nurse triage.
Method: A comprehensive symptom-based nurse triage system was introduced in June 1999 and data was collected prospectively on all non-routine contacts who were triaged up to March 2000.
Results: A total of 102 patients requested medical attention on 179 occasions, 73% of whom were triaged; 71% were on highly active antiretroviral therapy and 68% had CD4 counts >200 cells/µl. While 89% were registered with a GP only 7% had seen the GP with the same presenting complaint. Of those given a definitive diagnosis, the diagnosis was HIV-related in 19%, probably HIV-related in 7%, possibly HIV-related in 40% and not HIV-related in 34%. To obtain attention, 13% of patients telephoned, 54% walked-in and 33% did both. Of those who were triaged, 81% had a medical consultation, the remaining 19% being given nursing advice or referred by nurses to GPs, regular clinic doctors or elsewhere.
Conclusion: While defining conditions which may or may not be related to HIV can be complicated, this study demonstrates the potential for nurse triage in facilitating more appropriate use of services for patients requiring non-routine medical care.

P38

Sharps injuries among healthcare workers: management and outcome

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Introduction: In Portsmouth, a 24 hour on-call service is provided by staff in Genitourinary Medicine (GUM) for healthcare workers (HCWs) potentially at risk from acquiring HIV and other blood-borne viruses through occupational exposure to body fluids.
Objective: To assess the management of HCWs referred into the GUM sharps injury service.
Methods: Patients who were referred to the department following a potential exposure to blood or body fluids between 1 January and 31 December 2000 were identified retrospectively. Subjects were included if they had a documented percutaneous injury, or exposure of broken skin or mucous membranes to body fluids. A total of 133 subjects were identified; five were excluded from the analysis because of no exposure to blood-borne viruses.
Results: Of the 128 patients included in the analysis, 20 (16%) were male and 108 (84%) were female. A total of 78 (61%) staff worked in the community, 44 (34%) in an acute hospital and six (5%) were members of the public. The occupations of the subjects were: registered nurse, 56 (44%); healthcare support worker, 23 (18%); doctor, 16 (12.5%); dental nurse, 11 (8.5%); midwife, five (4%); dentist, four (3%); student healthcare workers, four (3%); domestics, two (1.5%); and others, seven (5.5%). Five (4%) HCWs commenced postexposure prophylaxis (PEP).
Conclusion: The majority (96.0%) of subjects in this study were not at significant risk of acquiring HIV occupationally. However, anxiety levels are very high, and therefore staff who provide advice should be knowledgeable about the risks and benefits of PEP. Prevention of occupational exposure is ideal. All HCWs should be aware of local reporting and management policies if a sharps injury occurs.

P39

Surviving AIDS: the experiences of people with AIDS who have responded well to HAART

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Background: Research in the US has shown that patients with AIDS in the pre-highly active antiretroviral therapy (HAART) era who have since had a positive response to HAART may experience mixed emotions in response to their revival of health. The aim of this study was to hear the experiences of a similar patient group within the UK.
Method: A qualitative approach was chosen, involving in-depth interviews with four participants with an AIDS diagnosis before August 1996, on uninterrupted HAART with an undetectable viral load. Interview data were analysed using an adapted version of Burnard's (1991) method of thematic content analysis.
Results: Participants expressed mixed emotions in response to this change in illness trajectory, which related to three broad areas: hope and future outlook, changes in quality of life and the need for social identity and support. In the absence of opportunistic infections, they experienced a catalogue of non life-threatening but debilitating problems with recurrent reference to the concept of uncertainty in illness.
Conclusion: The experience of revival is associated with mixed emotions, which need acknowledgement and consideration when working with this patient group. Specialist nursing skills and a questioning of how we measure 'good health' can further help meet these patients' needs. There are clearly limitations in such a small study. However, a larger study of uncertainty in HIV illness is long overdue.

P40

Viagra use and sexual risk behaviour in HIV-positive and -negative gay men in London

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Objective: To examine the use of viagra (sildenafil) and sexual risk among London gay men in London.
Methods: Nearly 800 gay/bisexual men (126 HIV-positive, 477 HIV-negative, 169 never tested) were surveyed in London in Jan–Feb 2000 for the use of sildenafil and non-concordant unprotected anal intercourse (UAI) with a person of discordant or unknown HIV status.
Results: About 20.0% (158/789) of the men had taken sildenafil in the previous 12 months. Significantly more HIV-positive men had taken viagra (36.8% HIV-positive, 19.2% HIV-negative, 8.9% never tested ($P<0.001$). Most men had used sildenafil recreationally and less than one-in-five sildenafil users had taken it on prescription. HIV-positive and -negative men who had taken sildenafil were no more likely to report non-concordant UAI while taking sildenafil than men who had never taken the drug ($P>0.3$). However, those who had taken sildenafil were more likely than those who had not to have also used recreational drugs ($P<0.01$), taken anabolic steroids ($P<0.001$) or report non-concordant UAI (but not necessarily while on the drug) ($P<0.03$).
Application of results: One in five gay men in this study had used sildenafil. While the use of sildenafil appeared to be associated with general risk-taking behaviour, there was no evidence that sildenafil *per se* led to high-risk sexual behaviour among HIV-positive or -negative gay men. Over one-third of HIV-positive men had used sildenafil; both they and their physicians should be aware of its potential interaction with protease inhibitors.

P41

Needlestick injuries amongst surgeons in the West Midlands

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Introduction and methods: The Worcestershire Infection Group (authors) are considering the use of pre-operative risk assessment to predict potential higher risk needlestick injuries, which may require postexposure prophylaxis (PEP). As a baseline, a questionnaire was sent all West Midlands-based surgeons to ascertain the frequency of needlestick injuries over the last year, high-risk incidents, advice regarding PEP, awareness of local guidelines and views on a formalised method of ascertaining the risk pre-operatively.

Results: 311/518 questionnaires were returned (60%), 160 from specialist registrars (SpRs) (51%) and 151 from consultants (49%). The average risk (AR) of a general surgical SpR sustaining a needlestick injury (total number of injuries/total number of surgeons) was 4.14 injuries/surgeon (145/35). For consultant general surgeons, the AR was 1.98 injuries/surgeon (158/80). For orthopaedic SpRs the AR was 1.14 (58/51) and for consultant orthopaedic surgeons, the AR was 1.28 (72/56). Seven of 311 (2%) sustained a higher-risk needlestick injury, including one who took PEP 12 hours after the injury and a further two who discussed the risk with Occupational Health. Only 99/311 (32%) were aware of local guidelines regarding PEP; 27% of respondents thought pre-operative risk assessment was a poor idea, 45% a good idea and 28% an excellent idea.

Comments and conclusions: Free text comments included the need to test all patients for blood-borne viruses pre-operatively, the difficulties in reporting needlesticks and the need for regular updates on guidelines. The data show a high frequency of needlestick injuries, especially amongst general surgical trainees, although few were higher risk. There is a need to improve awareness of guidelines regarding PEP.

P42

Antenatal HIV screening

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Objective: To determine the rate of uptake of HIV testing as part of the antenatal screening tests performed at the antenatal booking visit, following the introduction of an Opt-out screening program in June 1999.

Method: Between 1 August 1999 and 31 July 2000, data were collected retrospectively on the number of HIV tests performed from the antenatal clinic and the number of antenatal bookings in the Maternity Unit of a District Hospital. These were compared with the number of tests performed by the public health laboratory.

Summary: Of 3032 women booked for delivery during this period, 2712 (89%) had an antenatal HIV test performed as part of routine serology for syphilis and hepatitis B. All tests were negative, but two babies were born to mothers known to be HIV-positive before attendance at the clinic (both babies were HIV polymerase chain reaction-negative).

Conclusion: Although no positive cases of HIV were detected, these results show a high uptake of HIV testing and therefore the Opt-out method of antenatal HIV screening proved to be successful. This may help to considerably reduce the vertical transmission rate of HIV even further by detection and management at an earlier stage.

P43

Factors that may limit the acceptance of antiretroviral therapy by injecting drug users

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Objective: A comprehensive questionnaire was designed to assess the knowledge and understanding of injecting drug users (IDUs) regarding their HIV disease.

Results: Of the total IDU cohort, 20% (157 patients) participated in the study; 42% of these patients have been homeless in the past 5 years and 84% are unemployed; 72% did not complete second-level education and 10% are illiterate; 51% have siblings or parents with a history of injection drug misuse, and 25% have at least one HIV-positive sibling; 47% started using drugs before the age of 13 years, the most common initial drug being heroin (44%); 95% have attended for methadone maintenance therapy (MMT), with 39% currently attending for daily therapy. A significant number of these patients expressed a lack of knowledge of CD4 counts (54%) and viral loads (65%), and 57% of those questioned were receiving highly active antiretroviral therapy (HAART). There was a statistically significant association between patients receiving HAART and both attendance at a GP for MMT (P=0.005), and weekly take-outs of methadone (P=0.005), and between adherence to HAART and attendance for MMT (P=0.04).

Conclusions: This study highlights the chaotic lifestyle and often difficult social circumstances related to IDU. Such factors were not, however, associated with acceptance of HAART. The primary factor associated with both the acceptance of and adherence to HAART was regular and stable MMT.

P44

An assessment of current HIV adherence services in the UK

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Objectives: To examine current approaches to adherence support and quantify the use and value of adherence protocols/guidelines.

Methods: We interviewed a sample of 100 HIV/AIDS/genito-urinary medicine specialists who currently initiate highly active antiretroviral therapy and spend at least 33% of their time actively managing patients with HIV/AIDS.

Results: The most important criteria for achieving treatment success (scored from 1=not important to 5=very important) were: treatment fitting well into patient's lifestyle (4.7), regular viral load monitoring (4.4), the experience of the clinician/healthcare team (4.3) and adherence support (4.2). Of the specialists, 97% were personally involved in discussing adherence, spending 22% of consultation time on adherence issues and assessing adherence most commonly by patient self-report (88%). Other personnel involved included nurse (74%), other doctor (56%), health adviser (54%) and pharmacist (48%). A variety of tools were used to support adherence, including dosette boxes (53%), written information (44%) and verbal communication (42%). Twenty per cent of specialists followed adherence protocols or formal guidelines, including BHIVA guidelines (n=10) and clinic protocols/guidelines (n=5), and 75% had received no training on adherence. The most common ways specialists were kept informed about adherence issues were by attending conferences (87%), reading (71%) and learning from colleagues (51%). A large majority, 87%, of these specialists believed that national adherence guidelines would be valuable.

Conclusions: There is a need for training and direction within current adherence approaches. National guidelines could provide a valuable framework for healthcare professionals.

P45

A novel scheme of home delivery of HIV medicines

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Objective: A new scheme which enables patients who are stable on highly active antiretroviral therapy to receive home delivery of HIV therapy has recently been introduced at our centre. We assessed patient's attitudes to this scheme and the effect that participation had on adherence to therapy.
Methods: A pilot study at the Royal Free Hospital in November 1999 enrolled 21 patients for monthly delivery of antiretroviral therapy. Patients had to be stable on treatment for >3 months, and not on a trial or unlicensed drug. Questionnaires assessing satisfaction to the scheme were sent out at 3 and 12 months.
Results: In the first 12 months, two people changed therapy and three people came off due to inconvenience; 14 patients responded to each questionnaire. The results were generally very positive. At 3 months, 79% of patients felt that the scheme was more convenient, 71% felt that it had reduced the amount of medicine they stored at home, and the overall satisfaction rating was high. However, 28% of patients were slightly concerned about confidentiality issues. By 12 months, 79% were very satisfied with the scheme and the remaining 21% were fairly satisfied. The major advantages quoted were convenience, savings in time and not having to carry medicines home from the pharmacy. Those who noted a disadvantage with the scheme generally commented on the timing and frequency of deliveries. Patients stated that participation in the scheme had not affected their adherence to therapy, and viral loads remained low or undetectable in all patients who remained on the scheme.
Conclusions: This scheme has been well received, and has now been extended to over 200 patients. Some of the cost implications of this scheme will be discussed.

P46

Differences in perceptions of highly active antiretroviral therapy between people diagnosed before and after the advent of combination therapy

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Objective: To test the hypothesis that people diagnosed with HIV before the introduction of combination therapy have a more negative perception of highly active antiretroviral therapy (HAART) than those diagnosed more recently.
Methods: All patients attending Brighton clinics who are not taking HAART are invited to take part in this study through doctor referral. Participants are followed over 12 months and those who are offered HAART over this time period complete a validated questionnaire investigating their beliefs about the necessity of HAART and their concerns about taking HAART. Participants whose first diagnosis of HIV took place before 1995 (pre-combination therapy) are compared with those whose first diagnosis of HIV was during 1995 or later.
Results: Data have been collected from 35 participants to date, 13 of whom were diagnosed before 1995 and 22 since 1995. These groups did not differ significantly in terms of age, CD4 count, viral load or illness stage at treatment offer. However, those who were diagnosed before 1995 were less convinced of their personal need for HAART ($P< 0.05$) and were more concerned about potential adverse effects of taking HAART ($P<0.01$). There was also a trend for those diagnosed before 1995 to be more likely to decline HAART ($P=0.067$).
Conclusion: Patients who were diagnosed with HIV before 1995 have a more negative view of HAART and may be less inclined to accept antiretroviral treatment. We are conducting further studies to determine whether these findings are due to early experiences of monotherapy, or merely reflect a longer duration of diagnosis on perceptions of HAART. These factors should be considered when initiating or discussing HAART with this patient group.

P47

Systematic overview of adherence studies: findings and implications

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Objective: Adherence is seen as key factor in the success of highly active antiretroviral therapy (HAART). The literature on adherence is confusing. This review analyses all randomised controlled trial (RCT) interventions to report on efficacy. An overview is made of adherence levels, measures used, and predictors and correlates of adherence and non-adherence are collated.
Methods: A systematic review was made of all articles from 1996 to the end of 2000 on Medline and allied journal search. Two RCTs were identified, 23 studies providing data on levels, 24 on measures, and 19 on predictors. All studies were coded for geographic base.
Results: Adherence, even in the two RCTs, is wanting. No consensus exists on levels of acceptable adherence, but the literature suggests a cut-off point of 95%. Lower cut-off points need to be questioned. Most studies are cross-sectional and thus do not give long-term data. Methodologies rarely differentiate between regimens or those newly starting, continuing or changing regimens. Self report is the most common measure, although biological markers as well as mechanical devices are now being used with greater frequency. When studies correlate these markers with self-report, the correlation is generally good. There is a predominance of US studies. The only two RCTs emerged from Spain. It is difficult to generalise findings to other settings. There is limited consensus on predictors of adherence. Few studies concentrate on predictors of adherence rather than non-adherence. Many predictors documented in some studies fail to predict in others. The cluster may be similar to those associated with risk behaviour.
Conclusions: Interventions are effective, but too few exist for guidance. Prevention and adherence may need to be coupled and stressed in the ongoing management of people on HAART.

P48

Can the analysis of lung CD8 phenotype provide useful diagnostic information in HIV-infected patients with respiratory disease?

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Objectives: To assess whether the expression of perforin, interferon-γ and Ki67 in bronchoalveolar lavage (BAL) CD8 cells was useful in distinguishing different respiratory infections in HIV-infected patients.
Methods: Fresh BAL was obtained from HIV-positive patients with respiratory illnesses. One million CD45+ cells were fixed and permeabilised to allow intracellular staining. CD8 cells were stained with perforin, Ki67, CD38 and CD45RA. Another aliquot of 1 million cells was incubated with PMA and ionomycin to optimise intracellular cytokine staining for interferon-γ.
Results: Seven patients had tuberculosis (TB), four of whom were smear-positive. Five patients had *Pneumocystis carinii* pneumonia (PCP), one cytomegalovirus (CMV) and one had a probable immune reconstitution pneumonitis following an episode of treated PCP. Of the remainder, two had bacterial pathogens and in the rest no organism was detected in BAL. Two patients with smear + TB had IFN-γ production in 80% of CD8 cells. Three patients with PCP were strongly positive for perforin staining. The patient with CMV detected in BAL had intermediate perforin expression, while the patient with immune reconstitution pneumonitis expressed Ki67 in 85% of CD8 cells. In the remaining patients, perforin, IFN-γ and Ki67 were expressed in <5% CD8 cells.
Conclusions: The BAL CD8 phenotype appears to differ in some cases of TB and PCP infections in patients with HIV.

P49

Transient clinical deterioration in HIV patients with Pneumocystis carinii pneumonia after starting highly active antiretroviral therapy: another cause of immune restoration inflammatory syndrome?

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Introduction: Improvement in immune function produced by highly active antiretroviral therapy (HAART) may result in inflammatory syndromes (e.g. CMV, MTB, MAC). Three cases of *Pneumocystis carinii* pneumonia (PCP) showed a transient clinical deterioration after starting HAART. Full, intensive investigations for alternative diagnoses were negative and all made a good clinical recovery. This may represent a further cause of immune restoration inflammatory syndrome (IRIS).
Case 1: A 46-year-old gay man (PO_2 6.3 on air, CD4 26 cells/μl, viral load (VL) 130,913 HIV-1 RNA copies/ml) was treated with intravenous (IV) septrin/oral steroids with good effect. On day 17 he started stavudine (d4T)/lamivudine (3TC)/ritonavir/indinavir. On days 23–28, O_2 saturation decreased to 82% on air (temperature 39.5°C, worsening CXR, 2 week VL <200 copies/ml, CD4 82 cells/μl). Case 2: A 36-year-old gay man admitted to the intensive care unit (O_2 saturation 77% on air. CD4 9 cells/μl, VL 465,294 copies/ml) was treated with IV septrin/oral steroids with good effect. On day 15 he started d4T/3TC/efavirenz (EFV). On days 18–50 swinging pyrexia occurred (decreasing PO_2, worsening CXR, 2 week VL 1229 copies/ml, CD4 14 cells/μl). Case 3: A 37-year-old woman with respiratory distress (RR 38/min, CD4 33 cells/μl, VL 711,136 copies/ml) was treated with IV septrin/oral steroids with good effect. On day 15 she started zidovudine/3TC/EFV. On days 2–40 swinging pyrexia occurred (PO_2 6.9, worsening CXR. 2 week VL 2007 copies/ml, CD4 62 cells/μl).
Conclusions: Worsening PCP symptomatology was temporally related to the initiation of HAART associated with a marked VL fall, as in other immune-restoration disorders. Timing of HAART in PCP patients is vital.

P50

An attractive alternative to radiotherapy for intra-ocular lymphoma (IOL)

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Aim: The treatment of primary IOL remains controversial, with whole brain and ocular irradiation being standard practice. This treatment is associated with blindness, alopecia and mental deterioration, but may reduce late cerebral recurrence. Adjuvant intrathecal chemotherapy has also been used with limited success. Intravitreal chemotherapy for localised IOL preserves vision and has been used occasionally in the HIV-negative population although late cerebral relapse remains a risk. We describe the first case where this treatment has been used successfully in HIV-related IOL.
Patient and methods: A 53-year-old HIV-positive man complained of poor vision and floaters in the right eye. He was diagnosed with HIV in 1991 and started antiretrovirals in 1994. A vitreal biopsy revealed diffuse large-cell non-Hodgkin's lymphoma. Magnetic resonance imaging (MRI) of the brain and a lumbar puncture were normal, as was a computed tomography scan of the chest, abdomen and pelvis. A diagnosis of stage IE primary IOL was made. He was treated with six cycles of fortnightly intravitreal methotrexate. Over this period his vision improved and a repeat biopsy showed a complete response to treatment, the MRI brain remained normal.
Conclusion: This novel treatment is not well described, but is an attractive, less toxic alternative to radiotherapy.

P51

Prevalence of hepatitis in an Irish HIV drug-using cohort

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Objective: To prospectively study the seroprevalence of hepatitis in the HIV-positive injecting drug user (IDU) cohort attending the GUIDE clinic and to correlate seroprevalence of each infection with duration of HIV diagnosis.
Patients and methods: A total of 325 IDUs have been sequentially recruited to the study to date. Results of serological markers for hepatitis C (HCV) antibody (Ab), HCV RNA, hepatitis B (HB) surface antigen (HBsAg), HB core Ab (HBcAb) and hepatitis A (HAV) Ab were identified. Statistical analysis was by χ^2-tests.
Results: Antibody to HCV was detected in 275 (95%) patients; 75% of this population currently have detectable RNA to HCV. The percentage with detectable RNA increased significantly with year of diagnosis (P=0.01). Two hundred of these patients (69%) have been previously exposed to HAV. Chronic carrier prevalence to HBV as measured by HBsAg is 10.3%., and 252 (87%) have had previous exposure to HBV with a positive HBcAb. There was no statistically significant difference between year of diagnosis and HAV or HBV status.
Conclusions: The prevalence of HCV in our population is similar to that reported previously. The increasing prevalence of RNA detected with respect to year of diagnosis may be due to reactivation of latent HCV in hepatocytes. The high prevalence of both HAV and HBV suggests that this population should have screening serologies performed prior to routine vaccination.

P52

Unsuccessful treatment of CD20-positive refractory AIDS-related lymphoma with Rituximab

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Aim: AIDS-related non-Hodgkin's lymphomas (ARL) are B-cell tumours that frequently express CD20. Rituximab (MabThera) is a chimaeric monoclonal antibody combining murine variable regions and human immunoglobulin G Fc region that binds CD20, leading to cell destruction by complement-dependent lysis and antibody-dependent cell-mediated cytotoxicity (ADCC).
Patient and methods: A 34-year-old man presented with stage 4B ARL and advanced AIDS. He had extensive liver, spleen and lung involvement with diffuse large-cell lymphoma. He had been on antiretroviral therapy for 8 years, having received eight combinations including 10 different drugs and both protease inhibitors and non-nucleoside reverse transcriptase inhibitors. At ARL diagnosis his CD4 count was 3 cells/μl, and viral load 446,000 HIV-1 RNA copies/ml. He was initially treated with BEMOP/CA combination chemotherapy. However, this was poorly tolerated and there was clinical evidence of disease progression. Since the ARL expressed high levels of CD20, he commenced Rituximab therapy at 375 mg/m^2 weekly for 4 weeks. This was well tolerated, but resulted in profound suppression of circulating B cells (CD19 count <1 cell/μl 2 months later). Clinical and radiological response evaluation demonstrated disease progression of ARL.
Conclusions: Despite abundant expression of CD20, there was no response to Rituximab in this patient with chemotherapy-refractory ARL and advanced immunosuppression. Lack of response may, in part, be due to deficiency of cellular effectors of ADCC. Nonetheless, controlled randomised studies are under way to evaluate the value of Rituximab in combination with chemotherapy for the management of ARL.

P53

Pegylated interferonα-2b in HIV-related Kaposi's sarcoma

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Aim: We report the use of pegylated (monomethoxy polyethylene glycol) interferonα-2b (PEG-IFN), a long-acting conjugate form of recombinant interferonα-2b with improved pharmacological properties, in an HIV-positive patient whose Kaposi's sarcoma (KS) failed to respond to liposomal daunorubicin and to paclitaxel chemotherapy.

Methods: A 44-year-old man with no previous AIDS-defining diagnosis presented with extensive, histologically confirmed, cutaneous KS and tumour-associated oedema (stage T1 I0 S0). His CD4 count was 292 cells/μl and viral load (VL) 54,800 HIV-1 RNA copies/ml. He commenced highly active antiretroviral therapy (HAART) with didanosine (ddI), stavudine (d4T), nevirapine (NVP) and nelfinavir. Two months later, VL was undetectable and CD4 was 252 cells/μl. KS did not respond to initial HAART, five cycles of liposomal daunorubicin or five cycles of paclitaxel. Once weekly subcutaneous PEG-IFN at 2 μg/kg was started.

Results: An early subjective response to KS was seen after only five further injections, and after a total of nine injections, there was an objective partial response (ACTG criteria). No other local or systemic therapy was given for KS and he remains on PEG-IFN, ddI, d4T and NVP. A cumulative dose of 38 μg/kg PEG-IFN has so far been administered and he has reported flu-like symptoms, moderate emesis and depression. There has been no significant change in CD4, CD8, CD19 or VL during PEG-IFN therapy. Further studies are warranted to establish the efficacy of PEG-IFN in HIV-related KS.

P54

Reactivation of latent hepatitis B infection with HIV-related immunosuppression

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Background: Cellular immunity is important in the control of hepatitis B virus (HBV) infection. Reactivation of HBV infection after apparent resolution has been described with immunosuppression. The effect of HIV-related immunosuppression on HBV reactivation is unclear.

Method: Retrospective record analysis from two centres. Six cases of HBV reactivation occurred in HIV-immunosuppressed patients, some taking antiretroviral therapy (ART).

Results: All patients were male; four were white and two black African. All had symptomatic HIV, two with prior AIDS events. All were hepatitis B core antibody-positive and surface Ag (HbsAg) negative. In all, HBV reactivation was identified after abnormal liver function tests (LFTs). Two developed abnormal LFTs without ART. Both had very low CD4 counts (one AIDS) and became HbsAg/HBeAg positive. One later cleared HbsAg/HbeAg on ART. Three developed abnormal LFTs after 2–4 months of treatment when CD4 counts had increased and the viral load was suppressed. These had a transient LFT rise associated with HBV e-antigenaemia. In all three, LFTs normalised with clearance of e-antigen within 3 months. Only one patient was on a lamivudine (3TC)-containing regimen. In the last case HBV reactivation was noted 4/12 into ART (including 3TC) when LFTs became deranged. Retrospective testing of stored samples showed that the patient had become HbsAg/HbeAg positive prior to ART but this went unnoticed because LFTs were normal. The patient subsequently cleared eAg on ART.

Conclusions: Reactivation of latent HBV infection occurs with advanced HIV-related immunosuppression and can cause LFT abnormalities. In patients on ART who develop abnormal LFTs, repeat HBV serology testing can be important.

P55

Thermal threshold tests in HIV-positive patients

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Objective: To compare the thermal thresholds (TT) of HIV-positive patients (±peripheral neuropathy) with those of healthy controls.

Method: Patients were categorised as (1) no neuropathy; (2) symptoms of neuropathy, no signs and no previous medical history (PMH); (3) symptoms, no signs of PMH; or (4) neuropathy, by a consultant neurologist blinded to TT results. HAART, CD4 count and viral loads were also recorded. TT data were recorded by a research nurse and compared to values for healthy controls.

Results: 115 HIV +ve patients were studied, 79 males, 36 females, mean age 39 years. TTs results are shown below.

Group	Number	Median (IQR)
Healthy Controls	69	0.2 (0.1–0.6)
(1)	44	1.5 (0.6–3.2)
(2)	49	3.7 (1.7–6.6)
(3)	9	4.5 (1.2–6.1)
(4)	13	10.0 (2.5–10.0)

Patients with clinically definite neuropathy had significantly greater hot TTs than patients without clinical neuropathy. Using values from healthy controls, hot TT demonstrates a sensitivity of 0.85 and a specificity of 0.39. Examination may be normal in small-fibre sensory neuropathies and this is reflected in the low specificity.

Conclusions: Significant sensory neuropathy can occur in the absence of clinical signs. Hot TTs demonstrate an ability to discriminate between patients with and without peripheral neuropathy. Thermal threshold may be useful for early diagnosis of peripheral neuropathy.

P56

HIV quasi-species derived from the lung and blood are evolutionarily related despite compartmentalisation of resistance mutations

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Objective: To determine the diversity in HIV evolution and resistance mutations between the lung and peripheral blood.

Methods: Blood and bronchoalveolar lavage (BAL) samples were simultaneously collected from five HIV-positive patients on therapy. For each patient, four to seven sequences of reverse transcriptase (RT) were derived from peripheral blood mononuclear cells and BAL cells from approximately one quasi-species using limiting-dilution polymerase chain reaction (PCR). derived from each compartment. The phylogenetic relationship of the blood and lung viral variants was analysed.

Results: Sequence analysis from approximately one distinct virus per PCR reaction showed differences in resistance patterns between the lung and blood in four of five patients on antiretroviral therapy. In some patients, different resistance-associated mutations were present within one compartment as well as between compartments. Phylogenetic analysis demonstrated that the HIV RT quasi-species present in the lung and blood were evolutionarily related, despite differences in the resistance patterns. Analysis of intrapatient synonymous to non-synonymous nucleotide changes revealed a neutral selection pressure during the administration of antiretroviral therapy.

Conclusions: Differences exist between HIV quasi-species, both between the lung and blood, and within each compartment. These differences are not attributed to separate evolution between the two compartments, as demonstrated by phylogenetic analysis. Differences in mutations between the lung and blood may be due to differences in drug penetration, intracellular drug levels or phosphorylation of NRTIs. These data may help us to understand the basis of HAART drug failure.

P57

Outcomes of genotypic tests in clinical practice

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Objective: To evaluate the contribution of genotypic antiretroviral resistance testing (GART) in salvage patients to virological control and decision making.

Methods: A retrospective analysis of GART, assessing adherence to local policy, decision-making and outcome. Surrogate markers were assessed from time of genotyping.

Results: Data on 50/177 GARTs are presented; 81% of tests conformed to guidelines. Patients had received a median of three regimens (range one to eight) and the median therapy duration was 36 months (range 8–120); 37 (74%) patients changed therapy. The TruGene™ assay showed 79% nucleoside reverse transcriptase inhibitor, 57% non-nucleoside reverse transcriptase inhibitor and ×44% protease inhibitor resistance.

Time from genotyping	Median CD4 (cells/µl)	Median HIV RNA (log_{10} copies/ml)	BLQ (%)	1 log reduction (%)
Baseline, *n*=46	234	4.5	-	-
Week 12, *n*=39	189	4.5	2.2	30
Week 24, *n*=28	205	4.6	1.7	33
Week 48, *n*=27	183	4.5	2.2	26

Conclusion: The utility of GART in antiretroviral-experienced patients remains uncertain and further refinement is necessary.

P58

Retrospective audit of genotypic resistance testing in Edinburgh

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Objective: To review the appropriateness of requests for resistance testing, the proportion of failed amplification and the impact of resistance testing on virologic outcome.

Methods: We reviewed the case records of patients attending RIDU and Genito-Urinary Medicine (GUM) clinics who had HIV genotypic resistance assays (RAs) at the Public Health Laboratory Service Antiviral Susceptibility Reference Unit. We retrieved reasons for requesting RA, turnaround times and the antiviral responses to new antiviral regimens. A patient was deemed to have received a new drug if the results of a genotypic resistance assay did not show any mutations associated with that drug, even though the patient may have previously received it.

Results: Seventy-seven samples from 62 patients attending the HIV clinics at RIDU and GUM were sent for RA from April 2000 to November 2000; 23 samples failed to amplify and four samples had partial amplification. Data were analysed from 38 patients whose plasma was successfully genotyped. The average turnaround time was 4 weeks. Sixteen patients decided not to change their therapy after receiving the results of genotypic RA. One of two patients who received two new drugs for 3 months had <400 HIV-1 RNA copies/ml. Fifteen of 17 patients received three new drugs for more than 3 months; eight had <400 copies/ml and a further five had >1 log_{10} decrease in HIV RNA. All three patients who received four new drugs had <50 copies/ml by 3 months.

Conclusions: A significant number of plasma samples failed to amplify. Patients who received three or more new drugs had a good virological response following genotypic resistance testing.

P59

Clinical features of primary HIV infection

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Objective: To describe the mode of presentation, clinical features and diagnosis of primary HIV infection (PHI) in a patient cohort.

Methods: Patients who presented after July 1998 were identified from the Mortimer Market Centre HIV clinical database. They were eligible if they presented with either (1) an evolving HIV antibody profile or (2) a positive HIV antibody test or symptoms of PHI within 4 months of a negative HIV antibody result.

Results: We identified 26 patients (25 males) with a median follow-up of 11 (range 2–31) months (*n*=21). Six had a recent history of unprotected anal intercourse with either an HIV-positive partner (*n*=3) or a partner who had unknowingly seroconverted following a recent HIV-negative result (*n*=3). Thirteen presented before a positive HIV antibody profile, three before an evolving antibody response [p24 Ag (*n*=1), HIV proviral DNA positive (*n*=2)]. The median interval between the likely exposure date and onset of PHI-related symptoms or an evolving antibody profile was 22 (range 8–51) days (*n*=14). Initial viral loads ranged from 120 to >50,000,000 HIV-1 RNA copies/ml (median >500,000) and CD4 cell counts from 180 to 1200×10^6 cells/µl (median 590). Twenty-three patients described symptoms varying from mild (*n*=3) to a meningitic-like illness (*n*=4). Genotypic resistance tests (*n*=18) demonstrated zidovudine resistance (T215F/Y) in two cases and saquinavir and nelfinavir resistance (L90M, V771) in two other, linked cases. Six patients began highly active antiretroviral therapy at the time of PHI illness. Nine patients required psychological support, three of whom expressed suicidal thoughts and one attempted suicide.

Conclusion: A broad spectrum of clinical features is associated with PHI together with a high psychological morbidity. Transmission of HIV drug-resistant strains was demonstrated in four subjects.

P60

Modulation of HIV-specific immune responses by an efavirenz-containing therapeutic protocol in HIV-infected drug-experienced patients

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Objective: Analysis of the virological and immunomodulatory effects of a combination of efavirenz (EFV), nelfinavir (NFV) and stavudine (d4T) in HIV-infected highly active antiretroviral therapy (HAART)-experienced patients.

Methods: 18 HIV-infected, HAART-experienced non-nucleoside reverse transcriptase inhibitor (NNRTI)-naive patients (<500 CD4 cells/µl; >10,000 HIV-1 RNA copies/ml) were studied. The patients were treated for 10 months with EFV (600 mg/day) plus NFV (750 mg three times a day) and d4T (30 or 40 mg twice a day). We measured recall antigen-, HIV peptide-, and mitogen-stimulated proliferation and production of interleukin (IL)-2, interferon (IFN)γ, IL-4 and IL-10 and quantitation of cytokine messenger (m)RNA in unstimulated peripheral blood mononuclear cells at baseline and 2 weeks (t1), 2 months (t2) and 10 months (t3) during therapy.

Results: HIV-specific (but not mitogen-stimulated) IL-2 and IFNγ production was augmented and IL-10 production reduced in these patients. Immune modulation correlated with a reduction in plasma HIV-1 RNA and an increase in the CD4+ cell count. These changes occurred late in therapy (t2 and t3) and were confirmed by quantitation of cytokine-specific mRNA. Antigen-stimulated proliferation was only marginally influenced.

Conclusions: Therapy with EFV, NFV and d4T increases HIV-specific type 1 cytokine production and CD4 counts, and reduces plasma viraemia. EFV-including therapeutic regimens should be considered in advanced HIV infection.

P61

Immune reconstitution mimicking relapse of non-Hodgkins lymphoma in HIV

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Aim: Relapse following aggressive chemotherapy for AIDS-related lymphoma (ARL) is frequent, and may present with unusual extranodal features. Immune restoration following highly active antiretroviral therapy (HAART) may produce similar clinical findings. We present three cases of immune reconstitution mimicking relapse of ARL, emphasising the importance of histological conformation of relapse. All three patients developed suspicious features following a rise in CD4 count due to HAART.

Patients and methods: The patients were aged 28–52 years. Before the suspected relapse of high grade non-Hodgkins lymphoma (NHL), all three had started or changed HAART due to a suppressed CD4 count (10–51 cells/μl). Patient 1 developed lymphadenopathy, 4 years after stage 1B NHL involving the neck. The biopsy revealed follicular hyperplasia. Patient 2 was diagnosed concurrently with HIV and 4B NHL. He commenced HAART and chemotherapy and showed an excellent response by the NHL and CD4 count. After four cycles he developed extensive pulmonary infiltration due to *Mycobacterium tuberculosis*. Patient 3 developed a fever as well as cervical and para-aortic lymphadenopathy, 2 months after completing chemotherapy for 4B NHL. The biopsies revealed *Mycobacterium avium* complex.

Conclusions: These three cases demonstrate the need for a histological conformation of relapsed NHL to exclude other diagnosis, including immune reconstitution syndromes that may mimic recurrent NHL.

P62

True gynaecomastia, another immune reconstitution disease?

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Background: There have been several reports of gynaecomastia in HIV-1 seropositive patients but the pathophysiology is unclear. We have previously shown that true gynaecomastia can occur with all classes of antiretroviral drugs and now propose a unifying mechanism.

Methods: In a prospective study of all HIV-1 seropositive patients presenting between Nov 1999 and May 2000, 15 patients were identified, all of whom had breast ultrasound to confirm the presence of true gynaecomastia and underwent biochemical, endocrine and tumour marker estimation to exclude other causes.

Results: At the time of diagnosis of gynaecomastia the mean age, CD4 count and viral load of the patients were 42.1±2.8 years, 208±28 cells/μl and 14,3676±41,175 HIV-1 RNA copies/mL respectively. All patients presented with unilateral breast enlargement after a mean of 14.5±2.3 months on HAART. All had radiological confirmation of true gynaecomastia and the biochemical, hormone and tumour marker concentrations were normal. The patients were on differing antiretroviral regimens of two to five different agents. The mean CD4 count increase was 519.4±46.5% and the viral load was <50 copies/ml in all patients; 12/15 had spontaneous resolution of symptoms.

Conclusions. Gynaecomastia is associated with a decreased ratio of free androgens to oestrogens, but the endocrine profile of our patients was normal. After starting HAART, there is improvement in the T-helper cell cytokine response, specifically an increased IL-2 production which has been shown to increase breast tissue proliferation *in vitro*. Also, IL-6 has been shown to increase aromatase activity in breast tissue with a consequent increase in oestrogen available to stimulate breast growth. As all these patients were on successful HAART regimens, we hypothesise that successful immune restoration may result in altered breast tissue oestrogen availability and hence gynaecomastia.

P63

Virology and immunology of Kaposi's sarcoma-associated herpes virus in patients treated with highly active antiretroviral therapy

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Background: AIDS-associated Kaposi's sarcoma can resolve in patients treated with highly active antiretroviral therapy (HAART). This indicates that the immune system can control this disease and the virus that causes it, Kaposi's sarcoma-associated herpes virus (KSHV).

Objective: To investigate plasma KSHV viral load and the cellular and humoral immune responses to KSHV in HAART-treated patients.

Methods: KSHV serology and viral load were evaluated in 27 homosexual men starting antiretroviral therapy for the first time at baseline and every 3 months thereafter.

Results: Twenty-one of 27 patients were treated with a non-nucleoside reverse transcriptase inhibitor-containing triple regimen, and six with a protease inhibitor. Of the 27 patients: three had no follow-up, one for <3 months and 23 had a median follow-up of 9 months (range 3–15). Baseline: CD4 count 180×10^6 cells/μl (range 10–350), plasma viral load (VL) median 159,600 HIV-1 RNA copies /ml (range 4100–792,500). At 6 months, 18/19 had <50 copies /ml, median CD4 count 290×10^6 cells/μl (range 80–500). Six patients were KSHV antibody (Ab)-negative at baseline: one had no follow-up; three remained negative; two were positive on follow-up. Of 21 who were KSHV Ab-positive at baseline, two had no follow-up, 11 had a 2–16 fold increase in Ab titre and seven had a fall in titre or became negative (n=3). One of five patients with baseline KS was Ab-negative and became positive on HAART. Cutaneous KS lesions in two patients resolved on HAART alone.

Conclusions: Of homosexual men recruited, 78% were KSHV Ab-positive and most (61%) had increased KSHV Ab on HAART. Patients with KSHV may be baseline-negative and become positive on HAART.

P64

Limited thymic contribution in CD4 T-cell restoration during early highly active antiretroviral therapy

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Objectives: To measure T lymphocytes that have recently emigrated from the thymus before and during highly active antiretroviral therapy (HAART) to determine the contribution of the thymus to CD4 T-cell restoration during initial stages of therapy.

Methods: The T-cell receptor excision circle (TREC) assay was utilised to quantify recent thymic emigrant T-cell numbers in peripheral blood of 32 HIV-1 infected individuals in order to measure their thymic output before and during HAART. Viral loads, CD4 and CD8 T-cell numbers and naive and memory T-cell numbers were also measured.

Results: TREC levels declined in the first 8 weeks of HAART and increased after this point. Viral loads declined, while overall CD4 and CD8 T-cell numbers remained generally constant throughout the study period. Analysis of CD4 T-cell numbers in patients showing an overall increase in their TREC levels during treatment revealed an initial rise in cell numbers until week 4, after which a decline was observed until 8–10 weeks and increasing thereafter. CD8 T-cell numbers in these patients continually declined until 8–10 weeks, rising thereafter. A similar analysis of CD4 cell numbers in patients displaying an overall decline in TRECs during HAART revealed rises in CD4 T cells up to week 4, which remained constant thereafter. CD8 T-cell numbers in these patients showed a similar pattern to that of CD4 T cells.

Conclusion: Maintenance or increase in CD4 T-cell numbers during the first few weeks of HAART may involve some thymic contribution but appears to be largely due to expansion of existing cells in the periphery. The contribution of the thymus to the restoration of CD4 T cells becomes apparent, particularly in younger patients, during the later course of therapy, approximately 12–16 weeks post HAART.

P65

Relationship between lymphocyte proliferative responses and clinical, immunological and virological variables in patients before the commencement of highly active antiretroviral therapy

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Object: To identify any factors predictive of the strength of T-cell proliferative responses in patients naive to highly active antiretroviral therapy (HAART).
Methods: Peripheral blood mononuclear cells from 56 patients were collected before starting HAART. Lymphocyte proliferative responses (LPR) were evaluated to the following groups of antigens: recall antigens, mitogens and HIV-1 recombinant antigens. Database analysis was extracted for each patient on age, sex, duration of HIV, prior ADI, azole/aciclovir use and baseline CD4 count/HIV viral load (VL). Regression models were used to explore any association between variables and the strength of LPR.
Results: LPR to individual antigens correlated with those to all other antigens. No correlation was seen between the strength of LPR and baseline HIV VL or any clinical variables. There was a significant relationship between baseline CD4 and LPR for most individual antigens. Patients with the lowest strength LPR (<200 counts/m) had significantly higher baseline CD4 counts [mean 327, 95% confidence interval (CI) 314–340] than those with higher responses of >200 counts/m (mean 206, 95% CI 189–223) ($P<0.05$).
Discussion: This cross-sectional study showed that patients with the lowest proliferative responses to a range of antigens tended to have higher CD4 counts, contrary to the belief that proliferative responses are progressively weakened as the CD4 count falls, and may be related to 'stunning' of cellular immune responses in earlier HIV infection, overexpression of the T-cell regulatory response (e.g. 'tolerance') or related to the burden of antigen present. Follow-up is continuing.

P66

Depletion and infection of blood dendritic cells in patients with HIV-1

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Objectives: To monitor the effect of HIV-1 infection on the total dendritic cell (DC), myeloid DC (myDC) and plasmacytoid DC (pcDC) subpopulations.
Methods: Blood samples were obtained from HIV-1 positive patients at different stages of the disease but who were not on antiretroviral therapy. Blood DC numbers were determined by flow cytometry. DC were identified by high-level expression of major histocompatibility class (MHC) II and an absence of staining for CD3, CD14, CD16 and CD19 cells. The DCs were subdivided into two populations based on the expression of CD11c. The absolute number of DC/ml was estimated from the percentage of DC in peripheral blood mononuclear cells.
Results: We studied 37 patients at different stages of HIV-1 infection and compared them with 16 uninfected controls. DC numbers were reduced at all stages of HIV infection and with a more pronounced loss in those patients with viral loads above 2×10^5 HIV-1 RNA copies/ml. Both myDC (CD11c+) and pcDC (CD11c–) were reduced with increasing viral load. Analysis by flow cytometry showed that both populations of DC expressed CD4 and the chemokine receptors CCR5 and CXCR4, suggesting that they are potential targets for infection and that this may be one mechanism for the loss of DC in HIV-1 infected patients. Semi-quantitative polymerase chain reaction showed that a purified population of DC contains HIV-1 provirus.
Conclusions: DC are potent antigen-presenting cells. HIV-1 infected patients experience loss of blood DC numbers and this loss may contribute to disease progression. Therefore, therapeutic strategies should aim to restore the DC population.

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CD4 count prediction from CD4 percentage

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Background: It has been shown that the CD4 cell percentage is a better prognostic indicator of progression to AIDS than the CD4 count. CD4 counts, however, have been adopted for use and validated as a useful surrogate marker in various cohorts. On occasions we have had CD4 percentages assessed without a corresponding lymphocyte count to calculate the CD4 count.
Aims: To determine whether the correlation between CD4 counts and percentages in our cohort is high enough to predict the counts from the percentages when CD4 counts are unavailable.
Patients and methods: The Whittall Street Clinic HIV cohort database was used. It contained prospectively collected records of CD4 counts and percentages with over 1500 entries. These records were from a multicultural urban cohort in Birmingham, UK.
Results: There was a linear correlation between the CD4 counts and the percentage. A CD4% of 12 predicts a CD4 count of 514 (95% confidence interval 467–560).
Discussion: There can be no absolute correlation between the CD4 count and percentage because the count is dependent on the lymphocyte count and is subject to inter- and intra-individual variation. With a missing lymphocyte count in our cohort it may be possible to predict the CD4 count from the percentage, bearing in mind the above limitations.

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