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CONTENTS

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EDITORIAL

Conference attendance this month has taken us a little less far afield than usual, and we report from the 9th BHIVA meeting in Manchester.

A summary of the BHIVA 2002 treatment audit was presented, which gives a fascinating insight into what is actually happening in treating HIV in clinical practice in this country, and to what extent the national guidelines are being followed.

Revisions to the current BHIVA guidelines were also discussed, and these are available for comment from the first week of June on the BHIVA website, prior to final publication on the website in July and in HIV Medicine in October.

We also report on some of the presentations reflecting the diversity of populations with HIV, and in turn the diversity of issues they and their healthcare workers are facing in Britain today.

Our own UK-CAB meeting in May focused on TB coinfection, and access to treatment for UK visitors, refugees and asylum seekers. The reports from the meeting, together with slide and reading material are now on our website at:

http://www.i-base.info/ukcab/may03/

Finally on a completely different note, a big thank you is in order to photographer Wolfgang Tillmans whose exhibition “If one thing matters, everything matters” is currently on show at Tate Britain.

A beautiful limited edition print was made available for purchase at the preview of this exhibition to raise funds for i-Base.

i-Base does not receive any statutory or government funding - and continues to provide all services and publications free of charge - so we’re always in need of cash and especially appreciate funds raised through such an aesthetic route...

CONFERENCE REPORT

9th Annual British HIV Association Conference (BHIVA)

24-26 April 2003, Manchester

The 9th Annual British HIV Association (BHIVA) Conference was held from 24 to 26 April in Manchester and was attended by more than 650 clinicians and other healthcare workers and, thanks to the growing scholarship and assistance programme, a large involvement from UK community organisations which accounted for approximately 10% of registrations.

The meeting mainly provided a focus for UK research presentations.

The abstract book from the conference is available to download as a searchable pdf file from:

http://www.bhiva.org/conference.htm

UK 2003 audit and national standards of care

Simon Collins, HIV i-Base

One of the most interesting sessions at the meeting was the summary from the 2002 treatment audit. The audit is organised by BHIVA to evaluate the extent to which treatment guidelines are being followed in a wide range of 90 clinics across the UK - with current collective caseload of more than 21,000 patients. Participation in the audit is voluntary and is not compensated, and it is clear that clinic results will remain anonymous. Each clinic completes a summary from the most recent (25-50) case notes.

This year’s audit specifically focused on a survey of clinic practice and policies on starting treatment, follow-up of the 2001 audit, and arrangements for maternity care.

A rough breakdown of the participating clinics which provided regional and patient numbers is shown below:

No of pts	London region	Outside London	Total
1-100	6	55	62
100-500	14	25	39
>500	8	2	10

Increased caseload in >95% clinics

Firstly, fewer than 5% of clinics outside London and no clinic inside London reported either a similar or reduced caseload. Importantly, more than 50% of clinics, both inside and outside London, reported an increase of over 15% in patient numbers.

Access to treatment and care when starting treatment

When asked about local policies on starting treatment, 74% of centres said their policy was to follow BHIVA guidelines. Thirteen per cent have local policy/guidelines that supplement BHIVA. Four percent have no local policy/guidelines and nine per cent did not answer.

When asked about policy on adherence (and one of the BHIVA recommendations is for hospitals to have a policy on adherence), 34% had local policy/guidelines on adherence, 58% did not and 8% did not answer.

Currently there is very little indication that there are restrictions on the choice of ARV drugs. Eighty-eight per cent of clinics had no restriction, only 2% have restrictions on cost and a further 2% have restrictions due to clinic policy. (8% of clinics did not answer).

Follow-up of patients starting treatment for the first time (based on physician reply rather than patient notes) showed that 63% of centres see a patient again after one or two weeks and 29% between two and four weeks. Only 2% of clinics wait for longer than four weeks and 6% did not answer. However first viral load after starting ART is only provided within four weeks by 39% of centres. Eighteen per cent wait until six weeks, 18% until seven to eight weeks and a disturbingly high 18% wait until 10 to 12 weeks. (9% did not answer).

An early (two to four weeks) initial viral load test, to at least confirm antiviral activity, has been included as common practice in many clinics for several years and will be strongly recommended in this year's guidelines. It would be interesting to know whether an earlier revision of the guidelines could have improved this aspect of practice earlier.

Of 924 patients who started treatment for the first time, 56% were male and 44% female. Fifty-five per cent were Black-African and 36% white. Stated reasons for starting treatment included: disease progression (85%), prevention of vertical transmission (12%, and this was the sole reason for more than three-quarters of these patients), patient choice (9%), high viral load (29%) and recent seroconversion (3%).

Given the importance placed on starting treatment with a CD4 >200 cells/mm3 it is interesting to be able to look at the patterns for actual initiation of therapy. This audit showed that even among those with advanced disease, a significant minority of people starting treatment were not recently diagnosed. Ten per cent of those starting treatment at CD4 <50 and 20% of those starting treatment at CD4 50-100 had been diagnosed more than six months previously.

The audit was also able to highlight important pre-treatment testing, that should be integral to the effective use of HAART. It is noteworthy that 46% and 41% of clinics did measure blood pressure or serum lipids respectively. Although only 3% of clinics did not test for hepatitis B, 14% did not test for hepatitis C. Without these simple test results it is impossible to assess for cardiovascular risk or to monitor metabolic changes. Hepatitis status is essential prior to starting treatment for choice and dosing of individual drugs.

The figures for resistance testing may have been confused by methods of testing and storage, but the results are very disturbing for patient care. Only 6% of patients received resistance test results prior to starting treatment, with around 25% having a sample taken for storage. More than 50% clearly had neither a test nor sample stored. Given the minimal cost of storage and the importance of building a complete 'resistance history' by testing stored samples at future points of treatment failure, this is a very disappointing aspect of the audit.

Of the 25 patients for whom recent conversion was given as a reason for treatment and for whom the BHIVA guidelines clearly indicate the risk of infection with drug-resistant virus, only 16 were tested for resistance.

It is only possible to make general comments about the choices of combination therapy because a few confusing results cast doubts on the accuracy of recorded data. Although 65 different combinations were reported, 90% of patients were started on recommended combinations. With a backbone of two nucleosides, 60% used an NNRTI (with a 3:2 preference for efavirenz over nevirapine), 10% used a PI and 12-15% used a third nucleoside. The most non-recommended combinations were tenofovir-including (n=42) and triple-nucleoside plus NNRTI (n=36) regimens. Nine of the patients starting tenofovir had hepatitis B coinfection and seven of these patients also included 3TC in their initial combination.

Management of HIV and pregnancy

The audit was also used to assess current arrangements for testing pregnant women for HIV. Of 104 centres 10% offered an opt-in service, 88% an opt-out service and 3% a selective service. HIV clinician estimates for the percentages of women offered antenatal testing at 94 of these centres was:

% women tested	number (%) of clinics
0-30%	3 (3%)
30-60%	6 (6%)
60-70%	11 (12%)
70-80%	19 (20%)
80-90%	24 (26%)
>90%	31 (33%)

Feedback from 2001 audit

Although results from the audit remain confidential, an important part of the project is to offer individual reports back to clinics so they can assess their own performance, and this opportunity was taken up by fewer than half of the clinics participating in the previous audit.

Six per cent of clinics reported that the audit process changed their clinical practice.

Summary

Summary findings from this preliminary report were therefore that:

- most centres report >15% rise in their HIV caseload over past year
- 38% of centres do not test VL until at least six weeks after starting ART
- significant delays can occur between diagnosis and starting ART even for patients with extremely low CD4 counts
- BP, glucose and/or lipids were not measured before starting ART in half of patients
- although many different drug combinations were used, most patients started on 2NRTI/NNRTI or other standard HAART.

Ref: Brook G, BHIVA audit and updates. Symposium session. 9th BHIVA Conference, 24-26 April 2003, Manchester.

Outline of changes to UK guidelines for treating HIV in adults

Simon Collins, HIV i-Base

The bi-annual review of the UK treatment guidelines, produced by the British HIV Association, is already largely written, and Dr Duncan Churchill provided an outline of the committee's thinking for the main changes.

The purpose of guidelines is listed as to promote a uniformly high standard of care, to set out the strengths, weaknesses and relevance of research findings, to assist in discussions between purchasers and providers, to act as a basis for clinical audit and as a source of reference for physicians and HIV-positive people.

Key issues

- Treatment in primary HIV infection will be recommended if needed to relieve severe symptoms but is not generally recommended otherwise, unless as part of a clinical trial. Treatment during chronic infection remains largely determined by CD4 count, with recommendation to start treatment while still 200-350 cells/mm3 or at higher levels if symptomatic. Exact timing depends on various factors, including determinants of short-term risk.
- Considerations for recommending treatment regimens include ease of adherence and minimising toxicity, and should take account of individual factors, e.g. hepatitis B/C, risk of cardiovascular disease, diabetes, psychiatric disease, lifestyle.
- Recommended options for starting treatment remain based on the dual nucleoside backbone, plus either an NNRTI or a boosted-PI. The committee believes there is no definitive evidence on which to base a preference but accept that based on the most recent audit that clinicians currently favor NNRTI-based first-line treatment.
- Unboosted PI regimens will not be recommended for first choice due to poorer pharmacokinetics, and less convenient dosing.
- Triple nucleoside combinations previously favoured by the BHIVA committee such as Trizivir (AZT/3TC/abacavir) are not now recommended due to lower potency shown in recent trials. They will no longer be recommended even for patients with a low baseline VL (<50,000). d4T regimens are not recommended due to increased association with lipodystrophy.

- Use of resistance testing is recommended prior to starting treatment. In practice this means that people should receive or have a sample stored for later testing when diagnosed.
- Resistance testing is also recommended with any confirmed virological rebound or failure, when the likely cause of failure should be determined before deciding on subsequent treatment. This should prompt assessment of other factors such as resistance, adherence, and pharmacokinetics.
- If reasonable options are available, switch regimen as soon as virological rebound is confirmed (two consecutive viral loads >400), otherwise continue current therapy unless at high imminent risk. If at high imminent risk, switching treatment should be considered even if the next regimen is unlikely to be optimally suppressive.
- Interrupting or stopping treatment may benefit patients with high pre-treatment CD4 count (not specified in the overview) and undetectable viral load, but careful monitoring is needed. It is not recommended in treatment failure for those with other good options, although salvage patients with no good options, can consider entry into clinical trial of structured treatment interruptions such as Optima.
- Two new sections are to be included in the guidelines: one to cover monitoring tests and another to address patients who now find themselves using treatment combinations not now recommended in the guidelines (such as Trizivir or d4T).
- Therapeutic drug monitoring (TDM) is seen as being of value in specific circumstances, such as reducing toxicity, and adjusting doses in significant hepatic or renal impairment, and will be referenced as tabled recommendations.
- Sections on the management of side effects such as lactic acidosis, metabolic changes and lipodystrophy (to include a stronger recommendation for New-Fill), will be updated and finally, a short section will be included on drugs in development that are likely to be licensed over the next year.

The full guidelines are likely to run to 50 pages plus references, with detailed chapters on many important aspects of HIV care. A shorter summary will also be produced that outlines the main changes. It is hoped that this reduced summary will provide a clearer guide to the general approach to treatment.

The final guidelines together with the summary will then be available to download as a pdf file on the BHIVA website. They will be published in the October issue of HIV Medicine.

Ref: Churchill D - BHIVA treatment guidelines. Symposium session, 9th BHIVA Conference, 24-26 April 2003, Manchester.

C O M M E N T

Comments are invited and encouraged from clinicians, community groups, the pharmaceutical industry and other interested parties. As in previous years, these comments will be included on the website to provide a public discussion. The draft document will be posted to the internet in the first week of June at:

http://www.bhiva.org

Gender differences in rates and reasons for stopping treatment

Polly Clayden, HIV i-Base

Sapna Shah and colleagues from the Royal Free Hospital, London, compared rates and reasons for stopping treatment between men and women.

This retrospective audit was performed using data from 785 drug naïve HIV-positive patients (initiating HAART (either PI or NNRTI containing) between 1996 and 2002.

Comparisons were made between genders and different treatment groups – one PI, one NNRTI, two PIs, >one NNRTI and one PI and one NNRTI.

Women made up 24% of the group and they were mostly black African (63%), heterosexual (90%) and their median age was 32 years, while the men were primarily white (79%) and homosexual (75%) with a median age of 35. The investigators found that men initiated HAART eight months before women from first diagnosis and at higher CD4 counts. Forty-seven per cent of women vs 39% of men began therapy on a single NNRTI containing regimen and 50% of men vs 42% of women started with a single PI containing regimen.

There were no significant differences between genders in reasons for stopping therapy overall and median time to stopping was shorter for women than for men, 422 vs 675 days, but not significantly (p=0.2). However differences were reported across treatment groups. Women were 22%, 40% and 700% more likely to stop a single PI, a single NNRTI and a dual PI regimen respectively than men.

The investigators concluded, "Median times to stopping/switching a first HAART regimen were quite long. Rates of stopping may be higher in women."

Ref: Shah S, Smith C, Lampe FC et al. Gender differences in the rate of stopping highly active antiretroviral therapy (HAART). 9th BHIVA Conference, 24-26 April 2003, Manchester. Abstract P44

Maternal health, transmission and fertility

Polly Clayden, HIV i-Base

Good maternal health outcome following 218 deliveries

An oral presentation by Hermione Lyall from St Mary's Hospital in London evaluated long-term outcome for a group of 245 HIV-positive pregnant women from a multicentre cohort in London. [1]

As is the case throughout the industrialised world, thanks to greatly improved health and survival expectations, there has been a dramatic increase in the number of HIV positive women becoming pregnant in the UK in recent years.

Few studies have evaluated the longer-term health and survival of these women.

For this study the investigators performed a chart review of all women with an HIV positive diagnosis and prospectively recorded follow up in antenatal care in five London centres between January 1998 and December 2000.

The majority of the women studied were African (n=205) and the mean age at delivery was 30.4 years.

At the first antenatal visit 183 women were defined as CDC status A, 27 B and 19 C. Overall the mean CD4 count was 353 cells and median viral load 4,700 copies/mL. At delivery the mean CD4 was 413 cells and viral load 2,168 copies/mL. 158 mothers conceived on triple therapy; 115 commenced triple therapy during pregnancy - 51 used 'START' (short term antiretroviral therapy), 64 continued after delivery and 10 had an unknown treatment outcome - and 69 women received only zidovudine (ZDV, AZT, Retrovir) monotherapy prophylaxis.

Elective caesarean sections accounted for the vast majority of deliveries for women receiving both monotherapy and triple therapy - 81% and 70% respectively. In addition 6% of women receiving monotherapy and 12% receiving triple therapy had vaginal deliveries and10% of women receiving monotherapy and 18% of women receiving triple therapy had emergency C-sections.

At last follow up (median 18.1 months) median CD4 and viral load were 527 cells/mm3 and 795 copies/mL, and 410 cells/mm3 and 49 copies/mL, for women receiving mono and triple therapy respectively. Two mothers progressed to category C receiving triple therapy and one receiving monotherapy, and there was one maternal death in the triple therapy group, from lactic acidosis.

The investigators reported good maternal health overall and no evidence of adverse effect of ZDV monotherapy on maternal survival to 18 months. The investigators expect to generate future data from this cohort on transmission rates, time to start ongoing therapy, combinations of HAART used and longer-term outcomes. It would also be useful to evaluate the possible effect of any ZDV resistance generated by those women receiving ZDV monotherapy and the effect on future treatment options.

Seminal super-shedding…

Steve Taylor from Birmingham Heartlands Hospital presented some research on what he termed, with a snappy display of alliteration, "seminal super shedding"' of HIV…

In this study the investigators hypothesised that although the majority of men have lower levels of HIV in semen than in blood plasma, a minority appear to have HIV RNA in semen in excess of that in their blood plasma and that these 'seminal super shedders' may represent a group at greater risk of transmitting HIV-1. [2]

A group of 72 men, not currently receiving therapy, were enrolled. Overall they had a median CD4 count of 214 cells and 25 were defined as CDC status A, 17 CDC status B and 31 CDC status C, 44 were drug naïve and 28 had previous treatment experience.

Matched blood plasma and semen samples were obtained at the same time as carrying out tests for urethritis, determining viral load. The investigators defined seminal super shedding as SPVL/BPVL ratio >1.

They reported that none of the men had BPVL<400 copies/mL but 22/72 (30%) had SPVL <400 copies/mL despite detectable BPVL – this group were defined as non-shedders. 41/72 (58%) had detectable virus in semen – defined as normal shedders and 9/72 (12%) shed virus into semen in excess of blood - super shedders.

Of the nine that met the super shedder criteria, the investigators found that they had significantly higher SPVL compared to non super shedders (5.6 log 10 copies/mL vs 3.4 log/mL10, p<0.001), but their BPVL was not significantly different. They also

reported that seminal super shedders tended to be older – 48 vs 35 years (p<0.02) — and the presence of urethritis was significantly over represented in the super shedders compared to the other groups 3/9 (33%) vs 3/63 (4.8%) (p=0.02). There were no significant differences in BPVL >100,000, CD4 counts and CDC status between seminal super shedders and normal shedders.

The investigators speculated that this viral replication occurs locally in the genital tract and that these individuals may have a high probability of sexual transmission of HIV.

Sperm washing and fertility treatment in the UK

Two presentations from the Assisted Conception Unit at Chelsea and Westminster Hospital in London, described both the safety and efficacy of sperm washing and the increasing demand for this and other fertility services.

Carole Gilling-Smith reported that the unit's sperm washing programme (a safe reproduction technique for serodiscordant couples where the woman is HIV negative and the man HIV positive) had so far treated 53 couples since 1999. [3]

Both partners receive a sexual health and fertility screen; semen is then spun in a centrifuge and checked for HIV RNA. Following the success of these procedures, either intrauterine insemination (IUI) or *in vitro* fertilisation (IVF/ICSI) is performed – the latter if a fertility factor is diagnosed.

Thirty-eight couples received 94 cycles of IUI and 30 couples 42 cycles of IVF/ICSI. Pregnancy/live birth rates per cycle were 10.6% (10/94) for IUI and 23.8% (10/42) for IVF/ICSI. To date 15 children have been born and both mothers and children have had rigorous follow up with no reported seroconversions.

This service is largely accessed through self funding (91%), only five couples received NHS funding and more than 40% of couples referred were unable to proceed due to financial reasons. The cost per cycle is £625 and therefore prohibitive for many couples.

The investigators concluded that sperm washing at a specialist centre is a safe and effective risk reduction intervention. But they also noted: "Lack of NHS funding for this service may force couples to consider unprotected intercourse."

Additionally Leila Frodsham, from the same group, described an audit conducted of 294 UK GUM clinics concerning requests for this and other assisted reproduction techniques among HIV discordant/concordant couples. [4]

She noted that demand is increasing due both to an increase in HIV prevalence among the heterosexual population and the effects of HAART on both life expectancy and mother to child transmission risk.

The investigators had a 63% response rate to their questionnaire (186/294), in which 83/186 clinics had received requests for information concerning conception from patients (15,211 HIV positive patients are registered at 81/83 of these clinics). Over half 49/83 (59%) of these units had referred men for sperm washing and 42/83 (51%) had referred women for assisted reproduction. However, only 12/83 (14%) units had successfully secured HIV-prevention funds from local authorities for sperm washing. In addition 96% of the 83 clinics believed that a national database of units providing these procedures would be of benefit when referring patients.

They conclude that their survey highlights the high demand for fertility services for HIV positive couples, the need to improve current services to meet this demand and the need to make information available to referring physicians. The matter of cost being a deterrent is a serious one and health authorities must address this issue.

References

All references are to abstracts presented at 9th BHIVA Conference, 24-26 April 2003,Manchester.

1. Taylor GP, Sarner L, Khan W et al. AIDS-free survival of 218 HIV-infected women following pregnancy. Abstract O1.
2. Taylor S, Sadiq T, White D et al. Seminal super-shedding of HIV: implications for sexual transmission. Abstract O2.
3. Gilling-Smith C, Tamberlin B, Cox A et al. Sperm washing in the UK: evidence of safety and efficacy. Abstract O3.
4. Frodsham LCG, Boag F, Barton S et al. An estimation of the UK demand for fertility services in HIV-positive couples. Abstract O4.

Related links:

Presentation by Leila Frodsham to UK-CAB:
http://www.i-base.info/ukcab/oct/index.html

'Sperm washing' hope for HIV patients - BBC News:
http://ww2.aegis.org/news/bbc/2003/BB030411.html

C O M M E N T

Results from the Italian clinic where sperm washing was developed under Enrico Semprini clearly shows that this technique provides an important and safe way for a serodiscordant couple to have children where the male partner is HIV-positive and the female partner is HIV negative.

Although risks of transmission are reduced when a positive partner has an undetectable viral load in semen, viral load results from blood tests clearly do not reliably correlate and even single exposure risk can lead to HIV-infection.

The importance of providing sperm washing services as an option for such couples on the NHS should be prioritized as a health care and prevention issue.

Women: sexual function and relationships

Polly Clayden, HIV i-Base

Two posters from Keegan, Lambert and colleagues at St Bartholomew's Hospital, London, explored sexual functioning and relationships of HIV-positive women living in the UK. [1, 2] The findings from this study reveal a wide range of sexual difficulties including abstinence and avoidance of relationships.

For these studies, 82 HIV-positive women completed semi-structured interviews and questionnaires. Of the group participating, 75% were African and their mean age was 37.9 years and the mean length of time since their diagnoses was 68.5 months (range 4-191 months). Only 37% had an undetectable viral load and 19% had a CD4 count below 200 cells/mm3.

Twenty-eight per cent of women reported no sexual partners since diagnosis and 36% reported having had one partner since diagnosis. Time since diagnosis was not associated with having a sexual partner. A shocking 41% of women reported a history of sexual abuse, 34% reported past physical abuse and 6% reported that they were currently being abused.

In addition the women reported high levels of impaired sexual satisfaction - as defined by the Golombok and Rust Inventory of Sexual Satisfaction (GRISS) – predominately infrequency of sex (84%), avoidance (84%), non-communication (68%) and dysfunction (60%). The women also reported high levels of depression and anxiety.

The investigators reported high prevalence of sexual and relationship difficulties in this sample, which point to the need for more psychosexual and psychosocial interventions to address their needs. Clearly, given the high proportion of HIV-positive women from Africa in the UK, such interventions would need to be culturally appropriate to this population.

Association of torture and abuse with HIV transmission

More alarming still was a poster from Miah and colleagues from Newham Hospital, east London, documenting emerging patterns among their HIV-positive African women patients reporting rape and torture prior to seeking asylum and treatment in the UK. [3]

Approximately 80% of refugees worldwide are women and children and 50% of these women have experienced rape by soldiers or police. Many asylum seekers arrive in the UK having experienced such traumas and this pattern is reflected at the Sun Clinic at Newham.

The investigators illustrated this emerging pattern of HIV transmission associated with histories of torture (involving rape) and trauma of African women with case studies showing the problems of clinical management of such patients.

They reported that women with undisclosed histories of torture and trauma associated with HIV diagnosis have reported feeling retraumatised at the point of diagnosis due to the association; that language barriers and the nature of the experiences can result in non-disclosure to their healthcare team necessitating referral to a psychologist and in turn such difficulties with engagement with the medical system can impact on adherence, disclosure, sexual and mental health.

Clearly models of care for patients with high levels of distress, such as the one developed at Newham are essential in facing these challenges.

References

All references are to abstracts presented at 9th BHIVA Conference, 24-26 April 2003,Manchester.

1. Lambert S, Keegan A and Petrak J. Sexual functioning in HIV+ women. Abstract P24
2. Lambert S, Keegan A and Petrak J. Sex and relationships for HIV+ women. Abstract P27
3. Miah J, Poulton M, Lewis J et al. Emerging patterns of HIV transmission associated with experiences of torture and trauma in African women in East London. Abstract P19

Paediatrics: neurological and developmental outcomes

Polly Clayden, HIV i-Base

Rebecca Biggs from St Mary's Family Clinic, London, highlighted the importance of continual developmental monitoring for HIV positive children in an oral presentation. [1]

This study compared neurological and early developmental outcome of two groups of children under three years and earlier and later disease stages. Group 1 was defined as presenting with severe HIV disease other than encephalopathy (category

C) and Group 2 presenting with mild or moderate disease (category A/B).

A paediatric physiotherapist and a paediatrician evaluated the children's neurological functions, and development was assessed using the Bayley Scales of Infant Development II by a clinical psychologist and paediatric physiotherapist.

The investigators found 43% of children in group 1 (n=32, mean age at assessment 16 months) had abnormal neurological signs compared to 7% (n=31, mean age 18 months) in group 2. Twenty per cent of group 1 and 61% of group 2 had developmental scores within the normal range in both mental and motor functions.

The investigators concluded that in the era of HAART severe early HIV disease still relates to abnormal neurology with motor impairment and developmental delays, and that children are surviving longer with developmental needs. They stressed the need for regular developmental monitoring and these results have implications for community services.

Transition from paediatric to adult care

A poster from Dr K Miles and colleagues from Mortimer Market explored the (complicated and very much on the upswing) issue of HIV positive adolescents in transition from paediatric to adult care. [2]

This small study reports findings from semi-structured interviews with seven adolescents who have undergone transition from paediatric to adult HIV outpatient services.

Issues concerning stigma, new sexual opportunities and the loss of a lifetime healthcare team are all difficult factors for adolescents transferring care from paediatric to adult clinics. The investigators emphasised that "Neither a simple transfer to adult services nor allowing adolescents to 'drop out' of medical care is considered acceptable care for young people with HIV".

The feedback from those interviewed include a beneficial effect of including adult healthcare providers early on in the preparation for transition, concerns over the co-ordination of haemophiliac and HIV care (anecdotally this seems complex throughout adult care), and lack of preparedness for an adult and predominately gay clinic population. The benefits included a sense of independence, increased responsibility and the satisfaction of being treated as an adult. Those who had had a strong rapport with their paediatric HIV team experienced a sense of loss. Some found the transition 'easy' and others expressed concerns.

The investigators felt that this study supports the need for effective transition protocols and the development of adolescent-specific models of care to best facilitate this crossover from paediatric to adult care facilities and their ongoing care as adults.

References

All references are to abstracts presented at 9th BHIVA Conference, 24-26 April 2003,Manchester.

1. Lyall EGH, Foster C, Melvin D et al. Neurological and developmental outcomes in HIV-infected children presenting before 3 years of age. Abstract O5
2. Miles K, Prime K, Sudlow J et al. Bridging the gap between paediatric and adult HIV services. Abstract P21

The impact of migration, race and ethnic diversity on healthcare delivery and clinical outcomes in the UK

Polly Clayden, HIV i-Base

Three oral presentations and a number of posters highlighted issues of ethnic diversity in the UK and the impact of this on both healthcare delivery and clinical outcome.

Newly diagnosed women in Leicester

Dr Chapman from the GUM department at Leicester Royal Infirmary presented the results of an audit of newly diagnosed HIV positive women from January 2000 to December 2002. [1]

He reported that new diagnoses rose by 61% during this period in their area (the government's policy of 'dispersal' of asylum seekers has contributed significantly to this situation), and the aim of this study was to see if the national implementation of antenatal HIV screening has contributed to this rise and the impact it has had on services.

The investigators reported 129 newly diagnosed women during this period – of whom 31 (24%) were pregnant: "As this dispersal continues, more clinics will need to develop patient care pathways, with access to both healthcare and social-care professionals."

South Asians in London

South Asia has one of the fastest growing HIV epidemics in the world and to date there have been no data to describe HIV positive South Asians in the UK.

Sethi and colleagues performed a review of all South Asian patients (defining their ethnicity as Indian, Pakistani, Bangladeshi or Sri Lankan) presenting at four London hospitals between January 1985 and December 2002. [2]

Of the 116 patients identified 88 were men and 28 women. Their regions of origin included Africa (39%), the Indian subcontinent (35%) and the UK (16%). Mode of transmission included heterosexual 61 (53%), MSM 36 (31%), unknown 13 (11%), IDU 2 (2%) and transfusion 4 (3%) Their median age of diagnosis was 34 years and median CD4 298 cell/mm3, and heterosexuals were more likely to present late than gay men (CD4 214 vs 390 cells mm3 p=0,03) and to have an AIDS defining illness. They were also significantly less likely to be diagnosed in a GUM clinic (2/74, 3% vs 17/36, 47% p<0.001).

The investigators reported 129 newly diagnosed women during this period – of whom 31 (24%) were pregnant and antenatal screening identified 15 (12%). Of the 129 women 115 (89%) were infected outside the UK and 109 (95%) of in sub-Saharan Africa. 60 (55%) of these women are seeking asylum.

The investigators also noted that a large number of these women presented with advanced HIV disease, and that they required HAART either for themselves or to prevent mother to child transmission. And they added " As this dispersal continues, more clinics will need to develop patient care pathways, with access to both healthcare and social-care professionals."

HIV and black Caribbeans in the UK

Likewise, prevalence rates in the Caribbean are high. The UK has an estimated black Caribbean population of 612,000 and continuing immigration so inevitably the numbers of black Caribbeans living with HIV in the UK are increasing (almost six-fold since 1995).

Dougan and colleagues, on behalf of the Communicable Disease Surveillance Centre (CDSC), London, looked at data on new diagnoses received by the CDSC until 30 September 2002 and on diagnosed prevalent infections from the Survey of Prevalent Diagnosed HIV Infections (SOPHID). [3]

They reported 759 diagnoses of black Caribbeans since the beginning of the epidemic, the majority since 1998. Of these 531 (70%) were men and 228 (30%) women. Median ages at diagnosis were 33.7 years for men and 32.9 years for women. Regions of infection (recorded for 530 people) included 270(37%) probably infected in Latin America and the Caribbean and 194 (37%) in the UK. 297 (39%) were infected through sex between men and 407(53%) through heterosexual sex (of which 195 were men).

They also reported that SOPHID 2001 recorded 705 black Caribbeans receiving HIV-related treatment and care in England Wales and Northern Ireland, a 57% increase since 1999. In 2001 they recorded that 538 (76%) black Caribbeans with HIV lived in London.

In addition to reporting this increase the investigators stressed that "Targeted and culturally sensitive prevention methods are required to address this issue", and we would add targeted and culturally sensitive treatment information.

Another study evaluated subtypes, and other demographics, of black Caribbean patients at London's Kings College Hospital. [4] Aggarwal and colleagues collected data for 169 black Caribbean patients and 42 were subtyped using an in house assay.

They reported that 121 (72%) of the patients were men, 56 (46%) MSM and 41/48 (85%) of the women were infected heterosexually. Regions of origin included 73 (53%) Jamaica, 53 (39%) UK, and 11 (8%) elsewhere in the Caribbean. The median age at diagnosis was 31.5 years and the median CD4 count 316 cells/mm3; 18 (11%) had an AIDS diagnosis at presentation. The investigators noted that this is similar to the CD4 at presentation among their white patients (median 312 cells/mm3) but higher than their African patients (median 227 cells/mm3 p<0.05).

They report that 57.5% were subtype B, which was strongly associated with infection acquired through sex between men (60% vs 23% p<0.05). Non B subtypes included: five subtype C (four born in UK, one in Jamaica), two A (one UK, one Jamaica), two D (one UK, one Jamaica), one F (Jamaica), one H (Trinidad and Tobago), one CRFO2_AG (UK) and two B/C mosaics.

Non-B subtypes were therefore common among their cohort and the investigators pointed to the urgency for "in-depth studies into the emerging HIV epidemic among black Caribbeans in the UK."

Risk behaviour and the meaning of "resistance" in African patients in central London

Davidson and colleagues reported findings from the Padare project on behalf of the Mortimer Market Centre and African HIV Policy Network, London. [5] This study, conducted in the form of a questionnaire, aimed to assess risk knowledge, attitudes and behaviour in a group of HIV-positive African migrants living in London.

The questionnaire, distributed through two clinics and seven community groups elicited response from 214 HIV-positive Africans. Seventy-four per cent reported having had penetrative sex in the past month and of these 40% reported occasional or no condom use. Sixty-one per cent of respondents reported having had unprotected sex in the past year.

As an example of HIV knowledge, the investigators reported that only 18% were sure that they knew what "drug resistance" meant and 20% were unsure if "resistance' meant they could not transmit HIV to their partners. They continued: "Sixteen per

cent claimed they had been told they had developed resistance, with another eight per cent unsure whether they had been told this." And 45% of the sexually active study participants who had been told they had resistance reported inconsistent or no condom use in the previous month.

These findings suggest that healthcare workers and community groups, such as ours, need to do a better job concerning HIV information and misinformation…

Subtype, disease progression and response to treatment

Finally two studies from King's College and St Thomas' hospitals in London addressed some clinical aspects of an ethnically diverse cohort. [6, 7]

Philippa Easterbrook and colleagues compared the rate of immunological progression prior to antiretroviral therapy, on initiation of HAART and on virological rebound in patients with B vs non-B subtypes.

A group of 867 HIV-positive patients were subtyped using an in house assay. It found that 47.5% of patients were subtype B and 34.5% non-B, 5.5% were of mixed reactivity and 12.5% were either non reactive or below detectable limits of the assay (*env* gene sequencing was used to confirm exact distribution of non-B subtypes and mosaic strains).

CD4 count was recorded to determine disease progression and response to HAART. Response to HAART was assessed on time to viral load <50 copies/mL and rebound as time to >50 copies/mL.

Analyses of the subtypes revealed that 457 patients were B and 317 were non-B subtype. Of these 60 (19%) were A, 114 (36%) were C, 30 (9%) were D and 14 (4.4%) were infected with recombinant strains. Some 82.2% of recombinant strains were Africans from Sub-Saharan Africa (mostly Uganda, Zimbabwe, Nigeria, Ivory Coast and Ghana).

The investigators reported a similar rate of pretreatment CD4 decline and similar time to undetectable viral load across all subtypes.

Response to tenofovir in a highly drug experienced ethnically diverse cohort

McDonald and colleagues evaluated 48-week response to tenofovir containing salvage regimens in a group of 44 ethnically diverse and highly drug experienced patients.

The study group was 44 HIV-positive patients (28 men and 16 women) of which 38% were black African, 68% Caucasian and 45 black Caribbean with a median CD4 count of 224 cells/mm3. The mean number of previously used antiretroviral drugs was eight, mean number of regimen failures was four and mean number of months on HAART was 47. In addition the mean number of NRTI mutations with thymidine analogue mutations (TAMs) at baseline was two.

At 48 weeks 18 patients had a viral load <50 copies/mL (41%), two had a viral load >50 copies/mL but <400 copies/mL (5%), five viral load >400copies/mL (11%), eight were lost to follow up (18%) and 11 (25%) discontinued therapy. By ITT analysis virological control (viral load <400) was achieved in 46% at 48 weeks. CD4 counts increased by mean 118 cell/mm3 in patients who remained on treatment at week 24. The investigators noted that their results were "…despite a high prevalence of RT mutations known to affect tenofovir susceptibility."

References

All references are to abstracts presented at 9th BHIVA Conference, 24-26 April 2003,Manchester.

1. Chapman C and Dhar J. Migration and HIV: impact on service delivery. Abstract O6.
2. Sethi, G, Fox E, Williams et al South Asians with HIV infection in London: a growing epidemic? Abstract O29.
3. Dougan S, Payne l, Fenton K et al. HIV and black Caribbeans in the UK. Abstract O30.
4. Aggarwai I, Smith M, Geretti AM et al. HIV-1 infection among black Caribbeans in southeast London. Abstract P17.
5. Davidson O, Chinouya M, Ndawula L et al. Risk behaviour and the meaning of 'resistance' in a sample of HIV positive Africans accessing services in central London; clinicians be aware. Abstract P20.
6. Easterbrook PJ, Smith M, Mullen J et al. Relationship between HIV-1 viral subtype, disease progression and response to antiretroviral therapy. Abstract P59.
7. McDonald C, Kulasegaram R, Smith M et al. The impact of antiretroviral resistance on responses to tenofovir in an ethnically diverse population of highly antiretroviral drug-experienced HIV-infected patients in South London Abstract P1.

C O M M E N T

The UK government's ill-conceived and inhumane policy of dispersing asylum seekers around the country, on the basis that NHS care is supposedly equal across the UK, has contributed considerably to their often woefully inadequate standard of care. This results in interrupted treatment, ruptured patient-professional relationships and people being sent to areas that have limited or no experience of HIV treatment, with no account taken for necessary social support.

Related link: Issues of working with HIV positive refugees and asylum seekers: Linda McDonald and Badru Male presentation to the UK-CAB:

http://www.i-base.org.uk/ukcab/may03/asylum.html

High levels of gout may be linked to HAART

Graham McKerrow, HIV i-Base

London researchers reported to the BHIVA conference that they had seen a high level of gout in their HIV population from 2000 onwards, especially in patients receiving boosted protease inhibitors.

Researchers from the Mortimer Market Center and University College London, found that most of these patients had dyslipidaemia and clinical features of lipodystrophy. They conclude: "As gout is known to be associated with insulin resistance, atherosclerosis and visceral fat accumulation in the HIV-negative population, this suggests that gout may be another metabolic complication of HAART."

A retrospective analysis of 1,800 patient records was conducted. All cases of hyperuricaemi (elevated uric acid) attending the Mortimer Market Centre between 1 February 2000 and 1 February 2002 were identified from the hospital database. Notes were scrutinised using a standardised proforma, to identify predisposing factors for gout, HIV clinical history, lipodystrophy and laboratory markers.

Eighteen cases were identified, all of which had clinical manifestations of gout and elevated serum urate (mean 686, range 428–1552). Twelve patients had stage C disease and six stage B. Mean CD4 was 356 cells/mm3 (range 50–1100) and mean viral load (VL) 13,559 copies/ml (range below detection to 83,000).

Sixteen of the 18 were receiving highly active antiretroviral therapy (HAART) and had been on it for an average of 41 months (range 3–48). Eight had predisposing risk factors for gout (e.g. pyrazinamide therapy, haematological malignancy). Seven of the remaining 10 were receiving a boosted protease inhibitor (ritonavir (RTV)/saquinavir (SQV) n=5, RTV/indinavir n=1, RTV/amprenavir n=1), they had dyslipidaemia (mean triglycerides 542 mg/dl, range 373–783) and proven features of lipodystrophy. Patients with gout were significantly more likely to be taking boosted SQV than the remainder of the patients at the clinic (50% versus 10%, P<0.00001).

Ref: S Creighton, GP Kasidas, SG Edwards et al. Gout and HIV: a new facet of the fat redistribution syndrome? 9th BHIVA Conference, 24-26 April 2003,Manchester.Poster 12.

C O M M E N T

Elevated uric acid has been reported before in patients on antiretroviral combination therapy with or without lipodystrophy. This is most probably just another monocentric cohort. The prevalence is 1% or less, in which case an HIV-negative control may make sense or at least a comparison with an age-matched data subset on the prevalence of gout in London to put it into perspective.

TREATMENT ACCESS

Global Fund requires 'significant' new money

The US General Accounting Office (GAO) released a long-awaited 75-page report on the Global Fund. The views of the report are captured in its title: "Global Fund to Fight AIDS, TB and Malaria Has Advanced in Key Areas, but Difficult Challenges Remain."

The GAO is the audit, evaluation, and investigative arm of the US Congress. The report did not contain serious criticisms of the Fund as had been anticipated by some anti-Fund members of Congress. The report summarises its findings as follows:

- "The Fund has made noteworthy progress in establishing essential governance and other supporting structures and is responding to challenges that have impeded its ability to quickly disburse grants. A key challenge involves locally based governance structures, many of which are not currently performing in a manner envisioned by the Fund.
- "The Fund has developed comprehensive oversight systems for monitoring and evaluating grant performance and ensuring financial accountability and has issued guidance for procurement; however, the oversight systems face challenges at the country level and some procurement issues have not been finalised.
- "The Fund's ability to approve and finance additional grants is threatened by a lack of sufficient resources. Pledges made through the end of 2003 are insufficient to cover more than a small number of additional grants and without significant new pledges, the Fund will be unable to support all of the already approved grants beyond their initial two-year agreements.

- "Improvements in the Fund's grant-making processes have enhanced its ability to achieve its key objectives, but challenges remain. These challenges include ensuring that grants add to and complement existing spending on HIV/AIDS, TB, and malaria and that recipients have the capacity to effectively use grants."

Source: Reproduced from the Global Fund Observer Newsletter, a service of Aidspan.
http://www.aidspan.org/gfo

The full report is available to download at:
http://www.gao.gov/new.items/d03601.pdf

Commentary: A crisis the Board must confront

Bernard Rivers, Global Fund Observer

Unless a miracle takes place, many of the proposals to be approved in October in the Global Fund's third round of grants will have to be put on hold as a result of under-funding.

The Secretariat estimated a long time ago that Round 3 would require $1,600m. Of this, a mere $228 million has been promised. The remaining $1,372 million needs to be promised by October and in the bank by about the end of the year.

Dr Feachem, Executive Director, has always said that he assigns the highest priority to resource mobilisation, and has suggested that everything is under control. He informed the board's Resource Mobilisation Committee in April that "he was confident that the outstanding amount required to fund Round 3 would be met by donor countries."

Unfortunately, there is little evidence to support Dr Feachem's optimism. Indeed, almost no significant new pledges have been received by the Fund, other than from the US, during the 10 months since Dr Feachem became Executive Director last July. And most pledges that can be hoped for during the rest of this year will be for money to be received at least one year later.

The Fund was able to finance Rounds 1 and 2 because it had startup funding that was primarily generated by Kofi Annan. The current problems arise in part because the Secretariat and Board never developed a resource mobilisation strategy designed to get through the difficult transition from that startup phase to the point a couple of years from now where things can be expected to be easier because the Fund has proven that it can deliver results.

The likely failure to adequately fund Round 3 will have serious implications; but it must not lead to the death or marginalisation of the Fund. At the board meeting on 4-6 June, there must be frank talk about how to deal with the immediate need, and about how this crisis was allowed to arise; in addition, appropriate measures must be implemented to ensure it does not arise again.

The board would also do well to spend some time considering its own partial responsibility for the current situation. Board discussions and email exchanges have too often dealt with fine-tuned issues like what class of airline travel staff should use, or whether a precise balance has been achieved between North and South in Committee chairmanships, and have not focused sufficiently on big-picture issues.

Part of the problem is that some of the board members are losing interest in the fascinating experiment that the Fund represents. Economies are less strong than they were a couple of years ago; and donors worry that by giving money to the Fund rather than sending it directly to a few carefully-chosen governments, they have less control over the results; and they like that control, for a whole range of reasons.

What the Fund desperately needs is some inspirational leadership. The Secretariat staff are less than ecstatic with their own leadership. And the Board's Chair and Vice Chair - who have never met - have been engaging in too much long-distance bickering, at least until recently, in ways that have lost both of them some credibility within the board.

The Fund is remarkable in many ways; one of these is that its board is made up of governments from both developed and developing countries, in equal numbers, together with some non-government members. Such an innovative board, and the Secretariat that reports to it, can 'only' be effective and can 'only' achieve what millions of people need it to achieve, if the Chair, the Vice Chair, and the Executive Director are willing - indeed, determined - to set an example by working collaboratively and creatively, in a way that inspires the board and the Secretariat to do the same thing. Unless this happens soon, the future of the Fund is bleak.

Bernard Rivers is Executive Director of Aidspan and Editor of its GFO Newsletter.

Reproduced from the Global Fund Observer Newsletter.
http://www.aidspan.org/gfo

'Fund the Fund' launches campaign pack

The 'Fund the Fund' group, which is organising a popular international campaign to pressure the governments of rich nations to finance the Global Fund to Fight AIDS, TB and Malaria, has produced an advocacy guide to help groups and individuals

join the campaign. The group is urgently calling for US $1.4 billion so the Global Fund can finance a third group of projects.

The advocacy guide, now available to download from the website below, was created to serve as a guide to some of the activities that have already been planned for the campaign. It includes:

- A 'backgrounder' – Why do we need a Global Fund? What is the Fund's history? What is the Fund's future?
- Tips and suggestions on strategies and activities to campaign for the future of the Global Fund,
- A fact sheet about the Global Fund and its funding crisis,
- A draft 'sign up' letter to send to national governments,
- A list of resources of more information about the Global Fund and the 'Fund the Fund' campaign.

http://www.fundthefund.org

Senate approves Bush's $15 billion international AIDS bill

Graham McKerrow, HIV i-Base

The US Senate has approved president George W Bush's proposal to spend $15 billion on a massive international project to treat two million people and prevent seven million infections in 14 African and Caribbean countries.

The House approved the Bill by 375 to 41 with amendments that give it a more conservative tone. It provides for $3 billion a year for five years to be given to foreign HIV projects and $1 billion next year for the Global Fund to Fight AIDS, TB and Malaria.

The Bill endorses the controversial so-called ABC prevention model that advises: abstinence, be faithful, use condoms. One amendment included in the Bill specifically allocates one third of the prevention funding for abstinence and monogamy programmes. Democrats criticized this amendment as likely to detract from other prevention measures such as condom use and the Democrat leader in the House, Nancy Pelosi, said: "We must support what works." Another amendment strengthens the "conscience" language already in the Bill by ensuring that religious groups will receive US dollars even if they object to certain prevention measures such as condom use.

However, the Senate rejected Republican calls to prevent any of the money going to organisations that give advice on abortions, on condition that family planning and abortion programmes are run separately.

The Bill also responds to fears voiced by some Republicans that the Global Fund is inefficient by setting up a federal task force to monitor the Fund.

President Bush praised the House for passing the "historic" legislation that supports the proposals he made in his State of the Union addressing January. He went on: "Today's action is an important step toward providing critically needed treatment and care for millions of people suffering from AIDS, and proven prevention programmes for millions more who are at risk."

Links

US Clashes with World Health Organisation:
http://ww2.aegis.org/news/ips/2003/IP030416.html

US $15 billion approved by Senate:
http://kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=17498

Hooray for Bush! Wait . . . never mind:
http://www.aegis.org/news/sc/2003/SC030411.html

House Approves Major Global AIDS Bill:
http://ww2.aegis.org/news/ap/2003/AP030501.html

Information on the bill, H.R. 1298, can be found at:
http://thomas.loc.gov/030501

The HTB report on Bush's State of the Union address:
http://www.i-base.info/pub/htb/v4/htb4-2/Bush.html

GSK halves drug prices to 63 countries

Graham McKerrow, HIV i-Base

GlaxoSmithKline has announced a fresh round of price cutting that almost halves the cost of Combivir (3TC/lamivudine/Epivir and zidovudine/ZDV/AZT/retrovir) in developing countries from $1.70 a day to 90 cents – closer to the prices of generic rivals. The price in the US is $18 a day.

In those countries that qualify, and for those organisations that qualify for the new price reductions, the annual price for Combivir is £206, which compares to the WHO-approved generic version produced by Ranbaxy in India that sells for £167. Another generic version of the same combination, but one that doesn't have the WHO's approval, is sold by Aurobindo, also of India, for £128.

Poor countries now represent a considerable market for GSK. Last year, Glaxo supplied nearly 6 million tablets of Combivir to developing countries, the company said, up from about 2 million tablets in 2001.

Glaxo said it is able to reduce the drugs' prices because it is making them less expensively, as a result of improved manufacturing techniques and deals with some of the suppliers of raw materials that go into the medicines.

In addition to Combivir, GSK has also reduced the prices other HIV medicines. For example, 3TC (Epivir) is now available at 35 cents per day, and AZT (Retrovir) at 75 cents per day - reductions of 45% and 38% respectively.

GSK's new price cut was widely welcomed by, among others, the Global Fund to Fight AIDS, TB and Malaria and Clare Short, UK Secretary of State for International Development, but it also attracted immediate criticism. Euan Wilmshurst, Director of Action for Southern Africa, wrote to the Guardian newspaper saying: "We sincerely hope that GSK's price cuts for the anti-AIDS drug Combivir are not simply an attempt to muscle in on funds not intended for over-priced patented medicines."

He pointed out that the annual cost of the generic version produced by Ranbaxy, is almost 20% cheaper than GSK's Combivir following its latest price cut.

And Wilmshurst added: "Deep and sustained cuts in prices of medicines will only be brought about through competition with licensed generics manufacturers. If GSK truly wishes to contribute to the global struggle against AIDS, it should provide voluntary licences for the production of patented AIDS drugs in poor countries and should issue a public statement supporting the rights of developing country governments to provide healthcare by overriding drug patents."

Customers eligible for the new low prices include governments, non-governmental organisations (NGOs), aid agencies, UN agencies and international purchase funds like the Global Fund to Fight AIDS, TB and Malaria, operating in 63 named countries.

Links: Glaxo Halves Price of AIDS Drugs for Poor
http://ww2.aegis.org/news/re/2003/RE030427.html

GSK
http://www.gsk.com/media/pressreleases.htm

http://www.aurobindo.com

http://www.ranbaxy.com

COMMENT

With every move GSK makes it becomes clearer that they respond to three things: shareholders, share price and profit – and the greatest of these is profit. With the Global Fund attempting to raise $10 billion a year and the United States offering $15 billion for HIV treatment and prevention in poor countries over the next five years there is suddenly a huge market for antiretrovirals in poor countries. GSK – and it was not alone – once said dual pricing was impossible but with the manufacturers of generic drugs expanding into this growing market they, like other pharmaceutical companies, are eager for a slice of the pie.

The Global Fund has made clear it will fund projects that buy the best drugs at the lowest prices and President Bush recently said his $15 billion plan would take advantage of treatments now costing $300 a year – and when he said that only generics cost that little. The Global Fund and the president should both be praised for making clear that they are not going to pay the high western prices for treating poor people in developing nations.

Shareholders should also take a bow, both the institutional investors who, as we reported last month, are worried that the prices of shares in pharmaceutical companies could plummet unless they make treatments available to poor countries; and more politically motivated shareholders like The California Public Employees Retirement System (Calpers). Calpers owns about $760 million worth of GSK stock and in April attracted attention by demanding GSK cut its prices in poor countries.

GSK is the world's second largest drug maker and likes to throw its weight around – its very name is designed to intimidate, its turnover is bigger than many national GDPs – but even this giant is vulnerable to pressure. We can urge them to cut their prices further, but now is the time to look ahead to September when the World Trade Organisation holds its Ministers Meeting, and medicines are on their agenda. They must be persuaded to radically change the international patent system so that more countries can make, buy and distribute generic versions of drugs. It is not for the WTO to protect multinational companies against competition from smaller producers, and it is not for the WTO to enforce rules that let millions die from treatable illnesses.

Shareholders target PepsiCo over care for its employees in Africa

Graham McKerrow, HIV i-Base

A coalition of shareholders is pressing the soft drinks company PepsiCo to improve its care for HIV-positive workers in Africa. The shareholders, coordinated by the Interfaith Centre on Corporate Responsibility, has filed a resolution asking the company to detail the effect of HIV on the company's operations on its African soft drinks and snacks business and how the company intends to respond to the pandemic. They ask the board of directors for a response by October.

PepsiCo says its business in Africa is too small to warrant such a study and says African snack sales amount to less than 0.05% of the company's sales and assets. "The fact of the matter is we have very comprehensive programs that we offer our employees in connection with HIV and AIDS," said Dick Detweiler, a PepsiCo spokesperson.

Last year, activists targeted PepsiCo's main rival Coca-Cola, which has since extended medical benefits to more than 60,000 staff who work for the company and 40 bottling plants in Africa. Resolutions similar to the PepsiCo resolution have also been filed by shareholders of Colgate-Palmolive, Chevron-Texaco and Ford Motor Company, but these have since been withdrawn because these companies have agreed to discussions with the shareholders.

Links
http://www.iccr.org/products/proxy_book03/health&tobacco/rtpimpactaids_cat.htm

http://www.pepsico.com/citizenship/hiv/index.shtml

Burkina Faso to purchase generic drugs from Indian company

The government of Burkina Faso has signed a contract to purchase generic antiretroviral drugs from the Indian pharmaceutical firm Cipla. Health Minister Alain Yoda said the deal would bring down prices of AIDS medicine to between $37 and $70 per month. Under an earlier agreement reached with a European company, treatment cost up to $150 a month. However, prices of drugs remain "an obstacle for the treatment of a great number of people who really need them," Yoda said. About 6.5% of Burkina Faso's 12 million citizens are infected with HIV, according to a recent UN study. Currently only 675 people in the country are being treated with AIDS drugs, Yoda said. About 45% of the nation's population lives on less than $120 a year.

Source: CDC Summaries
http://www.aegis.com/news/ads/2003/AD030826.html

http://www.cipla.com

South Africa fails to accept $41 million from Global Fund

Richard Feachem, executive director of the UN-administered Global Fund to Fight AIDS, Tuberculosis and Malaria, says he is disappointed the South African government had not signed a deal to accept millions of dollars to combat the HIV pandemic.

In April, Feachem visited South Africa to sign an agreement for the release of US$41 million - the first installment of US$165 million to be released over five years - to fund programmes combating AIDS. But the South African government has repeatedly delayed signing the deal, citing "complex legal procedures," according to the South African Press Association.

"I have no words to express my dismay. It seems that the health ministry or whoever is responsible for this are fiddling while Rome is burning. People are dying," said Anglican Archbishop Njongonkulu Ndungane. South Africa's health department said in a statement that the deal "will, without fail, be signed" in May. "Programme implementation will begin by the end of May." The fund reached the deal with South Africa's government more than a year ago.

Source: CDC summaries

UK gives £15.7m to Burmese HIV project

The United Kingdom will give $15.7m to an international HIV care and prevention programme in Burma.

The donation is the biggest single grant to the project, which is administered by a group that includes representatives of the local population, UN agencies and donors. A UK government official said the transparency and accountability of the financial procedures were important. Other donors to the Joint Programme of Action for HIV/AIDS in Burma include Sweden, Norway and Denmark. The United Nations estimates that more than 400,000 people have HIV in Burma.

Links
UN epidemiological report: click on Myanmar (Burma):

http://www.unaids.org/hivaidsinfo/statistics/fact_sheets/all_countries_en.html#B

C O M M E N T

This grant reflects a growing mood among some governments, including the United States, to give money directly to foreign HIV projects. Donor governments feel they can have more direct control over the money that way than they can over money given to the Global Fund to Fight AIDS, TB and Malaria – even though donor governments sit on the board of the Global Fund.

Critics of direct funding say the money should be given to the Global Fund, so it can prioritise need and suitable projects on a global scale. It is also a waste of resources to duplicate bureaucracies to administer direct grants.

Death of South African AIDS activist fuels anger

A single mother who belonged to the activist group suing the South African government for refusing to provide antiretroviral drug therapy at public hospitals was buried in April after dying with AIDS. About 300 friends and activists, many wearing T-shirts with the message "Dying for Treatment," attended the emotionally charged funeral for Kebareng Moyeketsi, 32.

Believing that her death represents the plight of many young black South African women, some activists vowed to carry on with the civil disobedience campaign begun last month against the government. Mark Heywood, of the Treatment Action Campaign, said the group would march to the Johannesburg offices of the Human Rights Commission and the Commission for Gender Equality to demand a probe into Moyeketsi's death. "We believe her death is another example of preventable deaths," Heywood said.

ANTIRETROVIRALS

New 625mg formulations of nelfinavir

The US Food and Drug Administration has approved a new dosing formulation of the protease inhibitor Viracept (nelfinavir mesylate). Viracept has been available in 50 mg oral powder and 250 mg tablets. The new formulation of 625 mg reduces the pill burden from five-250 mg tablets twice a day to two-625 mg tablets twice a day, potentially facilitating adherence to treatment regimens.

Results of the bioequivalence study of the 250-mg tablet and the 625-mg tablet revealed increased bioavailability with the 625-mg formulation.

The sponsor, Agouron Pharmaceuticals, submitted clinical safety and pharmacokinetic data to the FDA providing evidence that the higher exposures do not pose a safety risk. However, diarrhoea may be more common in patients receiving this 625 mg formulation. No efficacy information was contained in this submission because it is unlikely that a more bioavailable formulation would be less efficacious.

Roche have developed a separate 625mg formulation of nelfinavir to be marketed in Europe, that will shortly be submitted to the European agency.

Source: FDA, USA
http://www.fda.gov/cder/approval/v.htm

i-Base guide to managing diarrhoea:
http://www.i-base.info/pub/guides/side802/dia.html

Calcium supplements for drug-related diarrhoea:
http://ww2.aegis.org/news/catie/2003/CATE-N20030405.html

C O M M E N T

Almost simultaneously Agouron and Roche have both produced separate, new, reduced pill formulations for nelfinavir. These both contain the same amount of nelfinavir but the formulations are *not* the same and the excipients used are entirely different. The Agouron formulation will only be available in the US. Results from clinical studies of the Roche formulation that will marketed in the rest of the world, showed a reduction in diarrhoea and were presented at the 4th Workshop on Clinical Pharmacology, and reported in last month's HTB.

An expanded access programme in the UK for the reduced tablet, but larger pill, for people with either intolerance or adherence difficulties, will be in early June 2003. European application for approval has not yet been submitted but Roche are hoping for licensing in early 2004.

Lopinavir suitable for TDM

Simon Collins, HIV i-Base

The use of therapeutic drug monitoring (TDM) for selected patient groups (interactions of new drugs, in treatment experienced patients, hepatitis coinfection, children etc) has allowed individualised dosing for both single and boosted PI-based regimens in some clinics in the UK and has widespread use in the Netherlands and France.

Although ritonavir-boosted levels of lopinavir were initially thought to produce trough levels safely exceeding the IC90 reducing the utility of TDM, inter-patient variability has shown that a few patients still absorb suboptimal levels.

One of the requirements for TDM to be safely used to recommend individualised dose adjustments, is the accuracy of any single measurement, and that drug levels within each patient – intra-patient variability - also remain relatively stable and consistent. This accuracy in a clinical setting is also determined by accuracy of recorded timing and patient variability of drug and food intake.

Ideally, for lopinavir/r, samples should be taken both at 12-hour post dose, (which for this drug may not be the actual trough as levels continue to drop post dose due to a short delay in absorption) and two-hours post observed dose.

Martha Boffito and colleagues from Liverpool University reported in the 2 May issue of AIDS on the intra-individual variability of lopinavir trough concentrations (Ctrough) prospectively measured by validated LC-MS in 25 HIV-positive out-patients (22 men, three women; median age 42 years, range 29-51), over a median period of 18 months (range 14-22). Blood samples were measured before the morning dose. One hundred and forty-three samples were analysed (5-9 for each patient).

Median lopinavir Ctrough considering all 25 patients ranged from 1,832 to 11,362 ng/ml (median 5,365). The median coefficient of variation of intra-patient variability was 35% (range 15-54).

Use of treatment was mixed (three were on first treatment, seven on second and 15 were multi-experienced). The median baseline CD4 was 204 cells/mm3 (range 94-433) increasing to 280 cells/mm3 (range 170-601) at the end of follow-up. Median plasma HIV-RNA level was approximately five logs (range 6,900-1,000,000) at baseline and was <50 copies/mL in 16 out of 25 subjects at the end of follow-up; the remaining nine subjects had a median viral load of 620 copies/ml (range 100-7900).

In this study, the authors' report that the variability determined for lopinavir, when co-administered with ritonavir in Kaletra, is of the same order of magnitude as that previously reported for nelfinavir and amprenavir when administered without ritonavir boosting. Consequently, even only a few determinations of plasma concentrations may be representative of individual exposure to PI, and may thus form the basis for dose adjustment.

Ref: Boffito M, Back DJ, Hoggard PG - Intra-individual variability in lopinavir plasma trough concentrations supports therapeutic drug monitoring. AIDS 2003; 17(7):1107-1108

C O M M E N T

Double PI combinations including lopinavir/r are another appropriate area for TDM. The most prominent example is the combination with amprenavir. In patients with partial resistance, TDM can be used to achieve higher trough levels and using the virtual phenotype approach to determine a virtual IQ may make sense. Patients with impaired liver function are another subset for use of TDM.

SUPERINFECTION

A case of intraclade HIV-1 superinfection by wild-type virus illustrates the potential to impact disease progression

Graham McKerrow, HIV i-Base

Californian and Scottish researchers report in the 2 May issue of AIDS on a case of intraclade HIV-1 superinfection by wild-type virus in the absence of antiretroviral therapy in a patient initially infected with drug-resistant HIV. They conclude that the substantially different in vivo viral growth characteristics they observed illustrate the potential for superinfection to impact disease progression.

The immunological response to HIV-1 infection has been postulated to impede superinfection with a second virus; however, a few recent reports have documented cases of HIV-1 superinfection in humans either from different viral clades or from the same clade. Kersten K Koelsch, of the University of San Diego, and colleagues set their objective to differentiate between coinfection and superinfection in a patient harboring a distinct wild-type HIV four months after primary infection with drug-resistant HIV.

They used detailed dye primer and clonal sequencing along with length polymorphism analysis to investigate the evolutionary

linkage between viral populations sampled at different time points.

They found that after a set point viral load of 6000 copies HIV RNA/ml, viral load jumped to 34,000 copies/ml at month four and, shortly after, to almost 200 000 copies/ml. At that time a second viral strain was first detected by dye primer sequencing of a *pol* fragment. These findings were confirmed by analysis of a 1300 bp *gag-pol* fragment and clonal sequencing and phylogenetic analysis of the V3 region. Length polymorphism analysis of the gp120 V4-V5 region showed that the second viral population was absent even as a minority population until month four, when it was found to be the majority population, and the initial variant was present only as a minority. Both strains were subtype B.

In their Discussion the researchers write: "Infection by viral variants with differing replication capacities and their variable susceptibility to the host immune response might be expected to have a significant impact on disease progression. Indeed, in the case described here, an abrupt increase in plasma viremia occurred coincident with the appearance of the second variant and consistent with the hypothesis that this second variant had greater in-vivo fitness than the initial, drug-resistant virus. The theoretical acceleration of disease progression that might result from a higher post-superinfection viral setpoint appears to be reflected in the steeper trajectory of the CD4 cell decline in this patient after superinfection.

"A second issue of importance is the impact of superinfection on treatment response. An obvious scenario for concern is that of a patient with drug-sensitive virus responding well to therapy who then becomes superinfected with drug-resistant virus. The transmission of drug-resistant virus is a common event. However, the case described here highlights a more insidious danger arising as a consequence of superinfection. In this case, standard drug susceptibility testing at late time points would fail to detect the occult drug-resistant virus. Nevertheless, if this patient were to initiate therapy, it seems likely that drug-resistant virus would quickly re-emerge."

The authors cite a handful of recent publications and conclude: "Together, these recent reports suggest that superinfection may occur more commonly than has previously been assumed, which has broad implications for HIV treatment, epidemiology, vaccine development and pathogenesis."

Ref: Koelsch K, Smith DM, Little SJ et al. Clade B HIV-1 superinfection with wild-type virus after primary infection with drug-resistant clade B virus. AIDS 17(7):F11- F16, 2003.

The full text of this article is available online following single free registration:
http://www.medscape.com/viewpublication/744_toc?vol=17&iss=7

C O M M E N T

Growing evidence affirms the previous plausibility of re-infection. The frequency of this remains difficult to determine. With the fragility of combination therapy dependent retaining drug sensitivity, drug absorption, food and drug interactions and adherence, the additional risk from reinfection is rarely suspected or investigated.

Large numbers of such cases are never likely to be reported, but this does not mean that they are only occurring infrequently.

ADVERSE EVENTS

Tenofovir side effects

Sean Hosein for CATIE news

Report from the 12th Annual Canadian Conference on HIV/AIDS Research (CAHR) 10 to 13 April, 2003.

Tenofovir (TDF, Viread) belongs to a group of drugs called nucleotide analogues, examples of which also include the following adefovir (Hepsera) and cidofovir (Vistide).

All three drugs are used to treat different viral infections. What they have in common is the potential to cause some degree of kidney damage.

In at least one clinical trial, about 5% of tenofovir users developed this problem. However, it is important to keep in mind that people who get enrolled in clinical trials for the testing of HIV drugs usually do not have other serious underlying medical conditions. In the real world outside of a clinical trial, people with HIV/AIDS (PHAs) can have other health-related issues, such as co-infections, complex treatment regimens and many years of exposure to therapies — all of which may increase the risk of side effects.

Focus on the kidneys

The kidneys filter the blood, flushing waste into the urine and reabsorbing important substances. When kidney damage occurs,

these organs may not work properly, which can cause waste to build up and/or cause the body to lose valuable nutrients.

Tenofovir users can develop higher-than-normal levels of creatinine in their blood and urine, suggesting kidney damage. Laboratory tests may also detect less-than-normal phosphorus levels in the blood, another consequence of kidney damage.

Questions remain as to what proportion of tenofovir users is at risk of kidney damage. To try to answer this question, researchers in Vancouver, British Columbia, collected and analysed data from patients attending HIV clinics who were in an expanded access programme for tenofovir. A research team member made a presentation about this study at CAHR.

The study team compared data from 322 patients who used tenofovir to data collected from 430 other patients who used the nucleoside analogue abacavir (ABC, Ziagen). What makes the researchers' work interesting is how they assess kidney damage. The Vancouver researchers consulted kidney specialists, who told them that creatinine levels greater than 1.5 times each patient's normal values should suggest that kidney damage was occurring. This way of reporting kidney damage is different from that seen in clinical trials of tenofovir. In those trials, attention was drawn to creatinine levels if they were so high they were judged to be "severe" or "potentially life-threatening." This can also be described as grade 3 or grade 4 elevations in creatinine.

Tenofovir toxicity risk

In analysing the data, the Vancouver researchers found that tenofovir users were about three times more likely than abacavir (ABC, Ziagen) users to develop higher-than-normal levels of creatinine in their blood. Another factor linked to having this problem was low CD4+ counts, roughly fewer than 150 cells. All in all, about 7% of tenofovir users in the Vancouver study developed some degree of kidney damage over an average of six months. A total of six patients had to stop taking tenofovir because of injured kidneys.

After listening to the presentation, another researcher from Vancouver in the audience announced that a patient in that city had been recently hospitalised and later died as a result of complications from severe kidney damage related to tenofovir-use.

Important considerations

These findings are preliminary and further analysis is needed to take into account other factors that may have had an impact on the results. For instance, there are a number of other drugs that can affect the health of the kidneys. Did tenofovir users in this study take some of these other drugs (see below)? If so, could these drugs have intensified tenofovir-related damage? Examples of drugs that can cause kidney damage and dysfunction include the following:

- aminoglycoside antibiotics – amikacin, gentamicin, paromomycin, streptomycin, tobramycin;
- other antibiotics – Septrin (Bactrim, co-trimoxazole, trimethoprim-sulfamethoxazole);
- antifungals – amphotericin B (Fungizone) and related formulations of this drug;
- antivirals – acyclovir (Zovirax), adefovir (Hepsera), cidofovir (Vistide), foscarnet (Foscavir), indinavir (Crixivan), Valtrex (valacyclovir);
- antiparasite drugs – intravenous pentamidine;
- NSAIDS (non-steroidal anti-inflammatory agents) – acetaminophen (Tylenol), ibuprofen (Advil, Motrin), indomethacin (Indocid), naproxen (Naprosyn).

About 10% of tenofovir users and about 20% of abacavir users in this study had previously used the protease inhibitor indinavir (Crixivan), which is also processed by the kidneys. However, exposure to indinavir was not a factor in the development of the kidney problems seen in this study.

Another factor for kidney damage was having a low CD4+ cell count. It was not clear how or why this could increase the risk of kidney damage. Some speculations: it is possible that people with low CD4+ counts were more ill than other patients and therefore more susceptible to drug side effects. Also, patients with low CD4+ cells could be exposed to more drugs (both for HIV and related complications), again increasing the risk for toxicity. However these theories are unproven.

Kidney health

Tenofovir may cause kidney damage by injuring the energy-producing parts of kidney tubules, called mitochondria, as does the nucleotide analogue adefovir. Ways of preventing tenofovir-related kidney damage were not mentioned in the presentation. However, if tenofovir does damage mitochondria, then perhaps a first step in testing ways to prevent this damage is to conduct test-tube experiments with kidney cells and antioxidants such as alpha-lipoic acid, L-carnitine, co-enzyme Q10 and N-acetyl-cysteine (NAC).

Ref: Harris M, Zalunardo N, Yip B, et al. Nephrotoxicity of tenofovir DF. 12th Annual Canadian Conference on HIV/AIDS Research, April 10-13, Halifax. Abstract 168.

be cleared through the Editor, The Community AIDS Treatment Information Exchange, Suite 420 - 517 College Street, Toronto, On M6G 4A2 Canada.

Links

The Community AIDS Treatment Information Exchange:
http://www.catie.ca

The Canadian Association for HIV Research:
http://www.cahr-acrv.ca/english/events/conferences.html

C O M M E N T

It is unclear from this report whether all creatinine elevations were counted or only the elevations occurring multiple times in a patient Presumably these elevations were then reversible when tenofovir was discontinued. Also there is no information about the time on treatment after which the elevations were observed in order to assess risk of cumulative toxicity.

Although tenofovir appears to be safe several reports of renal complications are beginning to emerge and the clinical relevance for the moment may be to avoid combinations with nephrotoxic agents until further data become available.

HIV-infected patients sustain acute myocardial infarction at a young age and have a benign in-hospital course

Reported series of patients have suggested that HIV-infected patients are at an increased risk of coronary artery disease (CAD), linked to the hyperlipidemia and insulin resistance associated with protease-inhibitor therapy. However, necropsy studies had demonstrated premature CAD in HIV-infected patients prior to the advent of protease inhibitors. Little data exist regarding the course of acute coronary events in HIV-infected patients.

The authors followed a series of 24 consecutive HIV-infected patients admitted for acute myocardial infarction (AMI) between 1998 and 2000. During hospitalisation, the patients were examined for recurrent ischemia, congestive heart failure, arrhythmia and death. Post discharge, patients were followed up for an average of 15 months for reinfarction; recurrent angina; the need for any angioplasty, bypass surgery or target vessel revascularisation for restenosis and stent thrombosis; HIV-related complications; and death. For comparison, the authors included a matched control group of 48 patients not HIV-infected. None of the patients in either group reported recent use of cocaine or anabolic steroids.

The HIV-infected patients with AMI were predominantly male (21; 88 percent), 47-9 years of age. Twenty-two (92 percent) were receiving antiretroviral treatment; 17 (71 percent), protease inhibitors; and 13 (54 percent), lipid-lowering therapy. With aggressive therapy, the lipid profile was similar in HIV- infected patients treated with protease inhibitors and those who were not. The mean duration of the infection was 10.7 - 4.4 years in patients with and 8.4 - 4.2 years in patients without protease inhibitor treatment.

The authors found that AMI in HIV-infected patients is associated with a favorable in-hospital outcome, not unlike the outcome in the matched control patients. This is likely due to the young age of the patients and the absence of significant haemodynamic compromise. Although both the HIV-infected and matched control patients had relatively benign hospital courses, with no deaths or reinfarctions reported, after discharge, HIV-infected patients had a higher incidence of reinfarction (4/20; 20%) and rehospitalisation for recurrent coronary event (9; 45%) than uninfected control patients in the approximately 15-month follow up. This study suggests that HIV infection is associated with an increased rate of restenosis after percutaneous coronary intervention. This association is particularly evident in patients with increased viral load, irrespective of protease inhibitor therapy.

The HIV-infected patients had lower low-density lipoprotein cholesterol and lower high-density lipoprotein values than HIV-negative patients. Otherwise, there were no significant differences in risk factors for CAD, ST-segment-elevation AMI, and AMI localisation between HIV-infected patients and control patients.

Dyslipidaemia associated with protease inhibitor therapy was considered as a significant factor for premature CAD in HIV-infected patients. The lipid profile of patients receiving protease inhibitors (71%) and lipid-lowering therapy (59%) was similar to the profile of HIV-infected patients not treated with protease inhibitors and control patients. Although the hyperlipidemia and insulin resistance associated with the use of protease inhibitors may contribute to the development of premature CAD, results of this study and others suggest that HIV infection is associated with CAD independent of the metabolic effects of antiretroviral therapy. This is supported by necropsy findings of premature atherosclerosis in a large percentage of HIV-positive patients not treated with protease inhibitors and in children who have died of AIDS.

The authors conclude that HIV-infected patients sustain AMI at a young age and have a benign in-hospital course. Although HIV-patients have a higher incidence of post-discharge coronary events, the intermediate-term mortality is low. Nevertheless,

the major determinants of prognosis likely remain complications associated with HIV infection.

Source: CDC HIV/STD/TB Prevention News Update

Ref: Matetzky S, Domingo M, Kar S et al. Acute myocardial infarction in human immunodeficiency virus-infected patients. Arch Intern Med 2003 Feb 24;163(4):457-60
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=12588205&dopt=Abstract

C O M M E N T

This is a small cohort, but it is interesting to put the relevance of MI into perspective.

Unfortunately because of the design of the cohort studies with a lack of an HIV-negative control, and the often unknown individual duration of the HIV-infection, current cohort studies like D:A:D or HOPS are unable to assess the influence of HIV-infection itself on CVD. A possible approach would be to match the HIV+ patients with individuals from the WHO MONICA project to have at least an HIV-negative control.

Cardiovascular and cerebrovascular events in patients treated for HIV infection

Metabolic abnormalities associated with HIV infection, including dysglycemia and hyperlipidemia, are increasingly prevalent, and there is concern about the possibility of an association with accelerated cardiovascular and cerebrovascular disease. In the current study, the relation between the risk of such disease and the use of antiretroviral therapy was evaluated.

Researchers conducted a retrospective study of the risk of cardiovascular disease among the 36,766 patients who received care for HIV at Veterans Affairs facilities between January 1993 and June 2001. Compared with typical patients with HIV in the United States, members of the VA cohort receiving services were more likely to be black (52.4%) and far more likely to be men (98.1%). The cohort was also slightly older (17.6% were less than 35 years old) and had less severe illness (36.7% were asymptomatic and had more than 500 CD4 cells/mm3 at diagnosis). A total of 23.9% had been previously treated at a VA facility for diabetes, hypertension, hyperlipidemia, or smoking, and 6.6% had been treated at a VA facility for vascular disease.

For antiretroviral therapy, 70.2% of patients received nucleoside analogues (NA), 41.6% received protease inhibitors (PI), and 25.6% received non-nucleoside reverse transcriptase inhibitors (NNRTI) for a median of 17 months, 16 months, and 9 months, respectively. Approximately 1,000 patients received combination therapy with a PI for at least 48 months, and approximately 1,000 patients received combination therapy with an NNRTI for at least 24 months.

Overall, there were 1,207 admissions for cardiovascular disease, 1,764 admissions for cardiovascular or cerebrovascular disease, and 2,006 admissions for or deaths from cardiovascular or cerebrovascular disease. Between 1995 and 2001, the rate of admissions for cardiovascular disease decreased from 1.7 to 0.9 per 100 patient-years, and the rate of death from any cause decreased from 21.3 to five deaths per 100 patient-years. Patient-level regression analyses indicated that there was no relation between the use of NAs, PIs, or NNRTIs and the hazard of cardiovascular or cerebrovascular events. However, the use of antiretroviral drugs was associated with a decreased hazard of death from any cause.

The fear of accelerated vascular disease need not compromise antiretroviral therapy over the short term, researchers concluded. Large increases in antiretroviral drug use by a large population of HIV-positive VA patients during the second half of the 1990s were accompanied by small decreases - rather than the feared increases - in the rates and hazards of cardiovascular and cerebrovascular events. However, the researchers cautioned that prolonged survival among HIV-infected patients means that longer-term observations and analyses are required.

Source: CDC HIV/STD/TB Prevention News Update

Ref: Bozzette SA, Ake CF, Tam HK et al. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 2003 Feb 20;348(8):702-10

Comment in N Engl J Med. 2003 Feb 20;348(8):679-80
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=12594314&dopt=Abstract

http://www.cdcnpin.org/scripts/News/NewsList.asp?strTempOrLive=Live

C O M M E N T

Conflicting results from studies looking at CVD in HIV-positive patients – notably the NEJM article above showing no increase in CVD and the recently presented data from D:A:D study showing an apparent cumulative risk for each year of treatment - continue to cause confusion

about the additional real risk that HIV treatment may add. The risk/benefit of HIV treatment is clearly in favour of treatment for people with low CVD risk but not so easily quantified when CVD risk is high (male, >45 years, family history, smoking, high fat diet, low exercise – and importantly contribution of increased lipids from ARV treatment.

Guidelines now generally include assessment for CVD risk prior to therapy, but give little practical help for how this should then related to decisions to prescribe treatment. Of concern is the finding that half the patients in the UK initiating HIV therapy for the first time last year, failed to have simple blood pressure recorded

Severe hepatotoxicity during ART: incidence, liver histology, and outcome

I

ssues concerning severe adverse events from combination antiretroviral therapy (ART) are becoming increasingly evident, limiting therapeutic benefits in a significant proportion of patients. Typical hepatic drug toxicity is exhibited by all classes of antiretrovirals; it is shown by a rise in transaminase levels and occasionally by signs of drug hypersensitivity or steatohepatitis. In the current study, all patients who initiated any combination of ART during an 18-month period were assessed to define prospectively the incidence and factors associated with the occurrence of severe hepatotoxicity (SH), as well as the histology and outcomes from SH during ART.

Seven hundred and fifty-five HIV-positive patients consecutively prescribed new ART were selected. Liver function tests were assessed at baseline, after one month, and every four months thereafter. Liver biopsy was recommended in case of SH (ie increase in liver enzymes greater than or equal to 10 times the upper limit of normal or five times baseline if markedly abnormal).

Twenty-six cases of SH were observed with an incidence of 4.2 per 100 person-years. SH incidence was not significantly different by treatment regimen (four per 100 person-years in patients treated with two nucleoside reverse transcriptase inhibitors (NRTI) plus one protease inhibitor (PI), six per 100 person-years in those treated with two NRTIs, and none in those treated with two NRTIs plus one non-nucleoside reverse transcriptase inhibitors (NNRTI). Patients developing SH during combination ART differed from those who did not by the following factors: they were more often male; had intravenous drug use as a risk factor for HIV acquisition; were younger; were more often coinfected with HCV, HBV, and HDV; and had higher baseline alanine aminotransferase and bilirubin values and longer prothrombin time. Anti-HCV and HCV RNA reactivity were detected in all but one of 26 patients with SH. HBsAg was detected in five patients, as was anti-HDV IgM. The patient without HCV-RNA reactivity showed HBsAg and HDV-Ab IgM reactivities.

Liver failure was rarely seen (1.1 per 100 person-years). Liver damage was invariably observed in patients with chronic viral hepatitis. Liver histology showed exacerbation of viral hepatitis in all 16 patients for whom a liver biopsy was available at the time of SH. A direct correlation was found between ALT increase and increase in CD4+ T-cell count in patients with SH. Death occurred during follow-up in seven of 26 patients (27%), all of who showed LF and baseline CD4+ count less than 200 cells/mm3 (7/7 patients = 100 percent vs. 8/19 patients without LF). Relapse of SH was observed after ART was recommenced in seven of 17 patients (41 percent). Five of these seven patients did not show further SH relapse after treatment with interferon.

Severe hepatotoxicity was related to preexisting chronic viral hepatitis followed by irreversible LF in a few patients, all with severe CD4+ T-cell depletion before starting ART. “Besides the fact that all patients with chronic viral hepatitis should be strictly monitored for liver damage after starting ART, this observation strengthens the importance of careful follow-up in patients with chronic hepatitis and a low CD4+ T-cell count. When the CD4+ T-cell count is 200 to 350 cells/mm3, the risk of SH resulting in LF may be low according to our data; thus ART could be started quite safely,” researchers concluded. “Antihepatitis pre- or co-medication could be an effective preventive or curative measure.”

Ref: Puoti M, Torti C, Ripamonti D et al. HIV-HCV Co-Infection Study Group. Severe hepatotoxicity during combination antiretroviral treatment: incidence, liver histology, and outcome. Journal of Acquired Immune Deficiency Syndromes (03.01.03) Vol. 32; No. 3: P. 259-267 - Thursday, May 01, 2003
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=12626885&dopt=Abstract

Source: CDC HIV/STD/TB Prevention News Update

Peripheral neuropathy in HIV disease: Lactate levels may help determine if nucleoside toxicity is a contributing factor

Paul Blanchard, HIV i-Base

With both HIV itself and antiretrovirals implicated in the development of HIV-related peripheral neuropathy it can be difficult to determine which may be the dominant aetiology in a particular individual. Given that nucleoside associated neuropathy may be related to nucleoside induced mitochondrial dysfunction, a marker of such dysfunction, blood lactate levels, might be useful in differentiating nucleoside induced from other neuropathies.

Bruce Brew and colleagues presented data on lactate levels in HIV neuropathy as a poster during the 8th Conference on Retroviruses and Opportunistic Infections (2001). It appears to be this data set, in an updated form, which has now been published as a research letter in the journal AIDS.

All outpatients at an Australian HIV medicine hospital department developing peripheral neuropathy were studied prospectively over one year and venous lactate levels and HIV viral load measured. Nucleoside neuropathy was diagnosed following exclusion of other likely causes and symptom improvement after cessation of the nucleoside. HIV neuropathy was diagnosed if clinical features were the same as for nucleoside neuropathy, except that patients were not taking didanosine, stavudine or zalcitabine (ddX nucleoside), and after exclusion of other likely causes. A control group consisted of patients without neuropathy, taking antiretroviral therapy (which may have included ddX) and with CD4 counts less than 200 cells/mL. The ability of raised serum lactate concentrations (>2.2 mmol/l) and detectable HIV viral load to discriminate between these groups was assessed using logistic regression. *(See Table 1)*

Table 1:

	ddX nucleoside with neuropathy (n=20)	HIV with neuropathy (n=10)	ddX nucleoside with no neuropathy (n=20)	No ddX nucleoside with no neuropathy (n=23)
Lactate conc. (mmol/l)	3.16 – 0.81	1.8 – 0.67	1.68 – 0.4	1.54 – 0.36
% lactate >2.2 mmol/l	90	10	15	0
HIV RNA (log copies/ml)	2.79 – 0.58	3.95 – 1.28	2.9 – 0.61	2.83 – 0.64
% less than 400 copies/ml	90	40	75	83

Logistic regression determined that an elevated serum lactate was 90% sensitive and 90% specific in discriminating between ddX neuropathy and HIV neuropathy. The researchers concluding that "…elevated serum lactate concentrations can be useful in the diagnosis of nucleoside neuropathy and its distinction from (HIV related) distal sensory peripheral neuropathy (DSPN), whereas the plasma HIV viral load is not, and indeed 40% of DSPN patients had a plasma viral load below 400 copies/ml."

Ref: Brew BJ, Tisch S, Law M. Lactate concentrations distinguish between nucleoside neuropathy and HIV neuropathy. AIDS 2003 May 2;17(7):1094-6.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=12700465

C O M M E N T

The authors of this study comment that in all 20 ddX neuropathy patients the neuropathy was considered to be related to stavudine. They also note that in these 20 patients a switch to either zidovudine or abacavir led to improvement in the severity of the neuropathy and normalisation of the serum lactate. Interestingly chart review revealed that the patients who developed HIV neuropathy with viral loads <400 copies/ml had development and progression of their neuropathy in the context of suppressed viral loads.

Results from in vitro studies with HepG2-cells published by Walker et al in AIDS 2002 and shown at the 4th Lipodystrophy Workshop demonstrate that a raise of lactate and mitochondrial damage as assessed by the appearance of cyclooxygenase in the supernatant must not be closely associated. Clinically a switch of a d-drug to another a non-d-drug would be the consequence even in individuals with "HIV"-peripheral neuropathy, because of additive toxicity or virological failure.

LIPODYSTROPHY AND METABOLIC COMPLICATIONS

Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women

Newly diagnosed diabetes mellitus (DM), exacerbations of preexisting DM, hyperlipidemia, and fat redistribution syndromes have been described among protease inhibitor (PI) users. In the current study, researchers examined the incidence of self-reported DM among participants of the prospective multicentre Women's Interagency HIV Study from 1994-1998, a period spanning PI introduction. The study assessed the epidemiologic relationships among diabetes, weight change, stage of illness, virologic response to therapy, and the use of specific antiretroviral medications among participants with no prior history of DM.

The HIV-infected and uninfected women (n= 1,435 and 350, respectively) were similar in median age (37 years vs. 36 years), race/ethnicity (55% vs. 52% African American, 26% vs. 30% Latina), and median follow-up time (2.91 years). The HIV-positive women had a lower baseline median body mass index than uninfected women (25.5 kg/m2 vs. 26.4kg/m2) and were less likely to be obese, defined as BMI greater than 30kg/m2 (23% vs. 33%). Among HIV-positive women, 27% had baseline CD4 counts below 200 cells/microliter and 34% had HIV RNA levels below 4,000 copies/mL. Median detectable baseline HIV RNA was 4.75 log10.

HIV-infected women were divided into three groups. PI users reported at least one PI, at least one nucleoside reverse transcriptase inhibitor (NRTI), and/or at least one non-nucleoside reverse transcriptase inhibitor (NNRTI). Reverse transcriptase inhibitor (RTI) users reported at least one NRTI and/or at least one NNRTI but never reported use of any PI. Women in the No ART group never reported using any PI, NRTI, or NNRTI.

There were 69 new cases of self-reported DM among 1,785 women who contributed 4,578 person-years (PY), an overall incidence of 1.5 per 100 PY. Per 100 PY, DM incidence was 1.4 among the HIV-uninfected women and 1.2, 1.2, and 2.8 in the RTI, No ART, and PI groups, respectively. The relative risk (RR) of reporting DM was highest among the morbidly obese (RR= 5.2) and the obese (RR= 2.8). Adjusted for BMI, women on PI therapy had a greater risk of reporting DM than women on RTI therapy (RR=2.2).

Incident DM and first PI use were reported at the same study visit for nine of 20 (45%) of the diabetic participants in the PI group. The remaining participants reported incident DM one (n= 3), two (n= 6), or three (n= 2) study visits after the first report of PI use. PI therapy was used continuously in 15 of the 20 diabetic participants. In the remaining five, PI use and incident DM were reported at the same visit, despite earlier interruptions in PI therapy.

Virologic response to therapy was determined for 86% of the RTI and PI groups. In the RTI group, virologic response occurred in 25% of diabetic participants and 28% of nondiabetic participants. In the PI group, virologic response occurred in 53% of diabetic participants and 52% of nondiabetic participants.

Frequency of zidovudine (AZT), stavudine (d4T), zalcitabine (ddC), didanosine (ddI), or lamivudine (3TC) use was the same for both diabetic and nondiabetic participants. There was no significant association between NNRTI use and DM. The frequency of individual PI use was also the same for both diabetic and nondiabetic participants. Among the 69 incident DM cases, only one reported use of megestrol.

Adjusting for known risk factors for diabetes and other HIV-related confounders, a significantly increased risk of DM in all multivariate models was associated with PI use, older age, and larger BMI category. Changes in CD4 cell count and viral load were not independent predictors of DM in HIV-positive women.

“This study found that PI use is an independent risk factor for self-reported DM, with a threefold increase in risk, a result consistent with other studies ... In view of the clinical benefits of PI therapy, concern about diabetes per se should not dissuade patients or practitioners from using this potent class of antiretrovirals. Routine screening for diabetes, particularly among older and heavier patients using PI therapy, is clearly warranted,” the authors concluded.

Ref: Justman JE, Benning L, Danoff A et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. J Acquir Immune Defic Syndr 2003 Mar 1;32(3):298-302
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=12626890&dopt=Abstract

Source: CDC summaries

C O M M E N T

These results should not be surprising, because the inhibition of glucose transporter 4 by indinavir has been demonstrated in vivo and in vitro. Another mechanism may be the inhibition of insulin secretion from the pancreatic islet cell. In HIV-negative individuals, as shown by Noor et al (AIDS 2002), indinavir rapidly induces insulin resistance. Interestingly RTIs induce reduced insulin sensitivity in about 25% of the patients compared to 50% on PI (Walli et al. Eur. J Med Res. 2002).

VACCINE RESEARCH

HIV vaccine symposium: more questions than answers

Kristen Kresge, amfAR

If it weren’t for the spectacular mountain scenery, vaccine researchers gathered at the recent Keystone Symposia in the Canadian Rockies may have come away a little depressed. One after another, the obstacles to finding an effective HIV vaccine

were illuminated. These arise from the virus's enormous genetic variation.

Undue optimism

David Weiner of the University of Pennsylvania Medical School began his talk by apologising for his inherent optimism - what he called a *faux pas* in an HIV vaccine talk.

Weiner's remark directly pertained to the most anticipated vaccine talk. In that presentation VaxGen updated the results for its phase III study of AIDSVAX. Although this HIV vaccine was unable overall to prevent infection or slow disease progression in a 5,000-person trial, VaxGen's attempts to cast the results in more favourable light has generated considerable controversy. The company announced in March that a subanalysis indicated that AIDSVAX did exhibit a protective effect in the African-American trial participants. But that conclusion pivoted on four black women who acquired HIV while participating in the trial's placebo arm.

"…It's highly unlikely that their story about the vaccine working in blacks is correct," Dr Dennis Burton (Scripps Research Institute, San Diego) said at Keystone. "You can see all sorts of effects in small numbers."

To bolster its argument, VaxGen promised a Keystone presentation on AIDSVAX-induced antibody production. The new results did not satisfy the critics: measured antibody levels were higher in black vaccine recipients than in the corresponding white males. Yet black men had equivalent HIV infection rates whether they received the vaccine or the placebo.

VaxGen also reported that women had higher antibody responses to AIDSVAX than men, regardless of race. But in non-black women, there were no new infections in the placebo group and one in the vaccine group. It does not appear from these results that antibody levels accurately indicate the extent to which a vaccine can protect against HIV.

Other presentations on antibody-eliciting vaccines were also discouraging. Researchers are now realising that a strong antibody response may be a necessity for an effective HIV vaccine. But reports at Keystone underscored the difficulty of finding antibodies able to neutralise the wily virus.

Dr Douglas Richman, a virologist and physician at Veterans Affairs San Diego Healthcare System, painted a bleak picture. Richman followed 19 HIV-infected volunteers for over 39 months after they contracted the virus. He found that most patients develop a strong antibody response soon after infection. But at every step along the way, the virus dodges the antibodies through its ability to mutate and escape detection. The mutations arise very quickly. Antibodies extracted from blood samples were unable to neutralise virus isolated from the same person only one month later.

'…The virus is escaping much more readily than anyone has realised,' said John Eldridge, Vice President of Immunology at Wyeth.

Moving forward

With effective antibodies elusive, attention returned to the vaccine candidates that rely on cellular immunity (killer T-cells that attack HIV-infected cells). Merck announced that it is going forward with its viral vector (MRKAd5, an adenovirus containing three HIV genes - gag, pol and nef). This vector, which creates a self-limiting mock HIV infection, looks more effective in animal studies than the company's nonviral naked DNA construct, either alone or in combination with MRKAd5.

Dr Emilio Emini, Senior Vice President of Vaccine Research at Merck, talked about the collaboration between Merck and Aventis Pasteur to combine an adenovirus-based vaccine with Aventis' HIV vaccine that utilises a canary pox vector (ALVAC vCP205). Participants in Merck's viral vaccine study who have already received the adenovirus vaccination will be rolled over into this new study and receive a booster vaccination of the canary pox vaccine.

In monkey studies, the combination of these two vaccine constructs induced a better immune response than when either was given alone. The clinical trial will begin soon, and Emini is hopeful that human volunteers will evidence a similarly enhanced immune response.

While Merck sets aside its nonviral naked DNA vaccine, Wyeth is moving its DNA vaccine forward into human clinical trials. The trial will combine the DNA vaccine with the protein interleukin 12 (IL-12; a cytokine secreted by macrophages that enhances type 1 cell mediated immune responses) and a viral vector boost (using a vesicular stomatitis virus with inserted HIV genes).

The human trial will begin early next year, and according to Eldridge: "The difference is going to be the cytokine." In animal studies, the addition of IL-12 triggered a greater antibody response, as well as a four- to six fold enhancement in cellular immunity.

Despite the obstacles encountered by HIV vaccine researchers, Emini remains confident of a successful outcome, though maybe not in the next five years. He remarked: "Everything is difficult until it's done."

http://www.amfar.org/cgi-bin/iowa/td/conf/record.html?record=89

Pushing the envelope: A new dawn for the role of antibodies in immune control of HIV?

Commentary by Gareth Hardy, HIV i-Base

While this years and last years Keystone Vaccine Symposia, specialising in HIV immunology, may have done little to encourage optimism that a successful vaccination strategy is on the horizon, important advances are being made in the understanding of why immunity to HIV is so hard to achieve. As a consequence of this, the sophisticated nature of HIV's immune evasion techniques may be laid bare, such that successful stratagems can be developed.

Pessimism is being drawn from the results of VaxGen's phase III trial of AIDSVAX and from the lack of any correlation between the magnitude of a vaccine induced antibody response and any evidence of protection from infection in this and other studies. Before we get too despondent we should take note that the perhaps falsely high expectations of these studies, especially AIDSVAX, have been based on early concepts of how immune responses in general and antibody responses in particular may confer a clinically relevant antiviral effect.

As reflected in the article above, our strategies in the past and still today often focus either on mobilising humoral immunity (antibody responses) or cellular immunity (killer T cells and related cell types). What is gradually becoming evident is that the immune system probably fails to control HIV not because both its main armaments are ineffective, but perhaps instead because it is fighting with one arm tied behind its back.

For many years immunologists have been divided into two camps; those who believe that antibodies that can neutralise the virus will hold the key to successful blockade of HIV replication and those who believe that CD8 killer (cytotoxic) T cells will do the job.

Both camps argued that with just a little tweek here and there, a bit of help and manipulation, things would come right with their respective armamentariums. This perspective is now set to be superceded by an almost Blairite third-way.

Many viral infections are quickly and efficiently eradicated by the combined force of both CD8 cytotoxic T cells and neutralising antibodies, as for example in flu virus infections. It is now becoming clear that in HIV infection this effective concert between the two arms of the immune system breaks down. This is because HIV has evolved a remarkable protective mechanism against neutralising antibodies (antibodies which bind the relevant parts of a protein to inactivate it or the organism to which it belongs). Unaided by the antiviral effect of successful humoral responses, CD8 cytotoxic T cells simply cannot keep up with viral mutation, displaying hyperactivated phenotypes and becoming exhausted.

At last year's Keystone Symposia David Watkins of the University of Madison, Wisconsin, USA, presented data on a vaccine strategy he is using in apes. This vaccine induced powerful responses from CD8 cytotoxic T cells that protected the apes from the usual very high viral loads experienced following infection. Despite this success it was not long before the little virus that was able to replicate in the presence of this response had mutated sufficiently and the CD8 cytotoxic T cell response became considerably less effective, thus allowing viral loads to increase unchecked in these animals. This of course underscores the problem faced by relying solely on robust CD8 cytotoxic T cells to restrict HIV replication and possibly prevent infection. The story is of course more complex than this because CD4 T helper cells, which pivotally initiate both antibody and cytotoxic T cell responses, are severely impaired in function through poorly characterised means and in number as a direct result of their destruction by HIV. Thus they are unable to effectively mobilise both antibodies and cytotoxic T cells, further impairing the efficiency and capability of both arms of the immune system.

A new understanding of the role of virus-specific antibodies in HIV infection is dawning, such that it is becoming tempting to believe that neutralising antibodies may hold a big part of the key to our previous and present failures with vaccination strategies. If antibodies could be induced which block viral replication, then perhaps the loss of CD4 T helper cells and exhaustion of CD8 cytotoxic T cells could be prevented leading either to indefinite containment of disease progression or otherwise to sterilising immunity.

The new understanding of just why neutralising antibodies fail requires us to appreciate HIV's envelope protein in minute detail. Robert Doms and James Hoxie of the University of Pennsylvania, Peter Kwong of the National Institutes of Health, USA, and Douglas Richman of the University of California, San Diego, USA have done precisely this and presented some of their findings at last years Keystone Symposia.

Gp120, the outer envelope protein of HIV, directly binds to CD4 and subsequently to other T helper cell surface molecules such as the chemokine receptors CCR5 and CXCR4. In order for gp120 to interact with its receptors CD4, CCR5 and CXCR4 it must have regions in its structure that recognise and bind them, of which the shape and chemical properties must not be subject to change by mutation, as is the case with much of the rest of the protein. These conserved regions of gp120 are the primary sites to which neutralising antibodies should bind and thus block gp120's ability to interact with CD4 and other cell surface receptors. Antibodies that bind other parts of gp120 do not neutralise it because they do not block gp120's essential function – to bind receptors on T helper cells – thus these are not neutralising antibodies.

Gp120's technique for evading neutralization in this way is somewhat multifaceted, but largely relies on a combination of high variability, spatial restriction of conserved epitopes and reconfiguration following CD4 binding. The CD4 binding site on gp120 is a bridging sheet tucked into a deep crevice. Large, highly immunogenic looping regions that constantly mutate from one

virus to another obscure this bridging sheet. While a given antibody may bind these looping regions and block the interaction of CD4 and the bridging sheet, easily affordable mutation of these regions in subsequent viral generations renders such a neutralising antibody clone ineffective. Thus the concept of broadly cross strain neutralising antibodies to these available sites is negated.

The CD4 binding site is however highly conserved and must remain so to maintain its integrity. While the CD4 molecule is a slender single chain molecule, antibodies are bulky, consisting of two chains. The crevice in gp120 in which the CD4 binding area resides is narrow, but allows the slender CD4 molecule to slot into position. In contrast antibodies that may be able to block the conserved CD4 binding site and neutralise gp120, regardless of quasi-species variation or mutation in other less important areas of the protein, are unable to gain access to the crevice because of their size.

Following interaction with CD4, gp120 undergoes structural changes, enabling other conserved but formerly masked areas to bind its second receptors: CCR5 or CXCR4. These changes temporarily expose other areas of the protein where antibodies can gain access and thus may be able to cross neutralise the multiple different highly variant gp120 molecules of different viral quasi-species. Such epitopes are referred to as CD4 induced or CD4i epitopes. Because these areas are exposed for a very limited time, such antibodies do not arise naturally. But if these new sites on gp120 can be introduced to the immune system in a stable form, such as in a vaccine, new neutralising antibodies should be induced which can block gp120, regardless of inter quasi-species mutation, and thus broadly inactivate free viral particles in a clinically relevant manner.

Thus the disappointment we experience when viewing VaxGens failure with the whole envelope protein preparation that was AIDSVAX, must tempered as we take on board the implications of our new understanding of the envelope. It is not the quantity of antibody a vaccine induces which is necessarily important in containing or preventing infection, but the quality and specificity of those antibodies. Unless an envelope vaccine presents something new to the immune system (such as reconfigured CD4i epitopes), we should probably expect to be disappointed.

Unfortunately, however, disappointment may not be all we experience with such results. There is some evidence that antibodies that fail to neutralise gp120 may be worse than merely ineffective. Indeed it may appear that non-neutralising gp120 antibodies actually enhance HIV infectivity and/or pathogenesis. Somewhat speculatively, the mechanism of such enhancement may lie in stabilisation of infectious HIV particles on the surface of antigen presenting cells in the lymphoid organs, or increased uptake and infection or disruption of dendritic cell populations.

At last years World AIDS Conference in Barcelona, Harriet Robinson presented work that supported just such a notion: that non-neutralising gp120-specific antibodies enhance HIV pathology (See HTB, vol 3, no. 7. Aug/Sept 2002. Immunology and Basic Science. Behind the headlines about vaccine research, pp 37). As postulated in that edition of HTB, we should be prepared to be disappointed by the results of trials that use whole envelope preparations.

The US military's announcement at the time that they are to go ahead with the largest phase III trial of an HIV vaccine, in 16,000 volunteers in Thailand, using AIDSVAX as a component of their vaccine strategy, may now be considered with even more caution.

Refs:

For an excellent recent review of the role neutralising antibodies in HIV infection see: Neutralizing antibodies against HIV - back in the major league. Flavia Ferrantelli and Ruth M Ruprecht. Current Opinion in Immunology. 2002, 14. 495-502.

For a review of the role of the HIV gp120 see: Gp120: Biological aspects of structural features. Pascal Poignard, Erica Ollmann Saphire, Paul WHI Parren and Dennis R Burton. Annual Review in Immunology. 2001, 19. 253-74.

OPPORTUNISTIC INFECTIONS

Anabolic steroid oxymetholone reduces wasting among HIV patients on HAART

Harvey McConnell, Doctors Guide Review

Oxymetholone, an anabolic steroid, appears to be effective in countering wasting among HIV-positive patients taking highly active antiretroviral therapy (HAART).

This finding results from a double-blind, randomised, placebo-controlled trial at the University of Essen, and the University of Bonn, Germany. Eighty-nine HIV-positive women and men participated.

Chronic involuntary weight loss is a serious problem among patients on HAART. The alterations in energy metabolism and endocrine regulation cause loss of lean body mass (LBM) and body cell mass (BCM).

There has been partial restoration of LBM in studies among HIV-positive men undergoing androgen replacement therapy, or treatment with recombinant growth hormone. However, these treatments have largely been ineffective among eugonadal individuals.

In the present study, the men and women with wasting were given oxymetholone 50 mg twice (BID), or three times daily (TID), or placebo for 16 weeks, followed by open-label treatment. Endpoints were body weight, bioimpedance measurements, and appetite.

The clinicians found that oxymetholone produced a significant weight gain of 3.0 – 0.5 kg in the TID group, and 3.5 – 0.7 kg in the BID group, while patients in the placebo group gained an average of 1.0 – 0.7 kg. Body cell mass increased 3.8 – 0.4 kg in the BID group and 2.1 – 0.6 kg in the TID group. This corresponded to 12.4T and 7.4% of baseline BCM, respectively.

The patients taking oxymetholone reported significant improvements in their appetite and food consumption, plus a reduction in feeling weak. The most important adverse event was liver-associated toxicity.

Overall, 35% of patients in the TID, 27% of patients in the BID oxymetholone group, and no patients in the placebo group, had a greater than five times baseline increase for alanine aminotransferase during the double-blind phase of the study.

Clinicians concluded that "the BID (100 mg/day) regimen appeared to be equally effective as the TID (150 mg/day) regimen in terms of weight gain, LBM and BCM and was associated with less, but still significant liver toxicity."

Source: Doctors Guide Review. April 1, 2003.

Ref: Hengge UR, Stocks K, Wiehler H et al "Double-blind, randomized, placebo-controlled phase III trial of oxymetholone for the treatment of HIV wasting." AIDS 2003 Mar 28; 17:5:699-710.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=12646793&dopt=Abstract

C O M M E N T

Anabolic steroids have however been proven to be ineffective in lipoatrophy and may worsen lipid profiles considerably (HDL decrease, LDL increase).

In addition pharmacologic application of anabolic steroids suppress the bodies natural production testosterone.

DIAGNOSTICS

Three-minute HIV test wins approval in China and the USA

Graham McKerrow, HIV i-Base

China and the United States have both approved a rapid, portable HIV testing kit that is cheap to produce, easy to use and gives results in three minutes. It is being compared to home pregnancy tests and could revolutionise HIV testing. After receiving distribution approval from China's State Drug Administration in February, a small Canadian biotech company is rushing to produce 400,000 rapid HIV tests for the nation. "The Chinese government has finally acknowledged this is a problem. Now they're trying to make prevention a priority," said Daniel Sham of the company MedMira. The US Food and Drug Administration approved the test in April.

The test, which costs about US$2.25 to manufacture, detects antibodies in the blood and shows two red lines for a positive result. Unlike conventional HIV tests, MedMira's test produces results in about three minutes. The Chinese order is for 400,000 tests to be distributed to clinics and hospitals.

The company said in a statement: "With the FDA approval, MedMira can market the *Reveal* Rapid HIV-1 Antibody Test for the detection of HIV-1 antibodies in serum or plasma. This test has a one-year shelf life at room temperature, the longest of any rapid HIV tests available in the United States. MedMira's test also produces highly accurate results substantially faster than any other FDA-approved HIV diagnostic test."

Stephen Sham, Chairman and CEO of MedMira, said: "We are very pleased to enter the United States market with the best rapid HIV test to date. Many countries view the approval to market of a diagnostic test by the FDA to be the gold standard of endorsement. Now that we have obtained this approval, we are very optimistic about the immediate expansion of MedMira's operations. We look forward to fulfilling the global diagnostic marketplace with our unique diagnostic products."

Sham called the earlier approval by China a landmark event for his company, which was founded in a university basement a few years ago. "This regulatory approval achieves one of the company's strategic goals of gaining access to large markets where the power of our technology can be used to make a difference in a significant public health campaign," he said.

Chinese HIV infection rates have surged, particularly in remote regions where IV drug use, prostitution, migration and blood transfusions have increased. In addition, China's blood supply was largely unregulated in the 1980s and many private agencies mixed supplies, reused needles and operated without sterilised equipment.

MedMira - which also manufactures diagnostic tests to detect hepatitis - signed a deal recently to supply 1 million tests to the Democratic Republic of Congo. Health Canada approved the test in 1998.

http://www.medmira.ca/news11.htm

New TB blood test shows promise

Scientists have developed a new diagnostic test for TB that experts say could help control the disease in the developed world by more accurately detecting infections before people get sick.

The study, published in the Lancet, indicates that the new tests detected latent infections more accurately than the standard skin-prick test used for a century.

The tuberculin skin-prick test is the cornerstone of TB control in developed countries, but it has many drawbacks. It involves injecting a substance under the skin on the arm and a technician reading the resulting bump a few days later. The test can give false positive readings in people who have had the BCG TB vaccine because antibodies are made in both cases.

The new test, developed by scientists at Oxford University in England, is a blood test using a different substance to stimulate a reaction. Instead of looking for antibodies, it detects the activation of immune system T-cells.

Researchers compared the new test with the skin-prick test on 535 children at a British school where a student was diagnosed with TB in 2001. Children who were exposed to the student with TB were significantly more likely to test positive with the new method, the study found. While the skin test was more likely to be positive in BCG-vaccinated children than in non- vaccinated children, there was no link with vaccination in the new test. The two tests reached the same conclusion in 89 percent of the children. When the results did not match, it was impossible to know for certain which test was correct. However, when the new test was positive and the skin test was negative, this was a strong predictor of TB exposure in the children. When the results were reversed, this was not a strong indicator of a child's exposure to TB - suggesting that isolated positive results from the blood test were more likely to be true positives than isolated positive results from the skin test, the scientists said.

Dr. Mark Perkins, a TB specialist at the World Health Organization, said about 95 percent of TB cases occur in the developing world, where a new diagnostic test for active TB is crucial because the current technology detects less than one- third of cases.

Ref: Ewer K, Deeks J, Alvarez L et al. "Comparison of T-cell-based assay with tuberculin skin test for diagnosis of mycobacterium tuberculosis infection in a school tuberculosis outbreak," is published in the Lancet (2003;361(9364):1168-1173)
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=12686038&dopt=Abstract

HEPATITIS COINFECTION

Genotype, enzyme levels, and viral load are clues to hepatitis C virus outcomes

Sonia Nichols, Hepatitis Weekly

Researchers in Germany report that viral genotype and load, as well as liver enzyme levels, are predictors for treatment outcomes in chronic hepatitis C. Their multicentre, retrospective investigation examined the data for 260 patients in Europe who were treated with pegylated interferon alfa, or with standard interferon. The patients, who underwent therapy for six to 12 months, also received ribavirin.

"A viral load at treatment week four above 450,000 IU/mL and at week 12 above 30,000 IU/mL was 100% predictive for virologic nonresponse in all patients," reported Thomas Berg and colleagues of Humboldt University-Berlin. Statistical analysis indicated that being of HCV of genotypes 2 or 3, having high levels of alanine aminotransferase before starting treatment, and having a low viral load at baseline were independent predictors for attaining a sustained virologic response.

"None of the latter three factors were predictive for sustained virologic response when analysis was restricted to the subgroup of genotypes 2- and 3-infected patients," Berg and coauthors wrote. They suggested that by as early as 12 weeks after therapy has begun, doctors can determine whether or not sustained virological response will occur using an HCV RNA cut-off level 30,000 IU/mL. "This algorithm recognises 53.7% of nonresponders previously identified at week 24 of treatment," they said.

Ref: Berg T, Sarrazin C, Herrmann E et al. Prediction of treatment outcome in patients with chronic hepatitis C: significance of baseline parameters

and viral dynamics during therapy," was published in Hepatology (2003;37(3):600-609).
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=12601358&dopt=Abstract

C O M M E N T

Similar observations for week 12 have been reported from the pivotal study for the approval of Pegasys published by Fried et al in NEJM 2002. The news from this study is the predictive value of week 4 response rather than week 12. These data may correlate well with a study from Ferenci et al from Vienna presented at last years AASLD where the viral kinetics in the first week of pegylated interferon were used to identify non-responders.

For the moment however week 12 seems to be the time to make a decision to stop or continue treatment based on virological response, because of the better documented data available. It has to be mentioned however that all the response data are based on 24/48 weeks of therapy and patients with a slow viral load decline may respond with prolonged periods of treatment.

Adherence and mental side effects during HCV treatment with interferon alfa and ribavirin in psychiatric risk groups

HIVandHepatitis.com

Psychiatric disorders or drug addiction are often regarded as contraindications against the use of interferon alfa in patients with chronic hepatitis C. The objective of the current study was to obtain prospective data on adherence to as well as efficacy and mental side effects of treatment with interferon alfa in different psychiatric risk groups compared with controls.

In a prospective trial, 81 patients with chronic hepatitis C (positive hepatitis C virus [HCV] RNA and elevated alanine aminotransferase [ALT] level) and psychiatric disorders (n = 16), methadone substitution (n = 21), former drug addiction (n = 21), or controls without a psychiatric history or drug addiction (n = 23) were treated with a combination of interferon alfa 2a 3 (Roferon A) MU 3 times weekly and ribavirin (1,000-1,200 mg/d).

Sustained virologic response (overall, 37%) did not differ significantly between subgroups. No significant differences between groups were detected with respect to interferon alfa-related development of depressions during treatment.

However, in the psychiatric group, significantly more patients received antidepressants before and during treatment with interferon alfa ($P < .001$).

Most of those who dropped out of the study were patients with former drug addiction (43%; $P = .04$) compared with 14% in the methadone group, 13% in the control group, and 18% in the psychiatric group. No patient in the psychiatric group had to discontinue treatment because of psychiatric deterioration.

The researchers conclude that the data do not confirm the supposed increased risk for interferon alfa-induced mental side effects and dropouts in psychiatric patients if interdisciplinary care and antidepressant treatment are available.

Preexisting psychiatric disorders or present methadone substitution should no longer be regarded as contraindications to treatment of chronic hepatitis C with interferon alfa and ribavirin in an interdisciplinary setting.

Ref: Schaefer M, Schmidt F, Folwaczny C et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *Hepatology* 37 (2): 443-451. February 2003.

C O M M E N T

This is a rather small study and patients were treated in a specialised center with a close collaboration of psychiatrists and hepatologists. In a well-controlled setting treatment of patients with psychiatric disorders including the use of antidepressants upfront may be feasible, but this is more difficult to recommend on a larger scale in less prepared centers.

It has to be stressed that interferon is causing depression in 15-20% of patients and suicides or psychotic decompensations have been reported multiple times. In addition hepatitis C is not a rapidly progressing disease for the majority of patients so risk and the likelihood of benefit (genotype, viral load, age etc.) should be carefully balanced.

Key to Hepatitis C virus persistence found

Scientists at two Texas universities have discovered how hepatitis C virus thwarts immune system efforts to eliminate it. The finding, published online today in Science Express, could lead to more effective treatments for liver disease caused by hepatitis C virus, says author Michael Gale, Jr, PhD, of University of Texas Southwestern Medical Centre at Dallas. Dr Gale and coauthor Stanley Lemon, MD, of University of Texas Medical Branch at Galveston, are grantees of the National Institute of Allergy and Infectious Diseases (NIAID).

“Persistent hepatitis C virus (HCV) infection is a major cause of liver disease worldwide and is the leading reason for liver transplants in this country,” notes NIAID Director Anthony Fauci. “The most prevalent form of HCV in the United States is, unfortunately, the least responsive to available treatments. Moreover, African Americans are even less responsive to therapy than Caucasians,” he adds.

The immune system has many ways to detect and fight off invading microbes, and microbes have just as many ways to elude and disarm immune system components. Through a series of experiments on cells grown in the laboratory, Drs Gale and Lemon defined the strategy HCV uses to evade the host’s immune response. As HCV begins to replicate in its human host, it manufactures enzymes, called proteases, which it requires to transform viral proteins into their functional forms. The Texas investigators determined that one viral protease, NS3/4A, specifically inhibits a key immune system molecule, interferon regulatory factor-3 (IRF-3). IRF-3 orchestrates a range of antiviral responses. Without this master switch, antiviral responses never begin, and HCV can gain a foothold and persist in its host.

Next, the scientists searched for ways to reverse the IRF-3 blockade. They applied a protease inhibitor to human cells containing modified HCV. This prevented the virus from making functional NS3/4A and restored the cells’ IRF-3 pathway. Follow-up studies have shown that once restored, the immune response reduced viral levels to nearly undetectable levels within days, according to Dr Gale.

The identification of this viral protease-regulated control of IRF-3 opens new avenues in both clinical and basic research on hepatitis C, notes Dr Gale. Until now, scientists had not considered the possibility that inhibiting this protease did anything more than halt viral replication. “Now that we know NS3/4A inhibition essentially restores the host’s immune response to the virus, we can assess hepatitis drug candidates for this ability as well,” Dr Gale says.

NS3/4A will be a valuable tool in further dissecting the roles of viral proteases and their host cell targets, says Dr Gale. For example, the scientists plan to use NS3/4A to hunt for the still unknown host cell enzyme responsible for activating IRF-3. Conceivably, Dr Gale explains, future therapeutic approaches to viral disease could involve boosting the activity of any key host enzymes that are found.

“Understanding the tricks that the hepatitis C virus employs to impair the immune system represents an important advance with potential implications for successful cure of those suffering from liver disease,” says Leslye Johnson, PhD, chief of NIAID’s enteric and hepatic diseases branch.

NIAID is a component of the National Institutes of Health (NIH), which is an agency of the United States Department of Health and Human Services. NIAID supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, illness from potential agents of bioterrorism, tuberculosis, malaria, autoimmune disorders, asthma and allergies.

News releases, fact sheets and other NIAID-related materials are available on the NIAID Web site at http://www.niaid.nih.gov/. (The paper will be available online at www.scienceexpress.org on April 17, 2003).

Reference: E Foy et al. Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. Science, April 17, 2003. DOI 10.1126/science.1082604.

Source: NIAID

http://www.nih.gov/news/pr/apr2003/niaid-17a.htm

COMMENT

This is conceptually interesting data, but to date no there is no animal model and no real cell culture system in which HCV can replicate as a whole virus. Replicon systems with artificial virus are used so far.

Interactions of immune system and the virus are difficult to extrapolate from cell culture to humans. This may limit the implications of any results as from the paper above. A serin-protease inhibitor from Boehringer Ingelheim is in clinical development and has demonstrated potent viral inhibition during 48 hours of application. All patients experienced a rapid viral rebound after cessation of therapy but this indicates at least initial antiviral activity.

OTHER NEWS

EMEA rejects recombinant Human Growth Hormone for AIDS-related wasting

Simon Collins, HIV i-Base

The European Medicines Evaluation Agency (EMEA) has rejected Serono's application to license its formulation of recombinant Human Growth Hormone, a compound with anabolic effects, (rHGH, non-proprietary name: Somatropin; tradename: Serostim) for AIDS-related wasting syndrome.

Serostim was designated as an orphan drug in August 2000, which allows for additional support from the European agency and reduced costs, for compounds to treat very low incidence diseases.

The reasons given for rejection by the Committee for Proprietary Medicinal Products (CPMP, the agencies scientific committee) included:

• Difficulty to identify a target population due to the heterogeneity in terms of body composition and antiretroviral (ARV) options included in Study GF 9037

• Doubts about the clinical relevance of the primary endpoints studied of improved work output and lean body mass (LBM). Although the questionnaire on the Quality of Life (QoL) showed improvements across all the domains it is still unclear what kind of a benefit might be expected from treatment with Serostim in a clinical setting.

• Long-term efficacy data under controlled conditions are lacking. These are considered necessary to determine the maintenance of the effect of Serostim or the rebound phenomenon, whether the therapy should be intermittent or systematic and whether there would be a need for dose adjustment.

• There is concern about the long-term safety profile of Serostim in the context of repeated courses of treatment in AIDS patients.

The drug received accelerated approval from the FDA for AIDS-wasting in the United States in July 1996.

Serono disagree with the EMEA interpretation of the trial results (which were presented at the IAS World AIDS Conference in Barcelona last year, Abstract ThPeB7352, and others).

Source: EMEA Press Release and Summary of Opinion

Links:

Serono Press Release
http://www.serono.com/media/stories2003/20030430_en.jsp?major=4&minor=1

Useful article on Human Growth Hormone
http://www.thebody.com/sfaf/winter03/hgh.html

C O M M E N T

The main problem with this study was the diverse patient population, with a minority of patients fullfilling the definition of true wasting. r-HGH has a clear anabolic effect in most study participants and this can reverse or stop the loss of lean body mass in HIV-positive patients who have experienced weight loss.

Side effects include induction of diabetes mellitus in patients with abnormal glucose tolerance and arthralgia, especially at the 6mg/day dose. Lipoatrophy may worsen due to subcutaneous fat loss.

Serono is also trying to get rHGH approved for lipodystrophy - reversal of buffalo hump and abdominal visceral fat have been reported during treatment, but symptoms generally return within a few months of discontinuing treatments

England faces soaring sexual infections, warns Adler

England is facing a "public health crisis" caused by dramatic increases in all types of STDs, according to the architect of Prime Minister Tony Blair's sexual health strategy. Professor Michael Adler, of the Royal Free and University College Medical School-London, said that unless there is political leadership, backed by money, the strategy for improving the situation could not get going. The Commons Health Select Committee's advisor painted a bleak picture of the nation's declining sexual health over the past 10 years.

The government has failed to meet almost all the targets set in "The Health of the Nation" in 1992, Adler wrote in the 1 April issue of Sexually Transmitted Infections. Chlamydia cases have risen 73 percent in the past five years, while cases of genital herpes rose 13 percent in the same period. The number of new HIV cases has increased dramatically and is expected to reach 33,930 by 2005. Infectious syphilis cases, which were rare in England, increased 374 percent since 1997, with 697 cases diagnosed in 2001. In the past 12 months alone, syphilis cases increased 116 percent.

Additionally, the rate of teenage conceptions among those under age 16 remained unchanged since 1992 - 8.3 conceptions per 1,000. That is well above the target of 4.8 conceptions per 1,000.

Adler said the ú47.5 million (US$74.6 million) the government allocated for its sexual health strategy would not even cover one aspect of the strategy: a Chlamydia screening program. Sexual health clinics are struggling to cope with demand, with some people in large urban centers forced to wait a month for an appointment. The number of consultants in genito- urinary medicine is 90 percent below target.

"We share Professor Adler's concerns about worsening sexual health and recognize that there are important public health issues to be addressed," said a Department of Health spokesperson. "This is why we have developed the first-ever national sexual health and HIV strategy." The £47.5 million announced with the strategy has been committed to support initiatives and help improve key services, he said.

UK campaign to remove Nonoxynol-9 from condoms and lubricants

Graham McKerrow, HIV i-Base

The National AIDS Trust (NAT) has launched a campaign for the removal of Nonoxynol-9 (N-9) from condoms and lubricants sold in the UK. N-9 is a detergent ingredient previously thought to have microbicidal properties.

NAT is lobbying the department of Health, regulatory authorities, British manufacturers, retailers and health promotion agencies, calling for an end to the production and distribution of condoms and lubricants containing N-9 and clarification on "the proper and limited use" of N-9 contraceptives. They are also calling for greater investment in the search for a safe, effective and affordable microbicide.

In an open letter to manufacturers, distributors and public authorities, NAT and seven specialists and eight other organisations say: "We are concerned that many people mistakenly believe that N-9 provides extra protection against HIV and STIs when used rectally, when in fact there is reason to think that the use of N-9 may increase risk of infection."

The launch of the campaign coincides with the publication in the journal AIDS of a new survey of 573 men who have sex with men (MSM) in California. The researchers found that 61% of participants had heard of N-9 and 83% of those had used it at some point. Of those, 67% had knowingly used N-9 during anal intercourse in the previous year. Of those who had used N-9 in the last year, 41% did so without using a condom because they believed or hoped it was protective.

Scientists have reported studies that have found N-9 was not protective against urogenital gonorrhea or Chlamydia infection and that it causes rectal mucosa disruption in humans, which may increase risk for HIV infection during anal intercourse.

The authors of the California survey write: "All MSM need to know about the dangers of using N-9 rectally." And they add: "Agencies and communities should work together to remove N-9 from products, venues, and websites that predominately serve MSM." They also call on manufacturers to provide warning labels specific to the rectal use of N-9 products.

Ref: Mansergh G, Marks G, Rader M et al. Rectal use of Nonoxynol-9 among men who have sex with men. AIDS (04.11.03) Vol. 17; No. 6: P. 905-909
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=12660538&dopt=Abstract

The NAT campaign briefing can be downloaded at:
http://www.nat.org.uk/

ON THE WEB

A guide to the best new reports and resources posted on the internet.

Guidelines:

US issues revised TB Guidelines

The American Thoracic Society, CDC, and the Infectious Diseases Society of America have released their first completely revised TB prevention, control, diagnosis and treatment guidelines since 1994. They are intended to advise public health

programs and health care providers on all aspects of the clinical and public health management of TB in low-incidence countries. The new guidelines focus on the latest aspects of therapy, including drug administration, fixed-dose combination preparations, monitoring and managing adverse effects, and drug interaction.

The management of HIV-related TB is complex, requiring expertise in both diseases. Expert management is especially important since HIV patients often take numerous medications, some of which interact with TB drugs.

Download pdf file:

http://www.thoracic.org/adobe/statements/treattb.pdf

Conference abstracts and reports:

Report from The 4th International Workshop on Clinical Pharmacology of HIV Therapy

http://www.natap.org/2003/clinPharm/day1.htm

Peter L. Anderson, Pharm.D.,

The 4th International Workshop on Clinical Pharmacology of HIV Therapy was convened March 27th to 29th, 2003 in Cannes, France. The discipline of clinical pharmacology involves the study of how/why human patients respond to drugs including the study of how humans absorb, distribute, metabolize, and eliminate drugs (termed pharmacokinetics), and how the drug affects the patient (termed pharmacodynamics).

The 12th Annual Canadian Conference on HIV/AIDS Research

April 10-13, 2003; Halifax, Nova Scotia, Canada

Report by Mark A. Wainberg, PhD

http://www.medscape.com/viewarticle/452970

On-line medical training

IAPAC I-Med Exchange

http://www.iapac.org/artdisplay.asp?catid=5&artid=641&m=P

http://www.iapac.org/capbuild.asp?catid=1103&m=P

The International Association of Physicians in AIDS Care (IAPAC) is re-launching and expanding “I-Med Exchange,” an innovative medical training program that makes use of Internet conferencing technology.

Presentations will be based on the IAPAC 15-module Global AIDS Learning & Evaluation Network (GALEN) curriculum.

I-Med Exchange sessions are scheduled to take place twice a month, are free of charge and open to all interested healthcare professionals. To participate, please view registration information at www.iapac.org.

For those healthcare professionals who lack access to the Internet, IAPAC-AFRO will be producing a CD compilation of I-Med Exchange sessions.

Guide to management of nucleoside/nucleotide analogue toxicities & side effects

HIV and Hepatitis.com have produced a Guide To Management of Nucleoside / Nucleotide Analogue (NA) Drug Toxicities & Side Effects that is posted in PDF format (196 KB/26 pages).

http://www.hivandhepatitis.com/email/na_guide/NAGuide.pdf

If you would like to have a hard copy of the Guide mailed to you, please e-mail your name and mailing address to steven@hivandhepatitis.com

Medscape articles:

Sexual Transmission of HIV-1: New Data from the 10th CROI

Stephen Taylor, MD, MRCP, PhD

http://www.medscape.com/viewarticle/455430

From JAIDS: Journal of Acquired Immune Deficiency Syndromes

HIV-1 protease and reverse transcriptase mutation patterns responsible for discordances between genotypic drug resistance interpretation algorithms

http://www.medscape.com/viewarticle/453562

Efficacy and treatment-limiting toxicity with the concurrent use of lopinavir/ritonavir and a third protease inhibitor in treatment-experienced HIV-infected patients

http://www.medscape.com/viewarticle/452536

Pharmacokinetics of once-daily saquinavir hard-gelatin capsules and saquinavir soft-gelatin capsules boosted with ritonavir in HIV-1-infected subjects

http://www.medscape.com/viewarticle/451766

Adherence to antiretroviral therapy and persistence of HIV RNA in semen

http://www.medscape.com/viewarticle/451767

From The AIDS Reader

Truth, lies and statistical tests - Graeme J. Moyle

http://www.medscape.com/viewarticle/451677

From AIDS

Volume 17, Number 7

Clade B HIV-1 superinfection with wild-type virus

http://www.medscape.com/viewpublication/744_toc?vol=17&iss=7

Volume 17, Number 6

http://www.medscape.com/viewpublication/744_toc?vol=17&iss=6

Statins and fibrates for the treatment of hyperlipidaemia

Phenotypic susceptibility and virological outcome in nucleoside-experienced patients receiving three or four antiretroviral drugs

Newsletters and reports:

‘Untangling the web of price reductions’ – MSF guide

Latest edition of this quarterly pricing guide to the purchase of ARVs for developing countries, produced and updated by Médecins Sans Frontières. Although the published date is April 24th, the document includes the new GlaxoSmithKline prices, announced last week.

French and Spanish versions are currently in progress and should be ready by the time HTB is printed. The document will be included as an annex to the WHO-MSF-UNICEF-UNAIDS document “Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS, May 2003” which will be released shortly.

Download the document at:

http://www.accessmed-msf.org/documents/untangling4thapril2003.pdf

Hopkins HIV Report – May 2003

http://www.hopkins-aids.edu/publications/report/report_toc_03.html

- FDA Approves Enfuvirtide (Fuzeon, ENF, T-20
- Enfuvirtide Access, Administration, and Patient Education
- The Optimal Use of Enfuvirtide
- Drug Profile: Enfuvirtide
- More From CROI
  - New Drugs: Full Pipeline, Steady Progress
  - Progress in Pharmacology and Drug Interactions
  - Cytomegalovirus Retinitis in 2003

GMHC Treatment Issues - April 2003

http://www.gmhc.org/living/treatment/ti1704/ti1704.html

- No-Care Equals Bad Care: A Talk with Sam Bozzette
- Testing HIV-Positive in New York City: 2001 HIV/AIDS Surveillance Report
- HIV Pathogenesis Reports From the 10th Retrovirus Conference
- HAART to Heart Talk: Continued controversy over HAART-related vascular disease risk
- ConFuzeon Reigns: More details of Roche's T-20 distribution plan
- A Report on the International Treatment Preparedness Summit
- You Have HIV… And You Have AIDS: Why are so many people coming so late to care?

amfAR Global Link – April 2003

http://www.amfar.org/cgi-bin/iowa/td/index.html

Global AIDS - The Private Sector Starts to Take Notice - Anne-christine d'Adesky

Psoriasis: Yet Another Challenge for HIV/AIDS Patients - Jeff Getty

Fighting for Their Health, India's Sex Workers Mobilize - Nicole Rajani

Co-infection:

Liver transplantation in HIV-infected persons

http://www.natap.org/2003/may/050603_1.htm

Full text of important and thorough overview article "Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease" by Neff GW et al, recently published in March 2003 issue of Liver Transplant. [Liver Transpl 2003 Mar;9(3):239-47]

Other links:

Catalogue of FDA approved drug products

Searchable internet source where you can search for official, up-to-date information about FDA approved brand name and generic drugs including those for the treatment of HIV/AIDS and related conditions.

http://www.accessdata.fda.gov/scripts/cder/drugcat/

MEETING ANNOUNCEMENTS

Dates for upcoming meetings are included below. Please check with their websites for full details.

UK Resistance and PK Workshops

5 - 6 June, 3-4 July and 27-28 November 2003

Three interactive educational workshops on resistance testing and pharmacological assessment in HIV have been organised, principally aimed at consultants, and specialist registrars.

Training, including detailed case studies, will be provided by Professor Clive Loveday and Dr Stephen Taylor.

Places are limited to 25 per course and registration fee of £50 includes overnight accommodation in London, plus all meals.

Please contact Mediscript on 020 8446 8898 for further details.

EASL rescheduled

The 38th Annual Meeting of the European Association for the Study of the Liver (EASL), previously postponed (from 29 March to 1 April 2003 in Istanbul, Turkey) due to the outbreak of war in Iraq, has been rescheduled and will now be held in Geneva, Switzerland, from 3 to 6 July, 2003. See website for details.

http://www.easl.ch/easl2003/

5th Workshop on Lipodystrophy and Adverse Drug Reactions and Lipodystrophy in HIV

8–11 July 2003, Paris, France.

Registration is now available on-line, including press, scholarship and community awards.

http://www.intmedpress.com/lipodystrophy

2nd IAS Conference on Pathogenesis and Treatment of HIV/AIDS

Registration is now available on-line, including press, scholarship and community awards.

13-16 July 2003. Paris, France.

http://www.ias2003.org/

PUBLICATIONS AND SERVICES FROM i-BASE

Guide to Avoiding and Managing Side Effects now available in Italian

This guide is now available in Italian, as well as French, Spanish, Chinese and English. The Italian version is available in pdf format from our website at

http://www.i-Base.info

This 36-page booklet is a comprehensive guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

It is written by people who are HIV-positive, who have been on most of the treatments, who have had many of the side effects and who have learnt to negotiate their own healthcare.

To order copies, see below.

UK-Community Advisory Board: new reports and presentations

The UK-Community Advisory Board (UK-CAB) is a network for community treatment workers across the UK. Each meeting includes two training lectures and a meeting with a pharmaceutical company.

The programme, reading material, reports and powerpoint slides from the presentations from the fifth meeting, held on May 2nd, are now posted to the i-Base website.

This meeting focused on:

- Access to treatment for UK visitors, refugees and asylum seekers - Linda McDonald
- TB and HIV coinfection - Dr Anton Pozniak
- T-20 - meeting with Roche

http://www.i-base.info/ukcab/may03/index.html

Transcriptions and slides of training sessions from previous meetings also on the site include:

Genetics, resistance and HIV – by Professor Clive Loveday

Approaches to Salvage Therapy – by Dr Mike Youle

Pregnancy, HIV and Women's Health - by Dr Karen Beckerman

Fertility treatment and sperm-washing techniques – by Dr Leila Frodsham

http://www.i-base.info/education/index.html

The i-Base web site

Our web address is:

http://www.i-Base.info

More than 500 people a day visit the site, where you can read all i-Base publications, fill in our readership survey, find details of the UK Community Advisory Boards (UK-CABs), learn about the organisation, our phone service and meetings, and access our archives and an incomparable range of links.

The site can also be used to order publications and regular subscriptions to be delivered by post or email (as pdf files).

Translations of 'Introduction to Combination Therapy'

This essential non-technical patient guide to combination therapy has recently been translated into Portuguese, Latvian and Slovak, by HIV-positive support organisations in those countries. The Portuguese version is available to download as a pdf file and reprint from the i-Base website:

http://www.i-base.info/pdf/guides/nonuk/COMBO_PORTUGUESE_jan03.pdf

For Latvian and Slovak copies please contact the i-Base office (see page 2).

Printed versions of this booklet are also available in English, French, Italian, Spanish, Chinese and Macedonian. The guide explains what combination therapy is, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and drug resistance and how to avoid it. To order copies, see below

Changing Treatment: a guide to second-line and salvage therapy

Updated January 2003. These treatment guides are reviewed every six months to ensure the latest information is available. Many factors contribute to whether a combination works and in salvage therapy it is important to look at all of these together.

The section on treatment strategies has been rewritten and updated and includes a new section on viral fitness and alternating treatment regimens. The information on expanded access and experimental treatments has also been updated.

Since the previous edition several new treatments have become available to use in salvage therapy and these are also included in the guide:

* T-20 has reported clear benefits for people resistant to other drugs. Marketing approval is expected in mid 2003 but in the meantime it is available in a limited early access programme.
* Atazanavir appears to increase cholesterol and triglycerides less than other PIs and is available in an early access

programme for people with raised lipids on current PIs.

* Tipranavir, a PI with activity against currently resistant HIV, will be available later this year in a limited early access programme.

For additional free copies, including bulk orders see below

Positive Treatment News (PTN)

The latest issue of Positive Treatment News, our magazine for positive people, looks at adherence (missed any pills recently, need any advice?), the latest information about side effects and treatments, and the benefits and risks of joining a drug trial or study.

There is also a detailed look at weight loss and what can be done about it, the official treatment guidelines, salvage therapy and treatment information provision for the African community. To order copies, see below.

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published 10 times a year in both printed and electronic versions.

Please see our website:

http://www.i-base.info

The printed version is available at most HIV clinics in the UK and is available free by post: see below for details.

Treatment information request service: 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can also mail or email copies of the latest research studies relevant to the caller.

For details call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by people who are HIV-positive and is open Mondays, Tuesdays and Wednesday from 12 noon to 4pm.

All calls are in confidence and are free within the UK.

Order i-Base publications via the internet, post or fax

People with internet access can use our site to order and receive publications. You can access our publications online or subscribe to receive our publications by email or by post; and you can order single copies or bulk deliveries by using the forms at:

http://www.i-base.info

Copies of publications can also be ordered by post or fax using the form on the back page of this journal. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), Positive Treatment News (PTN) and all our treatment guides and reports.

All publications are available free of charge — including bulk orders for the UK or single copies for other countries.

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Guide To Avoiding and Managing Side Effects *(August 2002)*
IN ENGLISH

1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____ _____ _____

Also available in FRENCH _____ SPANISH _____ CHINESE _____ _____ _____

Introduction to Combination Therapy *(August 2002)*
IN ENGLISH

1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____ _____ _____

Also available in several other languages - please state how many of each translation you require

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Changing Treatment - Guide to Second-line and Salvage Therapy *(April 2002)*

1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____ _____ _____

Positive Treatment News (PTN) *from Spring 2003*

1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____ _____ _____

Paediatric HIV Care - March 2001 - Report from i-Base Paediatric Meeting

1 ☐ 5 ☐ 10 ☐ Other_____ _____ _____

Adherence planners and side effect diary sheets - In pads of 50 sheets for adherence support

1 ☐ 5 ☐ 10 ☐ Other_____ _____ _____

Please fax this form back or email a request to HIV i-Base:

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