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EDITORIAL

The last issue of HTB for 2004 and first issue of 2005 includes conference reports from the Lipodystrophy Workshop and ICAAC and refers to the Boston Hepatitis meeting and the bi-annual Glasgow Congress held in November. Full coverage of the Glasgow meeting will be included in the next issue of HTB.

The conference coverage though is preceded by a letter issued by BMS to doctors in the US (but not so far in Europe) highlighting recent reports of problems when ddI and tenofovir are used together in a triple combination with nevirapine or efavirenz.

Until the data are more clearly understood patients should not start or switch to triple combinations using this nucleoside backbone, more difficult management decisions are discussed in the comment section following the letter.

It strikes us as a particular incongruity that a safety letter is issued in the US without comment in Europe, and also that dissemination of this information becomes the responsibility of community-based health media...

On a lighter note, HTB has just completed its fifth year - HIV i-Base was set up in 2000 - and as with every end-of-year issue we'd like to thank all our readers and funders for your support over the previous year and wish you all the best for the coming year ahead.

TREATMENT ALERT

Bristol-Myers Squibb (BMS) issued a "Dear Healthcare Provider" letter in the US, the text of which is included below.

Re: Important new clinical data: potential early virologic failure associated with the combination antiretroviral regimen of tenofovir disoproxil fumarate, didanosine, and either efavirenz or nevirapine in HIV treatment-naïve patients with high baseline viral loads

Dear Health Care Provider,

Bristol-Myers Squibb (BMS) Company is writing to advise you of important new clinical data regarding coadministration of Viread® (tenofovir disoproxil fumarate [TDF]), Videx® EC (didanosine delayed-release capsules enteric-coated beadlets [ddI/EC]), and either Sustiva® (efavirenz [EFV]) or Viramune® (nevirapine [NVP]). Data for EFV+TDF+ddI/EC are derived from an open-label randomized study (virologic failure in 6/14 patients) and a retrospective database analysis (virologic failure in 5/10 patients), while data for NVP+TDF+ddI/EC are derived from a retrospective database analysis (virologic failure in 2/4 patients).

Results from two recently conducted, investigator-sponsored trials by Podzamczer et al [1] and JM Gatell (written communication, July 2004) have demonstrated a potential for early virologic failure associated with this antiretroviral regimen in treatment-naïve HIV patients with high baseline viral loads. The mechanism of early virologic failure in these patients is unclear.

Early virologic failure appears to be limited to the specific combination of TDF + ddI EC + either EFV or NVP as there are data from registrational trials supporting the efficacy of EFV and TDF-based regimens as well as EFV and ddI EC-based regimens in treatment-naïve HIV patients. [2, 3, 4]

Additionally, a recent post-hoc analysis performed in treatment-experienced HIV patients with high baseline viral loads receiving a boosted protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors (NRTIs) demonstrated lower virologic failure rates in subjects receiving ddI/EC and TDF than those receiving another nucleoside analogue in combination with TDF, though significance testing could not be performed due to a small number of patients (n=55).

Based on this information:

- **clinicians should use caution when coadministering TDF, ddI/EC, and either EFV or NVP in treatment-naïve HIV patients with high baseline viral loads.**
- **further investigations are ongoing to better understand the clinical implications of these results.**

For further details on these studies, please refer to the following pages for study summaries.

Studies demonstrating early virologic failure in treatment-naïve HIV patients with high baseline viral loads

- The ININ Study [1] (Podzamczar et al): An open-label, randomized, multicenter, pilot study with a planned enrollment of 50 treatment-naïve HIV patients designed to assess efficacy and safety of TDF 300 mg once daily + ddI/EC 250 mg once daily (<60 kg: 200 mg once daily) + EFV 600 mg once daily compared with TDF 300 mg once daily + ddI EC 250 mg once daily (<60 kg: 200 mg once daily) + EFV 600 mg once daily + Kaletra® (lopinavir/ritonavir [LPV/r]) 400/100 mg twice daily. Of the 36 enrolled patients, 26 were available for follow-up at 3 months. Six of 14 patients (42.8%) in the TDF+ddI/EC+EFV arm experienced protocol-defined virologic failure*, versus 0 of 12 patients in the TDF+ddI/EC+EFV+LPV/r arm. Baseline viral load >100,000 copies/mL and advanced stage of disease (low CD4+ cell counts [<200 cells/mm³] plus CDC stage C or B3) were seen in all six patients with virologic failure but in none of the eight patients without virologic failure. Resistance patterns that included G190E/S (n=3), L74V/I (n=4), and K65R (n=2) mutations were observed at failure.
- JM Gatell et al (written communication, July 2004): A retrospective database analysis of 5,000 treatment-naïve HIV patients in whom therapy was initiated between October 2002 - March 2004 was performed. Fourteen patients were identified as having received a regimen of ddI EC 250 mg once daily and TDF 300 mg once daily, plus either EFV 600 mg once daily (n=10) or NVP 400 mg once daily (n=4). After 12 weeks of therapy, 5/14 patients (36%) experienced suboptimal (plasma viral load drop <2 log₁₀ copies/mL) response rates. Two additional patients (total 7/14, 50%) who were treatment-responders at Week 12 reached protocol-defined virologic failure at Week 24.†

The seven cases of virologic failure consisted of 2/4 patients receiving NVP- and 5/10 patients receiving EFV-containing regimens. At baseline, virologic failure patients had a median log₁₀ viral load of 5.8 (range, 4.7-6.0) copies/mL and a median CD4+ cell count of 126 (range, 24-281) cells/mm³. Four of the virologic failure patients exhibited the K65R and L74V mutations and all 7 exhibited one or more of the following mutations: L100I, K103N/R/T, Y181C, and G190E/Q/S.

Studies of treatment-naïve HIV patients with combination antiretroviral regimens containing EFV and TDF or ddI/EC

- Gilead Study 903 [2]: A 144-week, Phase III, multicenter, randomized, double-blind, active controlled trial in treatment-naïve HIV patients designed to evaluate the efficacy and safety of TDF compared to Zerit® (stavudine [d4T]) capsules, each in combination with 3TC + EFV.

At 48 weeks, similar efficacy was observed between the two treatment groups: EFV + 3TC + TDF (n=299), HIV RNA <400 copies/mL = 79% and <50 copies/mL = 76%; versus d4T + 3TC + EFV (n=301), HIV RNA <400 copies/mL = 82% and <50 copies/mL = 79%, ITT analysis. At 48 weeks, Study 903 showed comparable virologic efficacy (HIV RNA <400 copies/mL) in patients with baseline viral loads above and below 100,000 copies/mL (n=600; >100,000 copies/mL = 86% in the TDF arm and 85% in the d4T arm; <100,000 copies/mL = 87% in the TDF arm and 89% in the d4T arm). [5] These trends continued through 144 weeks.[6]

- **Study 301A** [3,4]: A 48-week, double-blind, active-controlled multicenter study compared Emtriva® (emtricitabine [FTC]) 200 mg once daily administered in combination with ddI EC 400 mg once daily (patients weighing <60 kg received 250 mg) and EFV 600 mg once daily versus d4T + ddI EC + EFV in 571 treatment-naïve patients. Thirty-eight percent of patients had baseline viral loads >100,000 copies/mL. In the FTC + ddI EC + EFV arm (n=286), 81% of patients had HIV RNA <400 copies/mL and 78% had <50 copies/mL at Week 48. In the d4T + ddI EC + EFV arm (n=285), 68% of patients had HIV RNA <400 copies/mL and 59% had <50 copies/mL at Week 48.

Study of treatment-experienced HIV patients with a combination antiretroviral regimen containing a RTV-boosted PI, TDF and ddI/EC or another NRTI

- BMS Study AI424-0457: A Phase III, open-label trial in which 358 treatment-experienced patients with multiple virologic failures were randomized to one of three boosted PIs (shown below) each in combination with TDF and one other NRTI (approximately half on ddI EC):
 - Reyataz® (atazanavir sulfate [ATV]) 300 mg + RTV 100 mg once daily or
 - LPV/r 400/100 mg twice daily or
 - ATV 400mg + saquinavir (SQV) 1200 mg once daily.

The ATV + SQV arm had statistically inferior results to those in the ATV + RTV and LPV/RTV arms, and will not be discussed. Interaction studies of ddI EC + TDF demonstrated increased ddI exposure when ddI EC 400 mg was administered one to two hours before TDF 300 mg and a light meal. Consequently, a protocol amendment specified ddI EC dose reduction to 250 mg (adults weighing 360 kg with creatinine clearance 360 mL/min) or 200 mg (adults weighing <60 kg with creatinine clearance 360 mL/min) once daily. By Week 24, approximately 2/3 of ddI EC subjects had reduced dosage to 250 mg.

Forty-eight week results were stratified according to baseline viral load and assessed for differences between ddI- and non-ddI-containing regimens. A post-hoc analysis using these data was performed on the subset of treatment-experienced patients with a baseline viral load 3100,000 copies/mL.‡

The two combined arms of ATV + RTV and LPV/RTV demonstrated a 33% (8/24) virologic failure rate§ through Week 48 in the ddI-treated group compared to 52% (16/31) in the non-ddI-treated group.

Please refer to the enclosed full prescribing information for Videx® EC (didanosine) Delayed Release Capsules Enteric Coated Beadlets and Sustiva® (efavirenz) Capsules and Tablets.

BMS is committed to providing you with current product information for the management of your patients with HIV infection. If you have any questions about this new information or require additional medical information, please contact the Virology Medical Services Department at Bristol-Myers Squibb Company at 1-800-426-7644 (select Option 3).

Sincerely,

Sally L. Hodder, MD

Vice President, Virology Medical Affairs, BMS

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- * Virologic failure in the ININ Study was defined as (1) reduction in viral load of less than 2 log₁₀ copies/mL at 3 months, (2) more than 1 log₁₀ copies/mL rebound from the nadir, or (3) viral load detectable at 6 months or later.
 - † Virologic failure in the Gatell et al study was defined as (1) plasma viral load drop of less than 2 log₁₀ copies/mL at 3 months or (2) viral load rebound less than 200 copies/mL for 2 consecutive measurements separated by at least one week, after an initial drop below 200 copies/mL.
 - ‡ Median baseline HIV RNA: ATV/RTV arm=4.44 log₁₀ copies/mL, LPV/RTV arm=4.47 log₁₀ copies/mL.
 - § Virologic failure rates measured by TLOVR (time to loss of virologic response) analysis.

References

1. Podzamczar D, Ferrer E, Gatell JM, et al. Early virologic failure with a combination of tenofovir, didanosine and efavirenz. Antiviral Therapy 2004 9:S172, Poster 156, 13th International HIV Drug Resistance Workshop; June 2004; Tenerife, Spain.
2. Viread® (tenofovir disoproxil fumarate) Prescribing Information. Gilead Sciences, Inc., June 2004.
3. Emtriva™ (emtricitabine) Prescribing Information. Gilead Sciences, Inc., July 2003.
4. Saag M, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naïve patients: a randomized trial. JAMA. 2004; 292:180-189.
5. Staszewski S, Gallant J, Pozniak A, et al. Efficacy and safety of tenofovir disoproxil fumarate (TDF) versus stavudine (d4T) when used in combination with lamivudine (3TC) and efavirenz (EFV) in HIV-1 infected patients naïve to antiretroviral therapy (ART): 48-week interim results. XIV International AIDS Conference; July 7-12, 2002; Barcelona, Spain. Oral Presentation LbOr17.
6. Gallant JE, Staszewski S, Pozniak A, et al. Long-term efficacy and safety of tenofovir DF (TDF): A 144 week comparison versus stavudine (d4T) in antiretroviral-naïve patients. XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Poster 4538.
7. Data on file, Bristol-Myers Squibb Company, Princeton, New Jersey.

C O M M E N T

This letter has so far been sent to US but not EU physicians, although both BMS and Gilead are discussing the data with the European regulatory agency and a response will not follow for at least another month.

There were also two studies at ICAAC addressing the same issues that are not referenced in the letter. See ICAAC reports from these studies later in this issue of HTB. Several other studies at the Glasgow conference presented further supportive data.

It is important to separate the virological failure interaction (Podzamczar/CORRS/Gatell), mechanism unknown, from the CD4 data (Negredo) which is likely to be related to a pharmacokinetic interaction, with the discordant CD4 response dependent on ddl dose. As regards low CD4 responses, there is interest with tenofovir inhibiting PNP (since PNP deficiency syndromes in childhood causes SCID-like immunodeficiency) - but low CD4s were not seen in the Gilead 903 study suggesting that this is a 'high dose ddl plus tenofovir' problem and not a 'tenofovir problem'.

Interestingly in the ICAAC poster from Barrios and colleagues (see ICAAC coverage below) patients with a CD4 decline, did not return to baseline even after reducing dose of ddl.

Until these results are more clearly understood, patients starting or switching treatment should clearly avoid the nucleoside combination of tenofovir and ddl.

Patients already successfully suppressed, should still probably switch one or other of these nucleosides, especially if this is a first line combination and convenient alternatives are available. This caution is for risk of cross class resistance should the combination fail in the future and also potential side effects linked to higher ddl exposure, including pancreatitis and lactic acidosis.

Although from a virological perspective this advice is most important in patients whose baseline viral load was >100,000 copies/mL and/or who are less than 100% adherent, the concern for toxicity will apply to all patients.

CONFERENCE REPORTS

6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (6th IWADRLH)

26-28 October, 2004, Washington

Simon Collins, HIV i-Base

This annual workshop, largely focused on lipodystrophy and metabolic complications, provides an opportunity to assess research developments over the previous year. It also addresses the implications on clinical practice, and to a more limited extent, the implications for clinical management. From a community perspective, this research is painfully slow, often based on in vitro cell studies and mouse and rat models.

The clinical approach for management of lipodystrophy is not addressed in a comprehensive way, but interesting individual studies, including treatment interventions, are usually included.

The meeting also includes invited lectures from expert in non-HIV related fields that gives useful insight into HIV-related lipids changes.

The areas covered in this report include:

- Nucleoside analogue-related mitochondrial toxicity and link to lipoatrophy: effect of non-thymidine analogues (abacavir and tenofovir)
- Nucleosides reduce PPAR-gamma: a role for rosiglitazone without thymidine analogues?
- Potential for uridine to treat mitochondrial toxicity: still only in vitro data
- 25% patients take Kaletra on an empty stomach: dietary advice often missed at 'centre of excellence'
- rHGH reduces central fat accumulation in adolescent lipodystrophy
- Weight loss is associated with elevated PBMC proviral DNA levels
- Coronary artery bypass graft is safe in HIV-positive patients but shows higher risk of longer term events
- Endothelial dysfunction similar in ARV-experienced and -naïve patients
- Pravastatin improves lipid profiles but not endothelial function
- Indinavir impairs endothelial function without insulin resistance
- Treatment interruptions improve lipids within four weeks: IL-2 has no metabolic effect
- Improvement of lipids following switch to tenofovir
- HCV coinfection linked to discontinuing ART due to toxicity

Abstracts from this meeting are already online as part of the excellent AEGiS conference abstract library.

<http://www.aegis.org/conferences/6thLipo/>

Unless stated otherwise, all references are to the Programme and Abstracts from the 6th IWADRLH meeting published in Antiviral Therapy 2004.

Nucleoside analogue-related mitochondrial toxicity and link to lipoatrophy: effect of non-thymidine analogues abacavir and tenofovir

Simon Collins, HIV i-Base

The most significant research into lipoatrophy over the last few years have come from several Australian research groups. The plausibility for the link between mitochondrial toxicity and lipoatrophy is convincingly strengthened by research that correlates peripheral and facial fat loss with reduced mitochondria cell number in adipocytes).

HIV itself may have an impact. There is a correlation of CD4 count and mitochondrial depletion in PBMCs in treatment naïve patients that improves following ARV treatment that includes ddC and ddI, that suggests HIV itself may also reduce mitochondria in adipocytes.

Last year, David Nolan's group reported mitochondria are similarly reduced in the following patient groups: d4T-treated > AZT-treated > ARV-experienced > ARV-naïve > HIV-negative with median mitochondria copies/adipocyte of 234, 537, 1169 and 1586 respectively, see also table below). Pathophysiological effects in adipocyte damage from fat biopsies in the same patients, showed progressively worsening adipocyte structure that correlated directly with reductions in mitochondria.

Longitudinal studies have shown differential impact of thymidine analogues. While BMI was 24kg/m² in each group, DEXA scan confirmed percentage of leg fat to be 12%, 17% and 24% in the d4T, AZT and naïve groups respectively.

This year, Nolan presented new data from 190 biopsies from just over 100 individuals, on the level of mitochondrial DNA content in adipocytes related to thymidine and non-thymidine analogs; with supporting chronology. Mitochondrial DNA levels at baseline had no correlation to CD4%, viral load, age or BMI.

Early mitochondrial depletion from d4T- or AZT-containing regimens (around -260 copies/cell per month; 60% reduction after 6-12 months), lead to adipocyte damage 3-12 months later, and subsequently symptomatic lipoatrophy over the next 10-40 months. This was statistically significant for both drugs, with the d4T causing twice the effect. Switching from d4T to AZT increased mtDNA.

Patients starting treatment with non-thymidine nucleosides, showed similar levels of mitochondria in adipocytes to ARV-naïve and HIV-negative patients. (non-significant reduction of -69 copies/cell/month; p=0.6) and people switching to from d4T to AZT or abacavir, or from AZT to abacavir saw mitochondrial number increase 3-11-fold over 1-24 months (p=0.01).

Table 1: Adipocyte mtDNA copies/cell by NRTI exposure

Exposure group	n	no. mt/cell	(range)	log mt/cell	
ART naïve	34	1427	(413-6570)	3.19	100%
AZT-containing	41	761	(94-2846)	2.89	49%
d4T-containing	35	250	(61-2287)	2.44	18%
non-thym					
(ABC or TDF)	19	1675	(916-4180)	3.23	

Switch studies from d4T or AZT to abacavir (Carr et al) have already showed reversal of leg fat, and the Gilead 903 tenofovir study showed low incidence of peripheral fat loss, and both clinically support the benefit of non-thymidine nucleosides. This study provided additional data to support the non-significance of mitochondrial involvement of these newer drugs.

Mitochondrial protein was statistically higher in d4T- and AZT-containing regimens (p=0.032 and 0.009 respectively, compared to naïve patients) and PPAR-gamma significantly lower (p=0.021, d4T compared to naïve), Gene expression represent total adipose tissue rather than adipocytes (approximately 30% adipocyte and 70% stromal-vascular, including pre-adipocytes. ICE/Caspase1 expression, involved in the induction phase of apoptosis or pre-adipocytes correlated with mtDNA (p=0.02) and d4T exposure (p=0.04), but not to abacavir or PI.

Lipoatrophy should therefore be viewed as a dynamic event that is confounded by individual changes in tissue expression over time as it becomes progressively more severe. Progression can be very rapid (ie leg fat reduced to 10% over 10 months treatment with d4T) and may continue after any switch in treatment.

Clearly not all nucleosides are equal and in vitro and in vivo studies seem to have produced a consensus agreement of greatest negative impact of d4T > AZT > 3TC > abacavir = tenofovir,

Ref: Nolan D. Differential effects of nucleoside reverse transcriptase inhibitor (NRTI) regimens on adipocyte mitochondrial DNA depletion in HIV-infected patients. Abstract 16.

C O M M E N T

We do not know the level of mitochondrial damage that triggers clinical symptoms, and there is still no data on the role of ddl.

While leg and arm fat may be reversible to some degree in some patients, this is a slow process dependent on individual regenerative capacity. Stankov and colleagues suggested that while both d4T and AZT affect adipocyte differentiation, only d4T is directly toxic to pre-adipocytes.

Nucleosides reduce PPAR-gamma: a role for rosiglitazone without thymidine analogues?

Simon Collins, HIV i-Base

Even earlier changes in gene-expression implicated in lipoatrophy were presented by Paddy Mallon and colleagues from St Vincent's Hospital, Sydney, who described changes in mitochondrial and nuclear gene expression in adipose tissue in 20 HIV-negative volunteers, randomised to standard dose dual nucleoside therapy (AZT/3TC or d4T/3TC) for 6 weeks. [1, 2, 3]

This group observed inhibition of mitochondrial RNA after 2 weeks that coincided with upregulation of genes relating to mt

transcription by 25-83% (mtTFA, NRF1, PCG1) and fatty acid oxidation by 50-55% (PPAR-alpha and LPL) and down regulation of PPAR-gamma (which is responsible for adipocyte differentiation and insulin responses) by 50%. It is notable that these changes occurred without significant changes in mtDNA appearance or depletion.

Monocyte mtRNA expression (COX1) also decreased by -38% to week 6 and persisted for a further 6 weeks after stopping study drugs.

These results showing an early change both in genetic expression both on production and development of fat cells on the one hand, and upregulation of mitochondrial transcription on the other, explain the link between nucleoside therapy and lipoatrophy, and also the increased rates of lipoatrophy when protease inhibitors (which also down regulate PPAR-gamma) are used in combinations with nucleosides.

The affect of thymidine analogues on PPAR-gamma may also explain the disappointing results given the theoretical promise of using rosiglitazone, a PPAR-gamma agonist, was used to treat lipoatrophy. [4] In a double-blinded randomised placebo study of 4mg rosiglitazone twice-daily showed no benefit over 48 weeks of the original study, or when follow-up was extended to 84 weeks.

C O M M E N T

An understanding that nucleosides could be acting at a later step to block any benefit from rosiglitazone, suggests that the rosiglitazone could perhaps be restudied without use of thymidine analogues.

1. Mallon PWG, Unemori P, Carr A et al. In vivo nucleoside reverse transcriptase inhibitors alter expression of both mitochondrial and lipid metabolism genes independent to HIV infection. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 15. Antiviral Therapy 2004; 9:L11.
2. Mallon PWG, Sedwell R, Unemori U et al. Changes in nuclear gene expression resulting from NRTI-induced inhibition of mitochondrial transcription reveal links between mitochondrial dysfunction and lipid metabolism. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 97. Antiviral Therapy 2004; 9:L56.
3. Mallon PWG, Sedwell R, Unemori U et al. Nucleoside reverse transcriptase inhibitors (NRTI) decrease adipocyte and monocyte mitochondrial (mt) messenger RNA transcription in the absence of changes in mtDNA or cell morphology. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 98. Antiviral Therapy 2004; 9:L56.
4. D Carey D, Workman C, Rogers G et al. Rosiglitazone for HIV lipoatrophy: 84 weeks follow-up. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 78. Antiviral Therapy 2004; 9:L46

Potential for uridine to treat mitochondrial toxicity: still only in vitro data

Simon Collins, HIV i-Base

Ulrich Walker from University of Freiburg and colleagues from INSERM and Pierre and Marie Curie Universite, Paris, presented interesting in vitro results looking at the effect of uridine on adipose cell function. [1]

At last years Workshop Walker presented interesting data were presented suggesting the potential for uridine to reverse ddC or d4T-associated mitochondrial dysfunction. The studies used Mitocnol, a dietary supplement derived from sugar cane, to raise levels of uridine. An in vitro study showed a protective effect in the presence of each drug in hepatocytes and normalised cell proliferation, lactate and intracellular lipids by adjusting mtDNA-levels to about 65% of NRTI-unexposed control cells. A single dose PK study showed that plasma uridine levels were achievable. [2]

The year data was presented on preadipocytes exposed to ddl or ddC +/- uridine for 21 days before and 7 days after differentiation. Without uridine, adipocytes showed reduced lipid accumulation containing reduced size and number of lipid droplets, and high rates of rates of apoptosis (by 5.6-fold and 2.2 fold in ddC and d4T exposed cells respectively).

Uridine had no effect by itself, but on ddC and d4T-exposed cells, normalised lipid morphology and rate of apoptosis.

Pharmacokinetic data was provided from a study in eight HIV-negative volunteers (4 men, 4 women) following single dose NucleomaxX (36g, dissolved in orange juice). Mean serum uridine levels increased from 5.6 uM at baseline to 152.0 uM (Cmax after 1.3 hours), dropping to 19.3 uM and 7.5 uM at 8 and 24 hours respectively. No side effects were reported. [3]

C O M M E N T

It was disappointing though not to have any further data in HIV-positive individuals at the meeting.

However, several larger studies in HIV-positive patients are already underway in Europe and the US, looking at countering mitochondrial toxicity in patients maintained on d4T- or AZT-containing regimens, and a further study in Germany is looking at NucleomaxX for polyneuropathy.

Uridine replacement may only be effective for lipoatrophy by abrogating an effect of ongoing nucleoside use and its mechanism of action

is not expected to help nucleosides such as ddl.

References

1. Walker UA, Capeau J, Caron M et al. Uridine abrogates the adverse effects of stavudine and zalcitabine on adipose cell functions. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 14. Antiviral Therapy 2004; 9:L10
2. Uridine as a potential treatment for NRTI related mitochondrial toxicity. See HTB Vol4No7 July/Aug 2004.
<http://www.i-base.info/pub/htb/v4/htb4-7/potential.html>
3. Walker UA, Venhoff N, Zilly M et al. Uridine pharmacokinetics of Mitocnol, a sugar cane extract. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 30. Antiviral Therapy 2004; 9:L21

25% patients take Kaletra on an empty stomach: dietary advice often missed at 'centre of excellence'

Graham McKerrow, HIV i-Base

A retrospective questionnaire/interview study of 63 patients taking lopinavir/ritonavir (LPV/r, Kaletra) at the Chelsea and Westminster Hospital in London found that only 43% were taking the drug with adequate food and just over a quarter of patients were taking Kaletra on an empty stomach.

Phillpot and colleagues aimed to interview a quarter of the clinics 500-odd patients taking an LPV/r-containing regimen by telephone questionnaire or at a routine clinic visit. In fact, only 63 (12.5%) patients were interviewed. 38 (60%) said they were told to eat with LPV/r, 20 (32%) said they weren't given any information and 5 (8%) couldn't remember.

A moderate fat meal (500-682 kcals) increases mean lopinavir AUC and C_{max} by 48% and 23% respectively relative to fasting, and this increased bioavailability is why Kaletra is recommended in prescription advice to be taken with food.

The researchers comment: "For those patients who said they were given guidance on how to take Kaletra, a greater percentage took it with the correct amount of food. However patient error must be considered when carrying out retrospective questionnaires and dietary recall."

Ref: Phillpot MN, Kabaroff E and Visser TL. Are patients given adequate dietary information when starting on a Lopinavir/Ritonavir containing HAART regimen? 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 86. Antiviral Therapy 2004; 9:L50.

rHGH reduces central fat accumulation in adolescent lipodystrophy

Simon Collins, HIV i-Base

Dr Alesandra Vigano was one of the first doctors to describe the incidence of lipodystrophy and reduced bone mineral density in her cohort of 100 children at University of Milan.

At this years Lipodystrophy meeting she reported results from a pilot study of growth hormone dosed at 0.028mg/Kg daily for 24 weeks in eight adolescents with visceral fat accumulation (defined as intra-abdominal tissue (IAT) content >41cm² by MRI scan at L4). This is less than the therapeutic rHGH dose for children with growth impairment. Abnormal glucose tolerance, diabetes or ongoing malignancies were exclusion criteria for the study.

Three boys and five girls with median age 15.7 years (range 13.7-18.5), with mean BMI 21 Kg/cm² with undetectable viral load on combination of 3TC/d4T+PI therapy for a median of almost seven years (range 64-83 months) received 24 weeks rHGH treatment and results were compared to 97 healthy HIV-negative children as a control group.

All children completed the course of treatment and experienced approximate mean reductions in trunk, leg, arm and total fat of -1.0, -0.1, -0.3 and -1.5 kg respectively, compared to increases of fat in each area seen in health controls.

Increases in mean lean mass of +1.5, +0.5, +1.6 and +3.1 kg in trunk, arms, legs and total lean mass were all significantly greater (approximately double) than lean mass increases in the control group.

IGF-1 levels (measured at week 4, 12 and 24) approximately doubled in all eight patients and although supraphysiological IGF-1 levels were detected in 5/8 (62%) of the patients and in 9/24 (37%) of measurements these levels were only 2-23% over upper limit normal. BMI, glucose and lipid profiles (fasting glucose, glucose and insulin AUC, HDL, LDL and total cholesterol, and triglyceride levels did not significantly change or worsen over the study period.

Side effects reported with adult use of rHGH (swollen joint and muscle ache or pain, carpal tunnel syndrome, nausea) were not reported. Notable bone mineral content also increased over 24 weeks (17.9 vs 19.5g, p=0.03).

4/8 patients achieved target of IAT <41 cm² and rHGH was not continued as maintenance dose. The other 4 patients continued treatment with a higher dosage of rHGH.

The authors concluded that rGHG was safe and effective at the studies dose in decreasing IAT and trunk fat and increasing lean mass in HIV-positive adolescents with ARV-associated central fat accumulation.

C O M M E N T

It was not clear in the study whether limb fat loss was caused by rGHG treatment or because HAART regimens continued to include d4T, 3TC and a PI.

Adult management of lipoatrophy has particularly shifted from continued use of d4T, and more recently also from AZT, in any patient with symptomatic lipoatrophy, and the use of other nucleosides would seem equally appropriate in children and adolescents, particularly strengthened by related studies at this Workshop.

Although switching therapies is likely to be an easy approach for lipoatrophy, there is not such a clear option for fat accumulation, and rGHG may therefore be an important option. The safety data from this study was reassuring.

Durability of response will be important, as fat accumulation has returned in around 50% adults patients using rGHG. Ongoing studies are looking at whether the response can be extended by lower dose maintenance regimens in these individuals.

Weight loss is associated with elevated PBMC proviral DNA levels

Graham McKerrow, HIV i-Base

Weight loss in the HAART era may be driven by residual HIV infection in cells of the monocyte/macrophage lineage, conclude Shikuma and colleagues from the University of Hawaii after a study involving 67 HIV-positive people, a subset of the Hawaii Aging with HIV longitudinal cohort study.

Catabolic cytokines such as TNF-alpha are often elevated in HIV-positive people who have received ARV therapy. Residual HIV infection in cells of the M/M-omega lineage have been found in ARV-treated people who have undetectable plasma HIV-1 RNA.

The researchers hypothesised that weight loss might be secondary to residual HIV infection in these cells with resultant increases in catabolic cytokine production and release.

They analysed the patients' PBMC proviral DNA copies/cell, select plasma cytokine levels and weight records over the last year of follow-up. Approximately 17% had weight loss > 10 %, 15% had weight loss from > 5% to 10%, 60% maintained stable weight (less than 5% gain or loss), and 6% gained weight.

PBMC proviral DNA levels were higher in those with weight loss > 5% compared to those with stable or increasing weight [median 8.9 vs 0.9 copies/106 cells; p=0.006]. Proviral DNA levels remained higher in the 52% of subjects with plasma HIV RNA levels < 50 copies/mL [median 8.9 vs 0.5 copies/106 cells, p=0.028]. Analysis of HIV DNA in subsets of PBMCs showed that the majority of proviral DNA copies in PBMCs were in activated (CD14+/CD16+) macrophages.

Ref: Shikuma C M, Valcour V, Ratto-Kim S et al. Loss of weight in the era of HAART is associated with elevated PBMC proviral DNA levels. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 57. Antiviral Therapy 2004; 9:L35.

Coronary artery bypass graft is safe in HIV-positive patients but shows higher risk of longer term events

Graham McKerrow, HIV i-Base

Coronary artery bypass graft (CABG) is a feasible and safe procedure in HIV-positive patients, conclude Boccara and colleagues at the French Italian Study on Coronary artery disease in AIDS patients (FRISCA-2). There was no difference in immediate postoperative outcomes between HIV-positive and HIV-negative patients. However, long-term follow-up showed higher rates of major adverse cardiac events (MACE) was significantly higher in HIV-positive patients due to an increased rate of repeat revascularisation procedure (reCABG and percutaneous coronary intervention [PCI]).

From 1997 to 2003 inclusive, researchers compared 22 HIV-positive and 42 HIV-negative control patients matched for age and gender who underwent CABG. They compared baseline characteristics, immediate results and clinical outcome (MACE: death from any cause, myocardial infarction, re-intervention and/or PCI) at 34 months.

Cardiovascular risk factors were nearly identical in both groups with a higher rate of hypercholesterolaemia (96% versus 74%, p=0.045) and hypertriglyceridaemia (82% versus 45%, p=0.005) in HIV-positive patients. Obesity was more frequent in the control group (33% versus 0%, p=0.001).

In the HIV-positive group, mean CD4 count was lower post-operation compared to beforehand (427 +/- 162 vs 503 +/- 200 cells/

mm³) but this was without clinical significance in the follow-up. Coronary multivessel disease (> 2 vessel disease) was present in nearly all patients (96% HIV-positive and 93% HIV-negative). Left Ventricular Ejection Fraction and mean number of grafts were also similar in the 2 groups (55%±10 versus 50%±14, respectively).

After one month, the rate of post-operative death, MI, stroke, mediastinitis, and re-intervention was identical in both groups. However, at 34 ±20 months follow-up, rate of occurrence of first MACE was higher in HIV-positive group. The only predictor of MACE at follow-up was HIV infection itself with a hazard ratio of 6.3 (95%CI 2.2-17.9, p=0.001).

Ref: Boccaro F, Cohen A, Odi G et al. Coronary artery bypass graft in HIV-infected patients. A multicentre case control study. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 115. Antiviral Therapy 2004; 9:L65.

Endothelial dysfunction similar in ARV-experienced and -naïve patients

Graham McKerrow, HIV i-Base

A Spanish study of 61 HIV-positive men on ARV therapy found endothelial dysfunction (ED) in 18%, a similar proportion to naïve patients. Its presence was independent of fat redistribution abnormalities, plasma adipokines, lipoproteins, immune status or use of PIs or NNRTIs.

Low adiponectin (AD) plasma levels are observed in patients on treatment with fat redistribution abnormalities (FRA) and low levels of adiponectin have been associated with impaired vasoreactivity in the general population. Previous studies found a significant relationship between use of PIs and endothelial dysfunction.

Estrada and colleagues in Madrid analysed the relationships between plasma AD, FRA, and endothelial function as measured by high-resolution ultrasound. Of the 61 ART-experienced people studied, 44.2% presented with FRA, most of them with lipotrophy.

Mean flow-mediated vasodilation (FMD) of patients on ARV treatment was 11.6% (IC 95%, 8.3-14.9) similar to control group, 11.7% (IC 95%, 7.4-16), p=NS. The proportion of patients who presented ED was similar between treated 11/61 (18%) and naïve groups 6/17 (35.3%) p=ns. There was a significant correlation between FMD and vasodilator response to nitrates (r=0.48, p=0.001). Plasma adiponectin, leptin, lipoproteins, insulin, CD4 lymphocyte count, HIV-1 viral load, did not correlate with FMD. Presence of fat distribution changes did not influence FMD values. Patients on PI or NNRTI showed similar FMD values. In multivariate linear regression analyses, only basal artery diameter significantly contributed to FMD.

Ref: Estrada V, Zamorano JL, Sainz T et al. Endothelial dysfunction, adiponectin plasma levels and lipodystrophy in patients on antiretroviral therapy. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 117. Antiviral Therapy 2004; 9:L66.

Pravastatin improves lipid profiles but not endothelial function

Graham McKerrow, HIV i-Base

Pravastatin improves the dyslipidaemia of HIV-positive people on ART but this does not translate to improved endothelial function (EF). Persistently elevated C-reactive protein (CRP) values suggest that there may be an ongoing stimulus towards cardiovascular (CV) risk that has yet to be elucidated, Sklar and colleagues in the United States conclude from a randomised, placebo-controlled, crossover study.

Twenty-three HIV-positive patients on stable ART completed the study to evaluate the effect of pravastatin (40mg) on endothelial function, which was assessed by flow-mediated vasodilation of the brachial artery.

At baseline, HIV-positive individuals demonstrated abnormal EF compared with an otherwise healthy, HIV-negative population (mean ± SEM, 7.0±0.5% HIV vs. 10.1±0.9 controls, p=0.002). Active treatment with pravastatin significantly reduced total cholesterol (mean -36±5 mg/dL, p<.001), LDL-cholesterol (-30±4, p<.001), and triglycerides (-69±25, p=.01). There was no effect on HDL-cholesterol or measures of insulin resistance.

Despite the overall improvement in metabolic risk profiles, pravastatin showed no consistent or significant improvement in EF (mean 7.0% on drug, 7.3% on placebo, P=0.68). CRP values were similarly unaffected (mean 6.3 on drug, 6.7 on placebo, p=0.85); there was no significant correlation between FMD and CRP at baseline (correlation coefficient = -0.16, p=0.45)

Ref: Sklar PA, Grubb JR, Voell JD et al. Endothelial dysfunction in HIV-infected patients on CART does not improve even when lipid profiles improve on pravastatin. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 24. Antiviral Therapy 2004; 9:L15.

Indinavir impairs endothelial function without insulin resistance

Graham McKerrow, HIV i-Base

Treatment for 4 weeks with indinavir (IDV, Crixivan) monotherapy markedly impairs endothelial function and insulin-mediated vasodilation, without significant impairment of whole-body glucose disposal, according to an American study. So it appears unlikely that insulin resistance plays a major role in the induction of endothelial dysfunction.

Dubé and colleagues hypothesised that IDV-induced endothelial dysfunction occurred because of IDV-induced insulin resistance. Their study assessed insulin sensitivity, endothelial function, and insulin-mediated vasodilation in 16 lean, healthy, male subjects before and after 4 weeks of IDV 800mg TID.

Subjects were 37 \pm 3 years old, with BMI of 25 \pm 1 kg/m², body fat of 19.6 \pm 1.9%, total cholesterol: 171 \pm 8 mg/dL; LDL-cholesterol: 98 \pm 7 mg/dL; HDL-cholesterol: 50 \pm 4 mg/dL; triglycerides: 140 \pm 39 mg/dL, and resting leg blood flow (LBF) of 0.207 \pm 0.015 L/min. There was no significant change in any of these parameters after IDV. Plasma adiponectin levels increased after IDV (16.4 \pm 2.2 ug/ml pre-IDV, 19.1 \pm 2.3 ug/ml post-IDV, p <0.05). Normal, robust endothelium-dependent and insulin-mediated vasodilatory responses were present at baseline. After IDV, there was a marked blunting of endothelium-dependent vasodilation (258 \pm 43% pre-IDV vs 60 \pm 13% post, p <0.05) and insulin-mediated vasodilation (70 \pm 10% pre-IDV vs 16 \pm 6% post, p <0.05). In spite of these dramatic effects on vascular function, there was no significant change in the steady-state whole body glucose-disposal rate with IDV (8.0 \pm 0.6 mg/kg/min pre-IDV vs 7.5 \pm 0.6 post, p =NS).

Ref: Dubé MP, Shankar SS, Considine RV et al. Marked impairment of endothelial function without insulin resistance in healthy men treated with the HIV-1 protease inhibitor indinavir. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 95. Antiviral Therapy 2004; 9:L55.

Treatment interruptions improve lipids within four weeks: IL-2 has no metabolic effect

Graham McKerrow, HIV i-Base

An American study was designed to evaluate the effects of IL-2 and treatment interruptions (TI) on lipid and glucose metabolism.

The 47 subjects were randomised to receive or not three 5-day cycles of IL-2, 4.5 million units sc BID every 8 weeks (n =23 and 24 respectively) for 18 weeks. Then, they discontinued ARV treatment until CD4 count dropped below 350 cells/mm³.

Three cycles of IL-2 did not affect lipid or glucose metabolism. After 48 weeks of TI there were significant decreases of triglycerides (from 172 mg/dl, -20%, p < .001), total cholesterol (from 213 mg/dl, -15%, p < .001), HDL cholesterol (from 41 mg/dl, -16%, p < .001) and LDL cholesterol (126 mg/dl, -12%, p =0.008). There were no significant changes in glucose or insulin levels or HOMA-IR (reciprocal index of homeostasis model assessment). Lipid changes occurred relatively early after interruption (within the first 4 weeks).

The researchers concluded that 3 cycles of IL-2 did not have significant metabolic effects on patients receiving stable ARV therapy. However, structured TI is associated with immediate and sustained decreases in cholesterol levels (both LDL and HDL) and triglycerides (TG). The effects on glucose and insulin metabolism were limited in this cohort.

Tebas and colleagues write: "A strategy of intermittent therapy can decrease the cardiovascular risk associated with ARV therapy and provide insight into which of the metabolic abnormalities observed in treated patients are HIV or ARV related."

Ref: Tebas P, Henry K, Cherng D et al. The metabolic effects of intermittent antiretroviral therapy with and without IL-2 (ACTG A5102). 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 20. Antiviral Therapy 2004; 9:L13.

Improvement of lipids following switch to tenofovir

Graham McKerrow, HIV i-Base

Switching patients with virologically controlled HIV infection to a simplified maintenance ARV regimen results in an improved lipid profile, according to the preliminary findings of a French randomised, multicentre trial of 143 patients.

Despite low lipid levels at baseline, switching to a tenofovir (Viread) based combination can mildly decrease total and LDL-cholesterol and significantly reduce triglycerides, according to Mercié and colleagues. They assessed the benefits of switching patients who had been on NNRTI- or PI-based HAART for >6 months and had viral load (VL) <50 copies/mL to either efavirenz+tenofovir or efavirenz+tenofovir+3TC.

Mean age was 42 \pm 10 years, 72% men and 28% women. Mean HAART duration at baseline was 3.7 \pm 1.9 years.

Median total and LDL cholesterol reduced from 5.3 mmol/l and 3.4 mmol/l by -0.4 and -0.3 respectively, both NS (p ~0.20); HDL did not change. Median triglycerides reduced from 1.4 mmol/l at baseline by -0.4 (p <0.004).

There were four serious adverse events (suicide attempt, pneumonia, dizziness and hepatic cytolysis), with two discontinuations.

Only one patient had VL>50 copies/ml (69 copies/ml at week 48). CD4 count increased by +23 (median CD4+ of 475/mm³ at baseline).

C O M M E N T

Although these results have generated interest related to the dual therapy maintenance arm it is unclear why this 48-week study merited an interim analysis and presentation at 36 weeks. The study continues and final results including lipodystrophy (evaluated by DEXA and CT) will be reported in 2005.

Ref: Mercié P, Trylesinski A, Cabié A et al. Improvement in lipid profile in HIV-infected virologically controlled patients switched to a simple QD regimen: Preliminary results of the COOL trial evaluating EFV/TDF vs EFV/TDF/3TC. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 82. *Antiviral Therapy* 2004; 9:L48.

HCV coinfection linked to discontinuing ART due to toxicity

Graham McKerrow, HIV i-Base

A European study of 1052 patients starting ART since 1999 found that those with HIV/HCV coinfection were more likely to discontinue all or part of their ART regimens due to toxicity and patient/physician choice than were HIV-positive patients without HCV. Moorcroft and colleagues in the EuroSIDA study group conclude that managing adverse events must remain a key intervention in maintaining HAART.

The study found that a year after starting ART, 65% of patients were still on their original regimen, 28% had changed and 7% had stopped treatment. The most common reason for discontinuation was toxicities (31%).

The incidence of discontinuation decreased over time by 18% per year (95% CI 11–24%, $p < 0.0001$). The main decline was among patients who discontinued due to toxicities and patient/physician choice. Patients with HCV had a higher incidence of discontinuation due to toxicities and patient/physician choice during the first 6 months of ART (incidence rate ratio (IRR) 2.14, 95% CI 1.05–5.92, $p = 0.035$) or after 6 months on therapy (IRR 2.09; 95% CI 1.02–4.28, $p = 0.044$) compared to patients without HCV.

Ref: Moorcroft A, Phillips AN, Soriano V et al. Why do patients with HIV stop antiretrovirals used as part of an initial highly active antiretroviral regimen? 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 74. *Antiviral Therapy* 2004; 9:L44.

Restorative treatments for HIV-associated lipoatrophy

Simon Collins, HIV i-Base

Although several posters focused on practical and corrective treatments for lipoatrophy, only a few studies provided new information.

The benefit and efficacy of New-fill (Poly-L-Lactic Acid, PLA, Sculptra) has already been covered extensively in HTB in reports from previous years meetings. None of the studies at this year's Workshop provided longer-term efficacy data or additional safety concerns to those already reported from those earlier studies.

Given that New-fill has been available for some years in Europe, and received FDA marketing approval in August this year, the most pressing issue largely remains access and reimbursement. Psychological well-being and improved quality of life have consistently improved in all studies.

In the UK, New-fill is increasingly available in some clinics, though there is a back-log for screening and treatment in the London-wide access funded by the pan-London consortium.

New aspects addressed at the meeting, included data on alternative treatments to New-Fill, and treatment of non-facial lipoatrophy - although there were only extremely limited data on each of these.

Polyalkylimide (Bio-Alcamid, Polymekon)

The action of New-Fill is to generate natural collagen growth to fill the gap left by the lost fat, with the active ingredient being quickly absorbed, and the resulting replacement collagen lasting upwards of two years.

Bio-Alcamid is an injectable biopolymer (pH 6.8-7.2) that is used as a filler, that is expected to produce permanent results, and this may have benefits for some patients. The supporting information says that once injected it becomes coated by a 'thin collagen capsule' that transforms it into an endogenous prosthesis. It is used in Europe mainly in private clinics for HIV-related lipoatrophy (including in the UK) and is a CE0123-marked product (ie passed certain safety standards), but does not have FDA approval. [1]

Results from private clinics using Bio-Alcamid for HIV-related lipoatrophy have been reported at previous lipodystrophy Workshops, but these studies have so far not been as closely monitored as the New-Fill studies. In addition to a longer effect, other interesting claims for Bio-Alcamid is that it can be used in higher volume applications (0.5-20cc), is suitable for non-facial lipoatrophy, and that it can be removed in case of 'over-filling'.

At the Workshop, Dr. Luis Casavantes presented a poster on 100 patients treated with Bio-Alcamid at a private clinic in Tijuana, Mexico [2].

Photographs are often the clearest way to judge how effective and natural the results are after treatment. The examples used in the poster at this meeting, though not reproducible in HTB, showed ten before and after shots of eight men and two women who started with severe facial lipoatrophy and achieved impressive and very natural final results after 2-3 treatments.

Treatment was reported as well tolerated and the facial deficits were "fully and permanently restored" after two to four sessions in 100% of patients. A sonogram after 4 months in one patient showed positioning of a gluteal implant and a biopsy sample after 8 months in another was used to show minor acute inflammation but no signs of chronic inflammation or granulomas. Recuperation time was reported as taking 0-3 days in all patients.

Finally, a set of photographs was included of buttock treatment, implanted in four sites in each buttock (total 425cc Bio-Alcamid), that showed substantial improvements in a 53 year old male patient.

The removable procedure for Bio-Alcamid, shown in the poster, is by puncturing the skin with needle and squeezing out unwanted filler. This has not been verified in clinical studies, and anecdotally, non-surgical removal may not always be so straight-forward.

Other approaches

Other approaches reported at the meeting included:

- Polymethylmethacrylate (PMMA, Artecoll), a compound that is neither EMEA nor FDA approved but which has been used in a clinic in Rio de Janeiro. [3] The poster presented results from 10 men and 12 women with lipoatrophy of the buttocks, legs, arms and pubis. Objective measurements (ultrasound, calipers etc) were not presented and photographic examples looked less successful than Bio-Alcamid, with most 'before' photographs showing far milder lipoatrophy.

Investigator claims and patient self-reports, included good efficacy with light to moderate pain lasting for two to three days, but until safety data are available for this compound and studies conducted in a more rigorous way, the inclusion in this HTB report is intended mainly to indicate the degree to which many compounds are already being used off-label and unregulated.

- Autologous Fat Transfer surgery (AFT) – where subcutaneous fat is collected usually from the abdominal area and transferred to the hollows in the face. This is a standard corrective surgical procedure that is generally more traumatic with greater recovery time. The limitations, apart from higher costs, include low availability of fat to harvest from many people who have facial lipoatrophy. It would be interesting to know whether the transported fat allows permanent generation of new and appropriate fat cells. One important caution, also reported at last year's meeting, is to not use fat associated with fat accumulation (ie brown fat taken from dorso-cervical pads. In four patients the transplanted fat has grown back at the same time as the shoulder fat returned, creating swollen cheeks that have not been re-correctable with liposuction. [4, 5]
- Polyacrylamide (PCA, brand names include Aquamid, Argiform, DermaLive) – which appears to have several disadvantages compared to polyalkylamide discussed above (ie has lower elasticity and cohesiveness, requires buffer to counter acidity, is less heat stable and less flexibility for removal)

The Italian researchers that have reported autologous fat transfer studies at this and previous Workshops, also provided data from a prospective, partially randomised study comparing New-Fill, AFT and polyacrylamide (patients who had insufficient fat to harvest were not included in the AFT randomization) in 59 patients at 24 weeks. [6]

Ultrasound (increase of 3-3.5mm in buccal thickness at 24 weeks) and photography provided objective measurement that were comparable in the three groups. Patient satisfaction showed no significant differences. 24-week is too early to assess the durability of each treatment and this will clearly be an important issue that could show benefits of specific treatments.

variables among the three study arms. However, they were careful to note that longer follow-up is necessary to determine the most suitable treatment in terms of durability.

C O M M E N T

There is a clear interest to evaluate Bio-Alcamid and other treatment in clinical trials, where results from all patients together with longer term follow-up can be considered, perhaps in comparison with other lipoatrophy treatments.

Although New-fill has generated successful results with severe lipoatrophy, this can take upwards of 7-8 sessions for some patients. A procedure that required fewer treatments and had greater permanence could be more tolerable and satisfactory in this patient group, who are also less likely to benefit from natural reversal of lipoatrophy, when the etiology is eventually understood. Cost clearly becomes an

important consideration, as does the pricing for each compound, when this number of treatments are required in severe cases.

Safety data from larger volume application, particularly non-facial use should also be collected prospectively.

The comparative benefits of different approaches is something that concerns patient, researchers and clinicians, with duration to 2 years being probably the minimum useful time point durability.

A meeting on the regulatory aspect of new treatments for lipodystrophy was organised by the Forum for Collaborative Research immediately prior to the meeting, and a report from this meeting was given at both at the Lipodystrophy Workshop and ICAAC conference, and included the aspect of durability as one of its recommendations.

The report from the Forum meeting is available from the website: <http://www.hivforum.org>

References

1. See information from the Bio-Alcamid website. <http://www.bioalcamid.com/news.htm>
2. Casavantes JC and Gottlieb M. Bio-Alcamid, a high-volume injectable prosthesis for facial reconstitution in HIV-related lipodystrophy: report on 100 patients. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 60. Antiviral Therapy 2004; 9:L37.
3. Serra MS and Oyafuso LK. Soft tissue augmentation with polymethylmethacrylate (PMMA) for correction of lipodystrophy related body fat atrophy. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 49. Antiviral Therapy 2004; 9:L31.
4. Guaraldi G, Orlando G, De Fazio D, et al. Autologous fat transfer for the treatment of HIV-related face lipodystrophy: a long follow-up experience. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 87. Antiviral Therapy 2004; 9:L50.
5. Guaraldi G, Orlando G, De Fazio D, et al. Long-term follow-up of graft hypertrophy after autologous fat transfer for HIV-related face lipodystrophy (hamster syndrome 1 year later). 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 90. Antiviral Therapy 2004; 9:L52.
6. Guaraldi G, Orlando G, De Fazio D, et al. Prospective, partially randomized, 24-week study to compare the efficacy and durability of different surgical techniques and interventions for the treatment of HIV-related facial lipodystrophy. 6th Lipodystrophy Workshop (6th IWADRLH), Washington. Abstract 12. Antiviral Therapy 2004; 9:L9.

CONFERENCE REPORTS

44th Annual ICAAC 30 October – 2 November, 2004, Washington.

Simon Collins, HIV I-Base

Over the last few years the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) has had a reduced focus on HIV. This year's meeting however included several important oral presentations and posters of interest.

ICAAC still maintains a restricted approach to making the research presented at these annual meetings available publicly. Although the website currently includes searchable abstracts, webcasts of many oral sessions, and the slides from some of these presentations, this is only for one month after the conference. The meeting is then available on CD Rom for around \$300, but the public access stops. Notably, this conference still refuses to allow these abstracts to join the online resource developed by AEGIS.org.

Unfortunately, abstracts that are currently available on the conference website are linked to pop-up windows, and this means that we are not able to provide direct weblinks for referenced articles in the way HTB does for routine conference coverage.

Abstracts can nevertheless be browsed and searched from the following unwieldy web address:

<http://www.abstractsonline.com/viewer/browseOptions.asp?MKey={CE64B3B3-6CEB-40D2-ACDF-14A2BE602044}&AKey={32093528-52DC-4EBE-9D80-29DAD84C92CE}>

Conference coverage also provided by the following sites:

<http://www.thebody.com/confs/icaac2004/complete.shtml>

<http://www.natap.org>

Abstract summaries organised by subject are provided by:

<http://www.hivandhepatitis.com/2004icr/icaac2004/main.html>

<http://clinicaloptions.com/hiv/conf/icaac2004/>

Unless otherwise stated, all references are to the Abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 30 October – 2 November 2004, Washington, DC.

Tipranavir in treatment experienced patients: results from RESIST-1

Simon Collins, HIV i-Base

One of the most anticipated studies at ICAAC was the 24-week results from tipranavir RESIST-1 study: Randomised Evaluation of Strategic Intervention in Multi-Drug Resistant Patients with Tipranavir, presented by Charles Hicks from Duke University, North Carolina. RESIST-2, the European sister study in slightly more experienced and resistant patients will be presented a month later at Glasgow.

Entry criteria for this study include triple class experience including exposure to at least two PI-containing regimens. This required genotypic resistance with at least one primary resistant mutation from 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M but not more than two Universal Protease Associated Mutations (UPAMs): at positions 33, 82, 84, 90. The primary endpoint for treatment response was 1 log or greater reduction in viral load at 24 weeks, with additional secondary analysis related to changes in viral load and CD4.

The study design randomised just over 600 patients to optimised background regimen (OBR) plus either tipranavir/r or comparator protease inhibitor (CPI). CPI (% patients) was LPV/r (61%), SQV (20%), APV (14%) and IDV (4%) with median baseline phenotypic sensitivity ranging from 76-fold (LPV/r) to 12-fold (APV). T-20 was used by 36% patients in the overall study.

Patients were generally advanced with median CD4 and viral load of 123 cells/mm³ (ranges, 1-860 and 1-1184) and viral load of 4.8 logs (range 2.3-6.1 and 2.0-6.3 logs) in the TPV and CPI arms respectively; with a median of 15 PI mutations in each arm. Gender and race balance was approximately 10% women/90% men ; 20% Black/ 80% White.

At week 4, by ITT analysis, approximately 60% and 40% of the patients in the TPV and CPI arms showed viral load reductions > 1 log, which by week 24 had fallen to 41% and 23% respectively (p=0.0001 from baseline to week 24). This highlights the difficulty of maintain responses in resistant patients without additional sensitive drugs. Median viral load change from baseline at week 24 was -0.88 and -0.28 log in the TPV and CPI arms respectively (p<0.001).

By ITT analysis, 34.7% vs 16.5% were <400 copies/mL and 25.1% vs 10.0% were <50 copies/mL in the TPV and CPI groups (both, p<0.001).

Virological failure drove the larger number of discontinuations in the CPI arm, when patients were then allowed roll-over access to tipranavir. 263/313 patient in the TPV arm remained on treatment at week 24, with 13 discontinuations due to virological failure and 25 due to side effects. 109/317 patients on the CPI arm discontinued due to failure and nine patients discontinued due to side effects.

Use of T-20 increased the chance of getting <400 or <50 copies/mL by up to 30% in either arm, with the additional increased benefit seen in patients using T-20 with tipranavir. 36% people in the study used T-20.

% of pts with undetectable viral load at 24-weeks:

	TPV/r	TPV/r+T-20	CPI	CPI inc.T-20
<400	34%	47%	16%	22%
<50	25%	33%	10%	14%

Median CD4 count increased by +36 cells/mm³ in the TPV and +6 cells/mm³ in the CPI arms at week 24 (P<0.001).

Side effects were evenly distributed between the two arms. Levels of grade 3/4 ALT (6.9 vs 1.3%), AST (4.6 vs 1.6%), triglyceride (22 vs 12%) and cholesterol (4 vs 0%) were all significantly higher in the TPV/r arms, but were mostly asymptomatic and resulted in few discontinuations.

The study concluded that tipranavir showed similar safety profile to other ritonavir-boosted PIs, with greater efficacy compared to CPI arms out to 24 weeks. The use of additional active drugs such as T-20 improved this virological response.

Ref: Hicks C et al. RESIST-1: a phase 3, randomised, controlled, open-labelled, multicenter trial comparing tipranavir/ritonavir (TPV/r) to and optimised comparator protease inhibitor (CPI/r) regimen in antiretroviral (ARV) experienced patients: 24-week data.

C O M M E N T

Results from the RESIST-2 study (in European patients) were presented at the Glasgow conference as this issue of HTB went to press, and were similar to this study. Only 11% patients used T-20 in either arm in RESIST-2.

Tipranavir is currently available in the UK through an expanded access programme. Doctors wishing to enroll patients in this programme or who have further questions should contact Sarah Jones at Boehringer Ingelheim 01344 741282 or 01344 742539.

Reverset: first data in patients with nucleoside resistance

Simon Collins, HIV i-Base

d-d4FC (Reverset) is a cytidine analogue reverse transcriptase inhibitor that has shown in vitro activity to HIV resistant to 3TC, AZT, tenofovir and other RTIs. First in vivo data, from exposure to 10 days monotherapy in treatment naïve patients, achieved mean viral load reductions of -1.77 log after 10 days exposure to 200mg dose, and was presented at the 2004 retrovirus conference. [1]

Results were presented at ICAAC on 10 treatment-experienced patients currently on failing treatment (viral load >1000 copies/mL; CD4 >50 cells/mm³) randomised 4:1 to add 200mg RTV or placebo for 10 days to their existing regimen. [2]

Previous treatment history in this group included 3, 1, 1 and 3 patients having failed 1, 2, 3 and 4 or more previous treatment regimens respectively. At baseline, 5/8 patients had 184V and 4/4 had 3 or more TAMS (41, 67, 70, 210, 215, 219). Two patients showed no RT mutations and none of the patients has the K65R mutation associated with tenofovir.

3TC was maintained by 6/8 patients in their regimen; 3/8 maintained AZT; 5/8 maintained tenofovir and one patient continued using each of ddl and abacavir.

Mean viral load reduction at day 10 was -0.80 ± 0.68 log from baseline of 4.11 ± 0.98 copies/mL with 7/8 patients showing ≥ 0.5 log reduction. This response was also seen in patients who maintained 3TC and who had M184V mutation at baseline. The mean reduction in people with 3-4 TAMS was around -0.4 log.

Incidence of headache, cold, and neutropenia was similar in Reverset and placebo arms. Increases in triglycerides, lipase and sore throat were reported in 4, 3 and 3 patients respectively who were receiving RVT (compared to no reports in placebo). A PK sub-study showed drug levels to be similar to previous treatment naïve data and plasma levels exceeded IC50 for most NRTI-resistant mutations.

COMMENT

This indication of short-term activity in treatment-experienced patients is extremely hopeful, especially given the previously curtailed RTI-pipeline, with hopeful compounds unable to overcome toxicity problems. Tolerability will also be critical to this compound.

A larger (n=180) international Phase 2b dose-finding study of Reverset is already underway.

References:

1. Tolerance and potent anti-HIV activity of Reverset following 10 days of monotherapy in treatment naïve individuals. 11th CROI, San Francisco. Abstract 137.
2. Murphy RL et al. Tolerance and anti-HIV-1 activity of Reverset following 10 days as add-on therapy to current regimens in treatment experienced HIV-infected individuals. 41st ICAAC, Washington, 2004. Abstract H-1130.

Poor response with tenofovir and ddl backbone causes early study termination

Simon Collins, HIV i-Base

A study from the Chelsea and Westminster Hospital, London, presented data indicating a poorer response when tenofovir and ddl are used together as dual nucleoside backbone.

This open-label study planned to randomise 100 treatment naïve patients to either tenofovir/ddl/efavirenz or 3TC/ddl/efavirenz but the study closed early following an unplanned interim safety analysis of the first 73 patients. The reduced dose of ddl (250/200mg $>/<60$ kg) was used throughout this study.

Although patients in each group were evenly matched by baseline CD4 and viral load, the tenofovir arm produced reduced virological responses and significantly greater earlier failure, defined as VL >0.5 log above nadir or development of new resistant mutations.

	3TC	tenofovir
Mean baseline CD4	160	173
Mean baseline VL	5 log	5 log
Results wk 4		
n	33	33
mean (SD) change VL	-2.7 (0.57)	-2.8 (0.87)
%pt >1 log	32/33 (97%)	29/38 (88%)

Results wk 12

n	23	29
mean (SD) change VL	-1.88 (0.4)	-2.04 (0.9)
n (%) pts VL rebound or new RT mutations	0/23 (0%)	4/29 (14%)

All patients failing the tenofovir arm had baseline VL >100,000 copies/mL and CD4 counts < 200 cells/mm³.

MEMS caps adherence monitoring confirmed 100% adherence in all the failing patients.

The poor performance of tenofovir/ddl, even when supported by efavirenz was clearly unexpected by these researchers. Although the combination failed in more advanced patients, together with other reports (see below) this should caution reliance on this dual nucleoside pairing in any three-drug combination,

No theoretical mechanism was suggested for the results of this study.

Re: Moyle G et al. Early virological failure in persons with viral loads >100,000 cps/ml and CD4 counts <200cells/mm³ receiving ddl/tenofovir/efavirenz as initial therapy: results from a randomised comparative trial. 41st ICAAC, Washington, 2004. Abstract H-566.

Paradoxical CD4 response with tenofovir and ddl backbone

Simon Collins, HIV i-Base

Several studies have previously reported a caution for toxicity or blunted immune responses in some patients using tenofovir and ddl together. A database analysis from Madrid, provided an indication for the likely mechanism, even though the results from the study were still too early to give an indication of risk in patients using tenofovir with dose-adjusted ddl

Barrios and colleagues from Hospital Carlos III, Madrid, presented an analysis of PI-sparing combinations including 100 patients who were using both tenofovir and ddl in their combination, compared to a similar number of patients using either drug separately or using neither drug. [1]

Some of the smaller studies that have already suggested a caution to using tenofovir and ddl together as a nucleoside combination were highlighted as background at the beginning of the presentation. [2, 3, 4]

As well as analysis by nucleoside, the study looked separately at response in treatment naïve patients and experienced patients switching to a simplified combination.

In treatment naïve patients CD4 response showed increases of +148 cells/mm³ over the first six months followed by a trend to drop back just below baseline of around 300 cells/mm³ by month 12. While this showed statistical significance (p<0.05 compared to baseline) patient numbers at 0, 6 and 12 months were 18, 17 and 10 respectively.

Patients switching to NNRTI simplification regimens with tenofovir/ddl showed an increase of +29 cells/mm³ which returned to baseline of around 570 cells/mm³ by month 12, with patient numbers being 263, 187 and 175 at the same time points. Of this group, 78 (45%), 54 (31%) and 25 (14%) patients lost >50, >100 and >200 cells/mm³ respectively. Patients were virologically suppressed prior to, and after the simplification switch.

Many of these patients did not dose reduce ddl (from 400/250mg to 250/200mg, depending on weight) after the interaction with tenofovir discovered. When the analysis looked at patient using reduced vs high dose ddl, the concern for naïve patients and the significance in decline in the switch patients was no longer significant.

Time on high dose ddl and weight were both statistically significant variables associated with CD4 decline in the multivariate analysis (p= 0.002 and p<0.001 respectively). Levels of plasma ddl at Cmin were neither predictive, nor significantly different between reduced and high dose ddl arms, but perhaps AUC and Cmax would have been more appropriate parameters to investigate.

As would be expected now, ddl/tenofovir with a third nucleoside performed particularly poorly, but again this is clearly no longer recommended practice.

Although reduced-dose ddl is now standard practice, and these triple nucleoside regimens are not used, the caution for paradoxical CD4 responses in virologically controlled patients using ddl/tenofovir were still reported in this study in significant number to warrant caution.

The hypothesis to explain these results was suggest that as both tenofovir and ddl are adenosine analogs, a synergistic effect of their metabolites could enhance mitochondrial damage, compromising energy output in CD4 cells, or by creating a cytostatic imbalance in the physiologic adenosine pool, impairing the turnover of CD4 cells.

COMMENT

The largest CD4 declines or most concern certainly appear driven by not using the recommended dose reduction of ddl to

250mg (200mg if weight <60kgs). This was well publicised and followed in the UK, when the PK interaction was first realised (see HTB Vol3no9, Nov2002 and Vol4No1, Jan2003).

This doesn't explain lower level CD4 declines seen in this study and reported elsewhere. Although the initial PK interaction of these QD drugs that lifts the requirement to take ddl on an empty stomach increase convenience, the choice of an alternative partner nucleoside for either drug would appear appropriate in patients who fail to achieve satisfactory CD4 responses.

References:

1. Paradoxical CD4+ T-cell decline in patients with complete virus suppression under tenofovir plus didanosine combination. 41st ICAAC, Washington, 2004. Abstract H-1132.
2. Martinez et al. Pancreatitis Lancet 2004; 364:65.
3. Garcia-Benayas et al – hyperglycemia; in press.
4. Negredo et al. CD4 declines. AIDS 2004; 18:459.

Tenofovir/FTC backbone outperforms AZT/3TC (Combivir) with efavirenz in treatment naïve patients; reduced toxicity drives ITT viral efficacy

Simon Collins, HIV I-Base

Results from a planned 24-week interim analysis of the Gilead 934 study were presented by Brian Gazzard from Chelsea and Westminster Hospital, London as a late-breaker. The bottom-line results had been press-released by Gilead several weeks before this meeting.

The study randomised 517 treatment naïve patients (from UK, Spain and the US) in a 1:1 ratio to background nucleosides of either tenofovir plus FTC taken once daily as separate pills or Combivir (AZT/3TC) taken twice-daily (Q12H). Efavirenz was the third drug for both arms. Primary endpoint is time to loss of virologic response at week 48, with follow up to 96 week. The study was designed with 85% power to show non-inferiority (13% difference). The intent-to-treat (ITT) analysis counted missing data, and patients switching treatment as failure.

This study had no entry restrictions based on CD4 count. Just over 40% of patients in each arm had baseline CD4 <200 cells/mm³, with 15% of TDF/FTC arm and 11% CBV arm having CD4 count <50 cells/mm³.

At 24 weeks, the time to loss of virologic response was significantly greater in the TDF/FTC arm using <400 and <50 copies/mL cut-off, and results are shown below.

Time to loss of virologic response at 24 weeks:

	TDF/FTC	CBV (AZT/3TC)	95% CI
<400 copies/mL	87%	78%	+1.9%, +14.9%
<50 copies/mL	73%	65%	+0.5%, +16.2%

Differences in the ITT analysis were largely driven by higher rates of discontinuations due to toxicity in the Combivir arm.

11% patients discontinued TDF/FTC. 3% of which was for toxicity, compared to 21% discontinuation in the Combivir arm, with 9% relating to toxicity. Renal safety was similar in each arm. A breakdown of grade 3/4 side effects is detailed below.

Summary of discontinuations due to adverse events:

	TDF/FTC	CBV (AZT/3TC)
n	255	254
Permanent d/c	11%	21%
Primary reason: a/e (n)	3% (24)	9% (38)
% d/c any side effect	3% (8)	9% (22)
anemia (n)	0	5% (14)
neutropenia (n)	0	1% (2)
fatigue	0	1% (3)
depression	<1% (1)	1% (2)

CD4 responses were not statistically different, Mean CD4 increases were slightly higher in the TDF/FTC arm (+129 vs +111 cells/mm³), but baseline CD4 counts were also slightly lower.

The resistance profile of patients viral load >400 at week 24) were analysed but there were only 10 and 8 patients with virological failure in the TDF/FTC and CBV arms respectively. Although there were small percentage differences approximately half failed with wild-type and half with either NNRTI +/-3TC resistance. Neither K65R nor TAMS were detected. Although eleven patients in each arm were found to have NNRTI resistance at baseline (reinforcing the importance of resistance testing naïve patients prior to treatment) they were excluded from this analysis.

C O M M E N T

The difference between these two regimens was largely driven by discontinuations related to side effects in the Combivir arm. Although this was an interim 24-week analysis, results from tenofovir registrational studies do not suggest a level of later toxicity-related discontinuations, that is likely to reverse these results. The final analysis from this study is still likely to be needed before widespread prescription change occurs. Intolerability to AZT, for example, would be overcome with a switch to tenofovir.

However, the association of AZT-related mitochondrial toxicity on adipocyte differentiation and subsequent risk of lipodystrophy highlighted in the Lipodystrophy Workshop report above, is a clinical advantage for not including AZT in initial regimens.

In the UK, this is likely to become further complicated by cost of treatment, where patients may continue to use AZT on the basis of lower cost, despite lower efficacy and tolerability. The pressure for this will increase when AZT comes off-patent in 2006.

For a further discussion of tenofovir plus ddI see:

http://www.natap.org/2004/ICAAC/icaac_08.htm

Ref: Gazzard B et al. The combinations of tenofovir DF (TDF), emtricitabine (FTC) and efavirenz (EFV) has significantly greater response vs fixed dose zidovudine/lamivudine (CBV) and EFV in antiretroviral naïve patients: A 24 week preliminary analysis. 41st ICAAC, Washington, 2004. Late breaker abstract H-1137a.

Limited stability of lopinavir/r (Kaletra) above 25 C

Simon Collins, HIV i-Base

Although Kaletra is generally stored in a refrigerator it retains potency for 2 months at a temperature of 25 C. This limits use for people who do not have access to refrigeration, particularly in hot countries.

Capparelli from University of California, San Diego and colleagues performed a small-scale proof of concept study in non-recommended higher temperatures, to evaluate use where refrigeration is not available, particularly in reference to Sub-Saharan Africa.

Kaletra capsules were incubated, individually and in a group of six, in high density polythene bottles, in high humidity, at 35 C and 45 C and contents tested for capsule stability and potency at day 1, 2 and 7 and week 2, 4 and 8.

Physical structure was maintained at 35 for 4 weeks but capsules become distorted by week 8, increasing in weight by 3% and 11% respectively. At 45 degrees the capsules melted together within a week. Potency compared to storage at 4 was >95% at week 4 at both 35 C and 45 C but fell below 85% by week 8.

The study concluded, that dispensing monthly supplies of LPV/r in climates up to 35 C where refrigeration is not available, would maintain potency, and use of this drug in wider settings than is currently available. It did not claim regulatory-standard assessment though, and highlighted the need for formulations that remain more stable at higher temperatures.

C O M M E N T

This was an eye opener and a great poster, and clearly there are storage problems in tropical countries. It would be interesting if future studies also addressed potency.

Equally interesting was the fact that the capsules gained weight – from absorbing water, in humidity. In view of this, there is a need to do bioavailability studies even when the capsules look okay, since alcohol in the caps may be lost and water gained, and this may affect absorption.

Ref: Capparelli E et al. Stability of lopinavir/r at elevated temperatures: relevance to HIV therapy in Sub-Saharan Africa. 41st ICAAC, Washington, 2004. Abstract H-868.

PK and drug interaction studies:

Atorvastatin requires dose reduction with tipranavir/r

Simon Collins, HIV i-Base

Richard Hoetelmans and colleagues from Tibotec reported an interaction between the investigational protease inhibitor TMC-114 dosed at 300mg BID with 100mg ritonavir BID, and boosted and atorvastatin (AVS) in HIV-negative individuals.

Atorvastatin levels are increased by TPV/r and a 10mg dose achieved around –15% exposure compared to 40mg AVS without TMC-114/r.

Similar reaction have been reported with other PIs and the recommendation for the study is to initiate AVS at 10mg and adjust based on clinical response.

Ref: Hoetelmans R et al. The effect of TMC-114, a potent next-generation HIV protease inhibitor, with low-dose ritonavir on atorvastatin pharmacokinetics. 41st ICAAC, Washington, 2004. Abstract H-865.

Once-daily T-20 is less effective than twice daily: lower potency is related to C trough

Simon Collins, HIV i-Base

In a cross-over study, for the first two weeks of treatment, 37 patients were randomised to start T-20 plus optimised background regimen, using T-20 either once- or twice-daily for the first 7 days and switching to the alternative dose for days 8-14. Once-daily dose involved taking two 90mg doses in the morning and twice-daily doses involved each 90mg dose taken 12 hours apart. PK was measured on days 6, 7, 13 and 14. More intensive PK at steady state was measured at 0, 1, 2, 4, 6, 8, 10, 12, 24 on days 7 and 14.

Total exposure (AUC) to T-20 and rate of clearance was similar in both schedules. While C max was approximately double when administered once-daily, C trough was also 57% lower than the BID level, and 40% of patients on the once-daily schedule had C trough levels below the target of 1.0ug/mL.

As resistance to T-20 is related to C trough, and patients using this drug are already dependent on achieving maximum response, this is a significant concern. Linear regression analysis also suggested that viral response was related to C trough and not AUC or C max. Tolerability was similar in once- and twice-daily arms.

Ref: Thompson M et al. Pharmacokinetic (PK), pharmacodynamic, and safety assessment of QD vs. BID dosing with enfuvirtide in HIV-infected subjects. 41st ICAAC, Washington, 2004. Abstract H-866.

Further genetic link to efavirenz absorption

Simon Collins, HIV i-Base

Further relevance to genetics and efavirenz (EFV) absorption were presented in a late breaker poster by Novoa and colleagues from Hospital Carlos III, Madrid.

Over 100 consecutive Caucasian adherent patients on EFV-containing combinations for over one month were studied with reference to codon 516 of the CYP2B6 isoenzyme. Median age was 40 years and 36% were coinfecting with HCV. 80% patients were men and 20% were women.

Genotyping showed 52% were wild-type GG (39 men, 13 women); 43% carried the heterozygote GT mutation associated with African patients, slower drug clearance and higher drug concentrations (36 men, 7 women); and 5% carried homogygote TT mutations (5 men). Mid-dose drug levels were measured by HPLC at 12 weeks,

The study identified a wide range of interpatient variability in efavirenz levels (0.33-6.88ug/mL, target range = 1.0-4.0 ug/mL). Median plasma levels were higher in patients with 516 polymorphism and highest in patients with homogygote TT variant. All patients with sub-therapeutic levels had the wild-type GG. 19% and 40% of patients with GT and TT variants respectively had drug levels > 4ug/mL associated with higher toxicity.

	G516G (wild-type)	G516T	T516T
Median (IQR) EFV levels (ug/mL)	1.71 (1.09-2.53)	2.6 (1.73-3.50)	3.57(2.55-6.07)
% sub-optimal (<1ug/mL)	19%	2%	0%
% toxicity (>4ug/mL)	5%	19%	40%

Neither age, gender or HCV coinfection, were associated with different efavirenz levels.

This supports earlier findings presented by two different groups at the Retrovirus conference earlier this years (see HTB Vol5No3, April 2004). Those studied highlighted the risk for higher efavirenz exposure in African of African/American patients, referring to both toxicity and risk for resistance due to extended periods of monotherapy on stopping efavirenz-based combinations.

The significance prevalence of GT and TT variants in these Caucasian Spanish patients indicates a higher influence of genetic factor for tolerance or efficacy than is probably so far recognised.

Ref: Novoa SR et al. Prediction of efavirenz plasma levels by determining the G516T polymorphism at the CYP2B6 isoenzyme – clinical implications. 41st ICAAC, Washington, 2004. Abstract H-584a.

C O M M E N T

The Novoa study is difficult to interpret since one third of the patients had Hepatitis B. However there appears to be a gene-dose effect TT>GT>GG.

Since genetic variation will have different effects on different populations, it is important to replicate these studies in diverse populations.

Long-term response to FTC in children Is similar to adults

Paul E Sax, MD, thebody.com

Gilead Study FTC-203 is an ongoing, open-label study designed to evaluate the antiviral activity of FTC (emtricitabine, Emtriva) in combination with other antiretroviral drugs in pediatric patients.

Study subjects received FTC at a dose of 6 mg/kg/day up to a maximum dose of 200 mg a day; either an alcohol-free oral solution or capsules were used. If treatment naive, the patient also received stavudine (d4T, Zerit) and lopinavir/ritonavir (LPV/r, Kaletra); if treatment experienced and receiving lamivudine (3TC, Epivir), the patient was given emtricitabine in addition to his or her other antiretrovirals.

A total of 71 naive and 45 experienced patients were enrolled. The mean age was 6 years old; the median HIV RNA was 4.5 log with a CD4+ cell count of 826. Fifty-three percent of the study participants were female and 69% were black. The proportion of patients achieving viral suppression at week 96 was as follows:

	Naive pts	Experienced pts
% pts VL <400	76%	69%
% pts VL <50	65%	55%

The only mutation to emerge among treatment-naive study subjects was M184V, the signature mutation of FTC. No data on tolerability was presented.

The results of this study suggest that FTC in pediatric patients achieves comparable antiviral activity to FTC in adults. As noted in adult studies of lopinavir/ritonavir with 3TC or FTC plus a third nucleoside/nucleotide reverse transcriptase inhibitor, the most likely mutation to emerge with treatment failure is M184V.

Ref: Harris J et al. Long-term virologic response and genotypic findings in HIV-1 infected pediatric patients receiving emtricitabine (FTC) once daily (QD). 41st ICAAC, Washington, 2004. Poster H-855.

Source: thebody.com

C O M M E N T

The preliminary data for FTC in children appears to be encouraging.

This study will hopefully hasten licensing and accessibility to FTC for children, which will provide an additional option for once daily combinations.

FTC liquid formulation is currently available in the UK on a named patient basis by contacting Rachel Hutchings at the medical department at Gilead Sciences on 01223 897345.

Side effects update: hypersensitivity, heart, bones

NATAP report 6 from the 44th ICAAC

Mark Mascolini, NATAP.org

The 44th ICAAC meeting featured a half-dozen interesting reports on antiretroviral side effects, including a possible way to predict hypersensitivity reactions to abacavir, news on lipids and the heart disease predictor C-reactive protein (CRP), and a study finding a higher risk of bone loss in African-American men with HIV than in men of other races.

Predicting hypersensitivity reactions to abacavir

A few years ago Simon Mallal's group in Perth identified genetic wrinkles that predicted a high risk of hypersensitivity to abacavir (1). Now researchers from four US clinics believe they've spotted a way to predict the reaction without gene testing. Sudden, unexplained drops in CD4 and CD8 counts appeared to herald hypersensitivity in this survey of 5 people starting abacavir (2).

Berrigno Rodriguez (Case Western Reserve University) and colleagues reported that 4 of the 5 people were enrolled in an AIDS Clinical Trials Group (ACTG) study of Trizivir (AZT/3TC/abacavir) with or without efavirenz and cyclosporine, an agent given to boost CD4 cells. Two of the 5 people studied took cyclosporine and 3 took efavirenz; 4 were men. They first had symptoms of hypersensitivity 4 to 22 days after starting abacavir, and the symptoms lasted 2 to 9 days. Unexplained plunges in CD4 and CD8 cells preceded or accompanied symptoms in 4 people and followed the onset of symptoms by 6 days in the fifth person.

- Average (range) CD4-cell drop: -166 cells/uL (-110 to -322 cells/uL)
- Average (range) CD8-cell drop: -465.2 cells/uL (-298.5 to -717.5 cells/uL)
- Average (range) total lymphocyte drop: -754 cells/uL (-465 to -1520 cells/uL)
- Average (range) white blood cell drop: -350 cells/uL (-1150 to +4100 cells/uL)

These T-cell plunges did not reflect loss of virologic control, a fall in platelets, or other blood disorders. Nor did these drops correlate with the severity of hypersensitivity reaction symptoms, time since abacavir therapy began, or use of other drugs including cyclosporine, efavirenz, or trimethoprim-sulfamethoxazole. T-cell counts returned to previous levels when the people stopped taking abacavir

Whether these T-cell ebbs are a specific feature of abacavir hypersensitivity or a result of the systemic illness that characterizes these reactions remains unclear. Rodriguez and coworkers speculated that the T-cell swoons "might represent cellular redistribution [out of the peripheral circulation and] to the areas affected by the inflammatory response." The quick rebound in circulating T cells after abacavir stops, they add, dovetails with that theory.

This phenomenon must be confirmed in bigger groups of people starting abacavir. Even if further study does confirm this finding, it probably would not be a practical predictive tool in the clinic because it would require intense T-cell monitoring in the first weeks of abacavir therapy. But unexplained T-cell slumps that clinicians do happen to notice in people starting abacavir may alert them to the possibility of hypersensitivity.

Low-down on lipid-lowerers for HIV dyslipidemia

Statins and fibrates can help lower cholesterol and triglycerides in people taking antiretrovirals. But as ACTG researchers reported earlier this year, pravastatin and fenofibrate-alone or together-helped few HIV-infected people reach National Cholesterol Education Program (NCEP) lipid goals (3). A smaller retrospective study of HIV-infected men in the Veterans Administration system confirmed that antilipid drugs rarely push cholesterol and triglycerides down to NCEP targets (4).

Jasmin Bhalodia (Campbell University School of Pharmacy, North Carolina) and colleagues studied 53 men cared for at the Durham VA Medical Center. All had total cholesterol or triglyceride readings above 200 mg/dL, all were taking antiretrovirals, and all took lipid-lowering drugs for more than 2 months. Twenty-seven men had tried pravastatin, 12 simvastatin, 7 gemfibrozil, and 1 atorvastatin. Thirty-seven were taking at least one protease inhibitor (PI) and 31 were taking a nonnucleoside, usually efavirenz.

Ten of the men (19%) had guidance from a specialty lipid management clinic, and 20 got dietary advice. Their ages ranged from 28 to 69 years (median 47 years), and they had a median of three risk factors for coronary artery disease. Twenty-seven of the men (51%) had clinical atherosclerotic disease or the coronary artery disease risk equivalent. Half were white.

Total cholesterol dropped 15% after 3 months of antilipid therapy and 13% after 6 months, both significant changes ($P < 0.05$). Triglycerides, meanwhile, dwindled by 8.5% after 3 months of therapy and by 19% after 6 months ($P < 0.05$). But among men with lipid measures at 3 and 6 months, only one quarter reached NCEP goals for total cholesterol or triglycerides.

Average total cholesterol measured 275 mg/dL before treatment, 233 mg/dL after 3 months of lipid-lowering therapy, and 228 mg/dL after 6 months. Triglycerides averaged 516 mg/dL before treatment, 508 mg/dL after 3 months, and 344 mg/dL after

6 months. Protective high-density lipoprotein (HDL) cholesterol rose slightly from 37 mg/dL before treatment to 40 mg/dL at month 6, while dangerous low-density lipoprotein (LDL) cholesterol dropped from 164 mg/dL to 132 mg/dL in that time.

Fosamprenavir's impact on HDL and triglycerides

Lipid analysis of treatment-naive people enrolled in the NEAT study of fosamprenavir (1400 mg twice daily) versus nelfinavir (1250 mg twice daily) found better gains in "good" HDL cholesterol in the fosamprenavir group (5). While triglycerides climbed over 48 weeks in the nelfinavir group, they stayed the same in the fosamprenavir group.

Jeffrey Nadler (University of South Florida, Tampa) randomized 166 people to start fosamprenavir plus 3TC/abacavir and 83 to start nelfinavir with the same two nucleosides. When treatment began, only 4% in the fosamprenavir arm and 3% in the nelfinavir group had an HDL level above the National Cholesterol Education Program's "negative risk" goal of 60 mg/dL. After 48 weeks of treatment, 27% taking fosamprenavir versus 10% taking nelfinavir had climbed into the salutary over-60 mg/dL bracket. The percentage of people with 40 to 60 mg/dL of HDL rose from 27% at baseline to 49% after 48 weeks in the fosamprenavir group, and from 21% at baseline to 43% in the nelfinavir group. Overall HDL cholesterol rose 37% with fosamprenavir and 22% with nelfinavir.

The two groups started treatment with nearly identical average fasting triglycerides: 150 mg/dL in the fosamprenavir arm and 152 mg/dL in the nelfinavir arm. After 48 weeks of antiretroviral therapy, the average in the fosamprenavir group had inched up to 152 mg/dL, while the nelfinavir group's average clambered to 200 mg/dL, the threshold of the NCEP danger zone.

How well does CRP predict heart disease?

Not very well in people with HIV infection, according to results of a 180-person case-control study presented by Peter Sklar (Drexel University, Philadelphia) and colleagues from five other sites (6). Earlier work by Sklar (7) and others (8) suggested C-reactive protein (CRP) could signal impending heart disease in people with HIV infection. But those studies linked CRP to other risk factors, not to actual cases of heart disease. The new case-control study confirmed that traditional risk factors remain strong predictors of so-called cardiovascular events in people with HIV, but CRP added nothing to their predictive power.

Defining cardiovascular disease as myocardial infarction, stroke, peripheral vascular disease, or coronary artery surgery, Sklar matched 60 HIV-infected men who had cardiovascular disease with 120 HIV-infected men of the same age who did not. Although the heart disease "cases" and matched "controls" had similar average CD4 counts (427 cells/uL for cases and 429 cells/uL for controls), the cases had a significantly shorter duration of HIV infection (4.0 versus 5.5 years, $P = 0.008$) and a significantly shorter time taking antiretrovirals (1.6 versus 3.4 years, $P = 0.007$). Not surprisingly, the men with heart disease had higher rates of cardiovascular risk factors than the controls:

- Tobacco use: 72% of cases versus 43% of controls
- Hypertension: 41% of cases versus 21% of controls
- LDL cholesterol: 138 mg/dL versus 112 mg/dL in controls

Median CRP measured 2.0 mg/dL (range 0.3 to 46.5 mg/dL) in cases and 1.3 mg/dL (range 0 to 39.9 mg/dL) in controls. But CRP did not correlate with cardiovascular disease in these men, whereas tobacco use ($P < 0.001$), LDL cholesterol ($P = 0.008$), and hypertension ($P = 0.005$) did.

Breaking the groups into thirds with low (0 to 0.7 mg/dL), medium (>0.7 to 3 mg/dL) or high (>3 mg/dL) CRP, Sklar found no significant differences between numbers of cases and controls in the three clusters. However, compared with low-level CRP, medium- or high-level CRP doubled the risk of cardiovascular disease. An analysis including both cases and controls linked higher CRP with traditional risk factors:

- Older age ($P = 0.007$)
- Tobacco use ($P = 0.04$)
- Higher total cholesterol ($P = 0.008$)
- Higher LDL cholesterol ($P = 0.001$)

But CRP didn't correlate with HIV-related factors like CD4 count, duration of HIV infection, or time taking antiretrovirals.

Finally, Sklar looked at the impact of CRP on two statistical models that predicted heart disease—one model resting on LDL cholesterol alone, and one model combining LDL cholesterol, tobacco use, and hypertension. CRP didn't enhance the predictive power of either model.

Low bone density in African-American men

A survey of 272 active members of the US military, veterans, and their dependents with HIV infection found a significantly higher rate of bone loss among African Americans than among others in the cohort (9). The findings apply mainly to men, who made up 84% of the study group. Most of them, 62%, were African American, while 28% were Caucasian, and 7% Hispanic.

PI therapy appeared to protect against bone loss in these people.

Only 14% of the study group smoked, and only 12% downed more than two alcoholic drinks a day. Duration of HIV infection averaged 3447 days, and the average CD4 count stood at 539 cells/uL. Average age did not differ significantly between whites (44 years), African Americans (40 years), and Hispanics (41 years).

Everyone in the study had a DEXA scan between August 2001 and October 2002. The researchers used World Health Organization criteria to define osteopenia (*t*score between -1 and -2.5) and osteoporosis (*t*score less than -2.5). They defined bone loss as osteopenia or osteoporosis of the hip or spine.

In a bivariate analysis three factors correlated with bone loss-being African American, less time with an undetectable viral load, and lower body mass index.

Factors not linked to bone loss in this analysis were gender, age, mean duration of HIV infection or antiretroviral therapy, mean days with a CD4 count under 50 cells/uL, lowest-ever CD4 count, current CD4 count, smoking, and PI use. Possibly because classic bone loss risk factors including steroid use, wasting, smoking, drinking, thyroid disease, and hypogonadism were infrequent in this population, the study did not tie them to osteopenia or osteoporosis.

In a multivariate statistical model controlling for smoking, African Americans were 1.7 times more likely than others to have any bone loss (95% confidence interval [CI] 1.1 to 2.9). Limiting the analysis to spine density, the researchers rated bone loss 2.3 times more likely among African Americans (95% CI 1.3 to 3.8). Hip bone loss alone did not correlate with race in this analysis. But in a model controlling for smoking, hip bone loss proved 4.2 times more likely in people older than 50 (95% CI 2.0 to 8.9) and half as likely in people who had ever taken a PI (95% CI 0.2 to 0.8).

Mark Mascolini writes about HIV infection (mailmark@ptd.net).

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CONFERENCE REPORTS

55th Annual Meeting of the American Society for the Study of Liver Diseases (55th AASLD)

29 October – 2 November, 2004, Boston, MA

Community attendance to this annual hepatic meeting which this year coincided with the ICAAC meeting reported above is generally less supported, and neither abstracts nor oral presentations are provided online.

Focussing on HBV, the meeting included comparative studies with existing treatments: mainly adefovir, lamivudine and peginterferon (pegIFN) plus a range of studies on new and pipeline HBV compounds including clevudine, emtricitabine (FTC), entecavir, telbivudine and alamifovir.

HCV-related studies included further results in HIV/HCV coinfecting patients from the APRICOT study, including data on histological response to pegIFN. Interesting data from the COPILOT study in HCV monoinfected patients suggested a benefit

in terms of prevented or delayed liver disease from low-dose (half-dose) pegIFN as maintenance therapy in patients who have previously failed IFN-based treatment.

The best coverage of studies from this meeting are on the following sites:

<http://www.hivandhepatitis.com/2004icr/aasld/main.html>

<http://www.natap.org>

<http://clinicaloptions.com/hep/conf/aasld2004/>

TREATMENT ACCESS

Generic ARVs and WHO prequalification list

Polly Clayden, HIV i-Base

Ranbaxy and Hetero withdraw antiretrovirals from WHO prequalified list

On 9 November WHO announced that Ranbaxy Laboratories had voluntarily withdrawn all its antiretrovirals from WHO prequalification. Three other Ranbaxy drugs were removed from the list earlier this year following findings of serious discrepancies in results from bioequivalence studies presented to WHO after inspections at the Contract Research Organisations (CROs) that conducted these tests.

A further announcement was made on 19 November that following an inspection by WHO, Hetero would withdraw six antiretrovirals from the list in order to review their bioequivalence data. Similar to Ranbaxy, Hetero evaluated the CROs it had used to conduct the studies, after receiving a warning letter sent by WHO to all manufacturers earlier this year, and found them non-compliant with international standards of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

Ranbaxy have presented WHO with a plan with proposed dates for the submission of new data for their products. The WHO statement says the first study is expected to be completed by December 2004. Likewise, Hetero will contract different CROs and submit new test results for the bioequivalence of the drugs "as soon as possible".

The WHO statement explains: "The irregularities found during the CRO inspections do not undermine the proven pharmaceutical quality of the medicines — including their purity and stability — but show that not all CROs can be relied upon as a source of evidence on the medicines' bioequivalence with their originator products."

They advise countries: "In principle, patients should suspend the use of de-listed medicines and switch to other prequalified products. However, if it is difficult to obtain alternative prequalified products immediately, it is recommended that patients continue the use of de-listed products. The risk of withholding treatment is higher than that of providing medicines whose bioequivalence is not proven but which have demonstrated quality and safety. A switch to non-prequalified products is not recommended, as their quality has not been documented by WHO."

The seven Ranbaxy products are: indinavir 400 mg capsule, blister (60, 100); lamivudine 150 mg tablet, blister (60, 100); lamivudine/stavudine 150 mg/40 mg tablet, Al strip (10), 60 in box; lamivudine/stavudine 150 mg/30 mg tablet, Al strip (10), 60 in box; nevirapine 200 mg tablet, blister (60, 100); stavudine 30 mg capsule, Al strip (10), 60 in box; zidovudine 300 mg tablet, blister (60, 100).

The Hetero products withdrawn are: stavudine 40 mg capsule; stavudine 30 mg capsule; lamivudine 150 mg plus zidovudine 300 mg tablet; indinavir 400 mg capsule; lamivudine 150 mg tablet; zidovudine 300 mg tablet.

And two Cipla antiretrovirals return to the WHO list...

Then on the 30 November 2004 WHO announced that it was reinstating two antiretrovirals manufactured by Cipla, in its list of prequalified medicines. The two medicines had been dropped from the list by WHO since May this year again due to non-compliance with international standards at CROs used by Cipla to conduct bioequivalence studies on the products.

Following the delisting, new bioequivalence studies were performed and further WHO scientific assessment and inspections have validated the results of these new studies, including the CROs involved, with all international requirements.

The two Cipla drugs are: lamivudine 150mg tablet, blister pack of 10; and lamivudine 150mg plus zidovudine 300mg tablet, blister pack of 10

Full announcements and Information and guidance for regulatory bodies, national AIDS programmes, doctors are on the WHO website:

<http://www.who.int/3by5>

More information on the WHO prequalification project:

<http://mednet3.who.int/prequal>

Two Cipla AIDS medicines back on WHO prequalification list:

<http://www.who.int/mediacentre/news/releases/2004/pr87/en/>

Ranbaxy withdraws all its ARVs from WHO prequalification:

<http://www.who.int/mediacentre/news/releases/2004/pr79/en/print.html>

C O M M E N T

In a Lancet editorial on November 20 the authors write: "So the latest news of the withdrawal of much-needed antiretrovirals from the prequalification list is both bad and good. Bad, obviously, for the patients and health carers affected locally. But good news because it shows that this little known part of WHO is effective and has teeth that can bite rapidly. QSM [Quality Assurance and Safety: Medicines] is a small team at WHO's headquarters that knows the importance of training local drug regulatory authorities, and has the ability to use international inspectors in local sites. And prequalification status means that some of the most important drugs are being made safely available in parts of the world where they are most needed." [1]

We would add that the process of reinstatement has been such a long one – the reinstated Cipla products were delisted in May – and the first delisted Ranbaxy products are not anticipated to be back until the spring.

Although not mentioned in the WHO statements, the generic companies are also seeking approval for their drugs from the FDA; Gregg Gonsalves from GMHC in New York raised (yet more) troubling issues of US unilateralism in an address to last month's Glasgow conference: "The US is driving countries to use brand name drugs, the Administration and its surrogates such as the Hudson Institute and Public Interest Watch have waged a successful campaign to undermine faith in the safety and effectiveness of generic ARVs. While there have been real issues about some of the bioequivalence studies of generic ARVs over the past few months, the US is using this to undermine countries' trust in the WHO on a more general level, implying that the WHO's entire system of evaluating ARVs is suspect. In fact, the US has set itself up to be the worldwide drug regulatory body and will evaluate generic ARVs through the US Food and Drug Administration, making itself the gatekeeper for the global community on which drugs do and do not get used widely across the world. In fact, Ranbaxy, a leading generic ARV maker has pulled all its drugs from the WHO evaluation process and is submitting its compounds for approval by the US FDA. Let's see how fast Ranbaxy's drugs are approved by the USFDA and how much of the market the company will lose as it waits for the blessing of the US government." [2]

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Cotrimoxazole reduces mortality and morbidity in HIV-positive children: joint WHO/UNAIDS/UNICEF statement

Polly Clayden, HIV i-Base

WHO, UNAIDS and UNICEF, guided by recent findings, have agreed to modify as an interim the current recommendations [1] for cotrimoxazole prophylaxis in children. This is based upon data - recently published in the Lancet [2] - from a double-blind randomised placebo-controlled trial in 541 children with HIV aged 1-14 years in Zambia, an area with high levels of bacterial resistance to this drug. After a median follow-up of 19 months, fewer children (28% vs 42%) had died in the cotrimoxazole group than in the placebo group.

It reads: "Cotrimoxazole remains important even with increasing access to ART, as its use can improve survival independently of specific HIV treatment. Current recommendations suggest it should be used before children require ART because it may even postpone the time at which ART needs to be started".

The statement recommends that cotrimoxazole should be given to:

All HIV exposed children (children born to HIV infected mothers) from 4-6 weeks of age (whether or not part of a prevention of mother-to-child transmission [PMTCT] programme)

Any child identified as HIV-infected with any clinical signs or symptoms suggestive of HIV, regardless of age or CD4 count.

The statement also makes recommendations on duration of prophylaxis, discontinuation, toxicity, dosing, follow up and other operational issues.

C O M M E N T

These results provide a valuable additional reason for HIV testing children with clinical features suggestive of HIV infection, as this is an affordable intervention that is available right now.

However it should be said that the 50% reduction in mortality seen with cotrimoxazole needs to be compared with the 500% reduction in mortality in HIV infected children given triple combination antiretroviral therapy. [3]

References

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<http://www.bmj.com>

Equitable access for antiretroviral treatment for women

Polly Clayden, HIV I-Base

The WHO and UNAIDS have issued a policy document on equitable access for ART for women concerning actions required to address gender issues in the scale up of ART.

The WHO press release explains: “Although 47% of people infected with HIV around the world are women and girls, there is currently no reliable information on how many of them receive treatment. Most countries collect general data on the number of people being treated, but this is generally not broken out by sex or by age. If countries are to ensure and monitor equitable access to treatment, they will need to collect data not only on who is becoming infected but also on how many men, women and children are getting access to prevention and treatment. ‘To ensure equitable access to prevention and treatment services for women and girls, it is important for countries to set their own national targets,’ said Dr LEE Jong-wook, WHO Director-General. ‘The targets must match the proportion of men, women and children who are living with HIV and in need of treatment.’”

The International Community of Women Living with HIV/AIDS (ICW) provided input to this document.

Ensuring equitable access to antiretroviral treatment for women policy statement downloadable as a pdf at:

<http://www.who.int/gender/violence/sixteendays/en/>

ANTIRETROVIRALS

US treatment guidelines updated

http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50

Updated guidelines on HIV treatment for adults and adolescents have been released by the U.S. Department of Health and Human Services (DHHS). Among the most important changes:

- Stavudine (d4T, Zerit) has been changed from a “preferred” to an “alternative” medication due to toxicity concerns, particularly facial wasting and neuropathy;
- The recently approved NRTI emtricitabine (FTC, Emtriva) has been added as an option to both the “preferred” and “alternative” lists of first-line regimens when used as part of a dual-NRTI backbone;
- The dual-NRTI backbone of tenofovir (Viread) plus lamivudine (3TC, Epivir) or emtricitabine is now recommended for protease inhibitor-based regimens as well as NNRTI-based regimens; and
- For asymptomatic, treatment-naïve patients with CD4+ cell counts above 350, the viral load recommendation to defer or to consider therapy has been increased from 55,000 to 100,000 copies/mL.

The new guidelines also feature discussions on HIV treatment in specific subpopulations of patients, including adolescents, injection drug users and patients coinfecting with hepatitis or tuberculosis.

Powerpoint Summaries of Updated DHHS Guidelines

Four sets of PowerPoint slide presentations, including author comments, are available from the AIDS Education and Training Centers (AETC) National Resource Center website.

Each slide presentation provides a review of the most important indications and recommendations together with speakers notes.

<http://www.aids-ed.org/>

- Comprehensive Guideline Summary (44 slides)
- Initiation of Therapy (56 slides)
- Changing Therapy (30 slides)
- Special Issues (52 slides) includes acute HIV infection, treatment for adolescents, treatment for pregnant women, injection drug users, patients with HBV and HCV coinfection, TB, prevention counseling.

Source: thebody.com

Roche discontinue plans for nelfinavir 625mg formulation

Roche has taken the decision not to introduce its Viracept (nelfinavir) 625 mg film-coated tablets. Recurrent manufacturing difficulties mean that an uninterrupted supply of this formulation could not be guaranteed for all patients. Roche believes that this is the most responsible decision to take and is in the best interests of patients and physicians.

The Viracept 250mg formulation is not affected by any manufacturing difficulties and remains an option in the therapy of HIV.

As a consequence of this decision we will be stopping all ongoing clinical trials. Patients in the UK receiving Roche Viracept 625mg via the Special Licence Scheme (SLS) should be transitioned to an alternative treatment, of which Viracept 250mg could be an option. This transition period of about 6 months (as agreed with the European regulatory body) should allow switching patients to an appropriate treatment without causing unnecessary inconvenience.

UK clinicians who currently have patients within the Viracept 625mg SLS or clinical trials are being informed of this decision and being asked to inform their patients at their next visit and switch them to an alternative treatment. All patients should have stopped taking Viracept 625mg by May 31st, 2005.

Roche is committed to continuing research, development and partnerships in HIV. We regret having to take this course of action and recognise that it could inconvenience patients and healthcare professionals but unfortunately it was not possible to overcome the problems involved in production.

For further information please contact Dr Cham Herath at Roche on 01707 366 7515 [dilruwan.herath@roche.com]

Source: PR Statement from Roche

C O M M E N T

This news will be a disappointment to patients who have been waiting for a lower pill count formulation with improved tolerability.

Although Agouron/Pfizer independently developed a different 625mg formulation for the US market, it was associated with poorer tolerability.

It is unlikely that the US formulation will be marketed in Europe.

HEPATITIS COINFECTION

Updated UK guidelines for HIV and Hepatitis coinfection

Updated guidelines are now available on the British HIV Association (BHIVA) website:

<http://www.bhiva.org>

The major changes for each section include:

HBV coinfection:

- Reformatted in the style of the ART guidelines.
- Treatment algorithms added.
- New, clearer definitions of when to treat and with what.

- High CD4: ideally treat according to liver biopsy result. Options are to use interferon if HBeAg +ve (non-cirrhotic) and abnormal LFT or adefovir in those who are HBeAg +ve or HBeAg -ve and HBV-DNA >10⁴ copies/ml (>10³ if cirrhosis)
- Low CD4 requiring ART: treat according to HBeAg status and HBV-DNA (as above). Can use tenofovir alone as part of HAART. 3TC/FTC are only recommended in combination with tenofovir.
- Updated clinical trial evidence and references.
- New information on investigations and vaccination.

HCV coinfection:

- Reformatted in the style of the ART guidelines.
- Recommended treatment is with pegylated interferon and ribavirin
- Non-pegylated interferon is no longer recommended
- Updated information on clinical trials and references
- Deletion of discussion on non-pegylated interferon
- Recommend avoid AZT and ddI in those on ribavirin.

IFN plus 3TC for coinfecting patients

CDC News Update

Treatments for patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B are associated with poor sustained responses, the study authors note. The resulting strategy of continued use of nucleoside and nucleotide analogues is associated with the risk of resistance and unknown long-term safety implications.

Researchers compared the effectiveness and safety of once-weekly 180 ug peginterferon alfa-2a plus placebo, peginterferon alfa-2a plus 100 mg daily lamivudine, and lamivudine alone in 177, 179, and 181 HBeAg-negative chronic hepatitis B patients, respectively.

After 24 weeks of follow-up, researchers found a significantly higher percentage of patients taking peginterferon monotherapy or combination therapy, compared to lamivudine alone, had normalization of alanine aminotransferase levels or HBV DNA levels below 20,000 copies/mL (peginterferon monotherapy: 59 percent and 43 percent, respectively; peginterferon plus lamivudine: 60 percent and 44 percent; lamivudine alone: 44 percent and 29 percent). Sustained HBV DNA suppression rates to below 400 copies/mL occurred among 19 percent of patients taking peginterferon monotherapy; 20 percent taking combination therapy; and 7 percent taking lamivudine alone.

Loss of hepatitis B surface antigen occurred in 12 patients in the peginterferon arms; no such clearance occurred in the group given only lamivudine. Patients taking lamivudine had fewer adverse events - including pyrexia, fatigue, myalgia and headache - than did patient groups taking peginterferon.

Patients had significantly higher rates of response, sustained for 24 weeks after cessation of therapy, with peginterferon alfa-2a than with lamivudine. "The addition of lamivudine to peginterferon alfa-2a did not improve post-therapy response rates," the researchers concluded.

Source: CDC HIV/STD/TB Prevention News Update, Monday, September 20, 2004

Ref: Marcellin P, Lau GKK, Bonino F et al. Peginterferon Alfa-2a Alone, Lamivudine Alone, and the Two in Combination in Patients with HBeAg-Negative Chronic Hepatitis B. New England Journal of Medicine (09.16.04) Vol. 351; No. 12: P. 1206-1217.

OTHER NEWS

ARV drug recycling project in UK

InterCare, a charity based in Leicester, has been providing unused dispensed medicines that would otherwise be destroyed to clinics in countries with limited access to medications mainly in Africa, for over 20 years.

Recently they have included ARV and HIV-related OI medications within their programmes.

The organization runs a strict quality assurance programme, based on recipient-driven requests. All medication is tracked and protected from commercial gain.

The project is particularly interested in working with doctors or pharmacists who work within HIV care at the moment and are

responsible for patient returned medications after a treatment change.

For further details please contact:

InterCare, 46 The Halfcroft, Syston, Leicester, LE7 1LD

Tel: 0116 269 5925 fax: 0116 269 6825

intercare@webleicester.co.uk

<http://www.intercare.org.uk>

ON THE WEB

Conference abstracts and reports:

AEGiS (AIDS Education Global Information System) has provided a huge library of AIDS information free to the world for over 12 years. Just one of its projects puts AIDS conference abstracts online, when no one else has done so.

<http://www.aegis.org>

There is an in interview with Sister Mary Elizabeth about the AEGiS online conference abstract database, in the current issue of AIDS Treatment News:

<http://www.aidsnews.org/2004/11/aegis-conferences.html>

7th International Congress on Drug Therapy in HIV Infection

November 14 - 18, 2004, Glasgow, Scotland

Several sites include early coverage of this meeting including:

<http://www.natap.org>

<http://www.hivandhepatitis.com/2004icr/7thcongress/main.html>

Medscape coverage:

<http://www.medscape.com/viewprogram/3602>

- Late-Breakers From Glasgow - Douglas Ward
- Viral Resistance to Antiretroviral Therapy - Jens Lundgren
- Adverse Events - Jens D. Lundgren
- Negotiating the Nucleosides on the Path to Simplicity - Douglas Ward, MD

XV Intl AIDS Conference, Bangkok

Mark Mascolini's report from the Bangkok Conference

<http://www.thebody.com/iapac/sept04/aids2004.html>

IAPAC conference articles are always essential reading, and a couple of months after most of the media attention has been forgotten, is sometimes the best time to re-read an in-depth report.

New Google research tool

<http://scholar.google.com/>

Google Scholar enables to search specifically for scholarly literature, including peer-reviewed papers, theses, books, preprints, abstracts and technical reports from all broad areas of research.

New web page on HIV drug deliberations

A new Food and Drug Administration Web page consolidates reports from HIV/AIDS-related advisory committee meetings to make accessing them easier. The site lists advisory committee meetings held since 1996; records are indexed by topic and

year. Meetings related to drugs, biologics and medical devices are documented.

The site will be updated to include records of future meetings.

Most records include the meeting announcement, committee rosters, briefing materials and transcripts. Visit

Advisory Committee Meetings related to HIV/AIDS and associated conditions

<http://www.fda.gov/oashi/aids/advisorycom.html>

Treatment Access:

Buprenorphine and methadone in the WHO essential medicine list

Proposals for the inclusion of buprenorphine and methadone in the WHO model list of essential medicines have now been posted on the WHO website. These pdf documents will be extremely helpful in supporting efforts to scale-up substitution treatment in the European region.

http://www.who.int/medicines/organization/par/edl/expcom14/buprenorphine/buprenorphine_msd_application17nov04.pdf

http://www.who.int/medicines/organization/par/edl/expcom14/methadone/methadone_collegeproblemsdrugdependence_letter.pdf

http://www.who.int/medicines/organization/par/edl/expcom14/methadone/methadone_msd_application17nov04.pdf

Update your WHO/EDM bookshelf

The latest version of the WHO Medicines Bookshelf CD-ROM, containing over 350 medicines-related publications, in English, French and Spanish, taken primarily from materials published by the Department of Essential Drugs and Medicines Policy (EDM), is now available. The e Bookshelf covers the Department's entire field of interest, including:

- access to essential medicines
- rational use of medicines
- national drug policy
- quality and safety issues
- traditional medicine.

Core publications from other sources are also included on the CD-ROM, with the kind permission of the organizations concerned.

For those in areas where Internet access is particularly slow or is unavailable, the Bookshelf was designed to serve as a self-contained medicines information resource. For this reason, a version of the Essential Medicines Library (20 MB) has been included on the CD-ROM. The Library includes the WHO Model Formulary, and the Library interface serves as a seamless gateway to a wide range of useful web sites, such as WHO clinical guidelines and United Nations price information resources, among many others.

The Bookshelf is available free of charge.

Write to: EDM Documentation Centre e-mail: edmdoccentre@who.int

Medical resources:

HIV InSite Knowledge Base: new chapters

<http://hivinsite.ucsf.edu>

Immunopathogenesis of HIV infection

<http://hivinsite.ucsf.edu/InSite?page=kb-02-01-04>

Changing antiretroviral therapy: why, when, and how

<http://hivinsite.ucsf.edu/InSite?page=kb-03-02-06>

Outpatient administration of intravenous therapies in patients with HIV infection

<http://hivinsite.ucsf.edu/InSite?page=kb-03-03-03>

Journal articles online at Medscape:

(requires on-time free registration)

AIDS

<http://www.medscape.com/viewpublication/744>

Volume 18, Number 15

- Immunologic and clinical responses to HAART over 50 years of age. Results from the French hospital database on HIV
- Cost-effectiveness of HIV PEP following sexual or injection drug exposure in 96 metropolitan areas in the United States

Volume 18, Number 14

- Proviral HIV-DNA predicts viral rebound and viral setpoint after structured treatment interruptions
- Response to HAART varies with age: the UK and Ireland Collaborative HIV Paediatric Study

JAIDS: Journal of Acquired Immune Deficiency Syndromes

http://www.medscape.com/viewpublication/878_index

Volume 37, Number 2

- Impact of HAART on anemia and relationship between anemia and survival in a large cohort of HIV-infected women: Women's Interagency HIV Study
- Progressive Multifocal Leukoencephalopathy (PML) in Patients on HAART: survival and risk factors of death

Community resources and publications:

Positively Aware: November/December 2004

Facing up to it: Bio-Alcamid as a facial filler to treat lipoatrophy - Matt Sharp

http://www.thebody.com/tpan/novdec_04/bio-alcamid.html?m72h#

PRN Notebook - September 2004

http://www.prn.org/prn_nb_cntnt/current.htm

- Novel viral markers predict HIV disease progression - Eric S. Daar, MD
- HIV drug resistance: new insight and updated practices - Daniel R. Kuritzkes, MD
- Coinfection with HIV and HBV: diagnosis and therapy - Marion Peters, MD
- View from the pipeline: the 2004 review of experimental antiretrovirals - Joseph J. Eron, MD

PRN Pre-press articles:

http://www.prn.org/prn_nb_cntnt/prepress.htm

- Mother-to-Child HIV transmission: national and international progress and challenges - Elaine J. Abrams, MD
- Herpes group viruses and HIV infection - Henry H. Balfour, Jr., MD
- From concept to care: pharmacokinetic boosting of protease inhibitors - Marta Boffito, MD
- XEN and the art of pharmacology: new learning from an old science - Charles Flexner, MD

RITA Treatment Alerts

The latest issue of the patient newsletter, HIV Treatment ALERTS!, mailed in October, is now online at The Center for AIDS website:

<http://www.centerforaids.org/rita/alerts.htm>

The issue includes recent treatment news including FDA updates and a look at HIV entry inhibitors, as well as regular features such as the Patient/Doctor Q&A, Bottom Lines, HIV 101.

i-Base training modules online in English and Russian

STEP is a pilot project of EATG, which is designed and implemented in cooperation with the All-Ukrainian Network of People Living with HIV, Central and Eastern European Harm Reduction Network, AIDS Foundation East-West (AFEW), International Harm Reduction Development Program (OSI), HIV i-Base (UK), Positive Movement (Belarus), and the Tides Foundation.

A workshop to train treatment advocates was held from 26-29 October in Kiev and the training material from the meeting is now online in draft format.

For more information please contact Svilen Konov svilen@eatg.org, or Mauro Guarinieri, mauro@eatg.org

The following training modules are available in English and Russian:

For the last version of the Manual in English and Russian:

<http://www.eatg.org/STEP/>

PUBLICATIONS AND SERVICES FROM i-BASE

All publications from i-Base are available free, individually or in bulk.

Please fax-back the order form on the back page of HTB or order online at:

<http://www.i-Base.info>

UK-Community Advisory Board: 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.

Reports and presentations for the ninth meeting, held on 31 May 2004, are posted to the i-Base website and are available in printed format. The training session at this meeting included an introduction to the immune system, a summary of community involvement in UK-based research into vaccines, microbicides and other new prevention technologies, an introduction to the International AIDS Vaccine Initiative, an update on post-exposure prophylaxis and updates on microbicides.

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

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

- An introduction to statistics, by Dr Caroline Sabin
- Genetics, resistance and HIV - Professor Clive Loveday
- Approaches to Salvage Therapy - Dr Mike Youle
- Pregnancy, HIV and Women's Health - Dr Karen Beckerman
- Fertility treatment and sperm-washing - Dr Leila Frodsham
- Access to treatment for UK visitors, refugees and asylum seekers - Linda McDonald
- Resistance, Lipodystrophy and IAS Report - Simon Collins
- TB and HIV coinfection - Dr Anton Pozniak

World CAB Report: focus on international drug pricing

Report from a meeting in February 2004 of community advocates and three major pharmaceutical companies that focussed on pricing issues and global access to treatment.

Available to download as a pdf file. See website below

The i-Base website

Our web address is

<http://www.i-Base.info>

All i-Base publications are available at our website, which is accessed by people all over the world; we have more than 5,000 successful page requests per week from about 80 countries on all continents.

The site gives details about i-Base, the UK Community Advisory Boards (UK-CABs), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as pdf files).

Introduction to Combination Therapy

This non-technical patient guide to treatment is available in 12 languages. It 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 how to avoid drug resistance.

Printed and pdf versions of this booklet are available in Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish.

Guide to HIV, pregnancy & women's health

This patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether you are on therapy or not and includes information for your own health and for the health of your baby.

The guide gives information on medication, Caesarean section and breastfeeding, as well as details of other sources of help. It is aimed at people in a wide range of circumstances including positive women thinking about having children and pregnant women who have recently been diagnosed HIV-positive.

Guide to changing treatment: second-line and salvage therapy

This is a non-technical patient guide to second-line and salvage therapy. This booklet helps patients in discussions with doctors, and covers what you can do if your viral load starts to rise, and the importance of considering or finding out why your current combination failed.

Guide to avoiding & managing side effects

This is a comprehensive 36-page 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.

Chinese, French, Italian and Spanish translations of this booklet are also available.

Italian treatment guides

We have Italian versions of our three treatment guides: Introduction to Combination Therapy, Guide to Changing Treatment and Guide to Avoiding and Managing Side Effects. For details of what is in each guide, see under the separate headings on these pages. The Italian guides are available in a single printed publication (to order ring the office on 020 7407 8488).

Treatment 'Passports'

These popular booklets are for HIV-positive people – whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

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 a printed version, in a pdf file that we can email to you, and on our website:

The printed version is available at most HIV clinics in the UK and is available free by post:

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 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 positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK.

Find HTB on AEGiS

AEGiS.com - the longest established and largest global resource of online HIV information - includes HTB in the regular journals that it puts online. You can find us at:

<http://www.aegis.com/pubs/i-base/2004>

The AEGiS daily email news service also carries i-Base conference reports.

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<http://www.i-base.info/forms/index.html>

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

h-tb

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HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website:

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