

The pdf version of HTB is fully hyperlinked, including contents page and referenced websites

November 2003

CONTENTS

(hyperlinked)

EDITORIAL	2
TREATMENT ALERT	2
• Important safety warning: high rate of virologic failure in patients with HIV infection treated with a once-daily triple NRTI combination containing ddI, 3TC, and tenofovir	
CONFERENCE REPORT	3
13th International Conference on AIDS and STIs in Africa (ICASA), 21-26 September 2003, Nairobi, Kenya	
• STIs in resource limited settings	
CONFERENCE REPORT	5
Reports from 43rd ICAAC, 14-17 September 2003, Chicago	
• ddI may retain activity in nucleoside experienced patients	6
• Studies and strategies with existing drugs	8
• Incremental progress with new antiviral drugs	10
• Newer nucleoside analogues show fewer adverse effects	13
PHARMACOLOGY STUDIES	
• Interaction between amprenavir and lopinavir thwarts triple PI salvage	14
• Vitamin C induces P4503A4 and reduces indinavir levels	14
• Indinavir levels reduced by omeprazole	14
• Boosted saquinavir PK in once-daily regimes	15
• Tenofovir drug-drug interactions	16
• Summary of other PK studies	17
TREATMENT ACCESS	17
• Global AIDS spending must double by 2005, says gloomy UN	
• GARPP requests permission from Boehringer to import generic nevirapine	
• Canada decides to lead the way in exempting AIDS drugs from patent laws	
ANTIRETROVIRALS	18
• Atazanavir 'named-patient' access extended in the UK and includes 150mg capsule	
• Another triple nuke failure: abacavir/ddI/d4T	
• FDA announces changes to ritonavir package insert	
TREATMENT INTERRUPTIONS	20
• Treatment interruption prior to five-drug regime shows no benefit at 48 weeks	
• Failure of alternating week-on and week-off therapy	
METABOLIC COMPLICATIONS	21
• Canadian study shows increased interventional cardiovascular procedures associated with HAART	
OPPORTUNISTIC INFECTIONS	22
• Valacyclovir is effective prophylaxis against herpes simplex	
WOMEN AND HIV	23
• Antiviral dynamics and sex differences of AZT and 3TC triphosphate concentrations	
• Women have a greater immunological response to effective HAART	
MATERNAL HEALTH & MOTHER TO CHILD TRANSMISSION	24
• Use of rapid HIV tests in labour	
• Eighteen month findings of HIVNET 012	
PAEDIATRICS	25
• Rituximab as single agent reversed paediatric Non-Hodgkins Lymphoma (NHL)	
• Perinatal antiretroviral treatment and haematopoiesis in HIV-uninfected infants	
COINFECTION	26
• Coinfected patients may require longer HCV treatment, irrespective of genotype	
OTHER NEWS	27
• New recommended standards for NHS HIV services	
• Vatican says HIV can pass through condoms	
ON THE WEB	28
PUBLICATIONS AND SERVICES FROM i-BASE	30

EDITORIAL

This is the third consecutive issue of HTB to lead with an FDA or EMEA drug warning letter.

The issue this month is that the triple-nucleoside combination of ddI/3TC/tenofovir failed to produce a viral load reduction >2logs by week 12 in a group of treatment naïve patients. It did however provide nearly all of them with their first set of drug-resistant mutations. It should be noted that the European version of this issue letter from Gilead also cautions against using ddI/3TC/tenofovir in treatment experienced patients.

Fortunately, this combination is unlikely to be currently widely used in the UK, and the caution against triple-nucleoside combinations in the 2003 BHIVA guidelines should limit any further prescribing of any triple-nucleoside combination in first-line therapy.

A further report of yet another poorly performing triple-nucleoside combination - this time with abacavir/ddI/d4T - is included on page 16.

The November HTB issue also includes a report on strategic treatment interruptions studies in resource-limited settings from the 13th International Conference on AIDS and STIs in Africa (ICASA).

STIs have now been well studied in countries which have widespread access to ARV therapy, and results from recent studies are reported on page 18-19.

These findings have not been particularly encouraging and the risk from resistance when stopping and restarting NNRTI-based regimens will apply wherever these studies are being run.

TREATMENT ALERT

Important safety information: high rate of virologic failure in patients with HIV infection treated with a once-daily triple NRTI combination containing ddI, 3TC, and tenofovir DF

This is new information as compared to the message sent to you in July 2003 by GlaxoSmithKline, regarding a different triple nucleosides/nucleotide reverse transcriptase inhibitors combination containing Abacavir, Lamivudine and Tenofovir DF

20 October 2003

Dear Health Care Professional,

In agreement with the European Medicines Evaluation Agency's scientific committee, the Committee for Proprietary Medicinal Products (CPMP) and the Irish Medicines Board (IMB), Gilead Sciences International Limited (Gilead) is writing to inform you of a high rate of early virologic failure and emergence of nucleoside/nucleotide reverse transcriptase inhibitor resistance associated mutations observed in a clinical study of HIV-infected treatment-naïve patients receiving a once-daily triple combination containing didanosine enteric coated beadlets (Videx[®] EC, Bristol-Myers Squibb), lamivudine (Epivir[®], GlaxoSmithKline), and tenofovir disoproxil fumarate (tenofovir DF, Viread[®], Gilead). Based on these results:

Tenofovir DF in combination with didanosine and lamivudine should not be used when considering a new treatment regimen for therapy-naïve or treatment-experienced patients with HIV-infection, and particularly as a once a day regimen.

Any patient currently controlled on this triple combination should be closely monitored for signs of treatment failure and considered for treatment modification at the first sign of viral load increase.

In a 24-week, single-site, pilot study [(N=24) 20 males; 4 females; median age (39 years), range (28 – 57 years)] designed to evaluate the safety and efficacy of a triple NRTI once-daily regimen of didanosine EC (250 mg), lamivudine (300 mg) and tenofovir DF (300 mg) in HIV-infected treatment-naïve patients, Jemsek et al. (oral communication, September 2003) have identified a high frequency of virologic failure (91%), which was defined as < 2 log₁₀ reduction in plasma HIV RNA level by Week 12.

Resistance testing was performed on 21 patients; 20 patients (95%) had M184I/V and 10 of these patients (50%) had K65R in addition to M184V. Of 19 patients who had phenotyping results available, all samples showed susceptibility to TDF (<1.4X WT), while 5/10 patients with K65R showed reduced susceptibility to ddI (>1.7X WT). As a result of this high early failure rate, the study was stopped.

The precise nature of any interaction leading to non-response in this study is not known.

Similar recommendations have been made and were communicated by GlaxoSmithKline in July 2003 regarding a different triple combination containing abacavir/lamivudine/tenofovir DF as an investigational once-daily regimen, in antiretroviral-naïve HIV-1 infected adults (Farthing *et al.*, 2003; Gallant JE *et al.*, 2003).

Gilead is committed to providing you with current product information for the management of your patients with HIV infection. You can assist us in monitoring the safety of our products by reporting adverse reactions, which should be advised to the IMB or Gilead at the address overleaf or by phone on + 44 1223 897 500, fax + 44 1223 897 290 or email at csafety@gilead.com.

For further information or a complete copy of the current Summary of Product Characteristics (SPC) for Viread, please contact me at the address overleaf.

Yours sincerely

Geoff Cotton, Medical Director

References:

Farthing C, Khanlou H, Yeh V, et al. Early virologic failure in a pilot study evaluating the efficacy of once daily abacavir (ABC), lamivudine (3TC), and tenofovir DF (TDF) in treatment naïve HIV-infected patients (oral presentation). Presented at the 2nd International AIDS Society Meeting, Paris, France, July 13-16, 2003.

Gallant JE, Rodriguez A, Weinberg W, et al. Early non-response to tenofovir DF (TDF) + abacavir (ABC) and lamivudine (3TC) in a randomized trial compared to efavirenz (EFV) + ABC and 3TC: ESS30009 unplanned interim analysis (oral presentation # H-1722a). Presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 14-17, 2003.

Source: Gilead Sciences

CONFERENCE REPORT

13th International Conference on AIDS and STIs in Africa (ICASA)

21-26 September 2003, Nairobi, Kenya

The ICASA meeting in Nairobi was founded in the late 80's to focus on HIV/AIDS and STIs in Africa and provides a forum for scientists, policy makers, political leaders and people living with HIV and their advocates. The 13 ICASA was attended by an estimated 7,000 delegates and included both scientific and socio-political sessions.

The conference website reminds us: "Current statistics show that about 29 million of the 40 million people infected with HIV worldwide are from sub-Saharan Africa. In the same region, about 55 per cent of those infected are women. While life expectancy has dipped to as low as 40 years, with some regions registering negative population growth. Thanks to HIV/AIDS. Yet, less than 33 per cent of countries in Africa have put in place National Strategic and Health Sector plans on how to tackle the epidemic and STI problems. Even those with the plans, only 11 of them are implementing them."

STIs in resource limited settings

Ben Cheng and Polly Clayden for HIV i-Base

Late breakers at the 13th International Conference on AIDS and STIs in Africa (ICASA) in September included early data from two ongoing structured treatment interruption trials in Africa presented by Cissy Kityo [1,2].

Intermittent therapy study in Uganda

This randomised controlled trial is to evaluate the effects of continuous HAART versus two intermittent approaches – seven days on/seven days off and five days on/two days off therapy – the study rationale being that this could reduce both cost and toxicities and have a practical role in developing countries.

Recruitment began in January 2003; the goal is to enrol 171 individuals (57 in each arm). The duration of the study is 72 weeks with six-weekly evaluation. The primary endpoint is the proportion of patients in each arm with viral load of <50 copies/mL at 72 weeks. Secondary endpoints include CD4 evaluation, laboratory evaluation of toxicities and reasons for change of therapy.

Inclusion criteria are as follows: patients must be on continuous HAART (2 NRTIs plus PI or efavirenz) for >90 days at enrolment with viral load of <50 copies/mL at baseline and CD4 >125 cells/mm³ within 30 days before randomisation. If CD4 count is <200 cells/mm³, patients must be receiving PCP prophylaxis, they should not be on a salvage regimen or receiving experimental antiretrovirals for >6 months (hydroxyurea allowed), nevirapine or abacavir.

And study termination criteria include: viral load >1000 copies/mL on two consecutive measurements, viral load >10,000 copies/mL on one single measurement, CD4 drop of >30% on two consecutive measurements, CD4 <100 cells/mm³,

malignancy (excluding MC-KS), serious HIV illness and permanent discontinuation of antiretrovirals.

As of September 116 patients have been screened (56% women) and 69 have enrolled and completed 12 weeks of the study (53% women). Median CD4 count is 261 cells/mm³ (mean 256 cells/mm³), with 69% having CD4 >200 cells/mm³. A total of 61% of patients are receiving d4T+3TC+efavirenz and 31% AZT+3TC+efavirenz.

Dr Kityo reported that of the 69 patients who have reached week 12, those with baseline CD4 >200 cells/mm³ on either of the intermittent treatment arms had a slight trend to have decreasing CD4 counts but their viral loads still remained undetectable. Those on either intermittent treatment arms with <200 CD4 cells/mm³ at baseline had a trend of increasing CD4 counts but this was less than those receiving continuous HAART.

There were five virologic failures: three using continuous HAART and two using interrupted therapy - one on the 7/7 arm (in a patient who did not take their d4T) and one on the 5/2 arm (who did not follow protocol).

There were no adverse events data presented. Dr Kityo reported that there have been some problems with adherence on the continuous arm because some of the individuals know that SIT may be a treatment strategy.

She concluded that these preliminary results show that short cycle intermittent therapy has maintained suppression of viral load while preserving CD4 counts in a small sample of patients, and that results are similar for patients with CD4 counts above and below 200 cell/mm³.

One of the issues that came up during the question/discussion period was the six weeks monitoring. If the study is to look for a 'cheaper' ARV strategy, then the rigorous monitoring adds a huge financial burden.

Development of antiretroviral therapy in Africa (DART) study

The aim of the DART study, which also began enrolment in January this year, is to compare routine laboratory and clinical monitoring (LCM) versus clinical monitoring only (CMO). A second randomisation will assess the risk and benefits of structured treatment interruption (three months on /three months off) or continuous therapy for those with CD4 >200 cells/mm³ after 24 weeks of HAART.

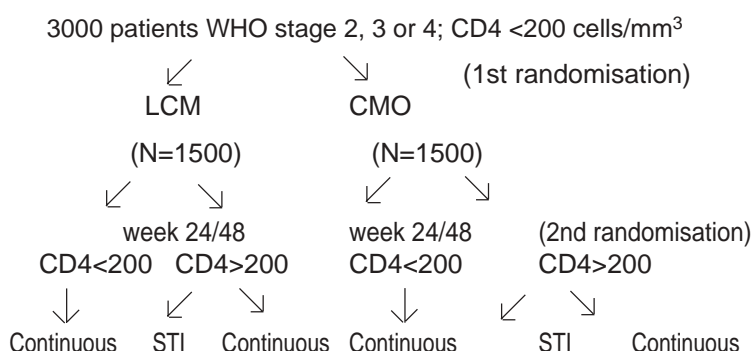
A pilot study involving 100 patients for the STI randomisation is built into the protocol in which 3,000 patients will receive triple therapy. The first-line regimen is AZT/3TC (Combivir) plus tenofovir and some patients will receive Combivir plus nevirapine. Second-line regimen is two NRTIs plus a boosted PI or nevirapine. Viral loads will be performed retrospectively and the results will not be provided in real time in this study.

The study is being conducted at two sites in Uganda and one site in Zimbabwe. Additionally, the Academic Alliance in Uganda is a satellite site. Follow up is four to five years.

As of 9 September 2003, 1,969 patients have been screened and 985 have been randomised to the first part of the study. The first patient to start the STI pilot study did so on 28 July 2003.

Baseline characteristics are: median age 37.2 years with 17% > 45 years median CD4 85 cells/mm³ (18% <25 CD4, 32% <50 CD4, 53% WHO stage 3, 19% WHO stage 2). Sixty-seven per cent of patients are women of which 14 individuals had previously received single dose nevirapine for mother to child transmission prophylaxis.

The study design is:



Dr Kityo reported a median change in CD4 cell counts after 24 weeks of 120 cells/mm³. Seven patients substituted d4T for AZT due to anaemia.

A decision about whether the second randomisation to the STI arm will be included will be made in early 2004 after results from the pilot STI phase are analysed. A similar trial to DART but for children and adolescents is being planned.

The investigators anticipate that: "The DART study will assess whether laboratory monitoring is necessary for effective ART

use, and whether toxicity can be reduced by STI without compromising efficacy.”

Links:

Further reports (many non-medical) from this conference are at:

<http://www.hdnet.org>

C O M M E N T

Although it is laudable to see a trial that will roll out to substantial numbers of African people, we are simultaneously seeing disappointing results with similar stop and start strategies reported from the “Staccato” and National Institutes of AIDS and Infectious Diseases (NIAID) studies reported on pages 17-18.

There are many outstanding questions for such strategies, notably resistance, complexities of adherence and, in this population particularly, stopping and starting therapy in people with very low baseline CD4 at initiation.

References

1. Kityo C and Mugenyi PN. A randomised controlled trial of short cycle intermittent versus continuous HAART for the treatment of chronic HIV infection in Uganda. Programme and abstracts 13th ICASA. Nairobi 21–26 September 2003. Abstract 1098929.
2. Kityo C. A randomised trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa: The DART trial. Programme and abstracts 13thICASA. Nairobi 21–26 September 2003. Abstract 1098933.

CONFERENCE REPORT

Reports from 43rd annual ICAAC

14-17 September 2003 in Chicago

The annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) may be becoming a less crucial conference for HIV research. However, some interesting studies were presented about both new and already licensed drugs.

The conference abstracts are available for a limited time on the conference website. Click on the ‘itinerary builder’ link for browse or search access to abstracts. All references in HTB coverage are to these abstracts.

<http://www.icaac.org/ICAAC.asp>

ddl may retain activity in nucleoside experienced patients

Simon Collins, HIV i-Base

A randomised study compared addition of either ddl (n=110) or placebo (n=68) for four weeks to current therapy of treatment experienced patients with detectable viral loads over 1,000 copies/mL. The primary endpoint was change in viral load between baseline and week 4. Resistance was analysed by genotype at baseline and week 4.

Median baseline viral load and CD4 count were 3.8 log copies/ML and 378 cells/mm³ respectively. Patients had a median of three thymidine analogue mutations and four nucleoside analogue mutations. Ranges were not provided for any of these baseline parameters.

After four weeks, patients receiving ddl (65% of who were ddl-experienced) had a mean reduction in viral load of –0.6 copies/mL, compared to a marginal increase in the placebo group. This additional viral pressure from ddl was sufficient for 31% and 11% of the ddl-receiving group for viral load to be below 400 copies/mL and <50 copies/mL respectively in the ddl-receiving group. The difference to the placebo group was statistically significant at <50 copies/mL level (p<0.01).

Viral response correlated closely with the extent of baseline resistance, with an approximate 0.6 log drop still reported with a median of four nucleoside-associated mutations (NAMs) and three thymidine-associated mutations. Tolerability was similar in each group.

C O M M E N T

Without more detailed presentation of treatment histories of these patients it is unclear whether this short-term viral suppression would be sustained. Data was not for example presented on any changes to the resistance profiles between baseline and week four. If introduction of ddl provided selective pressure for the return of archived virus from previous ddl and other nucleoside use, then the benefit is only likely to be limited.

If, however, it confirms antiviral activity with low-level nucleoside resistance, then this could provide an important boost for people who still fall just short of the potency required to reach and sustain an undetectable viral load. This is particularly important when constructing third-line and salvage regimens.

In addition, it is well documented that didanosine has good activity in monocyte/macrophage cell lines. HIV inhibition in these cell lines *in vitro* requires 100-fold lower drug levels than is required to suppress replication in lymphoblastic cells. Perhaps sensitivity to didanosine is selectively retained in these cell lines even in the presence of NAMs, giving additional benefit in nucleoside-experienced patients.

Ref: Molina JM, Marcellin AG, Pavie J. Didanosine (ddl) in treatment-experienced patients: Results from a randomised double-blind placebo controlled study (A1454-176 – JAGUAR). 43rd ICAAC, September, 2003; Abstract H-447.

Studies and strategies with existing drugs

David Margolis, NATAP.org

Monotherapy or no therapy at all: is this the new direction of HIV therapy?

As the pendulum governing prescription of antiretroviral therapy swings farther away from “hit hard and hit early” towards “the treatment is worse than the disease”, clinicians around the world are testing ways to minimise exposure to antivirals. Trials examining drug interruption or cycled therapy, as well as using fewer drugs, were presented. Clinicians should consider these concepts carefully, without forgetting the evolving benefits of potent, simpler, and less toxic drugs, or the difficulty of achieving full functional immune reconstitution once severe immunodeficiency has been allowed to develop, and recent evidence that minor populations of resistant HIV can expand when therapy is interrupted.

BASTA: when enough is enough

Maggiolo reported the interim findings of a treatment interruption study called “BASTA”. [1]

Patients durably suppressed to HIV-RNA <50 copies/mL with stable CD4 >800 cells/mm³ were randomised (2:1) to either interrupt or to continue their ongoing treatment. Therapy was to be restarted if CD4 count <400 cells/mm³. Of 114 patients enrolled, 76 stopped therapy while 38 continued it.

At roughly 20 months, about 25% of patients assigned continuous therapy had stopped therapy, presumably due to fatigue or toxicity. Multivariate analysis found that only the CD4 nadir value predicted CD4 cell decline ($P < 0.001$). For those whose lowest CD4 count was <200 cells/mm³, the median time to restarting therapy was 6.9 months. For those with a T-cell nadir of 200-350 cells/mm³ therapy was restarted in a median of 14.1 months, and 17.8 months for those with a nadir of 350-500 cells/mm³. No patient with a CD4 count nadir of >500 had to restart treatment.

This adds to the findings of previous clinic cohort observational studies that suggest that if one does not need HAART when HAART was started, it is safe to stop. Additional biomarkers that could aid in the identification of patients at low or high risk of progression off therapy are needed.

A second Italian group took a similar approach in an observational, retrospective, multicentre study of a group of 140 patients whose CD4 count pre-interruption was >500 cells/mm³, HAART for >12 months (median of 3.5 years), and a CD4 nadir >250 cells/mm³. [2]

Criteria for restarting treatment were: a confirmed CD4 count <350 cells/mm³ and the patient willingness. At treatment discontinuation, median CD4 count was: 804 cells/mL, median VL was 1.70 log₁₀ copies/mL.

At the time of the presentation 75 of 137 (56%) were still off therapy. Some 24.3% had experienced a CD4 decline to below 350 cells/mm³, and 22.1% restarted treatment before CD4 dropped below 350 cells/mm³. The median time to restarting HAART for any reason was 104 weeks (95% CI: 79-169). Median time was only 52 weeks, however, if CD4 at nadir was >350 cells/mm³. Independent predictors of therapy resumption were: CD4 nadir; months with undetectable viral load; slope of CD4 pre-ART and most recent VL vs the level at interruption.

A cost of interruption

But lunch is not free. Barreiro and colleagues presented findings for a cohort that had de-intensified therapy in which therapy was later re-intensified. [3]

One hundred and eighty-seven HIV+ patients on HAART (69 on PIs and 116 on NNRTIs), with CD4 counts >350 cells/mm³ and HIV-RNA <50 copies/mL substituted ddl 400 mg qd plus hydroxyurea 500 mg bid for their NRTI+NNRTI or NRTI+PI regimen. HAART therapy was restarted for viral rebound >10,000 copies/mL.

Overall, 21% of patients who moved to ddl-HU showed viral rebounds >10,000 copies/mL (19 on PIs and 20 on NNRTIs).

All patients who then resumed a PI-based regimen suppressed viraemia to <50 copies/mL. However, 55% (16 of 29) who restarted an NNRTI failed to attain HIV-RNA <50 copies/mL ($p < 0.001$). Genotypic analysis could not be performed in all failures, but NNRTI resistance did not predominate. However, this observation does add to the concern that if NNRTIs are discontinued in a suboptimal setting, their therapeutic potency may be lost. It is still unclear if strategies such as stopping NNRTIs one to two days before the rest of the regimen is stopped will avoid the induction of NNRTI resistance.

Back to monotherapy?

Gathe in Houston, with collaborators in Dallas, challenged the field by testing the safety and efficacy of Kaletra (LPV/r) alone in treatment-naïve patients. [4]

Gathe pointed out that monotherapy, if it could be shown to be effective, could avoid many of the high costs and synergistic toxicities of combination antiretroviral therapy. It should be noted that if multiple nucleosides can effectively control HIV replication in some patients, PI monotherapy with a sufficiently high barrier to resistance might control HIV as well.

Consenting patients enrolled in this open-label, unsponsored trial. There were no CD4 or VL criteria for entry, and 28 males and two females (White 60%, Hispanic 20%, Black 20%) who entered had a mean CD4 count of 169.5 cells/mm³ and viral load of 262,020 copies/mL. Lopinavir/ritonavir was dosed in a weight-based fashion, three capsules BID or four capsules BID if >70kgs. Patients intensified therapy at week 12 with saquinavir or tenofovir/3TC if desired.

At 24 weeks (or last observation) only one subject had not achieved <400 copies/mL HIV RNA. This subject had baseline VL 500,000 and had declined to a nadir of 1,510, but rebounded to 4,270 at week 32 when saquinavir was added. At that time genotype showed only L63P, phenotype was wild type, and an adequate LPV trough was measured.

However, two subjects were lost to follow-up, one was deported, two stopped therapy due to GI intolerance, one was nonadherent, and one had TDF/3TC added when active HBV was discovered. So by ITT, nine of 30 failures determined by viral load >400 copies/mL were seen by week 24 (70%). Twenty-one of 22 patients on treatment at 24 weeks had achieved <400 copies/mL (95%). No other significant AE's were reported and no triglyceride elevations >Grade 2 were observed.

Crixilop: two boosted protease inhibitors alone (Indinavir + Kaletra)

Of potential relevance to the concept of PI monotherapy, the Crixilop Cohort Study challenged the therapeutic potency of boosted PIs alone in a salvage setting. [5]

Staszewski and colleagues studied 23 heavily pre-treated HIV-positive patients in the Frankfurt HIV Cohort who were experiencing treatment failure with NRTI resistance or intolerance. Salvage therapy consisted of indinavir (800 mg bid) plus LPV/r (400/100mg bid) without additional RTIs or any other ART. All but one subject were male, with median age 40 years, prior exposure to 10.5 drugs and 3.5 PIs, viral load 5.2 log copies/mL, CD4 count 116 cells/mm³.

At a median follow up of 28 weeks, 17 (61%) patients remained on IDV/LPVr, eight discontinued due to IDV intolerance and three due to virologic failure. Viral load had declined 2.4 logs (range 1.30-5.6) and 1.9 logs (range 1.5-5.2) at weeks 12 and 24 respectively. The remaining six patients had no persistent response. Median CD4 count rose 70 cells/mm³ at week 24. IDV dose was decreased in six patients, and LPV/r doses in three due to intolerance.

Clearly many questions about the baseline PI sensitivity of these patients and the durability of this response need to be answered, but the initial virologic response in patients exposed to multiple PIs is impressive.

Vive la resistance

Weird viruses: NNRTI resistance is not always predicted genotype

Petropoulos reported the rare discovery of viral isolates with high-level resistance to HIV-1 NNRTIs when assayed by Virologics phenotype despite the absence of known NNRTI resistance mutations. [6]

In a dataset of 18,034 samples, 48 isolates were identified that exhibited >10-fold resistance to at least one NNRTI in the absence of well-characterised NNRTI mutations (98G, 101E, 103N/S, 106A/M, 225H, 230L, 236L, or any mutation at position 100 181, 188, 190 or 227). Of these 10 encoded K101P and 13 the combination of K103R and V179D.

The remainder of isolates contained other changes that have not yet been associated with NNRTI resistance. While this phenomenon is rare, it is useful to remember how much we have still to learn about the resistance of HIV to our drugs, and an illustration of the use of the phenotype assay to identify resistance not reported in a genotype assay.

The reverse could also rarely occur, as it is conceivable that rare isolates with clinical resistance may not demonstrate significant fold resistance in phenotype assays.

Is there a clinical consequence to the "pathway" of resistance?

Under the selective pressure of a given drug combination, a specific pattern of resistance mutations tends to emerge if therapy fails. It is not yet known if a given pattern or "pathway" predicts a durable or transient response to second-line therapy. Such knowledge might guide decisions about initial and subsequent therapy.

Van Houtte and colleagues examined prevalence and phenotypic resistance of RT mutation combinations found in over 31,400 clinical viral isolates from routine testing at Virco between January 2001 and February 2003. [7]

Two “pathways” to resistance against NRTIs with mutations 41L, 210W, and 215Y/F or 67N, 70R, and 219Q/E/N/R in HIV-1 reverse transcriptase have been suggested. The prevalence and phenotypic resistance of these combinations (termed NAMs or nucleoside analogue mutations) and the “non-pathway” 44D/E, 118I and 184V/I mutations in clinical isolates were examined. Resistance profiles came from Virco’s matched genotype/phenotype dataset.

Thirty-eight per cent of isolates have >1 NAMs (mean 2.7). Nearly half of these were phenotypically resistant to AZT (>4-fold). Median fold change in sensitivity to AZT in isolates with >3 NAMs ranges from three to 37 when the 3TC resistance mutation M184I/V was present, and from six to 52 when it was absent. The 41-210-215 “pathway” predominates in this data set (34% of the isolates) versus 67-70-219 (15%) with some overlap. Two-, three-, and four-NAM sets in the 41-210-215 pathway were on average more resistant to all NRTIs than those in the 67-70-219 pathway. Whether this predicts a poorer response to second-line therapy remains to be seen.

References

1. Maggiolo F, Ripamonti D, Gregis G et al. Individualised structured treatment interruptions: results of a randomised, controlled study (BASTA). 43rd ICAAC, September, 2003; Abstract H-448
2. Mussini C, Cozzi-Lepri A, Borghi V et al. CD4-guided treatment interruptions: a new therapeutic strategy. 43rd ICAAC, September, 2003; Abstract H-856.
3. Barreiro PM, de Mendoza C, Nez M et al. Negative impact of drug holidays in HIV-infected patients on non-nucleoside reverse transcriptase inhibitors. 43rd ICAAC, September, 2003; Abstract H-857
4. Gathe JC, Washington M, Piot D et al. Preliminary pilot data on the safety and efficacy of Kaletra (LPV/r) dosed alone for the treatment of HIV in ARV-naïve patients: greater than or equal 24 data. 43rd ICAAC, September, 2003; Abstract H-845.
5. Staszewski S, Dauer B, Gute P et al. The Crixilop Cohort Study: preliminary results from a salvage study of HIV-positive patients treated with indinavir (IDV) and lopinavir/ritonavir (LPV/r) without the addition of reverse transcriptase inhibitors (RTI). 43rd ICAAC, September, 2003; Abstract H-853.
6. Petropoulos CJ, Chappey C, Parkin NT et al. High-Level resistance to HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the absence of known resistance mutations. 43rd ICAAC, September, 2003; Abstract H-451.
7. Van Houtte M, Lecocq P, McKenna P et al. Phenotypic resistance and prevalence of specific nucleoside analog mutation combinations (NAMs) in reverse transcriptase in a dataset of recent HIV-1 clinical isolates. 43rd ICAAC, September, 2003; Abstract H-907

Source: NATAP.org

Incremental progress with new antiviral drugs

David Margolis, NATAP.org

Despite the proliferating frequency of meetings, it was encouraging to hear reports of steady advances in the development of new antivirals. Most exciting was the progress of multiple entry inhibitor drugs, creating optimism that we are moving towards combination therapy at the point of virus entry into the T cell.

CCR5 chemokine HIV co-receptor blocker: first report of anti-HIV effect in HIV-infected people

HIV requires a second receptor in addition to CD4 to enter cells. Drugs that effectively block this interaction are hoped for to add a new and highly potent class of antivirals to our armamentarium. Of the two most-often used chemokine receptors, CCR5 is the receptor primarily used by most HIV strains dominant in HIV-infected people, both during the initial process of infection, and throughout the course of disease. This receptor is therefore a therapeutic target of great potential, particularly as some immunologically healthy humans are born with the functional absence of CCR5. Blockade of CCR5 by a drug might therefore be well tolerated.

A safety study of Pfizer’s CCR5 antagonist in HIV-negative volunteers [1] showed that steady state drug levels were reached within seven days of dosing. 100mg and 300mg BID was well tolerated over 28 days of dosing.

There were no serious adverse events reported, and all treatment related adverse events were of mild or moderate intensity. No clinically significant increases in any laboratory safety tests including haematology, clinical chemistry or lipid profiles, and no clinically significant changes in 12-lead ECGs, blood pressure, or heart rate were observed.

Pozniak and colleagues then reported on the short-term antiviral activity of UK-427,857 [2].

Twenty-four asymptomatic, untreated HIV-positive patients with CD4 counts >250 cells/mm³ and plasma viral load >5000 copies/mL were treated with UK-427,857 for 10 days. Volunteers were given 25mg once a day, 100mg twice a day or placebo for 10 days and were followed for 30 days after drug was stopped.

Prior to dosing, patients were selected for this study that had predominant circulating viral populations that used the CCR5 receptor, rather than the other major co-receptor CXCR4 (seen most often in individuals with advanced AIDS). A concern is that blockade of CCR5-using viruses may lead to the selection and outgrowth of X4-using viruses, which might result in more rapid disease progression.

UK-427,857 was well tolerated with no severe or serious adverse events. EKG abnormalities, seen with some prior chemokine blocker candidates, were not found. Although the Pfizer team hopes to develop a drug without food restrictions, plasma levels are much higher when the drug is taken in the fasted state than with a high-fat meal. A study evaluating the impact of food on viral load reduction is ongoing. In this study, drug levels were also much higher and more stable at the 100 mg bid dose, rather than the 25 mg qd dose.

However, the 100mg bid dose of UK-427,857 yielded an impressive mean decrease in viral load of 1.42 log₁₀ in only 10 days, with a mean decrease of 0.42 log₁₀ at the 25mg QD dose. It was discovered that one patient harboured a mixed population of X4 and R5 viruses. This subject responded poorly to UK-427,857 monotherapy, and although viral load did not increase, a semi-quantitative assay suggested that the proportion of circulating X4 virus increased roughly 10-fold.

An accompanying presentation [3] showed UK-427,857 to be a potent inhibitor of R5 HIV-1 replication in the lab, and predictably inactive against X4 or R5X4 strains.

The drug's antiviral activity was unchanged despite increases in virus inoculum added to laboratory viral cultures, suggesting that viral load should not have a direct effect on efficacy in patients.

Recent laboratory studies suggest that R5 receptors are a limiting factor for HIV entry, and that multiple R5's are needed for the entry of a single viral particle. In other words, one individual may have 100 R5 receptors and another person may have 90 R5 receptors, but HIV may only need 50 R5 receptors for entry. Donor-to-donor PBMC variations (variations among study subjects) in host co-receptor expression did not affect potency in the study discussed in abstract H-875, indicating that "427" should be active regardless of individual variations in CCR5 expression or function. Currently, it appears that Pfizer must define the optimal dose for UK-427,857, and whether high levels of drug that saturate available R5 receptors are necessary, or whether sub-saturating doses will be equally clinically effective. However, the initial potent antiviral effects seen in short-term monotherapy are very encouraging. An important new antiretroviral may not be too far off.

T-20 to T-1249: a sequence of fusion inhibitors?

Lalezari [4] presented further follow-up on the activity and effect of the use of the second-generation fusion inhibitor T-1249 in subjects who had failed the first generation fusion inhibitor T-20.

Data on 25 patients was initially presented at CROI in February 2003. Fifty-three patients failing T-20 and other antivirals with a median baseline HIV RNA of 4.97 log₁₀ copies/ml received at least one dose of T-1249. These subjects had been failing T-20 for a median time of 66 weeks (range 28-165). All (52 or 53) whose virus could be amplified demonstrated T-20 resistance mutations and/or decreased susceptibility. Nevertheless, the median HIV RNA decline was 1.26 log (95% C.I. 1.40 to 1.09) after 10 days of therapy. No serious adverse events (AEs) related to T-1249 were seen, and site reactions and AEs were similar to T-20.

The authors suggested that this potent short-term response to T-1249 implied that sequencing of fusion inhibitor drugs after the development of resistance might be a viable clinical strategy. Certainly, more long-term data are needed. Alternatively, as T-1249 moves forward in development, the first use of this more potent agent may be preferable.

In a related presentation, Trottier [5] reported the 48-week response to enfuvirtide (T-20) in the TORO Trials.

As presented at CROI 2003 in February, heavily pre-treated patients (median 12 ARVs) were randomised to an optimised background (OB) regimen or to OB + enfuvirtide (ENF; 90 mg sc BID). The overall median viral load and CD4 count at baseline were 5.1 log copies/mL and 92 cells/mm³, respectively. At 48 weeks, 30.4% of patients (201/661) on ENF+OB had VL <400 copies/mL by ITT analysis. Most of these had responded by this criterion at 24 weeks, and maintained response, but a few (4.2% or 28 patients) dropped below 400 copies after 24 weeks and remained below 400 copies at 48 weeks.

These findings suggested a continuing clinical benefit of T-20 use with OB in this difficult-to-treat population. The challenges of a year of T-20 in the setting of advanced disease appear surmountable, and as with other antivirals, a clinical benefit may be reaped despite the gradual evolution of drug resistance.

Blocking the viral "handshake" with the T cell

Colonno and colleagues at Bristol first presented BMS-378806 ("806" for short) at the Resistance meeting in 2002. BMS are discontinuing 806 but pushing ahead with other candidates in their research and development programme of CD4 receptor inhibitors. The novel 806 small molecule is a specific inhibitor of HIV-1 attachment that blocks the interaction of the binding pocket of the viral envelope Gp120 with the CD4 receptor. The group presented further basic laboratory studies [6] aimed at illuminating the precise mechanism of blockade.

Their elegant work showed that 806 binding induces changes in the shape of gp120. Further, the shape-shifting forced by 806 may also affect gp120's ability to bind the CCR5 co-receptor. Lab studies suggested a synergistic antiviral effect when 806 was combined with a CCR5 chemokine co-receptor inhibitor or gp41 fusion inhibitor. Although BMS are switching the focus of their programme, the possibilities are exciting.

Developing NNRTIs

Hazen and co-workers from GSK added to the story of this new drug class [7] as first reported at CROI 2003.

GW8248 is a benzophenone and a potent NNRTI. A prodrug form of GW8248 with increased bioavailability and solubility is also under development. Like other NNRTIs, GW8248 inhibits HIV in the low nanomolar range. It is of great interest as it is active against a wide variety of NNRTI-resistant strains, including Y181C and K103N. GW8248 exhibited additive activities with other NNRTIs (NVP, DLV and EFV), was additive or synergistic with the activity of nucleosides, and generally synergistic with the activities of PIs.

To pose a very challenging laboratory test to GW8248, Hazen and colleagues tried to evolve a GW8248-resistant virus in the laboratory, starting with a K103N NNRTI pan-resistant virus. After eight serial passages of K103N-infected cells in the presence of sub-inhibitory concentrations of GW8248, GSK scientists were able to grow out a virus encoding new mutations at V106I, P236L and E138K that was 50-fold resistant to GW8248. This is a glass half-full, as while this experiment shows that resistance can develop, the fact that eight passages and three new mutations are required is encouraging.

The activity of capravirine (CPV), a novel NNRTI, was evaluated in combination with nelfinavir and two NRTIs in a Phase 2 study in HIV-infected, NNRTI-experienced patients [8].

It is hoped that CPV will have expanded activity against NNRTI-resistant HIV. Due to animal toxicities, this study was closed prematurely, but 36 patients chose to continue on open-label CPV. Of these 16 remained virologically suppressed (VL < 400 copies/mL) after 28 to 34 months of therapy. While 80% of the patient isolates demonstrated high-level resistance (>10-fold) to one or more of the approved NNRTIs, 70% remained susceptible (<10-fold resistance) to CPV. Despite its slow development, it is hoped that we will have more promising news about CPV soon.

References

1. Russell D, Bakhtyari A, Jazrawi RP et al. Multiple dose study to investigate the safety of UK-427,857 (100mg or 300mg) BID for 28 days in healthy males and females. 43rd ICAAC, September, 2003; Abstract H-874
2. Pozniak AL, Ftkenheuer G, Johnson M et al. Effect of short-term monotherapy with UK-427,857 on viral load in HIV-infected patients. 43rd ICAAC, September, 2003; Abstract H-443.
3. Macartney MJ, Dorr PK, Smith-Burchnell C et al. *In vitro* antiviral profile of UK-427,857, a novel CCR5 antagonist. 43rd ICAAC, September, 2003; Abstract H-875
4. Lalezari JP, Bellos N, Richmond G et al. Final analysis of T1249-102: T-1249 retains potent short term antiviral activity in patients who have failed a regimen containing enfuvirtide (ENF). 43rd ICAAC, September, 2003; Abstract H-444.
5. Trottier B, Arasth K, Henry K et al. Durability of response of enfuvirtide through 48 weeks in the TORO trials. Abstract H-835.
6. Lin P, Ho H, Fan I et al Impact of an HIV-1 attachment inhibitor on viral envelope Gp120. 43rd ICAAC, September, 2003; Abstract H-877
7. Hazen RJ, Harvey R, Ferris R et al. Characterisation of the anti-HIV-1 activity of GW8248 in combination with other anti-retroviral drugs and *in vitro* selection for resistance. 43rd ICAAC, September, 2003; Abstract H-445.
8. Hammond JL, Amantea M, Raber S et al. Long-term virologic response to capravirine in HIV-infected, NNRTI-experienced patients. 43rd ICAAC, September, 2003; Abstract H-871.

Source: NATAP.org

Newer nucleoside analogues show fewer adverse effects

Graeme Moyle, HIVandHepatitis.com

New data on the adverse effects of antiretroviral therapy were fairly thin on the ground at this year's ICAAC (September 14-17, 2003, Chicago, IL). However, there were valuable points raised, most notably with regard to the more favourable tolerability profiles of recently approved antiretrovirals and re-formulations of established agents. Notably lacking were new insights into the etiology and management of metabolic and morphological abnormalities.

Tenofovir (TDF, Viread) and the kidney: no evidence of harm from controlled data

Several clinical cohorts have reported clusters of individuals receiving tenofovir who have experienced elevations in creatinine, proteinuria or proximal renal tubular acidosis. In some of these reports, risk factors for these events appear evident, most notably prior proximal renal tubular acidosis during adefovir therapy. In some other case reports, renal toxic agents have been present, most notably fibrates, but authors of these abstracts chose to blame the renal dysfunction on tenofovir. Clearly, the best understanding of whether renal function abnormalities are more common during tenofovir use than alternative NRTIs will be derived from randomised controlled trials.

The GS 903 study is a double-blind placebo-controlled study comparing tenofovir (TDF) and d4T, each combined with 3TC and efavirenz, in treatment naïve individuals. The study has thus far completed 96 weeks of follow-up and detailed information regarding renal or possibly renal events was reported. Multiple ways of evaluating renal function during therapy were presented. In all cases no evidence of difference in events between tenofovir and d4T treated patients were observed.

The data presented looked at parameters including all graded episodes of creatinine elevation, mean change in creatinine clearance, episodes of proteinuria, glycosuria, and serum phosphorus. Additionally, for both proteinuria and serum

phosphorus, elevation of the number of individuals reporting abnormalities on two consecutive attendances was reported. Small numbers of individuals in both groups experienced transient episodes of creatinine elevation (3% of TDF and 2% d4T grade 1, 2% TDF and 0% d4T grade 2, 0% TDF and 2% d4T grade 3, no grade 4), proteinuria (12% of TDF and 16% d4T grade 1, 6% of each grade 2, no grade 3 or nephrotic syndrome) and serum phosphorus (3% each grade 1, 3% of TDF and 2% d4T grade 2, one individual in each group a grade 3 event) elevation.

For no event reported were differences observed between the randomised groups, either numerically or statistically. No episodes of Fanconi's syndrome were reported [1]. These data underline that renal events do occur during ART but ascribing these to TDF requires comparison with an appropriate control to be made. Case reports that do not investigate other possible causes of renal dysfunction, rule out concomitant agents associated with renal dysfunction and search for these events in matched subjects not receiving TDF should be treated with scepticism and caution.

Further data through 144 weeks of this study are anticipated for early 2004.

d4T extended release (Zerit XR)

The extended release formulation of stavudine (d4T XR) has been approved in a number of countries but not yet marketed due to production issues. The 100 mg once daily tablet leads to a slightly lower total exposure (with lower peak and higher trough values) of d4T relative to the standard formulation. (now called immediate release (IR)).

Equivalent efficacy has been demonstrated in two comparative studies that randomised treatment naïve individuals to either d4T XR or d4T IR in combination with 3TC and efavirenz. The 48-week results from these studies have suggested that there may be differences in the tolerability of the two d4T formulations, with fewer important adverse events in the XR arm.

Further comparative safety data from these two main studies, totaling 900 patients randomised equally to either d4T XR or d4T IR were reported. The average duration of treatment was 115 weeks.

Patients included in the studies had a median baseline CD4 cell count of 277 cells/mm³ and viral load of 4.8 log₁₀ cps/ml. Overall, rates of discontinuation from the studies were low with 12% of XR and 16% of IR patients discontinuing prior to week 48. Of these discontinuations 7% and 9%, respectively were related to adverse effects.

The most common treatment-related grade 2-4 adverse events were dizziness, rash, headaches, abnormal dreams, diarrhoea and nausea. Peripheral neuropathy (or 'peripheral neurologic symptoms' which included numbness, paresthesias, or pain in distal extremities) symptoms and physical signs were actively sought at each study visit.

Grades 2-4 neuropathy was reported in 4% of XR and 8% of IR treated patients. Only 1% of XR and 3% of IR patients discontinued d4T due to neuropathic symptoms.

Lipoatrophy has become a major obstacle to d4T use following several prospective studies that have indicated that regimens including d4T have a faster rate of fat loss over time relative to regimens based on AZT, abacavir or tenofovir.

Despite the possibility that this event is in part exposure dependent, no objective assessments of this event were included in the development programme for d4T XR. Specifically, baseline and follow up DEXA or CT scans were not performed. Lipodystrophy was not prospectively defined nor objectively confirmed. Events reported as lipodystrophy were 'investigator defined', similar to cases reported in the Gilead GS903 study.

Where lipodystrophy was reported, the investigator was asked to further define the event as 'lipoatrophy', 'lipohypertrophy' or mixed. 'Lipoatrophy' included events of facial, extremity, or subcutaneous fat loss. 'Lipohypertrophy' included increased abdominal girth, buffalo hump, lipomata and breast enlargement in women. Overall, lipodystrophy was reported in 11% of XR and 16% of IR patients (p=0.05), with lipoatrophy in 6% and 11%, lipohypertrophy in 3% and 2%, mixed syndrome in 2% and 3%, respectively.

Reports of 'gynaecomastia' (breast enlargement in males) were seen in 3% and 2% of XR and IR patients, respectively [2]. The data would indicate that whilst d4T XR may be somewhat less risky for lipoatrophy than the IR formulation, the event continues to be relatively common. Reports from the Gilead GS 903 study at 96 weeks have indicated that approximately 13% of patients in the d4T arm of that study have been diagnosed as having lipodystrophy by the investigator compared with just 1% of patients in the tenofovir arm.

Fasting grade 2 or more triglyceride elevations, an event that has been suggested to possibly relate to lipoatrophy, were reported in 5% in XR group as compared with 8% in IR group.

An event that is clearly related to mitochondrial toxicity is lactic acidosis. Several large cohort analyses have indicated that regimens containing d4T, and particularly those combining d4T and ddI, may be the greatest risk regimens for lactate elevation or lactic acidosis. This event however has been reported with all nucleoside analogue based regimens. So-called lactate events included 'symptomatic hyperlactataemia' (reported in two (1%) d4T XR and five (1%) IR treated individuals with one person in each group having lactic acidosis). The median time to presentation of lactate related symptoms was 44 weeks (range 34 - 57 weeks). Pancreatitis was reported in one (<1%) XR and four (<1%) IR patients [2].

In a pilot study of 22 individuals switching from AZT or d4T IR (with 3TC + Efavirenz) to a once daily regimen based on d4T

XR good tolerability over 24 weeks was observed relative to 21 patients continuing their original therapy. One individual in the continuation group experienced virological rebound. One individual in the XR arm stopped d4T XR due to dizziness. No other patients in the XR arm discontinued therapy. No differences were observed between the groups with regards to other clinical adverse events. Differences in laboratory toxicity were not observed. In particular, there were no changes in lactate or fasting lipid values following the switch. DEXA scans and objective evaluations of fat mass were not performed. Adherence, as measured by MEMS caps, did not differ over the first 12 weeks of therapy [3].

Switching d4T to tenofovir

Results of the Gilead GS 903 study suggested a difference in triglycerides and cholesterol existed between d4T and tenofovir when each is combined with 3TC and efavirenz. Patients in the study randomised to the tenofovir group had smaller rises in triglycerides total and LDL cholesterol and greater rises in HDL cholesterol than individuals who received d4T.

These effects were evident at both 48 and 96 weeks and resulted in fewer patients in the tenofovir arm initiating lipid lowering therapy relative to the d4T arm. It has not yet been demonstrated if these benefits are seen when tenofovir is used as a substitution agent for d4T or other nucleoside analogues.

Evidence of the improved safety of tenofovir relative to d4T was reported in a cohort of patients from Spain. Investigators reported data on 94 individuals in whom triglycerides values were available before and after switching. The values were reported non-fasting. Triglycerides values dropped from a mean of 458.11 mg/dl (95% CI 396.73-519.58) at baseline to 278.50 mg/dl (95% CI 248.85-308.15) at 12 weeks ($p < 0.001$). For changes in cholesterol, data were available on 70 individuals with results through week 12.

Cholesterol levels dropped from a mean of 265.73 mg/dl (95% CI 254.98–276.48) at baseline to 230.96 mg/dl (95% CI 220.26 – 241.66) at 12 weeks ($p < 0.001$). No virological rebound was reported after switching to tenofovir. No significant changes in CD4 were observed. The study suggests that randomised controlled investigation of the lipid benefits of tenofovir as a substitution agent for alternate nucleoside analogues is warranted.

Because some studies have suggested that triglycerides elevation in particular may be linked with the lipodystrophy syndrome, investigation of tenofovir in this setting is also warranted. This report from Spain did not provide details of any changes in patient morphology [4].

Abacavir + 3TC: a well-tolerated backbone

Several studies reported at ICAAC looked at the efficacy, tolerability and convenience of administration of abacavir plus 3TC. The pairing of these two drugs is well established from the use in their combination tablet with zidovudine, Trizivir. However, there are also plans for a combination tablet containing just abacavir and 3TC. This tablet has the potential for use as a once daily nucleoside pair.

Two studies combining abacavir and 3TC with efavirenz were reported. The first study CNA30024, compared this combination with AZT/3TC (as Combivir) plus efavirenz in treatment naïve individuals. The study included 324 individuals in the abacavir arm and 325 in the zidovudine arm with a median baseline CD4 cell count of 264/mm³ and a median viral load of 4.79 log.

Over the course of 48 weeks follow-up 13% of abacavir and 15% of zidovudine treated patients discontinued therapy due to an adverse event. The two drugs perform similarly from the efficacy standpoint although the abacavir group experienced a more substantial rise in CD4 lymphocyte count (208.5 cells/mm³) compared with the zidovudine treated patients (154.5 cells/mm³) over 48 weeks.

The most frequently reported grade 3-4 adverse events included rises in liver function tests (3% in each group), nausea (less than 1% and 2% for abacavir and zidovudine respectively), hypertriglyceridaemia (2% in each group), decreased white blood cell count (less than 1% and 2% respectively), and anaemia (0% and 2% respectively).

Events that led to discontinuation in the abacavir arm included abacavir hypersensitivity in 8%, with 2% discontinuing for nausea, 2% for rash and 1% for dizziness. Reasons for discontinuation in the zidovudine arm included anaemia in 4% with a further 3% discontinuing for each of dizziness, nausea and rash.

It is of note that this was a blinded study and initially investigators reported 10 (3%) patients in the zidovudine arm to have experienced the abacavir hypersensitivity reaction. Once the investigators were informed that these individuals were not taking abacavir these cases were adjusted [5]. Details of changes in lipids or assessments of changes in patient morphology were not reported.

The study defines the differences between abacavir and zidovudine. In general, patients initiating abacavir need only concern themselves with the adverse effect of hypersensitivity reaction. If this reaction is not experienced the drug appears to be very well tolerated. With zidovudine a wider range of problems are seen - most commonly anaemia, leukopaenia and nausea. If a simple screening test is established to rule out those individuals most likely to experience the abacavir hypersensitivity reaction one could potentially see the combination of abacavir and 3TC becoming preferred to Combivir.

A second advantage of abacavir and 3TC relative to Combivir is the potential for once daily dosing. This was explored in the

ZODIAC study (CNA30021) - a randomised, placebo controlled trial, comparing abacavir administered once daily with abacavir administered twice daily in combination with 3TC and efavirenz both administered once daily. A total of 384 individuals initiated abacavir once daily and 386 individuals twice daily. Participants had a median CD4 count of 262 cells/mm³ and median viral load of 4.9 log.

No differences in the efficacy were observed between the two dosing schedules of abacavir. Similar numbers of individuals discontinued therapy in each arm and no differences in the frequency of drug-related grade 2-4 adverse events were observed. Abacavir hypersensitivity was diagnosed in 9% of individuals in the once daily and 7% of individuals in the twice-daily abacavir arms. Symptoms at presentation of hypersensitivity also did not differ between arms [6].

Summary

NRTI preference is likely to change over the next few years as we see the appearance of new combination tablets and increasing evidence that combinations based on abacavir or tenofovir had improved tolerability relative to the thymidine analogues. Data presented at this conference indicate that both tenofovir and abacavir are well tolerated and have predictable adverse event profiles. Head-to-head comparisons of regimens based on tenofovir or abacavir are now required.

© Copyright 2002 by HIV and Hepatitis.com. All Rights Reserved. Reproduction for personal or educational use is encouraged and does not require permission. Written permission is required to re-print copyrighted articles but is almost always granted (email publisher@HIVandHepatitis.com).

References

1. Gallant J, Pozniak A, Staszewski S et al for the Study 903 Team. Similar 96-week renal safety profile of tenofovir DF (TDF) versus stavudine (d4T) when used in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral naïve patients. 43rd ICAAC, September, 2003; Abstract H-840.
2. Brett-Smith HM, Reynolds L, Bessen L et al. Two year analysis of stavudine extended-release/prolonged release capsules (XR/PRC) as compared to stavudine immediate-release (IR): efficacy and safety. 43rd ICAAC, September, 2003; Abstract H-855b
3. Portsmouth SD, Osorio J, et al. Once daily stavudine (d4T PRC) versus twice daily stavudine: a comparison of the efficacy, tolerability, safety and adherence. 43rd ICAAC, Abstract: H-842
4. Moreno S, Domingo P et al. Dyslipidemia improvement in patients switching from d4T to tenofovir. 43rd ICAAC, Abstract: H-843
5. DeJesus E, Herrera G, Teofilo E, et al. Efficacy and safety of abacavir (ABC) versus zidovudine (ZDV) in antiretroviral therapy naïve adults with HIV-1 infection (Study CNA30024). 43rd ICAAC, September, 2003; Abstract H-446
6. Gazzard BG, DeJesus E, Cahn P, et al. Abacavir (ABC) once daily (OAD) plus lamivudine (3TC) OAD in combination with efavirenz (EFV) OAD is well-tolerated and effective in the treatment of antiretroviral therapy (ART) naïve adults with HIV-1 infection (ZODIAC Study: CNA30021). 43rd ICAAC, September, 2003; Abstract: H-1722b.

43rd ICAAC: PHARMACOLOGY STUDIES

Interaction between amprenavir and lopinavir thwarts triple PI salvage

David Margolis, NATAP.org

Several studies presented at ICAAC drove home the important lesson that we cannot do without careful testing of novel antiretroviral regimens. Drug interactions on many levels are complex and unpredictable, and the "one from column A and two from column B" approach cannot be depended upon.

Adult ACTG Protocol A5143 was a carefully designed study to test the antiviral effect of combining GW433908 (Fosamprenavir or "908", the better absorbed prodrug of amprenavir nearing FDA approval) with Lopinavir/Ritonavir (LPV/R) in patients with PI resistance. PIs were given in combination with tenofovir plus one or two other nucleoside reverse transcriptase inhibitors (NRTIs).

Kashuba presented the findings of an open-label, steady-state PK substudy, performed in the absence of clear PK data to minimise subject risk. A planned independent interim review was performed after the first eight subjects were randomised to each arm. Surprisingly, both APV and LPV exposures were substantially lower in the double PI arm (LPV 12 hr AUC 92.97 ug/hr/mL (60.3-119.3) versus 48.05 ug/hr/mL (23.5-112.2) triple PI arm, and APV 12 hr AUC double PI 41.77 ug/hr/mL (33.1-55.1) versus 15.2 ug/hr/mL (4.6-41.3) triple PI). Ritonavir exposure was similar in all arms and tenofovir did not account for the lowered PI exposure. This study was closed upon this analysis, and this combination of PIs should be avoided until further data is available.

Arm A (n=8): LPV/R 3caps BID Arm B (n=8): 908/R 700mg/100mg BID Arm C (n=17); LPV/R 3caps BID + 908 700mg BID.

Ref: Kashuba A, Tierney C, Downey G et al. Combining GW433908 (fosamprenavir; 908) with lopinavir/ritonavir (LPV/R) in HIV-1 infected adults results in substantial reductions in amprenavir (APV) and LPV concentrations: pharmacokinetic (PK) results from adult ACTG protocol A5143. 43rd ICAAC, September, 2003; Abstract H-855a.

Source: NATAP.org

ally a well tolerated medication with a low pill burden and demonstrates potent antiretroviral activity. These characteristics

Vitamin C induces P4503A4 and reduces indinavir levels

Simon Collins, HIV i-Base

Douglas Slain and colleagues from University of West Virginia presented results from a diet-controlled longitudinal study PK study that found an interaction between Vitamin C and indinavir.

Seven HIV-negative volunteers were given four consecutive doses of 800mg indinavir every eight hours and baseline indinavir levels recorded hourly after the fourth dose. Following a washout period, Vitamin C was given at a dose of 1 gram/day for seven days with indinavir administration repeated for the last 36 hours. Dosing of Vitamin C and indinavir was separated by several hours.

Results showed a significant reduction on indinavir levels. C_{max} levels were reduced by -20% (p=0.04) and steady state eight-hour AUC by -14% (p<0.05). C_{min} levels were 32% lower from 265 ng/mL to 181 ng/mL although this parameter was not statistically significant (p=0.09).

C O M M E N T

These reduced levels are easily likely to be overcome in combinations where indinavir is used in regimens where it is boosted by ritonavir, and in practice this accounts for the majority of people still using this protease inhibitor.

However, although this study refers to high-dose Vitamin C, 1g doses are available over-the-counter and probably not unusual in people who believe in benefits of Vitamin supplements (ie in prevention of colds and flu). This interaction on a P4503A4 substrate could be just as important for other medications used in treatment and management of HIV metabolised in the same way.

Ref: Slain D, Amsden JR, Khakoo RA et al. 1, Effect of high-dose Vitamin C on the steady-state pharmacokinetics of the protease inhibitor indinavir in healthy volunteers. 43rd ICAAC, Sep, 2003; Abstract A-1610.

Indinavir levels reduced by omeprazole

Simon Collins, HIV i-Base

Indinavir levels were also significantly reduced when coadministered with the proton-pump inhibitor omeprazole. [1] It is generally thought that this would not cause a clinically significant interaction. [2]

The study randomised volunteers to either placebo or 20mg, 40mg of omeprazole for seven days and on day seven added either indinavir 800mg alone or boosted with 200mg ritonavir.

Indinavir 24-hour AUC decreased by almost half from 30.0 mg/hr/mL to 16 mg/hr/mL and 12-hour C_{min} decreased 55% from 82.3 ng/mL to 37.0 ng/mL.

C O M M E N T

This is another interaction that it is important to be aware of. It is not clear why 12-hour C_{min} was measured for unboosted indinavir which is prescribed on TID basis or why the choice of boosted dose of 200mg ritonavir was chosen as this is higher than most patients use due to increased side effects.

References

1. Rublein JC, Donovan BJ, Hollowell SB et al. Effect of omeprazole on the plasma concentrations of indinavir in HIV-negative subjects. 43rd ICAAC, September, 2003; Abstract A-1611.
2. University of Liverpool drug interaction charts.
<http://www.hiv-druginteractions.org/>

Boosted saquinavir PK in once-daily regimens

Simon Collins, HIV i-Base

Marta Boffito and colleagues from Liverpool University investigated steady-state PK of two once-daily boosted saquinavir regimens. Doses studied were 1600mg and 2000mg saquinavir, each boosted by 100mg ritonavir and drug levels were compared to those achieved in the same 18 HIV-positive patients on their original 1000mg/100mg twice daily regimens.

The interest in these possibilities is heightened by a new 500mg formulation of saquinavir that will considerably reduce the pill count.

Saquinavir was given with a 40g-fat meal on day one, then switched to 1600/100mg on day two and switched again on day 12 to 2000/100mg. Intensive PK was measured by HPMC on days 0, 11 and 22.

A summary of PK results are shown below in Table 1 but were skewed by one patient who had a Ctrough of over 3000ng/mL in 2000/100 mg arm. When this patient was excluded from the analysis the trough levels were reduced by 59% in the 2000/100mg once-daily arm compared to 1000/100mg twice-daily. Saquinavir AUC, Cmax and T1/2 increased by 30%, 136% and 29% respectively when excluding the outlier.

Although this is a small data set, trough levels at the 1600/100mg and 2000/100mg doses are clearly reduced compared to twice-daily dosing. Only one patient in each of the once-daily arms had a saquinavir Ctrough below the minimum effective concentration (MEC) target of 50ng/mL for treatment naïve patients.

The authors conclude that the higher drug exposure was driven by higher levels of absorption without evidence of increased toxicity (ALT, AST, glucose, TC and TG) in the short-term. Clearly longer follow-up is required in larger studies before this could be routinely recommended.

Table 1: PK parameters in eight HIV-positive patients

Parameter	Dose: saquinavir/ritonavir; Median (IQR)		
	1000/100 BID	1600/100 QD	2000/100 QD
Ctrough (ng/mL)	569	95	209
Range	138-2226 (250, 1178)	20-635 (57, 192)	31-3128 (100, 529)
Cmax (ng/mL)	2152 (1268, 3321)	2835 (1730, 2631)	4241 (3023, 5902)
AUC0-24hr(ng.h/mL)	28733 (14083, 46076)	17877 (1095, 34166)	31418 (22705, 55292)
t1/2 (hr)	3.31 (2.96, 4.90)	4.62 (4.09, 4.93)	4.47 (4.21, 5.43)

Ref: Boffito M, Dickinson L, Hill A et al. Saquinavir/ritonavir (SQV/r) pharmacokinetics (PKs) in HIV+ subjects: 1000/100mg BD vs 1600/100 and 2000/100mg once daily (OD). 43rd ICAAC, September, 2003; Abstract A-1612.

Tenofovir drug-drug interactions

Paul E. Sax, M.D. TheBody.com

Tenofovir (TDF, Viread) is generally a well tolerated medication with a low pill burden and demonstrates potent antiretroviral activity. These characteristics have led to its widespread use in clinical practice. Unlike other NRTIs, however, tenofovir use is associated with several drug interactions, most notably the reduction in levels of atazanavir (ATV, Reyataz) and an increase in levels of ddl (didanosine, Videx).

The pharmacokinetic studies presented here explore further potential drug interactions related to tenofovir, specifically related to lopinavir/ritonavir (LPV/r, Kaletra), abacavir (ABC, Ziagen) and oral contraceptives.

In the lopinavir/ritonavir study, 27 HIV-negative controls received an initial seven days of tenofovir alone at standard doses; they were then randomized to receive lopinavir/ritonavir both with and without tenofovir. At the end of 14 additional days, they were crossed over to the other treatment arm. Careful pharmacokinetic analyses were performed, and showed no change in lopinavir or ritonavir levels regardless of whether tenofovir was co-administered. In contrast, tenofovir exposure was increased by 32% when administered with lopinavir/ritonavir compared with tenofovir alone.

To explore whether this increase in tenofovir levels was clinically significant, the investigators reviewed renal and other safety data on 271 patients in the tenofovir expanded access programme who also received lopinavir/ritonavir. Five (1.8%) patients experienced serum creatinine changes leading to tenofovir discontinuation, with one developing Fanconi's syndrome with hypophosphatemia; this individual had a similar complication from high-dose adefovir (Hepsera) in the past.

While the data presented provide reassurance that tenofovir does not lead to a clinically significant reduction in lopinavir levels, the issue of lopinavir/ritonavir increasing tenofovir exposure (and possible toxicity) remains unsettled. This will require further analyses in larger populations of patients treated with this combination, controlling for other potential causes of renal dysfunction. In the meantime, patients receiving these two drugs in combination should have their renal function regularly monitored as part of their routine safety laboratories. Furthermore, the combination should be used with caution — and

appropriate tenofovir dose reduction — in those with pre-existing renal disease.

The triple-NRTI combination of tenofovir, abacavir and 3TC (lamivudine, Epivir) has shown surprisingly poor antiviral activity in two prospective studies: a single-arm study presented previously at this year's IAS meeting in Paris, and a comparative study presented at ICAAC. Potential (but still unproven) explanations for this include: 1) a tenofovir-abacavir pharmacokinetic drug interaction; 2) intracellular interaction, such as competition for a critical intracellular enzyme; or 3) low barrier to resistance via the K65R mutation. This pharmacokinetic study explored the first of these potential explanations.

Eight non-HIV-infected volunteers received a single 300-mg dose of abacavir while receiving either no other treatment or tenofovir 300-mg daily. Tenofovir and abacavir concentrations in plasma were measured, with calculated C_{max}, C_{min}, and area under the curve. The results showed that abacavir plasma levels were not affected by tenofovir, and that similarly, tenofovir levels did not differ from historical controls.

The results of this small pilot study suggest it is unlikely that a tenofovir-abacavir drug interaction is the cause of the suboptimal antiviral responses seen in abacavir-tenofovir-3TC treated patients, and that other explanations should be pursued. Furthermore, it enables clinicians to use abacavir and tenofovir together as part of a more comprehensive salvage regimen using other active drugs.

Hormonal contraception is an important and commonly-used medication in women with HIV infection. While tenofovir would not be expected to lead to suboptimal drug concentrations and lower contraceptive efficacy, this study explored this potential drug interaction.

Twenty-four HIV-negative women receiving norgestimate/ethinyl estradiol (Ortho Tri-Cyclen, OTC) were enrolled, with 20 ultimately eligible for pharmacokinetic analyses. OTC drug levels were assessed on study day one, with tenofovir 300 mg started on day 23. On day 29, both OTC and tenofovir pharmacokinetic measurements were repeated. The results showed that time curves for OTC levels with and without tenofovir were virtually superimposable, showing no significant drug interaction. Similarly, tenofovir levels were similar to those observed in prior studies.

The above three studies provide important data on use of tenofovir with three commonly used drugs. The precise mechanism of action accounting for the various tenofovir drug interactions remains under investigation, as does the explanation for the suboptimal response to the abacavir-tenofovir-3TC regimen.

Source: TheBody.com

References

1. Kearney B et al. The pharmacokinetics of abacavir, a purine nucleoside analog, are not affected by tenofovir DF. 43rd ICAAC, September, 2003; Abstract A-1615.
2. Kearney B et al. Pharmacokinetic drug interaction and long term safety profile of tenofovir DF and lopinavir/ritonavir. 43rd ICAAC, September, 2003; Abstract A-1617.
3. Kearney B et al. Tenofovir DF and oral contraceptives: lack of a PK drug interaction. 43rd ICAAC, September, 2003; Abstract A-1618.

Summary of other PK studies

David Margolis, NATAP.org

There were a large number of other PK and interaction studies included at the conference. Summary results are included below but please review the abstract for full details.

- No PK interaction was observed when FTC was administered with tenofovir or zidovudine.
- In a 35-day PK study of tenofovir and Kaletra, PK of lopinavir alone and RTV alone were unaffected by tenofovir. Tenofovir levels increased 32%, there were no serious adverse events reported. (In Study GS-908 TDF Compassionate Access Study (n=296), the incidence of confirmed changes in serum creatinine to >2.0 mg/dl or serum phosphorous <1.5 mg/dl was <1%. Five patients (1.8%; 5/271) experienced serum creatinine changes leading to TDF discontinuation: one patient developed Fanconi's Syndrome (also experienced during prior use of high dose adefovir).
- Indinavir requires acid for absorption. Patients should be cautioned not to use omeprazole with IDV unless IDV/RTV is used. This may be particularly important as proton pump inhibitors may become OTC medicines soon. However, ranitidine or Maalox did not affect levels of the amprenavir pro-drug 908, the investigation pro-drug of amprenavir.
- Atorvastatin has no clinically significant effect on 908. Coadministration of 908, alone or with ritonavir, significantly increases atorvastatin exposure. Atorvastatin doses < 20mg/day should be used with 908 or another statin that is less dependent on CYP3A4 metabolism should be considered.
- Both tenofovir and UK-427857, an investigational antagonist of the CCR5 receptor, do not affect the activity of oral contraceptives
- Coadministration of the lower dose of 250 mg ddl-EC with 400 mg atazanavir and 300 mg tenofovir with food results in adequate ddl exposure. However, atazanavir levels are significantly reduced when given with tenofovir (with or without ddl).

The addition of ritonavir may be required to overcome this, thus presenting challenges to the construction of a simple QD regimen that includes atazanavir.

- Saquinavir/ritonavir 2000/100mg once a day achieves levels close to 1600/100 twice a day, and might be studied for use in patients without PI resistance. However, trough levels at the end of dosing are unacceptably low when 2000/100 is given, particularly so if PI resistance is present.
- The intracellular half-life of the active metabolite of abacavir, carbovir, was reported to be 20.6 hours. This would be sufficient for once a day dosing of abacavir, and suggests that a mechanism other than insufficient intracellular drug concentrations must account for virological failure in recent studies using once a day abacavir/tenfovir/3TC.
- Lopinavir levels were reported from assays of 31 CSF-plasma pairs from 26 HIV-infected individuals taking lopinavir-containing antiretroviral regimens. LPV was detectable in the CSF at concentrations that exceed those needed to inhibit HIV replication.

TREATMENT ACCESS

GARPP requests permission from Boehringer to import generic nevirapine

Polly Clayden, HIV i-Base

The Generic Anti-Retroviral Procurement Project (GARPP) and the Treatment Action Campaign (TAC) Treatment Project have requested permission from the originator company Boehringer Ingelheim for the right to import generic nevirapine to South Africa. Refusal to grant this voluntary licence will lead GARPP and the TAC to apply to the Commissioner of Patents for compulsory licenses through the courts.

This request, made on 26 September, follows previous attempts from the TAC and Medicins sans Frontieres South Africa to obtain voluntary licences for nevirapine since 1999.

The Medicines Control Council (MCC) has already licensed generic nevirapine for use in South Africa and it can be purchased for just over R70.00 per month, compared to R410.00 for a month's supply of Boehringer's *Viramune*. But without Boehringer's permission importing generic nevirapine remains illegal.

Additionally the TAC and GARPP stress that Boehringer's exclusive licence prevents access to new co-formulated antiretroviral pills that can make combination therapy as simple as two pills a day

Ref: TAC Electronic Newsletter 28 September 2003

Global AIDS spending must double by 2005, says gloomy UN

Graham McKerrow, HIV i-Base

Although most countries are increasing spending on combating HIV, the resources that have been earmarked so far are "woefully inadequate", says the United Nations.

Spending is less than half the \$10 billion needed by 2005, and less than a third of the sum required by 2007. The organisation says that doubling resources by 2005 is necessary to tackle the disaster engulfing nations like India, which has the worst epidemic after South Africa.

A meeting of 10 heads of state and government, as well as many ministers and NGO leaders, at the UN's New York headquarters in September concluded that the crisis demanded "drastic action". The meeting heard progress reports from Kofi Annan, the UN secretary general, and the Joint UN Programme on HIV/AIDS, which said the global and national efforts to fight HIV were failing to meet the UN's own basic goals for prevention and care.

A special session of the UN General Assembly (UNGASS) two years ago set goals aimed at reversing the pattern of the pandemic by 2005. Mr Annan said it was "crystal clear" that on current trends none of the targets for 2005 would be met.

About 1 million people with AIDS receive antiretroviral treatment and the target is to treat three million by 2005 – the so-called three by five target – but to do so "we must change the way we think and change the way we act," said Lee Jong-wook, director general of the World Health Organisation.

There are seven million positive people in the Asia-Pacific region and yet more than a third of countries in the region have yet to adopt policies to treat people. Sub-Saharan Africa is the focus of much global publicity about its HIV disaster and yet few countries even have the resources necessary to prevent mother to child transmission. Few countries have introduced anti-

discrimination measures for people with, or at risk of contracting, HIV – measures regarded as essential to effective prevention and treatment.

The secretary general's summary of the meeting concludes: "While acknowledging the formidable obstacles before us, the conclusions of the panel were not pessimistic. We are learning more and more every day about what works, resources are increasing and political leadership is gaining steam. But we must stay on course – and redouble our efforts – to remain true to the [UNGASS] Declaration of Commitment adopted in this room just two years ago."

Link to United Nations statement:

<http://www.un.org/apps/sg/sgstats.asp?nid=516>

Canada decides to lead the way in exempting AIDS drugs from patent laws

David Spurgeon, BMJ

Canada's industry minister says his government will try by Christmas to exempt generic forms of drugs to treat AIDS and other drugs destined for poor countries from patent laws.

His announcement was followed by a statement from the organisation representing Canada's manufacturers of brand name drugs, saying it would help Canada "to show international leadership" in implementing last August's World Trade Organization (WTO) agreement to give poor countries access to cheap generic medicines to treat life threatening diseases such as HIV, tuberculosis, and malaria.

The minister, Allan Rock, warned that reaching this goal would not be easy, but he added: "We'll certainly do our best."

Murray Elston, president of Canada's Research-Based Pharmaceutical Companies, said his group "welcomed the WTO decision to strike a balance between addressing the needs of the poorest countries while ensuring the protection of intellectual property."

Canada's plan comes after a plea by Stephen Lewis, the United Nations special envoy to Africa on AIDS issues (and himself a Canadian) that Canada should show international leadership in making cheap drugs available to poor countries. Mr Lewis, who had earlier criticised brand name firms for resisting the plan, called Mr Rock's announcement a "very significant development."

Some people fear that it will take some time before some Canadian generic drugs can actually be shipped abroad. Jack Kay, president of Apotex, which is based in Toronto and is one of Canada's largest manufacturers of generic drugs, says manufacturers will probably need 18-24 months to apply for approvals from the federal health department, find raw materials, and set up production lines.

However, in the case of the anti-viral drug zidovudine, Apotex already had received government approval for its generic form and was producing it until last year, when the company lost a patent-infringement suit. Thus Apotex says it could probably start producing zidovudine again in a very short time.

The Canadian Generic Pharmaceutical Association said it was "very pleased" that the Canadian government was responding to its request and that of other organisations and individuals to allow Canada's generic drug manufacturers to participate in the WTO's plan.

Critics of the scheme have said that Canadian generic drug manufacturers will be unable to compete with generic drugs produced in India and Brazil. But Mr Lewis says demand for the drugs is rising quickly, and India and Brazil soon will not be able to supply enough. The World Health Organization wants to see three million people in treatment programmes by 2005, including two million people in Africa, where only 50 000 to 75 000 people are being treated now in such programmes. Lewis said he hopes Canada's move would prod other rich countries to take similar steps.

The plan has the support of the prime minister designate, Paul Martin, as well as the present prime minister, Jean Chretien, who is due to retire next February, and his cabinet.

Source: BMJ 2003;327:832 (11 October)

<http://bmj.bmjournals.com/cgi/content/full/327/7419/832-e>

ANTIRETROVIRALS

Atazanavir 'named-patient' access extended in the UK and includes 150mg capsule

Atazanavir, is a once-daily protease inhibitor from Bristol Myers Squibb that was approved in the US in June 2003. The UK

expanded access programme quickly enrolled, and unlike other countries the numbers for the programme were then capped. Access has now been extended through a new Individual Patient Supply (IPS) scheme, which allows doctors to request a drug for any patient who is considered in need. Administration costs are £360 per month – the licensed price is expected to be slightly lower.

Atazanavir is now available in 200mg and 150mg capsules, to enable patients to use a 300mg QD dose boosted with 100mg ritonavir.

Atazanavir is expected to be licensed in the European Union during the first quarter of 2004.

Doctors interested in this programme should contact Dr Ian Hitchcock at Bristol Myers Squibb on 020 8754 3684 or BMS main reception on 020 8572 7422.

Another triple nuke failure: abacavir/ddl/d4T

Simon Collins, HIV i-Base

The suboptimal performance of triple-nucleoside therapy (for Trizivir, and abacavir/tenofovir/3TC, see HTB vol 4 numbers 7 and 8) means that triple-nucleoside therapy is no longer a recommended treatment approach in UK and US treatment guidelines.

Results from this Danish study, reported in the 26 September issue of AIDS, including the triple-nucleoside combination of ddl/d4T/abacavir were similarly depressing and included an unexpectedly high level of side effects.

Comparison arms in the study were saquinavir/ritonavir and nevirapine/nelfinavir, both with AZT/3TC backbone nucleosides. The rationale for the study was to compare triple nucleoside, dual-PI and three-class therapy. In the discussion, the paper recognised that these regimes would not be chosen in 2003 but were options used for therapy in Denmark in 1999 when the study first enrolled.

Sixty treatment naïve patients were randomised to each arm, and although relatively closely matched the triple-nucleoside arm had a higher baseline CD4 count and fewer AIDS diagnoses. Median baseline CD4 and viral load count in the study as a whole was 161 cells/mm³ (range, 0-920) and 5.0 log copies/mL (range, 2.7-6.7).

However, by intent-to-treat analysis at week 48 only 43% of patients in the triple-nucleoside arm achieved viral suppression <20 copies/mL compared to 62% in the saquinavir/ritonavir arm and 69% in the nevirapine/nelfinavir arm. Odds ratio for achieving <20 copies/mL was 0.53 (95%CI, 0.33-0.83) and 0.25 (95% CI, 0.10-0.59) against each arm respectively.

When the analysis was broken down by baseline CD4 and viral load patients with the most advanced HIV disease performed comparatively even worse. Only 20% of patients with baseline CD4 counts <50 cells/mm³ achieved an undetectable viral load.

A particularly high number of patients changed treatment: in 63%, 58% and 45% of the triple-NUKE, dual-PI and three-class arms, predominantly due to toxicity. Grade 4 side effects occurred in 13%, 7% and 12% of these three arms.

Neuropathy was reported in 27% of the patients using abacavir/ddl/d4T, and hypersensitivity to abacavir suspected in 12%. Both these rates are higher than reported in ddl/d4T studies and abacavir studies respectively. Five patients in this arm (8%) had to discontinue due to increased lactate associated with clinical symptoms (abdominal pains, elevated liver enzymes), compared to an expected incidence of 1% in other d4T/ddl studies.

The authors suggested that in this study abacavir was adding to the mitochondrial toxicity associated with ddl and d4T although a convincing mechanism was not suggested.

Ref: Gerstoft J, Kirk O, Lundgren JD et al. Low efficacy and high frequency of adverse events in a randomised trial of the triple nucleoside regimen abacavir, stavudine and didanosine. AIDS 2003; 17(14):2045-2052.

FDA announces changes to ritonavir package insert

Revisions were recently made to the product labeling for Norvir (ritonavir) 100mg soft gelatin capsules and Norvir (ritonavir) 80mg/mL oral solution, marketed by Abbott Laboratories.

The changes address a Phase IV commitment to develop appropriate labeling for patients with hepatic insufficiency. Changes were also made to the Drug Interaction tables, including new information on the co-administration of Warfarin.

Other revisions include minor editorial changes such as renumbering of tables and consolidation of information into specific sections.

Source: NATAP.org

TREATMENT INTERRUPTIONS

Treatment interruption prior to five-drug regime shows no benefit at 48 weeks

Simon Collins, HIV i-Base

When the French GIGA-HAART study reported significant short-term benefits from a two-month treatment interruption (followed by an eight- or nine-drug GigaHAART regimen with PI drug levels optimised by therapeutic drug monitoring) compared to continuous treatment, the study was stopped early. [1] Whether this strategy resulted in longer-term benefit was therefore not established.

In the October 2003 issue of HTB we reported on a recent NIAID study that reported an increased risk of disease progression in patients who took a four-month interruption compared to patients using continuous therapy – and which was widely reported as discouraging any break in treatment.

The 1 October issue of the Journal of Infectious Diseases reports results from a Spanish group that provides additional data on this difficult option. [3]

In this study, Ruiz and colleagues randomised 46 heavily treatment experienced patients to either switch straight to five-drug salvage therapy (Kaletra, Fortovase 1000mg BD, abacavir, ddl, 3TC) (n=24) or to take a 12 week treatment interruption prior to the new five-drug treatment (n=22).

No differences between the groups were seen after six months (when reported at the 9th Retrovirus conference, Abstract 421) and similar responses are reported after one year in the HID paper. At week 48, 45% of patients in the interruption group and 46% of patients in the continuous treatment group had viral loads <50 copies/mL (p=0.619). No differences in CD4 cell counts were seen between groups at week 48 (p=0.734).

A complete reversion to wild-type genotype was detected in 35% of patients in the interruption group, and median genotypic mutations dropped from 10.8–4.8 at baseline to 3.8–4.2 after the three month interruption, but this did not affect the long-term virological response.

However, although this was a highly resistant group, they were also relatively healthy with baseline median CD4 and viral load counts in the interruption group of 383 cells/mm³ (84-783) and 4.3 copies/mL (range 3.2-5.3).

The only overall baseline factor associated with ensuing virus suppression was a lower number of nucleoside reverse-transcriptase inhibitor-resistant mutations (relative risk, 0.66; 95% CI, 0.47–0.93; p=0.021).

In this study an interruption prior to treatment produced no additional benefit to subsequent virological or immunological outcomes of the salvage regimen.

References:

1. Katlama C, Dominguez S, Duvivier C et al. Benefits of treatment interruption (TI) in patients with multiple therapy failures, CD4 cells <200 /mm³ and HIV RNA >50 000 cp/ml (GIGAART ANRS 097). XIV International AIDS Conference, Barcelona 7-12 July. Abstract WePeB5887. See HTB Vol3 No7.
2. Lawrence J et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. The New England Journal of Medicine 349(9):837-46 (2003). See HTB Vol4 No8.
3. Ruiz L, Ribera E, Bonjoch A et al. Role of structured treatment interruption before a five-drug salvage antiretroviral regimen: the Retrogene Study. The Journal of Infectious Diseases 2003;188:977-985

Failure of alternating week-on and week-off therapy

Simon Collins, HIV i-Base

Two recently published studies, each based on different interruption protocols, have both shown disappointing results, with higher rates of treatment failure and development of resistance.

The rationale for these studies was that HAART-induced viral suppression could maintain viral benefit to allow short periods off treatment, with potential benefits of reduced toxicity and cost.

The first study, from NIAID, published in 1 August issue of Journal of Infectious Diseases, looked at the effect of long-cycle structured intermittent therapy (SIT). Treatment interrupted for four weeks followed by eight weeks with HAART was compared to continuous HAART. The study was prematurely terminated to new enrolment because of the emergence of genetic mutations associated with resistance to antiretroviral drugs in five patients. After 48 weeks, there was no significant difference between groups in reduced toxicity. There was also no clear autoimmunisation effect by immunologic or virologic parameters.

Results from the Staccato Study, published as a fast track article in the 17 October issue of AIDS, led to the early termination of one arm of this large international study in which 600 patients (from Thailand, Switzerland, Australia, Argentina and Australia) who were on stable HAART (viral load <50 copies/mL, CD4 >350 cells/mm³) were randomised 1:1:1 to either

alternating one week on treatment with one week off, interrupting treatment and restarting by CD4 count or remaining on continuous treatment.

An interim analysis was performed after 150 patients had enrolled which included 36 patients in the week-on week-off arm with 8-week data. Overall, 19/36 (53%) patients failed using this regimen. Early failures (within 12 weeks) included three out of four patients on triple nucleotides in Switzerland, and in 11 out of 17 patients on ddI/d4T/saquinavir/ritonavir in Thailand. 'Late' failures (after 12 weeks) included two patients on nelfinavir/3TC/AZT, one on saquinavir/ritonavir/d4T and one on nevirapine/3TC/AZT. Of eight patients on efavirenz/3TC/AZT, one has failed.

In the continuous treatment arm of the study, only two failures have occurred so far in 37 patients ($P < 0.001$, compared to the one-week-one-1-week-off). In the CD4-guided arm, no failures occurred in 39 patients. The week-on week-off arm of this study has now been terminated.

1. Dybul M, Nies-Kraske E, Daucher M et al. Long-cycle structured intermittent versus continuous highly active antiretroviral therapy for the treatment of chronic infection with human immunodeficiency virus: effects on drug toxicity and on immunologic and virologic parameters. *Journal of Infectious Diseases* 2003;188:388-396
2. Ananworanich J, Nuesch R, Hirschel B et al. Failures of 1 week on, 1 week off antiretroviral therapies in a randomised trial. *AIDS* 2003; 17(15):F33-F37.

C O M M E N T

On these results, short course interruptions – guided more by cost than benefit regarding toxicity – are clearly ineffective, even allowing for some differences seen between regimens. Long-term interruptions, guided by CD4 count offer a longer benefit from toxicity, but it is unclear whether the cumulative risk from each interruption will prove similar to the week-on week-off arm but extended over many years. Will 50% of people fail after six interruptions irrespective of the time off therapy in between?

Additionally, there may still be utility in alternating, or cycling, regimens without interruption. The SMART study (*Ann Intern Med* 2003; 139:81-89) showed lower rates of viral load failure in the alternating arm compared to the continuous arms (NNRTI based and PI based). This strategy deserves to be investigated further using more contemporary regimens than those in the original study to see if the advantage of alternating holds in a more modern treatment context.

With UK guidelines suggesting that people who started treatment early by 2003, who have benefited from good CD4 recovery but are also experiencing side effects, may safely discontinue treatment and monitor, then the advice in the guidelines to switch to a combination that includes three drugs with similar half lives for the last two weeks of treatment, should also be noted.

METABOLIC COMPLICATIONS

Canadian study shows increased interventional cardiovascular procedures associated with HAART

Sean R Hosein, CATIE

In high-income countries, the availability of highly active antiretroviral therapy (HAART) has greatly decreased the risk of illness from AIDS-related complications. Although HAART can prolong life, it is not a cure. HAART also can have side effects; in some cases, users develop increased levels of fatty substances or lipids (cholesterol and triglycerides) and sugar in the blood. In theory, these changes increase the risk of developing cardiovascular disease (CVD)—heart attacks, strokes and other complications. Certainly if similar changes occurred in HIV negative people, they would have the same effect. But what exactly is the risk of severe CVD in HAART-users? To try to answer this question researcher Paula Braitstein and colleagues in Vancouver, British Columbia, conducted a study. According to their results, about 1% of users of anti-HIV therapy in that province needed surgery for CVD between the years 1995 and 2000.

Types of surgery

Researchers in Vancouver (including the British Columbia Centre for Excellence in HIV/AIDS) reviewed information in large databases on people with HIV/AIDS (PHAs) who had required surgery for CVD. The analysis of information focused between the years 1995 and 2000. During this time, the database of PHAs on therapy contained information on 5,082 people. Of these 5,082 PHAs, only 1% (63) was also registered in provincial cardiac registries during the same years. These 63 PHAs required the following procedures:

- 30 — open heart surgery
- 31 — coronary angioplasty (unclogging of the arteries)
- 36 — diagnostic coronary catheterisations (this involves sticking a thin tube into a vein to the heart and injecting dyes that appear on X-ray pictures that help doctors see clogged blood vessels and how well the heart works)

Among PHAs using HAART, at least half of these procedures occurred since 1999.

Trends

Over time and taking age into account, there was a trend for a steep increase in cardiac surgery after 1997 among PHAs. In contrast, among HIV negative people in British Columbia, the trend for cardiac surgery was generally stable, although there was an increase in the year 2000.

In PHAs, factors that were linked to having cardiac surgery included the following:

- Being older at the beginning of the study: for instance, PHAs who were 45 years old were at significantly greater risk of having CVD surgery than PHAs who were 37.
- Longer time on therapy: PHAs who were on therapy for an average of 4.5 years were significantly more likely to have CVD surgery than PHAs who had been on therapy for three years.

Other factors, such as gender, CD4+ cell count, viral load, number of drugs in an initial regimen, HIV risk group and adherence had no relation to the risk of CVD surgery.

The results of this study support the idea that use of HAART may increase the risk of CVD in some PHAs. Bear in mind that the risk of cardiac surgery (and severe CVD) was low in this study — about 1%. These results also support the fact that the benefits of HAART outweigh the risks.

The Vancouver study would have been strengthened if the researchers had been able to collect information on whether or not recipients of surgery were tobacco smokers or had family members who also had CVD, both of which increase the risk of CVD.

Although the study found a sharply increasing trend for cardiac surgery among PHAs since 1997, this trend may not continue indefinitely. As PHAs and their doctors become more aware of the risks of CVD, they may make use of strategies to help reduce their CVD risk, including dietary changes, regular exercise, programmes for quitting smoking and use of lipid-lowering drugs.

Source: www.catie.ca

Ref: Braitstein P, Yip B, Heath KV, et al. Interventional cardiovascular procedures among HIV-infected individuals on antiretroviral therapy 1995 – 2000. *AIDS* 2003;17:2071-2075.

Copyright 2003 - CATIE Treatment Update. Reproduced with permission. Reproduction of this article (other than one copy for personal reference) must be cleared through the Editor, The Community AIDS Treatment Information Exchange, Suite 420 - 517 College Street, Toronto, On M6G 4A2 Canada <http://www.catie.ca>

OPPORTUNISTIC INFECTIONS

Valacyclovir is effective prophylaxis against herpes simplex

Graham McKerrow, HIV i-Base

Valacyclovir is a more effective prophylaxis than acyclovir against recurrent herpes simplex in HIV-positive people, according to an international placebo-controlled trial.

The study could have significant influence on clinical practice because the researchers conclude that they have established an important treatment option for the management of genital herpes in HIV-positive patients, in the form of a convenient, twice-daily regimen that is well-tolerated.

Intravenous administration of acyclovir has previously been shown to be effective against mucocutaneous herpes in profoundly immunocompromised patients, and oral acyclovir has been shown to suppress genital herpes in a healthy population. Valacyclovir was developed to improve the bioavailability of acyclovir.

Two hundred and ninety-three positive subjects on stable antiretroviral regimens, with histories of symptomatic recurrent genital herpes, were enrolled in the randomised, double blind, placebo-controlled, multicentre trial in the United States, Canada and the United Kingdom.

The trial compared valacyclovir administered at 500mg twice daily with placebo, and was conducted between May 1999 and January 2002. Subjects were randomised in a 2:1 allocation (valacyclovir to placebo) to receive treatment for up to six months.

They were instructed to return to the clinic monthly and at first recurrence of genital herpes. Study drug was discontinued for subjects with clinically confirmed recurrence and they were treated with valacyclovir (1g twice daily) until they were healed. After treatment, they resumed suppressive therapy with open-label valacyclovir.

Of the 231 subjects who completed the study, 89 had a recurrence of genital herpes during the double blind phase of the study: 56/99 (57%) in the placebo group and 33/134 (17%) in the valacyclovir group. The proportion of subjects who had no recurrence of genital herpes at six months was significantly higher in the valacyclovir group than in the placebo group: 65% versus 26% (relative risk 2.5, 95% confidence interval [CI], 1.8-3.5).

The time to first recurrence of genital herpes was a median 59 days in the placebo group, compared with a median >180 days in the valacyclovir group (hazard ratio [HR] 5.0, 95% CI, 3.30-7.7).

Fifteen per cent (15/99) of subjects who received placebo, compared with 4% (8/194) of subjects who received acyclovir, reported a recurrence of oral herpes during the study.

Adverse event rates per exposure day were similar between treatment groups during the double blind phase: 2.2% for the placebo and 2.0% for valacyclovir; and a Kaplan-Meier plot of the time to first adverse event demonstrated a similar incidence in adverse events over time. Three serious adverse events, all in the same subject, were considered to be attributable to valacyclovir.

Fifty HSV-2 isolates were obtained from 48 subjects who had recurrence of genital herpes (but no pretreatment isolates were collected and no HSV -1 was isolated from genital specimens) and acyclovir resistance isolates were identified in three subjects (6.0%), all of whom had CDC stage C HIV disease. Two subjects in the valacyclovir group had a recurrence of genital herpes caused by a resistant isolate after three and 10 weeks respectively, of valacyclovir. One of these had received suppressive antiherpetic therapy, for about one year prior to the study. The third subject, who was in the placebo group but had received suppressive antiherpetic therapy for about four years prior to study entry, had a recurrence of genital herpes caused by a sensitive isolate after four weeks of doubleblind medication and a second recurrence caused by a resistant isolate after about 18 weeks of open label valacyclovir. All three people responded to a five day course of valacyclovir (1g twice daily).

In their discussion, the authors write: "It is believed that most physicians and patients will be reluctant to initiate long-term suppressive therapy for a low recurrence rate of one or two outbreaks per year. A rate of three or more recurrences per year would probably more resemble the use of long-term suppressive therapy in clinical practice. To increase the probability of reaching an end-point in our six-month study, subjects were required to have had a history of four or more recurrences during the previous year. In addition, when considering patients for suppressive therapy in clinical practice, the decision should not be based on the frequency of recurrences alone. The severity of recurrences and the potential for the activation of HIV in this patient group are also important factors."

Ref: DeJesus E, Wald A, Warren T et al. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus infected subjects. *The Journal of Infectious Diseases* 2003;188:1009-1016.

http://www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14513421&dopt=Abstract

<http://www.journals.uchicago.edu/JID/journal/issues/v188n7/30742/30742.html>

C O M M E N T

Although a head-to-head study has not been performed against acyclovir, valacyclovir has several advantages over acyclovir. It requires fewer pills and is potentially more effective, but is also more expensive than off-patent acyclovir.

Valacyclovir is also active against HIV-associated oral hairy leukoplakia (HLP) and Epstein-Barr virus (EBV) - See *Journal of Infectious Diseases*, 2003;188:883-890.

WOMEN AND HIV

Antiviral dynamics and sex differences of AZT and 3TC triphosphate concentrations

Polly Clayden, HIV i-Base

A report in the 17 October issue of *AIDS* investigates intracellular zidovudine triphosphate and lamivudine triphosphate concentrations in HIV-positive individuals, and the associations between these concentrations and patient characteristics and anti HIV activity.

Peripheral blood mononuclear cells (PBMCs) were obtained at multiple planned intervals from antiretroviral-naïve adult

patients enrolled in a study of zidovudine, lamivudine and indinavir, and triphosphate levels were determined by immunoassay and high-performance liquid chromatography and mass spectrometry. Plasma HIV-RNA, CD4 cell counts, and plasma drug concentrations were collected over 18 months.

Triphosphate data were available for 33 patients. The investigators found that the estimated half-lives of zidovudine and lamivudine triphosphate were seven and 22 hours, respectively. They noted that triphosphate concentrations were elevated in individuals with low baseline CD4 cell counts and higher in women than in men by 2.3 and 1.6-fold for zidovudine and lamivudine, respectively.

The investigators reported that women (4/33) reached an HIV-RNA level below 50 copies/ml in half the time that men did (median 56 vs 112 days, $p=0.02$). Of the four women, three were of African descent and there were no differences noted according to race/ethnicity.

They found that zidovudine triphosphate above 30 fmol/10⁶ cells to be independently predictive of time to below 50 copies/ml. Lamivudine triphosphate above 7,017 fmol/10⁶ cells was independently predictive of a sustained virological response ($p=0.0008$ at week 52).

Zidovudine and lamivudine triphosphate concentrations were independently associated with the antiviral activity of zidovudine, lamivudine, and indinavir. The investigators concluded: "The significantly elevated triphosphate concentrations in women and individuals with low baseline CD4 cell counts, groups that historically experience high rates of serious NRTI toxicities, provide a hypothesis for the pathogenesis of these events."

Ref: Anderson PL; Kakuda TN; Kawle S et al. Antiviral dynamics and sex differences of zidovudine and lamivudine triphosphate concentrations in HIV-infected individuals. *AIDS* 2003; 17(15): 2159-2168

Women have a greater immunological response to effective HAART

Polly Clayden, HIV i-Base

A retrospective analysis of data from 53 women and 60 men, published in the 5 September issue of *AIDS*, compared the immunological responses of women to men in patients with suppressed viral load <400 copies/ml at 24 weeks.

Of the patients analysed, 49% were described as African American, 30% Hispanic and 21% Caucasian. Thirty percent of both men and women were antiretroviral naïve. All patients in both groups received combination therapy.

Sixty one percent received a protease inhibitor and two nucleoside analogues; 30%, an NNRTI and two nucleosides and 5% used triple nucleosides.

On initiation of therapy, CD4 counts and viral load were similar in both groups but the mean CD4 count change was much greater in women than in men, 170 cells and 100 cells respectively ($p=0.0074$). Multivariate analysis failed to show any contribution of either the patients' age or initial viral load.

The investigators report: "Our data reveal that, among virological responders, women have a greater response." They report that the reasons for this are unclear and they note: "The larger increase in CD4 T-cells seen in women suggests that significant pathological differences may exist between the two sexes." They add: "Our findings warrant further investigation of the immunological differences between the two sexes."

Ref: Finkel DG, John G, Holland B et al. Women have a greater immunological response to effective virological HIV-1 therapy *AIDS* 2003 17 (13): 2009-2011

MATERNAL HEALTH AND MOTHER TO CHILD TRANSMISSION

Use of rapid HIV tests in labour

Polly Clayden, HIV i-Base

A research letter published in the 26 September issue of *AIDS* describes fast turnaround of point of care testing in labour and delivery using the OraQuick Rapid HIV-1 antibody test recently approved by the FDA.

Four Chicago hospitals, participating in the Mother Infant Rapid Intervention at Delivery (MIRIAD) Study, evaluated the difference in turnaround times between three hospitals where staff performed rapid tests on whole blood samples at point of care and a fourth where tests were performed in the hospital laboratory.

A total of 225 women were tested at the three hospitals offering point of care testing and 155 at the hospital using the laboratory. Standard enzyme immunoassay/western blot was used to confirm 100% of the test results.

The investigators report that the median turnaround time at the three hospitals using point of care testing was 45 minutes (range 30 minutes to two hours 30 minutes) and the hospital using the laboratory the median time was three hours 30 minutes (range 94 minutes to 16 hours) ($p=0.0001$). Turnaround time was defined as being the time that elapsed between drawing the participant's blood and her receipt of the test result.

The investigators concluded: "We found that point of care HIV testing was feasible, accurate and timely. It permitted previously undiagnosed HIV-infected pregnant women to learn their HIV status quickly allowing for the opportunity to administer intrapartum and neonatal antiretroviral therapy, a measure proven to reduce mother to child transmission."

Ref: Cohen MH, Olszewski Y, Branson B et al. Using point of care testing to make rapid HIV-1 tests in labour really rapid AIDS 2003, 17(14):2121-2124

Eighteen-month findings of HIVNET 012

Polly Clayden, HIV i-Base

A report published in the 13 September issue of *The Lancet* indicates that reduction of mother to child transmission achieved with single dose nevirapine at six-eight weeks (as demonstrated in earlier findings in the HIVNET 012 study) was sustained at 18 months follow up with an absolute reduction of 10.1% (95% CI 3.5-16.6) in breastfed babies [1].

Children in the nevirapine arm also had significantly lower risk of HIV transmission - 15.7% versus 25.8% in the zidovudine arm (mothers and babies receiving short course zidovudine prophylaxis) – and a greater probability of HIV free survival, 80% versus 70%.

In a commentary in the same issue Dr Karen Beckerman highlights concerns about the impact of debility of the caregiver on infant and child mortality. She also cautions against the probability of emergence of resistance for the mothers utilising this strategy that could prejudice future treatment options stressing that: "...we must ALL abandon the notion that universally acknowledged principles of antiretroviral therapy do not apply to pregnant women," and she suggests: "Why not modify the HIVNET 012 protocol to forestall the emergence of resistance?"

In her conclusion, she proposes: "Generic antiretrovirals, prepared in convenient single pill triple combinations for once and twice daily dosing are now available for less than US\$1 a day... Suboptimum single-agent and double agent prophylaxis protocols no longer have a justifiable place in the front lines of the global struggle against HIV/AIDS. It is up to all of us to focus on development of equitable distribution and effective use of these agents now. Once they are widely available, it may be too late."

References

1. Jackson JB, Musoke P, Fleming T et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child-transmission of HIV1 in Kampala, Uganda: 18 month follow up of the HIVNET 012 randomised trial. *The Lancet*. Vol 362 Number 9387 859-868. 13 September 2003
2. Beckerman KP. Long term findings of HIVNET 012: the next steps. *The Lancet*. Vol 362 Number 9387. 13 September 2003

PAEDIATRICS

Rituximab as single agent reversed paediatric Non-Hodgkins Lymphoma (NHL)

Simon Collins, HIV i-Base

Several adult studies have suggested that use of the monoclonal antibody rituximab, in addition to chemotherapy, may provide additional benefit in treatment of CD20+ Non-Hodgkins Lymphoma (NHL), although this is also associated with increased toxicity. [1, 2]

A research letter to the 26 September issue of *AIDS* reported a case of remission of HIV-associated paediatric NHL following treatment with rituximab alone. [3]

The 14-year-old congenitally infected girl was highly treatment-experienced having initiated monotherapy shortly after birth and HAART in 1996, with 16 treatment changes due to virological and clinical failure and extensive resistance. Despite combined prophylaxis the patient had HIV-related complications including systemic CMV, cryptosporidiosis, pneumocystosis and candidiasis. CD4 count was 77 cells/mm³ and viral load was 390 copies/mL.

Ultrasonography and CET scan disclosed massive involvement of multiple site visceral nodes with maximum size of 22-30mm and a highly malignant follicular NHL already at stage III-2 was diagnosed by biopsy. A cycle of chemotherapy with MACOP-B regimen only produced a very limited response.

A salvage treatment of four administrations of 375mg/m²/week of rituximab plus antihistaminic premedication was prescribed. A significant reduction in neoplastic bulk was noted after the first four-dose cycle. PET scans four months later showed

suspected residual mediastinal disease and prompted a second month's course of rituximab and lead to a negative PET scan at 10-months post diagnosis with complete disappearance of pathological superficial and visceral lymph nodes.

A further change in HAART (to ddl, d4T, LPV/r) led to a significant increase in CD4 count to 380 cells/mm³ and reduction in viral load to 9,800 copies/mL. The authors report that the patient has since been able to completely resume daily activities including returning to school.

C O M M E N T

Rituximab is now used in a pediatric population, if a tumor is CD20 positive. The normal dose is 375 mg/m² once weekly x four weeks), and combined with CHOP, seems to work well and is well tolerated.

This practice has come from copying adult treatment. The child should be reported with IVIG every other week for at least six months, since the mature B cells will get eliminated with this therapy.

HIV-associated NHL in children is rare it has not disappeared completely even with the introduction of HAART.

References

1. Boue F, Gabarre J, Costagliola D et al. CHOP Chemotherapy plus rituximab in HIV patients with high-grade lymphoma-results of an ANRS trial. 10th Conference of Retrovirus and Opportunistic Infections, Feb 2003. Abstract 805.
2. Tirelli U, Spina M, Bernardi D et al. Rituximab and infusional cyclophosphamide, doxorubicin, and etoposide: a safe and highly active regimen in HIV-related Non-Hodgkin's Lymphoma. 10th Conference of Retrovirus and Opportunistic Infections, Feb 2003. Abstract 804.
3. Manfredi R, Tadolini M, Fortunato L et al. Rituximab alone proves effective in the treatment of refractory, severe stage III AIDS-related non-Hodgkin's paediatric lymphoma. AIDS 2003; 17(14):2146-2148

Perinatal antiretroviral treatment and haematopoiesis in HIV-uninfected infants

Polly Clayden, HIV i-Base

A report from the French Perinatal Study published in the September issue of AIDS found that perinatal exposure to zidovudine might result in a small but significant and durable effect on haematopoiesis up to the age of 18 months.

The French Perinatal Study, established in 1986, prospectively follows infected and uninfected infants born to HIV-positive mothers.

In a longitudinal study, the investigators analysed haematological variables in 4,249 infants from zero to 18 months including haemoglobin, platelets, polynuclear neutrophils, total lymphocytes, and CD4+ and CD8+ lymphocytes. To perform the analysis they used non-parametric smoothing techniques. Modeling of repeated measures and non-linear evolution with age, with models combining natural cubic B-splines and random effects.

The investigators reported a transient reduction in haemoglobin levels in newborns exposed to zidovudine. Multivariate analysis taking into account age, prematurity, geographical origin, maternal drug use and maternal CD4 cell count, indicated that levels of the three other lineages were slightly lower until age 18 months in exposed than in not exposed infants ($p < 0.0001$ for each lineage). They report a negative relationship between the duration of exposure and each haematological variable.

Additionally, combinations of antiretrovirals were associated with larger decreases than zidovudine monotherapy up to 15 months of age. Similar, but less pronounced, patterns were found for the CD4+ and CD8+ subpopulations of lymphocytes.

The investigators concluded: "Zidovudine administered during the perinatal period may result in a small but significant and durable effect on haematopoiesis up to the age of 18 months." They also noted that the clinical consequence of these findings are probably minor or non-existent and: "A more detailed analysis of CD4/CD lymphocyte sub-populations (ie naïve/memory phenotype and function) could be of value as would long term evaluation."

Ref: Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C et al. Perinatal antiretroviral treatment and haematopoiesis in HIV-uninfected infants AIDS 2003, 17(14):2053-2061

HEPATITIS COINFECTION

Coinfected patients may require longer HCV treatment, irrespective of genotype

Simon Collins, HIV i-Base

Recent clinical implications for management of patients with Hepatitis C and HIV coinfection include an opportunity to recognise non-responders at 12 weeks, and therefore reduce exposure to unnecessary treatment, and at the other extreme, that a longer period of treatment may be necessary for others.

Vincent Soriano and colleagues presented further important data on response rates for 89 coinfecting Spanish patients who completed a course of PEG interferon plus ribavirin at standard doses.

Although 58% patients achieved >2log reductions in HCV viral load by week 12, only half of these patients achieved a sustained virologic response (SVR). None of the patients who had less than a two log drop at week 12 achieved an SVR.

Relapses occurred in 19 - almost one third - of the 58 patients who had negative HCV RCR at the end of the treatment period, and there were no significant differences in response between patients with genotype 2/3 and genotype 1/4.

The authors commented that the 100% negative predictive value for non-responders was previously reported in HCV monoinfected patients and could be used to discontinue a difficult to tolerate treatment. The higher relapse rate compared to monoinfected patients, particularly those with genotype 2/3 who rarely rebound, prompted the suggestion to extend treatment from six to 12 months in coinfecting patients with genotype 2/3 and from 12 to 18 months for those with genotype 1/4.

Ref: Soriano V, Perez-Olmeda M, Camino N et al. Clinical implications of the slower clearance of HCV-RNA under Interferon (IFN) plus ribavirin (RBV) in patients coinfecting with HIV and Hepatitis C virus (HCV). 43 ICAAC. Abstract H-1718.

C O M M E N T

This study highlights, as have studies with singular HCV infection, the reliability of early virological response (EVR) in predicting end of therapy responses (ETR) and sustained responses (SR). EVR is defined as an undetectable HCV-RNA or >2 log drop in HCV-RNA levels 12 weeks after starting therapy.

It is of note that despite EVR only half of these patients went on to achieve SRs and that 33% of patients with an ETR had a relapse on stopping therapy. The length of therapy was 24 weeks for genotypes 2/3 patients and 48 weeks for genotype 1 patients. The high relapse rate may be as a result of viral sanctuary sites or emergence of 'escape' quasispecies. If the former is true then extending treatment beyond the standard 24 or 48 weeks may be helpful in reducing relapse rates, as suggested by the authors.

The answer to this question, in part, may come from the currently ongoing Apricot study, which is due to report initial results early next year. In this study all patients irrespective of genotypes have received 48 weeks of therapy.

OTHER NEWS

New recommended standards of care for NHS services

Graham McKerrow, HIV i-Base

A 116 page document outlining standards for HIV services in the National Health Service was published in October by the Medical Foundation for AIDS and Sexual Health (MedFASH).

They are the first nationally agreed standards for England and have been endorsed by the Department of Health, the British HIV Association and the National Association of NHS Providers of AIDS Care, who all contributed to the funding of the recommendations. The standards have been compiled after consultations lasting two years.

The detailed standards cover HIV prevention, strategies for the early diagnosis of HIV infection, empowering people with HIV, access to specialist care and support services, local primary healthcare, integrated health and social care, comprehensive sexual health care for positive people, empowerment and support for pregnant women with HIV, adult and paediatric multidisciplinary care for children, families and their carers, in-patient care, and respite, rehabilitation and palliative care for people with HIV.

The recommended standards are aimed as guidance for service providers, commissioners and users of the NHS.

Dr Patrick French, a member of the government's Independent Advisory Group for sexual health and HIV, and chair of the expert group which helped develop the standards, said "About a third of people living with the virus do not even know they are infected and risk severe illness if not diagnosed. They may present with symptoms in a variety of healthcare settings, such as primary care or A&E. The recommended standards should help healthcare staff in such settings to work together with HIV specialists, and to access appropriate training and support through HIV service networks."

The full recommendations can be downloaded as a pdf file from:

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

Vatican says HIV can pass through condoms

Graham McKerrow, HIV i-Base

Unbelievably, the Vatican is telling people across four continents that condoms do not stop HIV because they are full of holes, according to a Panorama documentary broadcast on BBC1 TV in October. Some priests even say condoms are 'laced' with HIV.

Cardinal Alfonso Lopez Trujillo, president of the Vatican's Pontifical Council for the Family, told the programme in a filmed interview: "The AIDS virus is roughly 450 times smaller than the spermatozoon. The spermatozoon can easily pass through the 'net' that is formed by the condom. These margins of uncertainty ... should represent an obligation on the part of the health ministries and all these campaigns to act in the same way as they do with regard to cigarettes, which they state to be a danger."

The World Health Organisation has countered the Vatican's claims, calling them "incorrect" and "dangerous". The WHO says condoms can break or slip off but there are not holes through which the virus can pass. It says "consistent and correct" use of condoms cuts the risk of infection by 90%.

A scientific research group that included the WHO and the US National Institutes of Health, carried out research that found that "intact condoms are essentially impermeable to particles the size of STD pathogens including the smallest sexually transmitted virus".

Cardinal Trujillo dismissed the evidence, saying: "They are wrong about that ... this is an easily recognisable fact."

Panorama found the Vatican's advice repeated by Raphael Ndingi Nzeki, the archbishop of Nairobi, Catholic nuns and church leaders around the world. Gordon Wambi, the director of an HIV clinic in Lwak, near Lake Victoria, told the programme that the church had prevented him distributing condoms. "Some priests have even been saying that condoms are laced with HIV/AIDS," he said.

The Catholic Church has consistently condemned the use of condoms whether for use as contraceptives or for health protection.

More than 40 million people have HIV, most with no access to treatment.

Links

Transcript and online (RealAudio) access to Panorama

<http://news.bbc.co.uk/1/hi/programmes/panorama/3147672.stm>

UN Statement:

<http://www.un.org/apps/news/story.asp?NewsID=8534&Cr=&Cr1=>

ON THE WEB

Conferences and guidelines:

AIDS Vaccine 2003 Conference

September, New York, USA

The abstracts and posters for this conference are available at:

<http://aidsvaccine2003.org/2003/Files/glance.htm>

43rd ICCAC

For further coverage see the following sites.

HIVandHepatitis.com:

<http://www.hivandhepatitis.com>

The Body.com:

<http://www.thebody.com/confs/icaac2003/icaac2003.html>

NATAP:

<http://www.natap.org>

Medscape (requires one-time free registration):

<http://www.mescape.com>

Clinical care options:
<http://clinicaloptions.com/hiv/>

Newsletters and reports:

PRN Notebook – September 2003

Articles from the September 2003 issue of The PRN Notebook in both HTML and PDF formats are available online. Simple, free, one-time registration required.

<http://www.prn.org>

To switch or not to switch—when is it a question?

Steven Deeks, MD

An excellent article looking at data on clinical benefit for patients who are unable to construct a maximally suppressive regimen and who maintain >0.5 log below baseline, to continue a protease-containing but failing regimen. Explained largely by resistance and its effect on replicative capacity, and then virulence.

Also discussed is the more recent finding that PI-resistant induced decreases in replicative capacity may continue after discontinuation of PIs, allowing use on dual nucleoside therapy, and the use of complete and partial treatment interruptions to reduce further development of resistance rather than to promote a return to wild-type virus. Essential reading.

Feasible primary HIV infection screening: the North Carolina experience - Christopher D. Pilcher, MD

Transmission of drug-resistant HIV - Viviana Simon, MD, PhD

When two infections are better than one: the exceptional role of GB Virus-C in HIV disease - Hans L. Tillmann, MD

TAGline - October 2003

<http://www.thebody.com/tag/oct03/contents.html>

The diabolic science: VaxGen's claims of vaccine efficacy evanesce in Autumn's last light - Richard Jefferys

Medi Gap: congressional juggling of medicare drug coverage leaves many in the lurch - Letter to President Bush by William E. Arnold, Mark Harrington and A. Cornelius Baker

TAGline - September 2003

<http://www.thebody.com/tag/sept03/contents.html>

Rx Americas: antiretroviral therapy in Latin America: A good plan is hard to find - Richard Stern

Tragical realism: treatment coverage for selected countries - Richard Stern

ACTing UP for treatment access in Latin America - Richard Stern

Second shoe: Doha report - Anne Christine d'Adesky

HIV inSite Knowledge Base

Critical Care of Patients with HIV

Kristina Crothers, MD, and Laurence Huang, MD.

<http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-03-01>

Community-Based Care in the Developing World: Related Resources

Material on international community-based care programs.

<http://hivinsite.ucsf.edu/InSite?page=kbr-03-03-07>

HIV and hepatitis coinfection:

Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C.

http://www.natap.org/2003/sept/093003_10.htm

This is the study of 3,000 patients receiving one of 10 IFN based regimens assessing impact of PEG-IFN/RBV in fibrosis and activity in responders and nonresponders, and cirrhotics.

The findings are interesting and were reported in Gastroenterology. This report contains tables and charts from the published study.

PUBLICATIONS AND SERVICES FROM i-BASE

NEW: Guide to HIV, Pregnancy and Women's Health- November 2003

This patient guide aims to help 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.

To order copies, see below

NEW: Guide to Changing Treatment: second-line and salvage therapy

We have updated our non-technical patient guide 'Changing Treatment: a guide to second-line and salvage therapy', which is being distributed with this issue of HTB.

The guide is fully revised to reflect recent changes in UK and US treatment guidelines.

For additional free copies, including bulk orders, see below.

NEW: Introduction to Combination Therapy

In October 2003 we updated our essential, non-technical patient guide to treatment, 'Introduction to Combination Therapy', which 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.

To order copies, see below.

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.

The programme, reading material, reports and PowerPoint slides from the presentations from the sixth meeting, held on 8 August, are posted to the i-Base website.

This meeting focused on reports from the Resistance, Lipodystrophy and IAS Conferences.

In the afternoon session the CAB met with GlaxoSmithKline.

<http://www.i-base.info/ukcab/aug03/index.html>

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

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 techniques - Dr Leila Frodsham

Access to treatment for UK visitors, refugees and asylum seekers - Linda McDonald

TB and HIV coinfection - Dr Anton Pozniak

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

Treatment 'Passports'

These popular, handy booklets are for HIV-positive people – whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Such a record is useful when talking to different health care workers, changing clinics or changing treatments. Like all i-Base publications, it is available free as single copies or in bulk for volunteers and professionals to distribute to clients. Copies can be ordered using the form on the back page or by visiting our website (details below).

Guide to Avoiding and 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.

French, Spanish, Italian and Chinese translations of this booklet are also available. To order copies, see below.

The i-Base web site

Our web address is

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

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

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

Positive Treatment News (PTN)

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

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

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published 10 times a year in a printed version, in a pdf file that we can email to you, and on our website:

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

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

Treatment information request service – 0808 800 6013

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

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

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

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

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

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

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

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

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

h-tb

HIV Treatment Bulletin

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:

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

by sending an email to:

subscriptions@i-base.org.uk

or by fax or post using the form on the back page.

Editor in Chief: Paul Blanchard

Editor: Simon Collins

Associate Editor: Graham McKerron

Commissioning Editor: Polly Clayden

Medical Consultants:

Dr Sanjay Bhagani, Royal Free Hospital, London.

Dr Karen Beckerman, Bellevue Hospital, New York.

Dr Gareth Hardy, Royal Free Hospital, London.

Dr Saye Khoo, University of Liverpool Hospital.

Prof. Clive Loveday, International Laboratory Virology Centre.

Dr Graeme Moyle, Chelsea & Westminster Hosp, London.

Dr Stefan Mauss, Düsseldorf.

Dr Stephen Taylor, Birmingham Heartlands Hospital.

Dr Gareth Tudor-Williams, Imperial College, London.

HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments.

Some articles are reproduced from other respected sources and copyright for these articles remains with the original authors and sources, as indicated at the end of each article.

We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We also thank them for permission to distribute their excellent work and we encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

Articles written and credited to i-Base writers, as with all i-Base originated material, remains the copyright of HIV i-Base, but these articles may be reproduced by community and not-for-profit organisations without individual written permission and reproduction is encouraged. A credit and link to the original author, the HTB issue and the i-Base website is always appreciated.

HIV i-Base
Third Floor East
Thrale House
44-46 Southwark Street
London SE1 1UN
T: +44 (0) 20 7407 8488
F: +44 (0) 20 7407 8489

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

HIV i-Base is a registered charity no 1081905 and company reg no 3962064. HTB is also known as DrFax

HIV i-Base

Third Floor East, Thrale House, 44-46 Southwark Street, London SE1 1UN
T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489



Subscription Fax-Back Form

Name: _____ Position: _____

Organisation: _____

Address: _____

Tel: _____ Fax _____

E-mail: _____

Office use:

HIV Treatment Bulletin (HTB) by Email (PDF format) by Post

HIV Treatment 'Passports' - Booklets for patients to record their own medical history

1 5 10 25 50 100 Other _____

Guide To HIV, Pregnancy and Women's Health (November 2003)

1 5 10 25 50 100 Other _____

Introduction to Combination Therapy (October 2003)

1 5 10 25 50 100 Other _____

Also available in FRENCH, ITALIAN, SPANISH, PORTUGUESE, CHINESE, and GREEK
as pdf files on the i-Base website

Changing Treatment - Guide to Second-line and Salvage Therapy (November 2003)

1 5 10 25 50 100 Other _____

Guide To Avoiding and Managing Side Effects (August 2002)

1 5 10 25 50 100 Other _____

Also available in SPANISH as a print version and in FRENCH, SPANISH, ITALIAN, CHINESE
as pdf files on the i-Base website

Positive Treatment News (PTN) from Winter 2003

1 5 10 25 50 100 Other _____

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

1 5 10 Other _____

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

1 5 10 Other _____

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

020 7407 8489 (fax) subscriptions@i-Base.org.uk

h t t p : / / w w w . i - B a s e . i n f o