HIV-treatment bulletin

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HIV i-Base TREATMENT bulletin.5

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TREATMENT ALERT - Further safety warnings issued over abacavir

XIIIth International AIDS Conference

Durban, South Africa, 9 – 14th July 2000

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TREATMENT ALERT

The following warning letter was issued by Glaxo Wellcome Inc, Triangle Park , USA on 27 July 2000.

IMPORTANT DRUG WARNING

RE: Severe Hypersensitivity Reactions following reintroduction with ZIAGEN® (abacavir sulphate) Products

Dear Health Care Provider,

Glaxo Wellcome Inc. is writing to inform you of important new safety information about hypersensitivity reactions to abacavir, a nucleoside analogue reverse transcriptase inhibitor which, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection. Fatal hypersensitivity reactions are a described risk associated with the use of abacavir (Ziagen); patients who have developed hypersensitivity reactions upon abacavir rechallenge are at an increased risk of a hypersensitivity reaction, which may result in death.

Recent reports indicate that **severe of fatal hypersensitivity reactions can occur within hours after ZIAGEN reintroduction in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy.** In these reports:

- Hypersensitivity to abacavir was not recognised before abacavir therapy was interrupted.
- Most of these hypersensitivity reactions were indistinguishable from hypersensitivity reactions associated with abacavir rechallenge: short time to onset, increased severity of symptoms, and poor outcome (including death).
- Reasons for discontinuation of abacavir included interruption in drug supply and discontinuation of abacavir while treating other medical conditions.
- Severe or fatal hypersensitivity reactions occurred upon reintroduction when abacavir was discontinued for reasons unrelated to symptoms of hypersensitivity. In some cases, symptoms consistent with hypersensitivity may have been present before abacavir was discontinued, but may have been attributed to other medical conditions (for example, acute onset respiratory diseases, gastroenteritis or reactions to other medications).
- Hypersensitivity reactions occurred days to weeks following abacavir reintroduction in a minority of reports.

If abacavir has bee discontinued for reasons other than symptoms of hypersensitivity, and if reinitiation of Ziagen therapy in under consideration:

- The reason for a discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity is suspected, abacavir should **NOT** be reintroduced.
- If symptoms consistent with hypersensitivity are not identified, reintroduction should be undertaken with caution. Patients should be made aware that a hypersensitivity reaction can occur upon reintroduction of abacavir, and that reintroduction should be undertaken only if medical care can be readily accessed by the patient and others.

Please read the enclosed package insert for revisions in the **BOXED WARNING, WARNINGS, ADVERSE REACTIONS, PRECAUTIONS: Information for Patients** and patient **Medication Guide.** This information is provided to help you in the management of patients prescribed Ziagen Tablets or Ziagen Oral Solution.

Glaxo Wellcome is committed to providing you with the current product information for the management of your patients being treated with ZIAGEN. You can assist us in monitoring the safety of ZIAGEN by reporting adverse reactions to the Glaxo Wellcome Product Surveillance Department at 1-888-825-5249 or to the FDA MedWatch program by telephone at 1-800-332-1088, by FAX at 1-800-332-0178, via www.FDA.gov/medwatch, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Please refer to the enclosed revised prescribing information for ZIAGEN, If you have questions about the new information or want additional medical information about ZIAGEN, please contact the Glaxo Wellcome Customer Response Centre at 1-888-TALK2GW (1-888-825-5249).

Sincerely,

Marc Rubin, M.D.
Vice President, Therapeutic Development and Product Strategy
HIV, Infectious Diseases, and Hepatitis
Glaxo Wellcome Inc

C O M M E N T

According to Glaxo Wellcome (UK) this warning was based on 7 case reports in the US from patients who had interrupted abacavir-containing regimens for reasons other than hypersensitivity reaction. Two of these patients had been treated with abacavir for more than 6 weeks (one for 6 months, interrupting treatment for 3 weeks, the other for 5 months, interrupting treatment for 1 month).

Two of the reports were not accompanied by detailed histories but one of these was also believed to have been treated for long enough to be outside the normal hypersensitivity window period. The other three patients were still within this initial 6 week period when they interrupted treatment. They had received treatment for 4 days, 1 week and 4 weeks, interrupting treatment for 10 days, 2 weeks and 4 days respectively.

All hypersensitivity reactions in these patients resolved without fatality. A single case (not included in this group) with a fatal outcome was not associated with abacavir. This patient presented with pneumonia and SJS and was being treated with a multi-drug abacavir-including regimen.

All these cases had been reported to the CPMP who are now reviewing the data with the Glaxo Wellcome, but no action so far has been recommended in Europe.

Further guidance on management of patients taking abacavir is urgently needed and for the sake of patient safety we implore the CPMP and national pharmacovigilance agencies to look carefully at these new reports. If hypersensitivity can indeed develop without noticeable symptoms then for all patients any treatment interruption followed by reintroduction of drug must be undertaken with extreme caution and close monitoring.

The risk benefit ratio for the use of this agent in those with other antiretroviral options and who are not in immediate danger of disease progression should also be urgently reassessed and considered in any licensing decisions.

XIII International AIDS Conference

Durban, South Africa, 9 – 14th July 2000

The setting of this conference in South Africa, a country with more HIV-positive people than anywhere else in the world made it hard for us to ignore its context and merely concentrate on the scientific data. We were certainly not alone, indeed at the closing address; Stefano Vella described the conference as 'less of a clinical meeting and more of a political one' and spoke movingly about upholding their decision to hold it in Durban despite some opposition, 'mainly from those who are not here'.

It was a week of uplifting, eloquent, angry and emotional (and not so great) speechmaking. At the opening address President Mbeki successfully skirted round the practical issues and necessary interventions to combat AIDS and talked at length about poverty.

Undeniably, poverty aids the spread and inadequate treatment of disease, including HIV. Poverty produces conditions which facilitate the spread of the virus and makes currently available antiretrovirals a difficult, if not impossible, option. Prevention campaigns cannot succeed when poverty focuses the mind on the here and now, the next meal. Planning for the future becomes an impossible luxury. Poverty prevents access to treatments through lack of infrastructure, lack of a means to pay for treatments, and the public health and social difficulties which follow limited interventions.

The UNAIDS announcement of free supplies of nevirapine to reduce mother-to-child transmission was welcomed by many. But who will pay and care for the additional hundreds of thousands of babies saved from HIV-infections whose mothers remain untreated and condemned to certain disease and death. Intimacy with the struggles and peculiarities of the African situation allowed Mbeki to hint at the complexities and seemingly insurmountable barriers to alleviating the impact of AIDS in Africa. Complexities often overlooked by those demanding uncompromising access to treatment.

Concentrating on the wider issues has a tendency, however, to paralyse action. Action, which on an individual level can be immensely important. This perhaps is Mbeki and the South African governments dilemma.

Mbeki also neither defended nor refuted his recent interest in dissident theory disappointing many. 'One bullet, one dissident' declared one rather unambiguous slogan, displayed at a demonstration prior to the conference demanding more government action. Here it was particularly heartening to see important US treatment activists from TAG and Project Inform reclaiming their grassroots and marching with placards. And, although perhaps with motives that were not entirely spotless (two fingers to the government?), we heard Winnie Mandela's words much lacking from her compatriot's speech, 'HIV causes AIDS'.

In his closing address Nelson Mandela, speaking to a packed auditorium, commented that those infected must 'wish that the dispute be put on the back burner', and wisely pleaded for a 'move from rhetoric to action' to stop the 'terrible scourge of AIDS'.

Mother-to-child transmission, maternal health and women's access to care

Durban Reports by Polly Clayden, HIV i – Base

Mother-to-child-transmission

This was not a meeting that could be criticised for it's lack of women-specific research and the overwhelming majority of this dealt with the issue of mother-to-child transmission (MTCT) and prophylactic interventions. The subject provoked much heated debate and polarised opinion – from a triumph of HIV prevention to a callous disregard for the mothers' own health.

More than anything this issue underlines the vast disparity between north and south. While in the US use of words like elimination are now used in the context of vertical transmission [2] and the PACTG 316 trial is forced to stop because of it's extremely low transmission rate [3], in the developing world rudimentary programmes are only just beginning to be implemented. Hopefully much that is currently being mooted will form some important first steps (resistance notwithstanding) and not a complete solution.

We learnt that the Gates Foundation is about to donate millions (or is it billions?) of dollars to preventing MTCT and although babies are undoubtedly far more magnetic to philanthropists than adults (of both genders), this news sat uneasily among sessions addressing another major topic for the meeting – orphans. Perhaps a more utopian goal would be that of Treatment Action Campaign's slogan - 'Treat all HIV+ women'

HAART > ART > monotherapy > none

Two MTCT studies with a particularly clear message for industrialised nations with access to antiretrovirals were presented. Dr Karen Beckerman's group conducted a retrospective analysis entitled The impact of combination therapy on maternal health and pregnancy outcome of all the 99 known HIV-1 infected mothers and their infants born at San Francisco General Hospital and Moffit Long Hospital from January 1994 - December 1999 [4].

CD4 T-cell counts at baseline and delivery were available

for 71 mothers and viral load for 41 for their analysis. Prior to the use of combination antiretroviral therapy (ART), the mean CD4 count for the population dropped 39 cells/mm^3 from baseline to delivery. By 1997-9, 46 of 52 mothers elected to take 2, 3, or 4 drug combinations, resulting in a reduction of maternal viral load to undetectable in 26 and by an average of 1.5log10 copies/ml in the remaining 20.

Virological response improved amongst the mothers who used 3 drugs (HAART) 14/ 20 (70%) achieved an undetectable viral load compared with 11/33 (33%) mothers using two antiretrovirals or less. A mean CD4 gain of +102 cells/mm3 (P=0.043) was observed among treated mothers. Babies born to mothers who took two or more antiretrovirals during pregnancy were significantly less likely to be born before 37 weeks gestation (P=0.018) and showed a trend toward lower rates of low birth weight (P=0.18) when compared with mothers who had no antiretrovirals or zidovudine prophylaxis alone. Increasing maternal antiretroviral use was associated with a decline in vertical transmission. Overall the Caesarean section rate was 19%.

Length of rupture of membranes for greater than four and greater than 24 hours was significantly correlated with transmission (0 at <4 hours, 11% at 4-24 hours and 25% at >24 hours); however, this correlation was not evident among mothers receiving combination antiretroviral therapy during the antepartum period.

Of the six infants that were infected, 3 in 1994-96 were born to mothers who received either no therapy or zidovudine alone, and 2 to mothers who received either no prenatal care and were not identified in labour or 1 prenatal visit who was delivered by Caesarean section in 1997-99.

The investigators found combination antiretroviral therapy during pregnancy to be 'practical, feasible, well tolerated and beneficial... We conclude that combination antiretroviral therapy of maternal HIV-1 disease during pregnancy provides significant and life-saving benefits to both mother and baby'.

To further substantiate this, a large retrospective analysis from the Women and Infants Transmission Study (WITS) conducted at six sites in the US, collected data from 1492 mother and infant pairs over a decade prior to September 1999 [6]. This study set out to evaluate the effectiveness of potent antiretroviral therapies on reducing perinatal transmission of HIV-1 looking at the effect of antiretrovirals on viral load at delivery and the effects of different viral loads on MTCT.

Uninfected infants were defined as having no positive and at least 3 negative tests (the first at one month or over). Of the women that transmitted, antiretroviral use was described as follows: none 391 (26%); ZDV monotherapy (prior to 4/15/94) 206 (14%); ZDV monotherapy (after 4/15/94) 529 (36%); Multi-ART-defined as 2 NRTIs/and or NNRTI but without PIs 179 (12%); HAART- defined as any 3 drug or more combination including PIs 187 (12%). The transmission rates for each group were 80 (20.5%); 40 (19.4%), p=0.76; 41 (7.8%), p=0.01; 7 (3.9%), p=<0.01 and 2 (1.1%), p=<0.01 respectively.

Transmission rates were also stratified according to maternal viral load - at plasma HIV-1 RNA levels at delivery of >100,000 (122 women); 40,000 –100,000 (133 women); 3,000 – 40,000 (549 women); 400 – 3,000 (284 women); undetectable ie. <400 (216 women) with transmission rates of 38 (31.2%), p<0.01; 28 (21.0%), p<0.1; 62 (11.3%), p<0.01; 18 (6.3%), p<0.01; and 2 (0.9%), p<0.01 infected infants respectively.

Use of more complex therapy was associated with reduced rates of transmission and use of complex therapy was associated with reduced maternal viral load. On multivariate logistic regression analysis both increased complexity of antiretroviral therapies and reduced maternal viral load were associated with decreased vertical transmission. The investigators concluded that HAART>Multi-ART>ZDV>None.

d4T and ddI — New anti-retroviral options to prevent MTCT?

Amid many presentations showing the feasibility of interventions using ZDV/3TC or nevirapine for reducing MTCT in the developing world, one study looked at use of the (previously un-researched in this setting) nucleosides ddI and d4T. This research offers mothers and clinicians other possible antiretroviral options for reducing vertical transmission in resource poor populations.

Dr Glenda Gray's group aimed to evaluate the efficacy, safety, tolerability, and PK of oral d4T vs. ddI vs. d4T plus ddI vs. ZDV in HIV-1 infected mothers for the prevention of vertical transmission to their (formula-fed) infants [7]. 204 pregnant HIV-1 infected antiretroviral naive women from South Africa who were at weeks 34-36 gestation were randomised to oral prepartum and intrapartum treatment of either d4T, ddI, d4T/ddI, or ZDV, followed by 6 weeks of oral postpartum therapy of the same drug to their babies. This was an interim analysis of this ongoing study.

At six weeks the analysis of 197 women revealed transmission rates that were 4.2%; 1.9%; 2.0% and 6.3% in the d4T; ddI; d4T plus ddI and ZDV arms respectively. An intention-to-prevent analysis including all lost to follow up and infant mortalities showed 8.3%; 3.8%; 10% and 14.3% an overall average of 9%. 17% of women had an viral load of<50 copies/ml and 35% of <400 copies/ml at birth.

No significant treatment related adverse events were observed in either mothers or their babies. There is yet no resistance data for these strategies but they will be reported in the forthcoming final analysis.

Breastfeeding

There is still no clear consensus on the risk/benefits breast vs. formula feeding despite the number of presentations devoted to this topic. The most shocking findings on this subject, were reported by Dr Ruth Nduati collected from her randomised clinical trial to determine

the impact of breastfeeding on mortality in a group of HIV-1 infected women attending clinics in Nairobi [8].

425 women were randomised to either formula or breastfeed (212 in the breastfeeding arm and 213 in the formula feeding arm). 18 mothers from the breastfeeding arm and 6 from the formula arm died during follow up. At 24 months the probability of maternal death was 10.5% in the breastfeeding arm and 3.8% in the formula arm (p=0.02). 69% of the deaths in the breastfeeding arm were attributed to breastfeeding. Overall there was a threefold increased risk of maternal mortality associated with breastfeeding.

Findings from the PETRA trial attributed a significant number of cases of vertical transmission to breastfeeding in a cohort (70% breastfeeding population) receiving prophylaxis regimens [9]. 1754 HIV-infected women were randomised to one of the following arms: a] ZDV/3TC initiated at week 36 of pregnancy, then intrapartum and for both mother and baby for one week after delivery; b] ZDV/3TC intrapartum and one week after delivery – mother and baby; c] ZDV/3TC intrapartum only and placebo.

For both arms a] and b] transmission was reduced significantly at 6 weeks compared to placebo: 9.2%; 12.6% and 19.2% respectively and arm c] was no different from the placebo (18.4%). By 18 months no significant difference was found between arms - a] 20.7%; b] 24.4%; c] 25.7%; placebo 26.6%.

Note: 24 week data was presented at Durban by which time the placebo arm was discontinued (in December 98 after the publication of the Thai data [10].

The investigators are analysing the timing of the HIV-infection transmission at 6, 9 and 12 month of the babies' life. They hope to then develop feasible strategies to overcome this.

Finally one study presented a method by which HIV-infected women may express and pasteurise their breast milk in a domestic setting [11] Called Pretoria Pasteurisation it uses the principle of passive heat transfer and simple and inexpensive apparatus. This method resulted in undetectable levels of HIV-1 virus in expressed breast milk and research into this novel strategy is ongoing.

Resistance

Resistance data was presented from the PACTG 316 trial [12] - to evaluate the efficacy of nevirapine vs. placebo to reduce mother-to-child-transmission, for women also receiving open label antiretrovirals (not including NNRTIs). The nevirapine resistance mutation K103N was detected in 4/32 of women with viral loads >3000 and 3 women also had resistance mutations to the PIs in their regimens.

Also new data from the HIVNet 012 trials [13] revealed resistance mutations in 7/30 (23%) of women whose infants were HIV-infected. All women were found to have the K103N mutation and 1 woman also had the Y181C and another the Y181C and V106A. The K103N mutation was detected in 1 infant and the Y181C mutation was detected in 2 infants. The maternal infant genotypes were different for each mother-infant pair, which suggests that NVP resistant HIV-1 variants in the infants may have been selected by the NVP rather than transmitted from mother to child.

Both presenting authors Dr John Sullivan and Dr Brooks Jackson, respectively, emphasised that these findings about nevirapine resistance should in no way influence any decision to delay prevention strategies. Dr Sullivan stated, 'It should no way prevent implementation of this simple intervention for prevention of mother-to-child-transmission throughout the world', and Dr Jackson agreed and when questioned, concluded that 'It is important to recognise that treatment options are very rare in countries receiving this treatment'.

C O M M E N T

The finding that monotherapy ddI had such a strong impact on MTCT may be unexpected and deserves further investigation.

It may be that ddI, which works selectively in different cell-types to ZDV and d4T, has a disproportional impact on this mode of transmission.

Refernces:

1 UNAIDS – Report on the global epidemic. Geneva. June 2000-08-02

2 Hammett *et al*. Progress towards elimination of perinatal infection in the United States. XIII International AIDS Conference; Durban, July 9-14. Abstract MoOrC239

3 Fiore *et al*. Challenges in performing a randomised double-blind clinical trial: the European arm of the PACTG-nevirapine trial. XIII International AIDS Conference; Durban, July 9-14. Abstract TuPeB3248

4 Beckerman *et al*. The impact of combination therapy on maternal health and pregnancy outcome. XIII International AIDS Conference; Durban, July 9-14. Abstract MoPeB2198

5 Blattner *et al*. Effectiveness of potent antiretroviral therapies on reducing perinatal transmission of HIV. XIII International AIDS Conference; Durban, July 9-14. Abstract Lb01

6 Gray *et al*. Preliminary efficacy, safety, tolerability and pharmacokinetics of short course regimens of nucleoside analogues for the prevention of mother-to-child transmission of HIV. XIII International AIDS Conference; Durban, July 9-14. Abstract TuOrB355

7 Nduati *et al*. Impact of breastfeeding on maternal mortality among HIV-1 infected women. XIII International AIDS Conference; Durban, July 9-14. Abstract WeOrC495

8 Gray *et al*. The PETRA study: early and late efficacy of three short ZDV/3TC combination regimens to prevent MTCT of HIV-1. XIII International AIDS Conference; Durban, July 9-14. Abstract LbOr5

9 Shaffer *et al*. Short course zidovudine for perinatal HIV-1 transmission in Bangkok Thailand. Lancet 353:773-780, 1999.

10 Jeffery *et al*. Determination of the effectiveness of inactivation of HIV in human breast milk by Pretoria Pausteuisation. XIII International AIDS Conference; Durban, July 9-14. Abstract MoPeB2201

11 Sullivan *et al*. Genotypic resistance analysis in women participating in PACTG 316 with HIV-1 RNA >=10,000 copies/ml. XIII International AIDS Conference; Durban, July 9-14. Abstract LbOr14

12 Jackson *et al*. Selection of nevirapine resistance mutations in Ugandan women and infants receiving nevirapine prophylaxis to prevent HIV-1 vertical transmission (HIV NET 012). XIII International AIDS Conference; Durban, July 9-14. Abstract LbOr13

'The M in MTCT': Questions About HIV-Positive Mothers

Allan Rosenfield, dean of the Columbia School of Public Health, delivered a politically and ethically charged keynote to a July 10 symposium session on mother-to-child transmission (MTCT) of HIV. "Where is the 'M' in MTCT?" he asked rhetorically, before posing a series of ethical questions which were heatedly taken up by subsequent presenters and the standing-room-only audience. Some of his points:

- "The short course of ZDV preventive therapy uses the woman's body to confer treatment to the child, but gives no benefit to the woman," he began. "The short course therapy might increase viral resistance to drugs in the woman. If [she] never [gets] any other treatment, this is not important. But if she does, we may be increasing viral resistance to treatment. One thing we don't want to do with MTCT is make the woman's condition worse while reducing transmission. And I would say we don't have enough information on that."

- "Breastfeeding is even more complex," Rosenfield went on. "Which is the greater risk to the child?" he asked, referring to the lack of clean water and resulting diarrhoeal diseases and potential nutritional status deficits due to not receiving breast milk versus the risk of HIV transmission via the mother's milk.

- He posed "one final moral dilemma," asking, "If we're not going to treat the mother for her disease, and the likelihood is that the father already has the disease or has died, MTCT [prevention] does increase the number of orphans" He wondered aloud at the wisdom of creating "a generation of homeless children with no future."

- "The issue here is inequity." The impact of poverty must be addressed and prioritised by countries, he concluded, saying that the public health community must address the long-term issues while making the best decisions possible on short term programmatic issues surrounding MTCT.

Source: International Association of Physicians in AIDS Care. For more information visit the IAPAC website:

http:// www.iapac.org

PAEDIATRICS

First report of ABT 378/r use in children

Polly Clayden, HIV i-Base

The first paediatric data for ABT 378/r (lopinavir/ritonavir) was presented at this meeting. Using the liquid formulation of this new agent in a group of 100 children (comprising of 44 treatment naïve and 56 experienced, but NNRTI-naïve), the results look as promising as has been seen in recent adult trials. This will offer patients and clinicians an important new option in an area with more limited choice of antiretrovirals than that of adult subjects.

Study M98-940 is a phase I/II of co-formulated ABT 378/r, now branded *Kaletra*, at two doses in combination with NRTIs (and nevirapine in experienced subjects), in treatment naïve and treatment experienced paediatric patients. The mean average age of the children was 4.8 years (range 6 months to 10.2 years) for the naïve children and 5.7 years (range 8 months to 12.6 years) for the experienced group. Subjects were defined as naïve if they had received <3 months prior ARV therapy (or <1 week treatment with 3TC).

Both groups of children were randomised to receive twice daily doses of either 230/57.5mg per metre squared or 300/75mg per metre squared of ABT 378/r. In addition the naïve children received d4T and 3TC and the experienced ones received nevirapine and one or two open label NRTIs. All subjects were switched to the higher dose following an analysis of safety, tolerability and efficacy and week 3 pharmacokinetics.

At 24 weeks 82% of naïve and 66% of experienced children were undetectable (below <400 copies) by intent-to-treat analysis and their CD4 counts had risen by 328 and 335 respectively. Of the 100 children enrolled in the study there was only 1 discontinuation as of week 24, this was due to Burkitts lymphoma and problems with its treatment and not related to study drug. There were very few adverse events of probable relationship to study drug. Overall the presenting investigator Dr Violari described the results as 'very impressive indeed.'

Questions raised by the audience included the all-important one for paediatrics, 'But what does it taste like?' and the answer came back, 'It's not great, but the children got used to it, and it didn't cause anyone to stop their treatment'.

Reference:

XIII International AIDS Conference; Durban, July 9-14. Abstract. MoOrB177

Nelfinavir doses should be increased in infants less than 3 months

Polly Clayden, HIV i-Base

PENTA 7 is a phase I/II multi-centre trial to evaluate the efficacy, safety and pharmacokinetics of nelfinavir, used in combination with didanosine and stavudine in HIV-infected infants of less than three months of age [1].

Vertically infected infants with very high viral load appear to be more at risk for rapid disease progression and so early treatment is recommended. There has been limited paediatric pharmacokinetic research for nelfinavir, but recent data suggests that older children (age range 3 months to 13 years) need doses (mg/kg) 2 to 4 times

higher than adult doses to achieve similar plasma concentrations [2,3].

In this study the initial dose of nelfinavir was 40mg/kg TID (120mg/kg), but three months after its initiation, this was increased to 75mg/kg BID (150mg/kg) after the original dose failed to achieve therapeutic levels. Also BID dosing was implemented in line with adult studies showing comparable efficacy and better adherence with this schedule in comparison with TID. In addition didanosine and stavudine were given BID at doses of 100 mg/m2 and 1mg/kg respectively.

From September 1999 to February 2000, 9 pharmacokinetic studies were performed at steady state at least 2 weeks after initiation of the therapy on patients (N=8) aged between 1.5 and 7.2 months.

Important inter-patient variability was observed for Cmin and no correlation was found between this PK parameter and either the dose or the patient's age. Only 2 patients (aged 5.7 and 2.6 months) were considered to have the equivalent of the desired adult minimum therapeutic Cmin value (Cmin ->1000ng/ml). And among the 5 patients aged less than 4 months, only infants receiving a daily dose range of 130 to 150 mg/kg/d achieved the adult target value for AUC. Indicating that infants less than 3 or 4 months need higher doses compared to adults and older children to achieve therapeutic concentrations.

References:

1 C Litalien *et al*– Nelfinavir doses should be increased in infants less than 3 months. XIII International AIDS Conference; Durban, July 9-14. Abstract MoPeB2213

2 Krogstad *et al* Treatment of human immunodeficiency virus 1 in infected infants and children with the protease inhibitor nelfinavir mesylate. Clin. Infect. Dis. 28:1109-18; 1999

3 Brundage *et al*. Efavirenz and nelfinavir pharmacokinetics in HIV-infected children under 2 years of age. 7th Conference on Retroviruses and Opportunisic Infections. San Francisco, 1999. Abstract 382.

4 S Collins. Dr Fax 83. p 23.11.02.00

SWITCHING, SIMPLIFICATION & METABOLIC SIDE-EFFECTS

Metabolic and Lipodystropy issues: Confusion continues to reign

Reported by Graeme Moyle MD for NATAP

http://www.natap.org

Background

A definition for the lipodystrophy / lipoatrophy syndrome(s) to enable consistent case definition in studies does not currently exist. Reported clinical manifestations of the fat redistribution syndrome are heterogeneous and range from central or localised adiposity alone to peripheral fat wasting or combinations of both.

Central adiposity, at least in males, appears mainly secondary to visceral fat accumulation and may be best assessed by CT or MRI scanning. A range of approaches have been considered for management of fat redistribution and lipid abnormalities. These include:

- Diet modification and exercise programs
- Food supplements particularly acetyl-L-carnitine, Ubiquinone (co-enzyme Q-10) and riboflavin
- Hormonal therapies including growth hormone and anabolic steroids
- Lipid lowering agents such as statins, fibrates and omega-10 fish oils
- Insulin sensitising agents such as metformin and glitazones
- Cosmetic surgery
- Switching to alternative antiretrovirals with a perceived lower risk of the problems (see separate review)
- Structured treatment interruptions (see also separate review below)

Elevations in cholesterol and triglycerides have been reported in HIV-negative healthy volunteers receiving ritonavir monotherapy over a 2-week period, confirming that this agent has a direct effect on lipid handling.

Nucleoside analogues: Do available data support the mitochondrial toxicity hypothesis?

Nucleoside analogues have been occasionally associated with lactic acidosis and hepatic steatosis, which is thought to relate to mitochondrial dysfunction caused by these agents inhibiting mitochondrial DNA polymerase gamma. This problem has been reported with all the available nucleoside analogue combinations.

Inhibition of this enzyme has been suggested to also be important in the pathogenesis of fat redistribution syndrome. A difference in relative incidence of lactic acidosis or hyperlactatemia between combinations has not been established. In a cross sectional survey of 211 asymptomatic patients, 161 (76%) of whom were on nucleoside analogue therapy, mild hyperlactataemia (defined as 2.1-5mmol/l) was present in 23% of treated and 8% of untreated patients (Chi2 p=0.3). Serious hyperlactataemia (>5mmol/l) was observed in only one patient, which normalized without alteration of therapy.

Of the patients with hyperlactataemia, 19% of ZDV recipients therapy, and 28% of d4T recipients had hyperlactatemia [1]. The presence of elevated lactate in the absence of therapy is intriguing but may reflect laboratory issues, sampling variation (for example use of cuffs or not), use of other mitochondrial toxins (such as alcohol), familial mitochondrial disease, recent exercise or the possibility that HIV infection alone may impact

mitochondrial function.

A similar survey of 70 treated patients found lactate levels were >2.1 in 36% of patients and the anion gap widened in 19%. Three of 4 patients with lactate >3mmol/l and an anion gap of >12 had symptoms suggestive of drug toxicity such as fatigue, weight loss or myopathy [2]. In 8 patients with clinical lipodystrophy who were exercised to assess oxidative and glycolytic capacity in skeletal muscle tissue using ergometer cycling, oxygen consumption (VO2) and blood lactate (L) were measured. Before and after exercise, muscle biopsies were obtained to measure activity of citrate synthase (CS) and hydroxyacyl-CoA dehydrogenase (HD) to assess mitochondrial oxidative capacity.

The HAART treated HIV patients performed less work than healthy controls and had significantly higher baseline and post exercise lactates. Muscle biopsy data did not differ from controls. The absence of muscle abnormalities suggest that lactate elevations may have related to diminished hepatic clearance of lactate rather than excess production [3].

The physiology of the lipid metabolism was studied measuring lipid absorption, gastrointestinal lipid handling and lipid oxidation in 6 HIV positive individuals with established 2 years lipidaemia on treatment with a protease inhibitor (PI), 6 age matched healthy HIV negative controls. Additionally, seven HIV positive men were studied prior to treatment (study 1) after one month (study 2) on a PI containing regimen and again after three months (study 3). All patients were given a standard test meal and recovery of tracer in the breath as 13CO2 was determined hourly for six hours after the meal.

The rate of lipid absorption and oxidation were not significantly different between the pretherapy patient group and controls. However, the rate of lipid oxidation had increased at 3 months when compared with pretherapy. This rate was lower than in those who had established dyslipidaemia.

The authors concluded that prior to commencing PI lipid metabolism in HIV positive patients is normal. However, once on a PI containing regimen a progressive abnormality of lipid handling occurs in all patients with decreased peripheral uptake of lipid and enhanced oxidation. As the mitochondria are responsible for fat oxidation these data suggest that mitochondrial function is normal or may be increased to compensate for increases in circulating fat [4].

A small biopsy study of persons with fat redistribution and health controls, however, reported histological differences in the appearance of adipose tissue. Whilst mitochondria were abundant many abnormal forms were present with alterations of mitochondrial cristae and with lipid droplet accumulation in the cytoplasm [5]. These data are more consistent with some mitochondrial toxin at work although the need for more control data, particularly in older individuals where mitochondrial changes have previously been reported (the mitochondria deteriorate with age).

Prevalence of metabolic abnormalities: Too many confounders for clear conclusions

The problem with most available data on prevalence is that it is either retrospective or cross sectional and doesn't adequately correct for past treatment history. This may be particularly relevant if the appearance of fat redistribution is a delayed consequence of a particular drugs (as was seen with fialuridine and mitochondrial toxicity).

A German group evaluated 250 patients who commenced ART in 1996 (mean time since start of ART 36 months) using a standardized physician and patient questionnaire and visual analogue scales. Patients were mostly (80%) male with a mean age of 39 yrs. Physicians diagnosed lipodystrophy in 36-37% of the cohort [6]. Risk factors were analysed by univariate testing followed by multivariate logistic regression models of demographics, clinical history, CD4+ cells, viral load (VL), and treatment history.

Variables significantly associated with lipodystrophy in logistic models were: CD4+ nadir < 200/cells/mm^3 (OR 2.2, p > 0.05), treatment with d4T > 12 months (OR 2.2, p > 0.005), treatment with NNRTI > 12 months (OR 0.2, p > 0.05). Treatment with PI (OR 2.0, p = 0.03) and male gender (OR 0.4, p = 0.02). were significant in univariate but not in multivariate analyses [7].

Similar risk factors were evaluated in the Swiss cohort study. Data on abnormal body fat distribution reported by the patient, or by the visiting physician, were collected in the cohort. Serum levels of total cholesterol, HDL-cholesterol and triglycerides were measured at the time of each visit.

Out of 1379 patients treated with antiretroviral drugs, 585 (42.4%) developed signs of fat redistribution. Peripheral fat loss was observed in 386 (28.0%) patients, whereas 416 (30.2%) had signs of fat accumulation. In the analysis by cross tabulation, ZDV, 3TC and the combination ZDV + 3TC as part of HAART had a diminished rate of fat loss (Odds ratio (OR) of 0.5 (0.4-0.6), 0.8 (0.6-1.0), and 0.1 (0.03-0.5), respectively) relative to D4T and the combination DDI + D4T (OR of 2.1 (1.6-2.7), and 1.5 (0.4-6.5), respectively).

In regard to fat accumulation, a risk increase of 1.4 fold (1.1-1.8) was observed with indinavir, but not with other protease inhibitors. Lipid values were frequently abnormal: hypercholesterolemia (> 6.2 mmol/l) was detected in 28.4% and hypertriglyceridemia (> 2.3 mmol/l) in 37% of patients, although no specific associations were reported [8].

However, other cohorts did not find these significant associations. For example, in 118 HIV-infected patients on HAART including stavudine (n = 95) or zidovudine (n = 23) fat wasting was assessed by physical examination, regional fat distribution was estimated using four sites anthropometry and central adiposity was assessed by measurement of waist-hip ratio.

Both groups were well balanced with respect to age, sex, duration of HIV infection, risks factors for acquiring HIV

infection, prior AIDS defining conditions, duration of HAART, daily caloric intake, CD4 cell counts, viral load and percent with undetectable plasma viral load. The proportion of antiretroviral naive patients was significantly greater in the stavudine-treated group (26.7% vs. 0%, p = 0.01) but the mean time of exposure to NRTIs prior to HAART was not significantly different (46.9 ± 30.7 vs. 45.0 ± 32.1 months, p = .81).

The lean body mass and fat parameters of body composition were similar among the groups either when expressed in absolute numbers or when expressed as percentage of body weight. There were no statistically significant differences between the skin fold thickness measured at four different sites, nor were there between arm and leg or metabolic parameters. Visceral adiposity estimated through the waist-hip ratio was not statistically different in both groups [9].

Data examining the association of personal and/or family history of diabetes mellitus, cardiovascular diseases or obesity with the development of body habitus and metabolic complications were available from a US cohort of 175 patients (85% African American, 73% on PIs). Body habitus change was assessed by self report and measurement of waist-hip ratio plus unfasted lipids and glucose values.

In general, strong associations were observed with high cholesterol and family history of high cholesterol, high glucose and familial diabetes and history of obesity and raised BMI or waist-hip ratio suggesting that therapy may unmask familial conditions or accelerate their onset in susceptible individuals [10].

Management

Switching studies from this conference have been discussed in a separate report (see below). In general, improvements in insulin resistance, modest but incomplete improvements in lipids but not much change in peripheral lipoatrophy have been reported from changing to PI sparing regimens.

One study evaluated the impact of a planned treatment interruption on metabolic parameters. 26 men with viral loads <500 copies/ml for at least 12 months while on PI based HAART were studied. Parameters measured before HAART cessation and immediately prior to its reinstitution were: fasted cholesterol, LDL, HDL, triglycerides, oral glucose tolerance test with insulin levels, and anthropometrics (BMI, abdominal circumference, waist-to-hip ratio, sum of 4 skin folds). HAART was interrupted for a median 5.9 weeks (range 4.0-13.1). 13/17 had increased visceral abdominal fat at baseline.

There was a significant decrease in levels (mean±SD) of total cholesterol (194±47.3 vs. 160±29.4; p>0.0001), LDL (114± 32.6 vs. 95 ± 25.8; p = 0.0008), and triglycerides (261 ± 244.3 vs. 216 ± 267.3; p = 0.011) after the period of HAART interruption. However, there were no significant changes in glucose, insulin levels, or anthropometrics [11]. Thus, whilst some metabolic changes were rapid, clinical abnormalities, if reversible may require longer periods of treatment interruption than 6 weeks.

Growth hormone

Growth hormone has been suggested as a potential therapy particularly for fat increase manifestations of the syndrome. Several posters describing small series of patients supported this potential.

One study compared changes in body composition after 12 and 24 weeks of therapy and after therapy had been discontinued for at least 12 weeks. 14 subjects received open-label 6 mg/day recombinant human growth hormone. Measurements include DEXA scan for regional and total lean and fat tissue and MRI of the abdomen. Weight was similar at all time points. GH led to a gain in lean mass and a relative loss of fat. The loss of fat was greater in the trunk than in the arms or legs. Reduction in the intra-abdominal fat mass was observed. There were no additional benefits to >12 weeks therapy.

Unfortunately, benefit substantially regresses towards baseline after stopping therapy suggesting if benefits are to me maintained a maintenance dose of growth hormone needs to be established [12]. CD4 cell count and viral load benefits appear to be maintained and adverse effects of lipids or glucose handling are reported infrequently and resolve after treatment withdrawal [12, 13].

Lipid lowering agents

The elevation of cholesterol with HAART is principally in the LDL and VLDL fractions and in healthy volunteers has been suggested to be related to increased hepatic production of VLDL [14]. Inhibition of HMG-co-reductase in the liver diminishes de novo synthesis of cholesterol, the mechanism responsible for production of >50%of total body cholesterol. Inhibition of HMG-coA activates increased synthesis of hepatic LDL-receptors leading to increased clearance of circulating LDL [15].

The role of statins in drug induced hyperlipidemia is not established. Pravastation may represent the best choice of agent in the circumstance of protease inhibitor use as, unlike other statins it is not substantially metabolised by cytochromes p450 and has the lowest binding to plasma proteins of the statin agents [16]. Significant drug interactions with protease inhibitors have not been observed. ACTG A5047, reported the effects of ritonavir (RTV) + saquinavir (SQV) on statins levels: modest reductions in pravastatin levels were seen whereas atorvastatin levels rose 4-5 fold and simvistatin around 27-fold. Nelfinavir, or either ritonavir or saquinavir levels were not affected by pravastatin.

Atorvastatin also did not effect ritonavir or saquinavir levels but trend towards modest reductions in saquinavir levels were observed with simvistatin [17]. Thus simvistatin appears contraindicated with PIs. Statins are generally well tolerated agents with mild gastrointestinal effects being most commonly reported. The most important

adverse event is myotoxicity which may manifest as isolated creatinine kinase elevation, myalgia, myosotis myopathy or, most importantly, rhabdomyolysis [18].

In a randomised, open-label comparative trial of dietary advice alone or with 40mg od pravastatin (PS) in persons established on PI-based regimens with viral load (VL) <500cps/ml and cholesterol >6.5mmol/l (240mg/dl). All patients remained with VL <500cps/ml. Mean fasting cholesterol fell by 4% and 17% for dietary advice and pravastatin groups respectively.

The fall in total cholesterol in each group was accounted for entirely by reduction in LDL as HDL rose non-significantly by 0.6mmol/l in both groups. The reduction in LDL at week 24 was 1.24mmol/l (19%) with pravastatin and 5.5% with dietary advice alone. Weight, fasting glucose or triglycerides did not change significantly in either group. No significant clinical or laboratory events occurred [19].

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Switching Studies: Can viral load be maintained and metabolic or fat redistribution significantly improved?

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As antiretroviral regimens do not eradicate HIV infection, the current therapy paradigm involves a commitment to indefinite therapy. Long-term adherence to some regimens, particularly PI-based ones, is challenging due to requirements of high tablet volume, dietary restrictions and increased fluid intake. Improving the poor pharmacology of PIs by using booster co-therapies, such as low dose ritonavir improves administration characteristics but may also increase the number of important drug interactions. Additionally, ritonavir, and other protease inhibitors are known to cause elevation of blood lipids and may be less well tolerated in persons with hepatitis co-infections.

Short-term, effective therapy is associated with an increase in body weight and an improvement in nutritional status, although both plasma triglycerides, total and LDL cholesterol may elevate soon after therapy initiation. Longer-term (> 1 year) therapy has been associated with persistence of these lipid elevations, insulin resistance sometimes accompanied by new-onset diabetes mellitus, and abnormal body fat distribution. This may involve peripheral fat loss, localized or truncal fat gain or both.

It has not been clearly established if all these phenomena are inter-related although unifying theories have been proposed. Both PIs and nucleoside analogues (NAs) have been suggested to play a role in the pathogenesis of these changes and are hence both potential targets of switching strategies. Hypertriglyceridemia and reduced high density lipoprotein (HDL) cholesterol, but not diabetes mellitus or fat redistribution were recognized as complications of HIV-1 infection, and most typically wasting prior to the availability of PI.

A definition for the syndrome(s) to enable consistent case definition in studies does not currently exist. Reported clinical manifestations of the fat redistribution syndrome are heterogeneous and range from central or localised

adiposity alone to peripheral fat wasting or combinations of both. Central adiposity, at least in males, appears mainly secondary to visceral fat accumulation and may be best assessed by CT scanning.

Localised problems include breast enlargement, or development of cervical fat pads (or 'buffalo humps'). Peripheral fat wasting, generally presents with increased vein prominence as well as loss of facial fat pads such as the temporalis and naso-labial pads. The prevalence of these clinical manifestations is not known but appears to increase with time on antiretroviral therapy.

These changes have both significant psychological and social consequences for individuals with HIV infection. The conference included 2 studies evaluating the impact of fat redistribution on quality of life.

A German group evaluated 250 patients who had commence ART in 1996 (mean time since start of ART 36 months) using a standardized physician and patient questionnaire and visual analogue scales. Patients were mostly (80%) male with a mean age of 39 years. Physicians diagnosed lipodystrophy in 36% of the cohort. Patients with lipodystrophy all reported loss of quality of life in at least one of the measured domains: 63% for social contact, 68% on daily performance and sexuality and 83% on self esteem.

The authors also reported some specific physical changes were linked particular diminished ratings. For example, abdominal enlargement was significantly associated with diminished sexual and self esteem ratings, leg and arm changes with daily performance and social functioning [1].

In a survey of 74 attendees at a workshop on body shape changes where 78% of respondents reported body shape or metabolic changes thought related to ART, 30% of these individuals had changed therapy and 7% interrupted ART specifically due to these problems. In general (83% of cases), amongst those changing therapy, only the agent perceived as causative of the problem was changed. The authors, from Gay Men's Health Crisis New York, concluded that patient perceptions around metabolic and body shape changes are driving treatment decisions and potentially therapy outcomes [2]. These needs are driving a host of studies evaluating the outcome of therapy switches.

Given the known, theoretical and observational associations of metabolic and clinical changes with PIs, most of the studies currently reporting data have evaluated changes in HIV disease markers, clinical and biochemical parameters following changes from a PI based to a PI sparing regimen.

The reasons for considering switching to a PI sparing regimen include to address metabolic and fat redistribution problems but also:

- Improve adherence; reduce tablet load, remove food requirements, reduce dosing frequency
- Reduce the risk of clinically important drug interactions and;
- Managing an actual or possible PI toxicity including diarrhoea, recurrent renal calculi, etc.

In principle, two main outcomes should be looked at to evaluate the success or otherwise of switching. Firstly, that no harm is done and secondly, that benefit is gained. More specifically this can be measured as:

- Maintaining of virological control (most reported studies have focussed on patients with good virological control on PI-based therapy)
- Maintaining of CD4 responses (and immune function) and;
- Improving/resolving/preventing of toxicity — Improving adherence and quality of life.

Three drugs have been evaluated in switching studies. The non-nucleosides efavirenz (EFV) and nevirapine (NVP) and the potent nucleoside analogue abacavir (ABC). In general, the reports are not studies, per se, but observed clinical cohorts, thus the observations must be placed in the context of not knowing what would have had happened to a group of patients maintained on therapy.

Nevirapine

Several large studies have looked at switching to nevirapine. In one Spanish study, 91 patients (80% male) were switched to nevirapine after at least 3 months undetectable (<50) on PI therapy. Sixty four percent of them were on their first ever regimen. The reasons for changing PI included treatment simplification (41 patients), renal complications (24), lipodystrophy (20), hypertriglyceridemia (3), and gastro-intestinal disturbances (3). The mean CD4 count at change was 601 cells/mm^3 (range 80 to 1500). Ten patients (11 %) discontinued nevirapine: 8 due to intolerance and 2 because of sustained viral rebound at 24 and 36 weeks. Both responded to PI reintroduction. Additionally, at week 12, 7 patients showed minimal viral load rebounds (range 50 to 1700 copies/ml) returning to undetectable levels in 6 cases at 24 weeks. Analyses of risk factors for detectable VL were not reported. Mean CD4 rose at weeks 12, 24 and 36 by 1, 65 and 85 cells/mL, respectively. Whereas mean triglyceride at 12, 24 and 36 weeks fell by 125, 16 and 574 mg/dL, respectively [3].

A large 100 patients French cohort also evaluated switching to NVP in PI treated patients with plasma VL >20 copies/ml for >1 year. Data at month 3 on 72 patients indicated a significant rise in CD4 percentage (28.4% to 30.6%) and a rise in CD4 cells of 39/ mm^3. Seven patients (10%) had detectable viral load levels at month 3, available resistance data suggesting resistance only to NNRTI was present. There were no significant changes in cholesterol or triglycerides. Twenty one patients reported side effects following switch with 5 patients discontinuing nevirapine [4].

A further cohort of patients (mostly) switched to NVP yielded somewhat disappointing results. In this single centre Italian study, a total of 28 NNRTI-naive, PI-treated patients with a VL< 80 copies/ml for mean 21 months (range 7-33) and with metabolic toxicities were switched

Table 1.

	Mean CD4 (cells/mm^3)				Viral load (% <80 copies/mL)			
	0 wks	12 wks	24 wks	36 wks	0 wks	12 wks	24 wks	36 wks
Arm A (28 patients)	393	425	446	410	100%	73%	73%	75%
Arm B (27 patients)	345	376	398	405	100%	75%	80%	77%

to NVP (n= 24) or EFV (n=4). These patients (Arm A) were compared to a cohort who continued the PI-containing regimens (Arm B). The groups were well matched for age, sex, HIV risk factors, CD4 count when initiating PI therapy and switching therapy, and for the duration with an undetectable viral load.

Results after 36 weeks are reported in Table 1.

After 36 weeks of switching therapy mean values of cholesterol, triglycerides, and glucose were reported to have returned to within normal ranges. Whilst there was no statistical difference between the percent of patients with undetectable viral load in the two treatment arms, it is concerning that as many as 25% of patients in this cohort lost virological control, the majority in the first 12 weeks after switch [5].

Concern that switching therapy to nevirapine may be more risky in persons with prior therapy experience led one group to investigate this approach only in persons on their first regimen. In this study, 40 patients on PI regimens with undetectable VL for at least 6 months, switched the PI for NVP 200 mg bid. Nucleosides were maintained. 90% of the patients were men, with a median CD4 of 511 cells/mm^3. The median follow up was for 30 week. With regard to tolerability, 6 patients (15%) developed severe rash and were switched to EFV. One patient discontinued due to hepatitis, Only 1 patient (2.5%) lost viral control. Metabolic benefits were observed with 24 week results showing triglycerides had declined 44% ($p > 0.05$), HDL-cholesterol increased 26% ($p > 0.001$), and glucagon decreased 23% ($p = 0.01$). LDL cholesterol, glucose, insulin and proinsulin did not alter significantly. Hip and spine bone mineral density and truncal adiposity did not change [6].

Efavirenz

Similar data are available with EFV substituting for PIs. A German study evaluated this switch in 42 patients with median time on PI-regimen of 24 months (range: 6-41) (mean age: 43±9.4) with VL <50 cps/ml and CD4+ >200 cells/mm^3 at baseline. Baseline therapy switch included one PI in 23 patients (IDV: n = 13; NFV: n = 9; RTV: n = 1), and two PIs in 19 patients (RTV/IDV: n = 15; RTV/SQV: n = 1, NFV/SQV: n = 3). NRTIs were D4T/3TC(n = 29), or ZDV/3TC (n = 13). VL was undetectable for a median time of 12.5 months before substitution.

Therapy was changed due to adverse events to PI (n = 11), lipodystrophy (n = 20) and/or wish to simplify regimen (n = 15). VL of all patients (39 with available data, 2 lost to follow up) has remained <50 copies/ml and a significant reduction of CD8+/CD38+ cells from 66.9±17.1% at baseline to 60.5±18.1% at week 24. Non-fasting triglycerides showed a significant decrease from 322±212 mg/dl at baseline to 252±206 mg/dl at week 24, while values of HDL showed a significant improvement from 37±8 mg/dl to 43±9 mg/dl at week 24. Consistent with clinical trials data, 45.2% of patients reported nervous system symptoms during the first weeks of therapy with EFV [7].

An Italian study specifically investigated the effect on switching in persons with elevated triglycerides and viral load <500 copies/ml from PI to efavirenz. Patients continued with the same NRTIs. Thirty-one patients receiving either IDV (14), RTV (4), SQV (2), NFV (3) SQV+RTV (7) or SQV+NFV (1) for 19.8 +/- 8.2 months were enrolled. Before PI treatment their mean plasma triglyceride was 219 +/- 132 mg/dl. At switch this value was 718 +/- 453 mg/dl and was associated with lipodystrophy in 12 cases. Most patients showed reduction in triglycerides after switch.

After 1 month, tryglycerides had fallen to 362 +/- 233 mg/dl ($P< 0.004$), at 4 moths 325 +/- 157 ($P<0.008$) and at month 8 359 +/- 149 mg/dl ($P< 0.03$). Total cholesterol blood levels were unchanged. Mean HIV-RNA dropped from 90 copies/ml to 49.3 copies/ml after one month. At 4 months all patients were <50 copies/ml and at 8 months all but one patient was <50 copies/ml. CD4 T-cell levels increased from 525 cells/mm^3 to 625 cells/mm^3. Treatment with efavirenz was generally well tolerated; only one patient interrupted therapy because of dizziness [8].

A retrospective analysis of 40 patients who had been switched for any reason from PI-containing antiretroviral treatment (ART) to a regimen of two NRTI plus EFV reported data suggesting lipid levels may not improve impressively after switch to efavirenz but than viral control is generally maintained after switching. All 11 patients in this cohort who had a viral load below 50 copies/ml prior to switch maintained control over an observation period of 6 months. Median non-fasting cholesterol rose from 201 mg/dL (range: 71-426) at baseline level to 218mg/dl (range of change –49 to +156)($p = 0.01$); and triglycerides from 221 mg/dL (range: 66-1957) to 238mg/dl (range of change -433 to+853) ($p = ns$) [9].

Efavirenz or nevirapine

In another prospective, multicentre, non randomised study of 103 Spanish patients switched with a viral load <200 copies/ml (86% <50) (mean 12 months, range 1-34) on a PI regimen (mean 18 months range 4-35) switched to either efavirenz or nevirapine. Reasons for NNRTI choice were not stated. Twenty three percent of patients were on

their first regimen. After 24 weeks, 93% of 33 efavirenz patients and 87% of 70 nevirapine patients remained <50 copies/ml in the as-treated analysis, and 78% and 75% in the intent-to-treat, respectively.

Thirteen percent of patients withdrew due to adverse events. Median CD4 count increased from 502 to 591 cells/mm^3. Patients with a longer previous time on NRTI therapy (42 vs, 33 months), and a shorter time with undetectable HIV load (8 vs 12 months), had a higher rate of viral failure (efavirenz and nevirapine groups analysed together). Adverse events secondary to NNRTI were observed in 27 patients (31%), mainly hepatitis (9%) or rash (6%). Triglycerides and cholesterol levels significantly improved after switching to the NNRTI. For triglycerides from 321 to 246mg/dl (p = 0.01) and for cholesterol from 239 to 219mg/dl, p = 0.0001). Clinical manifestations of lipoatrophy were not noted to improve [10].

Efavirenz and abacavir

A further approach is to use two of these agents, thus potentially also intensifying the regimen. The safety, efficacy and impact on metabolic parameters of abacavir (ABC) + efavirenz (EFV) when substituted for a PI in persons viral loads with <50 c/ml, was evaluated in an open label, single centre study. To establish tolerability ABC was added at baseline then at week 6 EFV replaced the PI. Twenty-six patients have been followed-up for a mean 24 weeks.

Four discontinued at week 2 (3 for ABC-hypersensitivity; 1 for virological failure due to non-compliance). No grade 3 or 4 laboratory toxicities were reported. After stopping PI, all patients have remained <50 with stable CD4 counts. Mean fasting triglycerides, HDL- and LDL-cholesterol from the first 16 patients who reached wk 24 improved significantly compared to baseline. Two of 4 diabetic patients saw resolution of diabetes. Five of 8 patients with lipodystrophy self reported improvements, 2 stabilisation and one worsening of signs. [11]

Conclusions

There appear to be considerable benefits to switching from a PI-based regimen to a PI-sparing regimen. However resolution of clinical and metabolic abnormalities, which may arise during prior therapy, are incomplete. Patients appear generally pleased with the improved administration characteristics of the new regimens and improvements in quality of life have been reported. Clinical and metabolic benefits include a reduction in insulin resistance and subsequently intra-abdominal fat, and, most prominently, with nevirapine and (previously) abacavir, improvements in total cholesterol and triglycerides.

Cholesterol and triglyceride abnormalities may not resolve after switching to efavirenz although HDL:LDL ratio may improve. Peripheral or subcutaneous fat mass improvements are not evident in all studies reported to date. Weight gain, probably in part due to removal of PI-related dietary restrictions, has been observed and may lead to improvements in appearance. Lack of peripheral fat gain may in part relate to a contribution from nucleoside analogues to peripheral fat wasting.

Maintenance of virological control varies between studies. This may be due to two factors: the relative potencies of the drugs used, and the extent of prior drug exposure (or drug resistance) in patients entering the studies. In switch studies, all agents appear effective at maintaining virological control in persons with no history of prior treatment failure.

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Simplification strategies: Deintensification is not so easy

Reported by Graeme Moyle, MD, for NATAP

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The introduction of potent three (or more) drug antiretroviral therapy regimens (highly active antiretroviral therapy, HAART) has dramatically modified the natural history of HIV-1 infection. However, HAART regimens are unable to eradicate HIV-1 infection, thus establishing the current HIV therapeutic paradigm of giving antiretroviral therapy for an indefinite period. Initial studies evaluating treatment deintensification to more convenient maintenance

regimens following, generally, 24 weeks of induction to <50 copies/ml with HAART regimens have shown that maintenance is unable to maintain the suppression of HIV replication [1–3]. The failure in these studies may have been due an insufficiently long induction phase.

ADAM study: Extending induction to 50 weeks

In patients involved in the ADAM study [1], a second cohort of patients were evaluated to test the effect of a longer period of induction therapy on the feasibility of a treatment deintensification [4]. Antiretroviral therapy naive patients were treated with a 4 drug induction regimen (d4T + 3TC + saquinavir (initially as hard gel) (SQV) + nelfinavir (NFV)) for 26 or 50 weeks.

Randomisation at week 26 was discontinued following an interim analysis that showed inferior suppression of viral replication during maintenance therapy [1]. At week 50, patients were randomised to maintenance therapy (either d4T + NFV or SQV + NFV) or continued quadruple therapy if the plasma HIV-1 RNA levels at weeks 48 and 49 were both below the limit of quantification (<50 copies/ml). After randomisation, monthly monitoring of viral load in plasma was performed. Treatment failure was defined as two consecutive HIV-1 RNA measurements >100 copies/mL.

Of original 65 patients who commence the induction regimen, 16 patients had been randomised at week 26. Of the remaining 49 patients, 17 patients were randomised at week 50. Ten patients were randomised to either D4T/NFV (6) or SQV/NFV (4). In both arms one patient withdrew after randomisation. Treatment failure was observed in 4/8 patients who deintensified compared to 1/5 evaluable patients on quadruple therapy (p=0.56). In the patients randomised to deintensify at week 26 and at week 50, Kaplan-Meier analysis indicated time to > 400 HIV-1 RNA copies/mL in plasma was comparable. The authors concluded a longer period of induction does not postpone recurrence of viral replication following deintensification [4].

Simplification through dose modification

Given this disappointment, the next best thing may be to simplify regimen administration, reducing the frequency of dosing and/or tablet volume. Several studies looking at different drugs evaluated this possibility. Based on pharmacokinetic data presented last year [5] which indicated a dose of 100mg of ritonavir with 1200mg of indinavir resulted in higher indinavir exposure and a similar or higher trough level of indinavir to tid dosing a case-control study was performed at two Italian clinics. Patients on an indinavir-containing regimen and with viral load <50 copies/ml were offered change to once daily indinavir/ritonavir. Matched controls were selected based from the clinics database.

Twelve patient have completed 16 weeks of follow-up. Baseline characteristics included viral load <50 for 16 months and CD4 369 cells/mm^3. No viral rebound to >400 have occurred in simplification patients versus one in the control case. However, 2 simplification and 3 control patients have had a viral measurement >50 at week 16. It is not known if these represent 'blips' or not. Two simplification patients and one control have reported renal calculi [6]. This may have been expected given the peak indinavir levels reported for this regimen are around 80% higher than with tid dosing.

The pharmacokinetics of some NNRTIs and nucleoside analogues favour once daily (QD) dosing. Results of a Spanish study evaluating once daily ddI and nevirapine versus twice daily dosing, in each case with stavudine in asymptomatic antiretroviral naive HIV-1 infected patients with CD4+ T cell count >500 cells/mm^3 and viral load > 5000 copies /ml were also discussed today. Patients were randomly assigned to QD (N = 45) or BID (N = 44). Baseline characteristics were not presented.

The mean reduction in VL at month 12 was -1.84 (QD) versus -1.78 (BID) (p = 0.91) with the proportion of patients below 200 c/ml at 12 months by intent-to-treat (ITT) analysis being 73% (QD) and 68% (BID), and below 5 c/ml: (ITT) 40% (QD) and 45% (BID). No differences in CD4 count increase was observed. Tonsillar biopsies were performed in a subset of 11 patients with a plasma VL at month 12 below 5 copies/ml, 5 had detectable lymphoid VL (median: 7750 c/mg of tissue, range: 1020-33077). Eight percent of patients changed treatment due to side effects [7].

Whilst data support the use of once daily ddI and nevirapine in antiretroviral naive patients the lymphoid viral load data raise some concerns regarding the potential durability of this response.

Dual NNRTI's in once daily regimen

Another novel approach to once daily dosing was to combine the two once daily NNRTIs, efavirenz and nevirapine with ddI. The idea behind combining NNRTIs is that the total NNRTI exposure will be increased, potentially leading to additive antiviral effects. Limiting the nucleoside analogue load in this regimen may also have long term tolerability advantages.

This study evaluated fifteen treatment-naive and 11 treatment-experienced patients. Treatment was NVP (400 mg qd) plus EFV (600 mg qd) plus ddI (400 mg qd), thus no adjustment for a pharmacokinetic interaction which diminished efavirenz exposure around 30% was made (in an ongoing study of this combination efavirenz is dosed at 800mg/day with standard dose nevirapine). Amongst the treatment-naive patients the mean baseline VL was 4.59 log10 copies/mL, and the mean baseline CD4+ was 351 cells/mm^3; after 9 months of therapy, 12/12 evaluable patients had VL <400 copies/mL, and CD4+ had increased by mean 351 cells/mm^3. At baseline, 9/11 treatment-experienced patients had a VL <400 copies/mL, and mean CD4+ of 368 cells/mm^3; after 9 months, 9/9 had VL <400 copies/mL , and CD4+ had increased by mean 203 cells/mm^3. Five of the 26 patients (19%) discontinued therapy, 2 for rash, 3 for CNS effects.

This pilot study suggest that a double NNRTI therapy is a potentially attractive approach and further evaluation of once-daily NVP+EFV+ddI is warranted.

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Pharmacokinetic Enhancement: Simplification through combination

Reported by Graeme Moyle, MD for NATAP

http://www.natap.org

Pharmacokinetic enhancement involves the use of one drug to inhibit the metabolism of another, leading to improved drug exposure. The most popular candidate for this approach is ritonavir, which is a potent inhibitor of cytochrome (CYP) p450 3A, the liver and gut wall cytochrome responsible for metabolism of many drugs including other protease inhibitors (PI). Ritonavir increases exposure and slows the metabolism of other protease inhibitors leading to potential for using fewer tablets and having less frequent dosing.

It also removes the need for food restrictions and at least with saquinavir the need to separate dosing from buffered ddI. Furthermore, the interpatient variability in exposure with PIs is diminished when ritonavir co-dosing is used. Ritonavir is also known to inhibit p-glycoprotein, a cellular efflux pump. Inhibition of this pump may lead to increased cellular concentrations of other PIs and improved penetration into body compartment such as the brain. However, there are potential downsides to the use of ritonavir. It is known (as with other PIs) to increase (mostly) LDL cholesterol and triglycerides in what is probably a dose dependent manner. Inhibition of CYP3A may lead to interactions with other drugs the patient is prescribed or with recreational substances (such as MDMA/ecstasy and GBH). Additionally, the long-term consequences, if any, of chronically inhibiting CYP3A and P-glycoprotein is not known.

Whist the first studies if ritonavir enhancement were conducted with saquinavir, use of small or 'baby' doses (usually 100-200mg/day) of ritonavir with other PIs is increasingly standard practice and a co-formulation of 100mg bid with lopinavir (ABT-378) is currently in advanced development. Until this meeting, much of the available data on use of ritonavir with indinavir, amprenavir or nelfinavir was derived from either small pharmacokinetic studies or observational cohorts rather than prospective studies.

Two prospective studies presented today evaluated combining ritonavir and indinavir in subjects established on tid dosed indinavir and with viral loads <400 copies/ml. The studies differed in the dosing. Combining 400mg of each drug bid may mean that therapeutic levels of both ritonavir and indinavir are achieved, potentially giving a dual PI potency and is associated with lower indinavir peak levels, potentially diminishing the risk of renal calculi and crystalluria from indinavir. Using 100mg of ritonavir with 800mg indinavir bid is cheaper, uses fewer pills (3 bid versus 5 bid with 400/400) and has a lower risk of ritonavir related side effects such as lipid disturbances, nausea or diarrhoea.

The NICE study evaluated patients with HIV RNA <400 copies/mL in an open-label multicentre study comparing continuing indinavir 800mg tid to switching to 400/400mg bid of ritonavir/indinavir. A survey addressing adherence and convenience, was administered at the baseline and week 4 was the basis of the presentation. Efficacy data were not presented. The study has recruited 380 patients, 301 randomised to add ritonavir and 79 to remain on tid indinavir. After just 4 weeks 21% of those adding ritonavir and 15% remaining on indinavir alone have discontinued. Adverse events, mainly gastrointestinal, were the cause of discontinuation in 14% and 8% of patients, respectively.

The adherence survey at week 4 visit indicated that patients randomised to add ritonavir were missing fewer doses than they had reported missing prior to initiation of this regimen (p>.001). Additionally, they reported that it was easier to take the medication as prescribed, easier to take at the same time each day, and easier to coordinate with meals when compared to baseline (p>.001 in each case). Similar effects were not seen for patients who remained on indinavir alone. Thus, there seems to be a trade off with adding this dose of ritonavir between improved administration characteristics versus a modest increase in risk of toxicity.

A second study, this one called BEST, found a similar trade off existed with modifying dosing of indinavir to 800mg bid with 100mg of ritonavir. This randomised,

open-label, multicentre study testing whether switching in 326 patients with viral loads <500 copies/ml. 161 added ritonavir, 165 remained on indinavir alone.

All patients completed 3 months follow-up with 237 patients through week 24. Baseline characteristics of both groups were similar with CD4 counts of 407 and 440/mm^3 for tid and bid arms, respectively. Proportions of patients with plasma viral load <500 copies/ml at 6 months are:

	TID Indinavir	BID RTV/IDV
Intent to treat (%)	87%	88 %
Viral failures (number)	3	4

Adverse events requiring treatment interruption or discontinuation occurred in 7 versus 19% of patients. Nephrolithiasis developed in 5% versus 12% leading to treatment discontinuation in 1% versus 4%, respectively. The high rate of nephrolithiasis over a relatively short period of follow is disappointing and underlines the need for continued high fluid intake on this dosing schedule. Additional adverse events included nausea and/or vomiting which occurred in 2 versus 16% of patients, possible in part due to the use of liquid ritonavir during the first months of the study. No differences in triglycerides or cholesterol >3 times upper limit of normal were observed [2].

Pharmacokinetic studies ritonavir with amprenavir or nelfinavir

In evaluating the PK interaction between ritonavir and amprenavir three RTV-APV regimens were tested in 12 healthy volunteers per group: Group I 400mg Ritonavir + 450mg Amprenavir, group II 400/750 and group III 200/1200. Withdrawals, in all 19 cases due to amprenavir rash (despite excluding persons with known sulpha drug allergy) meant only seventeen subjects finished the 12-day study. Pharmacokinetic parameters were compared with historical controls taking the approved 1200mg bid dose.

PK parameters are shown in below:

.	Group 1	Group II	Group III	Controls
AUC mcg/h/mL	46	39	76	18.5
Cmin mcg/mL	0.57	0.63	1.74	0.28
Cmax mcg/mL	1.4	2.2	5.0	5.4

Group III had significantly higher mean amprenavir exposure than those of Groups I and II, but an elimination half-life 50% shorter. These data suggest ritonavir improves the PK profile of amprenavir with all three regimens yielding trough values at 12 hours above current recommended amprenavir dosing [3].

With nelfinavir, the possibility of once daily dosing with ritonavir was explored. Nelfinavir is not only metabolised by CYP3A but also by CYP2C19, an enzyme not significantly inhibited by ritonavir. As a result, only a modest enhancement of 17-49% in nelfinavir (plus M8 its active metabolite) exposure is achieved. A range of doses were evaluated. A dose of 200mg ritonavir and 2500mg nelfinavir produced a higher AUC and similar trough concentration of NFV (and a slightly higher nelfinavir + M8 exposure) to standard 1250mg bid dosing. Subjects receiving 100mg of ritonavir did not achieve comparable trough values to standard dosing.

These data suggest the feasibility for dosing nelfinavir plus ritonavir once daily [4] and warrant further clinical evaluation. Whilst with the current formulation the tablet load on the single occasion would be quite high (12 pills: 2 ritonavir plus 10 nelfinavir), however, a new formulation of nelfinavir as 625mg tablets could mean once daily PI therapy could be achieved with just six tablets

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TREATMENT INTERRUPTIONS & NEWER AGENTS

Commentary on STI Talk, Early Entry Inhibitor Research, Increase in Viral Replication Seen in Isolates in Presence of NNRTIs

Reported by Mike Youle, MD for NATAP

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The political agenda for change is by far the most important aspect of this meeting. Researchers have to some extent anticipated this and there appears to be a combination of acceptance that the first flush of excitement with HAART has been tempered by the rising incidence of side effects. On the other hand the economic imperative for those who can afford some therapy will drive strategies which examine intermittent, short term and low volume treatments.

Tony Fauci from the National Institutes for Health in Bethesda in a presentation reminiscent of a tele-novella heralded the importance of interruption of therapy (see also separate report below). Many in the audience, however, expressed concern that much like the 'Hit hard - Hit early' dictum which has now been discredited an early foray into this area, with sparse data (he presented less than double figure patient information) may drive a new treatment approach ahead of the science to support it. There will be further studies of this approach in the Late-breaker sessions.

[comment from Jules Levin, NATAP—In fact, in the Late Breaker sessions Mike Dybel of the NIH reported preliminary data on the 2 NIH studies—intermittent interruptions of a few days on therapy and a few days off therapy, and one month off therapy and 2 months on therapy—and was harshly criticized for presenting the data too soon. Many expressed concern that releasing preliminary data like this encourages patients to experiment with unproven treatment approaches and may put individuals at risk.]

So what more of the future approaches. In the sessions on New Antivirals and Targets, Guido Poli's group showed data on the B-oligomer of pertussis toxin (PTX-B) which is a non-toxic derivative of the toxin which appear to act at some point around fusion of HIV to the cell surface [1]. It appears to be a selective inhibitor of R5 fusion and deactivates CCR5 in activated primary lymphocytes and macrophages. Whilst it does not block fusion of X4 viruses it blocked infection of cells with recombinant HIV-1 particles pseudo-typed with R5, X4 or even VZV-G envelopes. Taken together the results suggest that PTX-B inhibited entry of R5 viruses and the accumulation and replication of both R5 and X4 viruses. As one researcher said in the session on fusion inhibitors it is vital we have agents which cover all viral strains so as to avoid a requirement for even more different agents to achieve suppression.

This work was augmented by Stefano Rusconi from the University of Milan, Italy [2]. He and his co-workers had examined the two chemokine receptor blockers AOP-RANTES, against R5 virus and met-SDF-1beta, specifically directed against X4 viruses. The isolates used to test this combination therapy approach were from two primary HIV-1 infected patients who exhibited tropism for one or other receptor. In the experiments single isolates or a 50:50 combination were examined in the presence of one or both receptor-blockers. As one might have expected the combination of agents worked the most effectively with inhibition rates of >95% whilst the single agents were less successful with repression rates of only 30-60%. These experiments further point to the necessity of approaching receptor blockade with R5 and X4 targeted compounds.

A third presentation, given by Huang from a New York based group spanning industry and academia, gave some further hopes of a cheap and effective new therapy [3]. Human lysozyme is an enzyme known to act against bacterial and viral infections, tumours and to alter host immunity. It appears also to have an inherent anti-HIV activity and thus is hypothesized to be a possible new candidate drug against the virus.

In these experiments limited proteolysis of lysozyme was undertaken to produce ten fragments of the original. Each of these was examined for antiretroviral activity in an in vitro inhibition assay. One 18-amino acid fragment appeared to hold all of the activity of the complete enzyme with 50% inhibition concentrations of 58-68nM. Further trimming of this molecule resulted in HL-9 consisting of an amino acid sequence RAWVAWRNR that required this sequence for maximal action and was reduced in potency if the R's were substituted for other amino acids. An elegant set of experiments characterized this as the optimal sequence for HIV suppression.

In addition to its antiretroviral activity this compound also inhibited the growth of cells infected by HHV-8 from AIDS patients with Kaposi's sarcoma. This appears a promising candidate as a new anti-HIV agent and it is non-toxic derived from human protein and has potent activity against a broad range of HIV isolates.

A study which was not presented except in abstract form but which holds interest for the assessment of drug action in the brain came from Kings College London [4]. In an in vitro assay utilizing mixed population of cells (neurons, microglia, astrocytes and oligodendrocytes) as well as relevant neuro-transmitters was established to most nearly mimic the cerebral environment. In to this HIV infection with the standard lymphotrophic IIIB strain was accompanied an increase in microglia but no neuronal loss, whilst the macrophage tropic strain SF-2 resulted in a 35% reduction in neuronal levels. Both of these effects were blocked by the addition of physiologically achieved concentrations of abacavir and zidovudine giving further evidence of the activity of these drugs in a compartment often felt to not be as suppressed as outside the blood–brain barrier.

The most potentially worrying presentation related to drug therapy, in my view, came from a single case report by Chris Petropoulos from Virologic found during phenotypic drug susceptibility testing [5]. Using the Phenosense assay an up to 400% increase in viral replication was seen when isolates from the patient were put in the presence of non-nucleoside agents. Analysis of samples from the subject prior to the use of NNRTI's suggested that novel genetic changes may have predisposed the virus to develop this phenotype. Clearly, apart from virus harbouring multiple mutations to zidovudine, the phenomenon of increase replication in the setting of antiretroviral agents has not been seen and with rising rates of resistance to NRTI's this is a phenomenon that should be actively looked for in laboratories testing resistance routinely.

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New Developments in Affordable Antiretroviral Therapy: Intermittent Treatment

Coverage provided by Calvin Cohen, M.D

http://HIV&hepatitis.com

A few years ago the focus of interest in HIV-treatment research was the search for regimens that could ultimately lead to eradication of HIV from the body. In the past year, however, there has been pessimism about the likelihood of this outcome, given how long HIV persists in some of the body's cells. Recent estimates suggest the possibility that it could take 60 years of continuous control of HIV replication to expect eradication to occur. Therefore, more research has started to focus on "stalemate," e.g. what can be done to augment the immune system and its capacity to control HIV itself, with fewer meds, or even no meds at all.

While some research, particularly in those very recently exposed to HIV ("acute infection"), has shown some promise, it is increasingly noted that immunologic control of HIV is difficult to recreate in more than a small percentage of those who are treated some months to years after seroconversion ("chronic infection"). This has led to the next potential phase of HIV treatment research; namely to define ways to both control HIV and the damage it causes, while using the least amount of medications to accomplish this, even if immunologic control isn't feasible.

One novel approach, presented here, is to use short cycles of medication in an attempt to control HIV with medication, but allow regular time off of antivirals. This is done partly to conserve resources in resource-poor countries, and partly in the hope that pauses will limit the cumulative side effects of medications. These pauses are done for short periods of time to prevent damage done to the immune system when medications are stopped and viral load rebounds.

One observation that underlies some of this work comes from studies which stopped antivirals in a NIH-sponsored trial presented last year. After about two weeks, virtually all participants saw a rebound in their viral load. However, for those with a viral load below detection who then stopped meds, it was noted that during the first week off meds there was very little if any return of detectable HIV. While it is virtually certain that there is some growth going on in that first week, the amount that is growing is so low as to not result in any obvious damage to the immune system. These observations have led to the following clinical studies.

Two studies from the NIH were presented with preliminary observations on just a few participants, and was presented by Dr. Mark Dybul. All study participants had a viral load suppressed to below 50 copies on a standard antiviral regimen. Starting with those who have viral load suppression is a key to this research, since stopping meds with a higher viral load potentially increases the risk of developing drug resistance to some of the antivirals. Three cycles of times "on/off" antivirals were studied. One was a cycle of two months on, one month off. Second was one week on, one week off. Third was a two-day on, five days off. Each had theoretically interesting reasons why it was worth further investigations.

The two day on/five day off cycle had only three participants studied before that approach was discontinued. It was found that there was some risk in not quickly re-establishing control of replication when going back on treatment using this schedule, and thus no further work is planned with this short cycle. The one week on/one week off cycle also had just a few (four) participants with information about their response out to about three months. To date, however, all were successful in re-establishing a suppressed viral load while on medication, and there was no loss of CD4 cells noted with this approach. While of great interest, it is cautioned that this approach should not be tried outside of research settings before more results are presented since there were significant concerns that these multiple rapid cycles might risk the development of medication resistance, and thereby threaten the longer term success of using antivirals.

Dr. Dybul also presented the results of a small study that cycled with one month off, two months on. Here, after two cycles, nine of nine participants were able to re-establish viral suppression after the two month "on" period. While there was some drop in the CD4 count in the first cycle off of medications, they noted less of a drop in the CD4 counts during the next cycle. However, there was little evidence that these patients had any increase in their immune response directed against HIV — these very early observations suggest that restoring HIV-specific immunity will be much harder in those treated after seroconversion than in those treated during the six month period following exposure to HIV.

The results of the Swiss/Spanish study are out to just about one year, and provide some of the best available data about the longer-term outcomes of an intermittent therapy approach. The cycle starts, as with all of these studies, after they first establish suppression of HIV to below 50 copies with standard antiviral combinations. Then, the cycle is to go off medication for two weeks, followed by eight weeks back on treatment. At one year, there was little evidence that continuous pulsing off meds

with this schedule leads to immunologic control, as they showed that during the one month time off, the 122 participants continued to have viral load returns during each "off" cycle. On average, the viral load came up to about 1,000 copies during each of the two-week cycles off medication, and didn't show a declining trend in the one-year period of the study. (It was also noted that during the first two-week interruption, about 12% had a viral load rebound over 100,000 copies.) However, while there was no evidence for decreasing peaks in the viral load over time in the majority of participants, there was a suggestion that in perhaps 20% of participants, there was some possible decline in the peak viral load off medication over the one-year period. Of those who successfully did re-establish virologic control, the CD4 counts were stable in this group for the entire one-year period, maintaining a mean of just over 700 cells/mm over this one-year period.

However, the study was not uniformly successful for all of those enrolled. Of concern is that about 15% of the group did not get a viral load back down to <50 copies after the eight-week re-treatment period, a finding which happened to about 5% of participants after each two-week interruption. Finally, they reported in one person that drug resistance to the medications taken did develop.

So where do these studies bring us? The larger Swiss study suggests that at best perhaps 20% of those who start treatment years after seroconversion might — through these cycles — have some improvement in immunologic control of HIV that leads to lower viral loads when off medication. In the remaining 80%, this cycle was not fully successful in that 15% did not get a viral load back down to <50 in the eight-week period back on medications. In addition, one person did develop drug resistance.

Perhaps if the re-treatment period were longer than eight weeks, more participants would be successful in meeting this goal. This may be important to accomplish since interruptions of medications may be riskier in those with higher levels of HIV growth, since in the time period that the medications are leaving the body, there is more of a chance that some of the virus will develop resistance to the medications. Alternatively, as in the NIH studies, the period of time off of medications could be shortened to just one week as a way to decrease the degree of viral rebound.

It is also important to emphasize that, except for the decrease in the amount of antivirals actually taken in these studies, it remains completely unknown which if any of these schedules might result in fewer long-term complications than what is seen in those who take antivirals daily. Thus, active ongoing research will be needed in order to provide guidance to those living with HIV infection and their providers about how to apply these initial observations.

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OTHER PRESENTATIONS

Cannabinoids effect on HIV-1 viral load and appetite

Simon Collins, HIV i-Base

Anecdotal benefits to appetite stimulation and stress relief (amongst other effects) ensure that a widespread use of marijuana amongst HIV-positive people in California (where there is also an established movement for legalisation for medical use). Donald Abrams and colleagues at University of California, San Francisco initiated a safety study based on a possible interaction with ARVs via CYP p450 or immune modulation via the CB2 receptor. The study looked at whether cannabis is associated with an effect on viral load, as well as short-term effects on endocrine function, appetite, energy intake and expenditure, body weight and composition.

In this randomised, partially blinded, placebo controlled 21-day study, 67 people (90% men) were randomised to either smoke cannabis, take oral dronabinol (a oral formulation of the active ingredient in cannabis) or take an oral placebo. All subjects were on a 'stable' combination, although only around 50% of people had undetectable viral loads at entry and 10% had counts about 10,000. Entry requirements for the study included previous use of marijuana – although not for the month prior to enrolment.

After three weeks, the study found small decreases in viral load (around 0.15 log reductions) in both the smoked and oral cannabis groups - although the broad definition of 'stable' treatment for entry criteria makes an interpretation of this result difficult. Still, it was an interesting finding, and most importantly viral load did not increase. People on the placebo arm had a reduction in viral load of 0.06 log. What was more significant was the average calorie intake – 4700, 4100 and 3600 calories a day in the marijuana, dronabinol and placebo arms respectively. This lead to an average weight gain of 3.5, 3.1 and 1.3 kgs over the three week study period.

	Calories/day		Weight (kg)	
	Mean	(95% CI)	change	(95% CI)
Marijuana	4771	(4630, 4911)	+3.51	(2.17, 4.86)
Dronabinol	4124	(4017, 4230)	+3.18	(2.24, 4.11)
Placebo	3619	(3545, 3692)	+1.30	(0.57, 2.03)

Three people left the study (1 receiving marijuana, two

receiving dronabinol) due to neuropsychiatric symptoms. No adverse events were reported in the placebo arm.

Reference

D Abrams, R Leiser *et al* – Short-term effects of Cannabinoids on HIV-1 Viral Load. XIII International AIDS Conference, Durban, July 9-14, 2000. Abstract LpPeB 7053.

IL-2 without HAART may delay need for antiretroviral treatment

Simon Collins, HIV i-Base

A pilot study run in the UK for the larger ESPRIT study (of IL-2 with HAART), looked at using IL-2 without background HIV treatment. Results were presented by Mike Youle in a late-breaker presentation.

IL-2 can boost CD4 counts and favourably alter immune function when used together with ARVs, and is recommended in the French treatment guidelines for anyone whose CD4 count remains below 200 after six months maximally suppressive HAART. There is a concern however that IL-2 also increases HIV-1 viral burden, if not supported by HAART. This study set out to look at whether there are benefits to using IL-2 alone, possibly as a strategy to delay using combination therapy.

36 treatment naïve individuals (35 male) were randomised (1:1:1) to receive either high dose IL-2 (7.5MIU, twice daily), low dose IL-2 (4.5MIU, twice daily) or no treatment. IL-2 was given sub-cutaneously for 5 days, every 8 weeks, for 24 weeks. Subjects who received IL-2 could then continue cycles on request. Baseline CD4 and viral load (averaged from last three pre-treatment results) in the IL-2 and control group were 445 cells/mm^3 and 476 cells/mm^3 and 4.4 log and 4.1 log respectively. The primary endpoints for the study were mean area under the curve (AUC) change from baseline CD4 cell count and plasma $\log_{10}$HIV RNA.

After 24 weeks people receiving IL-2 had significantly greater increases in CD4 increases than the control group by +148cells/mm^3 vs +25 c/mm^3 (p=0.001). By 48 weeks this increased to +232 cells/mm^3 vs +13 cells/mm^3 respectively (p = 0.02). Differences between the higher and lower dose arms were not significant (p=0.39). Surprisingly, there were no significant differences between the two groups in terms of changes in viral load although the change in viral load appeared to remain one log higher than the control arm.

IL-2 is certainly associated with significant side effects – similar to having a heavy flu during the dosing week, often requiring time off work. For the remainder of each two-month side effects are rare. 3 out of 12 patients discontinued treatment from the high dose compared to only one discontinuation in the low dose arm. I person in each arm left the study before receiving IL-2.

When IL-2 is used with combination therapy the CD4 increases produced are much stronger than in this study (around 300-400 cells/mm^3 over six months). However, the direction of the approach of this study was to determine if a significant benefit for people who will not or cannot use combination therapy as it is required. Delaying the initiation of ARV treatment, perhaps for several years, by maintaining CD4 count over 300, despite side effects for one in every eight weeks, is an option that some people may prefer and this approach deserves further study.

Reference

M Youle, M Fisher, M Nelson - Randomised study of intermittent subcutaneous interleukin-2 (IL-2) therapy without antiretrovirals versus no treatment. XIII International AIDS Conference, Durban, July 9-14, 2000. Late-breaker Oral Presentation LbOr28.

New potential dual NNRTI-based combinations

Simon Collins, HIV i-Base

Despite a concern over competition for the same binding site when using dual-NNRTI combinations, the potential for this approach excited many researchers and activists long before manufacturers agreed to collaborate on joint research, particularly in view of the benefits shown from dual-protease combinations.

A small pilot study from Los Angeles looked at a once-daily regimen of nevirapine/efavirenz/ddI in 15 treatment naïve and 11 treatment experienced patients. All three drugs were used at the standard daily dose, and although pharmacokinetic data would suggest increasing the efavirenz dose to 800mg QD would be necessary to compensate for an interaction with nevirapine, no alteration was made.

Baseline CD4 count was 351 cells/mm^3 (110 – 800, median 312) versus 368 cells/mm^3 (1 – 800, median 310) and baseline viral load was 38,600 copies/ml (range 576-180,000, median 33,000) and 2,000 copies/ml (<400-18,000, median <400) in the treatment naïve and experienced groups respectively. Results are shown below:

	naïve	experienced
N	15	11
<25 at 9 month	12/12	9/9
<400 at 52 wk	11/12	8/9
% <400 (on-treatment)	92%	89%
% <400 (ITT)	73%	72%
CD4+ (cell/mm^3)	+438	+367
Discontinuations	3	2

All patients became undetectable after nine months (including to less than 25 copies by 9 months). Each group started with an mean CD4 count of around 350 – and saw quite remarkable increases of around 440 and 370 in the naïve and experienced groups respectively.

There were five discontinuations due to side-effects (2 with nevirapine-associated rash and 3 with efavirenz-

associated CNS symptoms or insomnia). Although the study commented that there was no increased incidence of treatment-limiting side effects from combining two NNRTIs – even at 19% - the low numbers in this study make that difficult to assess.

If these results stand up to a larger trial (the 2NN study currently being run by NATEC includes UK sites and a double-NNRTI arm in treatment naïve patients) this PI- and nuke-sparing approach could be one of the pointers to changed treatment strategy that came out of the Durban conference. Given that cross-resistance generally limits the benefit from NNRTIs to one use only, if nevirapine and efavirenz produce an additive or even synergistic effect, this could play an important part in an overall approach to planning treatment strategy. It may also offer an important option now for in salvage therapy salvage therapy – dual NNRTIs were also included in the multi-drug mega-HAART protocol used by Julio Montaner – although with the caution that this should be supported in individual cases with concomitant drug level monitoring.

Reference:

W Jordan, R Jefferson, F Yemofio - Nevirapine (NVP) + efavirenz (EFV) + didanosine (ddI): a very simple, safe, and effective once-daily regimen. XIII International AIDS Conference, Durban, July 9-14, 2000. Abstract TuPeB3207.

Once-daily protease-based regimens

Simon Collins, HIV i-Base

An additional advantage of the above dual NNRTI study is that it involved a once-daily regimen, that is unlikely to require a rigid Q24H adherence. Because of their more favourable half-lives, once-daily regimens have usually been studied using NNRTIs and nucleosides, and often in the context of IVDU-related adherence.

Many companies have recently initiated studies using currently available protease inhibitors boosted with ritonavir, to see if they could be used in once-daily dosing. None of these has produced particularly convincing results that this is either safe or to be recommended – even for a study period. Although once-daily regimens have advantages, the main drive for this research has been from a commercial and marketing perspective rather than a more favourable pharmacokinetic profile and/or improved safety. QD dosing of nelfinavir, saquinavir, indinavir or amprenavir, by co-administration with ritonavir increase susceptibility to toxicity through higher Cmax levels whilst retaining trough levels generally at best similar to standard Q12H or Q8H dosing.

A late-breaker poster looking at QD dosing of nelfinavir with ritonavir did not lead to inspiring results. Six combinations of the two PIs were compared to the standard 1250mg BID nelfinavir in a 14-day PK study in 73 HIV-negative volunteers – only one of which (2500mg NFV/ 200mgRTV) produced comparable trough levels (and a slight improvement on levels of NFV M8.

There were 10 discontinuations over the 14 days of the study. Five due to adverse events including rash, oral lesion (2), pruritus and neutropenia (including two people from the standard BID NFV control arm. Nausea and headaches were reported in 50% people in the 2500/200 arm, although, interestingly this was the only group that reported no incidence of diarrhoea (20-30% across other groups). Other reasons for discontinuation were not given.

In this study, ritonavir only appeared to have a moderate effect on nelfinavir AUC (13-44%) and on AUC NFV M8 (17-49%). Cmax approximately doubled compared to the control arm when 2500mg nelfinavir was combined with either 100mg or 200mg ritonavir. Although there is a likely QD PI in development (no data was presented on this drug by BMS at Durban on 232,632), developing dual-PI regimens that have greater flexibility (forgiveness) to approach true BID rather than Q12H regimens is likely to be more beneficial. It has also often been pointed out that where adherence is an issue, a missed QD dose presents a greater risk than one missed from a BID regimen.

An Italian study switched patients on an indinavir-containing regimen with undetectable viral load (<50 copies) to a once-daily regimen based on IDV 1200mg / RTV 100mg. While viral load didn't rebound in the 12 patients evaluable at 16 weeks, 2/12 reported kidney stones, likely related to much increased peak IDV concentrations shortly after dosing.

References

P Hsyu, R Lewis, B Kerr – Parmacokinetics (PK) of Nelfinavir (NFV) after Once Daily Dosing in Combination with Mini Doses of Ritonavir (RTV) in Healthy Subjects. XIII International AIDS Conference, Durban, July 9-14, 2000. Abstract LbPe7049.

F Maggiolo, M Rizzi, G Finazzi - Once-a-day indinavir therapy in virologically controlled HIV+ persons XIII International AIDS Conference, Durban, July 9-14, 2000. Abstract TuPpA1155.

Mitochondrial DNA (mtDNA) damage in semen as surrogate marker for nucleoside analogue toxicity

Simon Collins, HIV i-Base

Mitochondrial damage is increasingly being linked to nucleoside toxicity, particularly lipoatrophy, peripheral neuropathy and lactic acidosis, yet there are currently no monitoring assays that can help in monitoring changes in mitochondrial DNA, or to use as a surrogate marker for the risk of future toxicity.

The most commonly affected tissues (muscle, fat, liver and peripheral nerve) are difficult and intrusive to sample, and blood is unsuitable as mitochondria are not present in red cells and low expression in leucocytes. Cellular mitochondrial division however occurs at a similar rate in semen to that of key affected tissue and spermatozoa contain relatively few mitochondria with a slower metabolic rate (and therefore highly consistent wild-type).

This prospective study presented by Dr Dush Mital from

the Birmingham Heartlands Hospital, analysed semen mtDNA in an HIV-positive man before and during HAART. Semen mtDNA was isolated using Puregene DNA isolation kit and analysed by mass spectrophotometry.

An initial treatment with 3TC/delavirdine/indinavir was quickly modified to ddI/d4T/nevirapine/hydroxyurea due to toxicity. After 12 weeks this was changed again, to 3TC/ZDV/nevirapine. Analysis of mtDNA (the long PCR result was shown on an agarose gel after electrophoresis viewed with ultraviolet light) showed wild-type both at baseline pre-treatment and after 12 weeks. At week 24 additional bands showed wild-type and mutant deletions. No nucleoside-associated toxicities were reported in this subject at any point in this study.

Although there is not a comparable sample for mtDNA toxicity analysis in women, the technology and expertise for developing assays should this prove successful are at a similar level to that required for viral load or resistance assays. The researchers have since expanded this research with a larger group of patients, including naïve and experienced patients with a well documented history, and a wider range of lipodystrophy symptoms, and will present data at the forthcoming 2nd Workshop on Lipodystrophy in Toronto in the Autumn.

Antiretrovirals and fertility - implications for couples looking to conceive

Simon Collins, HIV i-Base

The study reported above looking at mitochondrial toxicity in sperm, also presented data on the effect of several HIV treatments on sperm quality in an HIV-positive man before and after starting combination therapy. Multiple semen samples were taken prior to initiating HAART and then regularly at six monthly intervals. Sperm count and motility were analysed together with semen plasma viral load (NASBA nuclisens).

Sperm count dropped from 106 million/ml pre-treatment to 0.3 million/ml after 12 weeks on d4T, ddI, nevirapine and hydroxyurea. Six months after a second treatment change, dropping hydroxyurea switching ddI/d4T to ZDV/3TC sperm count had risen to 21 million/ml.

Similar dramatic changes were found in sperm motility.

	Pre-therapy	12 wks Rx (ddi/d4T/NVP/HU)	24 wks Rx (ZDV/3TC/NVP)
SPVL (c/ml)	12,000	BLQ	NA
Sperm count	106 x 10^6	0.3 x 10^6	21 x 10^6
Semen quality			
Rapid	57%	0%	7%
Medium	17%	1%	23%
Slow	7%	7%	6%
Static	19%	92%	64%

Hydroxyurea was believed to be responsible for the major changes in sperm count and motility in this study, and although this is only a single case study, the effect on fertility of different combinations is clearly important for couples looking to have children. This is an option many HIV-positive people are now able to consider (there are 'sperm-washing' clinics in both London and Birmingham for discordant couples) and who may want to adjust their treatment for a period with this aspect in mind.

Reference:

D Mital, J St.John, D White *et al* - Can semen quality and mitochondrial DNA deletions be used as a marker of nucleoside analogue toxicity? XIII International AIDS Conference, Durban, July 9-14, 2000. Abstract MoPeA2122.

Incidence of adverse events at 4 weeks correlates with adherence and virologic failure at 4 months

Simon Collins, HIV i-Base

Over one hundred presentations focused on adherence, inevitably overlapping with conclusions already reported in previous research. Nevertheless, all of these presentations were important and clinicians and investigators need to address the issue of integrating adherence support within every clinical care and trial setting.

An interesting presentation from the French APROCO study found that incidence of side-effects four weeks into a new therapy directly correlated with successful adherence 3 months later. 336 patients who received triple combination protease-based regimens (1 x PI + 2 x RTIs), and remained on the same treatment for more the first four months, self-completed a detailed questionnaire at months 1 and 4. This included a table listing 13 symptoms with space to include frequency, severity and related distress, as well as a section with more general questions. Adherence was defined as taking all prescribed pills over the four days prior to the clinic visit.

This careful approach to adverse effects produced a very accurate picture of the reality experienced by patients – 94% reported at least one symptom at M1, and 88% at M4. Fatigue and diarrhoea were the most frequently reported, 41% registered as mild and 7% as severe. A high median number of symptoms was 4 (IQR 2-6) at M1 and 3 (IQR 3-5) at M4 (the decrease over time was statistically significant with $p < 0.001$). There was also a general decrease in incidence as well as severity in all side-effects (except rash) between M1 and M4. Respectively, 81% and 75% were adherent at M1 and M4 ($p=0.03$). 66% patients were assessed as adherent at both visits and 10% were non-adherent at both visits.

The percentage of patients with undetectable viral load at M4 (< 500 copies/ml) was also significantly lower among

non-adherent patients (81% vs 70%; p = 0.03). Median decrease in viral load titres before and after initiation of HAART (M0 vs M4) was significantly lower among M4 non-adherent (1.6 log vs 1.1 log, p = 0.008). The number of self-reported symptoms was significantly associated with non-adherence at M4 - patients who were non-adherent at M4 had previously declared a higher number of symptoms at M1 (p = 0.006).

The relationship between patients reporting > 4 symptoms at M1 and non-adherence at M4 was also highly significant (OR IC95% = 1.93, 1.11-3.36). Adjustment was made in this analysis for other related factors such as history of previous treatment, younger age, unstable housing, poor social support, alcohol use etc. The decrease in the number of symptoms was only significant among the 252 adherent patients, p (ADH) <0.001 ; p (non-ADH) = 0.35.

Early identification of any patients experiencing side-effects, provides an opportunity to actively help manage these events, as well as incidentally to address adherence issues. Early identification of patients whose treatment is particularly difficult (>4 symptoms) and individual management of symptoms whether by concomitant medicines (anti-diarrhoeal, anti nausea etc) or the opportunity to switch to more tolerable ARVs, provides an opportunity to both improve levels of adherence and treatment outcome.

Reference:

B. Spire, S. Duran, F. Raffi *et al* - A high number of self-reported symptoms following HAART initiation is predictive of poor adherence at 4 months of treatment in HIV-infected patients. XIII International AIDS Conference, Durban, July 9-14, 2000. Abstract TuOrD332.

Prednisone and nevirapine rash

Simon Collins, HIV i-Base

Results of an uncontrolled study presented at ICAAC in 1998 found that using prednisone (40-50mg QD) during the first two weeks of nevirapine therapy led to a reduced incidence of rash (in 1/83 against 10/72 without prednisone). This led many clinicians to prescribe short courses of prednisone for patients starting nevirapine-based combinations.

In Durban, a Canadian study from Julio Montaner group found opposite results. This controlled open-label study in 138 patients (66 of whom were treatment naïve) randomised half of the group to receive prednisone (40mg QD) and half to receive nothing.

Analysis was performed after all patients had completed six weeks treatment - the risk period for NVP-associated rash. The incidence of rash was higher in the prednisone group (36% against 18%) most of which were mild to moderate severity. The majority of rashes were mild (55%) or moderate (9%). Serious rash only occurred in the prednisone group (9% vs 0%).

	Prednisone	no-prednisone	
Rash	36% (25/69)	18% (13/69)	*p = 0.022*
Serious rash	9% (6/69)	0%	

Reference:

J Montaner, M Gigliotti, P Cahn *et al*. The effects of a short course of prednisone (pred) on the incidence of rash associated with nevirapine (NVP, VIRAMUNE). XIII International AIDS Conference, Durban, July 9-14, 2000. Abstract WePpB1378.

The Prevalence of Hypogonadism in HIV-Infected Patients Receiving HAART

Coverage provided by Alvan Fisher, M.D for

http://www.HIV&Hepatitis.com

In this study we did a retrospective chart review of 88 male patients with HIV infection who had been on HAART for at least six months. Hypogonadism as defined by low serum-free testosterone (<15 pg/ml) was seen in 20%. Clinical wasting (weight loss >5% of ideal body weight) was prevalent in 42%. Hypogonadism was seen in 14% of patients without wasting and 30% of patients with clinical wasting. Also the majority of patients with moderate or severe wasting were not hypogonadal, but testosterone deficiency was seen more often in patients with more than moderate wasting. We concluded that testosterone deficiency in these male patients was lower than previously reported in other cohorts and did not correlate with wasting. Indeed, wasting may be the cause of testosterone deficiency.

Ref: Desyatnik M, Baaj A, Fisher A. The prevalence of hypogonadism in HIV-infected patients receiving HAART. TuPeB3180.

HIV-Related Malignancies

Coverage provided by Judith Feinberg, M.D for

http://www.HIV&Hepatitis.com

HPV (Human Papilloma Virus) is the virus that causes warts, including genital and anal warts, and chronic infection with certain strains of HPV has long been associated with precancerous changes that can lead to cancer of the cervix and rectum. Abnormal precancerous changes of both the cervix and anus can be detected by a simple Pap test. (The Pap test involves obtaining cells from the area with a wooden scraper, smearing the cells on a glass slide, staining the cells and looking for abnormalities with a microscope.) Two studies looked at HPV infection at different sites.

One study used a case-control design to evaluate risk factors for HPV in the mouth. In 1997-98, the frequency of oral lesions due to HPV at Grady Hospital in Atlanta was relatively stable, with 18 total cases seen over those two years. However, in 1999, 34 cases were diagnosed.

When the investigators matched their 52 cases with 104 control patients who were similar but did not have HPV disease, they found three factors that were associated with an increased risk of oral HPV: antibody to hepatitis B, a decrease in the viral load in the six months prior to the HPV diagnosis, and African-American heritage. Most opportunistic diseases related to HIV have decreased in frequency in the HAART era, so the increased rate at which this problem is currently being seen is puzzling. Longer term follow-up is needed to sort this out.

HIV-positive teenagers between 13 and 18 years old were evaluated for anal HPV infection, early precancerous changes and other STDs. The group included 83 boys and 265 girls. There were different risk factors identified for anal HPV infection and precancerous changes of the anus between the sexes. In adolescent boys, anal HPV infection was associated with having anal sex and with the presence of anal warts.

In adolescent girls, anal HPV was associated with the presence of both anal warts and external genital warts, but not with anal intercourse. When the investigators excluded the presence of warts at any site, then the most important risk factor for boys was sexual orientation, and the most important factor for girls was having fewer than 200 CD4 cells. When they evaluated the risks for the development of precancerous changes of the anus, the risks were again somewhat different for the two sexes. For boys, these changes were associated with being HIV-positive and with detection of HPV, and for girls the changes were associated with having more than one sexual partner and with anal HPV. These data indicate that it is valuable to screen sexually active HIV-positive teenagers for both HPV and for precancerous changes.

Ref: Blumberg H.M., King M.D.,. O'Daniels C.M at al. Emergence of oral HPV infection among HIV-infected patients in the HAART era (TuOrB304)

OTHER NEWS

$1bn drug deal creates debt for "tomorrow's AIDS orphans"

The United States has offered sub-Saharan African nations a $1bn (£666m) loan programme to buy anti-AIDS drugs. The new programme was announced in Washington last week by the congressionally funded US Export-Import Bank. It involves five year loans to 24 eligible countries at interest rates of about 7% a year. The offer has been condemned by Oxfam as "a debt that tomorrow's AIDS orphans will be forced to pay."

The US offer requires countries to buy drugs manufactured in the United States. Oxfam said that the loan would simply load more debt on countries that were already among the poorest in the world. "The deal amounts to a credit-line which locks poor countries into buying expensive patented drugs, when what they need is help to make or buy low cost generic equivalents," Oxfam said in press release. It continued: "The G8 nations promised last year to write-off $100 billion worth of poor country debt. But little of that has been delivered. For the US this week to offer these same poor countries another $1 billion of debt is wrong-headed." The debt owed by sub-Saharan African nations currently stands at $15.2bn.

"This offer has been publicised as an act of kindness toward Africa's 24.5 million sufferers of HIV and AIDS. In fact, the money will flow straight into the pockets of the US pharmaceutical industry," said an Oxfam spokesman. Oxfam accused the United States of setting up the deal to help the drug companies fight off competition from generic drugs that can be manufactured locally. Brazil and India, for example, currently manufacture anti-AIDS drugs at a fraction of the cost of those marketed by multinational pharmaceutical companies.

The companies consider these generic drugs to be a violation of intellectual property that the companies say is protected by patents and trade agreements enforced by the World Trade Organisation. The anti-AIDS drug stavudine, for example, costs $6.10 per daily dose in Uganda, where it is marketed by Bristol-Myers Squibb, but just 55 cents (36p) in Brazil, where it is produced generically. Brazil and India are among the few countries in the world that started local production of anti-AIDS drugs before the World Trade Organisation rules on intellectual property rights were applied.

"The best way to begin helping the poor countries of sub-Saharan Africa is to cancel their debt so they can invest in health, education, and development," an Oxfam spokesman said.

Ref: BMJ 2000;321:260 (29 July)

The Hepatitis Report

We would like to take this opportunity to recommend Treatment Action Group's The Hepatitis Report just completed by Michael Marco and Jeffery Schouten, M.D. This report is an excellent, detailed summary of where we are in the understanding of hepatitis C - transmission, prognosis, monitoring and treatment. It includes sections on HIV/HCV co-infection as well as information on HIV/HBV co-infection.

Interviews with researchers from around the world reveal candid and useful remarks. The research and policy recommendations are thoughtful, straightforward and absent of industry and institutional influence.

Every researcher, medical provider and person living with or affected by hepatitis C who wants to be fully up-to-date should read this outstanding report, available free at:

http://aidsinfonyc.org/tag/comp/heprpt.html

Evaluating Structured Treatment Interruptions: Rationale, Experience, Potential Risks, and Benefits

Veronica Miller, PHD, Director, Interdisciplinary HIV Research, J. W. Goethe-Universitat, Frankfurt, Germany

Summary by Tim Horn, Edited by Calvin Cohen, MD, MS, and Martin Markowitz, MD

Considering the growing number of drawbacks and uncertainties associated with chronic antiretroviral therapy, it should come as no surprise that both clinicians and patients have found a great deal of optimism in structured treatment interruptions (STIs). A number of researchers, including Dr. Veronica Miller, have hypothesized various rationales for discontinuing treatment in some HIV-infected patients, even for short periods of time:

- **Patients grappling with adherence issues.** Poor adherence has been identified as a leading cause of drug failure among patients receiving combination therapy. Stopping therapy in these patients, at least until barriers to adherence can be dealt with, might prove to be a short-term preventive solution to a long-term dilemma—multiple drug resistance.

- **Side effects.** There may be a benefit in initiating an STI to help control or reverse some of the long-term toxicities associated with HAART. It is still not known, however, if temporary cessation of therapy has any significant impact on side effects such as elevated liver function, peripheral neuropathy, or nutritional disorders (e.g., body-habitus changes or metabolic complications). A study, being conducted by the National Institutes of Health, is currently studying pulsed antiretroviral therapy as an approach to decreasing toxicities.

- **Pregnant women.** According to both the United States Public Health Service and the International AIDS Society-USA, antiretroviral therapy is of considerable benefit in reducing perinatal HIV transmission rates. However, few data are available to indicate that antiretrovirals are safe for a developing foetus during the first trimester of pregnancy when teratogenicity is most common. In turn, STIs may be a feasible option for HIV-infected women receiving HAART prior to pregnancy, carried through to the second trimester when such side effects are less common.

- **Patients with multiple-drug resistance and experiencing treatment failure.** Given the lack of effective options for patients with multiple-drug resistant HIV variants and few remaining treatment options, STIs have been suggested to be a worthwhile effort. As discussed by Dr. Miller, STIs in the setting of treatment failure appear to halt the evolution of additional mutations conferring drug resistance and, in many cases, allow for a shift to drug-sensitive wild-type virus.

- **Boosting HIV-specific cellular responses.** Preliminary data suggest that STIs may induce immune responses capable of controlling, albeit partially, HIV replication. This rationale was also discussed by Dr. Miller and may prove to be the most important benefit associated with STIs.

Full text available at:

http://www.prn.org/_frms/vol5/num2/miller_frm.htm

Source:

The PRN Notebook, June 2000, Vol. V, Num. 2.

Maintenance of Large Numbers of Virus-Specific CD8+ T Cells in HIV-Infected Progressors and Long-Term Nonprogressors.

The virus-specific CD8+ T cell responses of 21 HIV-infected patients were studied including a unique cohort of long-term nonprogressors with low levels of plasma viral RNA and strong proliferative responses to HIV Ags. HIV-specific CD8+ T cell responses were studied by a combination of standard cytotoxic T cell (CTL) assays, MHC tetramers, and TCR repertoire analysis. The frequencies of CD8+ T cells specific to the majority of HIV gene products were measured by flow cytometric detection of intracellular IFN-gamma in response to HIV-vaccinia recombinant-infected autologous B cells.

Very high frequencies (0.8-18.0%) of circulating CD8+ T cells were found to be HIV specific. High frequencies of HIV-specific CD8+ T cells were not limited to long-tern nonprogressors with restriction of plasma virus. No correlation was found between the frequency of HIV-specific CD8+ T cells and levels of plasma viraemia. In each case, the vast majority of cells (up to 17.2%) responded to gag-pol.

Repertoire analysis showed these large numbers of Ag-specific cells were scattered throughout the repertoire and in the majority of cases not contained within large monoclonal expansions. These data demonstrate that high numbers of HIV-specific CD8+ T cells exist even in patients with high-level viraemia and progressive disease. Further, they suggest that other qualitative parameters of the CD8+ T cell response may differentiate some patients with very low levels of plasma virus and nonprogressive disease.

Ref: Gea-Banacloche JC, Migueles SA, Martino L *et al.* J Immunol 2000 Jul 15;165(2):1082-1092.

European Drug Approvals

Amprenavir

Glaxo Wellcome has received European Union approval of its HIV drug amprenavir (Agenerase™), the company's first protease inhibitor (PI). Amprenavir, which would be used with other antivirals to treat HIV in adults and children, is already approved and marketed in the United States.

Enteric coated didanosine (ddI)

The European Union (EU) has approved Bristol-Myers Squibb's capsules of enteric coated ddI for once-daily administration. The capsules, are a new formulation of ddI which is resistant to gastric acid and therefore does not require the co-administered buffer agent. The buffering agent was thought to be responsible for much of the gastrointestinal intolerance associated with the previously approved version of the drug. The buffered ddI was originally approved in the EU in 1991.

Abacavir/zidovudine/lamivudine co-formulation (Trizivir™)

The European Union has awarded approval to Glaxo Wellcome for its co-formulated combination anti-HIV therapy Trizivir™. This is a combination of abacavir, zidovudine and lamivudine in one pill.

ABT-378/r (lopinavir/ritonavir)

Abbott Laboratories said on Wednesday that it has submitted an application to European regulators seeking approval for AIDS and HIV treatment ABT-378/r.

The Abbott Park, Illinois-based company said that the application was submitted to the European Agency for the Evaluation of Medical Products for review based on clinical data from studies conducted around the world. ABT-378/r (lopinavir/ritonavir) is a protease inhibitor (PI) and was filed under the trade name Kaletra.

The European regulatory submission of ABT-378/r is based on phase II and phase III trials in more than 700 patients from a broad range of treatment groups including those new to antiretroviral therapy, as well as those who have failed other drug regimens. The primary studies include 2 phase II trials in PI-naive and PI-experienced patients and a phase III study in naive patients. A phase I/phase II paediatric trial in 100 children was also included in the submission, Abbott said.

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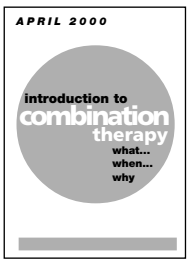

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