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EDITORIAL

The New Year, traditionally a time to look back and review achievements and acknowledge goals unmet, but also a time to look forward and institute change. This particular New Year welcomes a change for HIV i-Base and our "HIV Treatment Bulletin" publication. It accompanies a change in focus for myself, the editor, Paul Blanchard.

I have been involved with i-Base since it was formed in April 2000 by the former publications, editorial and meetings team from the AIDS Treatment Project (ATP). Myself, Raffi Babakhanian and David Campbell-Morrison founded ATP back in the pre-Vancouver days of 1996 spurred on by Mike Youle who highlighted the need for a UK treatment activist organisation.

I myself had initiated HAART in March 1996 after many years of antiretroviral scepticism (fuelled by personal observations of the effects of AZT on friends, the Concorde study results and the black days of the Berlin International Conference on AIDS). Reports were filtering through of some exciting new drugs, the protease inhibitors, and faced with a diagnosis of pulmonary KS and a CD4 count of zero it was either continued scepticism plus radio- and chemotherapy or a leap into the unknown.

The rest is, as they say, history. My miraculous recovery from the jaws of death was mirrored in others who were fortunate enough to gain early, compassionate access to these drugs. Mikes concern for improved access and knowledge about these advances, the lack of a UK community based organisation led by the HIV-infected, and the widespread conservatism and inertia of UK physicians and HIV commissioners - mono and dual therapy being widespread practice in the UK way past the Vancouver conference, were the driving force behind our efforts.

Raffi and David lobbied the pharmaceutical industry and organised meetings, I developed our first publication "Dr Fax", a fortnightly faxed newsletter of treatment advances and drug access issues. This went on over four years to evolve, with the change of organisation, into HTB as you know it today.

What you may not know, however, is how all of this happened on a "wing and a prayer" – no statutory recognition, short term on/off funding from pharmaceutical companies and our own struggles with infection, chronic ill health and treatment. I myself continued to maintain a full-time post in teaching throughout these years and it is here, in my "real job" as I call it that changes have led to the hand over of HTB.

The development of an osteopathic healthcare clinic for HIV-infection and the opportunity for PhD studies have proved incompatible with the burden of work associated with HTB and Simon Collins a regular contributor to HTB and veteran commentator on HIV treatment issues is taking over the reigns. With an editorial team including Graham McKerrow and Polly Clayden, Simon will continue the style and direction of HTB. I also hope to be a regular contributor on neurology and issues related to manual therapies, so I won't be leaving the gang all together.

This, my last issue as editor, contains extensive reports from the recent congress in Glasgow as well as the usual round-up of treatment news. We also include a feedback questionnaire to help you to inform us about your experience of HTB and any changes you might welcome. As long as challenges exist for both patients and physicians in coping with HIV and it's treatment, HTB and i-Base will continue to publish pertinent information to facilitate management and care. So until it is truly realistic to call HIV-infection a chronic manageable disease read on. Finally I would like to thank our team of medical consultants, especially Graeme Moyle and Stefan Mauss, and our fund raiser extraordinaire Polly Clayden whose dedication and hard work lightened the load.

CONFERENCE REPORT

6th International Congress on Drug Therapy in HIV Infection

17-21 November 2002, Glasgow, UK

Combination of three generic drugs in one pill meets bioequivalence criteria when compared with the branded drugs: Triomune vs d4T/3TC/NVP

Polly Clayden HIV i-Base

One of the most notable presentations at the Glasgow meeting was a pharmacokinetic evaluation of lamivudine, stavudine and nevirapine given as a fixed dose combination pill (Triomune) versus the same three drugs given separately in healthy human volunteers.

The study showed that Triomune met the requisite criteria for the conclusion of bioequivalence with regards to rate and extent of absorption.

Triomune is a combination pill manufactured by the Indian generic maker Cipla containing two NRTIs (stavudine 40mg and lamivudine 150mg) and one NNRTI (nevirapine 200mg), used twice daily.

This randomised, single dose study in 28 subjects, investigated the pharmacokinetic parameters between the triple combination product versus the respective reference products (originators drugs) in order to establish bioequivalence.

Dr Jaideep Gogtay and colleagues at Cipla in Mumbai, India, and at Lambda Therapeutic Research in Ahmedabad, India, reported that the drugs were administered under fasting conditions and a total of 26 serial plasma samples were collected up to 288 hours post-dose. Concentrations of lamivudine, stavudine and nevirapine were estimated from the plasma samples obtained after the administration of the test and reference formulations. Agents were considered bioequivalent if the 90% parametric confidence intervals constructed for ratios of means of log-transformed pharmacokinetic parameters AUC0-t and AUC0-t of the test and reference formulations were within the range of 80-125% and that for Cmax were within the range of 75-135% for all the three products, as per CPMP guidelines.

The investigators found that triomune "…met the requisite criteria for the conclusion of bioequivalence with regards to rate and extent of absorption." The ratios of AUC0-t and AUC0-t for the three drugs were from 96.6% to 104.8%.

This presentation provoked some practical clinical questions from the floor, including Graeme Moyle of Chelsea and Westminster Hospital, London, who asked how this product was managed considering that it is recommended patients naïve to nevirapine have a lead–in period of a 200mg daily dose for two weeks. (Answer: the product has a warning that it is not intended for use in patients who are just initiating therapy with nevirapine – Cipla also manufacture the three drugs individually).

David Burger then raised the issue of using a lower dose of 30mg BID for patients below 60kg. (Answer: there are two formulations Triomune 30 and Triomune 40).

The researchers wrote: "It is concluded that the single tablet formulation containing lamivudine150mg/stavudine 40 mg/ nevirapine 200 mg is bioequivalent to the reference compounds given separately."

Ref: Gogtay JA, Manek V, Nayak VG A pharmacokinetic evaluation of lamivudine, stavudine and nevirapine given as a fixed dose combination pill versus the same three drugs given separately in healthy human volunteers. 6th international Congress on Drug therapy in HIV Infection 17-21 November 2002 Glasgow Abstract PL8.4

COMMENT

Interestingly it takes a generic drug maker to take the most significant step in helping patients to better adherence - combining all three of the antiretrovirals necessary for an HIV treatment regimen in one pill irrespective of manufacturing source. Why can't western pharmaceutical companies put in the effort necessary to make this a reality for all patients? If alleviation of disease and suffering is the primary concern of these companies then collaboration and licensing agreements should be initiated to follow Cipla's lead. The lack of initiative and effort in this direction as well as the development of "incestuous" one company only co-formulations suggests that market share and competition currently take a higher priority than patient care.

We would strongly urge pharmaceutical companies to make efforts to collaborate, particularly regarding protease inhibitors and PK enhancement. Both tipranavir and fos-amprenavir require such PK enhancement to reduce pill burden, but why reduce pill burden on the one hand and then increase pill count on the other by not including ritonavir in a co-formulation? Patient needs are paramount here.

The International Federation of Pharmaceutical Manufacturers in Geneva, which lobbies on behalf of the multinational drug companies, issued a statement saying "it would be unfortunate if the current plague of substandard and counterfeit medicines spread" because generics makers were on the health organisation's list. Industry loves to confuse generic products (which are perfectly safe) with counterfeits.

It is legal in India to copy a medicine designed abroad and put it on the local market (as long as the companies can prove they use a different manufacturing process).

The scientific committee must be applauded for foregrounding this study at a conference with such a heavy pharmaceutical presence.

Link:
http://www.cipla.com/ourproducts/18/triomune.htm

An overview of the conference

Graeme Moyle, HIVandHepatitis.com

The 6th International Congress on Drug Therapy in HIV infection followed the format of the previous meetings, consisting predominantly of oral plenary sessions with 'experts' summarising the current state of the art in treatment-related issues, a small number of oral presentations of new data and a poster session extending to around 300 posters of data predominantly derived from European treatment centres.

Viral load testing

Over the evolution of viral load testing the lower limit of detection has declined from 10,000 copies/ml with the first Chiron assay, to 4-500 copies/ml, and most recently to the standard of less than 50 copies/ml. Studies such as the INCAS study demonstrated that there were benefits in terms of treatment durability in achieving suppression below 20 copies/ml relative to individuals who achieved suppression below 500 copies but remained above 20 copies/ml.

Evidence from studies examining viral evolution or LTR circles has indicated that ongoing viral replication occurs in a substantial subset of individuals who have viral loads repeatedly below 50 copies/ml. This begs the question as to whether there are further returns in terms of treatment durability or improved immune reconstitution in individuals who suppress viral load below five copies/ml (ie a further logarithm below the current cut-off).

This idea was evaluated in individuals naïve to antiretroviral therapy who initiated on a triple therapy regimen with Zerit (stavudine, d4T), Epivir (lamivudine, 3TC) and Kaletra (Lopinavir/ritonavir). The study used a modified Amplicor assay, which had a limit of quantitation of less than three copies/ml. Samples from patients with viral loads less than 50 copies/ml at which 24, 48 and 72 were analysed using this assay and the outcome of these patients after four years of follow-up was correlated with suppression.

The study included 100 individuals with a median baseline viral load of 4.8 log copies/ml and a median CD4 count of 326 cells/mm3. By intention to treat analysis at week 204, 71% of patients had a viral load less than 400 copies and 70% had a viral load less than 50 copies/ml, by on treatment analysis the proportions being 99% and 97%, respectively. Fifteen individuals met criteria of virological failure defined as two consecutive samples with viral load values > 400 copies/ml on therapy.

Patients who commenced therapy with viral load less than 100,000 copies or CD4 count greater than 200 cells/mm3 were more likely to achieve at least one viral load value <3 copies/ml. Stratification by baseline viral load above and below 100,000 copies/ml, 37% versus 72% of individuals achieved at least one viral load <3 copies/ ml and for CD4 cell count below and above of 200 cells/mm3, 37% and 67% of patients, respectively, achieved at least one <3 copies/ml viral load value.

Patients who achieved a viral load >3 copies/ml were no less likely to experience virological failure than those who had at least one or indeed multiple viral load values <3 copies/ml. Additionally, time to loss of virological response did not differ between individuals who achieved and those who did not achieve a virological response to <3 copies/ml.

These data would suggest that pushing the limits of detection of viral load assays lower than those currently available provides no greater return in estimating the likely durability of treatment effect and that a viral load value <50copies/ml is biologically meaningful. Whilst it is possible that at the low levels of viral [replication] evolution is occurring in individuals with detectable virus above three copies/ml but below 50 copies/ml, it does not seem to impact the treatment effect over the course of four years of follow-up.

Adherence

Several studies looked at the way in which adherence may be improved by manipulating characteristics of the treatment regimens. A survey of 504 HIV positive individuals across France, Germany, Italy, Spain and the United Kingdom reported a high level of interest in once a day regimens with patients anticipating that they would adhere to medication more successfully.

The small number of individuals in the survey who were on once daily regimens described fewer missed doses.

Perhaps the most interesting element of the survey was the preference for dosing schedules according to tablet volume. Individuals offered eight or more pills per day in two-thirds of cases preferred to divide the medication into twice a day dosing. As the number of pills in the regimen declined, an increasing preference for taking all of the medication at once increased, such that regimens involving six pills would be preferred once a day by 59 percent of individuals, for regimens containing four pills, 84% preferred once daily and regimens containing three pills, 92% of individuals wanted once daily dosing.

This suggests that if once a day dosing of antiretroviral medication is to become a common reality, consideration to making the regimen maximally compact remain important.

One way of doing this is to make combination tablets. The available combination tablets all involved pairs or triplets of agents all owned by a single company. A company from India presented bioequivalence data indicating that a fixed dose tablet of d4T, 3TC and nevirapine can be readily and cheaply made.

This combination tablet produced by Cipla Pharmaceuticals, is now providing triple antiretroviral therapy in some parts of the developing world at a price of one US dollar per day. The problem with such a tablet is that it breaches the patents and intellectual property held by the pharmaceutical companies that develop these products.

This may potentially act as a disincentive for pharmaceutical companies to develop new antiretroviral agents for fear that their return on investment or even the recuperation of their original investment may be impacted by companies that ignore patents. It therefore behoves the pharmaceutical companies to cooperate with each other to produce a wider range of combination tablets for availability in both the developing and the developed worlds.

A retrospective comparison of prescription refills in individuals receiving Combivir tablets compared with individuals receiving separate dosing with AZT and 3TC reported that adherence was substantially better and fewer therapy days missed in individuals who took the combination tablets relative to the separate dosing.

Other factors identified in the study by multivariate logistic regression that were associated with better adherence included male sex, having fewer than three antiretroviral pills per day, receiving a non-nucleoside reverse transcriptase as an additional

agent and having received therapy for less than 12 months.

In subgroup analyses, evidence that adherence to physician visits, absence of active psychiatric illness, alcohol or illicit drug use, and the presence of HIV symptoms were all important to adherence, and these profiles benefited from the use of the combination tablets.

Identification of individuals who may be at risk of poor adherence and management of factors which contribute to poor adherence prior to the initiation of therapy are likely to be important in managing treatment success.

In addition, this study underlines the value of combination tablets in easing the burden of therapy and reinforces the observation from studies in other areas of medicine that adherence declines with time and therefore should be something that is raised at every clinic visit rather than simply around the time of therapy initiation.

Once daily regimens

Data on several once a day regimens or potential once a day drugs were reported at the conference. The pro-drug of amprenavir, Fos-amprenavir (aka GSK 908) given as two pills once a day in combination with two pills of ritonavir showed similar responses to twice daily nelfinavir in antiretroviral naive individuals initiating therapy with a backbone of abacavir plus 3TC.

The Fos-amprenavir group reported a trend to better anti-viral effects in individuals who commenced therapy with very high viral loads (> 500,000 copies/ml). The tolerability of this agent appeared somewhat better than nelfinavir with a significantly lower rate of diarrhoea. However, somewhat greater elevation in fasting triglycerides was seen in the Fos-amprenavir group.

The two pills once a day protease inhibitor atazanavir was also discussed. Patients completing a randomised comparative study of atazanavir versus nelfinavir in first-line therapy (in which atazanavir was superior to nelfinavir at the cut-off of 400 copies/ml but not for the 50 copy assay) were switched from nelfinavir to atazanavir. Patients in this 'roll-over' study reported maintenance of virological control after switching and significant declines in total cholesterol (by 16%), LDL (by 21%) and triglycerides (by 28%) ($p< 0.0001$) as well as a significant increase in protective HDL (by 5%, $p< 0.05$). These data are in keeping with other prospective data that indicate that atazanavir is metabolically benign.

A review of safety information with the extended release formulation of stavudine (Zerit), which has recently been approved in the US, was also reported. The two main licensing studies for this agent (known as studies 096 and 099) both evaluated the efficacy of d4T XR with the current formulation of d4T in treatment naïve patients who also received 3TC and efavirenz. Across the studies 466 individuals received d4T XR and 467 individuals received the currently in use immediate release (IR) formulation.

No differences in adverse event rates of any grade or any relationship to treatment were observed. Discontinuations due to any adverse events were reported in 5% of d4T XR and 7% of d4T IR patients. Peripheral neurological symptoms thought related to study treatment were reported in 3% of d4T XR and 6% of d4T IR recipients, discontinuations due to neuropathy symptoms occurring in <1% of XR and 2% of IR patients.

Lipodystrophy, as assessed by investigators, was reported in 3% of XR and 5% of IR patients, with <1% of XR and approximately 2% of IR patients being specifically described as having lipoatrophy. Symptomatic hyperlactataemia or lactic acidosis occurred in three patients in the XR group and six patients in the IR group. Importantly, of the nine individuals who developed symptomatic hyperlactatemia or acidosis, most had known risk factors for this problem.

Of the nine individuals on d4T XR or IR who developed lactate problems, seven were female, three obese (BMI > 30) and four overweight (BMI 25 to 30). Taken together, these data suggest that the new formulation of d4T may have a somewhat lower risk of drug toxicities which have been suggested to be related to mitochondrial inhibition. More prospective data are needed to confirm this view. With regards to other adverse events within the studies, no differences were observed for shifts in haemoglobin, hepatic transaminase, lipase, or elevation of triglycerides.

Lipid profiles on therapy with protease inhibitors

The DAD study is a prospective study incorporating multiple HIV treatment databases and among more than 12,000 individuals includes 7,729 individuals currently receiving protease inhibitors. The most commonly used protease inhibitor regimens in the cohort are nelfinavir (Viracept) (2,574 individuals), indinavir (2,354 patients), and ritonavir-based double PI regimens (1,464 patients). The median cumulative exposure to protease inhibitors in the cohort is 30 months.

The study is evaluating cardiovascular risk factors and the possible impact of antiretroviral agents on cardiovascular disease. Of note, 44 percent of the patients in the cohort are current smokers and only 5% of patients are currently treated with either antiplatelet or lipid-lowering therapy.

Data presented at this meeting looked at differences at entry to the cohort between protease inhibitors with regards to dyslipidaemia. Dyslipidaemia was defined for total cholesterol, HDL, total cholesterol to HDL ratio and triglycerides by the cut-offs used in the USA national cholesterol education programme (NCEP).

The proportion of patients with a total cholesterol in the intervention range (greater than or = 6.2 mmol/litre) was highest in individuals receiving ritonavir or a ritonavir-based PI regimen (37.2% of individuals) and least in individuals receiving saquinavir (16%).

Rates of cholesterol elevation with indinavir (Crixivan), amprenavir (Agenerase) and nelfinavir (Viracept) were similar (23% to 25%). The proportion of patients with low HDL (< 0.9 mmol/litre) was highest amongst amprenavir-treated patients (41.9%) and least amongst nelfinavir recipients (20.4%).

The proportion of individuals with low HDL were similar amongst indinavir, Fortovase (saquinavir), ritonavir, and regimens containing two PI's (29 to 33%). With regards to the ratio of total cholesterol to HDL, elevated ratios (> or = 6.5) were observed most commonly in ritonavir-containing regimens (30.5 to 31.4%) and least common in saquinavir- (14%) and nelfinavir- (16%) treated patients with indinavir and amprenavir lying intermediate to those extremes (23.4% and 25.8% respectively).

With regards to triglycerides elevation (> or = 2.3 mmol/litre) saquinavir again proved the most benign of the agents (28.5% of individuals having elevated values) and ritonavir the most

problematic (61.8%). Of note, patients receiving amprenavir, a protease inhibitor often considered to have a "better than average lipid profile", triglycerides elevation was observed in 51.6% of patients, whereas elevation was only seen in 34.1% of indinavir recipients and 33.5% of nelfinavir recipients.

These data are consistent with previous smaller cohort studies that support the idea that saquinavir is the approved PI least likely to be associated with lipid elevation and regimens which include ritonavir have a greater chance of being associated with dyslipidaemia.

Pharmacokinetic evaluation of tenofovir and enteric-coated ddI

Mark Nelson, TheBody.com

Background

Tenofovir (TDF, Viread) is a nucleotide and ddI (didanosine, Videx) is a nucleoside. Both may be used as the backbone of HIV therapy with either a non-nucleoside or a protease inhibitor. TDF has been increasingly used in antiretroviral therapy following the results of study 903. This study looked at the regimen of TDF/3TC (lamivudine, Epivir)/efavirenz (EFV, Sustiva), and, at 48 weeks, more than 85% of study participants were able to reach a viral load below 400 copies.

Didnosine is a highly effective antiviral also available for once-daily dosing. However, due to the food restrictions with ddI (it has to be taken without food, in a fasted state), many individuals have chosen alternative therapies that they find easier to comply with. ddI has to be administered in the fasting state because the area under the curve (ie exposure) is reduced by approximately 25% when taken with food.

However, previous evidence has suggested that when TDF is dosed with ddI, a drug interaction occurs which leads to higher levels of ddI. Because of these results, it has been suggested that the dose of ddI should be reduced when used with TDF, and that it may be possible to remove the food restrictions with ddI. This would clearly lead to the possibility of an easy-to-take nucleoside/nucleotide backbone of TDF/ddI, which could be taken once daily, and ease the compliance problems associated with ddI therapy while providing a potentially highly effective backbone.

Aim

The aim of this study was to measure the pharmacokinetic (PK) interaction with ddI/TDF when administered together either with a light meal or in a fasting state.

Results

Twenty-eight individuals entered this study. Fourteen were male and 14 female. The majority were Caucasian. Administration of enteric coated ddI together with TDF either in the fasting state or with a light meal made no difference to the TDF PK. However, in individuals where ddI was administered at the full dose of 400 mg with a light meal, together with TDF, there was an increase in the Cmax (the maximum level of ddI reached) from 1,050 ng/mL to 1,720 ng/mL, and the area under the curve (ie total exposure) from 3,160 ng/mL to 5,060 ng/mL. No serious adverse events occurred during the study period over 15 days.

Conclusion

The conclusion of the study was that co-administration of TDF and ddI with a light meal did not alter the PK of TDF. The administration of ddI simultaneously with TDF and a light meal results in an elevated ddI exposure, suggesting that it is possible to administer ddI and TDF together with a light meal and that a reduction in ddI dosage is necessary.

Clinical implications

Unfortunately, no dosing alteration of ddI was suggested in this study, and further studies are ongoing. However, it appears that the administration of TDF and ddI is possible without reduction in ddI exposure if given together with a light meal. However, how they define "light meal" was not mentioned in the abstract. Whether "heavier" meals may alter the PK differently is therefore unclear. However, in the light of this data, many physicians have decided to reduce the dose of ddI to 250 mg in patients where TDF and ddI are administered within the same antiviral regimen.

Certainly at our unit at Chelsea and Westminster Hospital in London this has been common practice. We have not observed an increase in adverse events, and many patients have commented that minor ddI-related adverse events such as dry mouth, have either disappeared or been reduced by this dosing strategy. Some authors have suggested that even with the reduction to 250 mg there may still be a cause for greater ddI exposure and therefore more severe toxicities such as pancreatitis. This has not been observed at our unit.

The other advantage of this dosing strategy is that TDF, ddI and other once-daily drugs may be given as true once-daily therapy. Many patients have also commented on the relative ease of administration of such a regimen compared with when ddI was dosed with food restriction. Further studies are ongoing looking at different doses of ddI with TDF with food, and physicians and patients need to make their own decisions regarding the relative risk of dosing these drugs together as against the probable efficacy of such a regimen and ease of administration.

Ref: B.P. Kearney. Tenofovir DF (TDF) and Didanosine EC (ddI EC): Investigation of Pharmacokinetic (PK) Drug-Drug and Drug-Food Interactions. Poster 932, The 6th International Congress on Drug Therapy in HIV Infection

Source: The Body

Link:
http://www.thebody.com/confs/hiv6/hiv6.html

The advantages of fosamprenavir; comparing saquinavir/r to lopinavir/r; reducing viral load to <3 copies; AZT-d4T cross resistance; and rising HCV rates

Mike Youle, NATAP

Amprenavir once daily

The trials and tribulations of amprenavir have not been a happy story, consisting of a drug with a high-pill burden and frequent gastro-intestinal side effects, mainly diarrhoea and bloating. Fosamprenavir (GW433908, 908) is a new formulation with a distinct and now well-characterised resistance profile. The change in formulation allows for once daily dosing (QD) when combined with 200mg of ritonavir (RTV).

Schurmann and colleagues from the US, Europe and South Africa presented the SOLO study, a large multi-centre, randomised, open-label study in ART-naïve subjects which compared the efficacy and safety of 908/RTV QD vs nelfinavir (NFV) BID over 48 weeks [1]. Six-hundred and sixty subjects (649 treated) with plasma HIV-1 RNA ‡1000 copies/mL were randomised 1:1 to 908 1400mg/RTV 200mg QD or NFV 1250mg BID in combination with ABC and 3TC BID, and were stratified at entry by viral load >100,000 or <100,000 copies/mL. Subjects generally had advanced HIV disease at baseline: median HIVRNA of 4.8 log10 c/mL with 43% >100,000c/mL; median CD4 170 cells/mm3, 20% had <50 cells/mm3; 22% had a history of AIDS defining events.

Diarrhea was significantly lower in the 908/RTV group (9% v 16%, p=0.008), but the incidence of other drug-related side effects was comparable. Incidences of severe lipid abnormalities were low despite the use of low dose RTV (triglycerides: 6% v 2%; cholesterol: 1% v 0; 908/RTV v NFV respectively). These results show that the new version of amprenavir is at least as good as nelfinavir and that has a low pill burden. It would seem logical that those who are currently on amprenavir should switch to fosamprenavir when it becomes available in the clinic.

MaxCmin2: saquinavir/r vs lopinavir/r (Kaletra)

Another protease inhibitor based comparison study that had its first airing at this Scottish meeting was the MaxCmin2 trial that compared saquinavir soft gel/ritonavir 1000mg/100mg with lopinavir/ritonavir 400mg/100mg [2]. The study was conducted in a wide range of patients who were naive to treatment or who were undetectable with side effects or failing therapy but who were still sensitive to the boosted protease regimens.

The MaxCmin2 trial was designed to test whether the two protease inhibitors had differences in 48 week efficacy and safety profile among patients with a clinical need for a ritonavir-boosted PI treatment. All patients also received at least two (non) nucleoside reverse transcriptase analogues (NRTI's/NNRTI's). In the protocol, one interim analysis was planned when all patients had completed 24 weeks of follow-up. As per protocol, the Peto method of repeated significance testing was used to test for differences between the treatment arms, with a p-value of 0.001 used as the significance level for the interim analysis presented to the independent data safety and monitoring board (DSMB). Differences, which did not reach this level of significance, were considered not significant.

A total of 339 patients from 28 sites in Europe, South and North America were randomised from June 2001 to January 2002, of which 326 initiated the PI to which they were assigned to receive (the ITT/exposed population - ITT/e). Forty-nine percent of subjects were PI-naïve at entry (32% antiretroviral naïve), 32% were PI-experience and with HIV-RNA > 400 copies/mL and the remaining 19% PI-experienced but with HIV-RNA < 400 copies/mL. The median HIV-RNA plasma level was 4.6log10 copies/ml (40,000), and 21% had less than 400 copies/ml. Nadir CD4 cell count was relatively low with a median 98 cells/mm3. After 24 weeks of therapy, 55 patients (17%) had discontinued the assigned PI without differences between the two treatment arms at the p=0.001 level. The primary reason for discontinuation was clinical non-fatal adverse events (n=22). Only one patient to date has discontinued the assigned PI combination because of virological failure. However a switch from the randomised treatment was not mandatory for patients that experienced protocol defined virological failure. A total of 23 patients withdrew consent or were lost to follow-up, and 93% of the patients remained under follow-up.

The DSMB has recommended that the study be continued to the planned 48 weeks. For the overall study population, the proportion of patients with HIV-RNA < 400 copies/mL (ITT/e) at baseline, week 4, week 12 and week 24 was: 21%, 53%, 72% and 77%. If switch from randomised PI was counted as being not suppressed (ITT/e/switch= failure) then the corresponding numbers were 21%, 52%, 70% and 74%. Finally, in on treatment analysis 21%, 56%, 81% and 90%, respectively, had a HIV-RNA < 400 copies/mL. The median increase of CD4+ lymphocytes from baseline to week 24 was 81 cells/mL.

A total of 90 adverse events (AEs) of at least grade 3 were recorded up to the end of September 2002, of which 24 were considered at least possibly related to either of the study PI's. The time to develop the first adverse event of at least grade 3 was comparable in the two arms. There was no statistically significant difference at the p=0.001 level between the two treatment arms in AEs grade 3 or more.

So it seems that at the present this study has not picked up major statistical differences between these two boosted PI regimens and unlike MaxCmin 1 that compared boosted saquinavir at this dosage with indinavir/ritonavir 800/100mg twice daily there is not a difference in side effect profile. The final analysis of the week 48 data is expected in late 2003.

Reducing viral load <3 copies: Kaletra study

One enduring question at the moment is what is the effectiveness of suppression of HIV if you go to the current lower limit of detection of most HIV RNA viral load assays of 50copies/mL. In a study by King and co-workers this was examined using a new version of a viral load test, which can measure down to less than 3copies/mL [3]. Whilst the difference between 3 and 50 does not seem large this represents an entire log of viral load, equivalent to the difference between 30,000 and 500,000, which we know from other studies has a disease progression consequence. At the XI International HIV Drug Resistance Workshop in Seville, Spain, in July 2002, a group from San Diego showed that adding abacavir to the regimen of patients with long-term viral suppression between 2.5 and 50 copies/mL resulted in suppression to < 2.5 copies/mL in all subjects.

One hundred antiretroviral-naïve subjects were treated with lopinavir/ritonavir, lamivudine, and stavudine for 204 weeks,

and viral load was measured using <400 and <50 copies/mL assays at each visit. In addition, at weeks 24, 48, and 72, viral load was also evaluated using a modified version of the standard Roche Amplicor assay, in which an additional step in the measuring process enabled the detection of as few as 3 copies/mL of HIV-1 RNA. The likelihood of viral load rebound by week 204 was compared between those who achieved viral load suppression to < 3 copies/mL by week 72 (n = 54) and those who did not stay below 3copies/mL (n = 42).

At week 204, 72 subjects had a plasma HIV-1 RNA level < 50 copies/mL (by intention-to-treat analysis, missing equals failure), while 28 had discontinued therapy. There was no significant difference in the likelihood of viral suppression at this time between those with < 3 copies/mL by week 72, compared with those with > 3 copies/mL (86% vs 83%; P = .71, log rank test). The failure rates by year are shown in the Table.

Fifteen individuals had a viral load rebound during the follow-up period of which seven continued therapy with the same regimen and all these had viral load < 50 copies/mL by week 204. Of the eight subjects with virologic failure who then stopped treatment, genotypic resistance testing showed that no subjects had protease mutations, whilst two had had the M184V mutation associated with lamivudine use.

About 30% on this regimen developed grade 3 or 4 adverse events whilst the average increase in CD4+ cell count by week 204 was 440 cells/mm3, and appeared to be independent of baseline CD4+ cell count or starting viral load level.

This study suggests that a decrease in viral load to < 3 copies/mL might not associated with a better long-term virologic outcome to a lopinavir-ritonavir-containing regimen, compared with a decrease to < 50 copies/mL. However, the results do not address whether it may be advantageous either to intensify a regimen that is maintaining viral load at just under 50 copies/mL, or to prospectively aim to maintain viral load continuously below 3 copies/mL for a long period.

AZT-d4T cross resistance

Jaques Grassi and his colleagues from Gif-surYvette, France showed an interesting presentation on the intracellular metabolism of nucleoside analogue reverse transcriptase inhibitors (NRTI's) [4]. Using a novel technique the researchers showed that when zidovudine (AZT) is metabolised not only is the triphosphate active form of AZT made, AZT-TP, but also measurable levels occur of d4T-Tp the active form of stavudine (d4T). In 31 subjects blood was taken between 30 minutes and 15 hours after their last dose of AZT and intracellular levels of AZT-TP and d4T-TP were assessed. The later metabolite was found unexpectedly in all samples and represented between 3% and 30% of the total tri-phosphated reverse transcriptase inhibitor compared to AZT-TP. Thus giving one drug appears to produce some levels of another active anti-HIV drug. This work is supported by other observations in the test tube that show that d4T-TP is produced in cells cultured in the presence of AZT while d4T-TP was never detected in patients not receiving d4T or AZT but who were treated with other NRTI's such as lamivudine (3TC) or abacavir.

This observation indicates that d4T-TP could participate to the action and or toxicity of AZT and in any case brings a new light to the cross resistance observed between these two widely used NRTI's.

Rising HCV rates and sexual transmission

Following the enduring challenge of HIV there has been a recent realisation that hepatitis C virus (HCV) represents our next viral disease challenge; in fact, surveillance systems are not properly in place in most countries. For instance in Great Britain there are an estimated 300,000 HCV cases, over 90% of which are as yet undiagnosed, in comparison to approximately 33,500 people living with HIV, about 30% of whom are undiagnosed. The significance of sexual transmission in this emerging epidemic has been unclear but it appears now that there is incontrovertible evidence that this is an important method of acquisition, at least among men who have sex with men (MSM).

From the Chelsea and Westminster Hospital in London, Browne and co-workers presented some evidence that sexual transmission is responsible for an increasing incidence of HCV in HIV-infected individuals [5]. Cases of HCV were identified among subjects with a previously negative HCV antibody result that attended sexual health services from 1997 to 2002. There was a rise in the number of these HCV seroconvertors from zero during 1997 to ten in 2002. A total of 23 cases were identified, 22 of whom were male 21 known to be HIV-infected, including two who seroconverted to both viruses concurrently. Although four subjects gave a classic history of injection-drug use and needle sharing, 19 did not; these were all MSM, 15 of whom reported recent unsafe sex. Eight subjects in this cohort developed syphilis at the same time as they acquired their HCV.

All of the HIV-infected individuals diagnosed with HCV were identified by screening for HCV RNA among those with abnormal liver function, using stored blood samples to try to identify the date of acquisition. Routine antibody tests were also performed which were initially negative, with a median elapse rate from negative to HCV antibody positivity of four months (range 3-9.5 months). The rate of diagnosis of HCV among HIV-infected subjects found to have elevated liver function tests in the general clinic population rose throughout the time-period from 10.7% to 40%, a statistically significant change (P = .035, Chi-squared test). There appeared to be a significantly higher rate of diagnosis of HCV in 2002 compared to 1997, 5.1 cases/1000 patient years (95%CI 2.2-10.1) compared to 0 cases/1000 patient years (95%CI 0-1.2). This suggests that the HCV infection burden within the HIV-infected population has increased during that time.

This study raises a concern that the use of HCV antibody tests alone may not be sufficient to identify individuals who acquire HCV with only sexual risk factors or even in low incidence areas. Further epidemiological work addressing sexual acquisition is required to identify more clearly the risk factors for transmission as well as the outcomes of these infections. From a public health perspective, more aggressive surveillance studies should be performed, and health promotion messages need to be developed to educate those at risk.

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All references are from the Programme and Abstracts for the 6th International Congress on Drug Therapy in HIV Infection, 17-21 November 2002, Glasgow, UK.

http://www.hiv6.com/frames.htm

1. D Schürmann1, J Gathe2, I Sanne et al. Efficacy and safety of GW433908/ritonavir once daily in therapy-naïve subjects, 48 week results: the SOLO Study. Abstract PL14.4
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5. R Browne, D Asboe, Y Gilleece et al. Increased incidence of HIV positive individuals with acute hepatitis C due to sexual transmission: a new epidemic? Abstract P283

Source: NATAP

http://www.natap.org/

Promising data regarding DermaVir for therapeutic vaccine

Brian Boyle, HIVandHeptatis.com

There is a pressing need for simple and effective treatment strategies for HIV infection that result in long-term virologic control and avoidance of toxicities. Many novel therapeutic approaches are being explored.

One approach is in "leveraging the immune system" since boosting HIV-specific immune responses in chronic infection may offer a potential for synergy with antiretroviral drugs, enhancing durable control of viral replication.

In a study presented at the 6th International Congress on Drug Therapy in HIV Infection data regarding a novel immunotherapeutic, DermaVir, was presented. DermaVir delivers a replication and integration defective SIV/HIV DNA to dendritic cells after topical skin application. Unlike other vaccine technologies, DermaVir is designed to transduce Langerhans cells on the surface of the skin, which are "professional" presenting cells that stimulate CD4, CTL and naïve CD4 cell growth. Once the SIV/HIV DNA is present in the Langerhans cells, they then migrate to the lymph node and mature to antigen-expressing dendritic cells, and elicit SIV/HIV-specific T cell immunity.

In several animal studies, the therapeutic effect of DermaVir was evaluated in chronically SIV251-infected rhesus macaques that were randomised to receive intermittent structured treatment interruptions (STI) and highly active antiretroviral therapy (HAART) (three weeks on HAART and three weeks off) with or without DermaVir.

The investigators found monkeys that received DermaVir had excellent suppression of HIV replication during the STI periods, while those who did not receive DermaVir had very little, if any, virologic control during the STIs. The control of viral load during the STI in the DermaVir treated monkeys was associated with augmented SIV-specific CD8 and CD4 T cells. In these studies, DermaVir therapy did not show signs of toxic side effects.

Based upon these data, the presenter concluded: "The antiviral potency, topical application and infrequent dosing schedule make DermaVir a very attractive treatment option for HIV-infected individuals. Complementing the therapeutic efficacy of HAART with DermaVir immunotherapy could prolong the effectiveness of antiretroviral drugs and thereby delay development of drug resistance."

Phase I human studies using DermaVir will begin shortly.

Ref: Julianna Lisziewicz, Jianqing Xu, Mark Lewis et al. DermaVir: a new topical DNA vaccine for the treatment of HIV/AIDS. Plenary Session 7.2. 6th International Congress on Drug Therapy in HIV Infection November 17 - 21, 2002, Glasgow, UK

http://www.hiv6.com/frames.htm

Enfuvirtide (T-20): predicting success and modelling survival benefits

Graeme Moyle, NATAP

Enfuvirtide (Fuzeon, formerly T-20) has been evaluated into randomised, comparative studies in which individuals who have been experienced with all three approved drug classes were given a new antiretroviral regimen optimised by the use of resistance testing with or without enfuvirtide in a 2:1 ratio. Both studies, known as TORO 1&2, demonstrated substantial virological and immunological advantage to including enfuvirtide in the new treatment regimen. Characteristics associated with treatment response in the Toro 1 study were recently reported at the ICAAC conference. A similar analysis of the Toro 2 study was presented at the Glasgow conference. In Toro 2, 335 individuals received enfuvirtide with optimised background therapy and 169 individuals received optimised background therapy alone. The changing baseline viral load over 24 weeks was -1.43 log in the enfuvirtide recipients and -.65 in those who received optimised background alone. This advantage of 0.78 log was highly statistically significant ($p<0.0001$). Enfuvirtide recipients experienced a rise of 65 CD4 cells compared with just 38 in the control group. The number of individuals who reached a viral load less than 400 copies was 28% in the end for the enfurtide group and 14% in the control group, with 12% and 5% respectively achieving less than 50 copies/ml.

Subgroup analyses indicated that the benefits of the enfuvirtide were consistently observed in both male and female, white and non-white and all patients that were older and younger than 40 years of age. Of note, individuals who entered the study with an age less than 40 years experienced a more modest and not statistically significant advantage for enfuvirtide relative to background therapy alone, whereas in individuals who entered the trial with an age greater than 40 years, a greater and statistically significant advantage was observed.

When groups were stratified by baseline viral load less than or greater than 40,000 copies/ml and by baseline CD4 less than or greater than 100 cells/mm3, significant and consistent advantages to enfuvirtide over optimised background therapy alone were observed.

Using resistance information derived from baseline samples patients were given genotypic and phenotypic sensitivity scores whereby a score of one was given for every drug included in the optimised background that was likely to be active in the regimen. Individuals with a genotypic sensitivity score of two or more achieved the greatest reductions in viral load from baseline. However, individuals randomised to enfuvirtide had consistently larger reductions in viral load from baseline relative to those who

only received optimised background regardless of the genotypic sensitivity score. Similar benefits were seen when evaluating the phenotypic sensitivity scores, although individuals with phenotypic sensitivity scores of three or more in the optimised background therapy group in this analysis achieved similar responses to the enfuvirtide group, whereas the enfuvirtide group had significant advantage in those individuals entering the study with a phenotypic sensitivity score of two or less.

As reported in the analysis of the Toro 1 study, individuals naïve to Kaletra at baseline achieved larger reductions in viral load than those with prior Kaletra experience. When stratifying individuals by prior Kaletra experience, individuals randomised to enfuvirtide had significantly greater reductions in viral load from baseline both in individuals naïve to Kaletra and experienced with Kaletra at entry to the study.

In a multiple regression analysis investigating factors associated with the change in viral load from baseline to week 24, inclusion of enfuvirtide in the regimen was associated with an estimated 0.8 log reduction in viral load, factors including lower baseline viral load, higher baseline CD4 count, phenotypic or genotypic sensitivity score indicating greater number of active drugs in the optimised background regimen, and better adherence were associated with 0.1 to 0.3 log reductions in viral load. Individuals with prior Kaletra experience were estimated to have a 0.86 log smaller reduction in viral load than those naïve to Kaletra at study entry.

These subgroup analyses of the TORO 1 and 2 studies provide useful practical guidance as to how we should use enfuvirtide in clinical practice. The studies indicate that the best responses to a regimen containing enfuvirtide are seen in individuals with at least two and preferably three active agents to include in the accompanying regimen, and that treatment response may also be better if commenced with a relatively lower viral load and a higher CD4 count. Support for adherence appears critical, with a 10% increase in adherence in the Toro 2 study being associated with an estimated 0.11 log greater reduction in viral load. There are also issues about the use of Kaletra raised by the studies. If being naive to Kaletra at the time of initiation of enfuvirtide is truly critical to achieving the greatest virological response to an enfuvirtide containing regimen, then physicians may need to consider "saving" Kaletra for the time in the treatment sequence that they may plan to use enfuvirtide.

Results from the Toro 1 and 2 studies were placed in a complex mathematical model to estimate the advantage of enfuvirtide relative to optimised background therapy alone in delaying the time to development of an AIDS defining event or death. The model suggested that inclusion of enfuvirtide in the regimen would delay the development of a new AIDS defining event by approximately 1.5 years (from 3.3 years in the optimised background regimen to 4.8 years in the enfuvirtide containing regimen) and increase overall survival by 1.6 years (from 4.8 years in the optimised background alone regimen to 6.2 years in the enfuvirtide containing regimen). This information suggests that enfuvirtide is likely to be a highly cost-effective therapy and that it is likely to buy not only years of good quality (due to the prevention of new AIDS defining illnesses) but also time for new treatment options to become available.

Ref: Joep Lange, A Lazzarin, B Clotet et al. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs OB alone: week 24 response among categories of baseline (BL) demographics, treatment experience, and HIV antiretroviral (ARV) resistance. 6th International Congress on Drug Therapy in HIV Infection 17-21 November 2002, Glasgow, UK. Abstract PL14.3
http://www.hiv6.com/frames.htm

Source: NATAP
http://www.natap.org/

Virologic failure among treatment-naive patients taking tenofovir DF or stavudine in combination with lamivudine and efavirenz

Mark Nelson, TheBody.com

Gilead study 903 recruited over 600 patients to be randomly assigned to tenofovir (TDF, Viread)/3TC (lamivudine, Epivir)/efavirenz (EFV, Sustiva) and d4T (stavudine, Zerit) placebo or d4T/3TC/efavirenz and TDF placebo. The results of this study have been previously reported to have the highest rates of virological success of any clinical trial in HIV disease looking at HAART so far.

To recap, 87% of individuals in each arm, by the most strict analysis (i.e., intent-to-treat), had a viral load below 400 copies at 48 weeks. Eighty-two percent of patients in the TDF arm and 81% of patients in the d4T arm were undetectable by the 50-copy assay. CD4 count cell changes were similar in both arms. It is therefore difficult from this study to see any difference in efficacy between TDF and d4T when used in conjunction with 3TC, and EFV as regards virological or immunological efficacy.

However, it is important to remember that for effective and durable virological suppression, one must not only have powerful antiviral drugs, but also a regimen which is easy to comply with and which shows little long-term toxicity. In addition, in individuals who virologically fail a regimen, it is important to know the probability of sequencing to another effective regimen. Already presented is 903 toxicity data suggesting a reduction in potential mitochondrial-induced toxicity such as peripheral neuropathy and lipodystrophy and lower levels of cholesterol and triglycerides in the TDF arm.

Aim

The aim of this study was to describe the resistant mutations through to week 48 which occurred in both arms of the Gilead 903 study.

Results

Of the 299 patients who were recruited to the TDF arm, and 301 to the d4T arm, 29 individuals who had received TDF were classified as virological failures and 25 who had received d4T. Patients underwent genotypic and phenotypic resistant testing. The results of the genotype tests are shown below:

Development of Resistance Mutations Through Week 48 (ITT)

	Number of Patients (%)		
	TDF+3TC+EFV (n=299)	d4T+3TC+EFV (n=301)	p-value4
Virological Failures	29 (9.7%)	25 (8.3%)	0.57
Any EFV-R:	161 (5.4%)	12 (4.0%)	0.44
EFV-R alone	52 (1.7%)	4 (1.3%)	0.75
EFV-R+ M184V/1	4 (1.3%)	6 (2.0%)	0.75
EFV-R+ K65R	2 (0.7%)	1 (0.3%)	0.62
EFV-R+ M184V/I +K65R	5 (1.7%)	1 (0.3%)	0.12
M184VI alone 3	(1.0%)	1 (0.3%)	0.37
K65R alone	0 (0%)	0 (0%)	1.0
Wild type	103 (3.3%)	12 (4.0%)	0.82

1.K103N, V106M, Y188C/L or G190A/S/E/Q (K103N in 19/28; others more than 50-fold EFV-R with other mutations); three patients (all in TDF arm) had more than 4-fold efavirenz resistance at baseline and developed additional efavirenz resistance mutations.

2.One patient additionally developed D67G + K70E + V75L associated with more than 20-fold 3TC restack, but no TDF susceptibility change.

3.One patient had K1219Q at baseline, but did not develop any new mutations.

4.Fisher's exact test

In individuals with virological failure on TDF, 24% developed the signature mutation to TDF (ie the K65R), while in the d4T arm, 8% developed K65R. No mention of thymidine analogue mutations were found in either arm. Interestingly, less than half the individuals virologically failing their regimen had the M184V mutation and only 50% had EFV-resistant mutations.

In individuals who developed the K65R mutation while on therapy, the VIRCO antivirogram suggested continuing susceptibility in all individuals to AZT/d4T and to some individuals continuing sensitivity to ddI (didanosine, Videx)/abacavir (ABC, Ziagen) and also TDF. In vitro phenotypic analysis revealed that the K65R mutation was associated with hypersensitivity to AZT/d4T, full sensitivity to ABC if the M184V was not present and partial sensitivity if it was present. By virtual phenotype, five out of six individuals undergoing this test retained full sensitivity to TDF, three of whom also had the M184V mutation, which is known in vitro to hypersensitise the virus to TDF.

Clinical implications

The 903 study had remarkable results: high efficacy rates through to week 48 with less than 10% of patients in each arm undergoing virological failure. The high numbers of patients with wild type virus at the time of virological failure (35% in the TDF arm and 48% in the d4T arm) suggest that, in many cases, virological failure was not a true definition but may have been related to lack of adherence.

The evidence for poor compliance is increased with the low levels of non-nucleoside and 3TC resistance mutations in suggesting partial non-compliance within the regimen. Of the total number of patients entering the study on TDF, only 2.3% developed a K65R mutation, however this was 24% of all patients who experienced virological failure.

Discounting patients with wild type virus who may well have been poor compliers suggests that the K65R mutation may occur at a relatively high level in patients failing TDF. This is a much higher rate than in previous studies and an easy explanation is not forthcoming. Whether the escaping virus within this regimen preferentially selects for the K65R mutation, may be one explanation that needs to be looked at further.

Interestingly, in individuals developing the K65R mutation who experienced virological failure, a mean viral load decrease of 0.9 log from baseline, continued. By both virtual phenotype and true phenotype, patients with a K65R mutation were hypersensitive to AZT and d4T and had full or partial susceptibility to abacavir, and, in many cases — based on the results of resistance test alone — remained sensitive to TDF and ddI. Therefore it was not surprising that five of the seven patients experiencing failure with a K65R mutation, experienced virological success with a second regimen, two of which included TDF. Of the two patients who failed to respond to the second regimen, one was lost to follow up and one patient was known to be non-adherent.

Conclusions

The results of this study must not be taken out of context. In the Gilead 903 study, there were very few virological failures compared with any other study that has previously taken place, and clearly both regimens are highly effective. The study does suggest that TDF may select for the K65R mutation more readily than previously thought, and also it should not be discounted that no patient who experienced virological failure in the d4T arm selected thymidine mutations confirming a high barrier to resistance for d4T.

Ref: Michael Miller, Dion Coakley, Andrew Cheng,et al. Genotypic and Phenotypic Characterization of Virologic Failure Through 48 Weeks Among Treatment-Naive Patients Taking Tenofovir DF (TDF) or Stavudine (d4T) in Combination With Lamivudine (3TC) and Efavirenz (EFV). 6th International Congress on Drug Therapy in HIV Infection 17-21 November 2002, Glasgow, UK. Abstract P205

Source: The Body

Link:
http://www.thebody.com/index.shtml

Comparison of the efficacy and safety of tenofovir vs. d4T when used in combination with 3TC and efavirenz in ARV-naive patients

Mark Nelson, TheBody.com

Background

The 903 study compared tenofovir (TDF, Viread) against d4T (stavudine, Zerit) in combination with 3TC (lamivudine, Epivir) and efavirenz (EFV, Sustiva). Two hundred and ninety-nine

individuals received TDF/3TC/EFV and d4T placebo, and 301 individuals received d4T/3TC/EFV with TDF placebo. Patients were stratified by plasma viral load below or greater than 100,000 and CD4 count less or greater than 200 cells. This study is due to continue for 144 weeks.

Results

Patients who entered this study had a mean age of 36 years and, although the majority were white males, approximately 25% of study participants were female. Forty-six percent of participants in the TDF arm had a viral load above 100,000, while 43% in the d4T arm had viral loads above 100,000. Similarly, 39% of participants in the TDF arm had a low CD4 count and 38% in the d4T arm had less than 200 cells respectively. A very high number of patients continued this study for 48 weeks, with only 9% in each arm discontinuing the study.

This low discontinuation rate contributed to the rates of success seen in both arms, with 87% of individuals having a viral load less than 400 copies/ml, and 82% and 81% less than 50 copies/ml at 48 weeks. The CD4 count rise was 169 cells in the TDF arm, and 167 cells in the d4T arm. There was no effect of viral load or CD4 count on the efficacy in each arm.

Percentage of Patients With HIV-1 RNA <400 copies/mL at Week 48 by Baseline Strata

	TDF+3TC+EFV (n = 299)	d4T+3TC+EFV (n = 301)
</=100,000 c/mL HIV-1 RNA	87%	89%
>100,000 c/mL HIV-1 RNA	86%	85%
</=200 CD4 cells	84%	81%
>200 CD4 cells	88%	90%

Grade 3 and 4 adverse events did not differ through 48 weeks. In particular, there was some concern over the issue of the possibility of osteopenia and bone fracture in patients treated with TDF, however in this study only one patient developed a fracture in the TDF arm and, in fact, four fractured bones in the d4T arm.

Concerning laboratory events, there were marked differences between TDF and d4T in the incidence of raised triglycerides, cholesterol and lactic acid.

	TDF+3TC+EFV	d4T+3TC+EFV	p-value
Mean Change in Triglycerides (mg/dL)	+0.14	+ 0.95	-0.0001
Mean Change in Cholesterol (mg/dL)	+ 0.75	+1.47	-0.0001
Percent Lactate >2.2 mg/dL	4%	27%	-0.0001

There was also an attempt to quantify mitochondrial DNA reduction, which may lead to toxicities, including peripheral neuropathy, lactic acidosis, pancreatitis and, perhaps, most importantly, lipodystrophy. Mitochondrial DNA was quantified by nucleic acid extraction from PBMC in a sub group of patients in each arm and compared with a control group of 49 HIV-negative men. At baseline, individuals within both arms had lower mitochondrial DNAs than the HIV-negative males. This fact has already been noted in previous studies. When individuals are treated, mitochondrial DNA tends to increase, and individuals in the TDF arm returned to the same level as the HIV-negative men, while those in the d4T arm, although having increases in mitochondrial DNA, remained below the level of the HIV-negative and TDF-treated groups. This may explain the mitochondrial toxicities seen in the two groups.

Toxicities Potentially Associated With Mitochondrial Dysfunction Through Week 48

	TDF+3TC+EFV (n = 299)	d4T+3TC+EFV (n = 301)
(All grades)	9 (3%)*	30 (10%)*
Patients (%) with events	6 (2%)**	20 (7%)**
Peripheral Neuritis/Neuropathy	3 (1%)	11 (4%)
Lipodystrophy	0	3 (1%)
Pancreatitis	0	0

*p <0.001

** p = 0.013

Conclusion

High proportions of individuals in both arms achieved virological success and there were significant increases in CD4 counts. Both arms had a remarkably low discontinuation rate compared with other studies. Individuals who received TDF had fewer toxicities associated with mitochondrial dysfunction, potentially secondary to a greater increase in mitochondrial DNA than those treated with d4T. In addition, the TDF arm had smaller increases in cholesterol and triglycerides.

Clinical implications

Both the TDF and d4T arm achieved remarkable success, paving the way for us to say that the drugs that we have are sufficiently active and that the reasons for virological failure more and more are fear of development of toxicity and compliance issues. Both of the arms are or will soon be available as once-daily therapy. 3TC is now licensed to be utilised once daily and d4TXR will soon be licensed giving us the potential for two highly effective regimens.

However, the major reason for regimen failure both in cohort and clinical studies is toxicity. The lower rates of toxicity with TDF, particularly those associated with mitochondrial dysfunction would suggest that this may be a better choice of initial therapy than d4T. The lower increases in triglyceride and cholesterol may be explained by the fact that rather than d4T causing hyperlipidemia, TDF is protecting against the hyperlipidemia known to be associated with EFV. This theory would be backed up from unpublished data from the 902 and 907 studies suggesting that individuals who received TDF rather than placebo, in addition to background therapy, had a decrease from baseline of their lipids.

Whether the reduction in the increase in lipids in the TDF arm is of clinical significance can only be found by long-term follow up. Significantly fewer patients on the TDF arm than in the d4T arm had raised cholesterol, LDL and triglycerides as defined by limits

of the National Cholesterol Education Program Adult Treatment Panel.

Ref: Anton Pozniak, Schlomo Staszewski, Joel Gallant et al. Comparison of the Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) Versus Stavudine (d4T) When Used in Combination With Lamivudine (3TC) and Efavirenz (EFV) in HIV-1 Infected Patients Naive to Antiretroviral Therapy (ART) After 48 Weeks of Treatment (Study 903). 6th International Congress on Drug Therapy in HIV Infection 17-21 November 2002, Glasgow, UK. Abstract P1.

Link:
http://www.thebody.com/index.shtml

Source: The Body

Safety profile of tenofovir in treatment-experienced patients

Mark Nelson, theBody.com

Tenofovir (TDF, Viread) was originally studied in two trials - 902 and 907 - in which either TDF or a placebo was added to background antiviral therapy. As a result of the large number of individuals who received TDF in these studies, a lot of clinical experience with TDF has been gained. Individuals were followed up not only for virological efficacy but also for toxicities associated with this antiviral regimen. In both the 902 and 907 studies, a placebo arm was in place for the initial 24 weeks which allowed comparison of adverse events.

Results

Grade 3 or 4 adverse events or laboratory abnormalities were no more common in the TDF arm than compared with placebo. Indeed, the incidence of drug continuation in the study was 7% in the TDF arm and 9% in the placebo arm. Patients who received a placebo were switched to TDF at 24 weeks and all patients were followed for a mean of 95 weeks.

During extended follow up, the incidence of drug continuation in the study was 25%, although very few patients discontinued TDF due to an adverse event (9%). The most common adverse event seen was diarrhoea in 3% of patients. As for laboratory abnormalities, a raised creatinine kinase was seen in 15% of patients, elevated triglycerides in 13% of patients, a raised serum amylase in 9% of patients and a raised AST elevation in 8% of patients. None of these differed from the placebo arm.

There has been considerable interest in TDF's potential risk for renal and bone toxicity. Serum creatine of a grade 1 toxicity (ie mild) only developed in 1% of individuals receiving TDF during the first 24 weeks of therapy, a rate equivalent to that of a placebo. Overall, after 95 weeks, 6% of patients had developed a grade 1 toxicity, but only one patient developed a grade 2 (moderate) toxicity. Serum phosphate was measured as a possible marker of bone and renal toxicity and did not significantly differ between TDF and placebo. No patient discontinued the study due to TDF-related serum creatine elevation or hypophosphatemia.

In this study, the incidence of adverse events potentially associated with mitochondrial dysfunction was measured. During the first 24 weeks of therapy, 2% in the TDF arm and 3% in the placebo arm developed peripheral neuritis, and less than 1% in each arm developed pancreatitis or lactic acidosis. Of the two patients who did develop lactic acidosis, in addition to receiving TDF, both were also receiving d4T (stavudine, Zerit) or ddI (didanosine, Videx) concomitantly, either of which are associated with this adverse effect.

Conclusion

During the 24-week placebo-controlled period of 902 and 907, the safety profile of TDF appears similar to placebo.

Implications for clinical practice

TDF appears to have low toxicity, at least in the short-term. The mean follow up of patients to 95 weeks confirms this, although clearly longer follow up and maintenance of observation is of paramount importance as it is with all drugs. The safety profile of TDF has led many individuals to use TDF as a first-line agent, especially after the results of 902, or as a substitute agent. It is important when substituting TDF for other nucleoside analogues that we consider previous nucleoside non-suppressive treatment.

In a study from Chelsea and Westminster Hospital in London, of 40 patients who switched to TDF, it was virologically successful in 37. Of the three patients who failed the therapy switch, all had received previous nucleoside therapy in a non-suppressive regimen. Presumably then they were harbouring resistant mutations (especially important are the thymidine mutations 41 and 210 and the K65 mutation) which then were able to grow back when TDF was substituted for the nucleoside analogue. Although switching is often recommended to deal with toxicities and adherence problems, it is also important to make sure that we do not switch into virological failure.

Ref: Dion Coakley, Andrew Cheng, Shan-Shan Chen, et al. Safety Profile of Tenofovir DF (TDF) in Treatment-Experienced Patients From Randomized, Placebo-Controlled Clinical Trials. 6th International Congress on Drug Therapy in HIV Infection 17-21 November 2002, Glasgow, UK. Poster 910

Source: The Body

Link:
http://www.thebody.com/confs/hiv6/hiv6.html

TREATMENT ACCESS

Lancet special report examines direction new WHO director general should take on several HIV/AIDS-related issues

In a special report, the 4 January issue of the Lancet offers 12 opinion pieces that make recommendations as to the role the new director general of the World Health Organization should play, the issues that need to be addressed and the direction in which the organisation should proceed. Several of the pieces examine HIV/AIDS-related issues. Short summaries of some of these pieces follow:

Ken Bluestone, senior policy adviser, Voluntary Service Overseas: The HIV/AIDS epidemic places "unimaginable burdens" on the public health sector, as "more and more" trained health care professionals "succumb to the virus," Bluestone writes, adding that without these professionals, "the best international policies are meaningless." In order to "meet these challenges," WHO must "strengthen its resolve to maintain its independence and lead its member states, even at the risk of causing controversy." According to Bluestone, the agency is the "only global institution that has the remit to drive this agenda forward, yet has failed to do so convincingly." In conclusion, Bluestone writes that the new director general "must support and reinvigorate the advocacy efforts of the organization and provide a proper counterbalance to the interests of the pharmaceutical industry and wealthy member states".

Kenneth Roth, executive director, Human Rights Watch: The credibility of WHO's "advocacy of the right to health for all has been eroded in recent years" because of the organisation's "failure to challenge the pharmaceutical industry on access to medicines for people with HIV/AIDS." According to Roth, the new director general must "lead the organisation to stand consistently with those most deprived of health services" in order to "re-establish WHO's credibility".

Nathan Ford, access to medicines adviser, and Jean-Michel Piedagnel, executive director, Medecins Sans Frontieres: WHO must continue to speak out "in clear support of allowing medicine production and export as an exception to patent rights" in order to provide "affordable antiretrovirals" for the estimated 5.7 million people with AIDS "who currently need treatment but are left without." "In the face of rising infectious diseases such as AIDS, tuberculosis and malaria, and the increasing marginalisation of health problems that do not affect the developed world ... the importance of an international, independent organisation that is brave, aggressive and vocal in its defence of global public health has never been more important".

Harvey Dale, president, International Federation of Pharmaceutical Manufacturers Associations: Because "far more work is needed to improve access to health care and medicines," the new director general "will have to look more fundamentally at the problems and issues" surrounding patents for antiretroviral drugs and the "barriers to drug access in poor countries". According to Dale: "In its history, WHO has not, in its drug policies, focused sufficiently on the task of expanding access to inexpensive generic medicines that could make the greatest difference in reducing morbidity and mortality - and this fact does not bode well for success in the AIDS struggle as the patent debates are likely to subside over time".

Mohga Kamal Smith, health policy adviser, Oxfam GB: The "inadequate international response" in the fight against HIV/AIDS "demonstrates the lack of serious commitment to health of many governments in both developed and developing countries". Despite WHO's "long history of effective leadership on medicines," the "cutting edge advocacy in this area is being undertaken by non-governmental organisations". According to Kamal Smith, WHO "has not been outspoken on the preeminence of patients' rights to access to medicines over commercial rights in a worsening global health crisis". Smith concludes: "The issue of access to medicines will be seen as a benchmark of WHO commitment to the interests of poor people."

James Deane, executive director, Panos London: Because WHO has been "far from consistent" with its work on HIV/AIDS, the organisation needs to focus on three areas where it has "historically performed poorly: cooperation, communication and leadership". According to Deane, the new director general must "put institutional pride and profile emphatically in second place to coherence and cooperation across the UN system"; follow the lead of South Africa's Treatment Action Campaign, which "changed government policy and mobilised massive local and international public awareness"; and "engage in political and economic discourse, with all the vibrant debate and discussion this brings." The "priorities" of the new WHO director, Deane writes, are "intensely political, often controversial and require serious vision and leadership".

Free full text of all these reports is available online at:

http://www.thelancet.com/journal/vol361/iss9351/editorial_and_review

Source: KaiserNetwork Daily HIV/AIDS Report
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=15309

ANTIRETROVIRALS

Roche and Trimeris able to make enough enfuvirtide (T-20) for only 12,000 people this year, 32,000 next year, citing difficulties in the manufacturing process

Graham McKerrow, HIV i-Base

Roche and Trimeris have announced plans to produce enough enfuvirtide (formerly T-20), which will be marketed as Fuzeon, by the end of this year to treat between 12,000 and 15,000 people. The companies had planned to produce enough enfufirtide to treat 25,000 people by the end of the year but have encountered difficulties with the manufacturing process of this complex new drug.

Production will be stepped up to treat 32,000 people by the end of next year and 39,000 by the end of 2005.

Enfuvirtide, the first of a new class of drugs called fusion inhibitors, is currently available to fewer than 3,000 people through an international early access programme. The revised manufacturing targets include holding a half-year safety stock for each patient who initiates therapy with the drug.

Excitement about enfuvirtide centres on its ability to lower the viral loads of people who have HIV that is resistant to other drugs. While other antiretrovirals aim to stop HIV replicating, enfuvirtide is designed to block HIV from fusing with a host cell.

There are fears that it could cost $7,000 to $10,000 per patient per year, which would make it the most expensive anti-HIV drug. Some observers have even suggested it could cost $15,000. A spokesman for the company said: "Roche and Trimeris cannot comment on the price because it has not been announced. However, it can be expected that Fuzeon will be significantly more expensive than the most recently introduced AIDS therapies due to its structural complexity and its highly sophisticated manufacturing process."

Enfuvirtide is expected to receive its US licence in March. The companies say they now have enough data from the first three months of the commercial manufacturing process to provide an update on the progress to date. The following is the text of their statement.

"Fuzeon is one of the most complex and challenging molecules ever chemically manufactured on a large scale by the pharmaceutical industry. Roche and Trimeris have demonstrated that production of Fuzeon at large scale is possible and the first commercial scale production of Fuzeon drug substance has now been completed.

"Roche's manufacturing plant in Boulder, Colorado in the United States has been working 24 hours a day, seven days a week to meet the challenges required to manufacture this peptide - a complex molecule which requires more than 100 production steps. Initial commercial scale production yields were lower and cycle times longer than had been projected; however, subsequent improvements have been made so that yields have steadily improved to now consistently meet those derived from pilot plant projections.

"Plans are also in place to further improve production cycle times. A rate-limiting step has been identified in the manufacturing process, and plans have already been put in place to increase the capacity of this step, including the addition of duplicate equipment.

"In 2003: Short-term manufacturing estimates for Fuzeon are based on the current estimated ability to produce around two metric tonnes of Fuzeon in 2003 - equivalent to up to 20,000 treatment packs (one treatment pack equals one month's supply for one patient) per month by year end. This translates to supply for approximately 12,000 to 15,000 patients on Fuzeon by year end 2003.

"This number of patients is lower than would be calculated based upon the manufacturing output for the year due to the fact that approximately half a year 'safety supply' is allocated to every patient to ensure continuity of drug supply. We believe that a half-year safety supply is prudent given our early stage of commercial production and the severity of the illness being treated; however, we plan to evaluate the safety supply requirements as we move forward.

"In 2004: Annual production of Fuzeon is planned to increase to around 3.7 metric tons - equivalent to up to 39,000 treatment packs per month during mid-2004. After setting aside patient safety supplies, this will equate to up to a maximum of 32,000 patients on Fuzeon by year-end 2004.

"These figures are based upon the assumption that individual patient safety supply of approximately half a year is maintained and projected cycle times and yields remain on track. As we continue to gain confidence in the process and fill the distribution pipeline, we will evaluate the amount of safety stock required to maintain a continuity of supply.

"In 2005: It is expected that safety supplies will already be established and the manufacturing capacity can therefore supply up to 39,000 patients, based upon the improvements described.

"Fuzeon is the most clinically advanced in an investigational class of anti-HIV drugs known as fusion inhibitors. Unlike existing anti-HIV drugs that work inside the cell, Fuzeon has a unique mechanism of action that is designed to block HIV before it enters the human immune cell. Consequently, Fuzeon is active against HIV that is resistant to the currently available classes of anti-HIV drugs. Regulatory submissions for Fuzeon were filed in the US and European Union in September for the treatment of HIV-1 infection in combination with other antiretroviral agents. Fuzeon was granted priority review status in the US in October, establishing a target six-month review period. Marketing authorisations have also been submitted in Switzerland, Canada, and Australia.

"Because demand for Fuzeon is expected to exceed supply at launch, Roche and Trimeris will carefully manage allocation of Fuzeon, and are working with HIV physician and patient groups to develop a progressive launch plan. The details of this plan will be announced when Fuzeon is closer to launch."

Links:

http://www.hivandhepatitis.com/recent/experimental_drugs/100202j.html

http://www.natap.org/2002/9retro/day28.htm

http://www.rocheusa.com/newsroom/current/2002/pr2002080201.html

http://www.trimeris.com/news/pr/2002/020816.html

C O M M E N T

People with virus resistant to existing drugs will welcome the increased production of envufirtide. A sophisticated manufacturing process is required to produce this complex new drug and it is no great surprise that the companies have encountered unforeseen problems. They are to be congratulated on expanding the manufacturing plant to maintain production levels, even if at a lower rate than had been planned.

There remain serious worries about the cost of enfuvirtide with estimates varying from $7,000 per patient per year to more than twice that figure. Even the lower end would be twice the price of many other antiretrovirals. The companies should announce their price as soon as possible and, in order to avoid any appearance that they are making an undue profit, they should also publish the accounting costs of the drug.

Vertex Pharmaceuticals announces submission of NDA/MAA filings in US and Europe for amprenavir pro-drug (GW433908)

Vertex Pharmaceuticals Incorporated has announced that GlaxoSmithKline (GSK) has submitted a New Drug Application (NDA) to the US Food and Drug Administration (FDA) for marketing approval of GW433908 (also known as 908 or VX-175), an investigational HIV protease inhibitor in development for the treatment of HIV infection. GSK has simultaneously submitted a Marketing Authorisation Application (MAA) for regulatory approval of 908 in the European Union. The 908 compound was co-discovered by GlaxoSmithKline and Vertex Pharmaceuticals.

The submissions for registration include data from more than 1,100 treatment-naïve and treatment-experienced patients who have participated in Phase III trials to evaluate the safety and efficacy of 908 in comparison with two widely used HIV protease inhibitors. In clinical trials, 908 was dosed as two tablets in both once-daily and twice-daily regimens.

If approved, GSK will market 908 and Vertex will co-promote in the US and key markets in Europe.

Source: Vertex Pharmaceuticals Incorporated

C O M M E N T

GW433908 is the calcium phosphate ester prodrug of amprenavir, which is much more water soluble than the currently available *Agenerase* version of amprenavir. This amprenavir prodrug appears to be hydrolyzed to amprenavir and inorganic phosphate as it is absorbed through the gut epithelium. This new formulation is a 465-mg tablet, which would allow for a reduction in both the daily pill count and pill size.

Amprenavir itself is a protease inhibitor that is already approved for treatment of HIV infection. There are, however, formulation and pharmacokinetic shortcomings that limit its utility. Despite a relatively long plasma half-life, amprenavir must be given twice daily. Moreover, because of the relatively low solubility of this drug it is coformulated with a number of additives limiting capsules to 150 mg in size. Additionally these capsules are extremely large leading to difficulties in administration. The recommended dosage of amprenavir is 1200 mg (eight capsules) twice daily. The development of a more compact formulation of amprenavir would likely improve dosing convenience and tolerability

BMS submits new drug application for investigational protease inhibitior atazanavir

Bristol-Myers Squibb (BMS) has announced the submission of a New Drug Application (NDA) to the US Food and Drug Administration (FDA) for atazanavir, an investigational protease inhibitor under development for the treatment of HIV/AIDS in combination with other antiretroviral agents.

Atazanavir, currently in phase III clinical development, is an azapeptide viral protease inhibitor of HIV-1. It is the first protease inhibitor to be submitted with pharmacokinetic data supporting the potential for once-daily administration. The NDA includes data from more than 2,400 patients enrolled in clinical trials comparing atazanavir to widely prescribed drugs for HIV infection.

Source: Bristol-Myers Squibb Company

Europe and America approve once-a-day stavudine (d4T, Zerit)

Graham McKerrow, HIV i-Base

European and American authorities have approved a new once-a-day formulation of stavudine (d4T, Zerit) but it will not be launched until later in the year.

The new slow-release formulation will have slightly different names on each side of the Atlantic. In Europe it will be called stavudine prolonged release capsule (stavudine PRC, Zerit PRC) while in the US it will be know as stavudine extended release (stavudine XR, Zerit XR).

The new formulation was approved by the European Medicines Evaluation Agency, based in London, in October, and the US Food and Drug Administration followed suit on 31 December.

Bristol-Myers Squibb, the manufacturer, told HIV Treatment Bulletin that it was "validating the manufacturing process" which involved quality control checks on the capsules of tiny, coated beads of the drug.

There will not be an early access programme for the new formulation because the slow-release formulation is not regarded as a significant enough advantage over ordinary stavudine, said the company.

Stavudine PRC will be available in the following sizes: 37.5 mg, 50 mg, 75 mg, and 100 mg.

Stavudine PRC maintains measurable plasma concentrations for 24 hours after once-daily dosing. The recommended doses of stavudine PRC are 100 mg once daily for individuals weighing at least 60 kg and 75 mg once daily for individuals weighing less than 60 kg.

Once daily stavudine studies

In a randomised, controlled clinical study conducted in 783 treatment-naïve, HIV-infected individuals, stavudine PRC was comparable to the previously approved twice-daily formulation of the drug, according to Bristol-Myers Squibb. In this study, participants were randomised to either the extended release or standard formulation, in combination with lamivudine and efavirenz. The proportion of patients with HIV viral load levels below 400 copies/mL at 48 weeks was 79% and 76% for the extended release and immediate release-containing regimens, respectively.

For viral load under 50, the response rates were 55% and 57% for the new and old formulations, respectively. The tolerability and safety profile of the new once daily, extended release formulation is comparable to that of the previously approved twice-daily formulation, according to the company.

The study results were supported by a second, smaller study in 150 treatment naïve patients. It is widely believed that once daily formulations may help patients adhere to treatment regimens due to the increased convenience of the dosing schedule.

The full label for Zerit XR will soon be available at the FDA website.

http://www.fda.gov/cder/approval/index.htm

Source of study information: Richard Klein. Office of Special Health Issues. US Food and Drug Administration.

Link:
http://www.emea.eu.int/

Tenofovir as HIV prevention: study to reduce HIV transmission in sexually active adults

The Bill and Melinda Gates Foundation has announced that it has awarded Family Health International (FHI) a $6.5 million, three-year grant for a multinational clinical trial to evaluate an antiretroviral treatment as a novel approach to HIV prevention. The trial will focus on sexually active adults in resource-poor countries with high HIV incidence.

The FHI study is designed to evaluate the safety and efficacy of the antiretroviral tenofovir disoproxil fumarate (tenofovir DF) as a method of reducing the risk of HIV infection in sexually active adults who are regularly exposed to the virus. The study will also assess the acceptability of, and adherence to, a regimen of one tenofovir DF tablet taken once daily. Gilead Sciences developed tenofovir DF and is supplying the drug for this study. As an antiviral treatment, tenofovir DF has several characteristics that make it a promising candidate as a method of HIV prevention, including its safety, efficacy, pharmacokinetic and resistance profiles.

Although condoms are a proven method for preventing the spread of sexually transmitted diseases, including HIV, women often are unable to successfully negotiate the use of this method by their partners. Thus, the urgency for expanded prevention options is greatest for women. If shown to be safe and effective in this setting, tenofovir DF could be an HIV prevention method used by men or women.

"It is imperative that we not only strive to develop new drugs, but that we also consider new uses for existing ones, such as tenofovir DF, which has tremendous potential as a dual HIV treatment and prevention technology," said Ward Cates, president of FHI's Institute for Family Health. "Our goal with this unique study is to help guide public health decision-making that spurs the delivery of HIV prevention tools to men and women around the world."

"Convenient, reliable and effective methods of HIV prevention are urgently needed," said Helene Gayle, director HIV/AIDS and TB at the Bill and Melinda Gates Foundation. "Previous experience with antiretroviral therapy in reducing the acquisition risks in healthcare workers and newborns exposed to HIV gives us hope that they may be an effective method of preventing sexual transmission of HIV."

Dr Gayle serves as co-chair of the Global HIV Prevention Working Group, which this summer issued its blueprint for action. In its report, the working group highlighted the need for new, novel technologies to reduce transmission of HIV. The working group also underscored the importance of efforts that will empower women to decrease their vulnerability to HIV.

Source: FHI News Release

Link:
http://www.fhi.org/en/gen/releases/newsrel8.html

Boehringer chooses dose for phase III studies of tipranavir/ritonavir PI combination

Boehringer Ingelheim (BI) is developing tipranavir, the first non-peptidic protease inhibitor (NPPI). The company recently submitted preliminary results from ongoing Phase II clinical trials to the US Food and Drug Administration (FDA). This data is the basis for initiating the pivotal Phase III trials for tipranavir.

After reviewing the data from the Phase IIb dose optimisation study and other clinical studies performed to date, the FDA has concurred with BI's recommendation of 500 mg of tipranavir (TPV) taken with 200 mg of ritonavir (r) twice daily. This dose combination will be used in the upcoming RESIST Phase III clinical trials and other clinical studies.

Background on Choosing the Dose

The following three doses of tipranavir were studied in the Phase IIb dose optimisation study (BI 1182.52):

500mg /100mg TPV/r

500mg /200mg TPV/r

750mg /200mg TPV/r

These doses were chosen because data from earlier studies showed that each dose achieved:

- the preliminary target plasma concentration

- acceptable virologic suppression

- tolerable adverse event profile

Each regimen was given twice daily in combination with a genotypically-defined optimised background regimen. All eligible patients must have received drugs from both the NRTI and NNRTI classes, at least two protease inhibitor (PI) regimens and must have had virus containing at least one primary PI mutation prior to enrolment. BI examined viral load reductions through 14 days and safety endpoints through 28 days. The study was conducted at 85 sites in nine countries - the United States, Canada, Australia, the Netherlands, Italy, Spain, France, Germany and the United Kingdom.

The tipranavir, 500mg / ritonavir, 200mg dose was chosen as the optimal dose to pursue because data from the Phase IIb study showed that it provided the most favourable benefit/risk profile (ie viral load suppression and safety) in this highly treatment experienced patient population. These data will be presented publicly in February 2003 at the 10th Annual Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

The dose is now being inserted into the RESIST 1 and RESIST 2 study protocols, and these are being sent to investigators and Internal Review Boards/Ethical Review Committees.

Source: Boehringer Ingelheim

Links:

http://www.hivandhepatitis.com/advertisement/boehringer.html

http://www.hivandhepatitis.com/hiv_and_aids/hiv_exper_drugs.html#tip

METABOLIC TOXICITIES AND SIDE EFFECTS

Adipose tissue alterations develop early in antiretroviral therapy

Graham McKerrow, HIV i-Base

Adipose tissue alterations (ATAs) are a frequent and relatively early finding during first-line antiretroviral therapy, according to a study by researchers at the University of Milan.

The causes of ATAs remain incompletely explained so Dr Massimo Galli and colleagues at Milan's Institute of Infectious Diseases and Tropical Medicine, decided to assess the incidence of ATAs and to identify the associated risk factors in patients infected with HIV-1 starting their first-line antiretroviral treatment.

In a multicentre investigation, physicians were asked to assess the presence of ATAs at enrolment and every six months thereafter. The ATAs were considered all together and were also grouped as fat loss (lipoatrophy), adipose tissue accumulation (lipohypertrophy), and combined forms.

The study followed 655 patients over a median 86 weeks. One hundred and twenty-eight patients (19.6%) were diagnosed as having at least one morphologic alteration during the study period. The researchers note that female gender and positivity for hepatitis C virus were independently linked to an increased risk of developing morphologic alterations.

Galli and colleagues also report that age was an independent correlate of risk of developing ATAs. To have been injected through drug injection was a correlate of reduced risk of ATAs.

Stavudine (Zerit, d4T) exposure was predictive at borderline statistical significance of lipoatrophy, but not of the other ATAs. Indinavir (IDV, Crixivan) exposure was associated with a significantly higher risk of developing combined forms of tissue alterations.

The researchers also report that patients who started therapy with two nucleoside reverse transcriptase inhibitors and subsequently added a protease inhibitor during the follow-up had a significantly higher risk of having ATAs compared to patients who continued taking two nucleoside reverse transcriptase inhibitors.

Ref: Galli M, Cozzi-Lepri A, Ridolfo AL et al. Incidence of Adipose Tissue Alterations in First-Line Antiretroviral Therapy: The LipoICoNa Study. Arch Intern Med 2002 Dec 9;162(22):2621-8

http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12456235&dopt=Abstract

IMMUNOLOGY AND IMMUNOTHERAPY

Breadth of memory CTL response against HIV associated with immune control

The number of HIV antigens recognised by memory cytotoxic T lymphocytes (CTL) is a major correlate of viral control and tends to decrease with the duration of infection, study results suggest. According to the French investigators, these findings underscore the importance of incorporating a wide range of HIV antigens into therapeutic vaccines.

For their prospective study, Dr Yves Riviere, of Institut Pasteur in Paris, and his colleagues in the IMMUNOCO Study Group enrolled 148 HIV-infected patients between 1991 and 1992, prior to the advent of highly active antiretroviral therapy (HAART).

They evaluated blood samples annually until the end of 1996 for cytotoxic responses to seven antigens. One hundred and twenty-two subjects were assessed for viral load at least once during follow-up. Over the course of the study, none of the patients received more than two antiretroviral agents.

Approximately 75% of the subjects exhibited CTL responses against one or more proteins during the trial period, the authors report in the 6 December issue of AIDS. At baseline, 23% of subjects had CTL cells that recognised none of the proteins, while 8% had cells that recognised one protein, 32% had cells that recognised two, and 17% recognised three. None of the target antigens tested on its own correlated with disease progression.

The number of recognised antigens was associated with viral load at baseline ($p < 0.05$) and declined at an average of 0.14 protein per year. However, the rate of reduction increased to one protein per year when opportunistic infections were present.

Dr Riviere's group theorises that there is "a progressive exhaustion in the CTL capacity to proliferate and/or to kill specific target cells."

The diversity of CTL response was negatively associated with CD8 cell counts, but not with CD4 counts. The authors suggest that "CD4 T-helper cell depletion does not directly influence the loss of diversity in HIV-specific CTL responses."

In addition to the implications regarding vaccination strategies, the research team concludes that the study findings provide "new end-points for immune-based therapeutic strategies aimed at restoring a strong and protective immunity against HIV in individuals receiving HAART."

Ref: Chouquet C, Autran B, Gomard E et al. Correlation between breadth of memory HIV-specific cytotoxic T cells, viral load and disease progression in HIV infection. AIDS 2002 Dec 6;16(18):2399-407
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12461413&dopt=Abstract

Source: Reuters Health

Dendritic-cell vaccine elicits strong anti-SIV response in monkeys

In monkeys infected with simian immunodeficiency virus (SIV), vaccination with inactivated SIV-pulsed dendritic cells dramatically reduces SIV DNA and RNA levels, according to a report published in the 23 December online issue of Nature Medicine.

"This work demonstrates for the first time an effective and durable therapeutic vaccine for treating simian AIDS, which opens the possibility of treating human AIDS by vaccination," lead author Dr Wei Lu, from the Universite Rene Descartes in Paris, said in a statement.

The vaccine is created by harvesting dendritic cells from an infected animal and then treating the cells with a chemically inactivated form of SIV. These cells are then reintroduced into the animal to stimulate an enhanced anti-SIV response.

Previous reports have shown that pulsed dendritic cells can elicit a strong antiviral response in vitro. But until now, the efficacy of this technique in vivo has not been known.

In the current study, Dr Lu's team inoculated 14 rhesus monkeys with SIV. A few weeks later, 10 of the animals began receiving injections of inactivated SIV-pulsed dendritic cells. The four remaining animals received injections that contained non-pulsed dendritic cells.

By six weeks, monkeys treated with the pulsed cells had experienced a 50- and 1000-fold decrease in SIV DNA and RNA levels, respectively. Moreover, these reduced levels persisted for the remaining 34 weeks of the study. In contrast, no changes in SIV DNA or RNA levels were noted in the control group.

Further analysis of lymph node lymphocytes from the pulsed cell-treated animals revealed an inverse relationship between SIV DNA and RNA levels and SIV-specific T-cell responses, the authors note.

In contrast to highly active antiretroviral therapy (HAART), "therapeutic dendritic cell vaccines have no systemic side effects and need only a few subcutaneous injections," Dr Lu noted.

Dr Lu said that his team is currently preparing phase I/II clinical trial that "will tell us, within two years, whether a similar success can be reached in HIV-infected people." Also, "our research is now focused on improving these therapeutic vaccines in the monkey model with the ultimate aim of 'immunologic eradication' of SIV/HIV."

Ref: Lu W, Wu X, Lu Y et al. Therapeutic dendritic-cell vaccine for simian AIDS. Nat Med 2002 Dec 23; [epub ahead of print]
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12496959&dopt=Abstract

Source: Reuters Health

HIV infection causes fibrosis in lymphatic tissue, diminishing CD4+ pool

Chronic infection with HIV-1 causes severe fibrosis and scarring in the paracortical T cell zone of lymphatic tissues, which may explain why HAART fails to restore the peripheral CD4+ T cell count in some patients even when it results in good viral

suppression, researchers suggest. Their full report, "Collagen Deposition in HIV-1 Infected Lymphatic Tissues and T Cell Homeostasis," was published in the 15 October issue of the Journal of Clinical Investigation.

Examining lymph node biopsies in HIV-infected patients "has the potential to provide yet another look at how the body's immune defences are reacting to viral infection, and gives potentially prognostic information about what the impact of therapy will be," said lead author Dr Timothy W Schacker.

Schacker, of the University of Minnesota-Minneapolis, and colleagues prospectively studied inguinal lymph node biopsies of 11 HIV-infected patients who were HAART-naïve at baseline. Seven patients initiated HAART after the first biopsy; four chose to defer treatment.

Researchers noted significant depletion in the CD4+ T cell population in all samples at baseline. They also found evidence of chronic inflammation and fibrosis that altered the structural organisation of the tissue.

At one month and six months, investigators found improvement in the size and number of B cell follicles in three treated patients, and a general trend toward expansion of the CD4+ T cell numbers in lymphoid tissue. Yet, researchers found no improvement in three other patients who had also initiated HAART.

In one HIV-negative patient, less than 1% of the T cell zone area consisted of collagen. In infected persons, collagen comprised 2.2% to 19.9% of the T cell zone area. The study found a significant inverse relationship between the percentage area collagen and the size of the CD4+ T cell population in the baseline biopsies. The area occupied by collagen was not associated with other clinical markers of disease severity, including duration or stage of infection, baseline plasma CD4+ T cell count, or plasma HIV-1 RNA level. However, there was a significant relationship between the change in the peripheral CD4+ count after six months of HAART and the baseline percent area occupied by collagen, after controlling for baseline peripheral CD4+ count and viral load.

"In the state of chronic immune activation and inflammation from ongoing HIV-1 replication, there is damage and disruption to the lymph tissue microenvironment that results in the impaired recruitment, retention, and proliferation of CD4+ T cells," the investigators stated. They likened the fibrosis process to that found in the pathogenesis of cirrhosis in chronic active hepatitis B and C infection.

Schacker noted that such findings could be used to advise patients. "For example, if you were to perform a staging biopsy on a new patient, you could tell that patient, 'based on the evidence, we think your lymph tissue will suffer a significant amount of damage even though you have no clinical symptoms yet.' This individual you might want to put on HAART earlier rather than later to protect the lymph tissues."

He also suggested "something as simple as a nontoxic anti-inflammatory agent started immediately after infection could perhaps limit damage to the lymphoid space in a significant way."

Ref: Schacker TW, Nguyen PL, Beilman GJ et al. Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis. J Clin Invest 2002 Oct;110(8):1133-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12393849&dopt=Abstract

Source: CDC HIV/STD/TB Prevention News Update

Chronic immune activation: a lethal factor in HIV infection?

The theory that HIV causes T-cell dysfunction and T-cell loss by chronic immune activation has gained ground with the publication of a study that shows that persistent immune stimulation can cause immunodeficiency. "Chronic immune activation contributes to the depletion of the naive T-cell compartment and results in fatal opportunistic infections," reports senior researcher René van Lier (Academic Medical Centre, Amsterdam, Netherlands).

Van Lier and colleagues studied the effects of chronic immune activation using CD70 transgenic mice, which constitutively express CD70 - the ligand for the tumour necrosis factor receptor family member CD27 - on B cells. Transgenic expression of CD70 on B cells promoted effector T-cell formation, and mice showed progressive conversion of naive T cells into effector-memory cells, which led to a depletion of naive T cells from the lymph nodes and spleen. Despite having a hyperactive immune system, CD70 transgenic mice died aged six to eight months from Pneumocystis carinii infection, a hallmark of T-cell immunodeficiency (Nat Immunol; published online 9 December). "The persistent delivery of co-stimulatory signals was able to exhaust the T-cell pool and induced lethal immunodeficiency, in the absence of an active infection", explains van Lier.

"This is an elegant study", comments Lena Al-Harthi (Rush Medical College, Chicago, IL, USA), "that highlights the critical role played by immune over-stimulation in the progression of HIV". It is particularly interesting, notes Al-Harthi, that chronic immune activation leads to thymic accelularity, perhaps through induction of steroid hormones that lead to thymic involution. "This is especially relevant to paediatric HIV disease, where paediatric patients tend to progress much faster to AIDS than adult patients", she says.

Van Lier stresses that the cornerstone of the treatment of HIV-seropositive individuals remains reduction of virus replication, but adds that new and perhaps more effective drugs will be included in HAART cocktails. "The study suggests that treatment of hyper-immune activation may be beneficial in patients with viruses resistant to the current regimens. One option would be to target co-stimulatory molecules like CD70 that are up-regulated in HIV-infected people," he says.

The researchers are now doing two follow-up studies. One deals with the role of antigen in naive T-cell depletion. "We are testing if repetitive exposure to antigens together with excessive co-stimulation leads to depletion of antigen-specific T cells (CD4 and CD8)," explains van Lier. The second is investigating mechanisms of reconstitution - ie, role of thymus, peripheral homeostatic proliferation - and possible ways of influencing recovery.

Ref: Senior K. Chronic immune activation: a lethal factor in HIV infection? Lancet 2002 Dec 14;360(9349):1946.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12493267&dopt=Abstract

Source: www.thelancet.com

OTHER NEWS

Website run by a nun in a caravan is nominated for awards

Graham McKerrow

The AEGIS website, run by a nun from a caravan in California, has been nominated for awards for being perhaps the most exhaustive and accessible source of information on HIV.

The AIDS Education Global Information System was set up by Sister Mary Elizabeth Clark 12 years ago on a homemade computer in the 60ft mobile home she shares with her 91-year-old father in San Juan Capistrano. The free site has 750,000 documents, which Clark and two staff update daily. It receives 7 million hits a year.

Now AEGIS, which has an annual budget of $200,000, mostly from Boehringer Ingelheim, has been nominated for inclusion in UNESCO's Memory of the World Programme, which preserves the world's most important libraries and archives.

AIDS activist and playwright Larry Kramer has suggested Clark, aged 64, for an award from the American Foundation for AIDS Research.

Kramer told the Los Angeles Times: "She provides incredible and important information for my daily life, and I couldn't get along without it." When Bill Clinton was in power the executive office of the president of the United States checked the latest postings every morning.

Clark is no stranger to publicity, having enlisted in the US Navy as a man and in the US Army as a woman before becoming a nun. After 17 years in the Navy as Michael Clark, she had gender reassignment surgery and enlisted in the Army reserves. She was open about her transsexuality and the Army voided her enlistment. She sued and won a $25,000 settlement and an honourable discharge.

Raised a Christian, Clark then took vows of poverty, chastity and obedience at St Clement's By-the-Sea Episcopal Church in San Clemente, but within a week the bishop rejected her vows. Clark commented: "I made my vows to God, not a church."

Clark, who has also been married twice and fathered a son, still rises at 5am to upload reports to AEGIS but says she must now train others to continue the site without her.

Link:
http://www.aegis.org/

Infection by closely related HIV strains possible

A report of an individual infected with a second strain of HIV despite effective drug treatment following the first infection has researchers concerned.

"For the first time, we've shown it is possible for an individual to become infected with two closely related strains of HIV," says Dr Bruce D Walker, a grantee of the National Institute of Allergy and Infectious Diseases (NIAID) and a researcher at Massachusetts General Hospital and Harvard Medical School.

Published in Nature, these findings underscore the challenges vaccine developers face in creating a broadly effective vaccine against HIV. The first HIV vaccines may not prevent infection altogether, but rather may prevent HIV from causing disease by limiting the virus' ability to reproduce, explains Dr Walker. This case shows that a hypothetical vaccine against one strain of HIV may not necessarily protect the vaccinee against other, closely related strains.

"The implications of superinfection for an individual with HIV/AIDS are not yet clear," says Anthony S Fauci, NIAID's director. "However, there is little doubt what these new data mean in terms of public health: it is imperative that safer sex be practiced during each encounter, even when both partners are HIV-infected," he adds.

The new case involves a person whose HIV infection was kept in check for many months during structured treatment interruption (STI). In STI, antiviral therapies are frequently given during the early, acute stage of infection, but halted after the immune system has had time to adapt to the virus. Often, as in this case, a patient's immune system rebounds enough to keep HIV suppressed. "This patient's immune response against HIV was really quite robust," says Dr Walker. Thus, the researchers were perplexed when, after successfully suppressing HIV for close to one year, the patient's viral load suddenly shot upwards. Despite several more attempts to interrupt therapy, the patient was unable to hold the virus to previously attained low levels.

To understand why STI stopped working for this individual, "We dissected the immune system in very fine detail," says Dr Walker. First, he and his co-investigators examined HIV-made proteins taken from the patient at several points in time. They detected a difference between the amino acid sequence of the original infecting virus and the virus isolated after STI failed. Additional studies confirmed that the change resulted from infection by a second HIV strain well after the first infection.

The two strains differed in overall amino acid sequence by about 12%, "about what we'd expect for two strains in North America," notes Dr Walker. In comparison, the sequence difference between strains of various major subtypes, or clades, of HIV is about 30%. Although superinfection by strains from different clades has been reported previously, this is the first published report of infection by two strains from the same clade.

The picture became still more sobering when the researchers compared only those HIV amino acid sequences targeted by the immune system. Here, the strains differed by 50%. Consequently, a large fraction of the immune cells that had been produced previously and that had successfully tamped down the first virus were unable to recognise and react to the second strain. "We were stunned," says Dr Walker. "Essentially, the immune system was encountering two markedly different viruses."

The research did uncover a few bright spots, however. For instance, immune system cells called CD8+ T cells, appeared in new, strain-specific forms after the individual became infected with the second strain. This indicates an ability on the part of the CD8+ T cells to react appropriately to newly arrived HIV strains, even in conditions of chronic infection. Thus, researchers can remain cautiously optimistic that therapeutic immunisation to create broader and more potent immune responses in persons with chronic HIV infection may one day be possible.

Ref: Altfeld M, Allen TM, Yu XG et al. HIV-1 superinfection despite broad CD8+ T-cell responses containing replication of the primary virus. Nature 2002 Nov 28;420(6914):434-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12459786&dopt=Abstract

Source: NIAID News

Link:
http://www.niaid.nih.gov/newsroom/releases/hivinfection.htm

ON THE WEB

CONFERENCE REPORTS:

Report from the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

Joseph Cofrancesco Jr., M.D., M.P.H.

The Hopkins HIV Report - January 2003

- More on d4T
- PI Studies
- Treatments for Complications
- Implications of Lipodystrophy

San Diego was the site of the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, held 22-25 September 2002. This was a useful meeting for investigators exploring the long-term complications of HIV and its treatment. Though much of the data presented focused on *in vitro* studies and animal experiments, studies were presented that have important implications for HIV therapy and the management of treatment-related complications. This report focuses on the studies reporting human and clinical data.

Full text at:

http://www.aegis.org/pubs/jhopkins/2003/JH20030102.html

The science of side effects (or, who's afraid of 3T3-F44A2 cells?)

A report from the 4th Lipodystrophy Workshop.

IAPAC Monthly - Vol. 8, No. 11, November 2002

Mark Mascolini

Including:
- From bench to bedside
- From bedside to bench
- Hard science
- Hard arteries
- More good lipid and insulin scores with atazanavir
- Lipid subclass quiz (correct answer: efavirenz)
- Lipid liabilities with d4T
- HAART, the heart, and other muscles
- Hard choices
- Switching from d4T for atrophy and high lactates
- Diet and exercise: those who can, win
- Options for facial atrophy
- Alendronate for thin bones
- Statins popular, but how potent?

Full text at:

http://ww2.aegis.org/pubs/iapac/2002/ia021102.html

Medscape conference coverage, based on selected sessions at the 6th International Congress on Drug Therapy in HIV Infection, 17 – 21 November 2002, Glasgow, Scotland

Resistance and response to subsequent treatment following virologic failure of tenofovir-based therapy - Graeme Moyle

http://www.medscape.com/viewarticle/446683

Once-daily fosamprenavir/ritonavir appears comparable to twice-daily nelfinavir - W. David Hardy

http://www.medscape.com/viewarticle/446684

Efficacy of T-20 holds up across subgroups with varying demographics and disease status - W. David Hardy

http://www.medscape.com/viewarticle/446685

Nelfinavir Is less effective but better tolerated than ritonavir in advanced disease - Graeme Moyle

http://www.medscape.com/viewarticle/446686

Zidovudine is metabolized to stavudine triphosphate in human cells - Graeme Moyle

http://www.medscape.com/viewarticle/446687

Levels of abacavir and lamivudine in semen - Mike Youle

http://www.medscape.com/viewarticle/446688

Cellular expression of multidrug transporters only modestly affects intracellular PI levels - Graeme Moyle

http://www.medscape.com/viewarticle/446689

Lactic acid metabolism is affected both by baseline level and by HIV infection itself - W. David Hardy

http://www.medscape.com/viewarticle/446690

Sexual transmission of hepatitis C - Mike Youle

http://www.medscape.com/viewarticle/446691

4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

Donald P. Kotler

The 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV was held in San Diego, California, 22-25 September 2002, immediately before the 42nd ICAAC meeting. Of the two meetings, the most important presentations on lipodystrophy were at the workshop.

In general, the data presented were provocative but not definitive. There was progress in identifying the most relevant factors underlying the molecular and cellular changes associated with lipodystrophy, especially those related to protease inhibitors. The major focus of the workshop was on basic science, and very few treatment studies were presented. However, one theme that arose during the meeting was the concept that antiretroviral treatment may have several physiologic effects, some of which may be divergent.

This is a major confounding factor in the cross-sectional studies reported to date. However, results are becoming available from longitudinal studies of antiretroviral therapy, such as ACTG 384, and should further our knowledge of the development of lipodystrophy.

Including:

- Effects of antiretroviral agents on adipogenesis
- Effects of antiretroviral agents on glucose metabolism
- Effect of protease inhibitors on bone
- Basic science studies of atherogenesis
- Clinical studies of metabolic alterations
- Measurement of mitochondrial DNA
- Individual Susceptibility to Lipoatrophy
- Longitudinal Studies of Body Fat Distribution and HAART

Full text at:

http://www.medscape.com/viewprogram/2147_childindex

T-20: a model for novel anti-HIV drugs in development

Jeffrey Laurence

from The AIDS Reader

In September of 1993, Drs Wild, Greenwell, and Matthews of Duke University published a letter in an AIDS research journal describing a synthetic peptide directed against the gp41 transmembrane portion of the HIV envelope, which appeared to have remarkable antiviral activity in vitro. This 36-amino acid peptide, corresponding to residues 643 to 678 of the HIV-1LAI isolate, was originally designated DP-178. It later became known as T-20. Renamed enfuvirtide (Fuzeon) by its clinical developers at Trimeris and Roche, it belongs to a new family of antiretroviral drugs that inhibit HIV entry.

As noted in the original publication, the 50% inhibitory concentration of T-20 for HIV-1-mediated cell fusion, assessed by syncytia formation, was 0.4 nmol/L (1.7 ng/mL). This is very low, and unprecedented for a peptide. The area of gp41 against which it was directed shows limited genetic variability, and this variance did not appear to affect function. Specificity was illustrated by the fact that three-fold higher log concentrations of T-20 were required to block HIV-2 entry into target cells.

The conclusion of that original brief study was that T-20 “could serve as a lead compound in the discovery of both peptide- and nonpeptide-based drug candidates.” That turned out to be an understatement.

Full text at:

http://www.medscape.com/viewarticle/444890

Recent research in HIV infection: Part 1

Brian A. Boyle

from The AIDS Reader

The flood of developments in HIV research continues, and new data have recently been presented regarding some important issues in HIV therapeutics. These include what HAART regimen to start with, when that regimen should be started, and the impact and efficacy of simplified HIV therapy.

This column will provide summaries and analyses of these recent data. Data regarding the treatment of important coinfections, including herpes simplex virus infection, hepatitis B, and hepatitis C, will be discussed in Part 2.

Part 1 full text at:

http://www.medscape.com/viewarticle/444892

HIV/AIDS-related research at the 40th Annual Meeting of the Infectious Diseases Society of America, 24-27 October 2002, Chicago, Illinois

from Medscape HIV/AIDS

William G. Powderly

The annual meeting of the Infectious Diseases Society of America (IDSA) is increasingly associated with high-quality reviews by experts in the field. However, it is less likely to be associated with a large number of novel HIV-related abstracts because of the competition from other HIV-related scientific meetings in the summer and fall.

Nevertheless, a number of interesting and important observations could be gleaned from information presented at this year's meeting.

Including:

- Cardiovascular risk and HIV disease

- Treatment of HIV-associated hyperlipidemia

- Multiple protease inhibitors as salvage therapy

- Resistance testing in treatment-naive, chronically infected patients

- Predicting CD4+ cell count in resource-limited countries

- Clinical indicators of chronic renal failure

Full text at:

http://www.medscape.com/viewarticle/444549

HIV-associated sensory neuropathies

from AIDS, Official Journal of the International AIDS Society

[AIDS 16(16):2105-2117, 2002.]

Sanjay C. Keswania, Carlos A. Pardoa, Catherine L. Cherry, Ahmet Hokea,

Justin C. McArthur

Peripheral neuropathy has emerged as the most common neurological complication of HIV infection. There are several discrete types of HIV-associated neuropathy, which can be classified according to the timing of their appearance during HIV infection, their etiology and whether they are primarily axonal or demyelinating.

Some represent a consequence of HIV infection producing neuropathological damage [eg distal symmetrical polyneuropathy (DSP)], while others are related to opportunistic pathogens [eg cytomegalovirus (CMV) polyradiculitis]. An increasingly common group is that which occurs as a result of treatment toxicity [eg toxic neuropathy from antiretroviral drugs (TNA) and lactic acidosis syndrome].

Full text at:

http://www.medscape.com/viewarticle/445189

New HIV Insite Knowledge Base chapters

Pathogenesis of HIV-associated lymphoma

Valerie L. Ng, and Michael S. McGrath

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-06-03-01

Aspergillosis and HIV - Judith A. Aberg

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-05-02-02

Candidiasis and HIV - Carl J. Fichtenbaum, and Judith A. Aberg

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-05-02-03

Protease inhibitor double boosting - Jay F. Dobkin

from Infections in Medicine

Concepts in medicine sometimes cycle in and out of favour. Occasionally, something with a new name sounds novel but in fact may reflect an old idea, and every so often a practice adopted for one reason turns out to be useful for an entirely different rationale. The current trend toward combining multiple protease inhibitors (PIs) reflects these themes.

Central to these efforts has been Kaletra, the fixed combination of lopinavir and low-dose ritonavir, which opens the possibility of boosting another PI at the same time, usually saquinavir or amprenavir. In patients in whom initial regimens containing indinavir or nelfinavir fail, the addition of one of these agents to Kaletra seemed potentially useful because the key resistance mutations associated with these drugs were often absent.

Since the 100 mg of ritonavir contained in a standard dose of Kaletra could boost the levels of either amprenavir or saquinavir when used without lopinavir, the same effect was expected when the three agents were given together.

Full text at:

http://www.medscape.com/viewarticle/444857

Historical essays from Science:

Discovering the cause of AIDS - Stanley B. Prusiner

Free full text article:

http://aidscience.org/science/298(5599)1726b.html

A history of HIV discovery - Luc Montagnier

Free full text article:

http://aidscience.org/science/298(5599)1727.html

The early years of HIV/AIDS - Robert C. Gallo

Free full text article:

http://aidscience.org/science/298(5599)1728.html

Enhanced: prospects for the future - Robert C. Gallo and Luc Montagnier

Free full text article:

http://aidscience.org/science/298(5599)1730.html

Treatment of primary HIV infection

Eric S. Daar

from Medscape General Medicine [TM]

The natural history of HIV infection usually begins within weeks of a sexual or percutaneous exposure to the genital secretions or blood of an infected individual. The diagnosis of primary or acute HIV infection allows for counselling to prevent subsequent transmission to others and enrolment into immunopathogenesis studies. In addition, recent investigation suggests that the initiation of antiretroviral therapy during this stage of disease may have a profound influence on long-term virologic control.

Full text at:

http://www.medscape.com/viewarticle/443820

Lipodystrophy: lack of agreement on definition and etiology presents a challenge to research and therapy

Graeme Moyle

from The AIDS Reader

"I can't define it, but I know it when I see it," said Supreme Court Justice Potter Stewart when asked to define pornography. The sentiment of this response can be applied equally to lipodystrophy. Definitions of the lipodystrophy syndrome have proliferated more rapidly than successful treatments, adding confusion to an already complex area. It is now more than four years since the widespread recognition of the metabolic and morphologic changes observed during antiretroviral therapy. The morphologic changes can be highly stigmatising, and the metabolic manifestations may contribute to a range of morbidities. Anxiety about developing lipodystrophy may lead to risking HIV disease progression through delaying the commencement of therapy or deciding to stop therapy to prevent or manage the problems, and to risking long-term management through modification of established therapy to alternative regimens.

Full text at:

http://www.medscape.com/viewarticle/443422

Navigating resistance pathways

Daniel Kuritzkes

from The AIDS Reader

One of the most daunting challenges facing HIV-treating clinicians is the persistent spectre of treatment failure in their patients. There are several factors involved in the development of treatment failure in HIV-infected patients including preexisting resistant viral variants; the potency of the drugs used (and thus the barrier to resistance of each drug and the regimen as a whole); patient-specific factors, such as adherence; and pharmacologic factors. Host immunologic status is also important because the more advanced the disease is, the less likely it is that a complete response to antiretroviral therapy will occur.

These factors, when combined, can result in incomplete suppression of viral replication and, in the setting of persistent viral replication, a greater opportunity for drug resistance mutations to emerge. The emergence of these mutations initiates a cycle of less treatment efficacy, less viral suppression, more viral replication, and broader cross-resistance, which cycles back to less treatment efficacy and ultimately leads to failure of the regimen.

Full text at:

http://www.medscape.com/viewarticle/442763

PUBLICATIONS AND SERVICES FROM i-BASE

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

Included with this issue of HTB is the January 2003 edition of this 16-page guide. These treatment guides are reviewed every six months to ensure the latest information is available. Many factors contribute to whether a combination works and in salvage therapy it is important to look at all of these together.

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

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

* T-20 has reported clear benefits for people resistant to current drugs - marketing approval is expected in mid 2003 and prior to this will be available in a limited expanded access programme from early 2003.

* Atazanavir appears to increase cholesterol and triglycerides less than other PIs and is available in an expanded access programme for people with raised lipids on current PIs.

* Tipranavir, a PI with activity against currently resistant HIV, will be available during 2003 in a limited emergency access programme.

For additional free copies, including bulk orders see below

UK-Community Advisory Board reports and presentations

The UK-Community Advisory Board (UK-CAB) was set up by HIV i-Base last year as a network for community treatment workers across the UK and has so far held three meetings. Each meeting includes two training lectures and a meeting with a pharmaceutical company.

The training sessions from the August meeting, transcribed in full, are:

Genetics, resistance and HIV – by Professor Clive Loveday

Approaches to Salvage Therapy – by Dr Mike Youle

The October meeting covered:

Pregnancy, HIV and Women's Health - by Dr Karen Beckerman transcriptions are online at http://www.i-base.org.uk/education/index.html

Fertility treatment and sperm-washing techniques – by Dr Leila Frodsham (Powerpoint presentations are online at http://www.i-base.org.uk/education/index.html

Introduction to Combination Therapy

This guide explains what combination therapy is, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and drug resistance and how to avoid it, To order copies, see below

Guide to Avoiding and Managing Side Effects

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

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

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

Positive Treatment News (PTN)

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

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

HIV Treatment Bulletin (HTB)

This is the journal you are reading now; a review of the latest research and other news in the field. HTB is published 10 times a year on our website (http://www.i-base.org.uk/) and in a printed version. The printed version is available at most HIV clinics in the UK and is available free by post: see below for details.

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http://www.i-base.org.uk/

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

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

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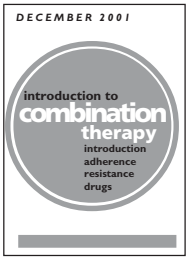

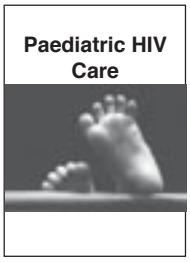

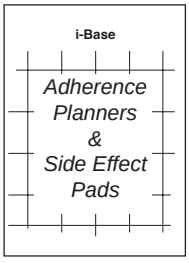

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