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CONTENTS

(hyperlinked)

EDITORIAL

The big story over the last month has been the ritonavir 400% "price hike" from Abbott in the US, which has provoked fury from activists and doctors alike. Although current prices will not increase for the moment in Europe the longer term implications for Europe are unclear at this stage, and it's feared things do not bode well for the new formulation.

An additional blow to salvage patients was the announcement from Roche that development of T-1249 has been suspended which will be particularly disappointing for those who have already developed resistance to T-20.

Good news though was the triumphant announcement by the treatment Action Campaign (TAC) that GSK and Boehringer have agreed to grant licences to generic companies to produce or distribute AZT, 3TC and nevirapine to sub-Saharan African countries in exchange for minimum royalties (see page 10)

Our next April issue of HTB will include extensive coverage of the 11th Conference of Retroviruses and Opportunistic Infections (CROI), held from 8-11th February in San Francisco. Abstracts from this meeting should be available on the conference website from the first week of February. Webcasts from many of the lectures should also be made available shortly after they have been presented.

http://www.retroconference.org

ANTIRETROVIRALS

Abbott raises price of ritonavir in the US by over 400%

Simon Collins, HIV i-Base

On 3 December 2003, Abbott Pharmaceuticals increased the US price of ritonavir by over 400%. This prompted an immediate response from both community and medical organisations that included withdrawing co-operation with Abbott projects and returning previous funding grants.

The increase is seen as an attempt to regain a higher percentage of the limited budget available for HIV drugs in the US and may be one of the largest price increases announced for any medication in recent years. A spokesperson for Abbott could not say whether the company had recently increased the price of any of its other drugs so substantially in the last few years.

Ritonavir now is widely used as a pharmacokinetic booster for other protease inhibitors. It helps produce more stable, constant and sustained drug levels and reduces inter-patient variability. Protease inhibitors boosted by ritonavir include lopinavir, indinavir, saquinavir, fosamprenavir and atazanavir and the pipeline compounds tipranavir and TMC-114. Although lopinavir is co-formulated with ritonavir in Abbott's protease inhibitor the price of Kaletra has not been increased.

These combinations are particularly important for treatment-experienced and salvage patients with few or no treatment options left. Although in the US a company can set its own price for a drug, legal advice is being sought on how the increase, which gives Kaletra an immediate cost advantage over other boosted protease combinations, can be challenged.

One community editorial said: 'What Abbott has done is unforgivable and will go into the history of the AIDS epidemic as a repugnant commercial manipulation that unnecessarily burdens people living with HIV/AIDS, especially those with fewer treatment options who can truly benefit from boosted protease-inhibitor therapy. Physicians, researchers, government officials, and patients should be outraged by these events and should take heed of such gross opportunism tainting the very nature and purpose of healthcare".

In a letter to Abbott, the AIDS Treatment Activist Coalition stated: "Instead of being grateful that Norvir still has therapeutic application and will enjoy continued sales, Abbott has apparently made an ultimatum that therapeutic options for salvage patients or even those who just need more potent therapy (arguably any patient with HIV) will cost, and cost dearly."

The letter continues: "Abbott has just changed the landscape of HIV/AIDS for the worse - is this what it wants to be known for? ATAC urges Abbott to reconsider its recent actions and to rejoin the battle against HIV/AIDS by advancing research and therapeutics until this scourge against humanity is conquered. Further, we challenge you to roll back the price of Norvir. Abbott has obviously regained its development costs many times over with this drug, which received full approval on the basis of a minimal development package and without an Expanded Access Program."

Also highlighted is the potential impact for next generation drugs that are being developed as boosted agents. Many patients have been hoping that tipranavir, a drug with activity against many protease-resistant viruses that is currently in Phase 3 studies, would become an important component of their treatment. The increased costs for the boosting component of these pipeline regimens (tipranavir, capravirine, TMC114) could jeopardize both clinical development and access post-approval.

In a comment to the Wall Street Journal, Abbott says that the sharp price increase is a long-overdue adjustment after years of being priced below other protease inhibitors, and that it invested a substantial amount in reformulating the drug. Abbott is

developing another formulation of ritonavir that will not require refrigeration.

The website of AIDS Treatment Activists Coalition (ATAC) provides further details of the community response, including HIV Medical Association and ATAC press releases: http://www.atac-usa.org/Abbott%20price%20hike.html

Abbott: http://abbott.com/hiv/hiv.html

C O M M E N T

There appears to be no justification whatsover for this price hike. It looks like a cynical and cruel manipulation of the marketplace to give Kaletra a cost benefit over any other PK enhanced PI.

Pharmaceutical companies are able to set their own prices for drugs in the US but it is not possible to comment on claims for research and development costs as independently audited breakdowns for these costs are never publicly available.

It certainly seems like Abbott wants to block the coadministration of once-daily saquinavir/r (see below) by this move to protect Kaletra, and this would explain the unchanged price for Kaletra. This seems logical because the US are their home market and boosting PIs is today a much wider used strategy in Europe compared to the US. A secondary effect may be to additionally boost its revenues by increasing the price of RTV 100 mg BID to a range usually matched by PIs dosed as true antivirals. Finally, it is a clear signal that the Meltrex formulation will be far more expensive compared to ritonavir at current European prices.

Abbott say that there are no plans to change the price for ritonavir in the UK which will be held stable in Europe until a new formulation of ritonavir is developed. They could not comment on the expected price for the non-refridgerated Meltrex formulation which may be available by 2005. If it is priced close to the new US price, this would be likely to increase the cost of tipranavir-boosted combinations to more than T-20.

Development of T-1249 put on hold

Simon Collins, HIV i-Base

On 5 January 2004, Roche and Trimeris, the companies that are jointly responsible for developing the fusion inhibitor T-20 (enfuvirtide, Fuzeon) announced that they have put on hold the development programme of the pipeline compound T-1249. [1]

T-1249 is a second fusion inhibitor in development, and in early studies had shown the potential for greater potency, once-daily rather than twice-daily dosing and activity over T-20 resistant virus. As with other HIV drugs, resistance to T-20 develops unless it is used in a combination with other active drugs.

Difficulties with producing an acceptable formulation are the main reason given for this decision. Although a large investment in the development of T-20 overcame many similar problems, the company does not believe that a similar investment in current approaches to T-1249 would lead to a drug that had a sufficiently beneficial profile over T-20.

Research will continue into new delivery options for T-1249 and other molecules. However, even if successful, in practice patients should not expect access to a second generation fusion inhibitor from Roche and Trimeris for many years.

Both companies were criticised for including the information about stopping T-1249 – clearly the most important news – within a 'forward-looking' statement about a new research agreement. [1]

The only ongoing study will continue for the 40 or so patients still enrolled, and patients still benefiting from T-1249 will continue to receive the drug even after the study closes, but the decision to suspend the research programme closes the door on T-1249 for new patients. This is particularly disappointing for people who have developed resistance to T-20. Early reports of T-1249 presented at the Retrovirus and ICAAC conferences in 2003, indicated that the compound had clear antiviral activity in T-20-resistant patients, whatever difficulties existed with the formulation. [2, 3]

It also has practical implications for patients who are using or considering using T-20 now. Without the promise of a second-generation drug in the pipeline, it becomes even more important to follow recent guidelines to use T-20 when supported by other active drugs, and many patients should either wait until new drugs are available to use with T-20, or use T-20 earlier in treatment failure, when sensitive drugs are still available.

Both BHIVA UK Guidelines and the London HIV Consortium have produced guidelines to this effect. [4, 5]

Use of T20 has been lower than initially predicted, possibly because it has to be given by twice daily injection, and is significantly more expensive than other treatments. Roche is expanding its community and medical education programmes to address these concerns.

Related links:
http://www.roche.com
http://www.natap.org/2004/jan/010704_02.htm

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3. Lalezari JP et al. Final analysis of T1249-102: T-1249 retains potent short term antiviral activity in patients who have failed a regimen containing enfuvirtide. 43rd ICAAC Conference, Chicago, September 2003. Abstract H-444.
4. http://www.bhiva.org
5. http://www.bhiva.org/consortium/consortium.html

C O M M E N T

The main explanation from Roche is that T-1249 has formulation problems and it is like injecting tooth paste, but it is hard to judge from outside if the disappointing sales results of T-20 may have at least facilitated this disappointing decision. It will be interesting to follow how Roche continues further development of T-20 in formulations to increase the half life and to optimize the administration.

Tenofovir/abacavir/3TC triple-nuke fails as maintenance regimen

Simon Collins, HIV i-Base

A research letter in the 13 December issue of the Lancet further highlighted the risk of using the triple nucleoside combination of abacavir/3TC/tenofovir, even as a as maintenance therapy. [1]

Serious concern over the potency of this combination led to the issuing of safety warning letters from Gilead and the EMEA last year, following significantly lower rates of viral suppression and higher rates of viral rebound in several studies. [2]

In a retrospective analysis from an observational cohort Hoogewerf and colleagues identified eight patients who had switched to abacavir/3TC/tenofovir and whose viral load was <50 copies/ml from their previous long-term ART (median 14·2 months, range 7·5–67·5). Nine other patients on the same combination were excluded because they had failed a previous combination treatment or because their viral load was already greater than 50 copies/mL at the time of the switch.

Treatment was judged to be failing if the viral load rebounded, confirmed by a subsequent sample. They tested genotype resistance in every patient who failed treatment. Five of the eight patients failed their treatment. The median time to failure was 130 days (range 54-160). The median viral load at the time of failure was just over 3000 copies/mL (range 314-37,597). Three patients are still being treated successfully with the combination after a mean of 199 days. The patients for whom treatment failed differed from those who were treated successfully in baseline viral load before ART (mean 445,000 vs 69,000 copies/mL respectively), baseline CD4 count before ART (mean 88 vs 177 cells/mm3), and in the average time on successful ART before switching (mean 10·8 vs 40·7 months), but too few patients were assessed for the results to be significant.

Genotype resistance at the end of the combination therapy in all five patients who failed treatment showed one patient had an M184I mutation, one a K65R mutation, one an M184V and a K65N mutation, and one a M184V and a K65R mutation. One patient did not have any of these mutations.

The authors conclude: "HIV-infected patients should not be given the abacavir, lamivudine, and tenofovir combination either as initial treatment in treatment-naïve patients, or as alternative treatments for successful ART regimens."

References

1. Hoogewerf M, Regez RM, Schouten WEM et al. Change to abacavir-lamivudine-tenofovir combination treatment in patients with HIV-1 who had complete virological suppression. Lancet. 2003;362:1979-1980. Dr K Brinkman (e-mail:k.brinkman@olvg.nl).
2. EMEA public statement on early virologic non-response in patients with HIV infection treated with tenofovir in combination with lamivudine and abacavir. See HIV Treatment Bulletin Volume 7 Number 4, August/September 2003.
   http://www.i-base.info/pub/htb/v4/htb4-7/TREATMENT.html

New data on viral load 'blips' and the link to replication

Bob Huff, GMHC Treatment Issues

You can be a "blipper" and still be chipper, suggests a study in the November 2003 issue of the Journal of Virology by Michele Di Mascio and her colleagues from the Los Alamos National Laboratory and the Aaron Diamond AIDS Research Centre in New York. Blips are usually thought of as occasional, transient episodes of low-level HIV RNA viraemia in someone who is adherent to their antiretroviral therapy and otherwise enjoys a well-suppressed viral load. Most people with HIV RNA below

50 copies/mL (undetectable) may have intermittent positive viral load test results at some time or another. But how common are blips, how long do they last, and what causes them?

Some have suggested that blips are due to the release of virions from reservoirs or protected sanctuaries in the body where replication of drug-sensitive virus continues at a low level. Others have reported that it's drug-resistant virus that makes for blips. Another theory is that an immunological event such as an infection suddenly increases the number of infectable immune cells and that blips are the resultant viral feeding frenzy. Whether due to any of these reasons or perhaps due to natural variations in drug levels in a person hovering on the margins of suppression, most studies, fortunately, have not found a long-term association between blips and loss of virologic control or disease progression.

Di Mascio's study looked carefully at the frequency and duration of blips above 50 copies/mL as recorded in 123 treatment naïve patients from eight different research cohorts starting a PI-containing regimen. The mean CD4 count at treatment initiation was 474 (+/- 254) cells/mm3. Overall, the analysis looked at an average of 26 viral load tests per subject over as many months, finding a wide variation in blip frequencies, with 41 patients showing no blips and one patient blipping at every other determination. The average number of blips per sample was 0.09.

The study found that blips were not due simply to assay variation or to chance alone but that different people inherently have different tendencies to blip. They next showed that, within the limits of monthly testing, having one blip does not predict having another and that blip arrival is substantially random. Furthermore, in the patients studied, neither the frequency nor amplitude of blips seemed to increase with time on therapy, which suggests that poor adherence was not responsible for these viraemic episodes.

There was a relationship, however, between blip frequency and baseline CD4 count, with those having more advanced HIV disease at the time of starting therapy being more likely to become blippers. The significance of this is not clear, although during the period of observation reported here no increase in blip frequency was seen.

Blips passing in the night

Perhaps the study's most striking finding is that blips may actually be viraemic episodes that last as long as a month, and that, depending on sampling frequency, a number of different blips could produce a pattern of viral load test results that appears as continuous viral breakthrough. An analysis of viral load measurements taken within 22 days of a blip, when fitted into a model, predicts a typical blip duration of 20 to 30 days. If blip episodes actually last this long, then even people with several consecutive detectable viral load determinations might actually be having a train of independent blips, and not sustained viral load throughout the period. Since even sequential blippers in this study generally did not progress to virologic failure, one might wonder how many consecutive blippers in real life have undergone unnecessary regimen switches because of what appeared to be sustained low-level viraemia to a clinician determined to maintain undetectability? While this work comes from the Theoretical Division of the Los Alamos lab, the practical implications of blips, blippers and blipping obviously require more and urgent research.

Replication rates and viral load

The different rates and amplitudes of blipping suggest that there is a great deal of individual variability in the replication rate of HIV, even when mostly suppressed by drug pressure. Another study reported in the November Journal of Virology investigated the relation between viral load and replication rate in individuals who are not taking antiretroviral drugs.

It's long been recognised that viral genetics plays a role in how aggressively HIV behaves in a host. The X4 coreceptor-using variant is particularly famous for kicking HIV immune damage into high gear. More recently it's been recognised that for people who have been on therapy and have developed drug-resistance, their mutant virus may be "less fit" than a wild type drug-susceptible virus. If so, then staying on a failing regimen may be clinically protective despite loss of viral control. Growth competition experiments have also shown that viruses from several long-term non-progressors were inherently less replication competent than viruses from people with normal rates of disease progression.

On the host side, the best known genetic trait that affects susceptibility to HIV infection and subsequent disease progression is a mutation found in a small segment of the population that limits or eliminates the CCR5 cell surface protein, an essential co-receptor for HIV entry. But this flaw in the CCR5 gene is not the only source of CCR5-dependent variability in HIV replication. Even in persons with two functional copies of the CCR5 gene there may be considerable inter-patient variability in levels of CCR5 expression at the cell surface. Individuals may also express different amounts of RANTES, a messenger protein that competes with HIV for using CCR5, with elevated l evels of RANTES associated with slower disease progression.

Different degrees of innate and acquired immunity to HIV may also play a large role in keeping HIV replication under control during the years of slowly progressing disease that follows primary infection. HIV-specific CD8 cells in particular are thought to help in controlling runaway HIV disease and it is hoped that one day a vaccine can be made to boost these protective cells.

The amount of virus found in the blood (viral load) is likely determined by a balance between the elimination of virus and the production of new virus. HIV-specific CD8 cells are generally considered the leading candidate for effecting viral elimination. But this theory remains shaky because most studies haven't found the expected correlation between the strength and

specificity of CD8 T-cell response and lowered viral load. If CD8s are mainly responsible for clearing out unwanted HIV, then why don't people with the most qualified CD8s always have the lowest viral loads?

Thomas Campbell and colleagues from the University of Colorado, Denver, sought to establish if replication rate was correlated with plasma viral load levels by performing two different kinds of replication rate assays on the viruses of 12 individuals with chronic HIV infection who were not receiving treatment. Eight of the 12 were treatment naïve and none of the participants had detectable drug resistance mutations.

Each individual's virus was cultivated in cell cultures for up to 10 days with assessments of HIV p24 protein production performed daily. Changes in the amount of p24 detected from one assessment to the next produced a growth curve that revealed each virus's particular replication dynamics. Typically, each virus had a daylong lag before any p24 production was seen. After p24 was detected, growth proceeded exponentially for the next six days or so. Finally, a plateau phase appeared after the sixth day when additional p24 production tapered off, probably due to saturation of infectable cells after day four.

In addition to the growth curves, the replication capacity of each virus's reverse transcriptase and protease enzymes were determined by genetic recombination techniques using a modified version of the Phenosense drug susceptibility assay.

The investigators found a strong linear relationship between replication rate and viral load that held true from 1000 copies to 100,000 copies/mL. Furthermore, they established that, among these 12 individuals, there was significant natural variation in rates of viral replication due entirely to viral qualities. Another interesting finding was that RT and PR replication capacity were related to the cell-based replication rate. This suggests that genetic variations in these wild type enzymes may be responsible for the different replication rates of different viruses, even in the absence of drug exposure.

One limitation to the study is that in cell systems the role of the host's genetics and immune system are removed, so an individual's actual response to their virus cannot be predicted from these results. This issue aside, however, the authors make a provocative suggestion that different viral replication rates may be obscuring measurements of immune-based factors that influence HIV viral load in the body. In particular, they suggest that CD8 cell responses, which have previously not correlated well with viral load, should be reexamined after controlling for replication rate. It's possible that the expected CD8 impact on viral load may only become clear after the "noise" of variation in replication rate has been reduced. If so, then this could help unlock one of the central mysteries of immune control of HIV and remove one of the stubborn stumbling blocks in the way of finding a vaccine.

References:

1. Di Mascio M, Markowitz M, Louie M, et al. Viral blip dynamics during highly active antiretroviral therapy. JVirol. Nov 2003.
2. Campbell TB, et al. Relationship between in vitro HIV-1 replication rate and virus load in plasma. JVirol,.Nov 2003.

Source: GMHC Treatment Issues, November 2003

http://www.gmhc.org

Invirase and Fortovase: new dosing regimens approved by FDA

The FDA approved, on 24 December 2003, new dosing regimens for the two available formulations of saquinavir, Invirase (hard gel capsule) and Fortovase (soft gel capsule). The newly approved dosing regimen for both Invirase and Fortovase is 1000 mg BID (twice a day) co-administered with ritonavir 100 mg BID.

For Invirase, the new ritonavir boosted regimen replaces the previously approved regimen. As stated in the revised label, Invirase should never be used without ritonavir.

For Fortovase, the ritonavir boosted regimen allows a reduced pill burden and ease of administration compared to the previously approved regimen. Unboosted Fortovase, however remains a dosage option for patients who are unable to tolerate ritonavir.

The approval of the new dosing regimens was based on pharmacokinetic and safety data. Both boosted regimens of saquinavir provide plasma concentrations exceeding that of unboosted Fortovase. Important changes in the Invirase and Fortovase labels include drug interaction information relevant to the co-administration of ritonavir.

The revised labelling will be available in the coming weeks through the index at:
http://www.fda.gov/cder/approval/index.htm

Source: FDA press release

C O M M E N T

Until now Invirase and Fortovase were one of the most expensive and least effective PIs when used according to the label. Now with an approved boosted setting at least in Europe the daily price will now decrease.

UK named-patient access to tipranavir

The named-patient access to tipranavir that started in Autumn 2003 is still continuing. Entry criteria for this limited programme include:

- Require tipranavir to construct a viable combination of anti-retroviral agents for therapy based on current treatment guidelines and the patient's previous anti-retroviral history.
- ‡ 18 years of age or is ‡ 13 years of age, with a total body weight ‡ 50kg.
- CD4+ count £ 50 cells/mm3
- HIV RNA ‡ 10,000 copies/ml

Patients taking or intending to take additional protease inhibitors with tipranavir and ritonavir are currently not eligible for named patient supply.

Clinicians should contact Sarah Jones in the medical division of Boehringer Ingelheim on 01344 742539 or 07776 483808 for further information regarding the programme.

FDA labelling changes for indinavir (Crixivan)

The following revisions to the package insert in the US were approved by the FDA in January 2004.

Precautions section: Tubulointerstitial Nephritis

"Reports of tubulointerstitial nephritis with medullary calcification and cortical atrophy have been observed in patients with asymptomatic severe leukocyturia (>100 cells/high power field). Patients with asymptomatic severe leukocyturia should be followed closely and monitored frequently with urinalyses. Further diagnostic evaluation may be warranted, and discontinuation of indinavir should be considered in all patients with severe leukocyturia."

Immune reconstitution syndrome

"Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (CART), including indinavir. During the initial phase of treatment, patients responding to antiretroviral therapy whose immune system responds to CART may develop an inflammatory response to indolent or residual opportunistic infections (such as MAI, CMV, PCP, or TB), which may necessitate further evaluation and treatment."

Drug interactions – contraindication with atazanavir (Reyataz)

"Both indinavir and atazanavir are associated with indirect (unconjugated) hyperbilirubinemia. Combinations of these drugs have not been studied and coadministration of indinavir and atazanavir is not recommended."

Revisions to the patient package Insert (PPI)

The following wording was added to the "What are the possible side effects of indinavir?" section of the PPI:

"In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from opportunistic infections may occur when combination antiretroviral treatment is started."

In the same section, under Marketing Experience, the words "and increased cholesterol" were added so that the revised text reads: "Other side effects reported since indinavir has been marketed include: allergic reactions; severe skin reactions; yellowing of the skin and/or eyes; heart problems including heart attack; stroke; abdominal swelling; indigestion; inflammation of the kidneys; inflammation of the pancreas; joint pain; depression; itching; hives; change in skin color; hair loss; ingrown toenails with or without infection; crystals in the urine; painful urination; numbness of the mouth and increased cholesterol."

Source: FDA press release, January 2004

TREATMENT ACCESS

Global Fund awards bring total to $2.1bn and supply ARVs to 700,000 people

Graham McKerrow, HIV i-Base

The third round of awards granted by the Global Fund to Fight AIDS, TB and Malaria amounted to another $623 million, bringing the total given and promised by the Fund to $2.1 billion over two years. The latest money given by the Fund is less than in the previous round, and less than was originally projected by the Fund.

The Global Fund expects the total money awarded so far to result, after five years, in 700,000 people on antiretrovirals which is triple the current coverage in developing countries, and 35 million people receiving voluntary counselling, testing and prevention services. The Fund dollars will also finance medical, educational and community care for 1 million orphans, treatment for 3 million people with TB, 22 million combination drug treatments for resistant malaria and 64 million bed nets to protect people from malaria.

In a statement, the Fund said its October 2003 meeting in Thailand focused on how to raise and disburse funds in "a time of scarce resources".

About 60% of the $2.1 billion so far awarded has been given to projects in Africa. The same percentage has been awarded for spending on HIV, with 23% of the money going to combat malaria. Almost half the money (46%) is allocated for drugs and commodities, 25% for human resources, 15% for physical infrastructure, 5% for monitoring and evaluation and 4% for administration. Half the money has been awarded to governments, 29% to non-governmental organisations and the rest to the private sector, faith-based groups, academic institutions and affected communities.

This year $2.9 billion is pledged to the Global Fund with another $1.9 billion promised for 2005-2008. The Fund estimates it will need $3.3 billion for 2004 alone.

Japan has announced that it will increase its contribution to the Fund this year from $40 million to $100 million bringing its contribution for 2002-2004 to $260 million. The US has promised $823 million for 2002-2004 and is considering increasing this sum. European pledges to the Fund total $1,691 million.

The World Health Organisation has declared that the Fund has a key role to play in financing the so-called "3 by 5" initiative to give 3 million HIV positive people access to ARVs by the end of 2005. There are 40 million people with HIV and it is estimated 6 million of them need treatment.

In January 2004 the Fund issued a call for proposals for Round 4, which have to be submitted by 2 April, and executive director Richard Feacham told the Global Fund Observer, an independent monitoring group, that the Fund hoped to receive large HIV-treatment-oriented proposals for Round 4.

"The world is now poised for a massive scale-up in antiretroviral therapy," he said, adding: "In every country that scale-up is urgent, timely and possible. The Global Fund exists to help finance that scale-up. So we very much hope to see large and ambitious applications for antiretroviral scale-up in Rounds 4 and 5." Round 5 is expected in 2005.

Global Fund the Fights ATM
http://www.theglobalfund.org/en/

Global Fund Observer (Aidspan)
http://www.aidspan.org/gfo/

WHO
http://www.who.int/en/

COMMENTARY: The Global Fund and treatment access in Latin America – a critical view

Richard Stern, Agua Buena Human Rights Association

The Global Fund to Fight AIDS, TB and Malaria offers promises and hope for many, but a view from the field in Latin America and the Caribbean indicates that when it comes to antiretroviral treatment access, the complications are many and the promises offered by the Fund are slow to be fulfilled.

In Ecuador and the Dominican Republic, prolonged internal disputes involving CCMs [the "Country Coordinating Mechanisms" which are national partnerships of government, PWAs, NGOs and other agencies] and Principal Recipients [of the Global Fund grants] have meant that even though their proposals were accepted by the Fund in January 2003, the grant agreements had still not been signed as of late November, and thus no money has been received. These countries compounded the problem by deciding to wait for Global Fund money to arrive before starting to purchase antiretrovirals for targeted populations. Thus, ironically, the existence of the Global Fund has actually delayed treatment access in these countries.

There is another problem, somewhat less dramatic, that has occurred in almost every country. NGOs that in the past might have tackled violations of human rights or gaps in treatment access now have to consider whether such activism could cause them to lose access to Global Fund revenue received by their local CCM. It is important to remember that in Latin America, prior to the Global Fund, only minimal amounts of financial support have been available for civil society through national AIDS programmes. The Global Fund appearing on the scene represents a potential "windfall" of resources, and the dynamics related to advocacy have changed considerably. The key factor here is that most CCMs are, in fact, government controlled, even if that is not the Fund's intention.

The domination of government in CCMs was dramatically illustrated in the Latin American/Caribbean Regional Meeting that

the Fund held in Panama in late November. Incredibly, only eight of 160 participants were People Living with HIV/AIDS (PLWAs). The Fund had instructed CCMs to make their own selection as to who to bring to the meeting, and only four out of the 20 countries present – Costa Rica, Bolivia, Colombia and Cuba – actually included PLWAs in their delegation.

One of the most interesting moments in the Panama meeting occurred on the final day when nearly a dozen international agencies marched to the podium to present themselves. Among them were USAID, PAHO, GTZ, UNAIDS, the World Bank, the Interamerican Development Bank, UNDP and UNICEF. Many of the agencies made references to the hundreds of millions of dollars they have invested in the AIDS pandemic. After the speakers had concluded their presentations, Julio Cesar Aguilar, a PLWA from Bolivia, commented: "I am grateful that almost all of the agencies on this stage are working to help us in Bolivia. But I wonder how it is possible that as yet not even one PLWA in my country has received ARV treatment?"

Eighteen months after the Fund began operations, Global Fund money has only led to some 800 to 1,000 people receiving treatment in Latin America and an additional 1,000 in the Caribbean. Most of these are in Honduras and Haiti, which had their proposals approved in Round One, and some are in El Salvador. Argentina and Chile may also be providing some ARV access with funds provided by the Fund, but ARV access in these two countries was nearly universal even before the Global Fund began to provide funds.

With the impending arrival of Global Fund money, it seems almost inevitable that there is intense competition and distrust between civil society and government, as well as between NGOs themselves. In two of the countries mentioned above, the fight about who was to be the Principal Recipient was taken by NGOs to the Fund's mid-level staff, and perhaps beyond, and this has resulted in delays which will set the process of actual disbursement of funds back as much as a year. Those who urgently needed ARVs in 2003 have had to wait until 2004. As many as 25% will not survive.

Another problem is that in some countries, NGOs that represent vulnerable populations such as gay/lesbian/bi/trans people are routinely denied legal registration, yet CCM regulations stipulate that only legally registered NGOs can benefit from Global Fund money. So, because of this Catch 22, these groups – which have a real ability to reach out to and conduct prevention work among their own populations – are supplanted by legally registered NGOs that suddenly appear on the scene and have no demonstrated track record in working with vulnerable populations.

Some of the accepted Global Fund proposals in the Latin American region were written by highly capable experts who joined forces with local CCMs only for the purpose of writing the proposal. In these cases, the accepted proposal does not always accurately reflect the country's national AIDS programme or its ability to put large amounts of money to good use in AIDS programmes. Some proposals reflect mainly the writing and technical skills of the outside consultants who drafted the proposals.

Another issue is that the few civil society representatives on the CCMs often are well intentioned but poorly trained regarding more technical issues of programme implementation and medication purchase. Many of the PLWA representatives come from backgrounds where they simply have not been trained in the necessary areas. This puts them at a tremendous disadvantage when facing government AIDS bureaucrats who may dominate decision-making processes in areas to do with ARV access and other "technical" issues.

The only feasible solution to the problems elaborated above would be greater active participation of the Global Fund in CCM activities and programme implementation. The Fund is reluctant to do this because it has limited staff and it wants local capacity to develop and national AIDS programmes to become self-sufficient. One possibility would be for this to happen in phases with, at first, much more support from trained experts whom the Fund could employ after a proposal has been approved.

To suddenly present a previously impoverished and not particularly well-trained AIDS programme with the prospect of millions of dollars is certainly well intentioned but can sometimes lead to all kinds of unforeseen problems, ranging from inadequate infrastructure to rampant manipulation and corruption. People living with HIV/AIDS need treatment today, not in a year or two, but without more active guidance and "hands on" participation from the Fund, situations that are destructive and lead to long delays in treatment access will undoubtedly continue to occur.

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Links: Agua Buena Human Rights Association
http://www.aguabuena.org/

COMMENTARY: **China starts long march against HIV**

Bernard Rivers, Aidspan, Beijing, November 2003

Until recently, there was little evidence that the government of China was serious about AIDS, despite its own forecast that today's one million people with HIV could reach at least 10 million by 2010. However, the Ministry of Health now appears willing to take some hesitant steps forward – although there is, as yet, little evidence that other ministries, or local government outside Beijing, are ready to act decisively.

The first signs of a change in spirit by the Ministry of Health came with China's Round 3 proposal to the Global Fund to Fight AIDS, TB and Malaria. The Country Coordinating Committee (CCM, a national partnership of government, NGOs PWAs and other agencies) proposed a programme costing $98 million over five years to provide care and treatment for 40,000 "former plasma donors" in rural provinces. In the mid-1990s, these people supplemented meagre incomes by repeatedly selling plasma at blood collection points which, it turned out, were practicing unsafe procedures, causing the blood sellers to become HIV-infected.

These people have been treated shamelessly. Local officials who profited from the plasma-selling operations took far too long to bring them to an end. Many of these officials remain in office to this day, sometimes promoting police crackdowns on HIV-infected villagers who protest at their dire plight. The central government wrings its hands and says that health and police activities have been delegated to local authorities and cannot be controlled from Beijing.

The government has at last led a successful initiative by the CCM to obtain Global Fund support for the provision of treatment to former plasma donors.

Prominently placed on the first page of the proposal was a statement that "the Ministry of Health is currently evaluating the potential financial and other consequences of providing universal free HIV/AIDS treatment to all those in China who cannot afford it." Then on September 22, speaking at the UN, China's acting Minister of Health, Gao Qiang, stated that the government has decided that it will indeed provide free treatment to all rural HIV/AIDS patients and poor urban patients.

This promise was repeated at several AIDS-related events in Beijing during early November. There was, on the one hand, an impressive spirit of openness. On the other hand, there was little discussion by government officials of the enormous hurdles that have to be surmounted if the government's desire to tackle HIV/AIDS is to be successful. As one speaker pointed out, the Ministry of Health – which has low status among government ministries – could not do all that is needed even if it tried to. Success will only occur if the desire for action moves 'up' from the Ministry of Health to the nation's top leadership; moves 'down' from the MoH to autonomous provincial and county agencies; and moves 'across' from the MoH to other ministries. Concern was also expressed regarding sub-optimal mixes of ARV drugs being used, and regarding high dropout rates from pilot treatment programmes.

The culminating point in the week's activities occurred on 10 November, with a visit by Bill Clinton to an AIDS conference at Tsinghua University. In the question and answer session, he was asked how physically close he has ever come to someone infected with HIV. Very close, he replied in a relaxed tone – handshakes, hugs, sometimes with patients who were close to death. After the Q and A session was over, one of the would-be questioners who had not been called upon jumped up and demanded to be heard. He said that he was 21, and had been HIV-positive for the past six years. Clinton answered his questions, and congratulated him on his openness. He then beckoned to the young man to come up on the stage, affably draped his arm over the young man's shoulders, and grinned at the flashing cameras as the audience applauded. The following morning, most of China's major newspapers showed this incident as the main photograph on the front page. It was the ultimate media moment.

The young man in question, Song Pengfei, became HIV-positive through receiving infected blood in a hospital operation. He and his family were then completely ostracised by society, and lived in poverty. His father fought tenaciously to publicise his plight and to obtain ARVs for him from foreign charities. Some years ago, Song was the first person in China to publicly state that he was HIV-infected. After he asked tough questions of Chinese officials at a foreign conference, he was blacklisted by the government. So there was poetic justice when a beaming Clinton took Song by the arm and got him to shake hands, in front of the cameras, with three government ministers, whose smiles seemed a little less perky than Song's.

The Global Fund grant is important because it represents a last-minute effort to help the former plasma donors before they die, and because it represents the first significant HIV care and treatment programme in China. However, the real test will be whether China builds on this and effectively tackles the flow of HIV infections from injecting drug users, via commercial sex workers, to the general population.

Bernard Rivers (rivers@aidspan.org) is Executive Director of Aidspan and Editor of its GFO Newsletter. He visited China several times last year to serve as facilitator to the team developing China's HIV proposal to the Global Fund.

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Link: Global Fund Observer (Aidspan)
http://www.aidspan.org/gfo/

WHO guidelines for use of ARVs in resource-poor settings

On 1 December 2003, the World Health Organisation launched the 3 by 5 Initiative, a new effort to scale-up antiretroviral therapy in the developing world, with an initial target of reaching 3 million people by 2005. Guidelines for use of ARVs in resource-poor settings were also published

These and other related documents are online at:

http://www.who.int/3by5/en/

Millions will benefit after GSK and BI license generic manufacturers to produce AZT, lamivudine and nevirapine

Graham McKerrow, HIV i-Base

Two of the world's biggest pharmaceutical companies have signed an agreement with a group of South African AIDS activists that will result in affordable medicines for millions of sub-Saharan Africans.

The ground breaking deal marks a triumphant end to a legal, political and media campaign against the companies, which, as we reported in the last issue of HTB, resulted in the South African Competition Commission finding that GlaxoSmithKline (GSK) and Boehringer Ingelheim (BI) had contravened the Competition Act by denying competitors access to essential facilities and by charging excessive prices.

The companies signed the agreement with the Treatment Action Campaign (TAC), the Congress of South African Trade Unions, other organisations, four people living with AIDS and four health workers. The activists say the agreement "goes well beyond what could conceivably have been won by pursuing the prosecution of the complaint under the Competition Act".

In October 2003, the Clinton Foundation brokered a deal that ensured that generic companies would sell triple combination therapy to sub-Saharan governments for $140 per patient per year. TAC says the new agreement between the activists and the companies means the Clinton deal can be implemented immediately.

GSK has agreed to grant licences to four generic companies to produce and/or import, sell and distribute AZT and lamivudine. BI will grant licences to three generic companies to produce and/or import, sell and distribute nevirapine. GSK and BI will receive royalties of "no more than 5% of net sales of the antiretroviral medicines". Before the agreement, BI was demanding royalties of 15% and GSK wanted 30%.

Previous agreements have applied to the supply of drugs only to the public sector but this deal covers the private sector as well. For the first time, the generic manufacturers will be allowed to export the drugs to all 47 sub-Saharan countries.

The agreement also allows the generic manufacturers to produce the drugs in combination with each other and/or other drugs for which they have licences, which will allow multi-drug fixed-dose combinations, currently made by separate companies, to come onto the market as single pills. The licences cover adult and paediatric formulations of the drugs.

The TAC has declared that in the event of GSK or BI not complying with any aspect of the agreement, they will return to court to have it enforced. The TAC has also warned the generic producers that it will monitor their prices as closely as it monitors the prices of brand name medicines.

The TAC has called on other major pharmaceutical companies such as Merck, Roche and Abbott to come to similar agreements

Link:
http://www.tac.org.za/

COMMENT

It is easy to knock the Global Fund for doing too little, too late and imperfectly but it is a slim machine that deserves credit for extracting more than $2 billion from rich countries and getting it out to projects in poorer countries. It is no mean feat to finance ARV treatment for 700,000 people, testing and counselling for 35 million and care for 1 million orphans as well as treatment for 3 million people with TB and the provision of 64 million bed nets.

Richard Stern's criticisms (above) of what is happening on the ground in Latin America are, however, serious and from a credible source, so the Global Fund needs to investigate them and respond.

South African activists are to be congratulated on another triumph in their long campaign for affordable treatments for the citizens of their own and neighbouring countries. Merck, Roche and Abbott should offer similar licences for generic producers and not waste time by waiting to be dragged through the courts and media, as did GSK and BI – at the cost of many lives and serious damage to those companies' reputations.

Companies, governments, NGOs and other agencies and individuals – the AIDS community - must now focus on the '3 by 5' target which, although it will take another two years to treat just half of those who need ARVs, sets the world an achievable goal and would represent significant progress.

This July the AIDS community will gather for the 15th International AIDS Conference, this time in Bangkok, and we will hold each other to

account as to just how much has been achieved since we met in Barcelona in 2002 and how to reassess our priorities. The conference banner is "Access for all" and we will learn from each others' experiences, not least from activists who have successfully confronted obstructionist government and multinationals.

Link:

http://www.aids2004.org/

Scaling up treatment access risks damaging national health systems, says WHO/UK report

Graham McKerrow, HIV i-Base

The HIV epidemic is increasing demands on already struggling health systems and undermining their capacity to provide services, says a review of the provision of antiretroviral therapy in poor countries, published in November 2003 by the World Health Organisation and the UK government. The problem is that the extra pressure leads to the breakdown of services because of "the attrition of health sector workers".

The report says: "Attempts to address the systemic impact of HIV/AIDS remain fragmented, confined to a few countries, and lacking the support of a coherent policy and resource framework. This will become more critical as countries move towards scaling up ART, since effective and efficient provision of ART will require well-functioning health systems."

However, the 105-page report goes on to say that if there is proper investment to address infrastructure, human resources and logistics weaknesses, "scale up of ART provision has the potential to strengthen systems and improve outcomes for non-HIV related conditions."

The report highlights a pilot programme in Thailand that has resulted in a stronger HIV service system, more commitment from health workers and greater community involvement.

Most countries, especially in sub-Saharan Africa, are taking a phased approach to the introduction of ART through the public sector, starting with provision through selected provincial and regional hospitals. For example, Botswana, the first African country to offer ART through the public health system, is rolling out the programme through hospitals at four sites. Nigeria started with an ARV programme operating at 25 health centres in 2002 and will expand it to 100 centres.

The report identifies shortage of staff as "a major constraint" to scale up, and says that in many countries, including those with high HIV prevalence rates, "the health sector is facing a crisis in human resources".

The report concludes that paying for the provision of ARVs solely through public sector financing is "unrealistic" in most poor countries. Many countries introducing ART will need to charge for services unless external funding is provided by the Global Fund to Fight AIDS, TB and Malaria or other sources.

Ref: Attawell K and Munday J. Provision of antiretroviral therapy in resource-limited settings: a review of experience up to August 2003. WHO and the UK's Department for International Development, November 2003.

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

http://www.who.int/3by5/publications/documents/dfid/en/print.html

Link:

http://www.healthsystemsrc.org

LIPODYSTROPHY AND METABOLIC COMPLICATIONS

Importance of dietary management in treating lipid disorders: soy diets may offer comparable effect as statins

Graham McKerrow, HIV i-Base

Studies in the United States and Canada emphasise the importance of dietary management in the treatment of lipid disorders, which can be just as effective as the use of statins.

DJ Jenkins and colleagues at St Michael's Hospital, Toronto, write in the November 2003 issue of Metabolism that combining a number of foods and food components in a 'portfolio diet' can lower low-density lipoprotein-cholesterol (LDL-C) similarly to statins. [1]

Reductions in LDL-C result from diets containing almonds, or diets that are low in saturated fat or high in viscous fibres, soy

proteins or plant sterols. The researchers combined all these into a 'portfolio diet' to see if they could achieve cholesterol reductions of similar magnitude to those reported in recent statin trials which reduced cardiovascular events.

Twenty-five hyperlipidaemic subjects were divided into two groups. One group (n=13) consumed a portfolio diet low in saturated fat and high in plant sterols, soy protein, viscous fibres and almonds, while the other group consumed a low saturated fat diet based on whole wheat cereals and low-fat dairy foods. LDL-C was reduced by 12.1%+/-2.4% (P<0.001) on the low fat diet and by 35.0% +/-3.1% (P<0.001) on the portfolio diet, which also reduced the ratio of LDL-C to high density lipoprotein –cholesterol (HDL-C) significantly (30.0%+/- 3.5%; P<.001).

The researchers write: "The reduction in LDL-C and the LDL-C:HDL-C ratio were both significantly lower on the portfolio diet than on the control diet (P<.001 and P<.001, respectively). Mean weight loss was similar on test and control diets (1.0kg and 0.9kg, respectively)."

A paper by Jenkins and colleagues in the July 2003 Journal of the American Medical Association (JAMA) reported that intensive dietary therapy may be just as effective in reducing cholesterol levels as the starting dosage of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) drug. [2] They randomly assigned 55 healthy hyperlipidaemic men and women to receive one of three treatments: a very low saturated fat diet based on whole-grain wheat cereals and low fat dairy foods (control group), the same diet plus lovostatin, 20mg/d (statin group), or a portfolio diet (see above). Based on data from 46 subjects in the four-week study, the authors report that the statin and dietary portfolio treatment groups had approximately 30% reduction in LDL-C compared with an 8% reduction in the control group.

In an editorial in the same issue of JAMA, James W Anderson writes: "These results are potentially important, given the expense, safety concerns, and intolerance related to statin use. Moreover, if confirmed in other rigorous investigations, these findings could have far-reaching implications for a large number of patients with dyslipidaemia; those who are motivated to adopt prudent diets might achieve meaningful lipid reductions without pharmacotherapy." [3]

The November 2003 issue of the Wellness Letter published by the University of California, Berkeley, commented "the portfolio diet is a good one" but under a section headed 'Pluses and minuses', it added: "If you are a vegetarian, the portfolio diet may seem easy; if you are accustomed to eating meat, poultry, fish, and dairy, it could be hard. And fish and low-fat or nonfat dairy products have their own cardiovascular benefits." [4]

KM Hendricks and colleagues at Tufts University School of Medicine, Boston, investigated dietary components that may predispose HIV-positive patients to develop fat deposition. [5] They evaluated differences in past dietary intake between HIV-positive men who developed fat deposition and those who did not. They had 47 cases and 47 controls from the Nutrition for Healthy Living cohort and compared food records from six to 24 months before development of fat deposition. HIV-positive patients without fat deposition had greater overall energy intakes (kcal/kg; P = 0.03) and greater intakes of total protein (P = 0.01), total dietary fibre (P = 0.01), soluble dietary fibre (P = 0.01), insoluble dietary fibre (P = 0.03), and pectin (P = 0.02) than did HIV-positive patients with fat deposition. Those without fat deposition also tended to currently perform more resistance training (P = 0.05) and to not be current smokers (P = 0.05).

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http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14522738&dopt=Abstract

COMMENT

The benefits of dietary treatment of lipids in HIV-negative individuals may differ substantially from the results in HIV-positive people with dyslipidemia due to antiretroviral treatment as this has a completely different pathophysiology. Practising a well balanced diet will not be wrong, but high flying hopes should be substantiated by controlled studies first.

The findings of the Boston study show that in HIV-positive patients the risk factors for lipoaccumulation are the same as in the general population which raises to the question how would these patients look without HIV? They would most probably more obese than matched controls. However the borderline p-values should be looked at with caution.

A recent paper in Medical Hypotheses suggested that very low fat diets may be a useful approach to HIV-related lipodystrophy. Excessive flux of free fatty acids after eating a normal diet may overwhelm the ability of peripheral subcutaneous adipocytes to store triglycerides. This manifests as hypertryclyceridaemia and fat redistribution to truncal and visceral stores. They go on to suggest that chronic exposure of tissues to high levels of free fatty acids (FFA's) may also induce insulin resistance. A very low fat diet (less that 15% of daily calories made up from fat intake) would reduce postprandial flux of FFA's, reduce LDL cholesterol and may help to reduce visceral fat deposits. Such diets are also known to have a beneficial effect on insulin sensitivity.

Ref: McCarty MF. Iatrogenic lipodystrophy in HIV patients - the need for very-low-fat diets. Med Hypotheses. 2003 Nov-Dec; 61(5-6): 561-6.
http://dx.doi.org/10.1016/S0306-9877(03)00230-5

Human histology and persistence of various injectable filler substances for soft tissue augmentation

The following is an abstract presented at the 33rd Annual Meeting of the Association of German Plastic Surgeons in Heidelberg, Germany, on 21 September 2002 and published online on 4 December 2003 by researchers at the University of California, San Diego, and the Institute of Pathology, Frankfurt.

An increasing number of soft tissue filler substances have been introduced to the beauty market outside the US which lack experimental and clinical data in support of their claim. Ten commercially available filler substances were examined for biocompatibility and durability: 0.1 cc of each substance was injected deep intradermally into the volar forearm of one of the authors and observed for clinical reaction and permanence. At one, three, six, and nine months the test sites were excised, histologically examined, and graded according to foreign body reactions classification. Collagen (Zyplast) was phagocytosed at six months and hyaluronic acid (Restylane) at nine months. PMMA microspheres (Artecoll) had encapsulated with connective tissue, macrophages, and sporadic giant cells. Silicone oil (PMS 350) was clinically inconspicuous but dissipated into the tissue, causing a chronic foreign body reaction.

Polylactic acid microspheres (New-Fill) induced a mild inflammatory response and had disappeared clinically at four months. Dextran microspheres (Reviderm intra) induced a pronounced foreign body reaction and had disappeared at six months. Polymethylacrylate particles (Dermalive) induced the lowest cellular reaction but had disappeared clinically at six months. Polyacrylamide (Aquamid) was well tolerated and remained palpable to a lessening degree over the entire testing period. Histologically, it dissipated more slowly and was kept in place through fine fibrous capsules. Polyvinylhydroxide microspheres suspended in acrylamide (Evolution) were well tolerated, slowly diminishing over nine months. Calcium hydroxylapatite microspheres (Radiance FN) induced almost no foreign body reaction but were absorbed by the skin at 12 months. Host defence mechanisms react differently to the various filler materials, but all substances - resorbable or nonresorbable - appeared to be clinically and histologically safe, although all exhibit undesirable side effects.

Since the mechanism of late inflammation or granuloma formation is still unknown, early histological findings are not useful in predicting possible late reactions to filler substances.

Ref: Lemperle G., Morhenn V and Charrier U. Human histology and persistence of various injectable filler substances for soft tissue augmentation. 33rd Annual Meeting of the Association of German Plastic Surgeons in Heidelberg, Germany, 21 September 2002.

C O M M E N T

This is an ambitious experiment and comparative studies for treatments for New-Fill will be important for patient choice. Dr Lemperle holds the patent rights for Artecoll.

OPPORTUNISTIC INFECTIONS

Treating oral hairy leukoplakia with high dose valacyclovir

Graham McKerrow, HIV i-Base

A study of 19 people (73% on HAART) with HIV-associated oral hairy leukoplakia (OHL) and Epstein-Barr virus (EBV) replication found that treatment with high dose oral valacyclovir (Valtrex), one gram every eight hours for a month, could inhibit productive replication of EBV. Walling and colleagues at the University of Texas report that in the majority of cases OHL was resolved and EBV replication was halted.

OHL was cleared in 89% of subjects. OHL and EBV replication recurred in two subjects and EBV replication alone was

detected in two more subjects. The researchers theorise that either the virus developed resistance and/or subjects did not take their medication as directed.

According to the research team: "Valacyclovir appears to be a generally safe and effective option for the short-term treatment of OHL in HIV-infected patients."

Ref: Walling DM, Flaitz CM and Nichols CM. Epstein-Barr virus replication in oral hairy leukoplakia: response, persistence, and resistance to treatment with valacyclovir. J Infect Dis. 2003 Sep 15;188(6):883-90.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12964120&dopt=Abstract

Stem-cell transplants help beat lymphoma

Sean Hosein, CATIE News

Partly because of their weakened immune systems, people with HIV/AIDS (PHAs) are at increased risk for certain tumours such as non-Hodgkin's lymphoma and Hodgkin's lymphoma. These tumours occur when cells of the immune system, mostly B cells, begin to multiply abnormally. Signs/symptoms of lymphoma can include unexpected tiredness, unintentional weight loss, fever, night sweats, swollen lumps in the neck, groin, or under the arms.

To help make a diagnosis of lymphoma, several procedures and tests are needed, including detailed pictures from inside the body using CAT scans or MRIs, blood tests, and biopsies of the tumour.

Lymphoma and HAART

In the time before highly active antiretroviral therapy (HAART) became available in high-income countries, the chances of survival after a diagnosis of AIDS-related lymphoma were low. Even with anti-cancer therapy, the average PHA survived for about six months. Now that HAART is available, survival after a diagnosis of lymphoma has been extended. In one study from France, researchers found that, on average, survival in the time of HAART rose to about 20 months after a lymphoma diagnosis. Moreover, researchers are testing new anti-lymphoma regimens, such as EPOCH, which appear to result in high rates of remission. For more details about EPOCH, please see CATIE's TreatmentUpdate 136 available at:
http://www.catie.ca/tu.nsf

While this statistic is encouraging, the fact remains that some PHAs with lymphoma only experience a partial remission or may not go into remission when first treated for cancer. To deal with this situation, researchers at several Italian hospitals have been testing a combination of stem-cell (CD34+) transplants and high-dose chemotherapy in 16 PHAs with lymphoma. Their results, published in the 1 December issue of the Journal of Clinical Oncology, suggest that these treatments can help some PHAs recover from cancer when first-line chemotherapy fails.

Why transplant stem-cells?

In addition to damaging tumours, chemotherapy damages the bone marrow – the site of blood cell production. So the doctors in this study came up with the idea of giving a stem-cell transplant to the subjects. Why stem-cells? Most cells in the body are specialised, for example, nerve cells, liver cells, skin cells and so on. But stem-cells are unspecialised cells that can turn into other types of cells. In the case of CD34+ stem-cells found in the blood, these can migrate to the bone marrow and turn into cells that specialise in producing other blood cells. By giving patients a transplant of their own stem-cells (collected before chemotherapy), doctors can then use a higher-than-normal dose of chemotherapy to achieve more intensive anti-cancer effects and not greatly worry about bone marrow damage in their patients. This combination of high-dose chemotherapy and stem-cell transplants is used in HIV-negative cases of lymphoma that do not respond to chemotherapy alone.

Before receiving high-dose chemotherapy, patients are given injections of the bone marrow stimulant G-CSF (granulocyte-colony stimulating factor, filgrastim, Neupogen). A few days later, stem-cells are collected from the blood and stored. After chemotherapy, the stem-cells are infused intravenously and they migrate to the bone marrow where they help it to recover and resume producing healthy blood cells.

Study details

Researchers recruited subjects between September 2000 and April 2003. All had AIDS-related lymphoma and had not experienced sustained remission with prior chemotherapy. The profile of the 16 subjects (two female, 14 male) at the start of the study included median age 39 years and CD4+ count 236 cells/mm3. Fourteen subjects were using HAART.

Upon entering the study, subjects received a course or two of normal-dose chemotherapy. The purpose of this was to assess if their tumours would respond to the treatment. If tumours did respond, this chemotherapy served to shrink them prior to exposure to much higher doses of chemotherapy. Once their bone marrow recovered from this round of chemotherapy, stem-cells were collected. At least one month after stem-cells were collected, subjects then received high-dose chemotherapy for a week. The drugs used for the high-dose regimen were carmustine, cytarabine, etoposide and melphalan.

Stem-cells were re-infused into subjects and one week after chemotherapy began, subjects were given the bone marrow stimulant G-CSF. In addition, doctors also prescribed several medications to suppress the development of bacterial, fungal and viral infections. All subjects remained on HAART while in the study.

Results

Six of the 16 subjects in this study did not receive a stem-cell transplant. Three subjects, two of whom had less than 100 CD4+ cells, died from rapidly worsening lymphoma. The bone marrow of three subjects was unable to produce stem-cells despite stimulation with G-CSF.

The research team reported initial results from nine of the 10 subjects (the 10th patient wasn't enrolled for a long enough time). Seven patients had a complete response (tumours disappeared) and two had a partial response (tumours shrank but did not disappear). About one year after having received a stem-cell transplant, six of the nine subjects remained alive. Most subjects experienced moderate or severe nausea/vomiting, diarrhoea and inflammation inside their mouths.

Because chemotherapy weakens the bone marrow, levels of disease-fighting cells are temporarily reduced and it is not uncommon for cancer patients receiving chemotherapy to develop infections. In this study, two subjects developed fungal infections in their throat and two subjects developed shingles.

Although CD4+ counts fell after high-dose chemo (to an average of 93 cells), by the sixth month of the study they rose to an average of 183 cells. Except for a few days when subjects stopped taking HAART because of side effects from chemotherapy, the average viral load remained below the 50 copy mark.

The researchers noted that six of the 10 subjects remained free from lymphoma for one year after receiving high-dose chemotherapy and a stem-cell transplant. Although the researchers found the results of this study promising, they caution that additional studies with longer monitoring times are needed to confirm and extend their results. Nonetheless, they suggest that high-dose chemotherapy can safely be given to HIV positive people with lymphoma. Although their research was about "salvage" therapy, because of the promising results the research team suggests that high-dose chemotherapy and stem-cell transplants be considered for use earlier in the course of AIDS-related lymphoma, as has been suggested for HIV negative people with lymphoma.

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PAEDIATRICS

Should treatment be started in all HIV-infected newborns?

Polly Clayden, HIV i-Base

A report from the HIV Paediatric Prognostic Markers Collaborative Study Group, published in the 15 November 2003 issue of the Lancet, evaluated the risk of progression to AIDS - with regards to CD4% or viral load and age - of HIV-infected newborns in the first year of life [1].

This study performed a meta-analysis of pooled individual patient data for 3,941 children participating in 17 cohort studies and randomised trials conducted in Europe and the USA between 1983 and 2002, receiving either no therapy or zidovudine monotherapy. Separate analyses were undertaken to determine the 12-month predictive value of CD4% and viral load for death (in both the presence and absence of AIDS) and progression to AIDS.

The investigators reported that in analysis of the predictive value of CD4%, 997 children progressed to AIDS or died without an AIDS diagnosis, compared to 284 children analysed by viral load; the numbers of deaths were 568 and 129 respectively. They reported a sharp increase in risk of death among children above two years when CD4% fell below 10%, and a poorer prognosis in children below two years than older children with the same CD4%. Additionally they reported 917 AIDS events

and that the relative frequency of these events was strongly age related. They cited an approximately three-fold higher risk of AIDS in a one year old child than in a five year old child and a difference of about six-fold for death.

For infants they reported very substantial rates of disease progression even at high CD4%: at six months for example a CD4% between 25% and 50% predicted a risk of developing AIDS within six months of between 25% and 13% and a risk of death between 8.5% and 4.1%

Viral load values greater than 100,000 copies/mL increased the risk of disease progression considerably at all ages but was a better predictor of disease progression at lower levels in older than in younger children. However, CD4 was a stronger predictor than both age and viral load.

The investigators noted: "The observation that neither CD4% nor viral load could identify children at low risk for disease progression lends some support to a universal treatment policy for infants, or at least the need for close observation to promptly detect clinical signs or symptoms preceding AIDS." Current European guidelines recommend that paediatricians "consider" treatment for all children less than one year of age, differing from the US guidelines, which advocate treatment for all at this age.

In a commentary from Dr Elaine Abrams and Dr Louise Kuhn in the same issue, the authors commend the study group, stating that their findings "…confirm collective experience and worst fears…For children under one year of age, the risk of progression to AIDS or death remains unacceptably high, even when immune degradation and viraemia are moderately well contained. CD4 T cells gradually decrease during early childhood from high values at birth, while HIV-RNA levels increase progressively, peaking during the first three to six months of life before decreasing slowly thereafter. With these developmental changes, it is not surprising that these markers are less informative during the first years of life."

The authors write that considering the findings from this study, arguments in favour of universal treatment for infants seem compelling and ask: "…is it feasible to treat children when they are most vulnerable and then stop treatment at a safer time?"

References

1. HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. The Lancet. Vol 362. 1605. 15 November 2003
2. Abrams EJ and Kuhn L. Should treatment be started among all HIV-infected children and then stopped? The Lancet. Vol 362. 1595. 15 November 2003

A risk calculator is available at:

http://www.peritrials.org/hppmcs

Tenofovir levels in children approach adult values

Mark Mascolini, IAS News

A study of tenofovir concentrations in HIV-infected, antiretroviral-experienced children starting this nucleotide analogue found steady-state exposures that approach those seen in adults taking 300 mg daily - approximately 3000 ng . h/mL.

The trial began with 18 children stopping a failing regimen and starting only tenofovir. Incremental dosing with 75-mg tablets aimed for a target dose of 175 mg/m2; the median administered dose was 208 mg/m2. Single-dose studies found a geometric mean area under the concentration-time curve (AUC) of 2150 ng . h/mL and a mean maximum concentration of 266 ng/mL.

Children then added other drugs to their regimen on the basis of treatment history and resistance patterns. Four weeks later, steady-state pharmacokinetic studies in 16 children showed a geometric mean AUC of 2920 ng . h/mL, which was significantly higher than the AUC in the single-dose study (P = 0.0004). The geometric mean maximum concentration at steady state measured 302 ng/mL.

Source: International AIDS Society
http://www.ias.se/article/show.asp?article=2566

Ref: Hazra R, Balis FM, Tullio AN et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. Antimicrobial Agents and Chemotherapy 2004; 48:124-129.

Study suggests paediatric dose of emtricitabine (FTC)

Mark Mascolini, IAS News

An open-label Phase I trial suggests that an FTC dose of 6 mg/kg (up to a maximum of 200 mg) for children will yield a drug plasma concentration equivalent to that in adults. A Phase II trial is further evaluating the 6-mg/kg dose.

The study involved 25 children, two younger than two years old, eight from two to five years old, eight from six to 12 years old, and seven from 13 to 17 years old. All children received single oral doses of 60 and 120 mg/m2 of the nucleoside in solution to a maximum of 200 mg. Children six years old or older also took a third dose of 120 mg/m2 in capsules.

The trial showed that pharmacokinetics of FTC are comparable in adults and children 22 months to 17 years of age. Plasma concentrations proved 20% higher with the capsule formulation than with solution. Using plasma area under the concentration-time curve (AUC) data at the 120-mg/m2 dose, researchers projected that a 6-mg/kg dose of FTC would produce AUCs in children comparable to those in adults given the standard 200-mg dose.

Source: International AIDS Society
http://www.ias.se/article/show.asp?article=2565

Ref: Wang LH, Wiznia AA, Rathore MH et al. Pharmacokinetics and safety of single oral doses of emtricitabine in human immunodeficiency virus-infected children. Antimicrobial Agents and Chemotherapy 2004;48:183-191.

HIV production in children with "undetectable" viral load

Mark Mascolini, IAS News

HIV replication continues in children whose viral loads cannot be detected by standard sensitive assays, and the virus produced remains susceptible to antiretrovirals.

Because viral replication continues at low levels in adults taking highly suppressive antiretroviral therapy, Robert Siliciano and Johns Hopkins colleagues wanted to see if low-level replication could be spotted in children, especially those who begin antiretrovirals shortly after birth. They looked for low-level viraemia with an ultrasensitive assay and searched for mutations conferring resistance to protease inhibitors with an assay that allows genotyping at viral loads as low as 5 copies/mL. These findings emerged:

- Low-level viraemia continued in children taking potent regimens, even those who begin therapy in early infancy.
- Suppression of viraemia in these children was so strong that HIV-1-specific antibody responses were "absent or minimal."
- Virus isolated at low levels lacked protease resistance mutations, even though many of the children took nelfinavir, which has a low barrier to resistance.
- The protease sequences detected resembled those of viruses in the latent reservoir of resting CD4 cells.

Source: International AIDS Society
http://www.ias.se/article/show.asp?article=2560

Ref: Persaud D, Siberry GK, Ahonkhai A et al. Continued production of drug-sensitive human immunodeficiency virus type 1 in children on combination antiretroviral therapy who have undetectable viral loads. Journal of Virology 2004;78:968-979.

Host genetic factors are important in disease progression in children

Graham McKerrow, HIV i-Base

Numerous host genetic factors play an important role in HIV disease progression in children, according to a report by researchers at the University of California, San Diego, La Jolla, California.

The authors believe their study of more than 1,000 US children represents the largest cohort of children perinatally infected with HIV-1 who have been evaluated for the impact that host genetics has on disease progression and neurocognitive impairment. It is an avenue of research that should lead to treatments being more closely tailored to individual needs.

Genetic factors have an impact on the susceptibility to HIV infection and the rate of progression to AIDS and death and on neurological impairment, the authors explain in the 15 November 2003 issue of The Journal of Infectious Diseases.

Stephen Spector and colleagues evaluated the effects of polymorphisms in CCR2, CCR5, and SDF1 in 1,049 children with symptomatic HIV-1 infection. They found higher mean CD4 lymphocyte counts and percentages, lower mean HIV-1 RNA levels, and higher mean cognitive-index scores in subjects with the CCR5-delta32 allele than in children not bearing this allele.

The researchers looked at children homozygous for wild-type CCR5, and found that mean lymphocyte percentages and mean cognitive-index scores were higher in those with the CCR5-59353-C/C and mean lymphocyte percentages were higher with the CCR5-59356-T/T genotypes. These polymorphisms, as well as those in CCR2, were not found to influence disease progression or neurological impairment.

The A/A genotype of SDF1-3' was associated with a doubling of the relative hazard for disease progression and with a significant increase in neurocognitive impairment associated with disease progression.

In a multivariate analysis, the strongest single predictor of disease progression among children with wild-type CCR5 was the CCR5-59029 genotype.

In their discussion the authors conclude: "Perhaps the greatest potential that research such as that presented in the present study has is to help guide treatment of HIV-1 infected individuals. As data accumulate regarding both host and virus genetic factors that have an impact on disease progression and neurological impairment, the potential exists that treatment can be individualised for each patient, thereby ensuring that optimal treatment is provided. In this regard, other genetic factors, including HLA types and polymorphisms that impact drug metabolism, also must be assessed, to determine the risk of disease progression and to optimise antiretroviral treatment. In combination, host and virus genetic data promise to provide important information for guiding the future clinical management of HIV-1 infected patients."

Ref: Spector S, Singh K, Barroga C et al Genetic influence of *CCR5, CCR2,* and *SDF1* variants on Human Immunodeficiency Virus 1 (HIV-1) related disease progression and neurological impairment, in children with symptomatic HIV-1 infection. J Infect Dis 2003;188:1461-1472.

HEPATITIS COINFECTION

London study finds sexual and intranasal transmission of HCV

Graham McKerrow, HIV i-Base

A cohort study of 23 HIV-positive gay men attending a London clinic with acute hepatitis C infection has found clinical and molecular evidence to suggest both sexual and intranasal transmission of HCV. Mark Danta and colleagues from the Royal Free Hospital also conclude that a higher CD4 count appears to predict spontaneous HCV eradication.

In a paper presented to the 54th Annual Meeting of the American Association for the Study of Liver Diseases in Boston, Massachusetts in October, the authors report that unprotected sexual intercourse was a universal risk factor in the cohort, 16 subjects (70%) reported group sex and fisting, 15 (65%) reported intranasal drug use, and four (17%) reported injected drug use.

The hypothesis of sexual transmission was supported by the fact that 10 (43%) had a documented STD (seven syphilis and one gonorrhoea) including two patients with acute HIV seroconversion. At the time of the report, five isolates had been sequenced and three appeared related by phylogenetic analysis, suggesting a common source.

Four patients eradicated HCV spontaneously, and they had significantly higher CD4 counts (810 versus 556, $p<0.05$) but there was no correlation with peak ALT or HIV viral load. Nine patients were treated with pegylated interferon and ribavirin.

In the last issue of HTB (Vol 4, No 10), we reported a different paper describing this cohort, and another study at the Chelsea and Westminster Hospital, both of which indicated an epidemic of acute HCV in London, transmitted sexually among HIV-positive men who have high-risk, unprotected sex with other men.

Ref: Danta M, Brown D, Jacobs M et al. Epidemiology of acute HCV infection in a London cohort of HIV positive homosexual males. 54th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, Massachusetts, 24-28 October 2003. Abstract 561

Link:

http://www.aasld.org/aasld/meetings.htm

(For abstract click on 2003 annual meeting, abstract viewer and search for 561)

C O M M E N T

Aggressive sex practices seem to be the key risk factor for transmitting HCV which is efficiently transmitted by blood. This explains too the intranasal transmission mainly associated with cocaine use.

HCV-coinfection is associated with diabetes and CD4 decline

Elizabeth R Jenny-Avital, for AIDS Clinical Care

Researchers recently recognised an association between hepatitis C virus (HCV) infection and diabetes mellitus. Several posters at the IDSA meeting have now demonstrated that HIV/HCV-coinfected patients are even more likely to develop diabetes than patients with either virus alone.

Jain and colleagues retrospectively reviewed 1,547 charts from patients attending an HIV outpatient clinic and found that 8.8% had glucose intolerance or diabetes, and 24% had HCV infection. In the univariate analysis, older age, black race, family history of diabetes, and BMI >25 kg/m2 were significantly associated with the presence of diabetes or glucose intolerance. In a multivariate analysis adjusted for age and race, the odds ratio for diabetes or glucose intolerance was 1.6 for patients with HCV-coinfection compared with patients with HIV infection alone. The odds ratio for diabetes or glucose intolerance among

coinfected patients was even higher when investigators controlled for elevated BMI and family history of diabetes, further demonstrating the independent association of HCV infection with the development of diabetes.

Butt and colleagues found that among 358 patients with HCV-infection alone, diabetes prevalence was 16%, whereas among 28 HIV/HCV-coinfected patients, diabetes prevalence was 29%. Receipt of PIs – which have been implicated in the development of glucose intolerance – was equally prevalent (73%) among those with and without diabetes in the HIV/HCV-coinfected group. However, the roles of HIV per se or PI exposure in this increased diabetes prevalence in coinfected patients compared with patients with HCV alone remain unclear. In a similar vein, Crane and colleagues determined risk factors for incident diabetes in 1,583 patients seen at an urban HIV clinic from 1995 to 2002. In the multivariate analysis, the odds ratios for the development of diabetes were 2.0 for HCV-positive compared with HCV-negative status, 2.7 for black compared with white race, 1.9 for PI-treated compared with PI-naive patients, and 1.05 for each year increase in age.

In other news on the coinfection front, cirrhosis may contribute to CD4-cell count decline in HIV-negative patients, potentially limiting the utility of CD4-cell count as a surrogate for HIV-induced immunosuppression in coinfected patients. McGovern and colleagues examined the relation between CD4-cell count and cirrhosis in 60 HIV-negative individuals, roughly half of whom were HCV-positive. CD4 counts <550, <300, and <200 cells/mm3 were observed in 65%, 28%, and 7% of these patients, respectively. However, the CD4-cell percentage was considered abnormal in only 7% of patients. In the multivariate analysis, only leukopenia was associated with a decreased CD4-cell count. The authors attribute these CD4-cell count declines to hypersplenism.

If HCV infection, in tandem with the severity of liver disease, drives down CD4-cell counts in coinfected individuals, the question becomes whether these CD4-cell counts have the same prognostic value as those in patients with HIV infection alone. To better elucidate the effect of HCV on this surrogate marker for HIV disease, future research should examine the incidence of AIDS endpoints in coinfected patients with low CD4-cell counts. As for the association of HCV-coinfection with diabetes, the clinical implications of these findings have yet to be fleshed out. However, data from future studies examining cardiovascular outcomes and dysglycaemia or insulin resistance in HIV-infected individuals should be analysed in light of patients' HCV status.

Dr Jenny-Avital is an infectious diseases specialist for the AIDS Consultation Service at Jacobi Medical Center in the Bronx.

References

1. Jain MK et al. Hepatitis C infection is associated with diabetes/glucose intolerance in HIV-infected patients. 41st Annual Meeting of the Infectious Diseases Society of America, San Diego, October 2003. Abstract 595.
2. Butt AA et al. Risk of diabetes mellitus in Hepatitis C and HIV infected patients. 41st Annual Meeting of the Infectious Diseases Society of America, San Diego, October 2003. Abstract 594.
3. Crane HL et al. Predictors of developing diabetes in HIV-infected patients. 41st Annual Meeting of the Infectious Diseases Society of America, San Diego, October 2003. Abstract 669.
4. McGovern B et al. Absolute CD4 T-cell subsets are decreased in HIV-seronegative patients with cirrhosis. 41st Annual Meeting of the Infectious Diseases Society of America, San Diego, October 2003. Abstract 603.

Source: AIDS Clinical Care Vol1 No12.
http://www.natap.org/2003/dec/122903_10.htm

DIAGNOSTICS

US approves new 10-minute HIV test

Graham McKerrow, HIV i-Base

The US Food and Drug Administration has approved a new, single-use 10 dollar, 10 minute HIV-1 antibody test, the Uni-Gold Recombigen, made by the Irish company Trinity Biotech PLC. It is the first testing kit to be approved by the FDA for use in plasma, serum and whole blood (venipuncture). The 20-minute OraSure test can be used only on whole blood.

The device, which tests a single drop of whole blood, serum or plasma, is only allowed to be used by clinical laboratory professionals in facilities that have suitable quality assurance programmes and Trinity Biotech wants to sell it to government programmes, physicians and hospitals for use following needlestick injuries and to test pregnant women. People being tested must receive printed information and counselling, and positive tests require confirmation. The company hopes to sell nearly 500,000 in the US this year alone. The test is already sold in Africa and Asia.

The FDA based its approval on company research involving more than 9,000 patient samples that detected 100% of HIV-positive specimens, and was 99.7% accurate on the negative samples.

Links: Trinity Biotech
http://www.trinitybiotech.com/EN/index.asp

FDA
http://www.fda.gov/

Product labeling will be available at
http://www.fda.gov/cber/products/testkits.htm

Rapid HIV tests offer economic advantages and convenience

Graham McKerrow, HIV i-Base

A cost comparison of three HIV testing technologies, conducted by researchers at the US Centres for Disease Control and Prevention and other institutions, concludes that rapid test protocols offer economic advantages as well as convenience, compared to the standard testing protocol. Donatus U Ekwueme and colleagues present cost estimates that should prove helpful to HIV programme managers and other public health decision makers who need information on these counselling and testing technologies.

More than 2 million HIV tests are performed each year at publicly funded clinics in the US. Clients do not receive results of one third of these tests because they don't go back to the clinic for them. Results of standard tests can take up to two weeks, but the use of newer, rapid tests improves the number of people who learn their test results. The researchers write that no study has systematically compared the costs of these newer technologies with standard tests so they compared three HIV counselling and testing protocols: the standard protocol and the one-step and two-step rapid protocols.

They calculated the intervention costs of counselling and testing services with each type of protocol and found that the one-step rapid protocol was generally the least expensive of the three. They also report: "The standard protocol cost less than the two-step protocol per HIV-positive client notified of his or her HIV status, but cost more per HIV-negative client. The sensitivity analysis indicated overlap in the cost estimates for HIV-negative clients, reflecting the generally similar costs of the three testing protocols. Taking into account HIV seroprevalence, the two-step rapid protocol would be less expensive than the standard protocol for most publicly funded testing programs in the United States."

Ref: Ekwueme D, Pinkerton S, Holtgrave D et al. Cost comparison of three HIV counseling and testing technologies. American Journal of Preventive Medicine (08.03) Vol. 25; No. 2:112-121
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12880878&dopt=Abstract

Use of total lymphocyte count (TLC) for monitoring response to antiretroviral therapy

HIVandHepatitis.com

CD4 cell count and CD4 cell percentage are key markers for determining disease progression and risk for opportunistic infection in HIV-infected patients.

These markers are of greatest use in treating the asymptomatic patient, in whom disease stage is more difficult to assess clinically and for whom laboratory measurements serve as guidelines for the initiation of therapy and opportunistic-infection prophylaxis.

However, providers in resource-constrained settings may not have access to this laboratory measurement or its cost may be prohibitive, resulting in the need for an alternative, surrogate marker. Given the decreasing costs and increased availability of antiretroviral therapy (ART) in the developing world, this is an issue of critical and increasing importance.

A number of previous studies indicate that the total lymphocyte count (TLC) may be useful as a surrogate marker of immune status in certain settings. However, controversy regarding the utility of the TLC remains.

A variety of recent small studies have sought to determine the utility of the TLC in predicting the stage of HIV disease. The majority of these studies indicate a positive correlation between TLC and CD4 cell count, although the specific data on correlation coefficients, sensitivity, specificity, and positive predictive value (PPV) have been mixed. In addition, the patient populations examined, parameters measured, and methods used for statistical analysis vary widely among the different studies.

TLC may have a role both in decisions about the initiation of ART and in the monitoring of immunologic response to ART in resource-constrained settings. There has been a wide range of findings in published studies, many of which have included small numbers of patients.

To summarise, a total of 15,102 patients enrolled in 15 different studies have been followed up to determine the ability of the TLC to predict the CD4 cell count and HIV disease stage. Eleven of these studies (which included a total of 11,713 patients) contained data that, overall, indicated support for the predictive ability of the TLC, whereas four have concluded that the TLC was not a reliable predictor of the CD4 cell count.

In contrast, only three different studies, with a total of more than 440 patients, have attempted to evaluate the use of TLC in monitoring the response to ART. All of these studies have produced data that, overall, support the use of TLC as a surrogate marker for CD4 cell count in monitoring patients receiving ART.

The authors conclude, "More convenient and less expensive technologies are needed as alternatives to currently available CD4 cell assays in resource-limited settings. Political pressure has been successful in reducing the cost of ART, and it needs to be extended to advocacy for reducing the cost of determining HIV disease stage and monitoring therapeutic outcomes."

Ref: Schreibman T, Friedland G. Use of total lymphocyte count for monitoring response to antiretroviral therapy. Clinical Infectious Diseases 38:257-262. January 15, 2004.

http://www.hivandhepatitis.com/recent/test/lymphocyte/011204_b.html

OTHER NEWS

Controversy surrounds British health plans for visitors to the UK

Graham McKerrow, HIV i-Base

The British government announced in December plans to withdraw the right of foreign visitors to the UK to receive free health care in the National Health Service – what has become known as 'health tourism'. The ban would apply to free treatment for all non-infectious diseases including HIV. The government is also consulting on whether or not to introduce compulsory HIV tests for asylum seekers and others seeking the right to remain in the UK.

Health Secretary John Reid told the Sunday Telegraph: "If there are emergencies here, and there are bone fide tourists dropping ill on the street, of course we will do what we have to do morally and legally. But we are not mugs. There is a difference between being civilised and being taken for a ride."

Some observers say 'Health tourism' costs the NHS £200 million a year, although this figure has been widely questioned, and results in other patients having to wait longer for treatment. The proposals would deny free treatment to business travellers and their dependents, failed asylum seekers, and HIV-positive people seeking long-term treatment. Emergency cases would remain exempt from charges. Reid said: "Visitors need to know they will be liable to be charged for treatment."

In a separate move, the government is consulting on compulsory HIV and TB tests for foreigners seeking permanent residence in the UK. The influential centre-left think tank the Institute for Public Policy Research has come out against the proposal, saying that screening for TB is ineffective and compulsory tests would be counter to public health by pushing the condition underground.

The IPPR says compulsory tests would:

- Compromise Britain's reputation for responding to HIV effectively,
- Contravene the European Convention and UN conventions,
- Lead to a false sense of security, and
- Would alienate and stigmatise HIV-positive people in a way that would increase the risk of infection spreading.

Links:

Original government proposal:

http://www.doh.gov.uk/overseasvisitors/nhschargesconsult.htm

IPPR report and summary:

http://www.ippr.org/publications/index.php?book=400

Doctors warn of death toll from silent epidemic of hepatitis C

Hospital specialists criticised the British government on 31 December for not acting to curb the spread of hepatitis C, which officials estimate has infected 200,000 people in the United Kingdom - four times as many as HIV - and infects more than 100 additional people each week. It is the main cause of liver transplants and is predicted to kill more people than AIDS by 2020. However, only a quarter of patients know they are infected, and only 1% receive treatment.

The Department of Health published a strategy for dealing with hepatitis C 18 months ago and promised an action plan by the end of 2002. Graham Foster, professor of hepatology at the Royal London Hospital, said, "There is much disappointment

at the lack of an action plan. Absolutely nothing is happening."

The Health Protection Agency announced that 5,901 cases of hepatitis C were diagnosed in 2002, up from fewer than 1,000 in 1994. Foster said over the next 10 to 15 years liver disease and cancer rates would soar if no action were taken.

New drug cocktails have increased the proportion of patients who can be cured to 60%, but since the virus is symptomless in its early stages, efforts must be made to test and identify people who are infected.

William Irving, professor of virology at Nottingham University, said, "There are a lot of people out there with hepatitis C and there is a window of opportunity to treat them now before they develop liver disease."

The blood borne virus can be spread through sharing needles, razor blades, toothbrushes and cocaine straws; tattooing; body piercing; and sex. It is 10 times more infectious than HIV via blood-to-blood contact, but less infectious than HIV via sexual contact.

ON THE WEB

A selection of the most important reports and resources posted to the internet over the last month is included below. Unless specified all material is available free and without paid subscription.

Treatment Access:

Untangling the web – 5th edition

MSF has released the fifth edition of 'Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries'.

This new edition incorporates all recent pricing and pre-qualification announcements, including those made by the WHO on 1 December 2003.

The fifth edition provides:

- updated information on prices for eligible countries, including both price per unit and price per patient per year for adult and paediatric formulations
- updated information and clarifications on the conditions and restrictions applying to these offers
- practical examples on how to use the document.

The document will not be printed but can be downloaded from the MSF Access Campaign website:

http://www.accessmed-msf.org/documents/5theditionuntangling.pdf

French and Spanish versions are in the pipeline and will be available soon.

Country analyses help inform national HIV/AIDS policies

The Country AIDS Policy Analysis Project develops and disseminates comprehensive analyses of HIV/AIDS in Ethiopia, Kenya, Malawi, Senegal, South Africa, Uganda, Tanzania, Zambia, Zimbabwe, Brazil, Cambodia, and India.

Managed by the AIDS Policy Research Centre at the University of California San Francisco and funded by USAID, the project links each analysis with national strategic plans for HIV/AIDS prevention, care, and support.

Analyses also include a detailed map and comparative table of 70 key HIV/AIDS and socioeconomic indicators.

http://ari.ucsf.edu/ARI/policy/countries.htm

Conferences and guidelines:

IDSA Guidelines for Treatment of Candidiasis

Published in Clinical Infectious Diseases, Volume 38, Number 2 (15 January 2004), these guidelines are not currently available free, but make many references to HIV-related candidiasis.

http://www.journals.uchicago.edu/cgi-bin/contents?CID+v38n2

Highlights of the 2003 16th Annual Conference of the Association of Nurses in AIDS Care (ANAC)

Medscape report by Sande Gracia Jones from this conference attended by over 800 HIV-specialist nurses in November 2003 in New York. Three themes are covered in the report: women as vulnerable populations for HIV; end-of-life issues; and complementary and alternative therapy.

http://www.medscape.com/viewarticle/466017

Vaccine research:

HIV vaccine trials network – meeting slides

Slides from selected presentations from meeting held in 22-24 October 2003, Seattle, USA.

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

- Epidemiology of HIV in IDUs: rationale for IDU participation in HIV vaccine trials
- Basic concepts in HIV vaccinology
- T-cell immunity and HIV
- HIV vaccine development & the Bill and Melinda Gates Foundation: a view of the field
- Involvement of injection drug users in prevention, treatment and research: vaccine development in former Soviet Union and Central and Eastern Europe
- The HIV/AIDS epidemic in the WHO European region
- Immunology and vaccinology - how do we relate it to current HVTN protocols?
- Env immunogens in candidate HIV-1 vaccines

Table of ongoing vaccine trials – updated to November 2003:

http://chi.ucsf.edu/vaccines/vaccines?page=vc-03-00

HIV inSite Knowledge Base

Updated or new chapters recently added to this thorough HIV online medical textbook.

- **Toxoplasmosis and HIV** - C. Subauste, MD. New chapter.

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-05-04-03

- **Radiographic Assessment of HIV-Related Diseases** - P. Goodman, MD. Updated chapter.

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-04-01-16

- **Safer-Sex Methods** - T. Lane, PhD, and H. Palacio, MD. Updated chapter

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-07-02-02

- **Renal Manifestations of HIV** - R. Rodriguez, MD. Updated chapter.

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-04-01-10

Journal articles available online:

Several important full-text articles from subscription-only journals are available without subscription on selected websites. Medscape requires a one-time free registration.

AIDS Clinical Care

HCV-coinfection is associated with diabetes and CD4 decline

http://www.medscape.com/viewarticle/464832

Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with HIV infection

http://www.natap.org/2004/jan/010504_06.htm

AIDS:

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

- An open-label assessment of TMC 125 - a new, next-generation NNRTI, for seven days in HIV-1 infected individuals with NNRTI resistance
- Monitoring of long-term toxicities of HIV treatments: an international perspective
- Expanding access to HIV antiretroviral therapy among marginalised populations in the developed world

NEJM:

- Once-daily valacyclovir to reduce the risk of transmission of genital herpes

http://www.natap.org/2004/jan/010504_13.htm

JAIDS:

http://www.medscape.com/viewpublication/878_toc?vol=34&iss=5

- Patterns of selective neuronal damage in methamphetamine-user AIDS patients

- HIV-1-infected antiretroviral-treated patients with prolonged partial viral suppression

Online medical lectures:

Critical Issues in HIV:

http://www.hivandhepatitis.com/essays/main1.html#hiv

Four excellent articles published by HIVandHepatitis.com as a part of a new series of online medical lectures.

Devising individualised HIV treatment strategies with resistance testing - Michael Youle

Management of HIV- and HAART-related lipodystrophy/metabolic syndromes - William G. Powderly

Adherence: the key to successful HAART - Brian A. Boyle,

Eight years of HIV protease inhibitor therapy: lessons learned and future directions - Charles Hicks,

Coinfection:

Insulin resistance is associated with chronic hepatitis C and virus infection fibrosis progression.

Gastroenterology December 2003, Volume 125, Number 6

“Hepatitis C virus may induce insulin resistance irrespective of the severity of liver disease, and this effect seems to be genotype specific. Further, our findings support the hypothesis that insulin resistance may contribute to fibrotic progression in chronic hepatitis C virus infection. “

http://www.natap.org/2004/jan/010604_04.htm

Newsletters and reports:

GMHC Treatment Issues – November 2003

http://www.gmhc.org/health/treatment/ti/ti1711.html

- Through the roof: the issues behind drug pricing
- One for the blipper: viral load and replication — where’s the link?
- ATAC meets FDA: warm and fuzzy in Rockville
- Some things never change: Carlton Hogan on demanding post-marketing monitoring of drug safety

PRN Notebook – December 2003

http://www.prn.org

- Rapid HIV assays and the diagnosis of new HIV infections
- Unraveling the mystery of long-term non progressors
- Therapeutic potential of RNA interference
- State of the ART: new DHHS guidelines

ACT-UP/New York histories published online

Sarah Schulman and James Wentzy have recorded a series of oral histories from 25 surviving members of ACT UP/New York.

Transcripts from 14 of the interviews are already available online as pdf documents and others will be added shortly.

http://www.actuporalhistory.org/interviews/

RITA

The latest issue of RITA! (volume 9, number 2) is online in pdf and html.

This issue, titled "HIV Treatment, Interrupted" reviews the last several years of structured treatment interruption (STI) and related research. Several essays on this topic by researchers and physicians are also included, as is a patient-oriented fact sheet on STIs.

http://www.centerforaids.org/

Contents include:

- HIV treatment interruptions: A review - Jennifer Newcomb-Fernandez, PhD
- Trying to make sense of treatment interruptions - Dorothy E. Lewis, PhD, and Richard E. Sutton, MD, PhD
- Is autovaccination dead? - Bernard Hirschel, MD
- Treatment Interruptions in the salvage setting: What have we learned? - Veronica Miller, PhD
- In memoriam - L. Joel Martinez 1953-2003

ACRIA Update – Winter 2004

Drugs! Drugs! Drugs! - An Overview of the Approved Anti-HIV Medications

http://www.criany.org/treatment/treatment_edu_fall03-win04update.html

The Winter 2004 issue of this newsletter includes new and updated fact sheets for every antiretroviral drug that is currently in use in a very easy to read format.

Forum for Collaborative HIV Research: new reports

http://www.hivforum.org

1. New Report: Sex and Gender and HIV – A Workshop Report

2. New Report: Protein Binding in Antiretroviral Therapies – A Roundtable Discussion Report [AIDS Research and Human Retroviruses 2003; 19:825-835]

3. New Report: Monitoring of long-term toxicities of HIV treatments: an international perspective [AIDS 2003; 17:2407-2417]

4. New Information: Alternative CD4 and Viral Load Testing Technologies

5. Standardised Data Analysis Plan and Call for Collaboration: Initiatives for Developing and Comparing Genotype and Phenotype Interpretation Systems

6. Information Source: Description of HIV Cohorts and Databases

7. Project updates – Presentation Slides: Presentations slides from our recent workshop on Racial and Ethnic Minority Issues in HIV (October 29-30, 2003) and QA/QC of CD4 and Viral Load Assays in the Resource-Limited Setting.

MEETING ANNOUNCEMENTS

UK Resistance and PK Workshops

26-27 February 2004

17-18 June 2004

25-26 November 2004

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

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

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

Please contact Mediscript on 020 8446 8898 for further details.

10th BHIVA Conference

15-17 April 2004, Cardiff.

For details contact Mediscript on 020 8446 8898 or BHIVA website:

http://www.bhiva.org

The meeting will be preceded by MRC CTU Annual Centres Meeting on 14 April 2004

PUBLICATIONS AND SERVICES FROM i-BASE

Introduction to Combination Therapy – in Russian

Our Introduction to Combination Therapy has been translated into Russian and is available in hard copy and on our website.

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

This non-technical patient guide to treatment is now available in 12 languages. It explains what combination therapy is, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and how to avoid drug resistance. Information about HIV treatment changes very quickly. You should only read information that is up to date. Be careful of information, whether printed or from the internet, that is not clearly dated.

When starting therapy it is important to choose a combination that is going to work for you. It must also be able to fit into your lifestyle. Getting as much information as possible before you start therapy is very important. It will help you make informed decisions about your therapy.

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

http://www.i-base.info/pdf/guides/nonuk/combo_PORTUGUESE_jan03.pdf

For Latvian and Slovak copies please contact the i-Base office on 020 7407 8488.

Printed versions of this booklet are also available in Bulgarian, Chinese, English, French, Georgian, Italian, Macedonian and Spanish.

To order copies, see below.

Italian treatment guides

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

Introduzione alla terapia di combinazione

http://www.i-Base.info/pdf/guides/nonuk/combo-ITALIAN03.pdf

Guida al cambiamento di terapia

http://www.i-Base.info/pdf/guides/nonuk/salvage-ITALIAN03.pdf

Como evitare e gestire gli effetti collaterali

http://www.i-Base.info/pdf/guides/nonuk/salvage-ITALIAN03.pdf

Guide to HIV, Pregnancy and Women's Health

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

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

http://www.i-base.info/pub/guides/pregnancy03/index.html

To order copies, see below

Guide to Changing Treatment: second-line and salvage therapy

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

Other sections include monitoring your new treatment, finding out what new treatments will become available, especially through expanded access programmes, how to keep up-to-date with the latest research, treatment interruptions, new drugs in development, and what you can do if you have a very low CD4 count.

To order copies, see below.

A Greek translation of the guide can be downloaded as a pdf file from our website:

http://www.i-Base.info

Guide to Avoiding and Managing Side Effects

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

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

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

Treatment information request service – 0808 800 6013

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

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

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

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

UK-Community Advisory Board: reports and presentations

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

Reports and presentations for the seventh meeting, held on 21 November 2003, are posted to the i-Base website. The training session at this meeting was an introduction to statistics, given by Dr Caroline Sabin from the Royal Free Hospital. In the afternoon session, the CAB met Gilead to discuss their new nucleoside FTC and recent drug interaction data involving tenofovir.

http://www.i-base.info/ukcab/nov03/index.html

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

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

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

Treatment 'Passports'

These popular, handy booklets are for HIV-positive people – whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Such a record is useful when talking to different health care workers, changing clinics or changing treatments.

Like all i-Base publications, they are available free as single copies, or in bulk for volunteers and professionals to distribute to clients.

Copies can be ordered using the form on the back page or by visiting our website (details below).

Positive Treatment News (PTN)

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

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

HIV Treatment Bulletin (HTB)

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

http://www.i-base.info

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

Find HTB on AEGiS

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

http://www.aegis.com/pubs/i-base/2003/

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

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

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

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

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

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

h-tb

HIV Treatment Bulletin

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

http://www.i-Base.info

by sending an email to:

subscriptions@i-Base.org.uk

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

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HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

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

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

Introduction to Combination Therapy *(October 2003)*

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

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

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

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

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

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

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

Positive Treatment News (PTN) *from Winter 2003*

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

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

1 ☐ 5 ☐ 10 ☐ Other_____ _____ _____

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

1 ☐ 5 ☐ 10 ☐ Other_____ _____ _____

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

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

http://www.i-Base.info