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Gender Inequality and AIDS

By Stephen Lewis
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There is one factor more than any other that drives me crazy in doing the Envoy job: it's the ferocious assault of the virus on women. We're paying a dreadful and inconsolable price for the refusal of the international community, every member of the community without exception, to embrace gender equality. And in so many parts of the world, gender inequality and AIDS is a preordained equation of death.

There's nothing new in that. It's irrefutably documented in encyclopedic profusion. The culture, the violence, the power, the patriarchy, the male sexual behaviour ... it's as though Darwin himself had stirred this Hecate's brew into a potion of death for women.

In so many parts of the world, gender inequality and AIDS is a preordained equation of death.

Just last Monday, February 2nd, 2004, I attended the first meeting, in London, of the newly-constituted Steering Committee of the Global Coalition on Women and AIDS, a Steering committee, I might add, of undisputed intelligence, influence and reach; a Steering Committee, several of whose members are women living with HIV and AIDS. The heading on the press release to stir media interest read: "HIV Prevention and Protection Efforts are Failing Women and Girls ... More young women are becoming infected by husbands and long-tem partners — female-controlled HIV prevention methods urgently needed". And then, during the presentations throughout the day, the ritual ghastly litany of examples defining a socio-economic-cultural gestalt that puts women at deadly risk.

Not in a million years would I challenge either the usefulness or intent of the Global Coalition. My problem, entirely independent of the Coalition, lies in the divide between the analysis and what's happening on the ground. I read the superb studies produced by Human Rights Watch, and I know that the gap between rhetoric and reality can be tolerated no longer. In the last two and a half years, traveling extensively on the African continent, I have seen virtually no improvement in the status of women. Virtually none. It's too painful for words. It makes me feel almost criminally complicit. I have come to the personal conclusion—and I admit it's personal—that it's time, truly and resoundingly, to take off the gloves. It's time for the respected UN community, for example, on the ground in countries, to join with the indigenous allies and groups fighting for women's rights to demand the visceral changes that are needed. It's time to abandon the fawning diplomatic deference. It's time to swallow the insufferable jargon, like 'mainstreaming gender' which serves to cement inequality by pretending that a process somehow transforms the lives women lead. It's not working. In Africa, of the ten million people living with HIV/AIDS between the ages of 15 and 24, nearly two-thirds are

women and girls. Please explain to me what is working.

The time has come to confront Cabinet Ministers openly, and demand that they promulgate or amend the laws on property rights and inheritance rights. It's time to put people in jail, for a good long chunk of life, for property-grabbing. If sexual violence leads to HIV and death, then it's time to use the entire apparatus of the state to enforce laws against rape; to stop putting the onus on the woman to fight off predatory male sexual behaviour, and move in on the oppressor with a vengeance. If male teachers molest young girls, make a spectacle of them. If early marriage is a death sentence, change the age of marriage and enforce it as though life depends on it, because life depends on it.

Women are the resilient force that sustains the continent, and they are being eviscerated by a virus.

It's time, in other words, country by country, to make the struggle for gender equality the cause celebre of the land. Give no quarter. Call press conferences, demand audiences with the political and religious authorities, form coalitions, take a tactical lesson from the Treatment Action Campaign in South Africa, demonstrate, boycott, rail, risk the possibility of being declared persona non grata by government, and if it happens, on this issue, wear it as a badge of honour. And should it happen, the cause of women will have been advanced.

It's all too much: too much sickness, too much sadness, too much death. Women are the resilient force that sustains the continent, and they are being eviscerated by a virus. And the world, there and here, largely inert, is watching it happen. Shades of the genocide in Rwanda.

You see, if we can make real gains in 3 by 5, and leverage the money for the Global Fund, and raise the intensity of focus on microbicides and vaccines, and understand that the pandemic has a woman's face, then we can begin to break the back of this appalling scourge. No one has to feel defeated. We just have to feel resolved. Doubtless it will require superhuman intervention: so much the better. It requires that level of magnitude to energize the world.

But even all of that said—and if it came to pass, it would be incredibly exciting—there remains one issue, growing inexorably, that is thus far intractable: the issue of orphans. I don't want to drive the nail through the wall; I've spoken a long time and must wind my way to the end. But it is important to understand that the millions of orphans are perhaps the most vexing inheritance of the pandemic. There are several African countries now, with more than a million orphans: it is without historical precedent; no one quite knows how to handle it.

In the last few months, I've had the enviable opportunity to accompany both Graca Machel and Oprah Winfrey on trips to Africa, primarily to assess the situation of orphans and vulnerable children. Graca Machel, who is seen by everyone as "Mama Africa", and has a formidable understanding of the continent was, I think it fair to say, overwhelmed at times by the sheer numbers and festering predicament of the orphans. Oprah, than whom it would be hard to find someone of greater worldliness, was equally shaken to her core. African communities are struggling valiantly to absorb the orphans as the families fragment and die, but given the levels of impoverishment, it's desperately, indescribably difficult.

And it's all becoming so strange. Now we have, pervasively, this phenomenon which AIDS has brought, of grandparents burying their children, and then living out their impoverished days looking after the orphan grandchildren. I was in Alexandra Township in Johannesburg in December, meeting with a large group of grandmothers heroically networking through their anguish: they had all lost almost all their children. It was a spirited if terribly mournful conversation. There was one grandmother who refused to speak until the end. And then, in a voice of wrenching and unendurable pain, she told us how she had lost all of her adult children, all five of her adult children, between the years 2001 and 2003. Five children in three years. She was left with four grandchildren, all of whom I later learned, are HIV positive. Two generations will disappear in an historical blink.

And where they don't disappear, these millions of orphans wander the landscape of Africa. These lonely youngsters are bewildered, angry, sad, frantically seeking nurture and affection, often hungry, homeless, significant numbers living with grandmothers or in child-headed households, countless numbers unable to go to school, a school being the single most valuable and supportive environment they could possibly have ... unable to go to school because they can't afford the school fees or the uniforms or the books. And when you lose your parents, who then hands down the knowledge and values from generation to generation? The orphan crisis is a crisis without parallel.

Somewhere, somehow, someday, the world has to understand what AIDS hath wrought. The understanding is not yet in evidence.

This is an excerpt from a plenary address delivered at the 12th Retrovirus Conference in San Francisco, February 8, 2004.

Khousalya Periaswamy

Interview by Bob Huff

What is the situation for access to antiretroviral (ARV) drugs in India now?

In April, the government started giving free ARV drugs in six high prevalence states in India, but only a few people are getting them so far. They are focusing on high prevalence states, but we need access everywhere. A few people are getting treatment, but they still don't have monitoring or education and the government workers are still not comfortable working with people with HIV.

The organization, INP+ (Indian Network of People Living with HIV/AIDS) is working nationally and within that we have an organization for working with women and children, which is called Positive Women's Network (PWN+), which I am in charge of. So INP+ and PWN+ are working closely together.

Indian generic drug companies are manufacturing low-cost ARV drugs for sale in Africa, but they are more expensive in India.

Yes, we are selling the drugs for $150 per year in African countries, but for $50 a month in our country. We have submitted a treatment proposal to the Global Fund, so if we get it then maybe we can interest our government in talking to the drug companies to get the cost down.

So far, around the country, 1,000 people are receiving the medicines for free from the government. They are planning that 100,000 people will get ARVs within a year, so we hope that that will be fulfilled. But we don't have all the money we need. So we are hoping that we will get money from the Global Fund, we are hoping for more outside money, and we are hoping that our government will also put some money towards treatment.

The government has recently changed and we want the new politicians to understand the importance of the free program and continue it. So, we are planning to go to the politicians and show them what is going on here and help them understand.

What drugs are the 1,000 people getting in the government program?

One of our pharmaceutical companies, Cipla, is providing a three-drug combination with nevirapine, lamivudine and zidovudine and another one with nevirapine, lamivudine and stavudine. These are three drugs in one pill. I can show you the medication that I take—It's by Cipla; three together. The separate drugs are also available, for children who need separate drugs. We don't have resistance tests and we don't have many CD4 tests and viral load tests because they are costly in our country. But we are hoping the Clinton Foundation will help us to get CD4 and viral load testing for high prevalence states. That may begin to happen in the next few months.

Where do people go to get treatment now?

The government is giving training for the government doctors. But the country is big and the state is big — I am from the Tamil Nadu state, and we have 30 districts in our state, but we have only one treatment center. That means in Chennai we are getting drugs in only one clinic and not in the other clinics. We hope that the other clinics will be getting the drugs too, but they don't have the proper resources in the hospital and they don't have doctors who are trained. The training is now going on for doctors and other healthcare providers.

A few people in India are getting treatment, but they still don't have monitoring or education and the government workers are still not comfortable working with people with HIV.

The CDC is helping train the government doctors and staff in our state. Before, we were seeing a lot of discrimination going on in the hospital, but now they are taking better care of the people. People from the positive networks are also there for counseling at the clinic, so there are many changes now. But most people don't have a doctor. There are only three doctors treating about 200 people, and there is no sharing of information between the government doctors and the private doctors.

People with HIV from the IPN+ state level network and the district level network are providing counseling, education and training for people living with HIV. At the state level network they are doing DOT training, care training, advocacy training and speaking out as positive people. It is peer education. Before the programs there was a lot of discrimination in the districts but now there are a lot of changes with the community people giving care to people. And the government is also supporting the Network, by giving space for their meetings.

We have separate support group meetings for women and children and then groups for men and women together. We have support group meeting where they can share their own experiences. And we have nutrition education programs and health education programs. And we have separate meetings for people who have started ARVs. We started a treatment education

program about eight months ago. People in the government ARV programs in the high prevalence districts are getting information about ARVs and how to take care of themselves. And we have some money for children's education.

What is the situation for women with HIV?

Women are vulnerable, but that is a global problem. In India, many women are not getting care and there are many orphans now. So many of the people infected in India are women — maybe half and half. Many are mothers. Most are between the ages of 19 to 30. In our culture they can marry at early ages; at 16 and 17 they can marry and have children.

We don't have many doctors who are women's specialists. For example, when the mother-to-child transmission prevention (PMTCT) program started in our country there was a lot of discrimination in the hospitals. Now that has changed a little bit, but the hospitals are still not providing full information and they are not giving women any help to take care of their children. They will give them the medicines while they are in the hospital, but after, the women are not coming back to the clinic.

The government program started in the STD clinics — the sexually transmitted diseases clinic, but there is a lot of stigma attached to that.

All pregnant women get HIV testing at the hospitals — not only government hospitals, but all the hospitals. But at the private hospitals they get no information and no counseling. And many in the private hospitals are tested without informed consent. Then if they have HIV, many private hospitals will discriminate against the women. Maybe they turn them away or maybe they refer them somewhere else. Some government hospitals have the PMTCT programs available and women may be referred there. But some women don't know their status and come in late at the time of delivery. After that they don't get follow-up.

Do they give these women who come in late nevirapine?

PMTCT treatment with nevirapine is available in some of the government clinics but not all of them. Information and counseling is available in some of these clinics but not all of the clinics.

Then why do they test if they don't treat to prevent transmission to the baby?

The doctors want to prevent themselves from becoming infected.

So children are still being born infected?

Yes. The government clinics have PMTCT treatment but the women don't know to go there

Women with HIV in India Speak Out

In March of 2002, a national consultation on women living with HIV/AIDS was organized by the Positive Women's Network (PWN+), Chennai, India in preparation for a study of the gender dimensions of HIV within a human rights context. The study produced a book entitled, "Positive Speaking: Voices of Women Living with HIV/AIDS" published by the United Nations Development Fund for Women (UNIFEM), South Asia Regional Office.

Despite a clearly enunciated commitment to women's equality in the Indian constitution, women, and especially women with HIV, remain marginalized. The purpose of the study was to make women's voices heard, since "what matters is women's capacity to speak up, demand that they be heard and succeed in motivating everyone concerned to take responsibility..." The study is based upon 21 testimonies of individual women's experiences, each with an analysis of the rights that had been violated, the consequences of those deprivations and discussions of specific opportunities to assert those rights, seek redress and better their situations.

Here is one excerpt from the story of Arti, age 26:

"During the pregnancy of my second child, the hospital took a test in the seventh month. They found I was positive so they told my husband that I should go to another hospital. I went to the doctor who had handled the delivery of my first child. He referred us to another hospital. When we went there for delivery we did not disclose our status, because we feared rejection and the hatred that would follow."

"At first my son was fine. One day he developed fever and started vomiting. We took him to the hospital and kept him there for 22 days. He had symptoms of epileptic fits also, so they gave him an injection and after 22 days he was discharged. He was fine for a week and after that he again developed dysentery. He died the same night. We had not revealed his status. But after his death we decided it was better to reveal my elder son's status so that he could get proper treatment. The doctor provided him with good care even after his status was known. But the fever did not stop and he was admitted to the government hospital for pneumonia."

"Though the doctors provided treatment, there was some problem when one doctor at the pediatric ward questioned why an 'STD case' was being kept in that ward. Previously when he was admitted the doctors used to treat him well. I feel that if right treatment had been given on time he would have lived longer. When my son was serious, the doctor was refusing to admit him. But the network members helped me. They got all the gloves and things like that and gave them to the doctor and asked her to admit my son. I was able to get treatment for him because we fought for it."

or if they are sent there they don't know why they are being sent to that clinic.

They get no information or education in the private hospitals. In the government hospitals, the counselors talk to people and say they can provide free testing. If interested, the women get an HIV test, but if they are not interested, the doctors in a government hospital will test them anyway. That has happened. If they were less than one or two months pregnant, they were told that they can abort the baby. We didn't have a choice to carry the baby. Now there have been some changes, and we can hope that more changes will come.

We don't have child specialists to take care of a child on ARV. That is another big task for us, to take care of the children. There are only two or three trained doctors taking care of children in all of India.

Are any public figures speaking out to help ease the stigma about HIV in India?

Previously some movie stars have spoken out on the prevention aspect but not on care and support. They are now making a Hindi movie where an actor plays an HIV positive person. Maybe that will help with discrimination. Before, though, movie actors would make HIV into a horrible joke. But we don't have anyone monitoring the media. They can do what ever they want and no one complains.

When did you start taking ARVs?

I started three years ago. My CD4 was 24 and I had a lot of diseases and TB and then Cryptococcus, but now I'm okay. My CD4 increased and I'm living! At that time the medicine was costly, but now it is less because of our advocacy at INP+. In our state, the state tax is waived on ARVs. Also, the AIDS Control Society has a medical shop with better prices; an outside medical shop would charge 20 percent more. Within our clinic in Chennai they are also 20 percent less; about $50 a month. I'm lucky because I can afford it, but not everybody can.

My CD4 was 24 and I had a lot of diseases and TB and then Cryptococcus, but now I'm okay. My CD4 increased and I'm living!

Khousalya Periaswamy is President of Positive Women's Network (PWN+) and Board Member of INP+

ARV Drug Procurement in India

Excerpts from a Letter to India's Minister of Health and Family Welfare

The Affordable Medicines and Treatment Campaign (AMTC), is a national campaign aimed at creating an environment that will ensure sustained accessibility and affordability of medicines and treatment for every individual in India.

We are writing this letter to seek your immediate attention and intervention to ensure adequate and sustained supply of antiretroviral (ARV) drugs for the free antiretroviral therapy (ART) programme. As you know, on 1st of April of this year Government of India initiated a free ART programme for people living with HIV/AIDS (PLHA) in the six high prevailing states (Andhra Pradesh, Karnataka, Maharashtra, Manipur, Nagaland and Tamil Nadu) and New Delhi. Even though, the first phase of the programme envisaged 15 delivery points, the present number of ARV delivery points is only seven (one hospital in each state). We estimate that at this pace the treatment plan will cover less than 1,200 PLHAs in the first phase. This is a minuscule number of the PLHA population currently in need of ART in these six high prevalence states. Further, this number is far below the overall target of providing treatment to 100,000 PLHAs within the first year of the programme.

We understand that the inadequate procurement of drugs is the main reason for the inadequate intake of the ART programme. As you are aware, the programme was launched with limited stock of drugs received from WHO, which is inadequate to meet the demand. We feel that only large-scale procurement of ARV drugs can address this issue. As you know, it is the Indian pharmaceutical companies that supply ARV drugs to majority of African and Latin American countries. Indian companies shook the international pharmaceutical industry and civil society by announcing the supply of ARV drugs for $340 per annum against the then international price of $12,000 per annum. These companies went further and are presently supplying ARV drugs for $140 per annum. However, the paradox is that ARV drugs are still not accessible to vast majority of Indian PLHAs. We seek your urgent intervention to end this inequity.

We also have information that the current stock of ARV drugs will be exhausted in July. Any discontinuance in the supply of drugs will have life threatening consequences to those people benefited under the programme.

Against this background, we request you to take necessary steps to achieve the following: To ensure the immediate procurement of ARV drugs before the exhaustion of current stock under free ART programme; to scale up the procurement of ARV drugs to meet the needs of those PLHAs who require immediate treatment; and to engage with the Indian pharmaceutical companies to bring down the price below $140 per annum to increase the accessibility of ARV drugs.

Keystone HIV Pathogenesis and Vaccine Development Report

By Gareth Hardy, PhD

This year's Keystone Symposia on Molecular Mechanisms of HIV Pathogenesis (X7) and HIV Vaccine Development (X8) was held in British Columbia's Whistler Resort, Canada, from 12–18 April 2004.

This highly specialised and relatively small annual meeting is often not attended by community activists or press. The focus on basic science means that much of what is presented and discussed has little, if any, direct implications for clinical practice. However, the meeting attracts some of the world's experts on HIV immunology and pathogenesis as a forum to exchange and discuss ideas and data. From year to year, the feeling of these meetings can shift from optimism and excitement, to a mundane business-as-usual mood, to an urgent knuckle-down and crack-on intensity. This year's meeting was somewhere between the latter two.

The meeting attracts some of the world's experts on HIV immunology and pathogenesis.

Of significant interest was a presentation entitled "Evolution of HIV is focused in HIV-specific CD4+ T cells" by the group of Dean Hamer at the National Cancer Institute together with the group of Daniel Douek at the Vaccine Research Center, both at the NIH in Maryland [1]. Douek has previously shown that HIV-specific CD4+ T cells harbour a large proportion of the pro-viral DNA that makes up the latent reservoir of virus in infected individuals. In this presentation Hamer not only showed that HIV-specific CD4+ T cells are infected, but that they are also activated by HIV itself. CD4+ T cells from patients treated with HAART early in infection (i.e. before any major loss of CD4+ count) were stimulated with HIV antigens p24 and gp120, with CMV antigen, or anti-CD3 (which stimulates all T-cells regardless of specificity), and the replication competent virus induced was sequenced. In addition pro-viral DNA was also sequenced from purified HIV-specific CD4+ T cells.

The sequences of HIV-1 envelope genes from viruses infecting HIV-specific CD4+ T cells was found to have an 8-12% divergence from the envelope sequences of viruses infecting CMV and anti-CD3 stimulated CD4+ T cells. Phylogenic tree analysis showed that these viral variants were diverse and distinct from viruses populating other CD4+ T cells. In general polyclonal (anti-CD3) stimulated CD4+ T cells appeared to have very homogenous sequences representing the original infecting strains, though during untreated chronic infection virus sequences were found to be highly heterogenous both in HIV-specific and polyclonal (anti-CD3 stimulated) CD4+ T cells. Hamer explained that the HIV present in HIV-specific CD4+ T cells continues to evolve even in individuals who initiated antiretroviral therapy shortly after they became infected.

Mathematical modeling based on these findings suggested that boosting HIV-specific CD4+ T cell frequency could increase viral load and decrease T cell functional help. The argument here is that while highly active anti-retroviral therapy may inhibit 99.9% of viral replication, the remaining 0.1% of virus that is replicating, is doing so in HIV-specific CD4+ T cells. The reason for this is logical enough: the population of CD4+ T cells that are most likely to be continually activated in HIV infection are HIV-specific ones, even in the presence of antiretroviral therapy, due to the ongoing presence of HIV antigen which stimulates them. Such activation of these cells subsequently leads to high turn over of the virus they harbour.

Though not particularly surprising, the implications of this data are profound. This may explain why one HIV therapeutic vaccine after another cannot induce sustained HIV-specific CD4+ T cell proliferative responses. Yes, we can induce those responses, but time and time again, they emerge as a transient phenomenon only to mysteriously disappear again. Such short-term responses are the hall mark of short-lived effector T cells which have a half life of 1–2 days, and not central memory T cells which should live for many years. The lack of generation of HIV-specific central memory T cells has been a perplexing mystery for a long time. These are the kind of T cells which protect us from re-infection with measles for example, or from any of the organisms we have been vaccinated against, years after inoculation. Although the jury is still out on the precise origin of central memory T cells, one popular current theory is that a small proportion of activated effector T cells will always survive to subsequently become resting (non-activated) long lived central memory T cells. The fact that this does not seem to happen to HIV-specific CD4+ T cells could be a very important component of why our immune systems fail to control and ultimately eradicate HIV. Indeed Hamer

explained that the half-life of HIV-specific CD4+ T cells, once activated, was less than 1 day, suggesting that all HIV-specific effector CD4+ T cells suffer the same fate. Hamer concluded that "The ability of HIV-specific CD4+ T cells to serve as a distinct reservoir for HIV growth and variation suggests that vaccines and treatments aimed at augmenting HIV-specific CD4+ T cell responses should be undertaken with caution." However many immunologists argue that we need to ensure preservation of these responses, perhaps by using more effective HAART regimens, which fully penetrate all anatomical and cellular compartments, thus preventing the small amount of virus replication that is taking place in HIV-specific CD4+ T cells. Indeed these responses need to be expanded in a manner in which they can be sustained, in order to help achieve long-term control of viral replication in the absence of anti-retroviral treatment.

Bruce Walker of Massachusetts General Hospital, Boston, Massachusetts, presented an update on his structured treatment interruption study in primary HIV infection. [2] Fourteen patients underwent up to three structured treatment interruptions. Treatment was restarted if the viral load increased to more than 5,000 copies/mL for more than 3 weeks or if the viral load increased to more than 50,000 copies/mL on any single occasion. Following interruption, 11 patients (79%) maintained control of viraemia for more than 90 days, despite lack of tissue types associated with protection. 57% achieved control of viraemia for 180 days, 43% for 369 days and 21% for 720 days. However over time there was a gradual decrease in CD4 counts and increase in viral loads. The total magnitude of CD8+ T cell responses increased 3.5, 2.1 and 1.78 fold at the first, second and third interruption and transiently detected HIV-specific CD4+ T cell proliferative responses declined with recurrence of viraemia. Walker concludes that "despite initial control of viraemia, durable immune control in persons following treated acute infection occurs infrequently".

In response to this, Dean Hamer made a passionate request to Walker that he would now denounce the practice of treatment interruptions, acknowledge the potential risks of drug resistant evolution within them, and agree that they offer limited real clinical benefit. However there was little agreement on this and Walker did not seem to share Hamer's view that structured treatment interruptions were dangerous.

One particularly interestingly element of Walker's data was his finding that CD8+ T cell responses measured by the release of the T cell cytokine interferon (IFN)-gamma in the ELISpot assay did not correlate with protection from viraemia in his patients. In contrast, measurement of HIV-1 specific CD8+ T cell proliferation revealed a very impressive correlation with protection from viraemia. Walker used a florescent dye called CFSE to stain CD8+ T cells, which binds to the cell membrane. With every round of division undertaken by proliferating cells the membrane bound concentration of CFSE halves. This assay is increasingly being used to measure cell proliferation in different laboratories. Walkers data using this assay concurs with previous data published by Migueles et al, [3] demonstrating that HIV-1 specific CD8+ T cell expression of the molecule perforin, which kills virus infected target cells, and is known to be deficient in HIV chronically infected individuals, correlates with CD8+ cellular proliferation. Thus while proliferation is coupled to effector function such as perforin production, what we are now experiencing is a gradually dawning understanding that IFN-gamma expression is not part of this picture. In fact we have known for some time that IFN-gamma expression is not linked to cellular proliferation, in the way that other cytokines, particularly interleukin (IL)-2 are. The implication here is that the commonly used IFN-gamma assay, now the assay of choice in many immunotherapy and vaccine trials, may not be telling us the correct information about functional T cell responses in HIV infection

Walker did not seem to share Hamer's view that structured treatment interruptions were dangerous.

Brigitte Autran of the Hôpital Pitié-Salpétrière, Paris, France, presented the results of the first international, randomised, double blind, placebo-controlled, phase-I therapeutic vaccination trial: QUEST. [4] Here 79 individuals with primary HIV-1 infection were treated with HAART >72 weeks before being randomised to one of three immunotherapy arms. Group A continued to receive ART alone, group B received the ALVAC-HIV(vCP1452) therapeutic vaccine in addition to ART and group C received both ALVAC-HIV(vCP1452) and Remune therapeutic vaccines in addition to ongoing ART. ALVAC-HIV(vCP1452) was given I/M at weeks 8, 12, 16 and 20 following randomisation in groups B and C and Remune was given I/M at weeks 0, 4, 12 and 20 following randomisation in group C. In all groups ART was discontinued 24 weeks following randomisation and patients were followed up for an additional 24 week period. The primary endpoint was a viral load <1000 copies/mL at week 48 (24 weeks after stopping ART) without restarting ART. Secondary endpoints were maintenance of viral load <400 copies/mL throughout the 24 week ART interruption and time to reaching viral load above

1000 copies/mL after stopping therapy. In all cases restarting HAART was considered failure in the intention to treat analysis.

Preliminary analysis of the data (vaccinated patients in groups B and C have not been unblinded) reveals that while vaccination successfully induced T cell responses measured by IFN-gamma ELISpot, the virological endpoints of this study all failed. In vaccinated patients the median p24 specific CD4 ELISpot response was 180 IFN-gamma responding lymphocytes per million peripheral blood mononuclear cells (PBMCs) (n=32) versus a median of 0 for the ART alone treated group (n=18) (p=0.006). The median CD8 IFN-gamma response to gag was similarly high for the vaccinated patients at 275 IFN-gamma responding lymphocytes per million PBMC (n=34) compared to 0 for the ART-alone treated group (n=18) (p=0.002). Of the 52 vaccinated patients, 15.4% reached the primary endpoint of a viral load <1000 copies/mL plasma at the end of the 24-week treatment discontinuation period. Of the 27 ART-alone treated patients 22.2% reached this endpoint. There was no statistically significant difference in these values. There was also no statistical difference in the number of patients achieving viral load <400 copies/mL during the ART discontinuation period or the median number of days to a viral load more than 1000 copies between the ART alone and vaccinated groups.

It is becoming increasingly clear that IFN-gamma production is not tied to T cell function in the manner we once thought it was.

The fact that vaccination here proved immunogenic in terms of T cell IFN-gamma responses, but yet failed to translate into any discernable clinical benefit further adds credence to the notion postulated by Bruce Walker that IFN-gamma is perhaps the wrong marker of immune function to be measuring in our immunotherapy trials. It is becoming increasingly clear from the published literature that IFN-gamma production is not tied to T cell function in the manner perhaps we once thought it was. Indeed it is possible that because of this, assays measuring IFN-gamma release tend to churn out lots of positive results. These are popular as everyone likes to show positive results. Thus IFN-gamma production assays validate the immunogenicity of various strategies tested, while these responses yield very little clinical benefit because they have limited or no functional impact that could affect long-term clinical outcome.

Walker advocates the CFSE dye dilution assay as an accurate measure of HIV-specific CD8+ T cell function. Functional assays for measurement of HIV-specific CD4+ T cells that offer clinically relevant alternatives to singly evaluating IFN-gamma production in the CD4 subset have previously been shown by other groups. Anna Vyakarnam's group at Kings College Hospital, London, demonstrate the superiority of IFN-gamma and IL-2 double positive intracellular staining by flow cytometry [5] and Frances Gotch's group at Chelsea and Westminster Hospital also in London demonstrate the superiority of the traditional lymphocyte proliferation assay which measures incorporation of radioactive labeled thymidine into the replicating DNA of proliferating cells [6].

If we are to get a handle on useful immune responses that candidate vaccines or immunotherapies should be inducing, we need to be using assays which correlate with clinical outcome. This means that immunology laboratories and investigators need to be a little more adventurous in terms of the assays with which they choose to evaluate their immunotherapy trials. Hopefully the work in this area already laid out by some groups will be verified in larger immunotherapy studies and by other groups in the not too distant future. But until then the incremental acquisition of failing immunotherapy data continues to generate a business-as-usual feel to not really understanding why our chosen immune-based interventions are not working. To this end I returned from British Columbia back home to England and to my London Immunology Lab, with a whole set of new plans for the way ahead, while the bars of the Whistler resort roared to the opening matches of a strange local game called "ice hockey" that was way beyond my comprehension.

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Medicare Drug Card Analysis

An examination of three GMHC clients, whose regimens typify the needs of people with HIV, shows that the discount card program is not comprehensive, lacks choice, and offers uneven savings.

Barry takes 4 prescription medications for HIV and pain management. Of the drugs covered by the lowest-price discount plan offered by Medicare, the following price comparisons were found:

Drug Name	Medicare	Drugstore.com	Canadadrugs.com
Celebrex	$151.56	$76.99	$88.72
Levaquin	266.28	97.93	149.56
Viracept	603.08	635.97	565.97
Zerit	329.75	316.24	259.08
Total Monthly Cost for Barry	**$1,350.67**	**$1,127.13**	**$1,063.33**
Barry's best bargain	*Most Expensive*	*Less Expensive*	*Least Expensive*

Total number of Medicare plans that cover all of Barry's drugs: 4

Patricia takes 6 prescription medications each day. Of the drugs covered by the lowest-price discount plan offered by Medicare, the following price comparisons were found:

Drug Name	Medicare	Drugstore.com	Canadadrugs.com
Epivir	$264.45	$269.99	$244.90
Hydrochlorothiazide	3.89	8.99	2.02
Retrovir	308.16	326.21	330.61
Total Monthly Cost for Pat	**$576.50**	**$605.19**	**$577.53**
Patricia's best bargain	*Least Expensive*	*Most Expensive*	*Less Expensive*

Patricia can purchase more of her drugs at one time through non-Medicare outlets.

Total number of Medicare plans that cover all of Patricia's drugs: 0
Number of Medicare plans that cover some of Patricia's drugs: 5

Jim has been on Medicare for 9 years and takes 12 prescription medications daily for HIV, high cholesterol, sleeplessness, and pain. Of the drugs covered by the lowest-price discount plan offered by Medicare, the following price comparisons were found:

Drug Name	Medicare	Drugstore.com	Canadadrugs.com
Elavil	$15.38	$10.99	$2.86
Famotidine	25.30	19.99	86.12
Lipitor	67.33	62.99	46.48
Naproxen	13.00	17.99	12.82
Reyataz	756.94	775.51	665.99
Total Monthly Cost for Jim	**$877.95**	**$887.47**	**$814.27**
Jim's best bargain	*Less Expensive*	*Most Expensive*	*Least Expensive*

Total number of Medicare plans that cover all of Jim's drugs: 0
Number of Medicare plans that cover some of Jim's drugs: 2

Analyses were conducted using prices listed on CMS's website www.medicare.gov, Drugstore.com's website, www.drugstore.com, and Canadiandrugs.com's website, www.canadiandrugs.com, on Thursday, May 20, 2004. Only drugs that were available from all three sources were compared. All prices in U.S. dollars.

Medicare-Approved Discount Cards Will Benefit Some

***Summary from* AIDS Treatment News**

Patients who are on Medicare and have income under 135% of Federal poverty level and are not on Medicaid probably should obtain one of the new Medicare discount cards that became available on June 1, 2004, because all these cards include $600 annual credit for prescription drug purchases for persons within that income limit. Unfortunately, this program is complex, no one yet knows how it will work in practice, and after choosing a card one is locked in until November 15. The most difficult part of the choice of which card to get may involve how it interacts with other programs, including ADAP, and pharmaceutical company patient assistance programs.

For the complete report, visit: www.aidsnews.org

Abbott's Norvir Price Hike is Bad Medicine

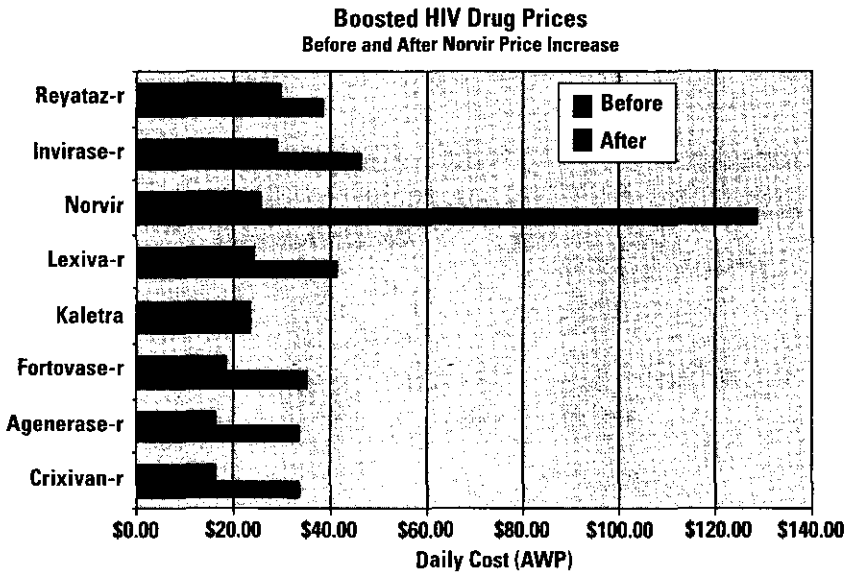
By Bob Huff
Statement at the NIH Public Meeting on Norvir

On May 25, 2004, the NIH heard public statements concerning a petition to invoke the march-in provisions of the Bayh-Dole Act on Abbott Laboratory's Norvir. The law says that patented inventions developed in part with public funds can be reassigned to other business entities if the patent holder does not make the invention available on reasonable terms.

In the first part of December 2003, the HIV/AIDS treatment community was shocked to hear that Abbott Laboratories was raising the price of its HIV drug, Norvir, five-fold. The price per 100mg pill would increase from $2.14 to $10.71 (average wholesale prices; $1.71 to $8.57, wholesale acquisition cost).

As you've heard, although Norvir was developed and approved by the FDA as an anti-viral drug—an inhibitor of the HIV protease enzyme—due to excessive toxicity, it is no longer used as such. Instead it is now used for an off-label indication in much lower doses to take advantage of one of its side effects, namely the inhibition of a metabolic pathway in the liver that effectively improves the concentration of other drugs in the blood. In current clinical practice, most other HIV protease inhibitors are "boosted" by Norvir, which increases their effectiveness. In other words, Norvir enables other drugs to work better.

Here is a before-and-after price chart that shows the eight approved HIV drugs that can be boosted by Norvir, and how the price increase has affected their overall cost. Note that the price of Norvir in its approved dosage as an antiviral is far out of proportion to the others. Also note that the price of the drug Kaletra, which is also made by Abbott and contains a small boosting dose of Norvir in each pill, did not change and is now the lowest price boosted protease inhibitor on the market. It is clear that the practical and intended effect of the Norvir price increase was to position Kaletra in advantage to its competitors.



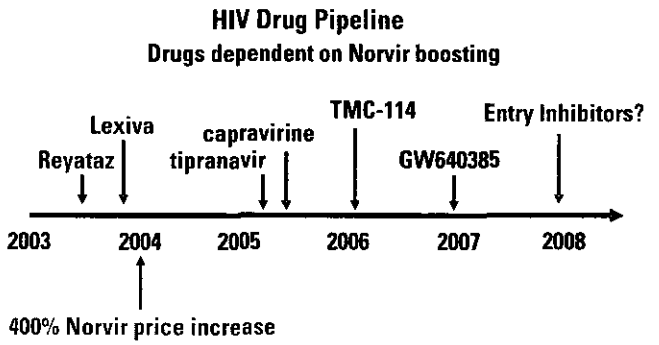
Here is another chart that shows a timeline for the development of some HIV drugs that require Norvir boosting. It includes two protease inhibitors that were approved last year (Reyataz and Lexiva) and several currently in development. It seems clear to me that the Norvir price increase was calculated to come just after these two new drugs received approval.

But I'm more concerned about the drugs that are still on the path to approval—and about potentially useful drugs that may now never enter clinical development—because they would be at the mercy of Abbott's monopoly on Norvir.

I would like to argue that Abbott's failure to make Norvir available on reasonable terms will adversely affect the development of new drugs that depend on metabolic boosting and will limit the amount of research that will be conducted on existing drugs that require boosting.

Abbott's abuse of their patent on Norvir will limit patient access to drugs, limit research, limit options for doctors and limit the innovation of new-generation drugs of this type. This is why we are asking the government to protect the public against Abbott's unreasonable use of the Norvir patents.

Before a pharmaceutical manufacturer decides to invest hundreds of millions of dollars into bringing a promising compound along the path to FDA approval, the company projects the mar-



ket for the drug over the entire expected life of the product. While this isn't easy, given the rapid pace of change in HIV therapy, it is necessary to forecast whether the drug will be competitive and will repay the considerable investment in clinical development. For the makers of Norvir-boosted drugs in the pipeline, Abbott's price increase has thrown these forecasts into chaos.

In seeking to mitigate the impact of the 400 percent increase in the price of Norvir, Abbott has announced it will make the drug available at the old price for research purposes to companies that are developing a drug that requires Norvir-boosting. However this offer expires once the new Norvir-dependent drug receives FDA approval and goes on the market.

Yet research on these drugs can not and must not end with approval. Post-market research, so-called Phase IV studies, are important to "fill in the blanks" about how a drug behaves in real-world settings and to provide controlled data that helps physicians make the most appropriate use of all the drugs in their armamentarium.

Much of this Phase IV research is mandated by the FDA and some is initiated by the company for marketing purposes. For the recently approved protease inhibitors, the 400 percent increase in the price of Norvir means that the cost of post-marketing research has now increased dramatically. One pharmaceutical executive estimated that the cost of post-approval research could go up by $20 million to $30 million. And this is for drugs that have already been approved, with FDA-mandated post-market research already planned and budgeted.

The impact on drugs still in the pipeline is far more insidious.

A drug company's Phase IV research commitments are decided in negotiations with the FDA. The FDA says it will grant accelerated approval based upon available safety and efficacy data, but only if the company will show a plan for continuing research on the drug after entering the market. These research plans are negotiated based on what the FDA would like to see and what the drug company can afford. The simple fact is that after the 400 percent rise in the price of Norvir, companies will not be able to afford as much post-market research. And the high price of Norvir will effectively tie the hands of the FDA in what they can ask of companies. This is going to hurt patient care.

There are four Norvir-dependent drugs in the pipeline that this will affect. Abbott's monopoly on Norvir means that there will be less post-marketing research and, consequently, less important real-world medical information produced on how to use these drugs, for example, in women, in people of color, in prisons, in combination with other drugs, in people with hepatitis infections or in people with liver or kidney disease. Much of this research will become too expensive.

Abbott's unreasonable terms for Norvir will inhibit innovation, restrict research, limit medical options and hurt people with HIV.

But my main concern is with what Abbott's monopoly on Norvir means for the future. One pharmaceutical executive I spoke to, in evaluating the impact of Abbott's action, posed this as a rhetorical question: "Who would risk developing a Norvir-boosted protease inhibitor after this price increase?" What he meant was that, not only will the high price of Norvir place any new Norvir-dependent drug into an uncompetitive price stratum, but

FDA Issues Warning Letter to Abbott over Norvir Pricing Spin

On June 10, 2004, the Food and Drug Administration issued a Warning Letter to Abbott Laboratories about a "false and misleading" cost comparison chart that Abbott had distributed to community groups in an effort to counter public outrage over the recent 400 percent increase in the price of their HIV drug, Norvir. The cost chart purported to show that Norvir, even at its new, higher price (the price for a single 100mg pill increased from $1.71 to $8.57 each) was the lowest priced HIV drug at its most commonly prescribed dosage. Although Norvir was originally developed as an HIV protease inhibitor, it is now used primarily at a much lower dose to "boost" the blood levels of other HIV protease inhibitors. At 100mg, Norvir is not active in on its own. Yet the chart implied that this boosting dose of Norvir was comparable to several full-dose antiretroviral drugs and even to one complete HIV regimen.

The FDA's letter stated:

"The cost chart is misleading for two reasons. First, it compares a subtherapeutic dose of Norvir (100mg once daily) to the labeled dosing regimes of other antiretroviral agents. Second, the chart implies that Norvir may be used other than in combination therapy, when it is not labeled for such use. Given by itself as a subtherapeutic dose, Norvir would likely have no antiviral activity and would place patients at risk for developing protease inhibitor resistance mutations."

"The cost chart misleadingly claims that Norvir has the lowest daily cost of all antiretroviral drugs and minimizes the risks of Norvir, and thus misbrands Norvir under 21 U.S.C. 352(a)."

Abbott was to respond to the FDA by June 25.

Abbott's unpredictable behavior has made depending on them or their products an unsupportable risk. It's difficult enough to project market conditions for new HIV drugs that don't need Norvir; it's very unlikely that a corporate market analysis will ever again justify investment in drugs of this type. In the words of another pharmaceutical executive, after the drugs currently in the pipeline empty out, "We've seen the end of the line for boosted protease inhibitors."

And that is a shame, because we desperately need new protease inhibitors to treat drug-resistant HIV. The so-called HIV salvage population is the fastest growing market segment in HIV therapy. Drugs with incremental benefits have continued to trickle onto the market over the past few years, but in practice, this has resulted in many patients simply adding the latest therapy onto a failing regimen, which starts the cycle of resistance all over again. Unless a person switches to multiple drugs that his virus is susceptible to, the development of resistance seems inevitable.

I believe Norvir should be considered a public amenity and be contracted to more responsible custodians.

For drugs in the protease inhibitor class —which are very durable HIV therapies— Norvir has assumed a crucial, enabling role by assuring that sufficient blood levels of the active antiviral drugs are achieved. Looking ahead, we can foresee the continued need for new protease inhibitors that will have novel resistance profiles, that will have less toxicity, and that are more durable. Some of the drugs in the pipeline have some of these qualities, but none has all of them. Most observers expect the protease inhibitors in the pipeline to continue towards approval because their sponsors have already made substantial financial commitments to their development. But how many important, useful, and desperately needed drugs will now never see the light of day—because of Abbott's monopoly on Norvir? Abbott's unreasonable terms for Norvir will inhibit innovation, restrict research, limit medical options and hurt people with HIV.

Finally, the pricing issue aside, Abbott has not been a responsible custodian of this drug. Although Norvir's usefulness is as a metabolic booster and not as a protease inhibitor as they had hoped, the company has not made the drug available in dosages that would optimize the use of Norvir for this purpose. With only a 100mg pill of Norvir available, many patients who would only require 50mg or less for boosting are being subjected to unnecessary toxicity.

Furthermore, Abbott has not sought FDA approval for Norvir as a metabolic boosting agent and continues to represent the drug in medically misleading terms—all the while encouraging continued off-label use.

Also, Abbott has, I have been told by several pharmaceutical executives, been unwilling to offer reasonable terms for licensing Norvir for co-formulation with other companies' drugs, even though a co-formulated pill is widely considered to help simplify drug regimens and improve patient adherence and therapeutic outcomes. Yet Abbott, in order to protect its own, more toxic Kaletra product, continues to resist this.

To sum up, Abbott has behaved unconscionably, and perhaps illegally, in increasing the price of Norvir, and in doing so they have abused the privilege of their patents.

- They have attempted to manipulate the market and restrict patient access to competing drugs that have less toxicity.
- They have increased the financial burden their competitors face in performing important post-market research.
- They have tied the hands of the FDA in how much post-market research can be required of drugs approaching approval.
- They have stifled innovation and have killed the market chances for any new drug candidate that would require Norvir.
- They have not been responsive to the medical need for safer and more rational doses of Norvir.
- They have refused reasonable offers to license Norvir for co-formulation into patient-friendly combinations with other drugs.

With at least ten HIV drugs dependent on Norvir to achieve optimal efficacy and minimal toxicity, I believe Norvir should be considered a public amenity and be contracted to more responsible custodians.

I'd like to note that I think the case of Norvir is an exceptional one, and that I fully support industry development programs that build on government funded research. It seems clear that the intent of the Bayh-Dole Act was to stimulate innovation, and in this it has been incredibly successful. But it also seems clear that a mechanism was provided to address abuse, and that, in Norvir, we are confronted with that rare case.

Under Abbott's monopoly control of Norvir, drug access (both to Norvir and to dependent drugs), patient care, innovation, research, and medical options are being restricted. The public interest would best be served by making this vital resource more broadly available under much more reasonable terms.

Drug News

By Bob Huff

Fixed-Dose Combinations

The FDA has granted a fast-track approval to Gilead's new co-formulated FTC/tenofovir pill. It should be approved by September 12. This is sooner than had been expected but the company says it has sufficient manufacturing capacity to begin shipping soon after that date. The FDA speeded up approval after prodding by treatment activists and a recognition that seemingly small advances, such as co-formulation, are worthy of accelerated approval, because it can mean a big difference in treatment outcomes for people due to the improved adherence that comes with simpler regimens. GlaxoSmithKline (GSK) expects to add a third co-formulated pill to its line-up with a 3TC/abacavir combo that will likely be approved in August. GSK pioneered the combo concept for HIV drugs with their AZT/3TC pill, Combivir, approved in 1997, and followed it with Trizivir (abacavir/AZT/3TC) in 2000.

The FDA acted after issuing a draft guidance document in May 2004 encouraging manufacturers to develop co-formulated regimens. Specifically they were responding to a controversy about the co-formulated pills produced by several Indian generic drug makers that are widely used in treatment programs in the developing world. These medications have been evaluated and "prequalified" by the World Health Organization (WHO) for purchase by private and government sponsored treatment programs. The generic all-in-one pills (nevirapine, AZT and d4T is one common combo) are preferred by programs operating in resource-poor regions because adherence is better, education and dispensing is simplified, and procurement problems are minimized. Also, the generics typically cost only about a tenth what their branded counterparts do. But representatives of the multi-national pharmaceutical industry, perceiving a threat to their markets, have been fostering the impression that these drugs are of inferior quality and have convinced the U.S. government to only buy drugs that have received FDA approval. With $15 billion promised by President Bush for his international AIDS program, known as PEPFAR (President's Emergency Plan for AIDS Relief), the drug companies have a powerful motivation to keep the generic makers out of the loop. But the practical result of their obstruction will be far fewer people receiving treatment and suboptimal outcomes for those who do benefit from the U.S.-sponsored programs.

The FDA, to its credit, stepped into the middle of this argument and has offered a fast track for generic makers to receive FDA review of their products, even if they are not approvable in the U.S. due to patent issues. While many feel that the WHO prequalification process is sufficiently stringent and that FDA review is superfluous, given the political climate and the power of the pharmaceutical lobby, it is unlikely that U.S. dollars will become available with out this extra step. Even so, the flap over prequalification of generics may prove to have been a feint, and the U.S. will simply continue to funnel money to the multi-national companies.

Generic, all-in-one pills are preferred because adherence is better, education and dispensing is simplified, and procurement problems are minimized.

One significant byproduct of the FDA's shift in thinking is that unprecedented collaborations between drug companies may now be in the works to produce new co-formulated HIV regimens in the U.S. and Europe. Simultaneous with the FDA statement, a joint press release from Gilead Sciences, Bristol Myers Squibb and Merck announced that they were in discussions to offer an all-in-one pill containing efavirenz (Sustiva), tenofovir and FTC. Merck is involved because they market efavirenz in certain parts of the world as Stocrin. Another announcement from GSK and Boehringer Ingelheim suggested that they were exploring a combination with nevirapine (Viramune), AZT, and 3TC. This is an amazing step forward (after years of protest that FDA regulations and anti-trust laws would make these collaborations impossible) but in a perfect world we would see Sustiva hooked up with Combivir and Viramune paired with Gilead's nukes, too. One size doesn't fit all.

Abbott

Abbott is looking ahead to a new once-a-day version of Kaletra and expects to show new data later in the year and file for FDA approval in the following months. The company is also cautiously excited about the early results from some small studies that have used Kaletra as a solo antiretroviral agent — without nuke backup. A company representative recently told investors that this could "change the paradigm for HIV treatment." Hopefully more data will appear at this year's ICAAC conference in October.

The company also says it is working on a new, more stable formulation of ritonavir that will not require refrigeration. The new process is said to employ Abbott's proprietary melt-extrusion (Meltrex) technology, whereby drug mole-

cules are stabilized in a solid dispersion within a special polymer that dissolves at a controlled rate. This could overcome one of the biggest limitations to using Kaletra in resource poor settings, which has been the need for a cold distribution chain. But don't expect this new product very soon. Typically, pharmaceutical companies start to introduce new formulations only when their patent protections begin to sunset. This allows them extend the market life of their branded products. Abbott's Kaletra patents don't begin to expire until 2012.

One dark cloud over the potential for using Kaletra in other parts of the world: a recent report found resistance to Kaletra developing fairly rapidly in a treatment naïve woman in South Africa who had Subtype C HIV.

Trimeris has announced that it is beginning studies of a needle-free injection system for the current generation of Fuzeon, and is moving forward with studies using the drug in a once-a-day regimen.

Trimeris

After a disappointingly slow start to the roll-out of their premier drug, Fuzeon (T-20, enfuvirtide), following approval in March of 2003, Trimeris is planning to make some improvements. Initially, distribution of Fuzeon was restricted because of limited manufacturing capacity and a desire by Trimeris' distribution partner, Roche, to be sure prescribers and patients had been properly educated about the techniques of reconstitution and injection. Its record breaking price also slowed acceptance by some third party payers (and even a year later it is not yet available through every state ADAP program). But the biggest impediment to an enthusiastic reception by patients is the need to inject the drug under the skin of the abdomen or arm, twice-a-day, every day. A high rate of injection site reactions has been reported, with symptoms ranging from redness to "golf ball size" nodules. Yet for those who can tolerate the routine, the drug has proven remarkably effective, even in people with extensive drug resistance to other classes of antiretrovirals.

Now Trimeris has announced that it is beginning studies of a needle-free injection system for the current generation of Fuzeon, and is moving forward with studies using the drug in a once-a-day regimen, although these improvements may not become generally available until 2006 or after. Trimeris is also pressing forward with the search for second-generation fusion inhibitors with better resistance profiles and more convenient dosing (possibly once-a-week) and says it may be able to announce a drug candidate by the end of 2004.

The company doesn't believe that the coming wave of oral CCR5 inhibitors will make Fuzeon obsolete. Since up to 40 percent of people with advanced HIV disease will have an X4-using virus that will not be susceptible to the new drugs, Trimeris thinks there will continue to be a place for fusion inhibitors in this population. They cite in vitro studies that show dramatic synergy between Fuzeon and other entry inhibitors when used in combination, and suggest that viral suppression could be achieved with only one tenth of the current dose of the drugs when used individually — at one tenth the cost. One needle-free shot, once a week, costing only $40 may be just the thing to turn Trimeris' fortunes around.

CCR5 Blockers

There are several CCR5 blockers/entry inhibitors in development, including Schering's SCH-D, Pfizer's UK 237, Glaxo's GW873140, and Progenics' PRO140. These drugs are keenly anticipated by people who have developed resistance to all drugs in the conventional classes and the FDA has seemed to signal that they favor larger, Phase III clinical trials in people with multi-drug resistant virus. But there may be a hitch. People with few remaining treatment options tend to be people with more advanced HIV disease. And the longer people have had HIV, the more likely they are to have evolved virus that is capable of using CXCR4, a development associated with accelerated disease progression. These people won't be helped by a CCR5 blocker and they may be put in danger if the drugs force a shift to X4-using virus that speeds up immune deterioration. The possibility of this risk would seem to favor first investigating the CCR5 blockers in a more recently infected population, where the X4 virus will be less common. To do this safely, though, a sensitive and reliable screening test to detect low levels of X4-using virus must be developed. All of this may call for a rethinking of how to test these new drugs.

One fallback position (though it will likely slow enrollment) may be to require Fuzeon for every trial participant as a "safety net" to catch any virus that achieves coreceptor binding. A bonus to this is suggested by a bit of recently reported data that found Fuzeon may also block X4 coreceptor usage, in addition to mucking up fusion.

Boehringer Ingelheim

BI is set to widen access to tipranavir, its salvage-oriented protease inhibitor, by the end of summer. The drug is active against HIV that has been exposed to most every other PI, which will be welcome news to the growing number of people who are searching among limited treatment options to cobble together some kind of

"salvage" regimen. Still, and this can't be stressed enough, a drug like tipranavir will work best over the longer term only if it is paired with at least one other drug that a person's HIV is susceptible to. For many, if not most, this is likely to be Fuzeon. One bit of disappointing news about tipranavir has surfaced: it seems to lower the blood levels of other PIs, making them unreliable partners, despite ritonavir boosting. Saquinavir in particular was seen to drop to subtherapeutic concentrations in the presence of tipranavir. This means that the emerging salvage strategy of using dual boosted PIs may not be possible with tipranavir.

Also, BI has announced that a clinical trial with alovudine (MIV-310), an NRTI targeting multiresistant HIV has recently begun. Continuing BI's foray into salvage therapy, alovudine (say it with a Cockney accent) was licensed from Medivir in July 2003. The trial has been designed to evaluate short-term antiviral activity and safety in patients with HIV resistant to multiple NRTIs. The trial is a dose finding study in patients infected with HIV resistant to multiple NRTIs and with detectable viral load. They will be treated for one month with alovudine added to their standard regimens.

Gilead

Gilead Sciences is working on a new prodrug technology that has the potential to all but revolutionize HIV protease inhibitor therapy. Prodrugs are "almost" drugs that are converted to their fully active form once they are in the body. The best known example is Glaxo's recently approved Lexiva, a prodrug of their earlier protease inhibitor, Agenerase (amprenavir), which suffered from poor solubility in the gut and required a large number of pills to simply get a sufficient amount of drug absorbed into the body. But Lexiva has a chemical modification that makes it much more soluble in the intestines than Agenerase, so fewer pills are needed to deliver an active dose to the bloodstream. Then, as Lexiva crosses the intestinal wall, the chemical modification is clipped by an enzyme there and the original, active drug goes on its merry way. The same potency is delivered with far fewer pills.

Now Gilead is working on a prodrug concept that goes one—if not two or three—steps further. The company's scientists have invented a chemical modification that specifically targets a drug to lymphocytes—precisely the kind of cells that HIV infects. The prodrug modification is clipped by an enzyme specific to these cells and only turns into its active form once it is in or around lymphatic tissue. Details of the enzyme involved and how all this works have not yet been published. So far Gilead has tested its prodrug concept with a modified form of tenofovir (Viread), which, in a short term clinical trial, effectively lowered viral loads with only a fraction of the usual dose required.

Gilead is also developing a new protease inhibitor that uses the prodrug trick. The chemical modification is tailored to let the prodrug be easily absorbed in the gut, and also let it dodge premature clearance by the CYP 3A4 enzyme system in the liver, so no boosting should be required. The active form of the drug would only get down to business after it is modified in its target cells, where it would be trapped. If this all pans out—and the PI version has yet to be tested in people with HIV—protease inhibitor therapy may take a quantum leap in terms of activity, tolerability and pill burden. The inherent efficiency of the prodrug system means that much smaller dosages are required, which could open the door for a three-in-one, PI-based, single pill regimen. The specificity for lymphocytes might mean that collateral toxicity to other cell types could be greatly reduced. In lab tests, the PI appears to have a similar resistance profile to that of tipranavir, which is active against many HIV strains that are multi-PI resistant. It is yet to be determined if the prodrug will reach infected cells in reservoirs or sanctuary sites in the body. Despite the exciting potential, it may be another year before we know if this prodrug technology will survive the boot camp of Phase I trials, and then another year or two until it becomes available, most likely in a tenofovir version first.

GMHC treatment ISSUES

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Scramble for Africa

By Gregg Gonsalves

In 1884, German Chancellor Otto von Bismarck called together the major western powers of the world to apportion control of Africa amongst them. At the time of the conference, 80 percent of Africa was still under traditional and local rule.

Now, 120 years later, the major clinical trials networks of the western world—that is, the half a dozen or so of these groups funded by the U.S. National Institutes of Health (NIH)—are set to carve up Africa, Asia and much of the developing world for the purpose of testing treatments, vaccines, microbicides and behavioral prevention approaches.

Of course, both the NIH and the investigators involved will scream that I am being singularly unfair: the new emphasis on clinical research on HIV/AIDS in the developing world will be a partnership between American investigators and their African, Asian, South American, and Caribbean counterparts and will bring much needed resources to these regions.

These clinical trials networks are getting ready to apply for funding, or "re-compete," for their next five-to-seven year cycle of federal support. Bureaucrats at the Division of AIDS are now furiously crafting a Request for Application (RFA) to guide those applying for the $400+ million in AIDS clinical research funding. The networks have been in existence for well over a decade and the scientists who lead them inhabit key positions in the world of AIDS research. Despite earnest invocations of partnership, the same group of U.S.-based researchers that has been in charge of clinical research on AIDS for many, many years will still be pulling the strings as their studies move to the global South (and they will not share or relinquish control easily).

While this stands as a moral outrage, it is a scientific one as well. There are key questions that need to be answered about treating HIV in the developing world concerning how to best use antiretroviral therapy in these settings, the impact of co-infections like tuberculosis and malaria, and best ways to deliver treatment where little health care infrastructure exists. All of these questions and the trials needed to answer them are far from the kind of high-tech, university-based studies that have been the focus of the American clinical research establishment. In fact, the researchers best positioned to develop a clinical research agenda for the developing world are those working there now.

The re-competition of the NIH's clinical trials networks is set to establish a new colonialism in AIDS research that is as unilateral as the administration's foreign policy. After cries of outrage from treatment activists, the Office of AIDS Research at NIH and its director Dr. Jack Whitescarver responded by bringing in a set of outside experts to draft some principles to guide their efforts. Initial drafts of these principles look promising, but the real problem lies at the Division of AIDS at the National Institute of Allergy and Infectious Diseases (NIAID) where deep parochialism, arrogance and lack of vision threaten to squander a precious opportunity to revamp this huge clinical research system.

So what is to be done? First, whether it wants to or not, DAIDS needs to ensure that researchers from the developing world have control over the scientific agenda of studies to be conducted in their countries. It simply isn't good enough to have "representation" from the developing world on decision-making committees of the major clinical trials networks—this is tokenism. Protocol design, administration and evaluation for studies conducted in the developing world can and should be conducted in the developing world—there is no reason it has to happen in Denver, Seattle, Baltimore or Bethesda.

Second, DAIDS should sequester a quarter or more of its annual clinical research budget for non-network-supported studies with a rapid review process. This would allow outside groups to apply for support to answer critical questions that the networks will not or cannot address. Indeed, there are some kinds of studies, particularly the operational research that will be vital to shaping the AIDS treatment programs of many developing countries, which standing networks are poorly suited to perform. This would also allow smaller, key studies to be performed without the onerous delays in protocol implementation that the existing networks are notorious for.

Third, DAIDS needs to ensure strong, external oversight of its clinical trials networks. The NIH Office of AIDS Research should be entrusted to establish an AIDS Clinical Research Advisory Group made up of leading researchers unaffiliated with funded networks and with strong representation from developing countries to provide guidance to the networks on a regular basis.

Clinical research on HIV/AIDS is one of the key engines for improving the treatment and prevention of HIV infection—the way it is conducted, by whom and what is studied have tremendous implications for the millions of us living with HIV/AIDS and those at risk. There are some momentous choices to be made in Bethesda this summer. Perhaps the leaders at the Division of AIDS will finally wake up to the enormous responsibility they now hold in their hands.