GMHC treatment ISSUES

NEWSLETTER OF CURRENT ISSUES IN HIV/AIDS

MAY 2003 VOLUME 17, NUMBER 5

Showdown at the X4 Corral

By Bob Huff

For most people, HIV infection, if not treated, causes a long, slow decline in immune capacity to a point when they become susceptible to dangerous opportunistic infections. In some, this decline can happen within a few years; for a few, it hasn't happened yet after 20 years. In the pre-treatment era, the average time for progression to death was about 11 years. Nowadays, this can be delayed by successful suppressive antiretroviral drug therapy, although, again, some people have terrific, trouble-free results while others never manage to get the full benefits of treatment.

This variability in the course of HIV disease and in the success of treatment can be due to a number of complex, intertwining factors. An individual's genetics may come into play: a small number of people lack crucial receptors that HIV uses to infect new cells and there are surely many more host factors involved that we don't know enough about. Different viral genetics can make a huge difference: a flawed HIV protein called Nef makes for a much less virulent virus, while infection with drug-resistant HIV bodes poorly for the success of therapy. The effectiveness of treatment can obviously guide the impact that HIV has and treatment efficacy is influenced by both host and viral genetics as well as personal and cultural factors.

The virus you start out with may not be the virus that causes trouble down the line.

But the virus one starts out with may not be the virus that causes trouble down the line. Early in the epidemic scientists recognized that HIV has two faces: one attacks a limited set of immune cells slowly and steadily, wearing down defenses over time. This form of the virus gives AIDS its reputation as a slow but relentless killer. But another form of the virus, one that eventually develops in about half of those with HIV, shifts the disease into high gear as it begins taking out T cells aggressively, causing rapid immune cell loss that can quickly plunge a person into a dangerous state of AIDS.

The differences between the two forms of HIV have been traced to a few simple mutations on one of the virus' outer envelope proteins responsible for latching on to new target cells. Most of the mutations occur in a region called the V3 loop of the gp120 protein. When HIV first attaches to a potential target cell, the gp120 protein hooks up with the cell's CD4 molecule, which is the main cellular receptor for infection. But attachment is not enough; the gp120 also needs to plug into a co-receptor molecule on the cell that helps pull the virus into contact with the cell's surface so the two can merge. In the slow form of the virus, the V3 loop of gp120 is able to connect with a cellular co-receptor called R5 (CCR5). This R5 co-receptor is found on mature T cells that have already been primed to fight infec-

tion as well as on immune system sentinels, the macrophages. The R5-using HIV may cause a slower-paced infection because it has only a limited set of target cells to infect and because it seems to replicate at only a moderate rate.

But if the V3 loop changes its chemical properties slightly, the virus starts to be able to use a different co-receptor called X4 (CXCR4). The X4 co-receptor is found primarily on immature T cells that are still being formed in the immune system's incubator, the thymus, and on newly activated T cells that have recently met their antigen. The shift to an X4-using virus speeds up T cell destruction dramatically. One study saw the rate of T cell loss increase by three. A classic sign that X4-using virus is on the loose is when infected T cells clump together to form giant cells called syncytium; X4 HIV used to be called SI type, for syncytium-inducing. But X4-using HIV is also able to kill T cells in subtle and coldly effective ways that are just being discovered.

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T cell depletion is the central problem—and central mystery—of HIV disease, and there are several contending theories to explain what's going on. The earliest explanation held that HIV infected and killed T cells directly, end of story. Then it was noted that although most T cells never become infected, they were still being removed. From the beginning, other scientists held that excess immune activation was responsible for running the T cell supply into the ground, possibly through exhaustion or self-attack. Some now think that apoptosis (programmed cell death) triggered by errant immune signaling, toxic viral byproducts or over-revved regulatory systems, is the main actor. Others argue that the T cells are simply retreating from the blood (where they are typically counted) back into hiding in lymph tissue. Most likely, several of these proposed mechanisms are overlapping and may operate at different stages of infection or under different conditions. One thing that surely heralds a change in the pace of T cell depletion is the shift from R5 to X4-using virus.

When the Shift Comes Down

The shift from R5-using to X4-using happens in stages and there are a few in-between forms of R5/X4 HIV that are able to use either co-receptor. As virulent as the X4 virus is, one of the mysteries of HIV is why newly infected people almost always carry the R5 virus exclusively. This may be because only the R5 virus is able to infect immune cells that patrol the mucous membrane frontiers where sexually transmitted HIV first takes hold. Yet even in people infected with blood-borne X4 HIV, there is a nearly immediate shift to the R5 variant in the new host. It's not clear why the R5 co-receptor is preferred at first; some have proposed an inhibitory factor, others think that macrophages are a preferred target, or it may be that R5-bearing mature T cells replicate faster and have not yet been exhausted in a healthy host. Although X4 T cells outnumber R5s, they may be outposted to tissues and less available to infection. Typically, the R5-using stage of infection can carry on for five or more years.

The reason for the shift is not clear. Some believe that the virus is trying to escape antibody attack directed at its R5-using site; others think that the virus simply starts to look for different co-receptors once the supply of mature R5-bearing T cells becomes too scarce. Once the shift begins, however, the use of X4 becomes more and more common until in a few people the body's predominant strain of HIV is using X4 exclusively. Clinically, this is bad news, for although antiretrovirals are able to suppress X4 HIV as well as its R5-using ancestor, T cell destruction now proceeds at an alarming pace. If the R5-using virus is like a sniper picking off selected target cells, the X4 virus is a weapon of mass destruction in the thymic maternity ward.

This may be one of the strongest reasons not to delay starting antiretroviral therapy too long: once the shift to X4 virus begins, it may be very difficult to recover lost immune capacity. One study found the shift often occurring in the 400–500 CD4 cell range. Another showed a greater rate of switching below 500 than above, with those in the 250-500 range switching at a rate similar to those in the 0–250 range. One day it could be common to test for co-receptor usage in the clinic; Virologic has developed a phenotypic test that classifies a virus as X4-using, R5-using, or dual type that could be available by 2004.

What is X4-Using HIV Doing in there?

A recent paper published in the *Journal of Virology* may shed some light on why the X4 strain is so destructive. Most of what we know about HIV comes from experiments conducted under laboratory conditions using cell systems and special viral strains that have been adapted to live and reproduce under artificial conditions. There is a limit to what these systems can say about a disease process that affects the complex interactions of immunity in living beings. This is why Andreas Jekle and colleagues from the Gladstone Institute of Virology and Immunology in San Francisco decided to use a model of infection that preserves much of the ecology of the T cell's environment, including a mix of cells at all

stages of maturity carrying either the R5 or X4 receptors, or both.

They began with lymphoid tissue harvested from children's tonsil operations then infected the tissue with various strains of X4-, R5- and mixed X4/R5-using HIV. They were particularly interested in looking for evidence of cell destruction caused by *apoptosis*, a natural mechanism of cell death than can be triggered by a number of internal or external factors. It had been recognized in the mid 1990s that apoptosis was a contributing factor in T cell depletion. Furthermore, it was noted that not only infected cells but also uninfected "bystander" cells were somehow receiving signals to activate their self-destruct mechanisms.

Jekle and colleagues began by looking for a few characteristic markers that appear whenever apoptosis has been activated. One of the first things they noticed was that signs of apoptosis were far more common among cells that were dosed with the X4- and dual X4/R5-using strains than among cells infected with R5-using HIV. Soon after apoptosis markers began to appear in the X4-infected system they noted that a large number of CD4 T cells were being depleted. Meanwhile, the R5-infected batch of cells only became slightly depleted. Although some studies have shown that CD8 cells were depleted in the presence of X4 HIV, in this study CD8 T cells were not depleted by either type of virus.

They then looked at how many cells had actually become infected with HIV. With the R5-using virus, the number of infected cells was low, and apoptosis levels, as was seen before, were also low. With the X4-using virus, the number of infected cells was similar to that of the R5 virus, but, as seen earlier, the number of cells with apoptosis markers was very high. It seems that the X4-using virus was able to stimulate cell death without directly infecting the cells. This phenomenon is called bystander apoptosis and in a number of other experiments it was shown that X4-associated apoptosis did not depend on establishing a productive infection, and that X4, but not R5, viral strains could induce widespread apoptosis in bystander CD4 T cells. Furthermore, the R5-using virus infected only CD4 T cells that carried R5 and produced a low level of apoptosis in these cells but caused no apoptosis in cells that lacked R5. In contrast, X4-using virus caused extensive apoptosis, predominantly in uninfected bystander cells, including some that also carried R5.

Since the only difference between the X4-using virus and the R5-using virus was a few changes in the V3 loop of the envelope protein, the investigators theorized that the interaction of the viral envelope with the cellular co-receptor was likely responsible for setting off apoptosis. They tested this by adding drugs that block X4-using virus from binding to the X4 receptor on T cells. They found that blocking X4 effectively protected the cells from bystander killing by X4 viruses. Treatment with an R5 blocker did not protect the cells. The authors concluded that binding of the gp120 viral envelope protein of an X4-using virus to the cellular X4 co-receptor was the trigger for bystander apoptosis in their tissue culture system. But is this true in living bodies as well?

In this experiment, a small number of X4 virus particles were able to deplete a large proportion of CD4 T cells—even when pre-treated by the reverse transcriptase inhibitor AZT. While AZT could prevent cells from becoming infected, it could not prevent apoptosis triggered by exposure to gp120. If this finding is also true in people, then the rapid drop in T-cells seen after the switch to an X4-using virus may be primarily due to the killing of bystander cells that never actually become infected. This may explain why some studies found that viral load does not soar when CD4 counts drop soon after the switch.

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Finally, since the immature T cells that are depleted by bystander apoptosis are the precursors to the mature cells, attacking X4-bearing cells may be shutting off the supply of T cells at its source. This could be another reason why only modest rates of T cell decline are seen during chronic infection with R5 virus, and why T cell depletion speeds up so much once the shift from R5 to X4 occurs. However, the authors caution, while the gp120 interaction with X4 seems to be necessary to induce apoptosis, there may still be other unknown factors that contribute to this effect. It is also not yet known if the gp120 must be bound to an intact virus for it to trigger apoptosis or if freely floating particles have the same effect.

"Pop" Stoppers

If blocking the binding of gp120 to a cell's X4 co-receptor can stop bystander apoptosis and the resulting rapid CD4 T cell depletion that occurs for some during the dangerous later stages of HIV disease, then X4 binding inhibitors could be a valuable form of salvage therapy for tens of thousands of people with AIDS. So what do we know about drugs that block X4?

A number of R5 binding inhibitors are being developed as HIV therapy. The R5 receptor is an attractive target because R5-using HIV is the pre-

dominant strain in life and has such a long, slow course of infection. Also, because some people are born without R5 receptors (a genetic anomaly that occurs in about 1% of Caucasians) and because rats modified to lack R5 suffer no overt ill effects, it's hoped that blocking R5 won't have toxic consequences. Effective blocking of R5-mediated infection, some believe, could preclude the need for having to ever deal with an X4-using strain. Yet there's been a great deal of concern that blocking R5 binding would push the virus to start using the X4 receptor, although that has not been borne out in laboratory studies. Still, that possibility makes the need for an X4 blocker even more important.

One of the drugs that Jekle and colleagues used in their experiment to show that blocking X4 stopped bystander apoptosis is called AMD3100. The drug had been recognized as an HIV entry inhibitor even before the R5 and X4 co-receptors were discovered in 1996. By 2000, several studies had shown that AMD3100 could not only block infection by X4-using HIV but could also arrest HIV-associated apoptosis. AMD3100 was explored in phase I clinical trials with HIV-infected people where it apparently showed limited activity against HIV. Unfortunately, heart rhythm abnormalities were detected in several patients and development of AMD3100 for HIV therapy was halted in 2001. The drug's sponsor, Anormed, of British Columbia, Canada, is now developing a new, orally available compound called AMD070 that is active in the laboratory against X4-using HIV. Human testing of AMD070 should begin this year.

One of the potential problems with blocking X4 is that it may perform some essential jobs in the body that shouldn't be messed with.

One of the potential problems with blocking X4 is that, unlike R5, it may perform some essential jobs in the body that shouldn't be messed with. It is also found on a greater variety of cell types than just immune cells. While mice born without R5 do okay, mice with the X4 gene deleted can't survive. And although AMD3100 has been scrapped for treating HIV, it has other kinds of biologic activity and is still under investigation for inhibiting cancers and accelerating recovery after heart attack—all of which suggests that indiscriminately blocking X4 may have unintended consequences. Finding highly specific medicinal molecules that block HIV co-receptor function without stepping on the toes of any of the receptor's natural tasks is the goal.

New Ideas, New Tools

The other type of X4 blocker used in the Jekle study was a monoclonal antibody that attached to the receptor and blocked access by gp120. One speculative idea is that perhaps a vaccine could induce the body to make its own anti-X4 antibodies, thus using the immune system to supply the therapeutic molecules.

A recent experiment has reported that "gene silencing" through RNA interference was able to suppress expression of the cell's X4 gene and block infection by X4 strains. This new technique gives a powerful tool for understanding the role these receptors play in the immune system and they may one day offer an approach to therapy. Another study observed that the viral protein Tat caused cells to display more CXCR4 receptors on their surfaces, possibly making them more susceptible to X4 virus. If this is significant, then perhaps a Tat inhibitor could be synergistic with an X4 blocker by reducing the number of X4 targets on a cell's surface. Another therapeutic avenue might be to stimulate the molecules that bind to R5 and X4 receptors in nature. These chemical messengers, called chemokines, send signals that also decrease the expression of the receptors on cells.

Resistance is Always with Us

One issue with co-receptor blockers—as with every other HIV drug—concerns the near certainty that viral resistance will develop after a while—and resistance to AMD3100 has already been shown to develop in laboratory experiments. When the drug was used against an exclusively X4-using virus, gp120 accumulated mutations that allowed it to use X4 in spite of the drug. But there are also suggestions that the mutations that allow escape from the drug also make the virus less fit and less pathogenic. In one experiment, all of the X4 isolates that evolved resistance to AMD3100 after serial passage in cell culture exhibited reduced fitness compared to wild type. In a clinical trial of AMD3100 in patients with dual X4/R5 HIV the virus simply switched over to using R5. Since all previous strains of HIV are likely to persist in viral reservoirs, blocking an evolved X4-using virus would probably tend to cause an earlier R5-using strain to eventually re-emerge. While not a perfect solution, having an active R5 strain may be better than the alternative.

Receptor blocking is still in its infancy, although several R5 blockers are moving forward in clinical trials. While resistance may be a problem, it may also provide an opportunity. One therapeutic strategy that is likely to come into greater use may be called "guided resistance," which seeks to back HIV into a corner of diminished fitness and destructive potential. Indeed this is already the only strategy left for many people with multi-drug resistant virus

who find that a failing regimen, if tolerable, is far better than no regimen at all. Since the virus appears impossible to eradicate, maybe shutting off one of its more destructive aspects, such as the shift to X4 type, can help to keep expanding the possibilities for living with HIV.

Until then, entry inhibitors will continue to have an important role to play in helping scientists understand the basic science of HIV pathogenesis and T cell depletion. It may be a race to see which avenue first benefits the greatest number of people: another new drug to suppress HIV or a new understanding that unlocks the secret to something much better.

Jekle A, et al., In Vivo Evolution of Human Immunodeficiency Virus Type 1 toward Increased Pathogenicity through CXCR4-Mediated Killing of Uninfected CD4 T Cells. J Virol, May 2003, p. 5846

Nevirapine-Based Fixed-Dose Combination ARVs

By Julian Meldrum
Wth commentary by Dr. Vijay Anthony Prabhu and Dr. Desmond Martin
Excerpted from HIV & AIDS Treatment in Practice (HATIP) #2

HATIP is a biweekly email newsletter intended for providers in resource-limited settings. For the full version of this article or to subscribe, visit: www.aidsmap.com

Advisory panel members include Dr. Vijay Anthony Prabhu (Chennai, India), and Desmond Martin (President, Southern Africa HIV Clinicians Society).

Fixed-dose combination antiretrovirals (FDC ARVs) are products that combine two or more active drugs in one tablet or capsule. In many countries, they now offer the cheapest available route to a complete and effective ARV regimen. There are many potential advantages of using FDCs. The most obvious are the simplification of what is supplied to and taken by individual patients and reduced potential for inappropriate sharing of drugs.

In a managed healthcare system where costs are shared, as is planned in Thailand, these drugs can free up resources to provide more expensive second- and third-line treatment options to those who need them, which is a universal benefit. Standardization of first-line regimens carries further potential benefits, including the development of simple education packages for healthcare workers and community members and possible economies of scale in laboratory monitoring tests.

Limitations at present include the lack of pediatric equivalents, inadequate provision for lead-in dosing and a number of other shortcomings concerning availability, packaging and provision for reporting adverse events.

This may be the right way to go for large-scale treatment programs, but there is still a distance to be traveled before the products are fully suited to that purpose.

Quality Issues and Availability

WHO's Essential Drugs and Medicines team has established a project to document the procedures and certification of generic facilities used to produce medicines for HIV and AIDS treatment that are not registered with the U.S. Food and Drug Administration (FDA) or European drug regulatory agencies recognized by the European Medicines Evaluation Agency (EMEA).

The Global Fund to fight AIDS, TB and Malaria has signaled that they will rely on this WHO list as a basis for approving the purchase of generic ARVs and other medicines, so the inclusion of products and of their makers on the list may have an increasing influence on their availability.

The Indian companies Cipla and Ranbaxy already have ARVs on the list; Hetero and Aurobindo products are being assessed. However, most of the products named are not listed by WHO. Ranbaxy's AZT/3TC is the one exception.

The Thai Government Pharmaceutical Organization makes drugs primarily for domestic use, with a high level of attention to quality control. It is supplying them in limited quantities to Cambodia, Sri Lanka and Laos, and has recently agreed to supply them to Indonesia. It is also supporting a number of African countries in establishing local manufacturing. Argentina, Brazil, China, Mexico and Vietnam are producing generic antiretrovirals, but with the exception of some AZT/3TC, these do not seem to include fixed dose combination products of the kind discussed here.

Affordability

Whatever the drug combination used, its success for an individual patient will depend on the ability of that person to take it consistently as prescribed.

Where patients are paying for their own treatment as in Kampala, inability to maintain those payments has emerged as the main reason for breaks in treatment, as reported at the 10th Retrovirus Conference in Boston by Byahihi-Tusiime. While the treatments discussed here are priced as low as $35 a month, they are still a long way from being affordable by most people with HIV. In Uganda, Molly Tumusiime reports there have been times when people went short of food to pay for ARVs, or missed out on ARVs to pay for monitoring tests. This is a powerful case for subsidizing treatment to make it genuinely affordable, as has been done in Senegal's pioneering treatment access program (described in Boston by Dr. Salif Sow)—and as is planned in Thailand.

Failing that, the strategy reported by YRG-CARE in India, of careful and thorough discussion with patients of their financial circumstances before starting on treatment may be helpful to some. However, this is a difficult role for hard-pressed clinical staff to assume. There has to be a limit to the clinic's responsibility, to ensure that the patient understands what treatment they need and how much it costs, and is able to access any support or discounts that may be available to them. Beyond that, it must be a decision for the patient themselves and their family.

Dr. Prabhu: ARV therapy has come a long way in India. The financial burden has steadily decreased and remains at around $35 per month for fixed-dose combination triple ARV therapy. The pricing of these potent drugs has received widespread publicity. Generic pharma companies proclaimed their social consciousness and responsibility by introducing these fixed-dose ARV drugs at lower prices. But in spite of intense pressure from different groups – positive patient networks, activists and others – these companies have not reduced prices any further, for a variety of reasons. The government does not help matters and continues to impose a sales tax on these drugs.

When patients are paying for their own treatment, I would agree with the Boston report from Kampala, that the main reason for breaks in treatment is the inability to maintain payments for ARV drugs even at low prices. AIDS and poverty go together. There is definitely a need for subsidizing treatment to make it genuinely affordable.

Fixed-Dose Products Now Available

AZT 300mg + 3TC 150mg + NVP 200mg
DUOVIR-N (Cipla Ltd)
ZIDOVEX-L-N (Imunus Aurobindo)

For lead-in dosing (or if NVP must be stopped):
AZT 300mg + 3TC 150mg—use separate drugs, or:
COMBIVIR (GlaxoSmithKline)
DUOVIR (Cipla Ltd)
VIROCOMB (Ranbaxy Laboratories Ltd)
ZIDOLAM (Genix Pharma/Hetero)

d4T 30mg + 3TC 150mg + NVP 200mg
GPO-VIR S 30 (Thai Government Pharmaceutical Organization)
STAVEX-30 LN (Imunus Aurobindo)
TRIOMUNE-30 (Cipla Ltd)
VIROLANS [capsules, d4T 30mg version] (Ranbaxy Laboratories Ltd)

For lead-in dosing (or if NVP must be stopped):
d4T 30mg + 3TC 150mg—use separate drugs, or:
LAMISTAR 30 (Genix Pharma/Hetero)
LAMIVIR-S-30 (Cipla Ltd)
VIROLIS [capsules, d4T 30mg version] (Ranbaxy Laboratories Ltd)

d4T 40mg + 3TC 150mg + NVP 200mg
GPO-VIR S 40 (Thai Government Pharmaceutical Organization)
TRIOMUNE-40 (Cipla Ltd)
VIROLANS [capsules, d4T 40mg version] (Ranbaxy Laboratories Ltd)

For lead-in dosing (or if NVP must be stopped):
d4T 40mg + 3TC 150mg—use separate drugs, or:
LAMISTAR 40 (Genix Pharma/Hetero)
LAMIVIR-S-40 (Cipla Ltd)
VIROLIS [capsule, d4T 40mg version] (Ranbaxy Laboratories Ltd)

All of the medicines listed above are taken as one tablet, twice daily (12 hour intervals), with or without food.

Availability

Dr. Prabhu: ARV fixed-dose drug combinations are available in major metropolitan cities and towns in India. Since only a handful of pharma shops dispense these ARV drugs, it is sometimes difficult to find out where they are or who dispenses them. Patients in the rural areas have to travel long distances to the neighboring big towns or cities, spending huge amounts of money, just to gain access to their drugs. Often the pharma shops run out of stocks especially at the end of the month or stock only certain brands and not others, not offering the entire range to the patients.

Dosing Schedules

Ideally, the only choices that should need to be made with these regimens are whether to start with AZT or d4T, and if it is d4T then to

choose a dosage (40mg or 30mg) on the basis of body weight (greater or less than 60kg). Unfortunately, it is not quite that simple in practice.

Lead-in Dosing: Starter Packs Needed

When nevirapine (NVP) is first started, it should be administered at half dose for the first 14 days, i.e. 200mg once a day instead of twice daily. However, the other drugs in the combination should be administered at full strength. It is clear that this often doesn't happen as it should.

As described by Dr. Martin, below, some patients are still starting on full-dose NVP, risking avoidable NVP reactions. Others have been started on one triple combination tablet a day, so the nucleoside analogues are under-dosed, risking selection for drug-resistant HIV. Hosseinipour reported in Boston that this was done in Malawi, when Triomune first became available in Lilongwe and Blantyre. Studies are now under way to find out whether this led to any avoidable drug resistance. Other patients are prescribed separate drugs for the initial period of treatment. However, as Dr. Prabhu explains, there can be serious problems with this, because the quantities in which the drugs are sold are not matched to how they are meant to be taken.

There is an obvious solution to all of these problems: combining two different fixed dose combinations (with and without NVP) in a blister pack, marketed as a "starter pack." Symbols on a 7-day, 14-dose blister pack could make it clear which tablet/capsule is the morning dose and which is the evening dose. This should be reinforced by clear written instructions in local languages. 7-day packs would also reinforce the point that the drugs must be taken daily (including at weekends) and make them convenient to carry. If patients have to pay for them, they should cost exactly the same as the triple combination drugs so there is no incentive to continue with the starter doses for longer than two weeks.

Dr. Martin: It is our experience (in southern Africa) that with Triomune, patients begin on the higher dose from Day 1. It appears that dose escalation is just too much bother for the physicians to explain and the cost of buying the separate drugs is not something they feel able to inflict on their patients.

Dr. Prabhu: The lead-in or build-up dosing schedule of NVP in combination with d4T/3TC or AZT/3TC is confusing for some patients. NVP is available separately in a container of 60 tablets, which with the lead-in dosage schedule leads to a wastage of about 15 tablets in the initial pill box. Patients do not seem to understand this and continue to consume NVP alone even when the LAMIVIR 30 mg pill box [which also contains 60 tablets] is empty at the end of the month. They feel they must finish both boxes before starting on the next and end up taking NVP alone [which carries a high risk of selecting NVP-resistant HIV], even after any amount of explanation! The patients end up paying hard-earned money for NVP that they cannot and should not use.

Other Packaging Issues

Dr. Prabhu: Certain patients who live far away [from where treatments are available] access their drugs through mail or courier. But on arrival at their home, the tablets are in powder form! These tablets are not packed for long journeys. Pill box covers are very loose and fall off at the earliest opportunity, making it very difficult to identify the drugs the patients are on, especially since doctors who prescribe these drugs do so in secret with no written prescriptions in the patients hands and no means of identification on the tablets themselves. Certain companies package their ARV drugs with a red AIDS logo boldly embossed on the packaging material, which patients find difficult to use, especially when they are traveling in public.

AIDS and poverty go together. There is definitely a need for subsidizing treatment to make it genuinely affordable.

Supporting Adherence

No matter how simple the treatment, it is still vital to spend time making sure that the patient understands how the treatment works.

Dr. Martin: It has been my experience that, provided adequate counseling is given prior to the commencement of ARVs, adherence to the regimens is remarkably good. This is often in the face of difficult work circumstances related to shift-work but the patients have been very innovative in developing strategies to remember their drugs. Clearly simplified dosage forms are preferable (twice-daily). Our experience has shown that the use of "the buddy system" has been the most effective. I think that in our populations where HIV is a rampant epidemic the patients who are able to access antiretrovirals do so with a commitment that will lead to impressive compliance. Peer counselors who themselves have had a turnaround in their disease can be very helpful.

Managing Nevirapine Skin Rash

The main risk associated with NVP, especially in the early stages of treatment, is a skin rash which in its most severe form (Stevens-Johnson syndrome) can be life threatening. Liver toxicity is also of concern and requires prompt action if detected.

If a rash develops, patients need to be advised to return to the clinic to evaluate it. If the rash is mild, then it may be best to try and treat through, so long as patients understand the need to return if the rash gets any worse. Treatment with corticosteroids does not help (in fact it may make it worse). If a rash is severe, or getting worse, then NVP must be stopped. Ideally, the nucleoside analogues should be continued for another week to try and prevent the emergence of virus with resistance mutations to NVP—so the possibility of using efavirenz (which is vulnerable to the same mutations) is kept open for the future. Liver toxicity is also a serious risk with NVP and monitoring for this is a key responsibility for prescribers.

The major reason why NNRTIs such as nevirapine are preferred to protease inhibitors for first line treatment is that they are more easily tolerated.

Dr. Prabhu: NVP skin rash is common, usually mild to moderate. Especially when it affects women and girls, much desperation sets in. The patients may already be suffering from HIV-related pruritic papular dermatitis from which they are seeking relief. Usually with the advent of ARV drugs, their rashes come under control, which can be a good indicator of the success of treatment. But if such a patient develops a NVP-associated skin rash, it becomes exceedingly difficult to distinguish failure of therapy from adverse drug reaction. Serial CD4 counts and HIV RNA viral loads are a luxury few patients can afford. Liver Function Tests might shed light on the subject by showing elevation of transaminases. Finally it boils down to a clinical decision taken on the table, to stop NVP or persist with it and manage the skin rash symptomatically. If the general condition of the patient continues to deteriorate, then it is obvious that ARV drugs are not working and NVP must be stopped and alternatives chosen. A risk versus benefit analysis, and knowledge of any prior ARV use, should guide the decision-making process.

Dr. Martin: Information regarding toxicities involving the liver, skin rashes or Stevens-Johnson Syndrome are lacking: while patients are warned, there is no proper system for reporting adverse events for these unlicensed products. Because these patients have limited financial means laboratory monitoring (liver enzymes) is not carried out in the vast majority of cases.

Downsides to Simplified Treatment?

The idea that HIV treatment can be reduced to one tablet, twice daily, is powerfully attractive to physicians as well as their patients. One risk is that "familiarity breeds contempt."

Dr. Prabhu: Generic pharma companies are as keen as any other to motivate and induce doctors to prescribe their drugs. "Prescriptions, doctor, for our product," "cheap and best," "reminders" are some of their slogans we hear day in and out. With all this pressure from pharma companies, and from patients who are desperate, it is very easy and simple to prescribe, but it needs more than strong will power, at times, to take a balanced decision not to prescribe.

I am no longer surprised to come across prescriptions for these drugs for a short duration of time, sometimes as short as a week's duration, as though we are treating a common cold! Sadly, the concept that, where HIV is concerned, therapy is life long is missing amongst a vast majority of general practitioners [in India]. So if one combination does not work, they just change to the other—very simple—with the result that we are soon back to where we started.

Dr. Martin: A source of concern is that the widespread and often sub-optimal use of regimens containing nevirapine will lead to resistance to the nevirapine component and compromise mother-to-child nevirapine-based transmission interruption programs.

How Effective are these Combinations?

The major reason why NNRTIs such as nevirapine are preferred to protease inhibitors for first-line treatment is that they are more easily tolerated (despite carrying risks, of which patients and providers must be aware). Superior virologic performance has also been reported, almost certainly because these combinations are less dependent than the protease inhibitors indinavir and nelfinavir, in particular, on taking treatment correctly in relation to meals.

One limitation is that NNRTIs are not effective against HIV-2 or HIV-1 group O viruses, so if these are present a protease-inhibitor based combination is likely to be needed.

A randomized trial that compared NVP, efavirenz, and a combination of the two drugs (the 2NN study, funded by nevirapine's maker, Boehringer Ingelheim), was reported at the Boston Retrovirus Conference. It found that NVP and efavirenz gave comparable results in terms of viral suppression. However, there were two deaths (from liver failure) among people treated with nevirapine, which reinforces the need for care in its use.

Following a series of trials which have shown efavirenz to be comparable or superior to protease inhibitors, these reports are important for providers to have confidence that the fixed-dose combinations now on offer can be as effective as more costly treatment options. There is also some data on the equivalence of various NVP

formulations, including generic ones. So far, this is reassuring.

Stavudine (d4T) vs. Zidovudine (AZT)

There is a groundswell of medical opinion, in countries where people with HIV usually start medical treatment at CD4 counts above 200, against using d4T as a first-line therapy. The prevalence of neuropathy and a (still-controversial) association between d4T and loss of fat (especially on the face) have relegated the drug to second choice for many. There is clearly a strong case not to prescribe higher doses of d4T than are needed. If a patient weighs less than 60 kg, the 30mg dose of d4T should be prescribed.

In settings where anemia is widespread (and closely correlates with mortality risk) and patients usually begin treatment at very low CD4 counts, the actual risks are different and it may not be unreasonable for doctors to prefer d4T as their first-line treatment.

The reason why more combinations have been launched based on d4T rather than AZT, is that the higher potency of d4T, by weight, makes it cheaper (per dose) than AZT. At a retail level, this translates to a difference of around $5 per month ($35 vs. $40), which clearly makes treatment more sustainable where patients pay for it.

Lipoatrophy has been seen in Thailand and India, and must be presumed to affect Asian populations as it does Caucasians/Europeans. There is some evidence from both longitudinal and cross-sectional studies that lipoatrophy is more frequent among Caucasians than among people of African descent. So the extent to which it will occur among African populations is still unclear. But for those who suffer from it, the implications will be much the same everywhere.

Dr. Prabhu: AZT is used by a large number of practitioners, though patient tolerance of AZT is low. Complaints of myalgia and headache are common, but what is worrying is development of severe anemia, for which blood transfusions are used enthusiastically with all the attendant risks. Management of ARV drug toxicity is difficult. When HIV is already far advanced and when clinical anemia is obvious, then d4T is the preferred drug. Peripheral neuropathy is painful and slow to respond. Cessation of d4T is sometimes the option chosen, but because of other limited options, dose reduction is attempted to see if it responds.

Dr. Martin: Scant attention is paid [in Southern Africa] to differing dosage forms for Triomune so that a number of patients are overdosed with the 40mg d4T dosage form and the risk of drug-induced neuropathy is increased; d4T-containing fixed-dose regimens used in the presence of treatment for tuberculosis will lead to increased occurrence of neuropathy.

Pediatric Dosing

Best practice in pediatric treatment relies on liquid suspensions, of which a limited range are available, often only in branded versions, at very high prices. For example, in Uganda, no generic suspensions are available, observes Dr. Henry Barigye. Even in India, there is no suspension available for d4T. Yet many babies and young children are anemic and have problems tolerating AZT.

Professor Norman Nyazema, a pharmacologist who has served as a senior technical advisor to the Medicines Control Agency of Zimbabwe, insists there can be no short cuts. Splitting tablets is unacceptable as a basis for licensing a drug for use in pediatric treatment, and if doctors use a drug beyond its license, the manufacturer cannot be held liable for the consequences. Companies that claim they are meeting public health needs by providing low-cost generic formulations must be pressed to provide a full range, including suspensions for pediatric use.

Companies that claim they are meeting public health needs by providing low-cost generic formulations must be pressed to provide a full range, including suspensions for pediatric use.

Dr. Prabhu: The lack of choice in pediatric formulations is particularly worrying, since with the increasing number of MTCT interventions that are taking place, more pediatric AIDS cases are being diagnosed. Only AZT, 3TC and NVP suspensions are available. Anemia, which is so common in children, makes it difficult at times to persist with AZT. d4T is chosen, but with lack of availability of pediatric formulations, adult tablets are split to provide for pediatric doses. This is not good practice, but in the absence of alternatives, we are left with no choice!

Short Course—Notes on HIV Drugs in Development

Raz-ma-TAZ

On May 13, 2003, an FDA advisory committee met outside of Washington, D.C. to consider the approval of a new protease inhibitor, atazanavir (ATV). The drug was mostly well received by the committee; efficacy in treatment naive patients was applauded and a recommendation for approval voted unanimously. The sponsor, Bristol-Myers Squibb (BMS), was congratulated by the FDA for testing the drug in diverse treatment populations and against formidable comparators.

But data for treating treatment-experienced patients was wanting. Although BMS put up slides about 24-week safety and efficacy of ritonavir (RTV) boosted ATV in treatment-experienced patients, the FDA hadn't enough time to review the data, and so it was not officially presented to the committee. Yet, there it was. So, while unboosted ATV was clearly inferior to Kaletra, no one can really say yet if boosting ATV with RTV fixes the problem—although many were inclined to believe that it does. There's a bit of mystery here, and I think that suits BMS just fine.

The lipid-neutral qualities of ATV are nothing short of amazing compared to others in the PI class, and this will drive acceptance by physicians. There is a danger of the drug being oversold as a remedy for lipodystrophy if BMS is willing to allow confusion between lipids and lipoatrophy to settle in — there's no proven link. Again, the lipid profile of ATV boosted with ritonavir was left in the shadows.

The unique resistance profile in treatment naive people is the icing on the cake. There's a lot more to learn about ATV resistance, but so far it's surprisingly good news. Hints of PI hypersusceptability after the I50L mutation emerges are the sprinkles on the icing. However, for people with prior PI mutations, none of this applies; they have their own pathway that leads to PI cross-resistance.

The concern over high bilirubin levels that caused reversible jaundice in a large proportion of trial participants is quieting down; expert consensus says it's not a problem in itself. But this drug is going to give quite a few people yellow eyeballs. Patient acceptance will be key.

Atazanavir also has a new brand name: Reyataz. Apparently someone thought this is better than Zrivada, the name that BMS had previously announced. A lot of people already call it "Taz" so the new name was probably selected to take advantage of that. More details from the hearing in the next issue.

Tipranavir Urgent Access

The Tipranavir (TPV) phase III clinical trial called RESIST 1 is in the process of opening at 31 sites in the U.S. for individuals with multi-drug resistant HIV. In addition, a small safety study has opened to provide access for people needing TPV who are not eligible for the large trial or who do not live near a city where the trial is being conducted. Unfortunately, due to drug supply problems, only 140 individuals will be accepted into the safety study, which has entry criteria of CD4 count below 50 and HIV RNA above 10,000 copies. Applicants who are eligible for RESIST 1 and live within 100 miles of a trial site will be excluded from the safety study. Patients on the safety study will be assessed monthly for tolerability and toxicity by the same criteria used in RESIST. Tipranavir is taken with 200mg ritonavir to boost blood levels of TPV. The safety study will only supply tipranavir; participants must obtain ritonavir from their treating physician.

A larger expanded access program that may be able to provide tipranavir for several thousand patients is planned for early 2004 if all proceeds well with the Phase III trials. Approval could possibly come by early 2005.

Patients who have access to Fuzeon (T-20) are eligible for RESIST and will be randomized separately to assure their even distribution within the trial, however patients may not add T-20 after beginning their RESIST regimen.

Alphaville

Schering has pulled a switch in their CCR5 entry inhibitor development program. SCH-C, which had been slowed by a concern with QT heart rhythm prolongation problems, has been shuffled back to let SCH-D take the fast track. Schering had downplayed the heart issue in meetings with community members, but much skepticism remained. SCH-D is a different molecule with much better activity in laboratory studies and, so far, no safety issues. Phase I trials are in progress. Recent reports indicate that only 1/10th the amount of SCH-D had similar activity to a given amount of SCH-C. Like every other HIV drug, however, resistance to SCH-D has been produced in lab tests. The switch is a disappointment because it pushes back Schering's entry inhibitor program by at least a year, but so far the new candidate seems to have a more realistic chance of achieving approval.

X4 Take 2

Anormed has filed an investigational new drug (IND) application with the FDA for its CXCR4 entry inhibitor, AMD-070. A previous Anormed compound, AMD3100, was dropped in 2001 after heart rhythm problems appeared during its first human trials. AMD-070 is a completely new drug with high specificity for CXCR4. In lab studies it effectively blocked HIV infection of X4-bearing cells by both X4 and dual X4/R5-using HIV. The drug is orally available and had a 10-hour half-life in dogs. First human study should begin this year.

Gilead's Viread International Access Program

By Bob Huff

Last December Gilead Sciences announced a plan to make their nucleotide reverse transcriptase inhibitor Viread (tenofovir) available to clinics and treatment programs in the developing world at an affordable price. Joe Steele, the architect of Gilead's plan, recently answered questions about the logistics and motivation for the program.

Gilead, Steele says, recognized the potential need for tenofovir beyond the U.S. because its dosing, safety and low-maintenance qualities were likely to be attractive to providers in limited resource settings. Wishing to avoid delay, they decided to launch a proactive access plan in anticipation of the need.

Initially, the Gilead program will address Africa, the less-developed countries (LDC), Latin America, Russia and Eastern Europe. The program was designed by Axios International, a technical assistance consultant specializing in healthcare issues for the developing world that had set up similar programs for Abbott and Boehringer Engelheim. But Gilead sought to design a program that could skirt some of the problems that have limited the impact of earlier programs.

The price for Viread through the program is $39 per bottle, roughly 10 percent of the U.S. wholesale price of $360 per bottle. The price does not include shipping, since purchasers may require flexibility in how they receive the drugs.

The cost of the drug has been set as the cost of goods plus the cost of administering the program. The mandate was to sell the drug for as low a price as possible with no expectation of making money. At this price, Gilead expects to lose money until 2006 or 2007, depending on how quickly volume sales develop, when prices will likely drop. With new money coming in from the Global Fund, the Bush initiative, and the Gates Foundation, a more rapid uptake of the program may lower prices sooner.

Recognizing that the standard commercial model of drug distribution would not apply, particularly in Africa, Gilead decided to forego traditional methods by not seeking product registration in the countries they want to serve. Instead they will sell the drug directly to NGOs, clinics and individual physicians to avoid the high mark ups taken by pharmaceutical distributors. Gilead will follow a model of named-patient sales to entities that have been vetted by Axios or a panel of regional experts that Axios has assembled. When it has been determined that a clinic is legitimate and has sufficient funding to offer a sustainable treatment program, they will be sold the drug.

The named-patient route avoids the need to gain full registration for Viread in every country where it could be useful. Clinic doctors need only to obtain an import license for their program's use. This could be as simple as demonstrating that the drug they wish to import has an approved package insert from the U.S. FDA.

After a program or clinic has been approved, and funds or a letter of credit has been received, the drug will be shipped from Gilead in San Dimas, California via DHL or a similar carrier. Reorders can be placed though the Internet.

After discussions with the FDA, Gilead decided to produce a white tablet version of Viread intended for the special program to distinguish it from the blue tablet approved in the U.S. It's hoped that this will offer some protection against diversion or re-importation of the discounted product to countries where Viread is marketed conventionally. It will be illegal to sell the white tablet in the U.S.

Who is this for?

This drug, while cheap, is not affordable to every program that would like to offer treatment. Until the large funding streams come online, the number of people receiving Viread is likely to be relatively small. Gilead has projected the need for Viread by taking an estimate of how many people in Africa need treatment currently, then estimating the rate at which people currently being treated will need a second-line or salvage regimen. Because of the cost, Viread will not be a first-line choice for many programs. Yet because the treatment situation in the next three years is so uncertain, Gilead plans to remain flexible with its plans while maintaining the overall goal of making their drug available to meet the need.

GMHC treatment ISSUES

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GMHC Treatment Issues is published twelve times yearly by GMHC, Inc.

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"Goodbye, America"

By Gregg Gonsalves

There was a joyous sing-along at a party closing the first regional meeting on AIDS activism for 17 states of the former Soviet Union, which took place in Minsk, Belarus, from May 7–10. Partially fueled by the camaraderie of working together over four days and partially by copious amounts of vodka, participants from each of the countries sang their national favorites (the Americans sang Lou Reed's, *Walk on the Wild Side*). There were two songs that all the Russian-speaking participants knew by heart: the old national anthem of the USSR and a song called "Goodbye, America." *Goodbye America* is about disillusionment with the United States and more broadly the West, in which the lure of Western culture and its forbidden fruits during the Soviet era turns out to be a mirage for contemporary Russians. "Goodbye, America—The place where I'll never ever be," goes the song, testifying to the fact that the "good life" the U.S. and the West symbolize remain out of reach for most people in the region. I couldn't help thinking that this song was an appropriate coda to a meeting that stressed the stunning lack of access to basic HIV treatments and diagnostics and the unwillingness of the West to intervene on any appropriate scale to assist these countries on the doorstep to Europe in confronting an epidemic that is exploding all around them.

The conference, "Increasing Advocacy Possibilities for the Rights of People Living with HIV/AIDS (PLWHA) in the Newly Independent States," was sponsored by the International Harm Reduction Development Program of the Open Society Institute, the Tides Foundation, the Ford Foundation and the Joint United Nations Programme on HIV/AIDS. Despite the grave situation in the region, the conference felt like a watershed event for the PWLHAs, drug users, sex workers, and gay men who gathered there from over 20 countries, to attend a training on advocacy skills and to strategize together about the needs for their communities.

While there are strong AIDS advocacy movements in a few countries in the region, particularly Ukraine, the idea of "acting-up" was new to many from the former Soviet states. By the end of the four days, the diverse group had settled on a few priorities for their work together: antiretroviral therapy access; access to harm reduction and substitution therapy (e.g. methadone); the reduction of stigma and discrimination towards PWLHAs and drug users; and the improvement of social services. Despite the obstacles they face, I was amazed by the participants' energy, intelligence and passion to move forward. Advocacy projects on issues identified at the conference will now be supported by a grant-making process. In a novel twist, the scope of projects to be supported and the proposals themselves will be reviewed by advocates from the region, with logistical support provided by the Tides Foundation, which has raised money and set up a fund to disburse the grants.

The former Soviet Union has the fastest growing epidemic in the world, yet the West has only recently taken notice of the looming catastrophe there. One cannot help think that there is a bit of queasiness by Western donors for an epidemic that is largely fueled by drug use. For instance, the U.S. government's aversion towards harm reduction, specifically needle exchange, and its own domestic policies on drug use, make it far easier to ignore what is happening in Eastern Europe and Central Asia, than to confront the irrationality of its approaches here at home. George Soros' Open Society Institute is a vital exception in the region and funds 65 percent of the harm reduction efforts there. Yet, in the context of the scarcity of other funding, there is little support for services for PWLHAs, much less HIV-positive drug users, which makes the harm reduction effort stand out like a sore thumb, exacerbating tensions between communities of drug users and those of PWLHAs.

The question "What is to be Done?" has a thorny history in the former Soviet Union, but unless great change comes to the region, the devastation will be tremendous. It's time for Western donors to step up and confront what is happening with a commitment of cash and resources, and particularly for the U.S. to give up its radically conservative vision of how to deal with drug use. Activists around the world also need to support our colleagues in the East and stand in solidarity with them as they begin the struggle that started to take shape a week ago in Minsk.