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HAART Version 2.0

By Bob Huff

What will a true second-generation antiretroviral drug be like? It's a common marketing claim and there have been several pretenders, but so far, failing to step cleanly away from the shortfalls of its forerunners has compromised every new bid for the title. Atazanavir is a fledgling protease inhibitor that may be just the ticket for knocking down virus levels in therapeutic newbies without incurring lipid problems—so long as its few toxic quirks remain benign. But what about folks whose ship of susceptability has long since sailed? Which criteria have to be satisfied for antiretroviral therapy to become truly effective, easy to live with, resilient, flexible and safe in the long run? And what are drug developers doing to try to get there?

Potency is at the top of everyone's wish list for a new antiretroviral. Reduction of viral load by at least 1.5 log copies within a few weeks is nearly an accepted standard for first line protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). The standard for nucleoside RT inhibitors (NRTI) tends to be a little less stringent, with 1.0 log drops in viral copy numbers often deemed very good. But it's clear from the gap in the proportion of trial subjects with viral load results below 200 copies and those below 50 copies that a lot of people on the fringes of suppression are barely getting by. A breakthrough in potency should be able to push viral replication down so far that virtually everyone who goes below 400 also goes below 50. That kind of potency would effectively arrest HIV activity whenever and wherever it kicks up and will be what it takes to hold out against the inexorable pressure of drug resistant viral mutants.

Several manufacturers are calling their drugs "second generation," but which ones have a shot at the title and which ones fall short?

There are other benefits to potency. A drug able to stop HIV in the test tube at very low concentrations may also be likely to work at doses far below the point where toxicity kicks in. Such a drug might also give the advantage of being far more tolerable in day-to-day use. And it's been demonstrated that tolerability is a big factor in keeping adherent to any particular regimen. This is the second big criterion where there's ample room for improvement: offer consumers an effective drug that they won't dread taking because of queasiness, loose bowels or nightmares, and they will vote with their feet. Good tolerability makes the bitter pill of lifetime HAART much easier to swallow.

The current Holy Grail of convenience is to achieve once-daily dosing with a coformulated product—all your pills in one, tiny tablet in the morning. (Did someone mention The Patch?) Dosing intervals depend on the rate a drug is cleared from the body by metabolism. Most protease inhibitors have had a tendency to activate the very mechanisms responsible for flushing drugs out of the body. The big exception is ritonavir, which has the opposite

effect. So powerful is ritonavir at slowing down the metabolism of PIs that its main use has turned out to be as an inhibitor of liver enzymes rather than an inhibitor of HIV. Unfortunately, PIs that rely on ritonavir for longevity have made a deal with the devil. Ritonavir brings with it tolerability problems as well as unpredictable interactions with other medications and uncertain but worrisome associations with long-term toxicity. Any drug that depends on ritonavir boosting to stay in the race is living in the past.

Offer consumers an effective drug that they won't dread taking because of queasiness, loose bowels or nightmares, and they will vote with their feet.

Which brings up another vexing quality: long-term safety. As the giddy flush of success during the first years of HAART tempered after lipodystrophy, lipoatrophy and cardiac risk factors began to show up, physicians and community members began questioning the underlying assumptions of the Hit Hard, Hit Early treatment dogma. They started looking for a middle path that treads a little more lightly without letting HIV get the upper hand. One problem is that the only way to uncover long-term side effects is to put people on drugs then wait and see; long-term effects are the most difficult aspects of drug therapy to pin down. But the consequences are finally being appreciated; if the mounting fears over cardiac risk have had a silver lining, it's that researchers are now more willing to use powerful research tools such as randomized trials in order to detect signs of toxicity before they begin cropping up everywhere at once. Nonetheless, consumer voices will need to grow louder before significant post-marketing and surveillance studies become routine responsibilities of bringing a new drug to market.

The other great long-term failing of most current generation drugs is the ease with which drug resistant mutations can erode their activity. In part, drug resistance stems from inadequacies in all of the previously mentioned criteria. A drug that inherently lacks potency will let HIV replicate in its presence, leading quickly to loss of susceptibility. Skipped doses mean inadequate drug concentrations, which can also drive resistance. And poorly tolerated drugs are more likely to be skipped than pills with benign side effects. Metabolic and genetic variations among individuals also come into play; drugs that never quite achieve maximum blood levels may dip below effective concentrations during the normal course of a day for some and not others. It remains to be seen if this variability becomes more problematic as dosage intervals are stretched to ever longer—and more convenient—periods. Interactions between agents affecting liver metabolism can play havoc with other drug levels. Finally, even people who have had excellent success on their regimens for many years may eventually take drug holidays due to fear about what is happening or might happen to the shape and constitution of their bodies. Unsupervised or ill-considered stopping and starting of therapy is another probable source of viral replication and resistance.

A truly next generation antiretroviral will not only need to have activity against the canonical HIV of yore—fast becoming a museum piece—but should also strike in a way that the multitude of variants resistant to existing drugs are also stopped cold. This dream drug would act against viruses from multiple worldwide subtypes and recombinations of subtypes, both from drug naïve and drug exposed persons. Even so, having flexibility against existing mutant strains isn't enough; the new drug will need to remain resilient against end runs by HIV genes freshly mutated against its particular shape and function. The ideal drug would block HIV at such a crucial step in its life cycle that no mutation could get by. Even if replication continued in sanctuary sites receiving sub-therapeutic concentrations, the drug should be able to stand up to low level sniping and hold fast.

Taken all together, it's easy to understand why coming up with a breakaway second generation drug is such a tall order. But that doesn't stop the pharmaceutical companies from trying—or from practicing wishful thinking. Several manufacturers have made or are making the claim for new drugs in their pipelines, but which ones have a shot at the title and which ones fall short?

Pipeline

While agents directed against new targets are exciting and a few candidates are on their way to the pharmacy, there's still a lot of room for improving inhibitors of the old standby HIV targets, reverse transcriptase (RT) and protease. (See *New Targets Bring New Challenges* for a look at future classes of ARV.)

Atazanavir is a protease inhibitor with efficacy comparable to current PIs in a treatment-naïve trial population. As a welcome step away from the ranks of existing PIs, atazanavir seems to have a minimal impact on cholesterol and triglyceride levels. In trials, asymptomatic, elevated, bilirubin levels occurred in a third to a half of trial participants and jaundice was observed in a few others. A genetic predisposition to these side effects has been proposed, suggesting that susceptible individuals may one day be identified before putting themselves

at risk. Moderate diarrhea was the main tolerability complaint. A recent bit of uncertainty over abnormal cardiac rhythmic patterns has brought out the caution flag for a very-large pre-approval access program that should have started by now. Otherwise, the drug seems to retain good activity against HIV with early-stage resistance to other PIs—although strains with multiple PI-resistance mutations probably become increasingly less susceptible to atazanavir. The good news is that viral strains developing resistance to atazanavir may still be susceptible to the existing lineup of PIs. Once-a-day dosing, low lipid toxicity and the ability to rescue emerging resistance with earlier protease inhibitors all contribute to the case for using atazanavir as a first-line agent. Its usefulness for PI failure and salvage situations is not as clear, however. Barring setbacks, Bristol Myers Squibb indicates the large expanded access program should begin shortly.

Tipranavir is a compound designed with a twist on the chemical structure that defined most earlier protease inhibitors. Although it has been tested in far fewer patients than atazanavir, tipranavir's most notable characteristic seems to be an ability to suppress multiply-PI resistant and wild-type virus with about equal efficacy. Primary resistance to tipranavir itself seems to be slow to develop. On the down side, tipranavir may share lipid-raising problems similar to earlier PIs. Furthermore, achieving sufficient blood levels to combat resistant strains and allow convenient dosing may require combining tipranavir with low-dose ritonavir, a strategy which brings the familiar set of cautions about tolerability, drug interactions and uncertain long term toxicities. In trials to date tolerability issues included gastrointestinal, neurologic and psychiatric effects.

Due to those limitations, tipranavir can't really be considered a second-generation product and it would probably never enjoy significant market acceptance if it is approved. But the drug deserves special attention because of its unique potential to patch over problems created by resistance to the first wave of PIs. It represents a solution that is urgently needed today: a lifesaver for people who've run out of treatment options. Tipranavir's conventional course of development has been limping along. Maybe the best plan for this drug is to fast track examining the dosage and safety issues, then to start making it available through compassionate use on a case-by-case basis before opening up an expanded access program for people unable to construct any other viable treatment regimen. This could conceivably start happening later this year. If sponsor Boeringer-Ingleheim is unable to consider taking extraordinary steps to move tipranvir forward, then perhaps an orphan drug development company could step in. This one is too important to treat as business-as-usual.

There are quite a few non-nucleoside reverse transcriptase inhibitors in the pipeline. The biggest failing of current generation NNRTIs is the ease with which resistant mutations develop that can also wipe out susceptibility to other drugs in the class. Coming up with a unique resistance profile is the principal goal of these newcomers.

DPC-083 is an NNRTI from Bristol Myers Squibb currently in Phase II studies in drug naïve patients. The agent is chemically similar to efavirenz with similar potency against wild-type HIV but has also shown activity against virus with efavirenz-resistant mutations. On the tolerability front, early trials have reported more episodes of rash but fewer problems with dizziness compared to efavirenz. DPC-083 is also a potent inducer of a liver metabolic pathway, which could mean drug interaction issues down the line. This drug doesn't seem to be running away from the pack, but as a transitional compound, maybe valuable lessons can

Second Generation Scorecard—Still Waiting

Drug	Potency	Easy to take and tolerate	Works against class-resistant HIV	Holds off new resistance	Long-term safety
atazanavir	~	✓	✓	~	✓✓?
tipranavir	~	~	✓✓	✓✓	?
FTC	✓	~	~	✓	?
DAPD	✓	~	✓✓	~?	?
TMC 125	~?	~	✓	✓?	?
DPC 083	~	~	✓	✓	?

~ similar to current generation ✓ some improvement ✓✓ big improvement ? too soon to say

be learned to help guide the development of future NNRTI candidates.

Two NNRTI drugs from Belgian biotech Tibotec have also appeared on the horizon. TMC125 is in very early development but has shown activity in brief studies with both drug-naïve as well as efavirenz-resistant individuals. Less is known about TMC120, another NNRTI, although short periods of dosing in people with HIV demonstrated activity.

As for new nucleoside analogs, two candidates from Triangle Pharmaceuticals merit watching. FTC (emtricitabine) is furthest along in development and may be offered to the FDA for review by the end of this year. FTC is chemically similar to 3TC and has similar potency against wild-type HIV. A longer half-life in the blood makes FTC a good candidate for once-a-day regimens. Unfortunately, overlapping resistance with 3TC means that people already resistant to its cousin won't benefit from FTC's convenience.

Further back in the pipeline is DAPD (amdoxovir), which may have excellent activity against AZT- and 3TC-resistant viral strains. Although resistance to DAPD itself can occur, it's still not certain how common or problematic that will be. It's thought that HIV with certain mutations conferring resistance to NNRTIs may actually become more susceptible to DAPD. On the whole, the drug remains attractive, especially for rescuing individuals with NRTI resistance, but its development has been slow. Triangle recently dropped one of its drug development projects and is moving FTC towards completion, so maybe DAPD is up for some long overdue attention from its sponsor.

Walk Don't Run

Last year, new enrollments to trials of capravirine, a NNRTI being developed by Agouron/Pfizer, were put on hold because of vascular inflammation observed in animal studies. No such toxicities have been seen in people who have received capravirine in clinical trials and people already on studies have continued to receive the drug. This agent is attractive because it promises to rescue individuals who have developed resistance to efavirenz (although not nevirapine). Early studies described gastrointestinal side effects, but significantly, did not report problems with rash.

Wipe Out

A number of drugs early and not so early in development bit the dust recently. Emivirine, an NNRTI from Triangle Pharmaceuticals was canned after data from large and expensive Phase III trials told the company that their drug was not potent enough to stand up in the marketplace. Triangle also pulled the plug on DMP-450 (mozenavir), a protease inhibitor that promised little more than existing PIs offer.

Several compounds in the Dupont stable acquired by BMS after their merger last year have been left on the moving van. Two promising protease inhibitors, DPC-681 and DPC-684 were dropped due to toxicity as has an NRTI candidate, DPC-817. One NNRTI candidate, DPC-961 was tabled after an unusual number of patients reported suicidal ideation. At a major conference two and a half years ago, Dupont billed two of their new NNRTI hopefuls, DPC-081 and DPC-083, as second generation breakthroughs; these too have now been quietly scrapped. Hopefully these stillborn progeny are part of the price to be paid before a stronger and gentler generation of HIV therapy finally appears.

New Targets Bring New Challenges

By Bob Huff

A new drug to block HIV at a new point in its lifecycle will be a welcome development. But approving a new drug from a new chemical class will also bring great uncertainties. It's not enough to simply be active against HIV, the new drug will also have to leave host functions alone and meet all of the other criteria for a medicine that is tolerable, easy to take, safe, and affordable. That's a lot to ask for a first time at bat. Advanced lead screening techniques and early use of better toxicity assays will hopefully accelerate the pace of developing the next generation of drugs. Still, the first wave of new-target drugs may go through a few false starts before they become useful medicines used in seamless combination with the older, more refined PI and RT inhibitors. Here's hoping one of these can knock the ball out of the park.

Information on new antiretroviral (ARV) drugs entering human trials was somewhat thin at this year's 9th Annual Retrovirus Conference in Seattle, but a few items stand out. Maybe the most encouraging news is that drug development is alive and chugging away on new products. Despite doomsday warnings by

pharmaceutical executives about having to pull out of HIV research if political pressure for affordable access to medicine threatens industry profits, there was evidence of commitments to develop new drugs for new HIV targets from Bristol Myers Squibb (BMS), Glaxo-SmithKline (GSK), Schering and Merck.

Researchers from Shionogi & Co., a Japanese pharmaceutical firm, presented a new inhibitor of integrase, an HIV protein that performs an essential step in the viral lifecycle. Integrase is one of the unique-to-HIV targets that have yet to be attacked with an effective drug. The big news in this presentation was the "GSK" logo that appeared in the corner of the slide. This means that HIV pharmaceutical leader Glaxo has joined the hunt for a novel integrase inhibitor... and if anyone has the capacity and know how to get an AIDS drug developed and moved through the pipeline, it's Glaxo. The drug is currently called S-1360. It is a *diketo acid* compound that has shown in vitro synergy with approved ARV drugs from every class. Merck also has a diketo acid integrase inhibitor that has previously been reported susceptible to site mutations in the enzyme; additional resistance mutations were also reported at this conference. Has the Shionogi compound gotten around this? S-1360 is proceeding with first human trials in a small number of HIV-infected individuals.

History shows that a new drug might enjoy glowing reports at one year's conference then never be heard from again; it's wise to reserve enthusiasm for agents that have at least entered full Phase II clinical development. In an example of the subtle scientific sniping that goes on at these conferences, a Merck researcher stood up after the Shionogi presentation and inquired about plasma protein binding for S-1360. Drug molecules can become gummed-up with proteins in the blood such as albumin. Protein-bound drugs aren't able to cross into the cells where they need to be and are ultimately eliminated from the bloodstream; too much susceptibility to protein binding in the body can eclipse a drug that shines in the test tube. Yes, S-1360 is highly protein bound, the Shionogi scientist admitted. Dare we hope that Merck has a new integrase inhibitor in the works that overcomes these problems?

The outlook for entry inhibitors is also looking better. T-20 from Trimeris/Roche is likely to be the first of this new class of drugs to be approved, although that may be up to a year from now. T-20 works by blocking HIV as it tries to insert itself into new cells. While a few posters filled out the clinical picture of what to expect from T-20, one detail incidentally slipped out in an unrelated talk by a BMS executive about their new entry inhibitor. Apparently the generic name for T-20 has been settled; initially known as pentafuside, T-20 will now be called enfuvirtide. (See *A T-20 Diary* in this issue.)

The new BMS entry inhibitor was another welcome surprise. Currently called BMS-806, the drug was discovered by screening a library of several hundred thousand variations on a chemical theme to detect potent anti-HIV activity. Eventually a few promising leads were narrowed down to number 806 which showed viral inhibition at concentrations that were not toxic to cells. The molecule is said to be highly specific for binding to the gp120 HIV envelope protein and probably interferes with attachment to cellular CD4. A green light so far, but experience with antibodies against the highly changeable gp120 protein tells us that the evolution of resistance may quickly become a problem. And in case you were wondering, BMS-806 is not highly bound by plasma proteins.

The other prominent entry inhibitors discussed at Retrovirus take a different approach to blocking viral attachment. Instead of sticking to the virus, they bind to receptors on a cell's surface that HIV uses to gain entry. Schering's SCH-C is in human trials and moving through a series of doses to find the best balance between activity and toxicity. Work is proceeding carefully because of abnormalities in a cardiac rhythmic parameter called QTc observed after volunteers received a single 600mg dose. A ten-day study of 25mg twice daily in 12 HIV-positive persons has been completed and a 50mg study is underway. At this point it seems that a slight prolongation of the QTc interval predictably occurs with increasing drug exposure, but it is too soon to say if this effect will doom the drug. After 10 days of SCH-C monotherapy at the 25mg twice-daily dose, mean viral load for the 12 patients had dropped by over 0.5 log.

SCH-C stops HIV from using the R5 receptor to infect new cells. A more virulent strain of HIV employs the X4 receptor, and is not inhibited by SCH-C. One fear is that using the drug could favor the evolution of X4-using mutants and actually accelerate disease progression. So far there is no evidence from test tube or animal studies that this occurs, but experience in human trials is the test that matters.

AMD 3100 is an entry inhibitor that acts on the X4 cellular receptor—the one that SCH-C doesn't attack. Although anti-HIV activity was noted in early clinical trials of the drug, studies

were stopped a year ago after failing to meet targets for reducing viral load. A look back at the data from those trials and a new analysis of the volunteers' viral genotypes suggest that some patients may have turned in a poor performance on AMD-3100 because they harbored a mixed population of X4 and R5 viral strains. The single individual infected solely with the X4 strain experienced respectable viral suppression. One question: If AMD-3100 acts on the viral phenotype that SCH-C does not, could one drug rescue the other in a synergistic fashion? In another AMD-3100 study presented at Retrovirus, increased heart rates combined with a lack of significant activity at the highest doses caused researchers to take pause. A new oral formulation will hopefully address toxicity problems seen with earlier infused versions of the drug. AMD-3100 may not be dead yet but its tiny biotech developer will surely have to partner with one of the big companies if this drug is to move forward.

For in-depth reports and more background, visit:
www.natap.org
www.aidsmap.com

Abstracts, posters and video from the 9th Annual Retrovirus Conference are available online at www.retroconference.org

T. Yoshinaga, et al. Persistence of Transmitted Drug Resistance among Subjects with Primary HIV Infection not Receiving Antiretroviral Therapy. 9th Retrovirus Conference, Seattle, 2002. Abstract 8.

M. Witvrouw, et al. Novel Mutations in HIV-1 Integrase Associated with Resistance to Diketo Acids. 9th Retrovirus Conference, Seattle, 2002. Abstract 573.

P-F Lin, et al. Identification and Characterization of a Novel Inhibitor of HIV-1 Entry - II: Mechanism of Action. 9th Retrovirus Conference, Seattle, 2002. Abstract 10.

J. Reynes, et al. SCH C: Safety and Antiviral Effects of a CCR5 Receptor Antagonist in HIV-1- Infected Subjects. 9th Retrovirus Conference, Seattle, 2002. Abstract 1.

D. Schols, et al. AMD-3100, a CXCR4 Antagonist, Reduced HIV Viral Load and X4 Virus Levels in Humans. 9th Retrovirus Conference, Seattle, 2002. Abstract 2.

C. Hendrix, et al. AMD-3100 CXCR4 Receptor Blocker Fails to Reduce HIV Viral Load by > 1 Log following 10-Day Continuous Infusion. 9th Retrovirus Conference, Seattle, 2002. Abstract 391.

A T-20 Diary

By Fred Gormley

Friday, March 1

Dear Diary,

Today my doctor informed me that my first dose of T-20 is just a week away! How I have yearned for this day! Scalding tears of joy spilled copiously down my face, onto my heaving, bountiful pectorals, drenching my grey Donna Karan cashmere sweater. What cared I: "Let the damage be done!" I exulted, whirling around my physician's office, gleefully tossing several other patients' files in the air. The precious fusion inhibitor would soon be mine and I would have closure to end all closures...

Well, of course not. One doesn't live in New York, wear all black, and reach the age of fifty (fourteen years aware of my positive HIV-status) to get exuberant about anything. What really happened was that, after waiting since...early December?...my shipment was coming in. As the result of a new study, I was the first of three people in Howard Grossman's office to get T-20. It wasn't easy, but the effort wasn't mine. From the time the protocol was announced, a Phase III open-label exploration of T-20's safety for people who have failed all other regimens, there were hurdles, the most aggravating of which was "call-in day". The pharmaceutical companies (Trimeris and Roche) set up a specific time when physicians around the country had to phone; availability was on a first-come, first-served basis, and there was limited drug to be had (see *Treatment Issues* Vol. 15 #4 detailing T-20's unique production difficulties). The volume of calls overwhelmed the insufficient phone lines, and getting through was hairy. And this was only to submit names! Each candidate was then reviewed as to appropriateness for the program. Several weeks later, I found out I had made it, and that the meds would come my way in February.

Don't think me overly blasé, but while I was gratefully anticipating this new tool against my AIDS, the intervening two months brought me distractions—or horrors—enough. I was receiving twice-weekly infusions of amphoteracin-B to fight a stubborn strain of candidiasis while recovering from a Christmastime bout of wasting, the most severe yet. And then, in the very beginning of January, my Mom died. At this writing, the weight's back, I'm still hooked up to the ampho, and the grief plays out its process. T-20 was something to look forward to, but eagerness for anything had been stomped right out of me.

Monday, March 4

The 'informed consent' has been signed! I kissed the precious document and clasped it to my chest as if each page were illuminated in lapis and gold...

Back in the doctor's office for the intake. Liza, the nurse-practitioner who administers all studies and trials in Dr. Grossman's office had given me an informed consent package the previous Friday and I'd read it during the weekend. It was one of the heftiest consent documents I'd ever put my hands on, though it was written in plain English rather than standard medico-legalese (example: "Can I be kicked out of the study?") And I don't know where I got the idea that this drug had fewer side effects than others, but with a brief pause over *stroke*... and I'd be willing to gamble on that... the downside passed my muster, which is to say that no one has reported growing antlers or such. The intake exam included an ECG, blood-drawing, a dipstick urinalysis and lots of questions. Liza handed me a videotape to view between then and when I picked up the meds.

Friday, March 8

The video! It answered all my innermost, private questions! I wanted to run to my Sony Wega and hug its big flat screen. So I did.

Whenever anyone *assigns* me something to read or view, I avoid it until the last minute, or never, if it's a high school book report. So the videotape waited until Friday morning, at which time I cozied-up with the procedures of self-injection.

There was nothing new here for me (except for the reconstitution process. T-20 is a protein, and its powdered form must be mixed with sterile water to be administered), so I concentrated on the tape's production values. Professionally done. High-quality video. San Francisco locale (every scene shot in open white rooms with crisp available light). And there's skin! The demonstration subject doffs his shirt to give himself a shot in his well-tended abs. The only treacly touch was the instructor, a young woman who's a little too upbeat for my jaded tastes at that hour and frankly could use her own dose of something to bring it down a notch. Minor distractions, but if I weren't already a long-time needle user (insulin, Serostim, Epogen, Procrit, testosterone) I would have missed the point entirely. How very "me".

At the doctor's office, I did my first hit under Liza's direction. No problems, but one potential annoyance, a possible future deal-breaker. The reconstitution takes 15 to 20 minutes if you tap the bottom of the vial and gently roll it around (no shaking!) and somewhat longer if you just let it sit. For someone like myself who greets the day with pills at 8 (no food!) pills at 9 (food!) protein shake, two packets of testosterone gel drying on my belly as well as the usual get-ready-to-go-out-the-door routine, another extended multi-step procedure (repeated at night) could quickly lose its charm and novelty. I'll bear with it, though.

Liza hauled out the accompanying supplies. YOU GET: One box safety syringes for mixing; one box safety syringes for injecting; a decent-sized sharps container; vials of sterile water; alcohol pads; the medication itself. BUT WAIT! THERE'S MORE: a small insulated bag for transporting chilled T-20 (must be refrigerated); instructions; an offer to participate in a marketing survey seventy-five days after your first injection ($50!) and a huge canvas tote bag to carry it all home in (by the way, nothing has a logo on it. They've finally learned!)

Sunday, March 10

So I've just given myself my fifth poke; no adverse reactions evident so far. Some people have complained about swelling under the skin at the injection site, but anything I've ever shot subcutaneously has given that effect; mine goes away within an hour. There was some itching with the in-office dose, and a vague feeling of momentary heartburn, which may have been coincidental. It'll go as it goes. It'll work or it won't or the results will be ambiguous, as most drugs are when you're on a heavy regimen. We'll see...

Que sera, sera...and yay!

Corrected Phone Number for HBV Trials

An article in the Nov/Dec issue, Low Dose Adefovir for the Treatment of Chronic Hepatitis B in HIV-Infected People, gave an incorrect phone number for obtaining information about participating in clinical trials for hepatitis B. The correct number is 1-800-772-5464, ext. 49905.

Life on HAART

By Michael Carter

Reprinted from AIDS Treatment Update, March 2002

For subscription information: atu@nam.org.uk or visit www.aidsmap.com

For the past four years I have been taking antiretroviral therapy. I've seen my CD4 count quadruple and my viral load fall from the high hundred thousands to below 50. It would therefore be easy to conclude that for me treatments have been a success. Not least because it is now well over ten years since I was diagnosed with HIV, and nine years since my first AIDS-defining illness. Quite simply, without my anti-HIV drugs I expect I would be dead by now, or in the last stages of advanced HIV disease.

However, even though my treatments have proved, according to my blood tests at least, a success, I am still very much aware of how serious a condition HIV is and the extent to which it impacts on my life and is likely to do so for the foreseeable future. I am still very medicalised. For a start, there are visits to the clinic every eight weeks for blood tests to monitor the success of my treatments, and their impact on my metabolism. This means that I'm seeing my consultant at least as often as I did in the days before I started taking my combination. What's more, my visits to the clinic last at least as long as they used to. But on top of that, treatments, combined with the length of time I have had HIV, mean that there are other medical issues which require me to visit the hospital.

In one week in late January this year, even though my CD4 count was over 600 and my viral load undetectable, I had to attend three separate outpatient clinics, none of them specifically HIV focused, to see specialists for the monitoring or treatment of conditions which have developed either as a consequence of my treatments, or as a consequence of having a potentially life-threatening illness for well over a decade.

Living with HIV has started to impact on my mental health; just as my lab results started to indicate that its damage to my immune system was being controlled, my mental health declined. I have had two major depressions since I started treatments, each of them as debilitating as any physical illness which HIV has caused. My consultant and the specialist HIV psychiatrist who he referred me to, have assured me that I am far from alone in experiencing mental health problems since starting treatments. For some people these problems have been the direct side-effect of their medication—depression, psychosis and vivid dreams are all recognized side-effects of efavirenz. For me the causation has been more indirect. I've been corroded by living with HIV for all these years. I've grown pessimistic, and the renewed hope of a future which treatments have provided me with has been compromised by the side-effects and uncertainty which accompanies them.

Fortunately, I've been spared any of the disfiguring body changes (lipodystrophy) which are caused by treatments, even though I've many of the factors which seem to be associated with it, particularly chronic infection with HIV and many years of antiretroviral therapy. A friend, however has not been so lucky, and as he put it: "It's the ultimate irony, you're spared dying of AIDS only to look like you are". Not surprisingly, another friend, who recently started his first combination, has been anxiously monitoring his body shape, fatalistically attributing changes in weight, or post-Christmas thickening of his gut, to early signs of lipodystrophy.

I've had my fair share of side-effects too, including the diarrhea which accompanied my first year on nelfinavir and felt like a tap being turned on in my bowel. Then there was the peripheral neuropathy in my feet and lower legs —the worst pain I've ever been in, and which still hasn't resolved three years after stopping the drug which caused it. And most recently I've been required to see a cardiologist after developing an irregular heart beat. As I neither smoke nor drink, eat a low fat, high fiber diet, rarely take drugs, have taken regular vigorous exercise since my teens, and currently run at least five times a week, this would seem to be without obvious cause. That's if I wasn't taking antiretroviral medication which has been shown to raise levels of fats in the blood (a risk factor for heart disease), particularly in people like me, with a family history of cardiovascular illness. So far the signs look good—I may well have bradycardia, a benign condition seen in people with low resting heart rates (particularly runners), but it's required numerous visits to the hospital and a heart rate-raising degree of worrying uncertainty just to get to this potentially hopeful diagnosis.

It is the uncertainty such as this which has become such an unsettling feature of my life on treatments. I am uncertain how long my current drug regimen will continue to work for. Indefinitely I hoped, until last week, when I was told that after years of being undetectable, my viral load was 125. Admittedly modest, but does it mean that I'm becoming resistant to my current combination?

It may well only be a 'blip,' but only more visits to the clinic and more tests will determine this.

Even though my treatments have caused problems, I have found a way of living with them. They're easy to take; twice daily with food (which I've realized can be something as easy to eat as a chocolate bar), and no longer cause any nausea or bowel problems. I don't relish the prospect of having to change to a new regimen. I can well remember the bewildering array of choices between different drugs and combinations which my doctor presented to me in the Spring of 1998 when I started my first regimen. Similarly fresh is the memory of the fretful decision I was asked to make a year later when it was clear that the d4T-related peripheral neuropathy was becoming unbearable, and I'd have to stop the drug despite having good lab results, and choose between AZT and abacavir. Neither of them appeared particularly attractive, well aware as I was of their respective side-effect profiles. In the end I went for abacavir, half expecting to experience the potentially life-threatening (though rare) allergic reaction.

Then there is uncertainty about how long the body can tolerate a chronic viral infection and potent drugs necessary to control it. Rates of cancer in people with HIV are being carefully monitored after some research suggested that non-AIDS-related tumors were more commonly seen in people with long-term HIV infection. As my consultant said to me: "It's another set of worries for you. First of all there was opportunistic infections. Then there was treatment choices, then side-effects, and now the possibility of other fatal illnesses."

Coupled with the medical uncertainty is a lack of security, particularly as regards employment and money. I've been in and out of work for the past decade, meaning that my CV has many gaping holes. My experiences with work have taught me that for me at least, having HIV does pose very real limitations on my employment opportunities. I have been severely ill, with both physical illnesses and depression, meaning that I have been forced to leave jobs. And even sustained periods of employment and good health have involved regular visits to the clinic, accommodated as far as possible outside the working day, but often at times of the day and with a frequency which even a sympathetic employer found hard to accommodate. Now in my mid-30s, I'm facing the possibility of a future of financial insecurity as life with a chronic and demanding illness leaves me ill-suited to a fast moving and competitive jobs market. With the safety net of benefits which accompanied the chronic illness of HIV disease long since removed, this could mean that chronic poverty may well become another unwelcome side-effect of my life on treatments.

It's also necessary to inject a bit of perspective here. The terrorists attacks in New York and Washington last year made many people feel less secure and worry about their employment prospects. In addition, it's become easy to blame HIV and treatment side-effects for just about every medical condition which raises its head. For example, I'd noticed some lines developing down my cheeks recently, and my instinct was to attribute it to treatment-associated fat loss, rather than look for a less sinister explanation, like aging—which is in fact the case.

With treatments has also come a redefinition of the way I perceive myself, and I think, the way others look at me. Although I have just written at length about some of the issues I have faced, there is no denying that I am likely to live for many more years, possibly as many as my HIV-negative peers. I'm to expect things from life, not least enjoyment and fulfillment and a determination to make the most of the years of life which treatments are hopefully offering me. I'm no longer prepared to accept the poor quality of life issues which accompany the day to day drudge of living with HIV. On the whole I've become a lot more open about my health. When asked in polite dinner-party chit-chat how I managed to get a housing association flat in central London I didn't try and dodge the question, or hedge the answer, but said simply "I've got AIDS." It killed further envious questioning. Similarly, I've become much more explicit about taking my medication in public, and now either honestly respond to inquiring glances about the handful of pills I'm downing, or simply ignore them, rather than apologetically lying about "vitamins" or scurrying off to the bathroom to take my medication in secret.

There are still limitations to my openness and honesty, not least that I've never told my parents I have HIV, maintaining elaborate fictions for their (or is it my own?) benefit about crucial aspects of my life. This is not because I fear that they'll reject me—I'm fortunate in knowing that they love me unconditionally—but because in some way I'm ashamed of having HIV. Luckily I've never had a bad reaction from a person who I've either told I'm positive or has guessed. But, the popular prejudice about the disease has, despite my best efforts at rational thought, penetrated deep into my consciousness. And this popular prejudice isn't only found amongst uninformed *Daily Mail* readers. Some recent correspondence to the British gay weekly *Boyz* showed that there's an unhealthy amount of prejudice directed towards people with HIV within the group most affected by HIV in the UK, gay men.

Having said that, because of treatments, and their success for me, I no longer feel I have the right to the sympathy and the allowances which people made before. I'm very aware of how hard it was for many of my friends and particularly my partner of ten years, to support me through what looked like it was going to be a terminal illness. To an extent, the problems I now face aren't as serious, and are more generic—lots of people live with serious illness which can be controlled with medication which causes nasty side-effects.

I want to make the most of the fact that treatments mean that very possibly I am alive when I expected to be dead. But to do this, I need to be honest. I've found living with antiretrovirals hard, often harder than life before treatments. But, like HIV, they're something which has become part of my life. I hope that at least some readers will identify with what I've written as they too, find a way of coping with, and making the most of, what life with treatments means.

Let Nevirapine Do What It Does Best

By Bob Huff

A single-dose of the AIDS drug nevirapine when taken at the onset of labor is a proven method for dramatically reducing rates of mother to child transmission (MTCT) of HIV. So why does Dr. Joep Lange, President of the International AIDS Society and vocal advocate for expanding the worldwide access to antiretroviral (ARV) drugs, take every opportunity to warn that resistance to nevirapine (NVP) can arise after single-dose use? His purpose is to raise this question: if single-dose NVP brings resistance, then should the drug be reserved exclusively for chronic treatment regimens and never used as a single-dose for preventing MTCT? Such talk causes shivers of alarm to dance through the networks of doctors and advocates working to extend ARV medicines to all corners of the world. But what is the basis for his nervousness?

Dr. Lange is correct that NVP resistance can appear after only one dose, but his conclusion about how to use this valuable drug is exactly wrong. NVP is very well suited for preventing MTCT. It acts quickly to lower viral load in the mother and the effect lasts for more than a day — enough time to protect a baby during labor and delivery. A single-dose given to the newborn continues the protection for up to a week. The drug crosses the placenta and appears in breast milk during the first critical days when the newborn receives its antibody-rich colostrum. No serious toxicity has ever been reported for single-use nevirapine, although longer-term follow up for children exposed to nevirapine at birth still needs to be performed. Though not as sure as an extended course of AZT or triple therapy to prevent transmission, in settings with limited prenatal care and little money to spend on medicines, single-dose NVP is cheap and effective.

Compare the profile of single-dose nevirapine to that of nevirapine used for chronic HIV infection. Severe rash has occurred in as many as 8% of people who start nevirapine therapy and some cases of liver toxicity have been fatal. These life-threatening side effects may not show up for several weeks or months after starting the drug. While close liver enzyme monitoring and careful medical management may be able to catch most incidents of toxicity before they become serious, this is precisely the kind of care likely to be scarce in resource-poor countries. Furthermore, there is some evidence that women on full-time NVP may suffer liver complications and serious rash at a higher rate than men. The toxicity problems are possibly due to the long half-life of nevirapine in the blood. The slow rate of clearance that makes nevirapine ideal for single-dose use during labor may cause trouble over time if blood concentrations accumulate to toxic levels during daily chronic dosing.

Dr. Lange's concern stems from the ease with which resistance can develop to nevirapine. As little as a single DNA mutation is sufficient to allow HIV to evade suppression by not only nevirapine, but also by efavirenz and delavirdine, the two other currently approved members of the non-nucleoside reverse transcriptase (NNRTI) inhibitor class of antiretroviral drugs. In one study, resistant mutations were observed in 30% of women eight weeks after single-dose nevirapine exposure. Dr. Lange is worried that women with the K103N mutation will never be able to use nevirapine, efavirenz or delavirdine as part of a chronic ARV regimen—should one become available to them in the future. Yet it's likely that having had resistance previously may not be a problem for women who only use NVP to avoid infecting their newborns. After the single dose has cleared the blood, the body's ecology no longer favors the nevirapine mutant. After a period of weeks to a few months, the wild-type nevirapine-susceptible virus should again overtake the woman's viral population. If she uses nevirapine during her next delivery, the fast acting drug should quickly suppress the dominant viral popu-

lation and lower her viral load to help insure a safe delivery. Since the nevirapine-resistant virus is now archived in latently infected cells, she may experience a bloom of the resistant strain, but not until the baby has been safely delivered. No reports of a second labor and delivery treated by nevirapine have yet been published, but real-world data should soon become available as several nevirapine MTCT pilot programs enter their third year.

In a study presented at the 9th Retrovirus Conference by Susan Little of the University of California, San Diego, the K103N mutation associated with NNRTI resistance persisted for up to a year in women who had been infected with drug resistant strains of virus. Dr. Lange, a convener of the panel that heard Dr. Little's presentation, was quick to ask if her findings should provoke a "rethinking" of single-dose nevirapine. Dr. Little agreed that the data was "extremely concerning."

Dr. Little found persistent NVP resistance in four of her six study participants. However, there is a crucial distinction that limits applying her observations to women who develop nevirapine resistance from drug exposure. Dr. Little's subjects were infected by sexual contact with partners who had been exposed to nevirapine and then transmitted a resistant strain. This means that her study patients carried a drug resistant clone and lacked an archived copy of a wild-type drug susceptible virus. For the drug resistance phenotype to disappear, a spontaneous N103K mutation had to occur then grow out as the dominant strain. This chain of events is far more dependent on the play of chance and environmental factors than is the process of an archived wild-type strain re-establishing itself after a few days of drug suppression. If anything, the spontaneous loss of N103 in this small group suggests that NVP resistant virus is less fit to replicate than the wild-type and argues for a quick rebound of drug-susceptible virus in most women exposed to single-dose therapy.

Since nevirapine resistance is so quick to develop, perhaps the real concern should be with the impact that widespread NNRTI resistance might have on successful efforts to prevent MTCT. Nevirapine resistance can be expected to rapidly arise in populations that adopt it as part of triple-drug ARV regimens. Even if adherence is near 100%, normal variations in absorption, metabolism and viral dynamics may allow virus replicating in the presence of nevirapine to quickly generate drug-resistant mutants. In resource-poor settings, viral load monitoring is likely to be minimal or non-existent. Therefore individuals failing nevirapine may be more likely continue on their failing regimens, perhaps infecting new individuals with NNRTI resistant strains—including women who could benefit from single-dose nevirapine when delivering their children. This would be the true tragedy, dimming one of the few therapeutic bright spots in the world AIDS crisis.

It is unquestionable that the best solution for stabilizing a family invaded by HIV is to not only give treatment to prevent MTCT, but also to provide continuing treatment to suppress virus in the mother and in other members of her family, including her children and husband. Indeed a new study of continuing ARV for mothers, called MTCT-Plus, is springing from the foundation of successful mother and infant research programs. These MTCT programs have moved forward because they have had the support and funding to successfully demonstrate results. Sadly, the lack of enthusiasm among drug companies, governments, foundations and the Global Fund for paying for chronic treatment means that the slow pace of bringing therapy to the vast majority of people who need it will continue to drag.

The unique suitability of nevirapine to prevent MTCT may be overshadowed in many minds by another of its attributes, its low cost. Nevirapine, whether supplied by Boeringer-Ingleheim or by a generic manufacturer, is by far the cheapest choice for the potent leg of a three-drug combo—and cost often looms larger than other issues when access to treatment is discussed. But proponents of universal therapy need to critically ask, is the cheapest drug really the best drug for the job? Despite the low cost of nevirapine itself, the expense for chronic dosing added to a nucleoside backbone, plus viral load and toxicity monitoring, will keep this regimen from being widely deployed for years to come. Meanwhile, the MTCT programs are reaching people, educating them, testing them and increasingly, treating them. Although confirmatory data about single-dose NVP used in subsequent pregnancies are eagerly awaited, it does a disservice to the most successful current efforts to expand HIV treatment in the developing world by promoting entirely theoretical objections.

S.J. Little, et al. Persistence of Transmitted Drug Resistance among Subjects with rimary HIV Infection not Receiving Antiretroviral Therapy. 9th Retrovirus Conference, Seattle, 2002. Abstract 95.

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EDITOR
Bob Huff

ART DIRECTOR
Adam Zachary Fredericks

TECHNICAL & MARKETING COORDINATOR
Fred Gormley

PROOFREADERS
Doug Goertzen
Derreth Duncan

VOLUNTEER SUPPORT STAFF
Edward Friedel

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GMHC Treatment Issues
The Tisch Building
119 West 24 Street, New York, NY 10011
Fax: 212/367-1235
e-mail: fredg@gmhc.org
www.gmhc.org

Canarypox in the Coal Mine

There's been a shakeup in the government's efforts to test a vaccine for HIV. First, the National Institutes of Health (NIH) cancelled plans by its HIV Vaccine Trials Network (HVTN) to launch a large, international study of an HIV vaccine next year. The reason? Disappointing smaller studies with a canarypox-based vaccine combination gave little reason to think it would do any better in an 11,000 person, eighty million dollar trial. This leaves the HVTN all dressed up with no date, its painstakingly built network of global partners standing idle.

Then came news the White House had heeded the advice of Secretary of the Army and recent Enron vice chairman, Thomas E. White, to shift responsibility for another large trial of a similar canarypox vaccine away from the U.S. Army and over to the NIH. This study, planned in cooperation with the Royal Thai Army, is slated to start in that country later this year. So the NIH is back in the canarypox business again—with little more chance of success than before.

What is the rationale for moving ahead with large, expensive trials before the underlying science to make an effective HIV vaccine has been solved? One answer: infrastructure. Beatrice Hahn, a widely-respected HIV scientist, explained the problem to Nature magazine: "They have made such an investment in training, infrastructure, technology transfer, assays and equipment that at this point it's impossible to pull the plug. This is more than just a vaccine trial" she said.

Indeed, it has the potential to be a disaster. The only thing worse than a minimally active vaccine bombing out in a ballyhooed trial is if it were actually believed to have had a benefit when it didn't. The Thai trial is designed to see if the canarypox combo can cut HIV infection rates in half. Proving that would be terrific—though highly implausible—but the problems start if some smaller, ambiguous, degree of protection is reported. In theory, even a modestly protective vaccine could have a significant impact on the pace of the epidemic over many years and large populations. But what would this news do to ongoing or planned trials for more sophisticated vaccine candidates? An ethical quandary over the "best proven treatment" means the landscape for testing vaccines would change altogether.

With a "proven" though marginally effective vaccine having set a standard, it's no longer ethical to conduct trials using placebo. You have to go up against what you already know works. To make an ethical comparison, all study participants would get the standard vaccine, and then only half of them would get the new, hopefully more effective vaccine. A trial's complexity is increased, its size and cost go up, and the time needed to get an answer now stretches out longer and longer. John McNeil, an architect of the surviving canarypox study, estimated that the planned 16,000-person Thai trial could balloon to require 100,000 people if there were a standard vaccine in the picture.

Meanwhile, the HVTN still lacks a mission for its global partners. Although many smaller studies are starting up, the most promising new vaccine candidates are several years from needing large scale testing. What can the vaccine networks do to justify their budgetary existence and keep their infrastructures intact? Must they wait for an AIDS vaccine? Or could they put their assays and equipment to work testing vaccines and preventive measures to combat other global heath disasters just as well?

The U.S./Thai collaboration on HIV vaccine research dates back a decade and is part of a longstanding partnership that has also tackled malaria and dengue virus. An effective vaccine for tuberculosis, malaria or pneumococcal infections would have dramatic health benefits for millions of people—with and without HIV. Vaccine candidates are languishing in under funded programs at the NIH, the Army and the CDC, as well as at laboratories throughout the world. The emerging capacity and infrastructure to conduct global vaccine trials is too important to let stagnate, but science and good sense demand spending that capital on a candidate with a chance to do some good in the broadest possible view. The time for a large HIV vaccine trial will come, but for now the networks should be thinking outside of the pox.