The Latest on Early Intervention

A “Hurry Up and Wait” strategy looks better than ever

October 1, 1998 By Dave Gilden

A friend named Steve tested positive last year and was thrown into turmoil. Yes, his life prospects suddenly darkened, but well-meaning friends thought they had the solution. “Everybody told me I should get right on combination therapy,” he says, “even though I had a low viral load and 1,100 T-cells.” Steve’s doctors, too, advised that he start treatment immediately to prevent his immune defenses from deteriorating further.

For years, the AIDS community has been quick to naysay denial -- the “you can’t run away from HIV by ignoring it” syndrome. But all along, a different kind of denial may have been developing: The bad news from last summer’s World AIDS Conference in Geneva was that triple-combination therapy can’t stamp out HIV. Leading researchers reported that there’s always some “residual” replicating virus even in those who respond best to therapy. This holdout HIV raises the specter that the slow evolution of drug-resistant HIV may be inevitable; sooner or later, the combinations may well fail.

Yet Geneva was not all doom and gloom: With careful planning -- this is key -- many can now control the virus for years, even decades. How quickly we forget that only the day before yesterday, medical discoveries extending survival for mere months were hailed as lifesaving advances. The details of a realistic strategy for managing HIV must be sorted out as people with HIV, their doctors and researchers together come to grips with the vanishing hope of viral eradication. Until then, the newly diagnosed -- like Steve -- will have to buck sharp public pressure in an effort to save their future options. “Treatment is a lifelong commitment,” he says. “I’m worried that if I fail on my first combination, no one will be able to tell me what to replace it with. I want to wait until they know better how to replace failing regimens.”

Since the advent of protease-based combination therapy in 1996, HIVers have been bombarded by all manner of guidelines and recommendations, ads and advice promoting early, aggressive treatment: Combine two nucleoside analogs and a protease inhibitor to suppress the virus to the point of undetectability, the “hit early, hit hard” dogma goes, and clear the virus out as early as possible. By now, the force of this “play to win” logic, as pre-eminent HIV researcher Dr. David Ho calls it, is overwhelming. “When you just play not to lose, you usually end up losing,” Ho aphorizes. But studies at Geneva offered compelling evidence that an “easy does it” strategy aimed at long-term control of HIV rather than outright eradication is likely more feasible.

Ho has enlivened many a conference since the Vancouver euphoria with his updates on the disappearing HIV population among his patients on combo therapy. But as he reinterprets his ever-new data, eradication just keeps receding further into the future. At first, Ho thought that the treatment time needed to achieve this lofty goal would be 18 to 24 months, then three or four years; last winter, he estimated that it might take as long as 20 years. In fact, the experience of people who stop therapy even after several years of undetectability indicates that a cure is nowhere in sight. A report in Geneva described the rapid resurgence of HIV in such people. After they interrupted treatment, their HIV doubled every 24 hours for the next 20 days. Others, including *POZ* founder Sean Strub in these pages last month, have described an even more disturbing viral rebound during "drug holidays."

Eradication enthusiasts have long had to accept the existence of so-called latently infected cells, which lead normal lives for years all the while secretly harboring HIV. Pioneers in this field, such as Dr. Robert Siliciano of Johns Hopkins University, have insisted that the fate of this long-dormant virus is to suddenly reproduce and burst forth only to be stymied by the antiretroviral cocktail. Still, some researchers disputed that this was in fact the last remains of HIV after these combos cleaned out the virus from active cells. Dr. Tony Fauci's group at the National Institutes of Health reported last fall that the drugs were not doing such a complete job of staunching HIV: A certain amount of viral replication was taking place after all. "People said that my patients were not responding to therapy as much as possible, but they were," Dr. Fauci retorted recently. Also, Dr. Mike Saag of the University of Alabama calculated that even at a viral load of one, there are 100,000 cells actively producing HIV at any one time in the body. Such daily production would dwarf the estimated one million latently infected cells -- only a few of which are turned on daily. But most experts doubted Saag's conclusions, too.

"Residual replication" was the talk of the Geneva conference. Several presentations, including one by Ho, introduced this concept to the medical mainstream. "The drugs must not be getting to certain cells or compartments, or there are problems with drug levels" is Ho's conclusion. He belittles the worry that this replication may lead to the gradual evolution of drug-resistant HIV, but Saag predicts a high likelihood of failure as treatment continues. "I've seen people with months of unquantifiable virus who suddenly have measurable virus," he says. "The initial response of most investigators would be to blame it on adherence, but I know some of these people haven't missed a dose."

If indeed a three-drug cocktail allows for HIV replication, maybe everyone should try four or more drugs -- whatever it takes to get viral loads below 50 copies, the limit of the new ultrasensitive viral-load assay. The extras that can be purchased in the pursuit of that much-fetishized "undetectable" now seem endless: And while you're adding drugs, why not also utilize the newly commercialized Virco resistance assays (at a cost of up to $1,330 per test) to make sure all the drugs really are effective against the HIV in your body. Then there's "therapeutic blood monitoring," which measures whether the drugs are reaching your bloodstream in optimum amounts. And don't forget to monitor the drugs' toxicities by submitting to frequent liver- and kidney-function tests as well as complete blood workups. The Geneva conference was awash in new strategies for alleviating so-called adverse effects. To take only one example, the class of

drugs known as statins can reduce the heart-threateningly high cholesterol levels seen in about half of all protease takers. But statins, of course, have their own side-effect issues. Meanwhile, human growth hormone (Serostim), a possible palliative for “protease paunch,” costs $1,000 a week, with third-party reimbursement problematic. In any case, it’s increasingly clear that as many as half of all those on three drugs have trouble following dosing instructions. Drug holidays are no isolated phenomenon. “Some people anecdotally have found greater potency with five drugs, but is it practical to do this for years?” Ho asks, citing both the question of adherence and the long-term toxicity issues.

As a complement to treatment, Ho and others are investigating the use of specialized “therapeutic” vaccines to stimulate anti-HIV immunity while keeping the virus suppressed with combo therapy. The hope is that once immunity is triggered, some or all of the drugs can be withdrawn, and the immune system left to pen in the remaining small amounts of HIV. With a cure unlikely, this immune-based method aimed at permanent “remission’’ -- Ho’s updated version of ”eradication" -- is a more attainable goal. And in fact, viral diseases are only rarely completely eradicated by the immune system. A few latently infected cells persist and are attacked by immune cells if they start producing virus.

Yet this vaccine concept remains totally speculative. Dr. Bruce Walker of Boston’s Massachusetts General Hospital pointed out in Geneva that a central player in the anti-HIV immune defenses, the T-helper CD4 cells genetically programmed to coordinate the attack, are wiped out by HIV in the first months of infection. So far, they seem unable to regrow, even after viral load is brought down radically.

Into the breach has leapt the Immune Response Corporation, which has experimented with a therapeutic vaccine for the last dozen years without yet producing definitive proof of its effectiveness. (This vaccine, which bears the trade name Remune and consists of killed HIV stripped of its outer envelope, was first proposed by the late Jonas Salk of polio-vaccine fame.) The advent of the highly active therapies has opened up a new role for the vaccine, which the company has been eager to explore. At the World AIDS Conference, Dr. Fred Valentine of New York University Medical Center presented the first results, showing what he called “enormous” newly acquired immune-cell responses to HIV in some 20 people after just two injections 12 weeks apart. Valentine insists that “we’ve shown that we can duplicate the magnitude of the response in long-term nonprogressors,” but few experts share his enthusiasm. Critics emphasize that all he truly found is that vaccine recipients’ cells respond to HIV in the test tube by activating and proliferating. Whether this response will prove protective when volunteers go off therapy remains unknown.

The current debate makes the important point that there’s no solid reason to hit the virus early and hard if no cure is in sight. The body can tolerate substantial viral levels with little apparent harm. One presentation in Geneva, by Dr. David Katzenstein of Stanford University, referred back to ACTG 175, an old trial of AZT, ddI and ddC, to remind attendees that people with both a viral load below 10,000 and a CD4 count above 300 nearly always remain free of major AIDS-defining conditions over a three-year period.

As Dr. Mike Saag has said, “If we can get viral loads below 5,000 and keep them there, patients generally won’t progress. There is study after study, with years of follow up, showing that. The problem is, it’s hard to keep patients below 5,000. If drug resistance develops, the natural tendency of HIV is to rebound above that level.”

Short of eradication, the big rationale for maximizing HIV suppression is that it prevents or delays the evolution of drug-resistant HIV strains. Yet there are other strategies for avoiding drug resistance. The most obvious is to put off taking the drugs altogether. But you can afford to do that only if your overall health is sufficient and if your viral load and, especially, your CD4 count are stable. This principle is suggested in the just-published, revised version of the HIV treatment guidelines put out by the International AIDS Society-USA, which Saag co-authored.’

The Geneva conference had no answers for such questions as how to drain the pool of cells containing latent HIV or how to block every last bit of viral replication. Indeed, studies found that the best antiviral combinations could drive HIV levels below 50 in only about half of the most-responsive patients -- those with no prior treatment and only moderate (less than 100,000) viral loads. Meanwhile, the conference yielded no solutions to complex toxicity and adherence problems. “I feel dazed and confused by the data. Providers are not very relaxed right now,” says Dr. Keith Henry, who directs a drug-resistant HIV clinic at a St. Paul, Minnesota, public hospital. “I now see patients resistant to all available and experimental drugs who were never sick -- and some never went below 500 in their viral load. In these cases, I say it is time for us to slow down here.”

In times of confusion, the appeal of adopting a “Hurry Up and Wait” approach is very strong. When protease inhibitors came out, many had lousy experiences with them because they had long followed aggressive-treatment advice. Their HIV gradually developed resistance to all the nukes that complement the protease inhibitors. Having “burned through” these older agents, their viral replication remained high when they added protease inhibitors, and they rapidly exhausted these drugs as well. Those who put off treatment did better.

In a plenary address to the Geneva conference, Treatment Action Group’s Mark Harrington described how he started therapy only after his health had deteriorated and his CD4 count had crashed. By then protease inhibitors were on the market. “I’m lucky I waited,” he said, showing off before-and-after slides of his lymph nodes, the center of HIV infection, to the packed hall. By the time he began treatment, HIV had seriously eroded their structure. Now, after two years with the lowest possible viral load, the nodes appear to be essentially restored. Indeed, the best news at Geneva was likely that the immune system seems capable of slowly repairing much of the damage it has suffered (with the possible exception being the anti-HIV immunity lost early on). According to French researcher Dr. Brigitte Autran, who has worked extensively on this subject, “the reconstitution of the CD4 cells depends only on the level of viral suppression” and even those with late-stage disease can slowly regenerate lost cells. The trick is to know how to pick the treatment strategy that is best for you, not rush to take combos at the earliest possible moment.

Delaying therapy may win you a couple of years while science elaborates wiser treatment

strategies that make better use of the available drugs. But what if your viral load already is rising and your CD4 cells declining? If you face present or imminent illness, “Hurry Up and Wait” is out of the question, but you can still develop a conservative strategy that both improves health and preserves future treatment options. This would be to use a regimen with as few drug classes (protease inhibitors, nucleoside analogs [nukes] and non-nucleoside reverse-transcriptase inhibitors [NNRTIs]) as possible, carefully choosing agents so as to avoid sparking cross-resistance to other drugs you might want to use down the pike. With 11 anti-HIV drugs now on the US market and another four available through expanded access, an impressive variety of such narrow but potent combinations are conceivable. Geneva provided several illustrations of what can be done.

One possible regimen is the nukes d4T (Zerit) and ddI (Videx), with or without hydroxyurea (Hydrea). d4T and ddI are less susceptible to drug resistance than many competitors, and hydroxyurea helps to boost their action, even against drug-resistant HIV. In a 117-person Argentinean study, d4T/ddI/hydroxyurea performed almost as well as many protease combinations in people without prior treatment and low viral loads. d4T/ddI by itself was quite respectable, too. Other regimens: a combination of the experimental NNRTI effavirenz (Sustiva) plus Crixivan or another protease inhibitor; a three-nuke combination of AZT, 3TC and the experimental abacavir; and several double protease-inhibitor regimens. With little overlapping resistance, these combos could gradually replace one another when HIV makes a comeback, allowing many years of health.

It’s possible that you can gain extra years of stable health by sticking with a combo that once worked better but now allows modest viral loads, according to reports from San Francisco General Hospital and elsewhere. But you might also be encouraging drug resistance. It’s hard to say which way the advantage lies, and current research is of too-little help. In his conference address, Harrington complained of the profusion of small, quick “industry-oriented” studies that produce some information on a drug’s ability to reduce viral load -- and then are terminated. The bemused attendees at the Geneva conference are still waiting for the studies that indicate drug regimens’ value in a clinical setting: when it is best to start, how long the drugs can be taken and which to switch to. The research so far has shown no end to the number of medical gizmos we can add to our lives, while the number of years we can add remains a mystery.

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