Research for the New Millennium

A five-point plan that HIVers can live with (Part 1 of a 12-part series)

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As we enter this millennial year, many people with HIV have much to be grateful for, and much more to hope for. No one should discount the profound improvements in health and survival achieved in the past two or three years. Yet no one should overstate just how far we have come, either. While the shiny happy-face media have already celebrated a self-declared "cure" and moved on, flesh-and-blood HIVers face a lifetime of problems, with no guarantees as to how long the newfound benefits will last. The work of science is by no means over. The current mix-and-match drugs—the 13 nukes, nonnukes and protease inhibitors of combo therapy—are nowhere near good enough. The simplest, least toxic regimens disappoint over the long haul. Side effects multiply. A degree of nonadherence is certain. Even without it, certain resistant mutations will inevitably lead to drug failure and viral rebound. Already many people are on their second, third or fourth regimen—and fast running out of options. And those in the know voice deep distress about the state of experimental drugs in the pipeline: It hasn't been this dry since 1984.

Where do we go from here? The agenda for the next five years in AIDS research should be grounded in reality—less casting about for some magic-bullet, miracle drug than determining the best strategies for the drugs already available. There's little reason to breathlessly wait for "more powerful" HAART (highly active antiretroviral therapy) when what we have provides truly profound suppression of HIV—but still fails to complete the job. Yet before we start down this path, PWAs, activists, federal officials and the drug industry all need first to agree on our goal. An "undetectable" viral load—however appealingly quantifiable—is not enough. The goal is, rather, for people with HIV to live out their normal lifespan, free of opportunistic infections and with the fewest possible drug-related side effects. To get there, research must focus on five fundamental issues.

1. We must test structured "drug holidays" as a means to extend the uses of therapy and patient tolerance.

It's currently widely assumed that an "undetectable" viral load, once achieved, must be sustained with constant diligence and expensive drugs for the rest of an HIVer's life—a pharmaceutical-company wet dream. Many people have been fed the fiction that missing a single dose or temporarily going off therapy will lead to immediate resistance and the failure of all future regimens. This is utter nonsense, as is the attendant expectation that the body can tolerate 20, 30

or 50 years' continuous use of multiple antiretrovirals. The main factor that contributes to resistance is inadequate or inconsistent doses. The only time when a person almost certainly won't develop resistance is when off therapy altogether, since without therapy there's no selective pressure to favor drug-resistant mutations. What is the evidence that people live longer if they don't take drug holidays or that they must remain on therapy for a lifetime? So far, absolutely none. What is the evidence that lifetime use of therapy is likely impossible? Let me count the ways: Lipodystrophy, elevated triglycerides and cholesterol, diabetes, liver disease, chronic diarrhea—and that's only after a few years' experience As time passes, it's all but certain that these and other problems will affect more and more people.
The total effect—the pros and the cons—of continuously using HAART must be weighed against the total effect of cycling on and off therapy. The best strategy may well include structured periods of rest from these highly potent meds in order to let the body recover from them and, once again, "do its own thing" with the virus while we monitor carefully. What's needed to test this strategy is a five-year clinical trial. But this is something no drug company wants to see and few researchers have the patience to conduct. Plenty of people are already taking drug holidays, but because we aren't studying this systematically, we've learned nothing.

2. We must study the question of why people who "fail" therapy still seem to prosper clinically.

This intriguing phenomenon has been reported anecdotally for two years now but is only beginning to get serious attention. Our obsession with undetectable viral load has caused science to deem it a "failure" any time a person's viral load is measurable. Patient-attentive scientists and physicians have begun pointing out that those for whom the drugs work only temporarily or partially very often do as well as those who achieve ongoing success in suppressing viral load. This is not to say that therapy is irrelevant. On the contrary, it may be evidence that HAART is more effective than we had thought. Any significant suppression of viral load (such as a half-log or more) maintained for 12 weeks or more, seems to result in lasting benefits for a great percentage of people. This suggests either that total suppression of viral load is unnecessary or that the drugs provide some independent benefit to the immune system. Most scientists believe the former more likely. If true, it's high time we stopped driving HIVers crazy over whether or not their viral load is absolutely, perfectly on-the-newest-available-assay undetectable. Although measurable HIV in the presence of therapy should, in theory, lead to resistance and viral reproduction, that's not always happening in the real world. The important question is the clinical outcome, and how best to achieve it. Once again, what's needed is a structured clinical trial.

3. We need to determine the feasibility of "purging" the body's remaining reservoirs of infected cells.

While many wonks have written off "eradication" as a chimera, it is far too early to do so. To date, it's true, the data show that despite the best and earliest antiretroviral treatment, HIV infection is sustained by a small population of virus-holding "latent," or resting, memory CD4 cells. As long as viral DNA remains integrated into these cells, the potential for active infection persists. Yet it's only when such cells wake up, or become active, that the immune system can recognize them as

infected, and it's only when they start to produce active virus that the drugs can act against them. The next step—testing methods of activating these cells—is already underway. What's less widely known is that the first human experiment began a few years ago—and produced startling findings. At last year's World AIDS Conference in Geneva, Dr. Anthony Fauci reported that a chemical means of activating these cells might be the administration of IL2, a well-studied immunologic therapy. He raised the question of whether people treated with HAART plus IL2 have any fewer of these latently infected cells than those treated with HAART alone. He and colleague Dr. Cliff Lane, who has studied IL2 for many years, recently pulled together both a group of 13 people who have used HAART plus IL2 and a retrospective control group of 13 others who had similar baseline characteristics but received HAART alone. They studied the two groups intensively, hunting for reservoirs of latently infected cells, and discovered a profound difference between the groups. The IL2-treated people had consistently and often dramatically lower levels of latently infected cells. Of even greater interest, a portion showed no evidence of latently infected cells at all—even after the scientists had searched twice through nearly a half billion cells. They are now searching in tissue sites as well. While no one is shouting "Eradication!," this finding is a big leap toward that goal. The most promising aspect of all is that this occurred in chronically infected people, not simply (as in many such cases) in those infected only weeks or months before treatment. Whatever Fauci and Lane's new data show, they will be applicable to the average HIVer. This high-priority research needs to be repeated and expanded post haste.

4. We need to start taking some people off therapy altogether.

Several researchers have been treating "acute infection" patients for up to two years. At this point, we need to know whether these people can now maintain adequate suppression of HIV without further therapy. Certainly, there is reason to think this is possible—in fact, it has already happened. Researchers in the United States and Europe are currently studying 10 people who have stopped therapy on their own without seeing a return of measurable viral load. One—the famous "Berlin patient"—has gone more than 18 months without therapy and without measurable viral load. And even if some virus returns, as long as it remains below some as-yet-undefined modest threshold, it might make sense for these people to stay off therapy. Media hype has popularized the hysterical notion that by quitting combo therapy, these people are dramatically risking their lives for science. Nonsense—HIVers do it every day. The worst-case scenario is that viral load skyrockets, in which case they go right back on therapy. There's no reason to expect that such a step leads immediately and irrevocably to resistance. To the researchers and patients involved, I say, "Just do it." At Harvard Medical School, a study led by Dr. Bruce Walker is now taking this bold step.

5. We must intensify the search for natural, biological methods of viral control.

If, unfortunately, it turns out that a lifetime of therapy is necessary to keep people with HIV healthy, it's clear that none of the drugs in our current arsenal is good enough to hit that bull's-eye. Yet we have learned that the body employs, at least temporarily, its own innate means to effectively suppress virus through a combination of antibody production, chemical messengers and HIV-specific cell responses. So this is where we should be looking, not just in the vats of Price-

Gouge Pharmaceuticals, Inc. Still, the amount of federal research dollars dedicated to this task is miniscule.

So the next five years in AIDS research must shift our focus from the promotion of the latest "wonder" drug to practical studies of realistic, long-term strategies. A new protease or, for that matter, integrase or tat inhibitor, is far less likely to get people through a lifetime than a well-thought-out plan. Simply by using the tools we already have in more ambitious ways, lifesaving outcomes are within our reach. In the end, these will serve us better than any fantasy of a single-drug cure.

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