# Hit Me, Baby, One More Time

Even as they debunk a much-hyped case of superinfection, researchers have finally launched a study to prove whether or not HIVers can be “twice bitten” by their nasty bug. Meantime, torn between courting drug resistance and playing it latex, HIV positive couples are going on horse sense -- and, likely as not, barebacking.

November 1, 2001 By Tim Murphy

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In a dramatic late-breaker at a big AIDS confab, Ottawa Hospital’s Jonathan Angel, MD, presented a grimly fascinating story. Patient A, an HIV nonprogressor for nearly a decade, abruptly saw his CD4 cells, which had always hovered at a lush 600, plummet, crossing paths with a suddenly skyrocketing viral load. HAART was no help -- strange in someone who had never before taken anti-HIV meds. In the course of things, Patient A told Angel about having had unprotected sex with a certain Patient B (now deceased), who, it turned out, was burdened with an apparently multidrug-resistant virus and was hurtling fast toward AIDS. On a hunch, Angel and his colleagues hit the lab, comparing the genetic sequence of both A and B’s current 1998 virus to a deep-freeze sample of A’s 1989 HIV.

To cut to the chase, A’s 1998 model looked not only significantly different from his older one but uncannily similar to B’s. Angel’s answer? It seemed very likely that A had been reinfected by B’s multidrug-resistant bug. Of course, the case would have to be confirmed, yada, yada.... But to everyone from nervous preventionistas to nervy skin-to-skinners, this was Big Stuff: the first human case suggesting that reinfection -- or its more dramatic moniker, superinfection -- was for real.

## THE BUZZ AND THE BUZZSAW

Not surprisingly, the media blew up Angel’s cautious presentation into ironclad proof of reinfection, issuing fire-and-brimstone warnings to HIVers lest they spread a dread “supervirus” impervious to all known meds. “Researchers Alarmed by Case of HIV ’Superinfection’: More Potent Strain Takes Hold in Stable Patient,” webmd.com warbled with nary a qualification, as did hivandhepatitis.com’s headline: “Second HIV Infection Causes Rapid Disease Progression in HIV Positive Gay Man.” Such leaps provoked many to agree with the AIDS Survival Project’s David Salyer, who wrote in the group’s newsletter, AIDS Survival News, “Since this kind of research has been going on for over a decade now, and this is the one and only documented case..., we would be better served by waiting for verification of Dr. Angel’s study before mounting a massive public health campaign.”

Fast-forward to August 2001, when Salyer and company got their follow-up from Bob Grant, MD, of the University of California at San Francisco’s prestigious Gladstone Institute of Virology. After

replicating lab research on patients A and B, Grant announced his findings at the CDC's annual HIV prevention conference. This time, not only did each of the two men's virus look strikingly less alike than before, but when gene sequences -- likely contaminated -- used in the Ottawa round were eliminated, there was no evidence at all that either patient even had drug-resistant virus. "The data was insufficient to prove that reinfection had occurred," Grant says. "As nearly as we can tell, the Ottawa case was not a case of superinfection."

But before the reinfection naysayers could let out a mass "Told you so!" and the reinfection faithful a chorus of injured pride, there were rumors of a second case, then a third...and as news spreads among AIDS researchers, the list of maybes will likely grow. And precisely because the specter of superinfection looms so large, with implications both for the treatment of people with HIV and for a possible vaccine, the Gladstone Institute recently joined forces with UCSF's Center for AIDS Prevention Studies (CAPS) to launch the CDC-supported Positive Partners Project -- according to Grant, "the only study ever designed to look for superinfection."

How? By enrolling a large cohort of HIV positive couples, recording their baseline viral profile and looking, year after year, for genetic changes that might indicate that one partner has acquired the other's strain of HIV (or, for that matter, somebody else's). At press time, the study had enrolled 18 couples and was about to do its first lab follow-up, according to project director Jeff McConnell, who hopes to enroll another 180 couples. "This is a study that a lot of people said was impossible," Grant says with pride. "It struck us as odd that they'd say that. But we've been able to do it simply by focusing on HIV positive people having active sexual lives. And a right to those sexual lives. And to all the information they need to make sexual decisions."

**BIG HAART, BIGGER STAKES**

But even as more light is shed, researchers warn, the reinfection question is riddled with all the same thorns that, for example, make it impossible to declare definitively whether condomless oral sex is safe -- or safe enough. First of all, "How do you prove a negative -- that something doesn't happen?" asks the CDC's Bernard Branson, MD, Positive Partners' project officer. Then there are technical problems -- reproducing viral DNA in a lab to confirm previous findings and having to discard lab results due to contamination. (It is worth noting that research in humans and monkeys provides what Grant calls "abundant evidence" that it is possible to be infected by a second strain of HIV before primary seroconversion -- that is, in the three-months-or-less interlude between exposure and infection to a first strain. Scientists dub this coinfection to distinguish it from the present mystery of reinfection.)

The crucial question about reinfection is not whether it can happen (most experts vote yes) but how often it actually does happen. "We don't need absolute proof that it doesn't happen," Branson says. "We need a whole bunch of evidence that if it happens, it's pretty rare or it doesn't cause much harm. I'm not in this for the scientific purity of thought."

So is reinfection rare, as leading researcher Jay Levy, MD, concluded in his seminal 1994 book, HIV and the Pathogenesis of AIDS? Branson seems to think so. "If you look hard at the places we're looking at, like San Francisco, where everyone screws a lot -- or at least it's reported they do," he

says, “if this were common, we would have seen far more of it by now.”

But Angel disagrees. “My sense is that [even] superinfection occurs probably commonly, but proving it is very hard,” he says. “For it not to occur, it would mean that a person’s immune system was perfect in being able to prevent infection by a virus. And those who already have HIV certainly have less-than-perfect immune systems.” Calvin Cohen, MD, research director of Community Research Initiative of New England, echoes Angel’s assessment: “The absence of proof of reinfection is not the proof of absence. There are plenty of reasons to hope that reinfection won’t happen -- but there’s little reason to expect it not to.”

Of course, that message was not much heard before the age of protease-powered combos, when many HIVers assumed that they could screw one another sans latex till the cows came home, there being nothing left to lose. Indeed, selling the bright side of viral enhancement, the late activist Stephen Gendin quipped in a June 1997 POZ column, “Membership has its privileges.” In those days, “there wasn’t much evidence of the efficacy of these new drugs,” Grant says. “Even if superinfection did occur, it didn’t really matter to anyone.”

But now reinfection, however theoretical, is right up there with lipodystrophy, maxed-out credit cards and career rehabilitation on the list of things HIVers get to worry about in return for a new lease on life. According to Angel, infection with an HIV strain resistant to at least one class of meds has climbed in urban areas from 0 to between 5 and 15 percent in just five years. And if reinfection does occur amidst such rising rates, Grant says, “you can easily imagine scenarios in which people acquire a second virus and their HAART fails.”

Yet even if drug-resistant reinfection is common, it doesn’t spell disaster for HIVers on HAART. “I doubt it’s a major reason for HAART failure,” says Angel, venturing that people on effective combos “have some anti-HIV immunity and are probably better able to prevent a second infection. And if they’re not on treatment and the first virus is already causing damage, the second will probably be less strong.” Others point out that drug-resistant strains, while often strong enough to be transmitted, don’t replicate anywhere near as rapidly as standard drug-sensitive (or “wild-type”) HIV. And a steady stream of new drugs in the pipeline shows promise in squelching virus that has mutated its way around current meds (see “Whatever Happened to Patient A?” below ).

**A COUNSELING CONUNDRUM**

Yet until a massive-cohort study like Positive Partners offers substantial evidence one way or the other, what’s a lusting-but-not-for-latex lovebird with HIV supposed to do? “I’m worried about the spin from this,” Grant confided to POZ just days before publicly debunking the theory of reinfection in the Ottawa case. “I do intend to remind people that HIV is just one of many STDs that HIV-seroconcordant couples may be discordant for.” He proceeded to deliver a perky bouquet of viral delights -- including HPV (anogenital warts), KS (Kaposi’s sarcoma), HSV (herpes), hepatitis B and C, syphilis and gonorrhea -- that can manifest more virulently in HIVers, accelerate HIV’s progress, make HIV more infectious and play a role in such disorders as liver failure or cervical/rectal cancer. (And note well: As abstinence-only congress members have recently roared, condoms aren’t as effective in preventing a skin-to-skin virus like herpes as they are a fluid-borne one like HIV or

hepatitis B or C.) “The take-home message simply has to be that superinfection may well occur,” Grant adds.

And yet. “If condoms would be disruptive to an otherwise good relationship...,” Grant trails off, and then adds, “Everyone has to weigh the value of the relationship.” Branson agrees: “If people with HIV were blithely told, ’You can’t ever have unsafe sex again because of reinfection,’ that’s an incredible burden.”

So, bedeviled HIV prevention “experts” are fielding questions and trying to provide answers across a vortex of knowledge -- all the more vexing in a field that has recently made tremendous strides in closing the information gap. When HIVers ask staff at AIDS Project Los Angeles if they can be reinfected, “in order to cover all the bases, we say yes, there is the possibility, and you should practice safe sex,” says David Pieribone, APLA’s associate director of education. “I don’t think there’s been a strong case made that reinfection occurs, but there’s the possibility. So from a public health perspective, I don’t think we would be responsible if we said anything else.”

**NO PEEPS FROM THE PEANUT GALLERY**

That is, if everyday HIVers are inquiring at all -- which, it appears, they do not. “At least as I sense it in this city,” says Alfredo Armendariz, who coordinates Stop AIDS Project’s information seminars for newly infected (largely gay male) San Franciscans, “there’s not that fear or concern. Mostly what I hear is ’I’m already infected -- reinfection’s a risk I can take.’” In the same vein, according to Noel Alicea, a spokesperson for New York City’s venerable Gay Men’s Health Crisis, its AIDS hotline has received just “a few calls” on the subject. Perhaps such a dearth of curiosity has kept other information centers from getting straight even what little there is to know about reinfection. When POZ queried a counselor on the anonymous hotline at Boston’s pioneering Fenway Community Health Center, the counselor clearly stated, “It is possible to get reinfected with HIV,” which is “quite scary because of drug-resistant virus.” When told that the latest research offered no strong evidence either confirming or denying reinfection, the counselor qualified this response as reflecting “what some doctors believe. I have to let callers know it is a strong possibility.” When asked if there were other concerns around unprotected sex between HIVers, like the commonly invoked one of other STDs, the counselor said, a bit disturbingly, “Not that I can think of.”

So, why aren’t HIVers storming the great towers of AIDS science demanding to know if viral lightning can strike twice? Frankly, my dear, they don’t give a damn -- or so it seems. Last year, shortly after news of the Ottawa case sent a chill through the medical community, anonymous HIVer “Mr. X,” in a contentious interview in the APLA mag Positive Living, defiantly declared, “I’d rather spend 10 years fucking around with other HIV positive guys and having a great time...than clench my butt and worry about that one-in-a-million chance of getting reinfected.”

A year later, his logic is alive and well among the positive and the restless. Already burdened with the physical and psychic toll of the virus’ proven demons -- from drug side effects to disclosure -- HIVers are saying “Basta!” to fretting over anything that still, to quote Chaka Khan and Rufus, ain’t nothin’ but a maybe.

New Yorker Luther (not his real name), 33, says that people in “the medical establishment,” not to mention his shrink, have told him that “I should always take precautions even though I’m infected. But they also reiterate that their primary concern is STDs, which to me has always implied that they don’t even buy reinfection.” Whatever the risks, he says, he doesn’t use condoms with other HIVers, “and I have yet to meet another poz guy who bothers, either. No one believes that it’s a threat. The trade-off seems worth it.” Fellow Manhattanite Trent (not his real name), 31, strikes a similar note: “I try not to get myself too worried about things that aren’t for sure yet. I figure if the experts can’t figure it out, I certainly can’t.”

Still, when asked if he would change his ways if “strong evidence” emerged that reinfection occurs, Luther snaps, “Of course” -- just as many HIV negative folks say that they will perform oral sex unless they know for sure someone is positive. Pietro (not his real name), 39, of Los Angeles, allows that he has only one misgiving about the bareback sex he’s had with other HIVers -- the single occasion when a guy revealed that he had multidrug-resistant HIV only after Pietro “took his cum.” And Trent, well into his first year of recovery from a crystal-meth addiction, concedes that when he barebacked recently, “I was very uncomfortable about not having used a condom. I think it’s due to caring about myself more than I used to.”

**LOVE WALKED IN**

Such dispatches come from gay-ghetto HIVers who aren’t riding just one stallion or haven’t yet chosen a favorite from the stable. But what about those, straight and gay, who’ve found their seroconcordant soulmate? This is when the hypothetical reinfection game gets real. For one thing, if reinfection can occur between any two HIVers playing raw, it’s more likely to happen between repeat offenders than a two-backed beast on a one-night stand. And the emotional stakes are higher, too. You may never know that your virus caused a handsome stranger’s treatment failure, or which handsome stranger caused yours. But all that is different with a lover -- that’s the “for better or worse” clause.

So learned David Salyer, of the afore-quoted AIDS Survival News column sniping at reinfection alarmists, when he began dating a guy who’s also positive. “Both of us were looking for something monogamous,” he says, “and both of us reject the idea of reinfection. So, after ruling out the possibility of exchanging any other STDs, we decided to abandon condoms. But my 15 years of condom use and all those safer-sex messages are deeply ingrained -- I’m still unable to ejaculate inside my partner!”

Conflicted impulses or no, Salyer and his boyfriend have enrolled in the Positive Partners study “because we wanted to be part of research that we believe will ultimately refute the theory of HIV reinfection,” Sayler says. “It’s time we got to the truth, and if that means I have to be a test animal, I’m OK with that.”

As with all things AIDS, in the absence of clear-cut answers what suffices are common sense, intuition and the wisdom gleaned from shared experience -- accompanied, of course, by love and desire, those twin forces that impel even as they imperil. Positive Partners’ McConnell has the last word: “A lot of the couples in our study have been given the impression over the years from their

doctors that reinfection really happens. Some believe that it does, but then say, 'Honestly, we don't care.' If the other shoe drops and we do ever confirm reinfection, it's still an open question what positive couples will do."

**Whatever Happened to Patient A?**

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Twenty years ago, we at least had a name and face to peg Patient Zero -- in the personage of French-Canadian airline steward Gaetan Dugas. But will we ever know the fate of Ottawa Hospital's Patient A, the long-term nonprogressor who last summer became the first documented -- but later debunked -- case of apparent HIV superinfection? At press time, Jonathan Angel, MD, the doctor who presented the case at an August 2000 conference, says that he knows *nada* of A's current condition or whereabouts.

Even more vexing than A's disappearing act is why, absent reinfection, a decade-long nonprogressor would suddenly take such a marked turn for the worse. Experts agree that it's because, uh,progression happens -- even among nonprogressors. "They may have had a defective virus that finally gets more fit. Or their host systemfinally collapses," UCSF's Bob Grant, MD, says, after mentioning a study that failed to find any common unifying viral or cellular trait among nonprogressors. The CDC's Bernard Branson, MD agrees that it's"very common" to see longtime healthy HIVers finally start trading CD4cells for viral load.

So far, so bad. But if A didn't inherit B's drug-resistant virus after all, why did he respond so slackly to HAART, which usually works best on pharmacological blank slates like himself? The answer may be that -- HAART-boosters, fasten your seat belts! -- "the cocktail"doesn't always work. "HAART is failing all the time," says Positive Partners' Jeff McConnell, adding that for 58 percent of HIVers on HAART, any one effective med combo will poop out within two years.

That's why pharma's race for new options should quicken. For example, Patient B's virus originally looked to be resistant to protease inhibitors (PIs) and NRTIs (nukes) but had never encountered NNRTIs (non-nukes) -- and, Angel says, that's exactly what he would put B on if he were alive today, along with Kaletra, a two-in-one PI (lopinavir and ritonavir) showing success in HIVers with failing regimens. Likewise, a patient with resistance to all three drug classes might respond well to power-PI Kaletra, tenofovir (the first nucleotideanalogue, see "Tenofovir") or one of another forthcoming class called fusion inhibitors.

The message to Patient A, wherever he is? Stick to your treatment, or get back on it...and drop us a line!

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