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AIDS drugs for HIV negatives:
the dangerous new trend in AIDS medicine

A January 22, 2006 article[1] in *The New York Times Magazine* promoted the idea that gay men – not just HIV positive gay men – but all sexually-active gay men (among others) should be given an AIDS drug, on the assumption that doing so would stop AIDS. The drug in question is called Tenofovir (brand name Viread), which the writer, Jon Cohen, described as "a drug that appears safer than the other AIDS medications on the market[1]."

Cohen asked, "Could the sexually active take antiretrovirals [AIDS drugs] to avoid contracting H.I.V. in the first place?" The answer is: Some people are willing to find out.

Cohen reports that "a recent survey conducted by the U.S. Centers for Disease Control and Prevention at Gay Pride events in four U.S. cities found that seven percent of those interviewed said they had tried it." The result? "A half-dozen studies are now under way that will determine whether these men are onto something."

This use of powerful AIDS drugs, in healthy young people who are neither HIV positive nor have AIDS, certainly needs a buzzworthy name to sell it, and it gets one: "PrEP!"—Pre-Exposure Prophylaxis. As in, Don't get HIV, get "PREP-ed!"

Andrew Sullivan, conservative, gay HIV-positive pundit, liked the idea, and wrote on his blog: "Why not put all HIV-negative men on a simple anti-retroviral regimen as a prophylaxis, rather than as a treatment?… My own view is that gay men, if the studies pan out, could and perhaps should embark on a proactive campaign to get as many sexually active men as possible on meds[2]."

Sullivan opined: "We're used to taking pills after we've become sick. Why not take them before – as a prevention technique?" Why indeed? Who could object to that line of thinking? Besides the FDA, which mandates that the manufacturer, Gilead Sciences, carry the following warning on the drug's package insert:

"VIREAD does not reduce the risk of passing HIV-1 to others through sexual contact or blood contamination."

Kind of a mixed message, don't you think? Maybe so for you and me, but not for the individuals and couples around the world who will be taking Viread as part of NIH (National Institute of Health) and WHO (World Health Organization) clinical trials.

I went looking to see what Viread would actually do for these young people. I found this at the doctor-run medical information website HIVandHepatitis.com[4]:

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[1] https://www.nytimes.com/2006/01/22/magazine/protect-or-disinhibit.html

"All of the RTIs, including Viread, are associated with a relatively uncommon, life-threatening toxic reaction called lactic acidosis and severe hepatomegaly with steatosis (i.e., acid in the blood and a fatty, enlarged liver)."

I found the same thing repeated on the manufacturer's FDA-mandated label (which they write in all capital letters, for some reason):

WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS [Tenofovir, 3TC, AZT, etc] ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS.

Doesn't sound good, but what does it mean? The AIDS Treatment Data Network[4] (a non-profit treatment advocacy group) explained it this way:

"Anti-HIV nucleoside analogs impair the function of mitochondria. This can lead to increased acid levels in the blood [lactic acidosis], and an enlarged fatty liver [hepatomegaly with steatosis]. The symptoms are severe nausea, shortness of breath and vomiting that does not get better." (Yikes!)

The warning at HIVandHepatitis.com goes a little further, explaining that that the drugs "can cause damage to DNA (genes) in the mitochondria (energy producers) of cells [which] may be the cause of many of the significant toxicities associated with each drug in this class."

But, they noted that Viread was, thus far, not as bad as other AIDS drugs: "There is preliminary, *in vitro* evidence that Viread is the RTI least likely to cause mitochondrial damage," but, they cautioned, "these data are not definitive in that regard."

"In Vitro," from the Latin for "in glass," literally means an experiment done in a glass container, but in practice it refers to any experiment done with laboratory machinery, as opposed to something observed in a human or animal.

Maybe that's what Cohen meant in the *Times'* story by "appears safer" – there is simply no long-term data available yet. At least that's the impression you get from reading the warning label, which states: "The long-term effects of VIREAD are not known at this time."

So, what do we know about the drug?

The FDA label explains that Tenofovir is a DNA chain-terminator[5]. It works by disrupting the normal replication of DNA in cells, in order to stop the replication of viruses, if any are there. Of course, in HIV-negative people, the only DNA chains available for "termination" belong to the cells, tissue, blood and bone marrow of the person taking the drug. This is probably why DNA-chain terminators have been so effective at causing anemia, bone marrow suppression, organ failure, birth defects and death in patients who have taken them[6].

The FDA reports that Viread also destroys bone:

"Twenty-eight percent of VIREAD-treated patients…lost at least 5% of Bone Mineral Density at the spine or 7% of Bone Mineral Density at the hip."

The FDA adds that the drug's effects "on long-term bone health and future fracture risk are unknown," although four people in one study developed "clinically relevant fractures (excluding fingers and toes[7])."

These illnesses: "Hepatitis, Renal [kidney] failure, Acute renal failure, acute tubular necrosis [blood vessel death], Pancreatitis, Fanconi syndrome [kidney damage]," were also associated with the drug. And the list goes on – "diarrhea, nausea, vomiting, flatulence, weakness," and on, "inflammation of the pancreas, dizziness, rash, kidney problems," and on, "The list of side effects is not complete."

The label also warns: "Do not take VIREAD if you are allergic to VIREAD or any of its ingredients," which is a little bit funny; I mean, how do you tell an allergy from a side-effect, like "vomiting that does not get better?" The warning continues, "If you suspect that you took more than the prescribed dose of VIREAD, contact your local poison control center or emegency room right away."

In that case, better tell poison control in Brazil, India, Thailand and Africa to get ready. That's where the NIH and WHO are enrolling participants for human trials with the drug. They're enrolling 1,200 healthy, sexually active, HIV-negative 18-29 year-old women and men in Botswana[8].

They're accepting "healthy volunteers" for a study in 1,600 HIV-negative drug users in Thailand[9], as well as 3500 people in India, Brazil, Malawi and Thailand, where the drug will be given to the HIV-positive partner from a "discordant" couple (that's where one partner tests positive, one tests negative), to see if it protects the other from contracting HIV[10].

The trials are also going on in the U.S., but not in young, healthy heterosexual couples. No, the study here specifically asks for 400 HIV-negative men who report any anal sex with a man in the last 12 months[11]. The "discordant" couples trial is also recruiting in the US, but, again, not for everyone. The trial is being held at the Fenway Clinic, Boston's gay health center.

The trials are placebo-controlled, so about half of the people enrolled will be taking the drug, and half (the placebo group) won't. Unless, I suppose, they *seroconvert* (become HIV positive) during the study. Then they too will be put on AIDS drugs.

That is, the participants will be subject to regular HIV testing throughout the length of the trial (and the couples' trial is slated to last over seven years). If they become HIV positive, they'll simply be put on the same drugs they were (or were not) taking to avoid becoming HIV positive. As you can see, it's quite an offer.

Where, one might ask, does an inspired idea like this come from? The answer: the streets of San Francisco. And I mean, the streets. The trial in that fair city, with 400 healthy, HIV-negative, gay and bisexual men, is being conducted Dr. Susan Buchbinder, head of HIV research at the San Francisco Department of Public Health.

The *Times* reported that Buchbinder decided to conduct the Tenofovir trials for two reasons. The first: "because Tenofovir PrEP had worked well in research monkeys." The second: "because she'd heard the anecdotes about underground use, including a cocktail known in street slang as the 3V's: Viread, Viagra and Valium." Street slang and pill-popping – a revolutionary inspiration for establishing international drug trials and medical policy, to be sure.

The details of the monkey research is also worth noting. AIDS researchers tried for a long time to study AIDS in chimpanzees, thinking that these primates, our nearest genetic relatives, would be the best subjects to help us unlock the riddles of the paradigm[12]. But it hasn't panned out.

As the *Times* reported in 2003:

"In the early days of the [AIDS] epidemic, scientists theorized that the chimp would be a useful model to study the disease in people….only to find that although chimpanzees could contract the AIDS virus, they rarely became sick from it. That distinction makes it hard to use the animals to test treatments or vaccines[13]."

So no chimps in the Center for Disease Control's (CDC) PrEP studies. Instead, they're using smaller monkeys called macaques. And doing so, they claim that Tenofovir will protect healthy heterosexuals from contracting a deadly STD. How have they accomplished this remarkable feat? By shoving some proteins up….well, you'll see.

Here's the title of the study: "Prevention of *Rectal SHIV Transmission* in Macaques by Tenofovir/FTC Combination[14]". Here it is again, in greater detail: "Tenofovir/FTC combination protected all 6 treated animals from infection after *fourteen repeated rectal SHIV exposures*[15]."

As a result, we now know that drugging six monkeys with DNA-chain terminators prevents them from testing positive, by some standard, for up to fourteen anal exposures of "SHIV." Gosh, I hope we at least bought them dinner.

But what's "SHIV"? The paper explains that SHIV stands for "Simian [monkey] Human Immunodeficiency Virus." But it's not just any old SHIV: "All animals were subjected to weekly rectal exposures with a low dose of SHIVSF162p3…"

And what is "SHIVSF162p3", you ask? Well, who knows? It's a molecular biology experiment. A laboratory construction of synthetic proteins and genetic material derived from bits and pieces of various monkeys and humans. So, you can see how this relates to heterosexual intercourse in young, healthy men and women in India, Botswana, Thailand and Brazil. Or to sex between healthy gay men [and other non-monkeys].

But there's another problem. These studies are being done with "Tenofovir/FTC." That's two drugs, not one. Two different drugs, because Tenofovir, on its own, didn't do what the monkey-rumpers wanted it to. So what's the point of giving Tenofovir to thousands of healthy individuals?

But even asking these questions can be dangerous. Criticism of AIDS research has typically been met with a forceful response. Asking questions like those posed above is called "denialism." A heavy charge like this tends to silence critics. But if, despite this warning, you still don't think Tenofovir PrEP is a good idea, it probably means one thing: you're not an AIDS specialist.

The *Times* asked Dr. Marcus Conant, a San Francisco AIDS clinician about the drug. His response? Conant "has high hopes that tenofovir PrEP will work wonders. Indeed, he already prescribes it to a half-dozen select patients."

"With my patients, it's not even ethical for me to wait for the science," Conant told the *Times*. "I can identify those patients who I know are at extremely high risk." (How does he do that? Easy, it's the ones who take street and prescription drugs in wild combinations.) Conant adds: "Should I wait for the scientific evidence to prove that it doesn't work before I give it to someone where it may work?" (No, why wait? What's the worst that could happen?)

So, will gay men take Tenofovir? A potential death sentence, a slow-drip of poison, as pre-penance for their cultural sin? I'm sure some will, and I'm sure some will feel grateful for the privilege. Like the 7% of people at Gay Pride parades. Andrew Sullivan stated that taking the drug would be "a way for HIV-negative men to do something which is not simply defensive in nature, and make decisions about their health in a moment outside the inevitable irrationality of a sexual encounter."

Sure, we'd hate to be irrational about sex. "Next up," he wrote: "Include vulnerable African American women in the discussion."

Of course – vulnerable black women! They'd hate to be left out of this. But I'm not worried. I'll bet we have drug studies lined up for them already.

References and Notes

Top Photo: Demonstration by ACT Up Paris at the 2004 AIDS Conference in Bangkok. HERE The sign reads "Tenofovir me fait vomir" – "Tenofovir makes me puke." More from the protest HERE

[1] "Protect or Disinhibit?" Jon Cohen, The New York Times Magazine, January 22nd, 2006. Cohen is the author of "Shots in the Dark: The Wayward Search for an AIDS Vaccine."

So where is the vaccine? Cohen writes in the *Times*' article: "Even if it works spectacularly well, tenofovir PrEP will not substitute for an AIDS vaccine, the holy grail of prevention research…Then again, no AIDS vaccine is on the near horizon." *Note the meaning here: no AIDS vaccine, so instead, we're going to drug perfectly healthy people*.

[2] Drugs and Negs Andrew Sullivan, The Daily Dish, a Time, Inc. blog.

[3] Viread Label Gilead Sciences/FDA.

[4] Viread – Cautions and Warnings from the doctor-run medical information site HIVandHepatitis.com. Viread – a Simple Fact Sheet – The AIDS Treatement Data Network.

These are two of the many HIV info and advocacy sites like Aegis.com and The Body.com often funded by pharmaceutical companies, providing information complied from FDA documents and studies.

[5] From the Viread label[3]: "Tenofovir diphosphate *inhibits the activity of HIV-1 reverse transcriptase* [a ubiquitous cellular enzyme found in human and animal cells, also used by retroviral particles] by competing with the natural substrate deoxyadenosine 5â€™-triphosphate *and, after incorporation into DNA, by DNA chain termination*."

[6] AZT, the premiere nucleoside analog, the basis for Tenofovir and at least a half-dozen other major AIDS drugs, has been studied at length. Get past the front page reporting about AIDS wonder drugs, and you find consistent reporting on the drug's overwhelming toxicity – anemia, bone marrow suppression, accelerated illness and death. For example:

"AZT has similar effects in children as in adults. We have previously documented that AZT accelerates the deaths of those taking that drug compared to HIV positive people who do not take AZT." (*The New England Journal of Medicine 324: 1018-1025, 1991*)

"Babies whose mothers had ZDV [AZT] exposure during pregnancy had a greater incidence of major malformations than those whose mothers did not. " (*J Acquir Immune Defic Syndr. 2000 Jul 1; 24(3): 249-256.*)

"Finally, survival probability was lower in children born to ZDV+ [AZT treated] mothers compared with children born to ZDV- [no AZT] mothers." (*AIDS. 13(8):927-933, May 28, 1999.*)

[7] Bone mineral density loss: U.S. Food and Drug Administration Viread (Tenofovir Disoproxil Fumarate) Labeling Revision

[8] Study of the Safety and Efficacy of Daily Tenofovir Disoproxil Fumarate for the Prevention of HIV Infection in Heterosexually Active Young Adults in Botswana (Study ID Numbers: CDC-NCHSTP-4321; BOTUSA MB04)

"This study will test whether taking a pill of tenofovir (an antiretroviral medicine) is safe for sexually-active young adults in Botswana without HIV infection and whether it will reduce their risk of getting an HIV infection."

Enrolling 1,200 people. Ages:18-29, "healthy and sexually-active." "Volunteers will be randomized to receive either Tenofovir or a placebo pill to take once a day. Volunteers will be seen monthly for at least 12 months to monitor for side effects and toxicities and to test their HIV status."

"Persons who become HIV infected during the trial will receive ongoing supportive counseling, CD4 and viral load monitoring, education about HIV infection/disease, and access to HIV care including free antiretrovirals when clinically indicated."

[9] Study of the Safety and Efficacy of Daily Tenofovir to Prevent HIV Infection Among Injection Drug Users in Bangkok, Thailand (Study ID Numbers: CDC-NCHSTP-4370)

"The primary goals of this study are to assess the safety and efficacy of daily tenofovir to prevent parenteral HIV infection among injection drug users (IDUs)."

Enrolling 1,600 people. Ages: 20-60. Both Sexes. Accepts Healthy Volunteers. "This is a phase II/III, randomized, double-blind, placebo-controlled study of the safety and efficacy of chemoprophylactic **tenofovir, administered orally once daily to IDUs**… Medication adherence will be measured as: rates, by interview and documentation on tenofovir adherence card, of participants taking at least six (86%) of **seven daily doses of study drug** each of the four weeks preceding the monthly study visit."

[10] A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus HIV Primary Care Versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 in Serodiscordant Couples (Study ID Numbers: HPTN 052)

"This study will determine whether anti-HIV drugs can prevent the sexual transmission of HIV among couples in which one partner is HIV infected and the other is not."

NOTE: *This is a precise inversion of the two related studies. Instead of asking whether a 'negative' person can avoid becoming 'positive', this study claims to see if a person who tests positive will be "less contagious" because he or she is taking Viread and up to seven other drugs. A remarkable claim, given that in 20 years of AIDS mayhem, the mainstream dogma has always denied the possibility that anything could make a person, once having tested positive, either be uninfectious or revert to negative (or live a normal lifespan*).

"Enrolling 3500 people. Ages: 18 years or above. Nevirapine; Tenofovir disoproxil fumarate; Atazanavir; Efavirenz; Didanosine, enteric coated; Stavudine; Lamivudine."

"**Breastfeeding is allowed at enrollment**; however, during the initial enrollment period, women may not be on a regimen containing study-provided atazanavir if they are breastfeeding" [*But the other 7 drugs are allowed – what do you think – better or worse than secondhand smoke*?]

"Participating couples will be enrolled for approximately **87 months** (**7 years, 3 months**)."

[11] Extended Safety Study of Tenofovir Disoproxil Fumarate (TDF) Among HIV-1 Negative Men (Study ID Numbers: CDC-NCHSTP-4323)

"The purpose of this study is to examine safety and tolerability of daily tenofovir use in HIV-uninfected men… Enrolling 400. Ages 18-60. Healthy biological male (male at birth). Reports any anal sex with a man in the last 12 months. Able to understand English."

Recruiting at the San Francisco Department of Public Health, SF, California, and the AIDS Research Consortium of Atlanta,Georgia.

[12] Hypotheses on the origins of AIDS: Chimp origin of HIV-1 Nature, 1999 | and a very different view on the psychological underpinnings of AIDS

[13] "For Retired Chimps, a Life of Leisure", Sheryl Gay Stolberg, The New York Times, January 7, 2003.

[14] "Prevention of Rectal SHIV Transmission in Macaques by Tenofovir/FTC Combination" (Heneine, Walid. Laboratory Branch Division of HIV/AIDS Prevention, CDC, Atlanta, GA). Presented at the 13th Conference on Retroviruses and Opportunistic Infections. Denver, Colorado. Feb 5 – 8, 2006) Summary

[15] CDC Abstract: Prevention of Rectal SHIV…. (ibid) "All animals were subjected to weekly rectal exposures with a low dose of SHIVSF162p3 (10 TCID50; 3.8×105 virus particles), which expresses an R5 tropic HIV-1 envelope that *resembles* naturally transmitted HIV-1 strains. Infection was monitored by serology and PCR amplification of *SHIV gag and pol sequences* from plasma and peripheral blood lymphocytes, respectively."

NOTE: *My reading of the study – it's more than a stretch from study to claim: These researchers postulate that some aspect of the SHIV construct causes the expression of a protein (in vivo? in vitro?) that "resembles" a protein which might be used by some retroviruses (what they're calling HIV) in humans. (What is it to "resemble a protein"?) At the same time, they're drugging the monkeys with Tenofovir/FTC, and injecting a gene/protein mixture into the monkeys' rectums. They then do PCR (Polymerase Chain Reaction – gene fragment copying tests) and antibody (blood, "serology") tests on the monkeys to see what kind of reaction occurs between the monkeys' blood and the test materials. They're testing for a sufficiently strong or weak reaction between what they take out of animals, (once they fill their rectums with SHIV) and the material in the test kits (those proteins and gene sequences they associate with the SHIV construct). It's awfully loose, speculative stuff, in my view, with too many a priori assumptions in place, to validate drugging healthy people with very strong drugs*.