RESEARCH INITIATIVE

Treatment *Action!*

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Letter from the Executive Director

Dear reader,

In this issue of *Research Initiative, Treatment Action* (RI*TA!*), we explore a novel and exciting use for anti-HIV medications: preventing HIV infection. This issue features two comprehensive reviews of what has come to be known as PrEP – preexposure prophylaxis – and two interviews with experts in the field.

In one of those interviews, Robert Grant (UCSF), principal investigator of the iPrEx placebo-controlled PrEP trial in gay and bisexual men and transgender women who have sex with men, offers further details of that research and his interpretation of key findings. Grant strongly argues that healthcare professionals should consider PrEP for anyone who states they want to find new ways to protect themselves or their partners from HIV, regardless of apparent or perceived risk factors.

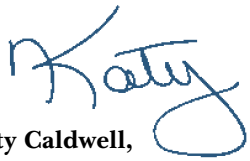
In a second interview, Raphael Landovitz (UCLA) explains how he and other clinicians have begun integrating PrEP into practice, fielding tough questions such as whether substance-abusing PrEP candidates should be offered PrEP.

The first review article analyzes the importance of adherence to once-daily Truvada as PrEP, the potential for less than once-daily PrEP, resistance risk with Truvada as PrEP, and cost.

The second review article provides the first exhaustive research-based analysis of kidney function and bone density risk with Truvada as PrEP in HIV-negative men and women who are most likely to consider PrEP.

With the number of new HIV infections in the United States holding steady at roughly 50,000 a year, we need safe, effective and state-of-the-art options for prevention. In this issue, you will find a comprehensive review of whether PrEP is one such option, and if so, how we might make it work.

Until there's a cure,



Katy Caldwell,
Executive Director
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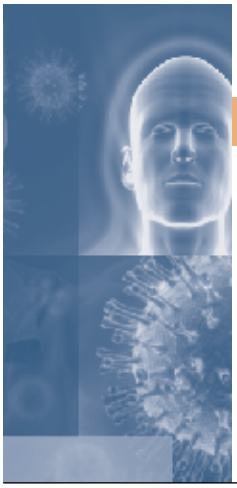

Who's prepared to make PrEP work?

By Mark Mascolini

Abstract: Tenofovir/emtricitabine (TDF/FTC) won FDA approval for preexposure prophylaxis (PrEP) after three placebo-controlled trials demonstrated that once-daily TDF/FTC lowers HIV acquisition risk in gay and bisexual men and heterosexual women and men. In the one trial that found no HIV protection with TDF/FTC PrEP in women, poor adherence largely explained that failure. Good adherence in the three successful PrEP trials enhanced the protective potential of this two-in-one, once-daily antiretroviral. Emergence of HIV resistant to FTC and/or TDF in PrEP users is unlikely—provided that people do not start PrEP when infected with HIV and that they do not take few enough doses to become infected but just enough doses to maintain meager drug levels. Placebo-controlled PrEP trials in gay men and heterosexuals found that study participants practiced safer sex after being randomized. But community-based research in the United States indicates that a substantial proportion of PrEP candidates would abandon condoms if they took a fairly reliable PrEP pill. Three modeling studies suggest TDF/FTC PrEP may not be cost-effective at current TDF/FTC prices with only moderate efficacy. But lower costs and higher efficacy could make PrEP cost-effective by current standards. Researchers are already testing future PrEP agents, which fall into three (sometimes overlapping) groups—current or investigational antiretrovirals with mechanisms different from TDF and FTC, longer-acting antiretrovirals that may be taken by mouth or injection, and longer-acting antiretrovirals suffused into vaginal rings.

PrEP will protect people from picking up HIV during sex if . . .

And after those ellipses one can append an arm-long list starting with "if PrEPpers take their pills often enough to maintain ample drug levels in target tissues" and ending with "if randomized trial data revealed so far hold true in the real world of sex, drugs, and outrageous fortune."

Four placebo-controlled trials involving 10,521 HIV-negative people unloaded a ton of data on PrEP (preexposure prophylaxis for HIV infection) with coformulated tenofovir/emtricitabine (TDF/FTC) or TDF alone. Considering these results and other findings, the US FDA approved TDF/FTC "in combination with safer sex practices for . . . PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk."[1]

Ten thousand sounds like a hefty number of PrEP trial participants, but it's not so big when you consider the biggest HIV risk group in the United States and countries with similar epidemics—gay and bisexual men or, in clinical argot, men who have sex with men (MSM). The four large PrEP trials with reported data—iPrEx,[2] Partners PrEP,[3] TDF2,[4] and FEM-PrEP[5]—involved only 6123 men, only 3912 of them assigned to TDF/FTC or TDF alone, and only 1251 of them MSM or transgenders assigned to TDF/FTC, all in iPrEx. (iPrEx stands for *Iniciativa Profilaxis Pre-exposición*.)

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More than half of all iPrEx men lived in Peru, while the United States contributed only 227 men to the trial, about 9% of the TDF/FTC arm and 9% of the placebo arm.[2] MSM account for almost two thirds of new HIV infections in the United States every year, and young black MSM bear the brunt of this high incidence.[6] Yet only 117 blacks (including 45 from South Africa) took TDF/FTC in iPrEx.[2]

Placebo-controlled PrEP trials reported in the past 2 years[2-5] offer little or no data on several other urgent questions about this much-bruited strategy:

- PrEP efficacy in heterosexual women outside sub-Saharan Africa
- PrEP efficacy in heterosexual men outside sub-Saharan Africa
- Whether US men and women will use PrEP
- How regularly US men and women will use PrEP
- Long-term TDF/FTC side effects in PrEP users
- PrEP efficacy with any type of PrEP besides TDF and TDF/FTC

iPrEx,[2] Partners PrEP,[3] and TDF2[4] yielded solid evidence that TDF/FTC PrEP substantially lowers the risk of getting HIV infection from a sex partner, especially when people take the drug regularly—as directed. But TDF/FTC did not protect high-risk Kenyan, South African, and Tanzanian women from HIV in FEM-PrEP.[5] And the VOICE trial in women of South Africa, Uganda, and Zimbabwe shut down its TDF-only arm early when results showed this strategy wasn't working[7]—even though TDF alone did protect women and men from HIV in Partners PrEP.[3] VOICE continued its TDF/FTC-versus-placebo faceoff, and results are expected soon. Poor adherence largely explained TDF/FTC failure in FEM-PrEP, as discussed below. What went wrong with TDF alone in VOICE will remain unknown until data from that trial are fully analyzed.

Partly because of these mixed results—and partly because participants in successful PrEP trials used condoms more and had fewer sex partners during the study—not all observers are convinced that TDF/FTC should have won a PrEP license from the FDA. The National Cancer Institute's Lauren Wood, a member of the FDA Antiviral Drugs Advisory Committee that considered TDF/FTC PrEP, voted no on all three proposed indications—for MSM, for HIV-negative people with a positive partner (HIV-discordant couples), and for other people at risk of picking up HIV during sex.[8]

In the context of contradictory trial results and lower sexual risk taking during the trials, Wood explained, "I found it difficult to get a sense of the additional benefit contributed by Truvada PrEP in reducing HIV transmission and would have liked to have had the effects of PrEP confirmed in a multiple logistic regression analysis of the data."[8] But Wood found herself in minorities in all three votes, which went 19 to 3 for the MSM indication, 19 to 2 with 1 abstention for the HIV-discordant couple indication, and 12 to 8 with 2 abstentions for the "other" indication.

This review will scrutinize what's known (and not known) about people who may try PrEP in the United States and countries with similar epidemics, whether HIV-negative people in the United States intend to use PrEP, FDA and Centers for Disease Control and Prevention (CDC) guidance on how to use PrEP, how often people must take TDF/FTC PrEP to protect themselves from HIV, the threat of riskier sex in PrEP users, resistance risk with inconsistent PrEP dosing, and prospects for PrEP beyond TDF/FTC.

PrEP means giving drugs to healthy people—always a concern when one of the drugs, TDF, has well-known and much-chronicled side effects if taken regularly by people with HIV. Whether HIV-negative people taking TDF/FTC PrEP daily—or perhaps less often—will end up with flagging kidney function or dwindling bone mineral density will not be known until enough people use it for a year or more. But hints can be garnered from long-term clinical studies of HIV-positive people and from what's known about likely PrEP users in the United States. A separate article in this issue of RI*TA!* will consider risk of long-term side effects in steady PrEP use. Interviews with Robert Grant and Raphael Landovitz will provide expert advice on these and other issues.

Who should use PrEP?

Year after year about 50,000 people in the United States get infected with HIV. In the CDC's most recent analysis, MSM (gay/bisexual men) account for almost two thirds of these new infections, while heterosexuals who don't inject drugs account for a little more than one quarter.[6] From 2006 through 2009, HIV incidence—the new infection rate—rose 21% in people 13 to 29 years old and climbed 34% in MSM that age. Over those years HIV incidence in 13- to 29-year-old black MSM vaulted 48% in the United States. HIV incidence has been surging among US MSM since the 1990s, the CDC figures.[9]

Among all African-American men—heterosexual or MSM—HIV incidence held steady at about 100 per 100,000 from 2006 through 2009.[6] Among African-American women HIV incidence remained at about 40 per 100,000 throughout the study period, about 4 times higher than incidence among Hispanic women and about 8 times higher than incidence among white women.

CDC advice to offer opt-out HIV testing to all 13- to 64-year-old people at routine medical visits[10] denotes an official stance that any sexually active person runs a risk of HIV infection. Does that mean anyone who has sex should consider PrEP? No. The CDC's 2011 PrEP interim guidance advised clinicians to confirm that a PrEP candidate "is at substantial, ongoing high risk for acquiring HIV infection"[9] **(Table 1)**. High-risk MSM, the CDC suggests, are those in regions with high HIV prevalence who often change sex partners or have concurrent partners. High-risk heterosexual women and men include those whose regular sex partners who have HIV.[11] FDA prescribing information for TDF/FTC PrEP says the following factors may help clinicians pinpoint high-risk men or women:[1]

- Inconsistent or no condom use
- Diagnosis of sexually transmitted infections
- Exchange of sex for commodities (such as money, goods, shelter, or drugs)
- Use of illicit drugs or alcohol dependence
- Incarceration
- One or more partners of unknown HIV status with any factor listed above

In an interview in this issue of RI*TA!*, iPrEx principal investigator Robert Grant (University of California, San Francisco) argues that providers should not get bogged down sorting through the nuances of high HIV risk in PrEP candidates. He maintains that "anyone who comes forward and says they're interested in finding new ways to protect themselves and their partners from HIV should receive prevention services, regardless of whether we can easily identify a risk factor." In another interview in this issue, Raphael Landovitz (University of California, Los Angeles) notes that people who use postexposure prophylaxis (PEP) more than once are also excellent PrEP candidates.

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CDC interim guidance also sanctions PrEP as "one of several options to help protect the HIV-negative partner in discordant couples during attempts to conceive."[11] But a woman should use PrEP during pregnancy only if the strategy is "clearly needed" because studies of TDF/FTC cannot rule out the possibility of harming the fetus.[1] Reproductive-age women should have a documented negative pregnancy test before starting PrEP and regularly during PrEP.[11] However, CDC interim PrEP guidance for heterosexuals also notes that the Antiretroviral Use in Pregnancy Registry and studies of pregnant women taking TDF or FTC "indicate no evidence of adverse effects among fetuses exposed to TDF or FTC."[11] Those guidelines state that breastfeeding women should not use PrEP.[11]

Because tenofovir saturates female genital mucosa less than it does colorectal tissue, and because TDF/FTC or TDF alone failed in the all-women FEM-PrEP[5] and VOICE[7] trials, some worry that TDF/FTC may not protect women from HIV as well as it protects men. But the 4747-couple Partners PrEP trial, with 38% of HIV-negative partners women, found equivalent protection with either TDF or TDF/FTC in women and men.[3]

Of course people who have HIV—or *might have* HIV—should steer clear of PrEP. Although regularly taken TDF/FTC does a great job warding off HIV infection, it can't control established HIV infection by itself and rapidly opens the door to resistance to FTC and eventually TDF. The FDA license stipu-

Table 1. Who should use PrEP—and who should not

People who might consider TDF/FTC PrEP	People who should not use TDF/FTC PrEP
■ People "at substantial, ongoing high risk for acquiring HIV infection"[9] ■ MSM in regions of high HIV prevalence who often change sex partners[9] ■ MSM in regions of high HIV prevalence who have concurrent partners[9] ■ Heterosexual men and women whose regular sex partners have HIV[11] ■ Heterosexual men and women and MSM with one or more of the following traits:[1] ➔ Inconsistent or no condom use ➔ Diagnosis of sexually transmitted infections ➔ Exchange of sex for commodities (such as money, goods, shelter, or drugs) ➔ Use of illicit drugs or alcohol dependence ➔ Incarceration ➔ One or more partners of unknown HIV status with any factor listed above	■ Anyone without a documented HIV-negative test immediately before starting PrEP[1] ■ Anyone with signs or symptoms suggesting acute HIV infection unless HIV RNA assay confirms negative status[1] ■ Anyone reporting unprotected sex with an HIV-positive person in past month unless HIV RNA assay confirms negative status[11] ■ Anyone not screened for HIV at least once every 3 months[1] ■ Pregnant women, unless PrEP is "clearly needed"[1] ■ Breastfeeding women[11] ■ Anyone with creatinine clearance below 60 mL/min[1] ■ Anyone taking adefovir (Hepsera) for HBV infection[1]

MSM, men who have sex with men. References appear at end of article.

lates that clinicians should prescribe PrEP only for someone with a confirmed HIV-negative test immediately before starting PrEP.[1] Prescribers should dole out enough pills for only 90 days of PrEP, and users should get retested before getting another 90-day supply.[11] CDC guidance says PrEP candidates should have an HIV antibody test or fourth-generation antibody/antigen test every 2 to 3 months to confirm their negative status.[9,11]

Because antibody tests do not detect acute HIV infection, any PrEP candidate with symptoms or signs of acute HIV infection (fever, fatigue, myalgia, skin rash) and anyone who reports unprotected (condom-free or broken-condom) sex with an HIV-positive person in the past month should be tested (by HIV RNA assay, a nucleic acid amplification test, or the fourth-generation antibody/antigen sandwich ELISA) to spot recent infection. If symptoms of acute infection crop up during a course of PrEP, TDF/FTC should be stopped immediately until testing reconfirms that the person does not have HIV infection.[1]

PrEP for high-risk MSM? Yes. For high-risk heterosexuals? Yes. But what about transgenders? The American Psychological Associations defines *transgender* as "an umbrella term for persons whose gender identity, gender expression, or behavior does not conform to that typically associated with the sex to which they were assigned at birth."[12]

A systematic review leaves little doubt that people born male who consider themselves women have high rates of HIV infection.[13] This analysis dissected 29 studies in the US-based HIV behavioral prevention literature that focused on male-to-female transgenders. Four studies that tested male-to-female transgenders for HIV found a prevalence of 27.7%, while 18 studies in which transgenders self-reported HIV status recorded a prevalence of 11.8%. African-American male-to-female transgenders had even higher HIV rates, whether tested for HIV (56.3%) or asked their HIV status (30.8%). Between one quarter and one half of male-to-female transgenders reported risky behaviors such as receptive anal intercourse without condoms, multiple casual sex partners, and sex work. Rates of HIV and risk behaviors were low among female-to-male transgenders.

About 15% of iPrEx participants, 366, identified themselves as "trans" or used female sex hormones, though few of them had sex-change surgery.[14] Eleven transgenders randomized to TDF/FTC and 11 randomized to placebo became infected, a result indicating that PrEP did not work in this group. In an interview in this issue of RI*TA!*, iPrEx principal investigator Robert Grant reported that transgenders in that trial appeared to have a tougher time with PrEP adherence than gay men, and he suggested that may explain why transgenders randomized to TDF/FTC did not have a lower HIV acquisition rate than those randomized to placebo. He stressed, though, that iPrEx didn't enroll enough transgenders to make a definitive call on this question.

Whether PrEP can block HIV in injection drug users (IDUs) also remains an unanswered question. The Bangkok Tenofovir Study, comparing once-daily TDF with placebo, enrolled 2400 IDUs and aims to have an answer in 2013.[15]

Because TDF may promote kidney toxicity, the FDA stipulates that no one with creatinine clearance below 60 mL/min should take TDF/FTC for PrEP.[1] If creatinine clearance falls in someone taking TDF/FTC for PrEP, the FDA advises clinicians to "evaluate potential causes and re-assess potential risks and benefits of continued use" of PrEP.[1]

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CDC experts advise clinicians to screen PrEP candidates for hepatitis B virus (HBV) infection, to vaccinate people susceptible to HBV, and to treat those infected.[9,11] Hepatitis can flare when people with HIV and active HBV infection start or stop anti-HBV antiretrovirals, so HBV-positive people must be monitored closely when starting or stopping TDF/FTC PrEP. Although FDA prescribing information for TDF/FTC notes that the two-in-one pill is not licensed for chronic HBV infection,[1] CDC PrEP guidance says clinicians can consider TDF/FTC for HIV prevention *and* HBV treatment in coinfected people.[9,11]

Providers should not prescribe TDF/FTC for anyone taking adefovir (Hepsera), an antiviral related to TDF, for HBV infection.[1] **Table 2** summarizes key screening and follow-up tests providers should perform when deciding whether to prescribe TDF/FTC PrEP, and whether to continue, according to CDC interim guidance for MSM[9] and heterosexuals.[11]

Table 2. Test and retest—screening and follow-up advice for PrEP providers[9,11]

Before prescribing:

- Confirm that candidate has substantial, ongoing, high risk for acquiring HIV infection.
- Document negative HIV antibody test(s) immediately before starting PrEP.
- Test for acute HIV infection if candidate has symptoms consistent with acute infection.
- Determine if women are planning to become pregnant, are currently pregnant, or are breastfeeding.
- Counsel women that TDF/FTC safety for infants exposed during pregnancy is not fully assessed but no harm has been reported.
- Do not prescribe PrEP for breastfeeding women.
- Confirm that creatinine clearance is at or above 60 mL/min by Cockroft-Gault formula.
- Screen for and treat sexually transmitted infections (STIs).
- Screen candidates for HBV; vaccinate susceptible people; treat active infection regardless of decision to prescribe PrEP.

When prescribing PrEP:

- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that person remains HIV-uninfected.
- For people with active HBV infection, consider using TDF/FTC both for HBV therapy and for PrEP.
- Provide risk-reduction counseling, PrEP adherence counseling, and condoms.

After PrEP has begun:

- Every 2 to 3 months, perform an HIV antibody test and document negative result.
- Every 2 to 3 months, assess risk behaviors and provide risk-reduction counseling and condoms.
- Every 2 to 3 months, assess STI symptoms and, if present, test and treat for STIs.
- Every 6 months, test for STIs even if patient is asymptomatic and treat as needed.
- Three months after PrEP begins, then every 6 months while on PrEP, check blood urea nitrogen and serum creatinine and calculate creatinine clearance.
- At each follow-up visit for women, conduct a pregnancy test. If woman is pregnant, discuss continued PrEP use.
- Evaluate and support PrEP adherence at every follow-up visit—and more often if inconsistent adherence is identified.

Will at-risk men and women use TDF/FTC PrEP?

Before TDF/FTC won PrEP approval and before most PrEP trial results became widely known, limited research addressed awareness of PrEP and likely use by gay and bisexual men and heterosexual men and women in the United States or countries with similar epidemics.

Two published surveys of HIV risk perception and PrEP awareness in heterosexual US men and women visiting sexually transmitted infection (STI) clinics found inverse correlations between actual HIV risk and self-perceived risk—and moderate interest in PrEP, depending on how the question was asked.[16,17] Both of these surveys were completed, however, before publication of iPrEx results,[2] before release of the two key PrEP efficacy studies in African heterosexuals,[3,4] and before approval of TDF/FTC PrEP.

An anonymous survey of 494 people attending a Chicago STI clinic found that 409 (83%) had a high risk of HIV infection (by predefined criteria).[16] While 63% of the study group were men, 70% were black, and 88% were heterosexual. Median age stood at 30 years. Among 359 heterosexual high-risk participants in this August-to-October 2010 survey, 301 (84%) thought they had *low or no* risk of HIV infection. Although this group had a good understanding of HIV transmission, fewer than 20% reported consistent condom use during vaginal, oral, and anal sex.

Among the 359 high-risk heterosexual participants, 299 (83%) said they would take a pill for PrEP, including 84% of men and 82% of women.[16] But lower proportions would take a PrEP pill once a week (76%) or once a day (63%). Half of these people (51%) said they would don condoms as often with PrEP as without, while 23% said they would wear condoms more with PrEP and 20% would use condoms less with PrEP. People with lower education levels were 5 times more likely to express no interest in PrEP (adjusted odds ratio [aOR] 4.97, 95% confidence interval [CI] 1.26 to 19.67, $P = 0.02$). People with low HIV risk perception tended to declare no interest in PrEP ($P = 0.10$).

A similar survey of 225 men and 174 women visiting a South Carolina STI clinic in 2009 and 2010 included 358 people who answered a question about PrEP knowledge.[17] Median age of this study group stood at 24.5, 89% were black, and 90% identified themselves as heterosexuals. As in the Chicago study, clinic attendees with a higher risk of HIV infection thought they had a *lower* risk. Specifically, compared with people who had 1 sex partner in the past 3 months, those with 2 to 4 partners were more than twice as likely to disagree with the statement "I believe I am at risk of getting HIV" ($P = 0.0003$).

One third of these South Carolina residents (32%) somewhat agreed with the statement, "If I had to it would be very difficult for me (or my partner) to both use condoms and take daily pills to prevent HIV infection," while a slightly higher proportion (38%) strongly disagreed with that statement.[17] Compared with women, men were almost 3 times more likely to agree that simultaneous condom and PrEP use would be tough (adjusted odds ratio 2.78, $P < 0.001$). Gay and bisexual men had almost a 7 times higher chance of knowing about PrEP than heterosexuals in 2011 (OR 6.7, 95% CI 1.70 to 26.1).

Research dating back a half-decade suggests that US gay and bisexual men relish the possibility of PrEP more than high-risk heterosexuals—though some postPrEP approval evidence does not bear out that suggestion. A survey of 227 HIV-negative men

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in the Boston area, 46% of them white, found that only 43 (19%) had heard of PrEP in 2007, though 1 pioneer had already tried it.[18] But after researchers explained PrEP and its preventive potential, 168 men (74%) averred that they would adopt this then-novel strategy.

A 2009 (pre-iPrEx) survey of 50 Los Angeles gay and bisexual men in 25 HIV-discordant couples found that 40 (80%) voiced "positive and enthusiastic comments regarding this new prevention strategy," although they did not expressly state their willingness to take a *daily* PrEP pill.[19] Most of these men (80%) belonged to a racial or ethnic minority, one third reported unprotected receptive anal intercourse, and two thirds reported unprotected insertive anal intercourse. These men frankly admitted one of the reasons they found PrEP appealing was the opportunity to avoid HIV and condoms at the same time. If PrEP were available, one study participant predicted, condom use "would probably change dramatically, 100% less use, more than likely." These same men evinced some shrewd concern about potential barriers to ready PrEP use, including cost, possible side effects, risks posed by missing doses, and needing a prescription and a negative HIV test.[20]

An Internet survey of US MSM conducted early in 2011, after release of iPrEx results, determined that 83% of HIV-negative men claimed they would use a PrEP product with 44% efficacy[21]—the overall protective effect found in iPrEx. A US Internet-based survey of 398 at-risk gay men before iPrEx results became known and 4558 men after iPrEx results showed that only 12.5% of men in the pre-iPrEx group and 19% in the post-iPrEx group knew about PrEP.[22] But once researchers explained PrEP to these men, 76% in the pre-iPrEx contingent and 78.8% in the post-iPrEx set expressed interest in using PrEP.

For this second study, men were recruited from a multinational social networking site for MSM.[22] Age averaged 40.2 in the pre-iPrEx group and 39 in the post-iPrEx group. Respective proportions of whites were 82.1% and 84.0%. Only 2.2% and 3.2% were black. Only about 6.5% of men had only a high school education or less. Multivariate analysis determined that interest in using PrEP was associated with older age (OR 1.01, 95% CI 1.00 to 1.02, $P = 0.01$), self-perceived risk of HIV infection (OR 1.20, 95% CI 1.13 to 1.27, $P < 0.0001$), and unprotected anal intercourse with one or more male partners (versus no anal intercourse) (OR 1.41, 95% CI 1.11 to 1.79, $P = 0.004$). Notably, men aware of *post*exposure prophylaxis had 45% lower odds of being interested in PrEP (OR 0.55, 95% CI 0.43 to 0.71, $P < 0.0001$).

The apparent appeal of PrEP to MSM, compared with high-risk heterosexuals, could reflect their greater awareness of this strategy through personal and digital networking. The University of Cincinnati's Judith Feinberg, who chaired the FDA hearing on TDF/FTC PrEP, worried whether PrEP will be "limited to persons who are well-informed and have good insurance, rather than reaching those at highest risk?"[23]

But now that PrEP is a prescribing reality, anecdotal evidence suggests few at-risk people in the United States are rushing to start a once-daily prophylactic pill. In an interview following this article, UCLA's Raphael Landovitz says he's had two referrals of PrEP candidates, and his colleagues in Los Angeles report a similarly meager flow of "early adopters." In an interview immediately following this article, iPrEx principal investigator Robert Grant reports that perhaps one provider in every clinician audience he talks to about PrEP across the country has started prescribing. These experiences suggest that

MSM enthusiasm for PrEP in preapproval surveys may not carry over to everyday practice—at least not right away. Raphael Landovitz suggests men may be waiting for a PrEP regimen that does not require daily dosing.

Whether MSM actually use TDF/FTC PrEP when someone puts it in their hand may depend on age and education. Analysis of tenofovir or FTC intracellular concentrations in iPrEx (in which 9% of participants lived in the United States) found measurable levels in 25 of 65 men (31%) under 25 year old and in 31 of 68 (46%) who were 25 or older.[24] Eight of 30 men (27%) with less than a secondary education had detectable drug inside cells, compared with 43 of 103 men (42%) with secondary or higher education. And adherence has a big impact on how well PrEP works, as the next section describes.

PrEP protects men and women—but adherence is critical

Two consistent themes emerged from the four recent and fully reported placebo-controlled PrEP trials—iPrEx,[2] Partners PrEP,[3] TDF2,[4] and FEM-PrEP[5]: TDF/FTC PrEP cuts the risk of picking up HIV during sex, and it cuts that risk more when people take TDF/FTC regularly.

In FEM-PrEP, the one trial that failed to find protection from HIV with TDF/FTC PrEP, adherence largely (though probably not entirely) explained that failure.[5] This study of 2120 HIV-negative women in Kenya, South Africa, and Tanzania ended early when interim analysis tallied 33 HIV infections in the TDF/FTC group and 35 in the placebo group. Self-report and pill counts indicated good adherence, but drug-level testing did not. Measuring tenofovir and FTC in plasma samples with an assay that has a lower limit of 0.25 ng/mL, FEM-PrEP researchers considered 10 ng/mL of tenofovir as evidence that a woman had taken TDF in the past 48 hours. Among women assigned to TDF/FTC who became infected with HIV, only 7 of 27 (26%) met that target at the beginning of the infection window, and only 7 of 33 (21%) met the target at the end of that window. Among women assigned to TDF/FTC who did not become infected, only 27 of 78 (35%) met the tenofovir target level at the beginning of the infection window, and only 35 of 95 (37%) did at the end of the window.

Why did FEM-PrEP women take their PrEP pill so irregularly? One reason seems to be that enrollees did not think they had a high risk of HIV infection. Nearly three quarters of women (70%) believed they had no or low risk of HIV infection in the coming month when asked to rate risk at the baseline visit, as did 74.8% at the last follow-up visit.[5] Yet these women averaged 3.7 vaginal sex acts in the past week and 1.9 sex acts without a condom in the past week. All women had one or more vaginal sex acts in the past 2 weeks or more than one sex partner in the past month. The researchers speculated that this perception of minimal risk may account for the low adherence observed. These investigators concluded that they "were unable to accurately assess the effect of TDF-FTC on HIV acquisition or safety because of low study drug adherence, which may be an indication that a daily pill-taking regimen will be difficult for some populations."[5]

Among 29 heterosexual women and men who became infected in Partners PrEP despite assignment to TDF or TDF/FTC, only 9 (31%) had detectable tenofovir in plasma at the visit when they tested positive.[3] In contrast, 82% of 902 plasma samples from a randomly selected 198 PrEP takers who did not become infected had detectable tenofovir concentrations. Detectable versus undetectable tenofovir was

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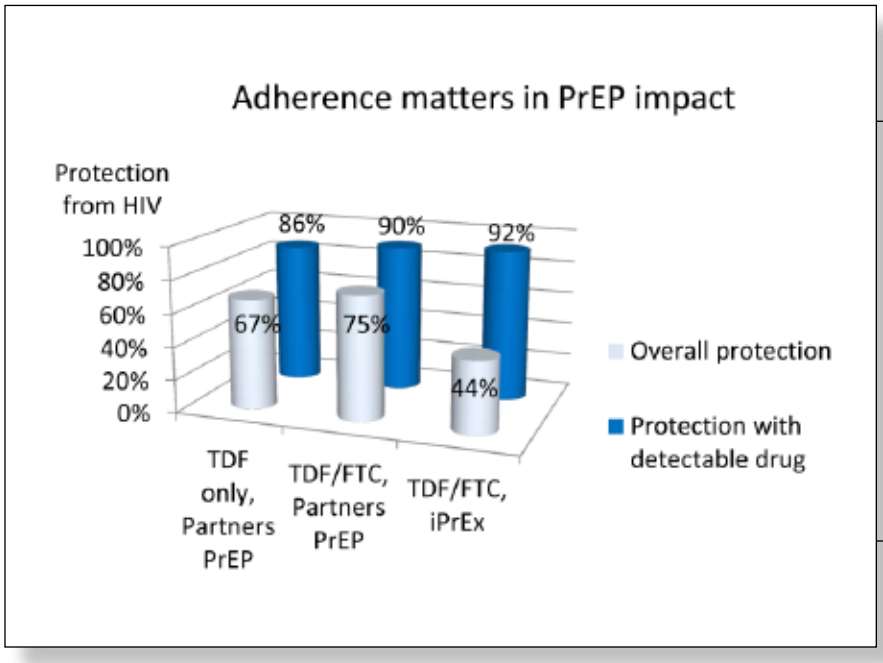

Figure 1. When tenofovir and/or FTC could be detected in plasma of Partners PrEP[3] or iPrEx[2] participants randomized to study drugs (versus placebo), calculated protection from HIV infection was higher than in overall protection results in those trials.

associated with a relative HIV risk reduction of 86% in people assigned to TDF and 90% in people assigned to TDF/FTC (**Figure 1**). For comparison, overall risk reductions were 67% with TDF PrEP and 75% with TDF/FTC PrEP.

In TDF2, 2 of 4 people randomized to TDF/FTC who became infected had detectable tenofovir and FTC in plasma at the visit just before HIV seroconversion.[4] In contrast, among 69 PrEP takers who did not become infected, 55 (80%) and 56 (81%) had detectable tenofovir and FTC in samples matched by date with the 4 PrEP takers who did get infected. Geometric mean plasma levels in seroconverters versus nonseroconverters were 0.3 versus 30.6 ng/mL for tenofovir ($P = 0.007$) and 0.5 versus 103.3 ng/mL for FTC ($P = 0.009$).

The impact of PrEP adherence on protection also proved telling in iPrEx men and transgender women who have sex with men.[2] Overall, TDF/FTC PrEP lowered HIV acquisition risk 44%. iPrEx investigators measured tenofovir and FTC levels in everyone assigned to TDF/FTC who became infected and in a matched subset of PrEP takers who remained free of HIV. People with detectable drug levels had a 92% lower risk of HIV acquisition than did those with undetectable levels (**Figure 1**). iPrEx investigators found that protective concentrations of TDF and FTC continue rising through the first 3 weeks of PrEP use. iPrEx investigator Robert Grant explained in an interview in this issue of *RITA!*, "If people want the maximum level of protection" from TDF/FTC PrEP, he advised, "they should take it daily."

An FDA analysis presented at the agency's PrEP hearing found that iPrEx participants with measureable intracellular drug concentrations had an 87.5% lower HIV risk than participants taking placebo.[25] Remember that only 9% of iPrEx participants lived in the United States. When the iPrEx team measured tenofovir diphosphate levels in blood cells, they found the drug in 94% of US men versus 43% of non-US men, a highly significant difference ($P < 0.001$).

CDC interim guidance stresses that iPrEx results "provide strong evidence that support for adherence to the prescribed medication regimen must be a routine component of any PrEP program."[9] The two sets of CDC guidance—for gay or bisexual men[9] and heterosexual men and women[11]—both advise clinicians to provide adherence counseling when PrEP begins and to check adherence at every follow-up visit, or more often if poor adherence becomes apparent. In approving TDF/FTC for PrEP, the FDA ordered Gilead Sciences, the manufacturer, to run a trial evaluating adherence and how it affects HIV risk, emergence of resistant virus, and side effects. "An effective tool used incorrectly or inconsistently is reduced to an ineffective tool," cautioned Lauren Wood, an FDA PrEP panelist who voted against a PrEP license for TDF/FTC.[8]

Prospects for intermittent PrEP dosing

PrEP trial results reviewed in the preceding section leave little doubt that spotty adherence to once-daily TDF/FTC imperils chances of protection from HIV. As Robert Steinbrook (Yale School of Medicine) wrote in his recent PrEP review, TDF/FTC "is not an effective morning before pill or morning after pill, to be taken as needed by uninfected persons."[26] But animal studies, other research, and iPrEx itself dangle tantalizing evidence that intermittent TDF/FTC dosing—if planned well and practiced faithfully—could offer reliable HIV prophylaxis, at a lower cost and a lower side effect risk (**Table 3**).

Table 3. Intermittent TDF/FTC PrEP strategies considered or being studied

Strategy	Completed on ongoing trial	Results
Subcutaneous FTC plus high-dose TDF 2 hours before and 24 hours after exposure to simian HIV (SHIV)	Tested in macaques rectally challenged weekly with SHIV[27]	Protected 6 of 6 macaques from 14 rectal SHIV challenges
Oral TDF/FTC 1, 3, or 7 days before sexual exposure and 2 hours after exposure	Tested in macaques rectally challenged weekly with SHIV[28]	As protective as daily TDF/FTC
Doubled dose of oral TDF/FTC 2 hours before or after sexual exposure	Tested in macaques rectally challenged weekly with SHIV[28]	Fully protective (but dose 24 hours after exposure not protective)
Oral TDF/FTC four times weekly	Assessed in modeling study by iPrEx investigators[29]	Provided intracellular drug concentrations high enough to protect as well as one dose daily
Oral TDF/FTC on Monday, Friday, and within 2 hours after sex versus daily dosing	Assessed in placebo-controlled trial enrolling Kenyan MSM and female sex workers[31]	MEMS-measured adherence 83% with daily dosing, 55% with intermittent dosing, and 26% with postsex dose
Oral TDF/FTC before and after sexual exposure or twice-weekly with a postsex boost	Being tested in HPTN 067, the ADAPT study[32]	Trial enrolling MSM in Thailand and women in South Africa
Two oral TDF/FTC doses within 24 hours of sex, one dose during sex, plus one dose 24 hours after sex	Being tested in ANRS IPERGAY trial[33]	Trial enrolling MSM in France and Canada

MEMS, Medication Event Monitoring System; MSM, men who have sex with men.
See text for full discussion of trials and results.

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CDC investigators rectally challenged macaques with simian HIV (SHIV) once weekly for 14 weeks as the monkeys received one of three daily regimens of FTC or TDF/FTC or subcutaneous FTC plus high-dose TDF given 2 hours before and 24 hours after SHIV exposure.[27] All six macaques given the before-and-after subcutaneous shot remained free of HIV through the 14-week challenge period. In another study these same researchers also rectally exposed macaques to SHIV once weekly for 14 weeks, but the TDF/FTC dosing strategy was different.[28] An oral dose of TDF/FTC 1, 3, or 7 days before rectal exposure and 2 hours after exposure proved as effective in forestalling infection as daily dosing. A two-dose regimen given 2 hours before or after SHIV exposure—with doubled TDF/FTC concentrations—proved fully protective. But a postexposure dose 24 hours after rectal challenge did not block SHIV in these monkeys.

Modeling work by iPrEx pharmacologist Peter Anderson (University of Colorado) yielded evidence that taking TDF/FTC PrEP four times a week may have protected MSM study participants virtually as well as once-daily dosing.[29] Compared with placebo, daily TDF/FTC dosing hoisted intracellular drug concentrations high enough to cut HIV acquisition risk 99%, according to this model. Four doses weekly packed enough drug into cells to trim the risk 96%. But twice-weekly dosing produced intracellular drug levels high enough to lower HIV risk only 76%. iPrEx investigators and others still recommend daily TDF/FTC PrEP, however, because it offers some forgiveness for missed doses, while forgiveness with four-times-weekly dosing approaches the razor's edge.

Jonathan Volk (Department of Public Health, San Francisco) and colleagues at other institutions observed that intermittent PrEPping could improve adherence, cut costs and side effects, and make sense for people who "only perceive themselves to be at risk at certain periods (eg, weekends, vacations), and thus are not willing to take a daily pill."[30] But TDF/FTC dosing just before and after sex, as in the macaque studies, will work only for people who have sex fewer than three times a week (otherwise you still need near-daily dosing) and for people who plan sex ahead of time and have TDF/FTC on hand.

To see how many MSM plan their sexual forays far enough ahead to make before-and-after dosing feasible, Volk and coworkers recruited 1013 HIV-negative men from two social networks, facebook and black gay chat (bcglive).[30] Study participants were at least 18 and reported anal sex with another man in the past 12 months. They completed an online survey about sex in the past year shortly after iPrEx results became known. Most men (70%) were white, 13% were Hispanic, 8% were black, and 9% had another racial or ethnic background. More than half (56%) said they did not use a condom the last time they had anal sex, 34% had anal sex during the preceding weekend, and 36% had anal sex on a least 1 weekday in the preceding week. Half of these men (50.4%) reported no advance planning before their last sex, 8.2% reported planning only minutes in advance, and 22.4% planned only hours in advance. All told, then, 81% of these men would not benefit from a PrEP regimen that requires dosing more than a few hours before sex; but the 1 in 5 men with a more structured sex calendar may.

One completed placebo-controlled trial of intermittent PrEP—in HIV-negative Kenyan MSM and female sex workers—found that these people had a hard time remembering less-than-daily dosing and especially postsex dosing.[31] The trial involved 67

MSM and 5 female sex workers randomized to daily TDF/FTC or to three doses—one Monday, one Friday, and one within 2 hours after sex. Researchers monitored adherence with the Medication Event Monitoring System (MEMS), and monthly follow-up continued for 4 months. The study took place in late 2009, before release of iPrEx, Partners PrEP, and TDF2 results. Two thirds of study participants reported transactional sex, and nearly two thirds reported receptive anal intercourse in the past 28 days. Median MEMS adherence measured 83% with daily dosing but dropped off to 55% with intermittent dosing. Median MEMS adherence to any postsex dose was only 26%.

HPTN 067, the ADAPT study, is recruiting participants to compare two intermittent TDF/FTC PrEP schedules with daily dosing: before and after potential HIV exposure or twice-weekly dosing with a postsex boost.[32] Study participants are Thai MSM and South African women. A PrEP trial that hopes to enroll 1900 MSM in France and Canada will compare placebo with two TDF/FTC pills within 24 hours before sex, one pill *during* the period of sexual activity, and one pill about 24 hours after sex.[33] It will be interesting to see if these MSM do better planning sex than the MSM surveyed in the United States.[30]

At the FDA PrEP hearing, iPrEx principal investigator Robert Grant stressed that PrEP candidates should be told to take one TDF/FTC tablet daily because that's the only course that's been tested and because it's probably easier to remember than intermittent schedules. But all the PrEP studies so far—and the recruiting intermittent trials—involve TDF/FTC, a once-a-day drug. As detailed in the final section of this report, drug developers are hard at work devising agents that might be injected once monthly or loaded into vaginal rings that last as long.

Resistance risk with TDF/FTC PrEP

PrEP trials so far indicate a low risk that HIV resistant to FTC or TDF will emerge in someone taking this two-in-one pill to stave off infection. The reasons are simple: If HIV-negative people take TDF/FTC PrEP on schedule, they will avoid infection, and *no virus means no resistance*. If HIV-negative people miss

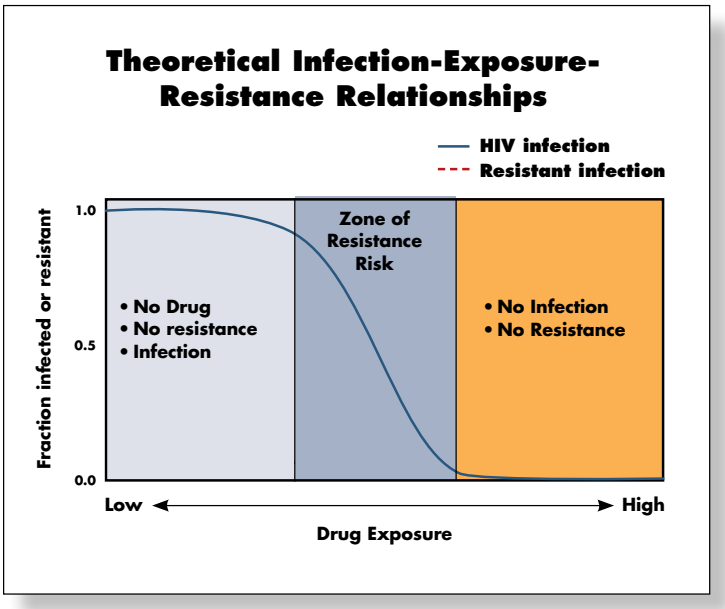

Figure 2. *Left:* If someone taking TDF/FTC PrEP misses too many doses, drug levels will fall and that person may become infected with HIV. But facing little or no TDF or FTC in the newly infected person, the virus will not be pressured to evolve to mutant strains resistant to TDF or FTC. *Right:* If a person takes TDF/FTC PrEP regularly, levels of the drug will be high enough to prevent infection—and without virus there can be no resistance. *Center:* But there may be a "zone of resistance risk" between low and high TDF/FTC levels that permits infection at drug levels still high enough to select resistant virus. (Illustration courtesy of John Mellors, University of Pittsburgh.)

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enough TDF/FTC doses and become infected, resistant virus will probably not evolve because *no drug means no resistance*.

But that "probably" needs some explanation. At the FDA PrEP hearing, HIV resistance expert John Mellors (University of Pittsburgh) cautioned that there may be a grey-area TDF/FTC level that permits infection but also leaves enough circulating drug to select resistant virus (**Figure 2**), though Mellors added that this possibility "appears to be uncommon."

So uncommon that HIV apparently did not nose out that route to resistance in PrEP trials analyzed so far. Although researchers did spot resistant virus in a few TDF/FTC takers in iPrEx,[2] Partners PrEP,[3] and TDF2,[4] these people all appeared to have undetected HIV infection when they started PrEP. CDC PrEP guidelines stress that PrEP candidates must have a documented negative HIV antibody test "immediately before starting PrEP medication."[9,11] Providers should also look for signals of acute HIV infection, which may not register on a standard antibody test.

While prescribing PrEP for someone with undetected HIV infection poses a clear resistance risk, continuing PrEP in a negative person who picks up HIV also poses a danger. PrEP trials minimized the latter possibility by testing PrEPpers for HIV once a month,[2-4] Whether clinicians manage to screen PrEP users for HIV even every 2 or 3 months, as recommended,[9,11] remains unknown. In a thoughtful review of PrEP pointers for providers, Douglas Krakower and Kenneth Mayer (Harvard Medical School and Fenway Institute) suggested that home HIV testing (which costs $40 per test) may prove a useful adjunct to clinical screening for PrEP users.[34]

Once someone starts PrEP, HIV risk counseling assumes paramount importance. CDC PrEP guidelines map out a three-pronged approach for PrEP prescribers (**Table 2**): (1) assess risk behaviors and provide risk-reduction counseling and condoms every 2 to 3 months, (2) assess STI symptoms every 2 to 3 months and treat STIs, (3) test for STIs every 6 months even in people with no STI symptoms. Avoiding STIs lowers HIV risk by preventing mucosal lesions that offer a portal to HIV if PrEP adherence falters.

What's the chance that someone taking TDF/FTC PrEP will pick up an HIV variant resistant to one or both of those drugs and so become infected? Low, according to a modeling study involving MSM in the United Kingdom.[35] This analysis by researchers from the UK HIV Drug Resistance Database and the UK Collaborative HIV Cohort (UK CHIC) figured that population prevalence of TDF/FTC-resistant virus in infectious individuals in 2008 lay at 0.9%, and resistance levels dropped throughout the 2005-2009 study period. Population prevalence of virus resistant to FTC stood at 1.6%, and prevalence of virus resistant to FTC *or* TDF stood at 4.1%.

Research in the United States also shows waning rates of HIV bearing mutations that spawn resistance to TDF (K65R) or FTC (M184V/I). A study by Gilead investigators parsed resistance data in 107,231 HIV sequences filed in the database of a large reference lab from 2003 through 2010.[36] Over that period prevalence of K65R fell by half, from 4.3% to 2.1%. Over the same years prevalence of M184V/I dropped even more, from 44.0% to 17.9%. Coincident with these dips, the Gilead team traced a prescription shift away from lamivudine (associated with M184V/I) plus zidovudine and toward TDF plus FTC.

Recent US research also shows an ebb in transmission of resistant virus from before 2003 to 2007,

though that trend may have bottomed out in 2007 and 2008.[37] This analysis deciphered 1585 viral sequences from HIV-positive antiretroviral-naive people in the CNICS cohort in Birmingham, Boston, Cleveland, San Diego, San Francisco, and Seattle. Among these viral samples, 225 (14.2%) harbored one or more resistance mutations. In contrast, a European-Israeli analysis covering 2002 through 2005 charted an overall 8.4% prevalence of transmitted resistance mutations in 2687 people, with declines in protease inhibitor and nonnucleoside mutations but a stable prevalence of nucleoside-related mutations (4.7%).[38]

In the US cohort study prevalence of transmitted mutations dropped from 1.2 per viral sequence before 2003, to 0.76 in 2003, and gradually down to 0.22 in 2007.[37] But the rate inched back up to 0.37 per viral sequence in 2008. Overall prevalence of transmitted 3TC/FTC mutations at reverse transcriptase positive M184 stood at 2.52%, compared with an overall 0.19% prevalence of TDF-related mutations a K65.

If PrEP catches on, there's no doubt that a few users will wind up with resistant virus, either because they start PrEP when already infected or get infected with enough TDF or FTC in their body to engender viral evolution to a resistant strain. How will that bump in resistance prevalence affect overall resistance prevalence? There's only one way to project an estimate: make a model. That's what Cleveland Clinic investigators did, modeling the impact of an optimistic scenario (75% PrEP efficacy, 60% coverage of the susceptible population, and 5% inadvertent PrEP use in infected people leading to emergence of resistance), a realistic scenario (50% PrEP efficacy, 30% coverage, and 10% inadvertent PrEP use), and a pessimistic scenario (25% PrEP efficacy, 15% coverage, and 25% inadvertent PrEP use).[39]

The model does not consider a specific PrEP agent, though the researchers say they used "resistance-related input estimates that would be expected for a single antiretroviral drug used for PrEP such as tenofovir."[39] And the model does not consider a combination PrEP agent, such as TDF/FTC. **Figure 3** shows that an optimistic PrEP scenario would boost total resistance prevalence in a population of sexually active people by only 2.5% in the 10 years after PrEP rollout, a realistic scenario would hoist the resistance total 9.9%, and a pessimistic scenario would expand resistance prevalence by 42.3%. The inverse rates of infections prevented are equally dramatic.

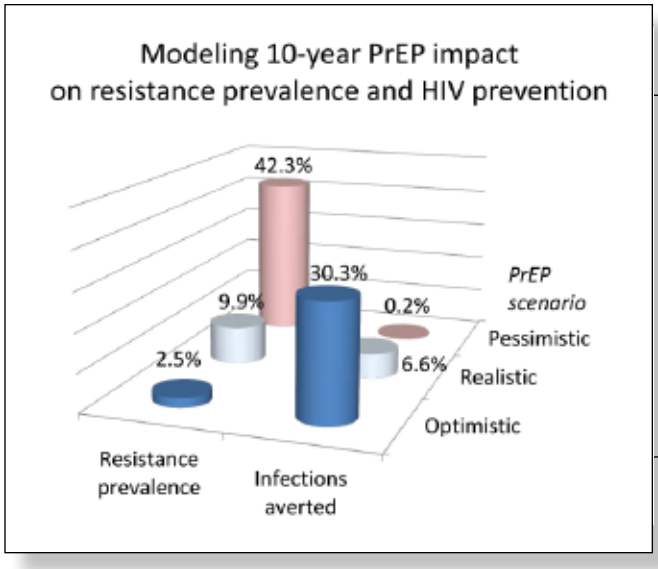

Figure 3. Optimistic, realistic, and pessimistic PrEP scenarios (see text for explanation) would have dramatically different impacts on additional prevalence of resistant virus in that population 10 years after PrEP rollout, according to results of a modeling study by Cleveland Clinic researchers.[39] The relative impacts on HIV infections prevented would be equally striking.

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Will PrEP make people discard condoms?

For many gay men and high-risk heterosexuals, the answer to that question is yes, recent research shows. Although so-called risk compensation or disinhibition did not occur in the iPrEx and Partners PrEP trials, that finding may not translate smoothly into the hurly burly of busy sex lives.

While 60% of iPrEx MSM reported having receptive anal sex without condoms before the trial began, that rate fell to about 30% at study week 12 and stayed right there through week 144.[40] When MSM entered iPrEx, 16% had an STI. During the trial STI incidence measured 12.6 per 100 person-years in the TDF/FTC arm and 12.2 in the placebo arm. About one quarter of Partners PrEP participants (27%) said they had condom-free sex in the month before enrolling, and that proportion sagged steadily to about 10% at month 30.[41]

But everyone knows how people behave in clinical trials may not mirror how they behave in day-to-day life, for at least three reasons. First, people who sign up for clinical trials are probably better self-motivators than people who don't. Second, iPrEx and Partners PrEP participants had A-to-Z risk counseling before the trials, then they made monthly follow-up visits where they got condoms and got reminded about shunning risk. And three, during the trials participants didn't know if TDF/FTC PrEP would work and whether they were taking the antiretrovirals or placebo. Average Jacks and Jills getting counseled quarterly (at best) and taking a drug they know works pretty well may be less prudent.

FDA product information stresses that TDF/FTC "is indicated *in combination with safer sex practices* for pre-exposure prophylaxis" (emphasis added), but few at-risk people will read the product information and many will combine TDF/FTC with *riskier* sex practices.

If he started PrEP, one Los Angeles gay man told researchers, "I could engage in more risky behavior because I now have that extra layer of confidence and protection."[19] Another proposed that he "would probably end up thinking well, after taking [PrEP] for a while, like a month or two, I would probably feel like okay I can stop using condoms because it would've built up in my body apparently." But one man said if his provider prescribed PrEP, "I would not negate condoms just because I was on the pill. I would still take that extra precaution."

In this pre-iPrEx study of 50 MSM in HIV-discordant partnerships, almost two thirds said they would probably engage in riskier sex behaviors if they had 90% effective PrEP, a level close to the 92% recorded in iPrEx men with detectable drug in plasma.[19] Almost as many men, 60%, predicted they would abandon condoms if they started PrEP. This is a small study and included only members of discordant partnerships, so the findings may not apply to all gay and bisexual men in the United States. But the results suggest PrEP prescribers will have hard work keeping PrEP users sheathed in latex.

In a larger study 630 substance-using MSM in Chicago, Los Angeles, New York, and San Diego fielded questions about a theoretical PrEP pill before anyone knew what iPrEx would find.[42] One third of these men (34.1%) would feel free to forgo condoms during insertive anal intercourse if PrEP were effective "at least half the time or more but not [effective] almost always or always"—roughly paralleling the overall iPrEx efficacy result. The same midrange level of PrEP would encourage 15% of these men to abandon condoms during receptive anal sex. Even *higher* pro-

portions of men said they would have unprotected receptive anal sex (28%) or unprotected insertive anal sex (51%) with PrEP that protected them from HIV "less than half the time." Compared with white men, black and Latino MSM were more willing to rely on less effective PrEP to avoid condom use.

A post-iPrEx online survey of 1155 US MSM recruited from facebook and black gay chat (bcglive) found that a 44%-effective PrEP pill (overall efficacy in iPrEx) would not change condom use in 75% of respondents—and 51% said they had unprotected anal intercourse the last time they had sex.[43] Another 7% said they would use condoms less often with 44% effective PrEP, 8% claimed they would use condoms more often, and 10% said they wouldn't use PrEP. One third of these men felt they would face increased pressure to shun condoms if they took PrEP. Almost three quarters of respondents (73%) were white, while 7% were black and 12% Hispanic.

Two studies offer some insight into how PrEP may affect risk behavior in heterosexual men and women. One survey involved 235 men and 125 women considered at high risk of HIV infection while attending a Chicago HIV clinic. Fifty-four men (23%) and 17 women (14%) said PrEP would make them use condoms less, while 109 men (47%) and 74 women (59%) said they would use condoms at the same rate with PrEP.[16] But only 38% of men and 33% of women reported using condoms all or most of the time during vaginal sex, and only 25% of men and 19% of women used condoms all or most of the time during anal sex. On the brighter side, only 54 men (23%) and 7 women (6%) foresaw having more sex partners if they took PrEP.

A similar 2009-2010 survey in a South Carolina STI clinic quizzed 225 men and 174 women, 89% of them black and 90% identifying themselves as heterosexual.[17] One third of survey respondents (32%) somewhat agreed that they or their partner would find it "very difficult to both use condoms and take daily pills to prevent HIV infection." On the other hand, 38% strongly *disagreed* with that statement. Men were 3 times more likely than women to foresee difficultly with simultaneous PrEP and condom use.

But at the end of the day should anyone be surprised that people who don't use condoms much—if at all—would suddenly *start* using them if they had a pretty good PrEP pill? PrEP candidates—people with "substantial, ongoing high risk for acquiring HIV infection"[9]—have that high risk precisely because condoms rarely show up on their shopping lists. As South African HIV prevention researchers Salim and Quarraisha Abdool Karim observed in an essay on these questions, "PrEP is most appropriate for the target populations where condom use is low or non-existent."[44]

How much will PrEP cost, and who will pay?

TDF/FTC PrEP isn't cheap. Pharmacychecker.com lists monthly tabs ranging from $580 to $3180 for brand-name Truvada. Even if PrEPpers take TDF/FTC only 4 days a week, for example, at a cost of $20 per pill that adds up to $4160 a year, and at list price the cost would be much higher. If a person doesn't have insurance that will pay the bill, Douglas Krakower and Kenneth Mayer write, "out-of-pocket expenses are likely to be prohibitive for many high-risk persons."[34] Gilead Sciences set up a PrEP Medication Assistance Program for "eligible HIV-negative adults in the United States who do not have insurance," their Website says. People can find out if they qualify by calling 1-855-330-5479 Monday through Friday between 9:00 AM and 8:00 PM Eastern time.

Los Angeles clinical investigators Theodoros Kelesidis and Raphael Landovitz estimate that "the cost

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of providing [TDF/FTC] PrEP to the 100,000 most at-risk people in the US could exceed $1 billion each year at current retail prices, which would exceed the CDC's current HIV prevention budget just with this intervention alone."[45] Three studies tried to reckon the preventive power and cost-effectiveness of TDF/FTC PrEP among gay and bisexual men in the United States.

A 2008 modeling study of PrEP in US MSM figured the cost of once-daily TDF/FTC—plus monitoring and care—at $11,740 per person annually, and drug costs made up 91% of that tally.[46] This model devised by Imperial College London investigators aimed to figure HIV cases prevented and cost-effectiveness of daily TDF/FTC PrEP among MSM in New York City over the course of 5 years. They figured costs based on the average wholesale cost of coformulated TDF/FTC in 2007. The model weighed different combinations of protection mechanism, efficacy, adherence, and population coverage. The researchers also modeled the impact of the three R's—risk compensation, resistance, and renal impairment.

A PrEP program targeting 25% of high-risk New York City MSM would prevent 4% to 23% of the 19,510 infections predicted in the 5-year window.[46] More than half of averted infections would involve men not taking PrEP but protected because of lowered HIV prevalence in the community. Across the range of input assumptions, TDF/FTC PrEP proved cost-effective 75% of the time at a threshold of $50,000 per quality-adjusted life year (QALY) gained and 87.5% of the time at a threshold of $100,000 per QALY gained.

In 2009 researchers from Yale School of Medicine and other institutions calculated cost-effectiveness in MSM across the United States, with a base-case assumption of 50% TDF/FTC efficacy and a monthly cost of $753.[47] This model also factored in the potential impact of differences in efficacy and risks of resistance, toxicity, and behavioral disinhibition.

In an MSM population averaging 34 years in age, daily PrEP would cut lifetime HIV infection risk from 44% to 25% and boost life expectancy modestly from 39.9 to 40.7 years.[47] But at a steep cost of $298,000 per QALY saved, TDF/FTC PrEP would not be cost-effective in the base-case model. Cost per QALY saved dropped substantially to $107,000 if PrEP efficacy rose from 50% to 90% (about the rate among men with detectable drug levels in iPrEx), to $114,000 if drug costs got halved, and to $189,000 if the target population age fell to an average 20 years. But in an "extreme toxicity scenario," cost per QALY saved soared to $1.5 million. These investigators concluded that "with improvements in efficacy, targeting, or pricing, [TDF/FTC PrEP] may . . . be cost-effective by current US standards."

In 2012 Stanford University researchers modeled the infection risk and cost-effectiveness of TDF/FTC PrEP in the general population of US MSM 13 to 64 years old and in certain MSM subgroups.[48] The base-case scenario set TDF/FTC PrEP efficacy at 44%—the overall iPrEx result. Dispensing PrEP to 20% of US MSM would trim the new-infection rate by 13% and add 550,166 QALYs over 20 years at $172,091 per QALY gained. For high-risk MSM with an average of 5 partners per year, PrEP would cost only $50,000 per QALY gained, but prescribing PrEP to all high-risk US MSM for 20 years would balloon healthcare costs $75 billion over current outlays. If the daily cost of TDF/FTC dropped to $15 or PrEP efficacy lay above 75% (as it did in adherent iPrEx men), PrEP for the general US MSM population would cost less than $100,000 per QALY gained.
One might formulate the following bottom line from all three studies: PrEP could prevent many

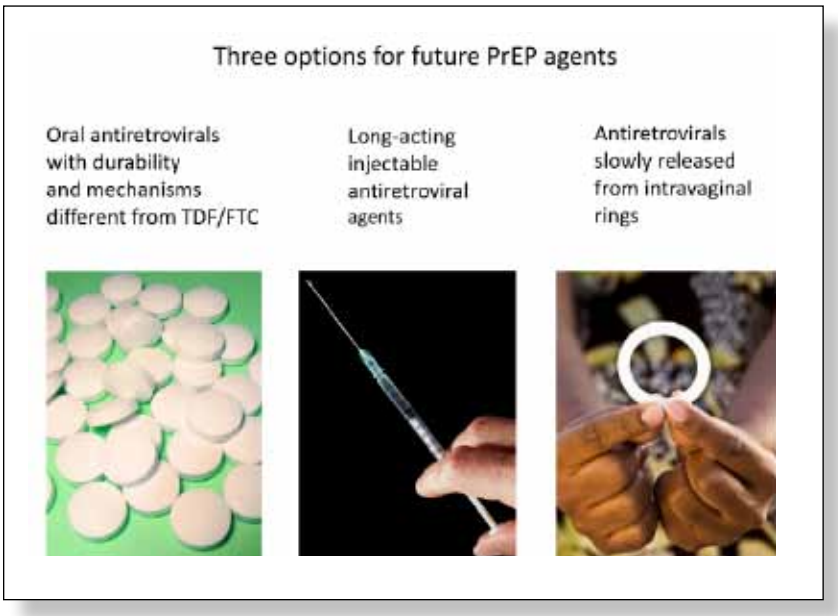
HIV infections in US gay and bisexual men over the next decade or so, but it costs a lot and may not be cost-effective at current TDF/FTC prices and if PrEP has only moderate efficacy. But lower costs and higher efficacy—including levels achieved by adherent men in iPrEx—could make PrEP cost-effective by current standards.

And who will pay for PrEP? Insurance companies will pay, iPrEx investigator Robert Grant affirmed in an interview in this issue. "The payers in the United States have decided not to require HIV testing results before paying for antiretroviral medications," he noted, "and they do realize this means they are paying for PrEP." Of course many people with the highest risk of HIV infection do not have insurance.

Prepping for PrEP's future

Years from now, healthcare providers and others in the know will look at TDF/FTC PrEP the way they look at zidovudine today—as an esteemed bellwether that may retain some niche function. Drug developers and clinical investigators are already well along in refining and testing new PrEP agents they hope will be more protective, safer, and easier to take than a once-a-day TDF/FTC pill.

So far future PrEP hopefuls fall into three (sometimes overlapping) groups—current or investigational antiretrovirals with mechanisms different from TDF and FTC, longer-acting antiretrovirals that may be taken by mouth or injection, and longer-acting antiretrovirals suffused into vaginal rings (**Figure 4**).



Falling into the first category, the CCR5 antagonist maraviroc thwarts HIV infection at an earlier step in the viral replication cycle than reverse transcriptase inhibitors like TDF and FTC. NEXT-PrEP (HPTN 069) is a US double-blind placebo-controlled trial aiming to enroll 400 MSM and 200 heterosexual women to compare the 48-week safety and tolerability of daily maraviroc, maraviroc/FTC, maraviroc/TDF, and TDF/FTC.[49]

Figure 4. Researchers are hard at work devising and testing PrEP agents that could improve on the activity, durability, and tolerability of TDF/FTC. (Pill and needle/syringe photos from Wikimedia Commons. Intravaginal ring photo from International Partnership for Microbicides (***http://www.ipmglobal.org/sites/international.ixm.ca/files/attachments/RING_BACKGROUNDER_%20ENGLISH.pdf***).

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Nonnucleoside reverse transcriptase inhibitors are well known for their long half-lives, a property Janssen hopes to exploit in long-acting formulations of rilpivirine (TMC278LA) and dapivirine (TMC120). A study of a single intramuscular TMC278LA injection recorded high concentrations in plasma, genital tract fluid, and vaginal tissue of 27 HIV-negative women studied in London.[50,51]

A single 600-mg intramuscular injection of rilpivirine suspended in nanoparticles remained in circulation for 84 days in 10 HIV-negative women and 6 HIV-negative men tested by the same investigators.[52] Vaginal tissue concentrations of rilpivirine were slightly lower than cervicovaginal fluid levels, but concentrations in male rectal tissue were higher than in rectal fluid. A phase 1/2 study of TMC278LA for PrEP ended early because of "additional safety information."[53]

Long-acting dapivirine is being studied both as a directly applied vaginal gel and in a vaginal ring, either alone[54] or with maraviroc.[55] Ideally, such rings could be inserted once a month, as contraceptive vaginal rings are today. In a double-blind placebo-controlled trial of a monthly dapivirine vaginal ring, 280 healthy, HIV-negative, sexually active women tolerated the ring well, and no serious safety concerns related to the ring arose.[56] Two parallel phase 3 placebo-controlled trials of dapivirine are testing a once-monthly dapivirine ring in more than 5000 African women.[57]

Three studies have tested antiretrovirals in intravaginal rings inserted in sheep—the protease inhibitor saquinavir,[58] tenofovir plus maraviroc,[59] and the integrase inhibitor raltegravir.[60]

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Putting PrEP into practice: adopt an attitude of discovery

An interview with **Robert M. Grant, MD, MPH**

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Dr. Grant is the protocol chair for the Pre-Exposure Prophylaxis Initiative (iPrEx) trial,[1] the first placebo-controlled trial to demonstrate partial protection from HIV infection with oral preexposure prophylaxis (PrEP). His lab at the Gladstone Institute of Virology is studying the biological and social implications of PrEP, the impact of low-level resistance to antiretrovirals, and HIV superinfection. Dr. Grant earned his MPH in epidemiology at the University of California, Berkeley and his MD at the University of California, San Francisco. With more than 26 years of experience in HIV clinical care and research, he has authored more than 100 peer-reviewed publications. In 2012 *Time* magazine named Dr. Grant one of the world's 100 most influential people for his research on HIV prevention.

Who should try PrEP?

Mascolini: For whom should US clinicians prescribe PrEP?

Grant: Broadly speaking, PrEP is for people potentially exposed to HIV infection. In the United States one key group consists of young men of color in urban centers that have an identified epidemic. PrEP candidates also include their partners, who may be women, and other people potentially at risk for acquiring HIV.

I think the most important point is that PrEP is for people *who want it*. Anyone who comes forward and says they're interested in finding new ways to protect themselves and their partners from HIV should receive prevention services, regardless of whether we can easily identify a risk factor. I say that because most of the language that we use about "risk groups" and "risk factors" is stigmatizing, off-putting, and insulting. It seems to me that if someone has come forward and says, look, I want PrEP, or I want to explore this, the answer should be yes. If anyone says, I want to find ways of keeping myself free of HIV, the answer should be yes.

Mascolini: Are you saying that if a man or a woman seeing a healthcare provider says they want PrEP, the provider shouldn't say, well, how many sex partners do you have, or do you use condoms consistently?

Grant: It's fine to explore these issues and to engage in such a conversation. But I think many clinicians are not prepared to have a nonjudgmental discussion about numbers of partners and sexual practices and similar issues. Clinicians need to think seriously about whether they're prepared to have a nonjudgmental conversation with a patient. If they are prepared, then by all means that kind of conversation can be useful.

This field is evolving rapidly. I think we need to help healthcare providers learn more about sexual health and ways of promoting sexual health in nonjudgmental ways. That process takes some time. In the meantime, when someone asks for prevention services, the answer should be yes.

Mascolini: Do you think heterosexual men and women with some risk of HIV infection are going to use PrEP in the United States?

Grant: Yes, I think they will sometimes. Certainly for heterosexual couples with one negative and one positive partner who desire pregnancy, PrEP is a very attractive option. Another alternative is suppressive therapy for the infected partner, which is also highly effective in preventing transmission.[2] But sometimes the negative partner may not have complete faith in their partner's ability to take antiretroviral therapy in a fully suppressive way. In those cases PrEP becomes an additional safeguard to allow intimate sex and pregnancy while lowering the risk of HIV transmission.

Identifying heterosexuals who need HIV prevention services has been a challenge in the United States. Again, I think that if we can find less stigmatizing ways of talking about HIV and sex, people will be more willing to come forward and ask for prevention services if they need them.

Mascolini: So far PrEP clinical trials that enrolled heterosexuals took place in Africa.[3-5] Can US and European clinicians be sure PrEP will work in heterosexual men and women outside Africa?

Grant: Yes. The Partners PrEP study[3] and the TDF2 study[4] both demonstrated that oral TDF/FTC is highly effective in heterosexual populations. Both of those studies were done in Africa, but the biology of heterosexual transmission is very similar around the world. I think that in heterosexual populations, as with gay men, adherence to PrEP is very important. It will not work if it is not used, and we've seen that in our research.[1,3-5] PrEP will fail if it's not used sufficiently to attain detectable drug levels in the body.

Mascolini: iPrEx had a small contingent of transgender participants, and your iPrEx abstract for the 2011 IAS meeting showed no protection of transgender participants.[6] Should clinicians consider PrEP for male-to-female transgender people?

Grant: I think they can consider it. In iPrEx we found that transgender women had detectable drug in their blood less frequently than other subgroups. We believe the trans subgroup in our study had more difficulty with adherence and that likely explains the lack of protective effect in that subgroup.

Importantly, there were insufficient numbers of trans women in iPrEx to know whether PrEP can work for them, so we're not sure yet whether PrEP efficacy is similar in trans women compared with gay men. But I think PrEP with tenofovir/emtricitabine [TDF/FTC, Truvada] is an option for trans women. Certainly, they should be aware that there's less information available about how well it works for them and that adherence was particularly challenging for trans women in iPrEx, we think for social reasons.

Everyone should realize that PrEP is highly effective if taken, but it is harder to take than people imagine. It does require taking a pill a day. People have to be organized to build that into their lives. They have to have an ongoing relationship with their healthcare provider.

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PrEP adoption, reimbursement, and side effects

Mascolini: Do you have a sense of whether many clinicians are starting to prescribe PrEP in the United States?

Grant: I think it's just beginning. As I go around the United States giving talks, typically there's one clinician in every room in virtually every city I've visited who is currently prescribing PrEP. But it really hasn't taken off as a common practice. I think providers are still trying to learn how best to use it and how best to inform people's decisions about whether PrEP is right for them.

Mascolini: When you give these talks around the country, what are the primary PrEP concerns your audiences ask about?

Grant: They're concerned about who should be offered PrEP, and I usually emphasize that people who want it should be offered PrEP. People's initiative is really the key thing to nurture at this point. We're trying to build a prevention initiative across the country so that we can see an AIDS-free generation.

Clinicians are interested in long-term as well as short-term side effects, as well as tolerance issues. They want to know when to start and when to stop PrEP. Does it have to be taken daily? Are there alternative regimens that are just as good? And then the practical questions: Who's going to pay for it and how can it be made available within our existing healthcare system?

Mascolini: Are third-party payers paying for PrEP?

Grant: I believe they are all paying for it. The payers in the United States have decided not to require HIV testing results before paying for antiretroviral medications, and they do realize this means they are paying for PrEP. Preventing HIV infection potentially saves 40 years or more of antiretroviral therapy costs. People who are taking antiretroviral therapy for infection still have an excess risk of cancer and heart disease, which obviously cause a lot of suffering, but they're also very expensive conditions to treat.

Insurance companies are very happy to see money spent on HIV prevention—it saves them money in the end. So generally they've been supportive of PrEP. The payers are not advertising that they have positive policies regarding PrEP, but they certainly have decided to pay for it the way they have been so far.

Mascolini: What are you telling providers about the potential risk of side effects with Truvada PrEP and what they should be watching for if they decide to prescribe it?

Grant: The side effects that we see most frequently are short-term side effects, and it's important to be aware of them. Trials indicate that somewhat less than 1 in 10 uninfected people who start Truvada PrEP will have some sort of symptom—nausea, abdominal cramping, dizziness, or headache. Typically these problems occur in the first week or 2 of PrEP use, and they resolve if people continue taking their medications. Some reassurance through that first period can help people decide whether they want to continue trying to take PrEP.

It's useful to have a check-in visit after 2 or 4 weeks of PrEP use just to see how it's going. At that visit, clinicians can see whether people decided to actually take

the pill and whether those who did are having that start-up syndrome, which is reminiscent of the start-up syndrome that may occur when people start taking antiretroviral drugs for treatment of HIV. Making PrEP users aware that this syndrome can occur and that it usually resolves spontaneously is important for early adherence.

There were no excess moderate to severe side effects in people taking PrEP versus those taking placebo in the phase 3 trials.[1,3-5] We did see that a small number of individuals taking Truvada PrEP had elevations in their serum creatinine, which is an indicator of renal function. We agree with the CDC's recommendation that serum creatinine should be monitored in people taking PrEP.[7,8]

If serum creatinine increases more than 50% above baseline or if serum creatinine is abnormally high, the first thing to do is to recheck the blood test, because most serum creatinine elevations will resolve without stopping the drugs. If there's a confirmed increase in serum creatinine, we do recommend that PrEP be stopped and that serum creatinine be allowed to return to normal. If it does return to normal, PrEP can be restarted with careful monitoring.

We saw elevated serum creatinine in about 1 in 200 PrEP users in iPrEx.[1] It's rare, but if a clinician is writing prescriptions for 200 PrEP users, they may see 1 or 2 people who have confirmed elevations in serum creatinine.

Finally we saw an average 1% loss in bone mineral density in people taking Truvada PrEP.[1] This average change in bone mineral density occurred in the first 6 months of PrEP and did not progress with ongoing exposure to PrEP, and it was not associated with an excess in bone fractures. The FDA package insert indicates that the preventive use of these drugs can cause a small decrease in bone mineral density, and people who have risk factors for osteoporosis might consider DEXA scanning during PrEP use.

We did not see any change in fat distribution in HIV-negative people taking Truvada PrEP in iPrEx.[1] There had been concerns that lipodystrophies might occur with Truvada PrEP—that we might see the kinds of fat redistribution observed in people taking antiretrovirals for HIV treatment. But we did not see anything like that in people taking PrEP.

Risk of intermittent PrEP, and research priorities

Mascolini: Is there a danger that people will use Truvada PrEP as a presex or morning-after pill?

Grant: We think Truvada PrEP is most useful when it's taken daily, so we recommend that people who want to protect themselves by using PrEP should take it daily. There is interest in intermittent dosing, but we emphasize that one pill is not enough for protection: Protective concentrations of the drugs continue to increase over the first 21 days of use, so if people want the maximum level of protection they should take it daily.

Will people try to take this in a more casual way? I think it's too early to know. We do know and have published in *Science Translational Medicine* that people in iPrEx were protected by PrEP even though adherence was less than perfect.[9] The drug concentrations that we observed in iPrEx were commensurate with 3 to 7 doses per week, yet we did see high levels of protection in all people who had detectable levels of drug in their blood, even if drug levels were relatively low. Although people should try to take Truvada PrEP

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daily, there is some forgiveness for missing some doses, especially if people are taking it daily. If they try to take it just before and after sex, that may provide some protection, but there's no forgiveness if they miss the preexposure dose or the postexposure dose or if they take it a little late—the regimen becomes fragile if people try to take it just pre- and postexposure.

Mascolini: What are the priorities for ongoing PrEP research?

Grant: The main priority is how to make PrEP easier to use. We do have studies in the field looking at nondaily Truvada regimens: Can people take it pre- and postintercourse?[10] Can they take it twice a week with a postintercourse boost?[11] [See "Prospects for intermittent PrEP dosing" in the article preceding this interview.] PrEP formulations that can be used in different ways are important to develop, perhaps an injection once a month.

Not everyone was able to tolerate Truvada in PrEP trials. The vast majority of people who took Truvada PrEP could tolerate it, but some people didn't. So alternative antiretrovirals, possibly maraviroc or raltegravir, should also be explored. Some antiretrovirals, such as the nonnucleoside dapivirine, have very long half-lives. Discovering whether they can be used as PrEP is also very important.

Key findings from the iPrEx study of TDF/FTC PrEP[1]

- 2499 men and transgender women who have sex with men enrolled in Peru, Ecuador, South Africa, Brazil, Thailand, and the United States
- Participants randomized to once-daily TDF/FTC or placebo
- Half of participants (47% TDF/FTC, 53% placebo) 18 to 24 years old
- Almost three quarters of participants (72% TDF/FTC, 73% placebo) Hispanic
- About 10% of participants (9% TDF/FTC, 10% placebo) from US (San Francisco or Boston)
- Average number of sex partners in last 12 weeks: 18
- Unprotected receptive anal intercourse in past 12 weeks: 59% TDF/FTC, 60% placebo
- Any grade 3 or 4 adverse event: 12% TDF/FTC, 13% placebo
- Elevated creatinine: 2% TDF/FTC, 1% placebo
- Overall decrease in HIV acquisition risk with TDF/FTC: 44%
- Decrease in HIV acquisition risk with TDF/FTC with at least 50% pill use*: 50%
- Decrease in HIV acquisition risk with TDF/FTC with at least 90% pill use*: 73%
- Decrease in HIV acquisition risk with detectable TDF/FTC in plasma: 92%†
- No significant between-group difference in protection on the basis of region, race or ethnic group, male circumcision, education level, alcohol use, or age

*Determined by study-drug dispensation and returns.

†Decrease 95% after adjustment for reported unprotected receptive anal intercourse.

Mascolini: What are you looking for in iPrEx OLE—the open-label extension of the iPrEx trial?

Grant: iPrEx OLE (***http://www.iprexole.com/***) is fully enrolled with 1770 individuals. We offer PrEP to everyone, and we follow them whether or not they choose to protect themselves with PrEP. We are looking at who chooses to take PrEP and who chooses not to, and we will measure HIV infection rates in both groups. Over the 1.5 years that we will follow this cohort, we are hoping that all 1770 participants remain free of HIV, regardless of how they chose to protect themselves from HIV.

Among people who start PrEP in this open-label format, we want to learn how well they adhere to the regimen and how their sexual practices might change: Do they stop using condoms? Do they have more sexual partners? Or rather do they focus more on intimacy with one or a few partners? We see that people do change their sexual practices and their sexual goals when they start PrEP, but interestingly the change is often in the direction of seeking more intimacy with fewer partners rather than the opposite. Our overall goal is to discover what people will do when PrEP becomes a real opportunity accompanied with real information about what the pill is, how effective it can be, and how safe it is.

Mascolini: Is there anything we didn't discuss that you think prescribers or PrEP candidates should know?

Grant: PrEP is a new approach. We're still discovering a lot about it, so having an attitude of discovery with potential PrEP users is appropriate. Let's explore for whom this is a good intervention, how long they want to take it, and how well they can achieve their goals by PrEP or alternative means. I think an attitude of exploration is appropriate, and I think it's equally important to move away from stigmatizing language. We need to stop thinking in terms of "risk groups" and "risk behavior" and start appreciating people for who they are and for their desires to remain healthy and socially engaged.

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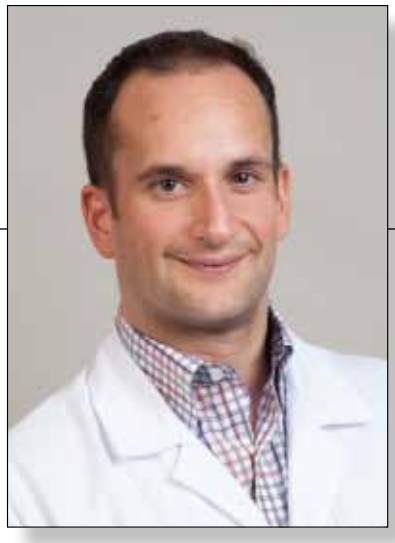

How PrEP will roll out in practice (slowly, so far)

An interview with **Raphael J. Landovitz, MD, MSc**

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In his 16 years as a physician and clinical investigator, Dr. Landovitz has earned a strong reputation for his research on medical prevention of HIV infection and the impact of such interventions on risk behavior. As co-director of the Combination Prevention Core at the Center for HIV Identification, Prevention, and Treatment Services and the UCLA Center for Clinical AIDS Research & Education, he conducts research through the HIV Prevention Trials Network (HPTN) and the AIDS Clinical Trials Group (ACTG), which awarded him the John Carey Young Investigator Award in 2010. Dr. Landovitz holds an undergraduate degree from Princeton University and earned his MD from Harvard Medical School and his MSc from UCLA. Before moving to Los Angeles, he served as chief resident at Brigham and Women's Hospital in Boston and medical co-director of the Vietnam-CDC-Harvard Medical School-AIDS-Partnership (VC-HAP), which trains Vietnamese physicians in HIV care and treatment. (He speaks Vietnamese and Spanish.) Dr. Landovitz heads the Los Angeles County PEP Demonstration Project and collaborates with the City and County of Los Angeles, and Friends Community Center. His innovative work in HIV prevention includes prevention practices among gay men who use GRINDR (a GPS-based networking application MSM use to find sex partners) and combination HIV prevention with postexposure prophylaxis and contingency management for substance use among methamphetamine-using men.

Mascolini: Can you summarize the demographics, sexual behaviors, and substance use habits of HIV-positive and negative populations you care for and study in Los Angeles?

Landovitz: Our clinic cares for about 900 HIV-infected men and women on the west side of Los Angeles. We're broadening the scope of our care and research involving HIV-uninfected individuals at risk for HIV infection. With the medicalization of HIV prevention, we're working to learn how to best deliver prevention and care services as the domain of who provides prevention care continues to evolve.

Our clinic's HIV-infected population is approximately 42% non-Hispanic white, 34% African American, and 22% Latino. Although I don't have aggregate data on sexual and drug use behavior for this patient

population, I can give you some data from certain studies we've done in people with HIV: 44% of that population had ever used any illicit substances, and 36% reported ever having used stimulants. In terms of sexual risk behavior, about 30% of that study population reported some unprotected sexual activity with a partner of unknown HIV status in the last year.

For the HIV-negative but at-risk individuals we see, I can cite some data from studies of people who requested HIV postexposure prophylaxis (PEP) at our community-based program. That population is almost 95% male, and 85% men who have sex with men (MSM). Almost two thirds, 62%, sought PEP after receptive anal intercourse. This population is 48% Caucasian, 35% Latino, and 8% African American.

PrEP interest and uptake in Los Angeles

Mascolini: Do HIV-negative at-risk men in your area know about PrEP and do they want to try it?

Landovitz: We have had very few requests for PrEP in our clinic. I've surveyed other HIV providers on the west side of Los Angeles, and they too have had precious few requests for PrEP. We were a little surprised by that. The majority of these few requests have come from men who are in serodiscordant relationships and seem to keep their fingers on the pulse of what's current.

Here is Los Angeles we've only recently begun to be involved in clinical trials of PrEP. We were not part of the iPrEx trial in MSM[1] or the early open-label study that came out of iPrEx, the iPrEx OLÉ rollover protocol. The HPTN 069 protocol comparing PrEP regimens containing tenofovir/emtricitabine to maraviroc-containing regimens[2] (**Table**) is the first clinical study activity in Los Angeles. In the wake of the iPrEx results, we've had a number of community forums and engagement meetings to disseminate the results and initiate discussion about how PrEP could or should be used in the context of larger prevention programming.

We've done some combination prevention work at two community-based sites in Los Angeles, one at the Gay and Lesbian Center and one at the Oasis Clinic, which is in South LA. As part of this work, we developed a community-based 1-year nonoccupational PEP demonstration project that we parlayed into an ongoing public health service delivery program sponsored by the Division of HIV/STD Prevention (DHSP) in the County Department of Public Health. We are ramping up a PrEP demonstration project that will be deployed at those sites, but it has not begun yet.

Our PEP work indicates that 3% to 5% of PEP users asked for PEP more than once, and we think those people are excellent candidates for PrEP. In my mind PEP should be a one-time emergency intervention after a condom breaks or isn't used in a particular situation. The counseling that surrounds an episode of PEP should help prevent someone from ever requiring PEP again, and certainly not to require PEP frequently. I believe recurrent PEP users would be better served by PrEP. At the same time, we have to continue studying this recurrently at-risk population—to understand how to modify the behaviors that cause them to be persistently at risk and allow potential PrEP users to come off PrEP, because nobody wants to be on PrEP forever.

Mascolini: Have you and your colleagues figured out how to make PrEP part of your practice, and have you established any sort of PrEP use protocol?

Landovitz: We've talked about how PrEP might be part of larger HIV prevention programming. I think we all agree that PrEP should not be seen or promoted as an isolated intervention: PrEP may be an

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HPTN 069: Safety and tolerability of four prep regimens in MSM

Status
- Recruiting
- Estimated primary completion date January 2014

Primary outcomes
- Occurrence of grade 3 or 4 adverse events through 48 weeks
- Tolerability as assessed by time to permanent discontinuation of treatment through 48 weeks

PrEP regimen arms
- Maraviroc plus emtricitabine (FTC) placebo plus tenofovir (TDF) placebo orally once daily
- Maraviroc plus FTC plus TDF placebo orally once daily
- Maraviroc plus FTC placebo plus TDF orally once daily
- Maraviroc placebo plus FTC plus TDF orally once daily

Key inclusion criteria
- Born male and 18 or older at screening
- Receptive or insertive anal intercourse without condoms with at least one HIV-infected male partner or male partner of unknown HIV status within 3 months of study entry
- Creatinine clearance 70 mL/minute or higher
- No alcohol or substance use that the investigator believes would interfere with the study

Key exclusion criteria
- One or more reactive HIV test results at screening or enrollment
- Use of antiretrovirals for PEP or PrEP within 90 days before study entry
- Ongoing intravenous drug use
- Weight over 300 pounds

Participating sites
- California: UCLA Care Center, Los Angeles; San Francisco Vaccine and Prevention Center
- Maryland: Johns Hopkins Adult AIDS Center, Baltimore
- Massachusetts: Fenway Institute, Boston
- New York: Cornell University, New York City
- North Carolina: University of North Carolina, Chapel Hill; Wake County Health and Human Services, Raleigh
- Ohio: Case Western Reserve University, Cleveland
- Puerto Rico: Puerto Rico-AIDS
- Pennsylvania: Hospital of the University of Pennsylvania, Philadelphia; University of Pittsburgh
- Washington, DC: George Washington University
- Washington State: University of Washington, Seattle
- For detailed study information and study site contacts: ***http://www.clinicaltrials.gov/ct2/show/study/NCT01505114***

appropriate adjunct to other prevention efforts and may be appropriate for certain targeted populations, but we should not prescribe PrEP and send people off with the impression that PrEP alone is sufficient to mitigate HIV acquisition risk.

We're trying to funnel any PrEP referrals to providers who have kept up on the literature and have a comprehensive understanding of combination prevention programming. Such programming might involve referring people to other services, including mental health services, substance use treatment services, and intimate partner violence services. At the same time, we believe combination prevention includes condom provision and education and adherence counseling. In that context we can do some risk stratification for who appears to be at ongoing risk for HIV acquisition despite other interventions and then consider PrEP as an adjunct to all these other efforts.

I'm one of those people handling PrEP referrals, and so far I've seen two consultations for preexposure prophylaxis since the FDA approval of Truvada for PrEP. So at least in a controlled medical environment on the west side of LA, we're not seeing a lot of demand for PrEP.

Mascolini: Do you think this low demand means PrEP candidates are on an early part of the PrEP learning curve, or does it mean people just aren't interested in taking a pill to prevent HIV infection?

Landovitz: It's probably multifactorial. I think people are probably much less interested in taking a *daily* pill, and some adherence data from the placebo-controlled iPrEx,[1] Partners PrEP,[3] and TDF2[4] trials bear this out. [See the first article in this issue.] Others may believe it's just not feasible to take a daily HIV-prevention pill for any number of reasons.

My personal feeling is that there's not going to be widespread uptake and interest in PrEP—at least in the MSM communities who dominate the epidemic on the West Coast—until a PrEP agent is available in a depot or sustained-release formulation. My experience talking to patients and interacting with other providers suggests that the analogy to women taking daily birth control does not appear to be a compelling one for gay men. So I think the game changer will be a depot or long-acting formulation—or at the very least a much more sophisticated understanding of what sort of more intermittent dosing might be effective and safe.

Mascolini: What proportion of PrEP candidates you see have insurance that will pay for PrEP?

Landovitz: In our PEP experience with HIV-negative but at-risk people, 60% of those seeking PEP at our community-based sites are uninsured. Our PEP demonstration project is designed to have no cost to people seeking that service. I suspect this PEP population is similar to our potential PrEP population. People who are well-informed early adopters, who have private insurance and private doctors, will access PrEP in those contexts and aren't waiting for a publicly funded demonstration project.

Considering substance abuse and PrEP side effects

Mascolini: Have you or any providers you know in the area actually prescribed PrEP for anyone?

Landovitz: I've prescribed it to one man in a serodiscordant couple outside of a study context. We have a growing number of people enrolling in the HPTN 069 study[2] for whom we've prescribed PrEP. Because HPTN 069 is a fairly intensive study, these are largely people in serodiscordant relationships or individuals who want to give back to the community

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by furthering research about PrEP and who simultaneously perceive themselves to be at high risk of HIV acquisition. But that view is a little bit skewed because our clinical practice does not see uninsured patients and so does not reflect the evolving US epidemic.

Mascolini: You've reported frequent substance abuse in your population of HIV-uninfected MSM. Will you be less likely to prescribe PrEP for men with substance abuse problems?

Landovitz: That's an extremely challenging question. In LA methamphetamine appears to be driving a large portion of the MSM HIV epidemic, so stimulant users may be a population for whom PrEP could be particularly effective, if there were a way to deploy it successfully and safely. My group and some of my colleagues have done some pilot work trying to use post-exposure prophylaxis in stimulant users for exactly that reason.[5] We found that you can get PEP time-to-initiation and adherence rates in methamphetamine users comparable to those in the general population by combining PEP with a contingency management program in which people are given voucher-based incentives to abstain from stimulant use during the course of PEP treatment.

But we're still struggling to figure out how to optimize a PrEP regimen that requires daily adherence in a population with clear adherence challenges. Most people assume that the poor antiretroviral adherence we see in HIV-positive substance users will also be true in an HIV-uninfected population of substance users. I think it's an unanswered question that needs to be studied. For now, I would personally be reluctant to prescribe PrEP for this population outside of a study context because we're so acutely aware of how adherence-sensitive the efficacy of this intervention is.

Mascolini: How will you consider kidney and bone risk factors when deciding whether to prescribe Truvada PrEP?

Landovitz: I think that's a critical question. The phase 3 randomized PrEP data raise some serious concerns about both those safety areas. [See the following article in this issue.] The 1% loss in bone mineral density over 1 year recorded in some trial participants is extremely concerning in a healthy population, especially considering the poor adherence rates in PrEP trials. What would be the rate of bone mineral density loss in a more adherent population? I don't think we know.

I think PrEP trial data on bone mineral density changes would give a provider pause in using Truvada-based PrEP in someone with risk factors for low bone mineral density. Perhaps PrEP candidates with these risk factors should receive up-front vitamin D and calcium supplementation, and maybe they need more frequent DEXA scans during PrEP use. But I think we don't know exactly how to use these diagnostic tools to stratify people. It's an important area of research that needs to be clarified before Truvada PrEP is implemented in a widespread way.

The risk of renal toxicity with Truvada PrEP is also an unanswered question. All of the randomized controlled PrEP trials selected extremely healthy populations with excellent baseline renal function. I don't think we know what the renal adverse event rate is going to be in real-world populations. Even the PrEP demonstration projects rolling out now are going to have fairly restrictive creatinine clearance and glomerular filtration rate criteria for entry, so they will still not give a full picture of the toxicity spectrum. But toxicity results from these projects should be closer to what we will see in practice because the study populations will be a little more diverse. We're hoping to enroll 30% to 40% African Americans in our demonstration project, and African Americans have

increased rates of hypertension and baseline renal dysfunction. So we hope to get a broader experience with how Truvada PrEP may affect HIV-uninfected African Americans at risk.

I think it's incumbent on those who are running these demonstration projects to build in careful safety monitoring that will provide a full and clear picture of toxicity now that the efficacy of this intervention has been established.

Talking to PrEP candidates about adherence and condoms

Mascolini: How do you counsel PrEP candidates on the importance of adherence?

Landovitz: I think it's really challenging. We're partnering with some of the smartest adherence experts in the country and the ones with the most experience in biomedical prevention-related adherence. We're working with Rivet Amico from the University of Connecticut, who was the adherence and behavioral specialist in the iPrEx study. So we're benefitting from her longitudinal experience with that group.

We need to be very careful to explain to PrEP candidates that all available data strongly suggest that the medication works best when taken every day. For that reason we cannot recommend that people skip any doses. At the same time we want people to report their medication-taking behavior realistically because we want to understand why people do or don't take the medication regularly. The best and most honest information we can provide is that the medication does not work if you don't take it, and that the more regularly you take it, the better it works.

Mascolini: What are you saying to PrEP candidates about condom use?

Landovitz: I fear that many individuals will look at PrEP as an alternative to condoms. Mathematical models clearly suggest that if individuals choose to use PrEP only and not use condoms, there is the potential for an increase in HIV incidence.[6,7] I find that frightening.

We have to remind everyone that no prevention intervention is 100% effective and the best way to protect oneself is to use condoms and to consider PrEP a back-up strategy if a condom fails or for whatever reason doesn't get used in a particular instance. But PrEP should not be thought of as a substitute for the protection afforded by condoms. If that weren't compelling enough, many other infections that can be transmitted sexually are not prevented by PrEP.

Mascolini: Do you want to add anything on concerns or observations you may have on how PrEP may be used in practice?

Landovitz: The biggest concern I have that I'm hearing from communities is that disparities between those who have access to HIV care and treatment and those who don't will only be enlarged by the medicalization of HIV prevention. There is concern that those disparities will widen the chasm between racial and ethnic communities who do and do not have access to HIV care and treatment.

I think it's critical for those of us who are studying and considering how to implement PrEP to make sure that doesn't happen. Partnership with communities in the study and dissemination of PrEP information is the only way to ensure it's done equitably. I'm far from saying that we in LA have found the optimal or even the right way to do that. But that is one of our main missions in reaching a comprehensive understanding of how to use this intervention.

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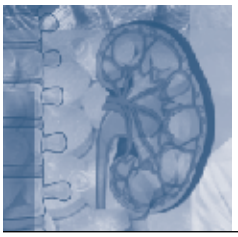

Weighing risks of TDF/FTC PrEP side effects in people without HIV

By Mark Mascolini

Abstract: Prescribing tenofovir/emtricitabine (TDF/FTC) as PrEP raises questions about side effect risks in HIV-negative people. Side effects that arise in the first weeks of PrEP—nausea, abdominal cramping, vomiting, dizziness, headache, and fatigue—usually resolve without withdrawing TDF/FTC. But providers should alert PrEP candidates to these possible problems so they do not stop PrEP unnecessarily if side effects occur. Cohort studies that enroll HIV-positive people and similar HIV-negative people at risk of HIV infection offer unique insights into risks of two well-known TDF side effects, impaired kidney function and declining bone mineral density (BMD). This research indicates that many HIV-negative PrEP candidates have risk factors for kidney and bone complications, but these people do not appear to have higher than normal rates of kidney and bone problems in published studies. Through 1 to 2 years of follow-up, placebo-controlled PrEP trials found higher rates of declining kidney function and BMD in HIV-negative people randomized to TDF/FTC. But these problems affected only small proportions of people assigned to TDF/FTC during these trials. In HIV-positive people, some research indicates that TDF-linked kidney toxicity improves when TDF stops, but a 10,000-person Veterans Affairs study found that it may not. Another prospective study of HIV-positive veterans figured that every year of TDF use boosts the risk of osteoporotic fracture 12%, while other cohort studies and trials confirmed dwindling BMD with TDF therapy but found no greater fracture risk. TDF/FTC PrEP should not be prescribed for people with creatinine clearance below 60 mL/min, and pre-PrEP DEXA scans of BMD may be prudent for people with a past fracture or other bone risk factors.

"I probably wouldn't take [PrEP] because I know HIV medications are very strong and if you don't have to take them why would you? And I'm healthy, so why would I do damage to my body to protect myself but I still got a chance of getting [HIV], when I can just use a condom and continue what I've been doing?"[1]

Those keen questions by a gay man in Los Angeles, reported in a study by UCLA investigators,[1] neatly encapsulate the dilemma faced by people who may take tenofovir/emtricitabine (TDF/FTC) preexposure prophylaxis (PrEP) and by people who may prescribe it. Plenty of precedent sketches out the risks healthy people face when taking prophylactic agents—from short-term chloroquine to ward off malaria to regular hormonal agents to prevent pregnancy.

Hormonal contraception, in fact, offers a trenchant reverse analogy for TDF/FTC PrEP. Hormonal contraception, especially injected hormonal agents, may *boost* the risk of HIV acquisition and transmission.[2] But because data on that question are inconsistent and contraception offers such clear family-planning benefits, the World Health Organization decided that women using progestogen-only injectable contraception "should be strongly advised to also always use condoms, male or female, and other HIV preventive measures."[3]

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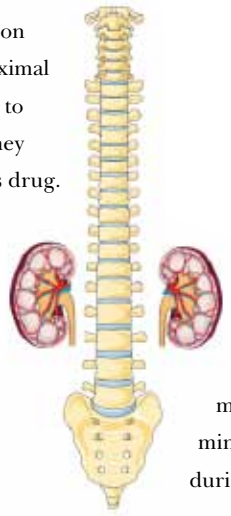
In contrast, TDF/FTC PrEP clearly cuts the risk of HIV acquisition,[4-6] but it does so at the risk of TDF-related toxicity and so requires pre-PrEP side-effect screening and regular check-ups during PrEP (see Table 2 in the first article in this issue). Like hormonal contraceptives, TDF/FTC PrEP should also be taken "in combination with safer sex practices,"[7] because it does not erect an impervious firewall against HIV.

Probably the most hallowed tenet of medicine—and one echoed often at the FDA hearing on TDF/FTC PrEP—adjures clinicians trying to help their patients to avoid hurting them first. A PrEP-specific translation of that dictum, penned by Myron Cohen and Lindsey Baden (University of North Carolina and Brigham and Women's Hospital), puts it this way: "Providing a daily medication to healthy, HIV-uninfected persons demands an extraordinarily high degree of safety."[8]

Emtricitabine ranks among the safest medicines dispensed, but everyone knows TDF poses a threat of serious long-term toxicity to a handful of people taking it to treat HIV infection. Will people without HIV face the same risk?

Possible mechanisms of kidney and bone toxicity with TDF

TDF accumulation in the renal proximal tubulae appears to account for kidney toxicity with this drug.



TDF-induced perturbation of cellular DNA synthesis and gene expression may explain bone mineral density loss during TDF therapy

Because follow-up in PrEP trials generally falls short of 2 years, only informed guesswork can approach an answer to that question. But thanks to round-the-clock HIV research, the guesswork addressing this question is highly informed. Over the years, HIV investigators created and endlessly canvassed cohorts of HIV-positive people paired with HIV-negative contemporaries sharing similar behaviors, lifestyles, sociodemographic nitty-gritties, and—in the end—a worrying risk of HIV infection. These well-studied HIV-negative people are among today's top PrEP candidates. The Multicenter HIV Cohort Study (MACS) of US gay and bisexual men with and without HIV and the Women's Interagency HIV Study (WIHS) of US women are eminent examples. PrEP studies of HIV-negative people who run a high risk of getting infected provide another font of plumbable data.

Together, data from this research offer much more than a passing glance at rates and risks of two TDF-related toxicities in HIV-negative people: impaired kidney function and waning bone mineral density (**Figure 1**). This article offers a detailed analysis of kidney and bone findings in people without HIV—as well as in people with HIV who took TDF for years.

Figure 1. Research suggests possible mechanisms for the much-studied impact of tenofovir disoproxil fumarate (TDF) on kidney and bone mineral density: Kohler JJ, Hosseini SH, Hoying-Brandt A, et al. Tenofovir renal toxicity targets mitochondria of renal proximal tubules. *Lab Invest.* 2009;89:513-519; Grigsby IF, Pham L, Mansky LM, Gopalakrishnan R, Mansky KC. Tenofovir-associated bone density loss. *Clin Risk Manag.* 2010;6:41-47. Kidney and spine illustrations from Servier Medical Art: ***http://www.servier.co.uk/medical-art-gallery/***.

Short-term side effects of TDF/FTC PrEP

Although providers worry about the long-term risk of compromising kidneys or depleting bone mineral with TDF/FTC PrEP taken for 2 years or more, both clinicians and PrEP candidates should realize that TDF/FTC can have short-term side effects, including nausea, abdominal cramping, vomiting, dizziness, headache, and fatigue.[4-6,9] These problems typically arise in the first week or 2 of PrEP, then often disappear in the next few weeks. In an interview in this issue of R*ITA!* Robert Grant, who headed the iPrEx PrEP trial,[4] compares these problems to the "start-up syndrome" seen when people start antiretrovirals for treatment. These vexations can have a big impact on care if they sway people to skip doses or stop their drugs altogether.

Clinicians would be wise to alert PrEP novitiates that these ailments may arise and that they usually resolve without stopping TDF/FTC. Robert Grant even suggests that providers schedule a "check-in visit" 2 to 4 weeks after a person plans to start PrEP—both to see if the person actually started taking the pill daily, and if TDF/FTC caused any aches or pangs.

FDA prescribing information for TDF/FTC lists three adverse reactions reported in at least 2% of people randomized to TDF/FTC PrEP and more frequently than in those randomized to placebo—headache, abdominal pain, and weight loss.[7] A few other problems affected at least 2% of TDF/FTC takers and a similar proportion of placebo recipients: diarrhea, back pain, depression, and anxiety. "Unintentional weight loss" of 5% or more affected 34 people in the TDF/FTC arm of iPrEx and 19 in the placebo group ($P = 0.04$).[4]

An angle on long-term side effect risk with TDF/FTC PrEP

How healthy are HIV-negative people who may take TDF/FTC PrEP in the United States? And what's their risk of subpar kidney function and ebbing bone mineral density? Because many sexually active people—and all injection drug users—run some risk of picking up HIV, it's impossible to generalize about at-risk people as a monolithic group. But the Multicenter AIDS Cohort Study (MACS), the Women's Interagency HIV Study (WIHS), and other population-based analyses in high-income countries offer plenty of insight on HIV-negative gay and bisexual men and women in danger of getting HIV infection.

By and large, people who put themselves on a collision course with HIV are not paragons of good health. Because people with the highest risk of picking up HIV during sex are those who have lots of sex—often without condoms—this group shoulders a high burden of other sexually transmitted infections, including hepatitis C virus (HCV) infection, an oft-noted risk factor for deliquescing bone density and chronic kidney disease. In the United States, young black men who have sex with men (MSM) account for a burgeoning proportion of new HIV infections,[10] and blacks run a higher risk of kidney disease than whites. Young white and black MSM with lots of sex partners often have other habits that threaten their health—smoking, drinking, and downing recreational drugs that range from the innocuous to the caustic. In the United States, WIHS findings and other data indicate, women with a high HIV risk are often poor, overweight, and members of minorities with off-and-on access to health care.

If one compiles a list of classic risk factors for low bone density and chronic kidney disease (**Table 1**), that catalog includes an array of variables common among US men and women with a substantial risk of HIV infection. Both MSM and high-risk women can claim many of the behavioral risk factors. HCV and other chronic infections occur often among risk-taking gay and bisexual men, while disadvantaged women with a high HIV risk are prone to diabetes,

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hypertension, high cholesterol, and cardiovascular disease. Unbalanced diets in at-risk poor women can result in vitamin D and calcium deficiency. Vitamin D insufficiency and deficiency are virtually endemic in sedentary populations with meager sun exposure.

The TDF/FTC PrEP dose is the same as the treatment dose—one Truvada tablet daily, 300 mg of TDF plus 200 mg of FTC. Whether PrEP users will adhere to that prescription remains open to question (as discussed in the preceding review article in

Table 1. Classic risk factors for low bone mineral density and chronic kidney disease

Low bone density risk factors	Chronic kidney disease risk factors
Demographics/family history	
Older age	Older age
White race	Black race
Asian race	Asian race
Female sex	Native Americans
Previous fragility fracture	Family history of chronic kidney disease
Family history of osteoporosis	
Physical factors	
Low weight	Overweight
Anorexia	
Low estrogen or testosterone	
Thyroid problems	
Behaviors	
Smoking	Smoking
Alcohol	
Methadone/opiates	
Physical inactivity	
Dietary and related factors	
Vitamin D deficiency	
Limited sun exposure	
Low dietary calcium	
Other conditions and medications	
Diabetes mellitus	Diabetes mellitus
HCV infection	HCV infection
Chronic infection	High cholesterol
Chronic kidney disease	Hypertension
Corticosteroids (such as prednisone, cortisone)	Cardiovascular disease
Anticoagulants, anticonvulsants, antipsychotics, cyclosporines, glitazones, gonadotropin-releasing hormone agonists, methotrexate, proton pump inhibitors	Kidney stones or kidney infection; sickle-cell anemia; autoimmune disorders (such as lupus, scleroderma)

Sources: Centers for Disease Control and Prevention. National chronic kidney disease fact sheet 2010. ***http://www.cdc.gov/diabetes/pubs/factsheets/kidney.htm***; Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2005;40:1559-1585. ***http://cid.oxfordjournals.org/content/40/11/1559.long***; McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. *Clin Infect Dis*. 2010;51:937-946. ***http://cid.oxfordjournals.org/content/51/8/937.long***; Mayo Clinic. Osteoporosis. ***http://www.mayoclinic.com/health/osteoporosis/DS00128***; Mayo Clinic. Chronic kidney failure. ***http://www.mayoclinic.com/health/kidney-failure/DS00682***; National Institutes of Health. US National Library of Medicine. Medline Plus. Osteoporosis. ***http://www.nlm.nih.gov/medlineplus/osteoporosis.html***; National Institutes of Health. US National Library of Medicine. PubMed Health. Chronic kidney disease. ***http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001503***/.

this issue). But if they take TDF/FTC PrEP for 2 or 3 years, they may run the same toxicity risk as people who take TDF/FTC daily for chronic HIV infection—though perhaps not quite. People with HIV may face a slightly higher risk of side effects because HIV itself may affect kidney function and bone density, because HIV-positive people may have higher rates of other conditions that threaten kidneys and bone, and because HIV-positive people may be taking more nonantiretrovirals that pose toxic threats to kidneys and bones. So reviewing the impact of TDF/FTC in HIV-negative people enrolled in PrEP trials—and appraising kidney and bone health in other PrEP candidates—should yield some insight into long-term toxic risks with this double drug. After those analyses, this article weighs evidence on long-term TDF toxicity in people taking antiretroviral therapy.

Kidney function in PrEP users and candidates

FDA regulators recognized the kidney threat posed by long-term TDF when they stipulated that TDF/FTC PrEP should not be used by "HIV-uninfected individuals if creatinine clearance is below 60 mL/min."[7] In iPrEx,[4] Partners PrEP,[5] and TDF2,[6] PrEP users took TDF—often inconsistently—for medians of 1.2, 1.9, and 1.1 years in the primary published reports, and TDF did provoke some renal wrinkles in these HIV-negative study participants (**Table 2**).

In the iPrEx trial of MSM and transgender women, investigators recorded 41 creatinine elevations during follow-up, 26 (2%) in people randomized to TDF/FTC and 15 (1%) in those randomized to pla-

Table 2. Key findings on kidney health in HIV-negative at-risk people taking or not taking TDF

Transaminase elevations affected 2% of iPrEx participants randomized to TDF/FTC and 1% randomized to placebo.[4]
Ten creatinine elevations—7 in the TDF/FTC group—led iPrEx participants to stop their study drug. Nine resumed their assigned regimen.[4]
Four Partners PrEP participants randomized to TDF or TDF/FTC and 1 randomized to placebo stopped study drug because of declining creatinine clearance, but overall creatinine and phosphorous abnormalities did not differ between study arms.[5]
Renal side effect rates in PrEP trials must be interpreted in the context of the relatively low adherence reported in these trials.
Creatinine clearance was normal in gay and bisexual HIV-negative at-risk men in a MACS study, but 37% had hypertension and 13% had diabetes, risk factors for chronic kidney disease.[12]
Among HIV-negative at-risk women in the HERS cohort, 6.6% had renal lab abnormalities, compared with 21.7% of HIV-positive women in that study. [15]
Among HIV-negative at-risk women in HERS, many had two chronic kidney disease risk factors: 47.5% tested positive for HCV and 24.2% had hypertension.[15]

HERS, HIV Epidemiology Research Study; MACS, Multicenter AIDS Cohort Study.

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cebo, a difference approaching statistical significance ($P = 0.08$).[4] Eighteen creatinine elevations (44%) remained in the normal range, and 36 elevations (88%) disappeared on the next test. Five people randomized to TDF/FTC (5%) and none randomized to placebo had creatinine jumps on more than 1 consecutive test. Ten creatinine gains led iPrEx participants to stop study drug, 7 in the TDF/FTC group and 3 in the placebo group. Nine people resumed their assigned regimen.

In the Partners PrEP trial of HIV-discordant African couples, frequency of creatinine or phosphorus abnormalities did not differ between the TDF arms and the placebo arm.[5] Three people taking TDF alone and 2 taking TDF/FTC had grade 2 or 3 creatinine elevations, with both frequencies below 1%. Four Partners PrEP participants stopped TDF or TDF/FTC because creatinine clearance dropped below 50 mL/min, while 1 stopped placebo because of declining clearance. Seven Partners PrEP participants permanently stopped their assigned regimen, 6 of them because of grade 2 renal toxicity (3 taking TDF alone, 2 taking TDF/FTC, and 1 taking placebo). Grade 2 and 3 drops in phosphorus affected 8% and 1% taking TDF alone and 8% and 1% taking TDF/FTC.

Table 3. Kidney risk factors in HIV-negative but at-risk men and women

Men in MACS[12] (n = 150)	Women in HERS[15] (n = 425)
One third black	Half black
Hypertension in 37%	Antihypertensive therapy in 24.2%
Diabetes in 13%	HCV in 47.5% Renal lab abnormalities in 6.6%

HERS, HIV Epidemiology Research Study; MACS, Multicenter AIDS Cohort Study.

In the TDF2 study of high-risk heterosexual African women and men, 1 person (0.2%) randomized to TDF/FTC and none randomized to placebo had a creatinine elevation, while 23.2% randomized to TDF/FTC and 26.2% randomized to placebo had low phosphorus.[6]

A phase 2 trial of TDF alone versus placebo to prevent HIV infection in high-risk women of Cameroon, Ghana, and Nigeria collected primary safety data from two sites.[11] Comparing 363 women randomized to TDF and 368 randomized to placebo for 210.2 and 217.6 person-years of follow-up, researchers recorded no grade 2, 3, or 4 creatinine elevations in either study arm. There were 13 grade 1 elevations in the TDF group (6.5 per 100 person-years) and 15 in the placebo group (7.1 per 100 person-years). Phosphorus drops also proved uncommon and did not differ between groups.

Together these findings suggest that TDF taken as PrEP for 1 to 2 years poses only a small risk of negative kidney marker changes, and by some (but hardly all) measures that risk was greater with TDF or TDF/FTC than with placebo.

What about kidney health in people not taking TDF but with more than a passing risk of HIV infection, in other words, PrEP candidates? Multiple PubMed searching strategies turned up two reports of kidney function in such people, one in men and one in women (**Table 3**).

The study in men involved 738 HIV-positive and 150 HIV-negative gay and bisexual men in MACS.[12] MACS is an ongoing prospective study of gay and bisexual men with and without HIV infection recruited in Baltimore, Chicago, Pittsburgh, and Los Angeles.

The 6972 cohort members, including 3501 men with HIV, make study visits twice a year. This cross-sectional analysis involved men with serum creatinine and urine protein excretion measured between September 2006 and April 2007. One third in each group was black, and 2% or fewer injected drugs. The HIV-positive and negative men had similar chronic kidney disease risk factors, except that a higher proportion of HIV-positive men had HCV infection (10% versus 4%) and high liver enzymes. Proportions with diabetes were similar in the HIV-positive and negative groups (10% and 13%), while more than one third in each group (38% and 37%) had hypertension, another kidney disease risk factor.

A significantly higher proportion of men with than without HIV had proteinuria (17% versus 2%, $P < 0.01$). Median creatinine was similar in the two groups (1.0 mg/dL without HIV and 0.9 mg/dL with HIV, $P = 0.41$), while median cystatin C, an alternative kidney function marker, was significantly higher in the HIV group (0.76 versus 0.85 mg/dL, $P < 0.01$). Median estimated glomerular filtration rate (eGFR) using serum creatinine was similar in the two groups (103.1 mL/min without HIV versus 105.2 mL/min with HIV, $P = 0.78$), while eGFR using cystatin C was significantly greater in men without HIV (108.0 versus 94.6 mL/min/173m^2, $P < 0.01$).

The National Kidney Foundation lists normal eGFR as above 60 mL/min,[13] while labtestsonline.org gives 90 to 120 mL/min as normal.[14] Either way, both HIV-positive and HIV-negative men in this MACS analysis fell within the normal range as a group. Interquartile ranges also fell entirely within the 90-to-120 normal range for both groups of men with both eGFR estimating formulas.

The HIV Epidemiology Research Study (HERS) prospectively monitored HIV-positive women and HIV-negative women with a high HIV risk recruited in Baltimore, the Bronx, Detroit, and Providence.[15] An analysis involving 885 HIV-positive women and 425 without HIV who made twice-yearly visits from 1993 through 2000 tracked overall and condition-specific hospital admissions, including admissions for diabetes mellitus and nonacute renal conditions. About two thirds of women in the positive and negative groups were between 31 and 44 years old; 61% of positive women and 53% of negative women were black, and 17% and 15% were Hispanic.

While 21.7% of HERS women with HIV had renal lab abnormalities, 6.6% of HIV-negative women did, a highly significant difference ($P < 0.0001$).[15] The hospital admission rate for nonacute renal causes was more than 14 times higher in women with than without HIV (rate ratio 14.4, $P = 0.0033$). Diabetes admissions were 3.6 times more likely in women with than without HIV ($P = 0.04$). Overall admission rates were 54.9 per 100 person-years in the HIV group and 15.1 per 100 person-years in the HIV-negative group. In 2009 the hospital discharge rate for all US women was 13.8 per 100 person-years, according to the CDC.[16] So the overall admission rate for HIV-negative women in HERS is largely in line with the general-population rate.

Although these HERS findings indicate that US women at risk of HIV infection have lower rates of kidney problems and kidney-related and overall hospital admissions than women with HIV, other findings show that both groups had high rates of two renal risk factors. About one quarter of women with and without HIV (27.0% and 24.2%) were taking antihypertensives, a nonsignificant difference. Hypertension quintupled the risk of nonacute renal hospital admissions in women with HIV (rate ratio 5.1, 95% CI 2.1 to 12.4); the researchers did not perform a similar analysis for HIV-negative women. While 61.4% of HIV-positive women tested positive for HCV antibody, 47.5% without HIV had a positive HCV antibody result ($P < 0.0001$). Drug injection probably

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accounted for the high HCV prevalence, as 60.7% of HIV-positive women and 54.1% of HIV-negative women had an injection history.

Together these two studies suggest that US men and women at risk of HIV infection do not have more compromised kidney function than the general population. However, the high hypertension prevalence in MACS men and HERS women without HIV offers a vivid example of kidney threats faced by prime PrEP candidates. The same can be said for the high HCV-antibody positivity rate in HIV-negative HERS women.

Kidney changes with long-term TDF therapy

The medical literature is loaded with studies of how TDF does—or does not—affect kidney function when taken for several years by people with HIV (**Table 4**). Because of differences in study populations, design, and follow-up time, these analyses yield varying, and sometimes seemingly contradictory, results.

The biggest TDF-kidney study involved 10,841 HIV-positive US veterans, almost all of them (98%) men.[17] While 40% of this nationally representative sample had taken TDF, 60% had not. Median age in this prospective study was similar in TDF takers and TDF naives (45 and 47), and similar proportions were black

Table 4. Key findings on kidney health in HIV-positive people on long-term TDF

In a prospective 10,841-person US veterans cohort, every year of TDF therapy independently raised the risk of proteinuria, rapid kidney function decline, and chronic kidney disease, and these changes were not readily reversible after TDF stopped.[17]
A Spanish study of 183 people with TDF-associated kidney impairment found that kidney markers improved in 69% after TDF stopped, including 59% in whom key markers returned to normal.[18] An 80-person US study charted improving kidney function in 76% of people who stopped TDF.[19]
A US multicenter study of 3329 people determined that TDF plus a ritonavir-boosted protease inhibitor (PI) (but not TDF alone or a boosted PI alone) independently raised the odds of eGFR below 60 mL/min, which it did in 5.7% of patients.[20]
A EuroSIDA analysis of 6843 people determined that TDF and three PIs each independently raised the risk of chronic kidney disease.[25]
Meta-analysis of studies comparing TDF regimens with non-TDF regimens found an average 3.92 mL/min lower creatinine clearance in TDF takers, along with a 0.7% higher risk of acute kidney failure.[22]
A UK study of 3439 people with HIV found that, among those who started TDF, being 50 or older boosted the odds of chronic kidney disease 5.4 times, while an eGFR of 60 to 75 raised the odds 17.2 times.[26]

(47% and 51%). Among kidney risk factors, baseline hypertension prevalence was 39% without TDF experience and 38% with TDF experience, diabetes prevalence 7.9% and 6.8%, abnormal lipids 15% in each group, HCV positivity 17% and 14%, proteinuria 21% and 19%, and smoking prevalence 19% and 18%.

The VA team examined associations between TDF use and time to three kidney endpoints: (**1**) proteinuria (two consecutive urine dipstick measurements at or above 30 mg/dL), (**2**) rapid decline in kidney function (at least 3 mL/min annual decline), and (**3**) chronic kidney disease (eGFR below 60mL/min). Median follow-up before an endpoint was reached stretched from 3.9 years for the proteinuria endpoint to 5.5 years for chronic kidney disease. TDF-treated veterans took the drug for an average 1.3 years.

Multivariate analysis that considered demographics, HIV-related factors, other illnesses, and other antiretrovirals figured that each year of TDF therapy independently raised the risk of all three endpoints (**Figure 2**). The risk of chronic kidney disease jumped by one third for each year of TDF therapy. Having chronic kidney disease, diabetes, or hypertension before starting TDF had little further impact on these kidney endpoints in people taking TDF. And stopping TDF during follow-up did not reverse these three signals of kidney toxicity (see note **17A**).

The VA investigators suggested their findings "provide strong evidence that tenofovir may cause clinically significant toxicity to the kidney that is not reversible,"[17] adding that "the balance between [TDF] efficacy and probable adverse effects requires further study." Further study is certainly in order for people taking TDF to prevent HIV rather than treat it. The researchers noted that their analysis is limited by their inability to measure eGFR directly, and no one can say whether the findings apply to women as well as men.

Two small single-center studies found, however, that impaired kidney function usually does improve when people stop TDF.[18,19] The larger of these two studies, from Barcelona, found that TDF-associated kidney deficits reversed course in well over half of those who stop the drug.[18] The study involved 183

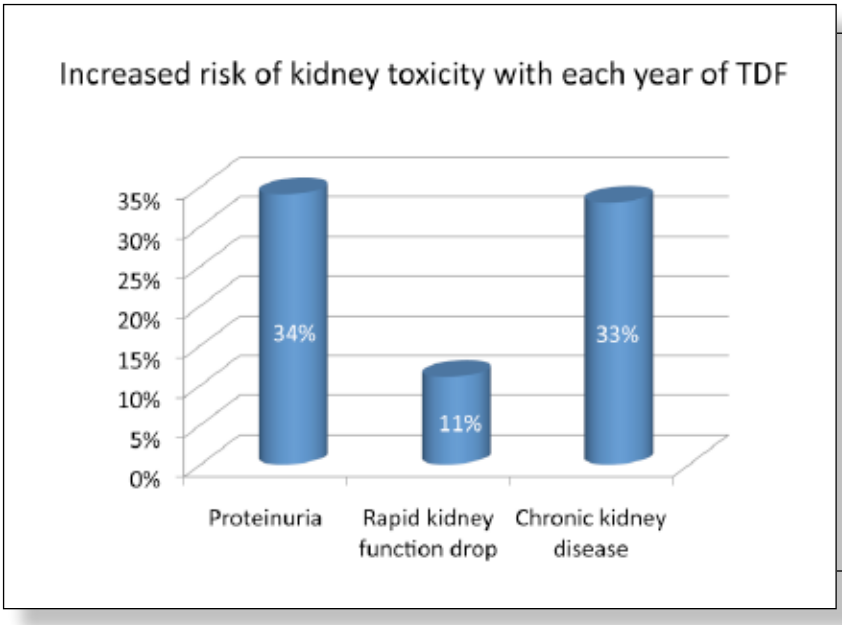

Figure 2. Each year of TDF therapy independently raised the risk of three kidney dysfunction endpoints in a study of 10,841 HIV-positive US veterans, 98% of them men and half black.[17] Endpoints are defined in the text, and risks are calculated as hazard ratios (proteinuria 1.34, 95% CI 1.25 to 1.45, $P < 0.0001$; rapid decline in kidney function 1.11, 95% CI 1.03 to 1.18, $P = 0.0033$; chronic kidney disease 1.33, 95% CI 1.18 to 1.51, $P < 0.0001$).

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people, 85% of them men, with a median age of 44 (interquartile range [IQR] 40 to 50). This group took TDF for a median of 39 months (IQR 22 to 63) and endured baleful changes in kidney markers during that time. The researchers used logistic regression to evaluate factors associated with a return to normal kidney markers, which they defined as eGFR at or above 60 mL/min, creatinine at or below 1.20 mg/dL, phosphate at or above 2.69 mg/dL, proteinuria below 30 mg/dL, and glycosuria below 20 mg/dL in people without diabetes.

A median of 22 months (IQR 13 to 49.5) after people stopped TDF, renal values returned to normal in 59% of this group, improved without reaching normal benchmarks in 10%, and did not improve in 31%. Median time to reaching normal values measured 4 months (IQR 2 to 15.75). Follow-up time stood below 12 months in 30% of people with no improvement in kidney values. Higher nadir CD4 count predicted higher odds of returning to normal kidney function (odds ratio [OR] 1.002 per 1-cell increase, $P = 0.034$), as did higher CD4 count when TDF stopped (OR 1.033 per 1-cell increase, $P = 0.030$). These associations, the researchers proposed, suggest "a role of preserved cellular immunity in renal recovery" after stopping TDF.

The second single-center study involved 80 people with TDF-associated kidney toxicity at an inner-city clinic in Chicago, including 86.5% with increasing serum creatinine and/or declining eGFR, 11% with proteinuria, and 2.5% with Fanconi syndrome.[19] The investigators defined improved renal function as (**1**) eGFR rising to or above the baseline value, (**2**) qualitative or quantitative improvement in proteinuria, or (**3**) improvement or normalization of parameters defining Fanconi syndrome. Most study participants (84%) were men, and 74% were black. Median age stood at 53 years, and TDF duration averaged 27.4 months. Two thirds of the TDF regimens included a protease inhibitor (PI). Forty-nine people (61%) stopped TDF and 31 (39%) continued.

Kidney function values improved in 37 of 49 people (76%) who stopped TDF versus 17 of 31 (55%) who did not. Kidney disease progressed to end-stage renal disease in 2 of 49 people (4%) who stopped TDF. Multivariate analysis determined that stopping TDF nearly quadrupled odds of renal recovery (OR 3.76, 95% CI 1.26 to 11.27, $P = 0.02$). Factors that did not affect chances of recovery in this analysis were diabetes, hypertension, and use of other nephrotoxic drugs.

The VA investigators suggested that different mechanisms of TDF-induced kidney damage may explain why impairment improves in some people but not in others who stop TDF.[17] TDF accumulation in the proximal renal tubule may be reversible, they proposed, whereas active tubular necrosis and tubulointerstitial scarring may not.

A large and long US multicenter study found a link between chronic kidney disease and regimens containing TDF plus a ritonavir-boosted PI, but TDF/nonnucleoside combos or a boosted PI without TDF did not send kidneys out of kilter.[20] The study involved 3329 adults in HIV care who had at least one creatinine reading before and after starting antiretroviral therapy. One quarter (24.9%) took TDF with a ritonavir-boosted PI, 35.1% took TDF with a nonnucleoside, 11.9% took a PI without TDF, and 28.1% took a nonnucleoside without TDF. Median age stood at 40 years, 38.5% of study participants were black, and 18.7% were women. Rates of kidney disease risk factors were moderate to low—16.1% had hypertension, 14.9% had HCV infection, and 3.2% had diabetes. Median follow-up spanned 4.8 years, including a median of 23 weeks before antiretroviral therapy and 143 weeks on treatment.

Analyses adjusted for kidney risk factors determined that black race, HCV infection, and lower CD4 count and higher viral load during antiretroviral therapy swelled the risk of chronic kidney disease.[20] Overall, antiretroviral therapy was associated with a slower eGFR decline. But taking a TDF/PI regimen (compared with a nonnucleoside without TDF) more than tripled the odds that eGFR would fall below 60 mL/min (OR 3.35, 95% CI 1.40 to 8.02, $P = 0.006$). Still, after 4 years taking a TDF/PI regimen, eGFR fell that low in only 5.7% of patients. Severe chronic kidney disease (eGFR below 30 mL/min) developed in only 16 people through more than 10,000 person-years of follow-up. Taking TDF without a boosted PI or taking a boosted PI without TDF did not independently hike the odds of an eGFR below 60 mL/min or 45 mL/min.

What about renal safety of TDF when combined with the integrase inhibitor raltegravir in previously untreated people? The STARTMRK trial randomized antiretroviral-naive people to raltegravir or efavirenz, both with TDF/FTC.[21] After 3 years of follow-up, none of 281 people randomized to raltegravir and 1 of 279 randomized to efavirenz had creatinine levels at or above 1.9 times the upper limit of normal.

A meta-analysis of 17 studies comparing TDF regimens with non-TDF therapies found an average 3.92 mL/min lower creatinine clearance in TDF takers (95% CI 2.13 to 5.70) in 11 studies reporting that outcome.[22] In 8 studies risk of acute renal failure was 0.7% higher in the TDF group (95% CI 0.2 to 1.2), but TDF takers did not have a higher rate of chronic kidney failure or end-stage kidney failure requiring long-term dialysis. Three of these studies had 86 to 96 weeks of follow-up, and 4 had 104 to 520 weeks. Renal function declined less in randomized trials than in observational studies, and less in people starting first-line TDF than in treatment-experienced people. This meta-analysis yielded no evidence that TDF heightened the risk of severe proteinuria or hypophosphatemia.

Among the longest individual studies of TDF in people with HIV are an international randomized trial comparing TDF/FTC with zidovudine/lamivudine (ZDV/3TC), each with efavirenz,[23] an international randomized trial comparing TDF with stavudine in previously untreated adults,[24] a EuroSIDA analysis of chronic kidney disease,[25] and a study of HIV-positive people at two UK centers.[26] (The meta-analysis[22] included three of these studies.[23,24,26]) Side effect findings in the TDF trials must be interpreted with the understanding they excluded people with creatine clearance below 50[23] or 60[24] mL/min, people taking other kidney-toxic drugs,[23] and people with a history of "clinically significant bone disease."[23] As noted in the meta-analysis of 17 studies discussed above, renal function appears to drop less in randomized trials than in observational studies.[22]

The first trial involved 517 antiretroviral-naive adults, 14% of them women, with a median age of 37 years. Everyone had an eGFR above 50 mL/min when the trial began and creatinine below 1.5 mg/dL.[23] After 144 weeks, more people stopped ZDV/3TC than TDF/FTC because of adverse events (11% versus 5%, $P = 0.01$), and no one dropped out because of kidney trouble. One person in the TDF group had a confirmed grade 1 creatinine elevation through 144 weeks, while 2 in the ZDV arm had a confirmed grade 2 elevation. Median eGFR dropped 12 mL/min (from 110 to 98 mL/min) in the TDF group while rising 1 mL/min (from 105 to 106 mL/min) in the ZDV group, a significant difference ($P < 0.001$).

The trial that established TDF efficacy in antiretroviral-naive people randomized 299 to TDF and 303 to stavudine, each with lamivudine and efavirenz.[24] About 20% of participants were black. After 144 weeks of follow-up creatinine rose above 2 mg/dL in 2 of 296 randomized to TDF and 2 of 296 ran-

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domized to stavudine. Similar proportions in both arms had proteinuria (above 30 mg/dL) by week 144: 18% in the TDF arm and 23% in the stavudine arm. Creatinine clearance rose by an average 2 mL/min in the TDF group and 7 mL/min in the stavudine group through 144 weeks. No one dropped out of the study because of TDF-related kidney toxicity. A 1111-person 3-year analysis combining results of these two TDF trials[23,24] determined that fewer than 1% in the TDF arms and the comparison arms had confirmed creatinine elevations above 1.5 mg/dL or serum phosphorus below 2 mg/dL.[27]

A EUROSIDA analysis of 6843 adults with at least three creatinine measures and a median follow-up of 3.7 years (IQR 2.8 to 5.7) found that TDF and three PIs—atazanavir, indinavir, and lopinavir—independently raised the risk of chronic kidney disease, defined as a confirmed eGFR falling below 60 mL/min or a 25% drop in eGFR for people starting below 60 mL/min.[25] After adjustment for traditional risk factors, each year of TDF use raised the risk of chronic kidney disease about 15% (incidence rate ratio 1.16, 95% CI 1.06 to 1.25, $P < 0.0001$).

The UK cohort study involved 3439 HIV patients seen at two centers between January 1998 and December 2005.[26] Follow-up ranged from 104 to 520 weeks. Among 843 people who took TDF during the study period, chronic kidney disease (eGFR below 60 mL/min for at least 3 months) developed in 26 people (3.1%), compared with an overall incidence of 2.4% in this study group. Of the 22 people who stopped TDF during follow-up, 21 did so because of kidney concerns. In people with chronic kidney disease, taking TDF was tied to a 3.7-fold faster decline in kidney function. And among people who started TDF during the study period, being 50 or older boosted the odds of chronic kidney disease 5.4 times, while an eGFR of 60 to 74 (versus 90 or higher) raised the odds 17.2 times.

Implications of studies of kidney function in PrEP candidates and TDF takers

Only the bold would try to wrest overarching conclusions from the data payload explored in the preceding two sections. But a few suggestions seem feasible.

First, the limited studies of kidney function in HIV-negative people with a possibly high risk of infection offer no evidence that PrEP candidates, as a group, have notably fragile kidneys just waiting for a nephrotoxic insult.[12,15] But in the MACS study of HIV-positive and negative gay and bisexual men, the negative group had concerning rates of two kidney risk factors—hypertension (37%) and diabetes (13%).[12] And although HIV-positive women in the HERS analysis had a significantly higher rate of renal lab abnormalities than HIV-negative women, more than 1 in 20 women in the negative group did have such warning signals.[15] Findings like these buttress FDA[7] and CDC[28,29] advice to screen PrEP candidates for creatinine clearance, to probe for other kidney risk factors (including smoking) before prescribing TDF/FTC, and to continue monitoring kidney function in PrEP takers.

PrEP trials showing low rates of creatinine elevations or phosphorus slumps in HIV-negative people randomized to TDF offer some reassurance.[4-6,11] Remember, though, that these trial participants got monitored more than PrEP takers would in clinical practice, and that follow-up in these trials ranged from 1 to 2 years.

Clinical trials and cohort studies of HIV-positive people taking TDF found low to modest rates of elevated creatinine, slowed creatinine clearance, or chronic kidney disease.[23-27] But three large cohort studies in the United States and Europe linked TDF therapy to possibly ominous changes in kidney markers,[17,20,25] though one of the US studies discerned a higher risk of chronic kidney disease with TDF only in people also taking a ritonavir-boosted PI.[20]

The study tying longer TDF use to three unpropitious kidney outcomes in US veterans raised the additional concern that these ill-trending renal markers did not improve readily when TDF stops.[17,17A] These investigators cite two other studies confirming incomplete reversibility of TDF-linked kidney changes, though one of these studies involved only 24 men[30] and the other was cross-sectional.[31] And two single-center studies documented improving kidney markers in most people with compromised kidney function who stopped TDF.[18,19] Still, prudent prescribers will keep the veterans findings in mind when evaluating people for PrEP and charting their progress.

Bone mineral density in PrEP users and candidates

FDA regulators[7] and CDC experts[28,29] do not suggest screening all PrEP candidates for bone mineral density (BMD) before starting TDF/FTC PrEP. But, without differentiating between TDF/FTC for PrEP or HIV therapy, the FDA counsels prescribers to check BMD in people with "a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss."[7] Prescribing information suggests "supplementation with calcium and vitamin D . . . may be beneficial" for people with a high risk of bone loss but notes that this strategy remains unstudied.

PrEP trials offer a look at BMD changes and fracture risk in HIV-negative people randomized to daily TDF, and the literature features several analyses of bone changes in HIV-negative people at risk of HIV infection or people with newly diagnosed HIV (**Table 5**). PrEP trial data on TDF-related bone toxicity must be interpreted cautiously because of the poor TDF/FTC adherence reported among many trial participants.

The iPrEx PrEP trial of HIV-negative men and transgender women who have sex with men[4] included a bone substudy of 503 participants, summarized in the Truvada license.[7] People randomized to TDF/FTC had greater declines in BMD than those randomized to placebo; these drops ranged from –0.4% to –1.0% across total hip, spine, femoral neck, and trochanter. Bone mineral changes migrated back toward baseline values after TDF/FTC stopped. While 6% of iPrEx participants randomized to placebo lost at least 5% of spine BMD during follow-up, 13% randomized to TDF/FTC lost that much. But fracture rates did not differ between the TDF/FTC group and the placebo group (1.7% and 1.4%), and BMD changes did not correlate with fractures.

In the TDF2 PrEP trial of high-risk Botswana men and women, people in the TDF/FTC group had significantly greater BMD drops in the forearm, hip, and lumbar spine than did people randomized to placebo.[6] But fracture rates did not differ between the two groups (1.1% with TDF, 1% with placebo) through a median 1.1 years of follow-up. The Partners PrEP trial of TDF and TDF/FTC PrEP in HIV-discordant African couples did not measure BMD. But again fracture rates during a median 1.9 years of follow-up were similar in people randomized to a TDF regimen and those randomized to placebo (0.8% and 0.6%).[5,7] Fractures were even less frequent in the FEM-PrEP trial of African women, 0.1% in the TDF/FTC group and 0.2% in the placebo group.[9]

These placebo-controlled trials of TDF/FTC PrEP are unanimous in finding no excess fracture incidence with TDF/FTC PrEP versus placebo during 1 to 2 years of follow-up. But BMD did decline significantly more with TDF than with placebo in iPrEx[4] and TDF2.[6]

A pre-iPrEx placebo-controlled trial of TDF PrEP in gay and bisexual men in San Francisco offers admonitory data on bone risk in US men who may take PrEP.[32] Before anyone swallowed a single pill, DEXA scanning determined that 20 of 210 men (10%) had a BMD z score at or below –2.0 at the L2-L4 spine,

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Table 5. Key findings on bone health in HIV-negative at-risk people taking or not taking TDF

BMD declined more with TDF than with placebo in the iPrEx trial,[4,7] the TDF2 trial,[6] and a TDF PrEP trial in gay men in San Francisco.[32]
In iPrEx 13% of participants randomized to TDF/FTC lost at least 5% of spine BMD.[7]
During 1 to 2 years of follow-up, no PrEP trials found a higher fracture rate with TDF than with placebo.[4-7,9]
Bone-related side effect rates in PrEP trials must be interpreted in the context of the relatively low adherence reported in these trials.
One in 10 gay/bisexual men in a TDF PrEP trial in San Francisco had low BMD when they entered the trial at a median age of 40—before they started taking TDF.[32]
Half of HIV-negative but at-risk men at a median age of 55 had osteopenia or osteoporosis in New York City.[34]
Seventeen of 33 men with primary HIV infection in the Netherlands and averaging 38 years in age had osteopenia or osteoporosis.[35]
Prevalence of low BMD was only 19% among HIV-negative at-risk women averaging 44.5 years of age in a New York City study.[36]
A WIHS cohort analysis of premenopausal women with and at risk of HIV logged similar BMD declines and similar low fracture incidence in the two groups through 2.5 years of follow-up.[39]
Another WIHS study recorded a similar fracture incidence in premenopausal women with and without HIV (1.8 and 1.4 per 100 person-years) through 5.4 years of follow-up.[40]
Methadone maintenance raised chances of low BMD in two studies of HIV-positive and negative women[36,38] and in one study of HIV-positive and negative men.[34]
In the studies highlighted above, rates of low-BMD risk factors were high in both women and men at risk of HIV infection.

BMD, bone mineral density.

total hip, or femoral neck. These men had a median age of about 40. Taking amphetamines inflated the odds of low BMD almost 6 times (OR 5.86, 95% CI 1.70 to 2.20), and using inhalants (poppers, amyl nitrate, nitrous oxide, glue) more than quadrupled the odds (OR 4.57, 95% CI 1.32 to 15.81). Men who took multivitamins, calcium, or vitamin D had lower chances of deficient BMD than did men not taking these supplements.

These researchers tracked BMD changes in 184 men, half of whom began TDF or placebo after a 9-month

hiatus to appraise changes in pill-associated risk behavior.[32] Compared with men who started placebo or no study drug, those starting TDF had a 1.1% net drop in BMD at the femoral neck ($P = 0.004$), a 0.8% decline at the total hip ($P = 0.003$), and a 0.7% dwindling at the L2-L4 spine ($P = 0.11$). After 24 months, 13% of men randomized to TDF versus 6% randomized to placebo or taking no study drugs had more than a 5% fall in BMD at the femoral neck, a nonsignificant difference ($P = 0.13$).

The investigators believe their findings "suggest that low BMD may pre-date HIV infection among men at risk for acquisition of HIV, and use of tenofovir in these individuals leads to a small but statistically significant decline in BMD."[32]

A MACS cohort analysis of HIV-positive and at-risk gay or bisexual US men at least 30 years old found a similar osteoporosis-related fracture incidence in the HIV-positive and negative groups.[33] But after statistical adjustment for body mass index and race, men with HIV had a higher fracture incidence starting at age 50. This analysis involved 5106 men who made study visits every 6 months at some point between 1996 and 2011. Age averaged 45.2 in men with HIV and 47.5 in men without HIV, and respective proportions of whites were 70% and 82%. In the HIV and no-HIV groups, 31% and 24% smoked and 42% and 45% smoked at the past.

During follow-up the MACS team counted 53 FRAX-defined fractures in the HIV group and 50 in the HIV-negative groups for crude incidence rates of 0.15 per 100 person-years with HIV and 0.13 per 100 person-years without HIV. But after statistical adjustment for body mass index and race, incidence was higher in HIV-positive men than negative men 50 to 64 years old (1.78 versus 0.74 compared with 30- to 39-year-olds) and higher in HIV-positive men than negative men 65 or older (3.50 versus 2.44 compared with 30- to 39-year-olds) (**Figure 3**).

A New York City study compared BMD in men with HIV and at risk of HIV, all of them at least 49 years old (median 55).[34] This study involved 328 HIV-positive men in the Cohort of HIV at-risk Men's Prospective Study (CHAMPS) and 231 HIV-negative cohort members. HIV-negative men had a high risk of HIV infection because they injected drugs or had high-risk sex. Most men (89%) used illicit drugs, and 56% were black. High proportions of HIV-positive and negative men had classic risk factors for low BMD, including 90% who smoked or once smoked, 47% in a methadone maintenance program, 30% who used heroin in the past 5 years, 52% who exercised less than once a week, and 54% with serum testosterone below 300 ng/dL.

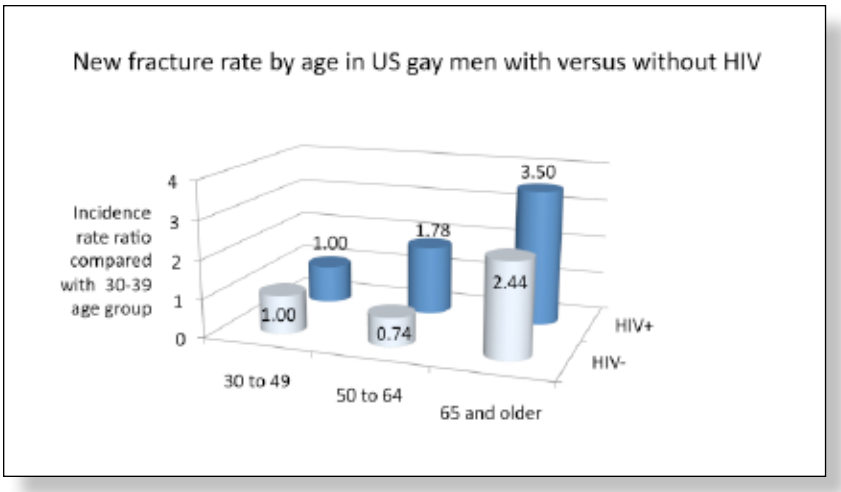

Figure 3. Compared with US gay and bisexual men from 30 to 49 years old in the Multicenter AIDS Cohort Study, risk of new osteoporosis-related fractures was higher in HIV-positive men than in HIV-negative men from 50 to 64 years old or 65 and older.[33]

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Of the 559 men studied, 299 (54%) had osteopenia or osteoporosis, and that rate did not differ significantly between men with and without HIV (55% versus 51%, $P = 0.4$).[34] The osteopenia rates in these men were similar to national estimates among white men 50 and older. But the proportion of men with osteoporosis in this study, 14%, was higher than in the general population.

Statistical analysis adjusted for age, weight, race, testosterone level, and prednisone and illicit drug use found lower BMD at the femoral neck and lumbar spine in men with than without HIV. HIV infection, older age, nonblack race, lower weight, low testosterone, prednisone use, heroin use, and current methadone maintenance were independently associated with low BMD at the femoral neck, lumbar spine, or both sites. Osteopenia or osteoporosis independently raised the fracture risk, but HIV infection did not.

A Netherlands study of 33 young men just infected with HIV found that more than half had osteopenia or osteoporosis.[35] Some evidence from this study hinted HIV itself accounted for low BMD in at least some of these men, but other evidence suggested low BMD preceded HIV infection in these men.

Of the 33 men assessed, 30 were gay or bisexual, none were injection drug users, and none had HCV or HBV infection.[35] Their age averaged 38 years, and their body mass index averaged 22.7 kg/m^2 (within the normal range of 18.5 to 24.9). Only 1 man had taken antiretrovirals—for 9 days—when DEXA scans measured BMD of the lumbar spine, femoral neck, and total hip. Low BMD risk factors abounded in these men: Twenty-six men (79%) were white, 22 (67%) currently used drugs, 18 (55%) smoked, and 7 (21%) downed more than 3 alcoholic drinks a day. Ten men (30%) had low osteocalcin levels, which may betoken flagging bone formation. Twelve men (36%) had broken a bone before getting infected with HIV. About half of these men also had some bone-boosting habits—multivitamin use by 17 men (52%) and strenuous exercise for at least 20 minutes at least 3 times a week by 19 men (58%).

Average lumbar spine t score (–0.8) and z score (–0.7) and average femoral neck t score (–0.5) were significantly lower than in a reference population. Fifteen of 33 men (45%) met World Health Organization criteria for osteopenia, and 2 of 33 (6%) met osteoporosis criteria. "These numbers," the authors observed, "are much higher than would be expected in a relatively young male population like ours."[35]

Can recent HIV infection—and the resulting lofty viral load—explain low bone density in these men? Or did their multiple bone risk factors, maybe coupled with genetics, account for these formidable rates of osteopenia and osteoporosis? Perhaps both. But it's hard to dismiss the big list of risk factors—including an impressive fracture history—these men brought into the study. One statistical analysis these researchers ran suggested spiking viremia during primary HIV infection did contribute to low BMD in these men: Linear regression analysis adjusted for age and body mass index saw a link between higher viral load and lower total hip t score (β –0.2, $P = 0.02$). But reduced BMD in these men could not be tied to biochemical evidence of brisk bone turnover or systemic inflammation, which the researchers noted might be expected during primary HIV infection. Citing the San Francisco study of HIV-negative gay and bisexual men,[32] the Dutch team proposed their findings also raise the question "whether it is actually the recent HIV-1 infection causing rapid bone loss shortly after transmission, or whether these bone disorders predate HIV infection and are caused by other risk factors."[35]

Several studies scrutinized bone variables in HIV-negative women with some risk of HIV infection. A 2001-2003 study of HIV-positive women and negative women at risk of infection found that HIV independently raised the risk of low BMD, but only in nonblack women.[36] Overall prevalence of low BMD in these middle-aged women (27% in the HIV group and 19% in the negative group) lagged national estimates of osteopenia and osteoporosis, perhaps because of the high proportions of black and overweight women in this cohort.

The study involved 263 women with HIV and 232 without HIV in the New York City-based Menopause Study, a longitudinal analysis of menopause and its impact on women with and at risk of HIV infection.[36] The women averaged 44.5 years in age; racial/ethnic proportions were 59% and 44% black in the HIV and no-HIV groups, 34% and 42% Hispanic, and 6% and 12% white. Only 8% of women were postmenopausal, though about 74% were rated perimenopausal (older than 40 and not amenorrheic). Proportions of overweight women (25 to 29.9 kg/m^2) were 36% with HIV and 22% without HIV, and respective proportions of obese women were 32% and 62%.

Moderately high proportions of these women—61% with HIV and 54% without HIV—reported regular exercise, though a similar proportion—53% in both groups—reported watching more than 4 hours of TV daily. High proportions (63% with HIV and 72% without HIV) smoked, while 27% and 19% had smoked in the past. About 8% of women had used prednisone, and about 15% had used estrogen. About 20% had an earlier fracture. Drug use was not rare in women with or without HIV: heroin in past 5 years (22% and 33%), cocaine in past 5 years (44% and 45%), and current methadone maintenance (23% and 44%).

Compared with HIV-negative women, those with HIV had significantly lower BMD at the femoral neck and lumbar spine, significantly lower t scores at both sites, and significantly lower z scores at the femoral neck. But low BMD affected these women less often than women in the general population. While 51% to 70% of white women in the US at least 50 years old have reduced BMD (up to 50% with osteopenia and 20% with osteoporosis),[37] nonblack women in this study group had a 25% prevalence of osteopenia and a 5% rate of osteoporosis. The researchers suggested the low overall rates of reduced BMD in their cohort (27% of women with HIV and 19% without HIV) reflect the high proportion of black women (who have a diminished risk of low BMD compared with whites) and the "extremely high prevalence" of overweight and obesity.

Linear regression analysis determined that HIV independently raised the risk of low BMD (defined as a t score at least 1 standard deviation below the average peak bone mass in young adult women) at the femoral neck and lumbar spine (β –0.026, $P = 0.02$; β –0.041, $P < 0.01$). Classic independent risk factors were older age, nonblack race, low weight, prednisone use, cocaine use, prior fracture, and methadone maintenance. In race-stratified analyses, HIV was independently associated with low femoral neck BMD (β –0.04, $P < 0.01$) in nonblack women, but the HIV association did not hold in black women. In women with HIV, neither nucleosides nor PIs were associated with low BMD.

This New York Menopause Study in women[36] and the New York CHAMPS study in HIV-positive and at-risk men[34] both linked methadone maintenance to low BMD. A recent comparison of BMD in HIV-negative women on methadone and healthy controls

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confirmed a lower total hip BMD in the methadone group, but not lower lumbar spine or femoral neck BMD.[38] The study involved 11 young women taking methadone after heroin addiction and 30 healthy women without a heroin problem and not taking methadone. Ages ranged from 20 to 29 in the two groups, and the methadone group had taken this agent for 1.5 to 9 years (median 3). No women in either group had former or current low weight, though average body mass indices leaned toward the lower end of normal (21.9 kg/m^2 with methadone and 20.5 kg/m^2 without). Women taking methadone had other bone risk factors, including smoking, alcohol use, and cocaine use. DEXA scans found equivalent BMD in the spine and femoral neck in the methadone group and the comparison group, and marginally lower total hip BMD in women on methadone maintenance ($P = 0.054$ for BMD, $P = 0.049$ for t score). The researchers proposed that "long-term methadone substitution in HIV-negative women seems to slightly affect bone mass density."[38]

Two analyses of BMD and fractures in premenopausal women with HIV and at risk of HIV infection found lower BMD in the HIV group but no difference in fracture rates.[39,40] Both studies come from the Women's Interagency HIV Study (WIHS), which recruits HIV-positive and at-risk women in the Bronx, Brooklyn, Washington, DC, Los Angeles, San Francisco, and Chicago.

The first study involved 100 women with HIV and 68 uninfected women who had DEXA scans of the femoral neck and lumbar spine at visits separated by a median of 2.5 years.[39] At the first visit women with HIV had 5% lower BMD at both sites, but the annual drop in BMD through follow-up did not differ between groups. Statistical analysis adjusted for age, weight, and BMD at the initial visit confirmed similar BMD declines in women with and without HIV. Self-reported fracture incidence was nonsignificantly higher in the HIV-negative group (1.03 versus 0.74 per 100 person-years without and with HIV, $P = 1.0$).

As in other studies of US women at risk of HIV infection, this WIHS contingent carried more than a few bone risk factors: 65% smoked at the first visit and 78% ever smoked, 56% drank alcohol, 46% ever used cocaine, 23% injected drugs, 31% tested positive for HCV, and 5% had diabetes.[39] On the plus side—as far as BMD is concerned—body mass index averaged 30.2 kg/m^2, in the obese range. And 26% of women took vitamin D. Low weight and alcohol use were associated with low BMD in the whole study group. In HIV-positive women, CD4 count and antiretroviral class did not predict declining BMD.

A larger and longer comparison of mostly premenopausal HIV-positive and negative WIHS women found a fracture incidence of 1.8 per 100 person-years in women with HIV and 1.4 in women without HIV, a nonsignificant difference ($P = 0.18$).[40] Median follow-up measured 5.4 years. Multivariate analysis did not tease out an association between HIV infection and fracture in this study. And HIV-positive women had a bone-risk disadvantage compared with HIV-negative women because they were older (average 40 versus 36 years, $P < 0.0001$), weighed less (74.5 versus 79.7 kg, $P < 0.001$), and were more likely to be postmenopausal and to have HCV coinfection. Hip and wrist fracture incidence rates in the HIV-positive women (0.2 and 0.3 per 100 person-years) were similar to hip and wrist fracture rates in the general population of premenopausal women in the United Kingdom.[41,42]

As in the smaller WIHS study,[39] HIV-negative women in the larger analysis[40] had their share of low-BMD risk factors: 51% smoked, 21% rated themselves moderate or heavy drinkers, 19% had a prior fracture, 14.5% had HCV infection. In the plus column, 28%

took vitamin D. Bivariate analysis of the entire study group linked an array of classic risk factors to incident fracture: older age, white race, self-reported menopause, prior fracture, HCV infection, higher diastolic blood pressure, cigarette smoking, and injection drug or opiate use.

Bone changes with long-term TDF therapy

Two longitudinal studies and three randomized trials implicate TDF in BMD loss in HIV-positive men and women (**Table 6**). A large Veterans Affairs (VA) analysis determined that every year of TDF use inflates the risk of osteoporotic fracture 12%.[43] The longitudinal studies and trials did not tally fracture rates or found no higher rate with TDF than with other regimens.

The VA study involved 56,660 US veterans seen from 1998 through 2009, 98% of them men.[43] Two thirds took antiretrovirals for at least 1 month. During follow-up 951 vets had an osteoporotic fracture, ascertained by ICD-9 code and defined as the first new spine, hip, or wrist fracture "selected on the basis of their likelihood of being related to osteoporosis." Veterans who sustained fractures were generally middle-aged and only moderately older than those who did

Table 6. Key findings on bone health in HIV-positive people on long-term TDF

A prospective study of 33,439 US veterans determined that every year of TDF use boosts the risk of osteoporotic fracture 12%.[43]
Longitudinal analysis in a US Nutrition for Healthy Living Study involving 283 men and 96 women linked TDF use to an average 2.04% drop in total BMD among men and an average 1.74% drop in premenopausal women.[44]
Longitudinal analysis of 483 men and 188 women in Spain determined that taking TDF at the time of the most recent DEXA scan raised odds of declining BMD more than 40%.[45]
After 3 years of follow-up in a 517-person trial comparing TDF/FTC with ZDV/3TC in previously untreated adults, fracture rates were low and similar in the two treatment arms.[23]
After 3 years of follow-up in a 602-person trial comparing TDF/3TC with stavudine/3TC in previously untreated adults, BMD waned more at the lumbar spine and hip with TDF/3TC, but fewer people in the TDF group broke a bone.[24]
After 96 weeks of follow-up in a trial that randomized antiretroviral-naive adults to TDF/FTC or ABC/3TC, BMD declined more at the spine and hip in the TDF group.[46] Fracture rates did not differ between the two arms.

BMD, bone mineral density.

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not (46 versus 44 years). People with fractures were more likely to be white (57% versus 45%) and more likely to smoke (56% versus 32%), have diabetes (25% versus 15%), have a body mass index below 20 kg/m² (49% versus 33%), and have HCV infection (51% versus 31%) ($P < 0.0001$ for all comparisons).

The VA investigators sized up fracture risk factors in two multivariate models; the first factored in race, age, tobacco use, diabetes, body mass index, chronic kidney disease, HCV status, and cumulative exposure to TDF, abacavir, zidovudine or stavudine, any boosted PI, and any nonnucleoside; the second model added concomitant exposure to other antiretrovirals. Neither model considered other possibly telling variables, such as exercise, vitamin D or calcium, or use of steroids, alcohol, or illicit drugs; and the researchers could not evaluate BMD. Because the cohort included few women, results may not apply to them.

Through an average follow-up of 5.4 years, both multivariate models figured that every year taking TDF hiked the osteoporotic fracture risk 6%, but in both analyses the 95% confidence interval just crossed 1.0 (0.99 to 1.12 in model 1 and 0.99 to 1.14 in model 2).[43] When the researchers limited the analyses to 33,439 vets who entered the cohort in the combination antiretroviral era (starting January 1, 1996), every year taking TDF independently upped the fracture risk about 12% (model 1 hazard ratio [HR] 1.13, 95% CI 1.05 to 1.21, $P = 0.001$; model 2 HR 1.12, 95% CI 1.03 to 1.21, $P = 0.011$). Adding a boosted PI to a TDF regimen inflated the risk slightly more (HR 1.16, 95% CI 1.04 to 1.30). Cumulative antiretroviral use did not make fractures more likely, but several classic risk factors did: white race, older age, tobacco use, and body mass index below 20 kg/m².

Longitudinal analysis of total body BMD in HIV-positive men and women in the Nutrition for Healthy Living Study linked greater bone loss to steroids and two antiretrovirals—TDF and didanosine.[44] The Nutrition for Healthy Living Study is a prospective cohort of HIV-positive adults living in Massachusetts and Rhode Island. This analysis included 283 men and 96 women seen between August 1996 and September 2003 who had at least two whole-body DEXA scans at least 1 year apart. Median age was 42.7 in men and 39.4 in women; 59.4% and 34.4% were white, 25.4% and 51.0% were black. Smoking rates were high in both men and women (43.3% and 66.7%), as was a history of injection drug use (32.2% and 44.8%). Among women, 17.7% were postmenopausal. While 30% of men reported strength training in the previous week, only 11.6% of women did.

Statistical analysis adjusted for age, race, sex, menopause, and smoking linked greater loss of total BMD to TDF use, longer didanosine use, prednisone or hydrocortisone use, lower body mass index, and lower albumin.[44] TDF use conferred an average 2.04% drop in total BMD among men and an average 1.74% decline in premenopausal women. Strength training mitigated loss of total BMD.

A longitudinal study of 671 antiretroviral-treated people in Spain included 483 men (72%) and 188 women, only 18 of them (10%) postmenopausal.[45] Median age for the whole group was 42.1 years, median time on antiretroviral therapy 7.4 years, and median time on tenofovir 2.2 years. Almost half of the study group (47.5%) had osteopenia, and almost one quarter (23%) had osteoporosis.

Among people who took TDF for 1 year or less, 20% had osteoporosis, while in those who took TDF for more than 5 years, 37% had osteoporosis.[45] Taking TDF at the time of the most recent DEXA scan upped the odds of declining BMD 44% (OR 1.44, 95% CI 1.03 to 2.20, $P = 0.03$). Among 105 people with at

least 5 years of follow-up, DEXA scans confirmed progression to osteopenia in 18% and to osteoporosis in 29%. Odds of BMD loss or progression to osteopenia or osteoporosis rose with longer time taking TDF (OR 1.08, 95% CI 1.03 to 1.14, $P < 0.0019$), longer time taking a PI (OR 1.18, 95% CI 1.12 to 1.24, $P < 0.0001$), and current PI use (OR 1.64, 95% CI 1.35 to 2.04, $P < 0.0001$)

Through 144 weeks of follow-up in the 517-person international trial comparing TDF/FTC with ZDV/3TC (both with efavirenz) in antiretroviral-naive adults, 6 people in the TDF group and 8 in the ZDV/3TC group broke a bone.[23] Trauma caused all fractures, and the investigators attributed none of the breaks to study drugs. The researchers did not report changes in BMD. This trial excluded people with a history of "clinically significant bone disease."

After 144 weeks in the trial comparing TDF/3TC with stavudine/3TC in 602 previously untreated adults, researchers charted a greater drop from baseline lumbar spine BMD in the TDF group (−2.2% TDF versus −1.0% stavudine, $P = 0.001$).[24] BMD faded even more at the hip in both study groups, and the difference between groups approached statistical significance (−2.8% TDF and −2.4% stavudine, $P = 0.06$). The researchers noted, though, that BMD waning generally occurred through weeks 24 to 48 then stabilized. Five people randomized to TDF and 11 randomized to stavudine broke a bone during follow-up.

ACTG protocol A5224s was a substudy of a trial that randomized antiretroviral-naive adults to TDF/FTC or abacavir (ABC)/3TC with open-label efavirenz or atazanavir/ritonavir.[46] Of the 269 study participants, 229 (85%) were men, and median age was similar across the four arms (38 years overall). Almost half of enrollees (47%) were white non-Hispanic, 33% were black non-Hispanic, and 16% were Hispanic. Almost one third (32%) broke a bone in the past.

After 96 weeks spine BMD decreased significantly more in the TDF/FTC arms than in the ABC/3TC arms (−3.3% versus −1.3%, $P = 0.004$), as did hip BMD (−4.0% versus −2.6%, $P = 0.024$).[46] ABC/3TC plus efavirenz was the only combination not linked to a significant 96-week drop in spine BMD. From study entry to week 48, declines in BMD were greater with TDF/FTC than with ABC/3TC at the lumbar spine (−1.66%, $P = 0.005$) and hip (−1.43%, $P = 0.007$). But from weeks 48 through 192, mean percent change in BMD per year did not differ between the two groups. Regression analysis that factored in age, sex, race/ethnicity, and pretreatment viral load, CD4 count, and body mass index reckoned significant associations between ABC/3TC (versus TDF/FTC) and greater BMD at both the spine (parameter estimate 1.90, $P = 0.003$) and hip (parameter estimate 1.28, $P = 0.033$) at week 96. About 1 in 20 people had a trauma-related fracture during 96 weeks of follow-up, but neither fracture rate nor time to first fracture differed by treatment assignment.

Implications of studies of BMD and fractures in PrEP candidates and TDF takers

What can one make of the bone data medley from studies of people who run some risk of HIV infection and may consider TDF/FTC PrEP? First, the PrEP trials themselves show that taking TDF to ward off infection depletes bone mineral density—but only in small proportions of people during these trials' 1 to 2 years of follow-up.[4,6,7,32] And taking TDF for PrEP had no impact on fracture risk during any of these placebo-controlled trials.[4-7,9,32]

How longer-term TDF PrEP will affect bone health depends on how consistently people take their PrEP pills and what other bone risk factors they have. Sev-

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eral studies of HIV-negative but at-risk men and women in the United States and the Netherlands leave no doubt that people likely to consider PrEP bear a hefty burden of low-BMD risk factors,[32-36,38-40] including cigarette smoking, use of alcohol and injected or noninjected drugs, methadone maintenance, lack of exercise, previous fractures, diabetes, and HCV infection.

A study of HIV-negative gay and bisexual men recruited for a TDF PrEP trial in San Francisco found that 10% had low BMD of the spine, total hip, or femoral neck before they started PrEP, and that taking amphetamines or inhalants boosted the risk of low BMD.[32] This finding resonated in a Dutch study of men (91% gay or bisexual) with primary HIV infection, 45% of whom had osteopenia and 6% of whom had osteoporosis.[35] The researchers found mixed evidence on whether the spiking viremia of acute infection caused or contributed to this high rate of depleted BMD or whether that rate could be more firmly tied to pre-HIV risk factors. Rates of osteopenia or osteoporosis were high and similar in 49-year-old and older HIV-positive and negative but at-risk men in a New York City study (55% and 51%).[34] A large majority of men in this study, 89%, used illicit drugs, and 47% were on methadone maintenance.

Together these findings indicate that middle-aged male PrEP candidates in the United States and perhaps Western Europe—including gay men and drug injectors—may have compromised bone health before starting TDF/FTC PrEP. Clinicians considering PrEP for men like these would do well to heed FDA advice to check them for "a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss."[7] A pre-PrEP bone scan may be in order for some men. Notably, the early San Francisco PrEP trial found that men taking multivitamins, calcium, or vitamin D trimmed their risk of low BMD.[32] And the FDA suggests calcium or vitamin D supplements may have a role in slowing BMD decline.[7]

Unlike these studies of men at risk of HIV infection or with acute HIV infection,[32-35] studies of at-risk mostly premenopausal US women in two cohorts did not find an undue burden of osteopenia or osteoporosis.[36,38-40] Two studies saw links between methadone maintenance and low BMD in women[36,38] (as did one in HIV-positive and at-risk men[34]). All these studies recorded lofty rates of classic bone risk factors in women with and without HIV, and these risk factors inflated the odds of low BMD in statistical analyses. Providers discussing PrEP with women should review the list of bone risk variables in **Table 1** and might consider DEXA scanning, vitamin D, and calcium for women with an apparently high risk.

Three longitudinal studies of HIV-positive people were unanimous in linking TDF use to either a higher osteoporotic fracture rate[43] or to dwindling BMD.[44,45] The large Veterans Affairs study that established a magnified fracture risk with TDF is limited in that it could not determine changes in BMD; it could not clinically confirm fractures, which were ascertained by ICD-9 codes; and almost all study participants were men.[43] The two much smaller longitudinal studies that confirmed declining BMD in people taking TDF did not report fracture rates.[44,45] A Spanish study tied TDF use to progression from normal BMD to osteopenia or osteoporosis through 5 years of follow-up.[45] Three randomized trials found equivalent or lower fracture rates with TDF regimens than with comparison regimens.[23,24,46] But two of these studies con-

firmed greater declines in BMD with TDF combinations than with non-TDF combinations.[24,46] In the two trials that tracked BMD, the dips occurred mostly in the first year of therapy and then stabilized.

Bottom line: low TDF toxicity risk, but caution advised

Anyone who prescribes antiretrovirals or scans FDA prescribing information for TDF[7] knows that this reverse transcriptase inhibitor can muddle kidney function or deplete bone mineral. Gilead Sciences, TDF's maker, plainly acknowledges the drug's toxic potential in its full-tilt development of GS-7340, a defanged TDF facsimile the company hopes will stymie HIV better than TDF but with less toxic sting.[47-50]

Although two large randomized trials left no doubt that TDF has a cleaner safety record than the nucleosides it displaced, zidovudine and stavudine,[23,24,27] long-term TDF therapy clearly poses some kidney and bone risk. Some research indicates that TDF-linked kidney toxicity dissipates when TDF stops,[18,19] but a 10,000-person Veterans Affairs study found that it may not.[17] Another prospective veterans study figured that every year of TDF use boosts the risk of osteoporotic fracture 12%,[43] while other cohort studies and trials confirmed dwindling bone mineral density with TDF but found no greater fracture risk.[23,24,44,46] TDF PrEP trials showed that the drug leaves a thin toxic trail in kidney and bone of HIV-negative people, though toxicity rates were low during the 1 to 2 years of follow-up in these studies.[4-6,9,32]

Cohort studies leave no doubt that men and women at risk of HIV infection have histories full of kidney and bone risk factors, summarized in **Table 1**. And some—but hardly all—studies of HIV-negative people disclosed an above-average rate of kidney and bone disease in these people.

PrEP prescribers should keep all this in mind when pondering risks and benefits of TDF/FTC with PrEP candidates. And they should follow FDA and CDC advice to avoid PrEP in people with creatinine clearance below 60 mL/min and to consider DEXA scans for candidates with a past fracture or other bone loss risk factors.[7]

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