Unmasking the Bare Bones of HIV Preexposure Prophylaxis

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2015 marks an important milestone in the struggle against human immunodeficiency virus (HIV)/AIDS. Almost 20 years ago, effective combination antiretroviral therapy (cART) became available and significantly altered the outcome of HIV infection, transforming an essentially uniformly fatal infection into a manageable, chronic illness that continues to challenge patients, care providers, and the scientific community [1].

People still become infected with HIV [2, 3] as effective prevention remains elusive. In the absence of an HIV vaccine, other means of HIV prevention have been investigated. The practical application of the “treatment as prevention” hypothesis significantly decreases new infections in at-risk individuals [4]. Antiretrovirals are highly effective for preexposure prophylaxis (PrEP) of HIV infection [5]. It is anticipated that PrEP, as part of a multipart program of HIV prevention options, will impact the incidence of new infections.

PrEP’s safety profile is a particularly important consideration as a primary prevention therapy. It is thus noteworthy that the available regimen for PrEP, the daily use of a fixed-dose combination of oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF), contains tenofovir (TFV). TFV causes renal toxicity, via a proximal tubulopathy, and bone demineralization, by increasing bone turnover and altering bone metabolism, in a minority of patients [6]. In general, low bone mineral density (BMD) occurs more frequently in treated HIV adults than in seronegative individuals [7]. Low BMD is associated with an increased risk of fragility fractures [8, 9]. The etiology of low BMD is multifactorial, including both HIV- and cART-related factors [10], plus common causes of low BMD, as occurs in seronegative persons [11], including low body weight [12]. Currently available cART regimens are associated with a BMD decline of 4%–6%, generally occurring in the 4–6 months after starting treatment, and which is nonprogressive [10]. TFV-HAART is associated with greater BMD loss compared with non-TFV regimens [7]. Significantly, TFV-HAART has been associated with an increased fracture risk compared with other regimens in some studies [13].

In this context, Mulligan et al have published in this issue of Clinical Infectious Diseases an illuminating study of the effects of FTC/TDF on dual-energy X-ray absorptiometry (DXA)–determined BMD in seronegative men who have sex with men (MSM) [14]. How does this analysis inform our judgment as PrEP is rolled out? Several studies of PrEP have already raised concerns about BMD loss with FTC/TDF. Liu et al showed an overall BMD decline of <1% at the spine and hip in a small study of MSM receiving TDF alone [15]. Thigpen et al [16] showed similar small BMD changes in a larger study of heterosexual men and women in Botswana receiving FTC/TDF that was stopped early because of logistic considerations. Mulligan et al’s study provides us a comprehensive, internally valid analysis. Subjects were enrolled in a DXA substudy of the parent Preexposure Prophylaxis Initiative (iPrEx) Study, a large, multinational randomized, double-blind, placebo-controlled trial of FTC/TDF involving 2499 MSM [5]. Subjects receiving FTC/TDF had a 44% reduction in HIV incidence compared with patients on placebo. In the DXA substudy, 498 mostly young subjects randomized to placebo or FTC/TDF were followed for a median of 24 weeks. Overall results showed a small but statistically significant difference in the change in BMD between placebo and treated subjects of −0.9% and −0.6% at the lumbosacral spine and hip, respectively. As with other TDF-cART studies, this occurred mostly during the first 24 weeks.
of treatment with no further important BMD change during follow-up. After treatment termination, follow-up scans showed that treatment vs placebo differences at both the spine and hip persisted despite a return toward baseline BMD in treated patients. The number of confirmed post-treatment fractures was similar in both groups although follow-up was short and the total number of fractures was small.

Careful analysis of the DXA substudy reveals details relevant to the generalizability of the findings. Almost 50% of the study subjects were aged <25, whereas only 14% were older than 40; <15% were black or African American, and 10% were female. No information is provided concerning whether substudy subjects were representative of the parent cohort. Despite the multinational character of the parent study, these results may not be readily applicable to at-risk persons living in either the United States or sub-Saharan Africa where the demographics of HIV differ. The small number of older subjects in the study is particularly noteworthy. The age at HIV seroconversion is increasing. This fact, along with the near-normal survival of treated patients today, contributes to the overall median age of 50 of HIV patients in industrialized countries [17]. Arnsten et al showed that men with a mean age of 56, at risk for HIV, have a prevalence of low BMD ranging from 40% to 75%, which triples their fracture risk [18]. A further important finding in Mulligan et al’s study is that pretreatment BMD was low at the spine and hip in 12% and 2% of participants, respectively. This may contribute to the clinical impact of further treatment-related loss of BMD, although low baseline BMD was not a risk for further treatment-related BMD loss. Is the low baseline BMD an unexpected finding? In a 2010 study of 33 untreated, mostly white MSM in Amsterdam, with a mean age of 38, DXA, performed within 1 month of HIV primary infection, showed that 45% of subjects were osteopenic and 6% osteoporotic [19], which was associated with increasing age. The authors speculated that the bone changes could have predated HIV infection. In a study of adults from Botswana, 70% of whom were aged <24 years, 7% had low hip and lumbar spine BMD, which was greater than the expected prevalence of 2.3% [20] and was related to being underweight. Although in Mulligan et al’s study, subjects had a normal BMI of 23, recent studies show an overall increase in the BMI of all untreated HIV patients, particularly among African-American and Hispanic females, in whom the prevalence of obesity mirrors that of the general population [21]. Similar trends are reported in both uninfected and seropositive South African females [22], whose baseline BMI of 26 was in the overweight range. The iPrEX DXA substudy does not clarify how FTC/TDF will affect BMD in either older persons or those with increased body weight.

Notwithstanding the increased BMD at both sites seen in the posttreatment cessation follow-up DXA scans at 24 weeks, the net difference between treatment arms remained negative at both sites, although significantly so only at the hip. Longer follow-up may provide reassurance that the early BMD loss is reversible. The observed inverse relationship between intracellular TFV-DP concentration and BMD changes provides further validity that FTC/TDF has an independent effect on BMD in uninfected subjects.

Data on possible undetermined confounders will inform future analyses. Hepatitis C coinfection, important in many at-risk subjects, may play a role in determining fracture risk [23]. Similarly, vitamin D deficiency occurs as commonly in HIV patients as in the general population and may increase risk of BMD loss [24].

How does this important study help us to safely manage persons eligible for PrEP who may take it either for extended periods of time, or on an intermittent basis? It is reassuring that the actual loss of BMD was minimal, and appears to be mostly reversible. The low documented fracture risk is not necessarily reliable given the short follow-up but may be accurately determined using the FRAX calculator (www.shef.ac.uk/FRAX) in subjects aged >40 years, in whom this been validated. The new knowledge presented in the current study will be contextualized in light of emerging options about other pharmacological options for PrEP. A new tenofovir prodrug, tenofovir alafenamide (TAF), has similar virologic and immunologic effects to TDF in early studies and is associated with less renal toxicity and significantly less BMD loss at the spine and hip [25]. It is too soon to speculate on TAF’s role in the therapeutic armamentarium of PrEP. Other antiretrovirals with possibly less BMD toxicity undergoing assessment for PrEP include maraviroc and rilpivirine.

In sum, Mulligan et al have provided us with careful analyses relative to important knowledge gaps in the safety of an effective strategy for PrEP. This study also clarifies what further information is required to address safety issues. It thereby will surely add meat to the bare bones of knowledge in this rapidly evolving field.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

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