EPH162

Modelling the Long-Term Bone Health Impact of TDF/FTC PrEP in Adolescent MSM

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Key Takeaways

- **Whilst the short-term impact of TDF/FTC PrEP (Pre-Exposure Prophylaxis) on Bone Mineral Density (BMD) has been observed in clinical trial data, modelling is required to understand the long-term implications for bone health.**
- **This is particularly important for adolescent MSM (Men who have Sex with Men) who may have a significant risk of HIV acquisition and therefore PrEP need but are also at a critical age for BMD accrual prior to reaching Peak Bone Mass (PBM).**
- **A simulated cohort was used to assess the modelled impact of TDF/FTC-based PrEP use in adolescents on lifetime bone health based on data from the ATN 110 and ATN 113 clinical trials.**
- **Periods of high adherence to TDF/FTC protect against HIV acquisition but could lead to BMD loss that may only be partially reversible, resulting in lower lifetime BMD trajectory and higher risk of osteopenia and osteoporosis in later life.**

Introduction

- Daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is highly efficacious at reducing the risk of acquiring HIV through sexual contact when taken with high adherence[1]. However, TDF/FTC PrEP also has known impacts on bone mineral density (BMD)[2].
- Adolescent MSM may have significant risk of HIV acquisition and therefore a need for PrEP but are also at a crucial age for BMD accrual prior to reaching Peak Bone Mass (PBM).
- MSM also have lower BMD compared to other males by age, putting them at greater risk of osteopenia and osteoporosis in later life[3].
- In a study of HIV-negative young men aged 15–22 on TDF/FTC PrEP, significant declines in BMD were observed over 48 weeks of exposure. When TDF/FTC PrEP was stopped, BMD began to recover, but bone density did not fully return to baseline in the younger participants even 48 weeks after discontinuation[4].
- These findings raise the possibility that TDF/FTC use during the crucial bone-building years could lead to a lasting deficit in bone density.
- Here, modelling is used to synthesize available data on the natural history of BMD, characteristics of TDF/FTC PrEP use and the observed clinical effects of TDF/FTC PrEP use on BMD to project long-term bone health outcomes.

Table 1. Key Model Inputs

Parameter	Value Mean (SD)	Reference
Absolute change in total hip BMD from baseline to 24 weeks of PrEP use (g/cm^2)	-0.0082 (0.0218)	Derived from [5]
Absolute change in total hip BMD from baseline to 48 weeks of PrEP use) (g/cm^2)	-0.0165 (0.0216)	Derived from [5]
Absolute change in total hip BMD from PrEP discontinuation to 48 weeks after discontinuation (i.e., during the bounce-back period) (g/cm^2)	0.0107 (0.0403)	Derived from [4]
Total proximal femur BMD in 12-15-year-olds (g/cm^2)	0.964 (0.162)	[6]
z-score for Total Hip of HIV-negative MSM	-0.1 (0.7)	[3]

Methods

- A microsimulation model was used to project total hip BMD changes in a cohort of 50,000 young Black MSM between ages 15 to 70.
  - BMD trajectory is known to differ by race/ethnicity. Black males were the majority group in the clinical trials used to inform the study and have higher BMD throughout the life course, therefore providing the most conservative base case.
  - Total hip BMD was tracked as the categorization of osteoporosis in adults is based on T-scores at the hip.
- The impact of different TDF/FTC PrEP use scenarios on PBM at approximately age 20 was assessed. To assess the longer-term impact, t-scores were calculated at ages 50, 60 and 70 and used to assess the prevalence of osteoporosis and osteopenia at these ages.
- Key model inputs are summarized in Table 1 and described further below.

Natural History of BMD in the absence of TDF/FTC use

- The natural history of BMD was derived from NHANES data[6]; reflecting typical bone development during adolescence, the achievement of peak bone mass by the early 20s, and bone loss in later adulthood.
- Additionally, the cohort BMD mean was calibrated so that the average z-score at baseline was slightly below 0 to reflect reports that MSM may have marginally lower BMD compared to other males[3] .

Modelled TDF/FTC PrEP Use Scenarios

- All scenarios assumed high adherence during periods on TDF/FTC PrEP (i.e., one tablet per day), which represents a conservative "worst-case" for bone loss but "best-case" for HIV prevention.
- In "continuous TDF/FTC PrEP" scenarios, individuals remained on daily TDF/FTC for a fixed duration of 1, 2, or 3 years starting at age 15. In "intermittent TDF/FTC PrEP" scenarios, monthly discontinuation and reinitiation probabilities were derived from Hojilla et al[7].

Impact of TDF/FTC PrEP use on BMD

- The change in BMD with TDF/FTC PrEP use is based on a substudy of the Adolescent Trials Network (ATN) studies 110 and 113 – which measured BMD changes over 48 weeks of TDF/FTC PrEP in adolescent MSM [4,5].
- When individuals discontinued TDF/FTC PrEP, the model applied a "bounce-back" effect: a partial recovery of BMD toward the individual's projected natural trajectory once TDF/FTC was removed. [4]
  - This improvement was applied at a constant rate within a period equal to the TDF/FTC PrEP use duration after stopping TDF/FTC PrEP but capped at two years in total.
  - After this bounce-back period, BMD was assumed to progress at the standard age-related rate again.

Impact on HIV Acquisitions

- To assess the benefit/risk profile of TDF/FTC PrEP, the model simulated HIV acquisitions alongside bone outcomes.
- A baseline HIV incidence rate of 4.70 per 100 person-years was assumed; representative of data from MSM at high risk of HIV acquisition in the absence of PrEP[8].
- When TDF/FTC PrEP was introduced, HIV acquisitions were probabilistically averted.
- Given the conservative assumption of perfect adherence during use, TDF/FTC PrEP was assumed to be associated with the 0 per 100 person-year incidence from the iPrEx trial reflecting daily TDF/FTC PrEP use[8].

Results

Short-Term Bone Health Outcomes

- During continuous TDF/FTC PrEP use, total hip BMD declined relative to the natural growth trajectory, leading to a lower peak BMD by approximately age 20 (Table 2).
- Three years of continuous TDF/FTC PrEP (ages 15–18) led to a 21% lower mean BMD at age 20 relative to Base Case (no TDF/FTC PrEP use).

Table 2. Simulated peak hip BMD at age 20 under various adolescent TDF/FTC PrEP use scenarios, and percentage difference compared to no TDF/FTC PrEP Base Case.

TDF/FTC PrEP Use Scenario	Mean BMD at 20 (g/cm^2) ± SD	% Difference vs. No TDF/FTC PrEP
Natural BMD progression (No TDF/FTC PrEP use)	1.150 ± 0.223	— (reference)
1 year continuous	1.056 ± 0.201	–8.17%
2 years continuous	0.950 ± 0.138	–17.39%
3 years continuous	0.911 ± 0.155	–20.78%
1 year intermittent (on/off)	1.067 ± 0.209	–7.22%
2 years intermittent (on/off)	0.986 ± 0.172	–14.26%
3 years intermittent (on/off)	0.953 ± 0.183	–17.04%

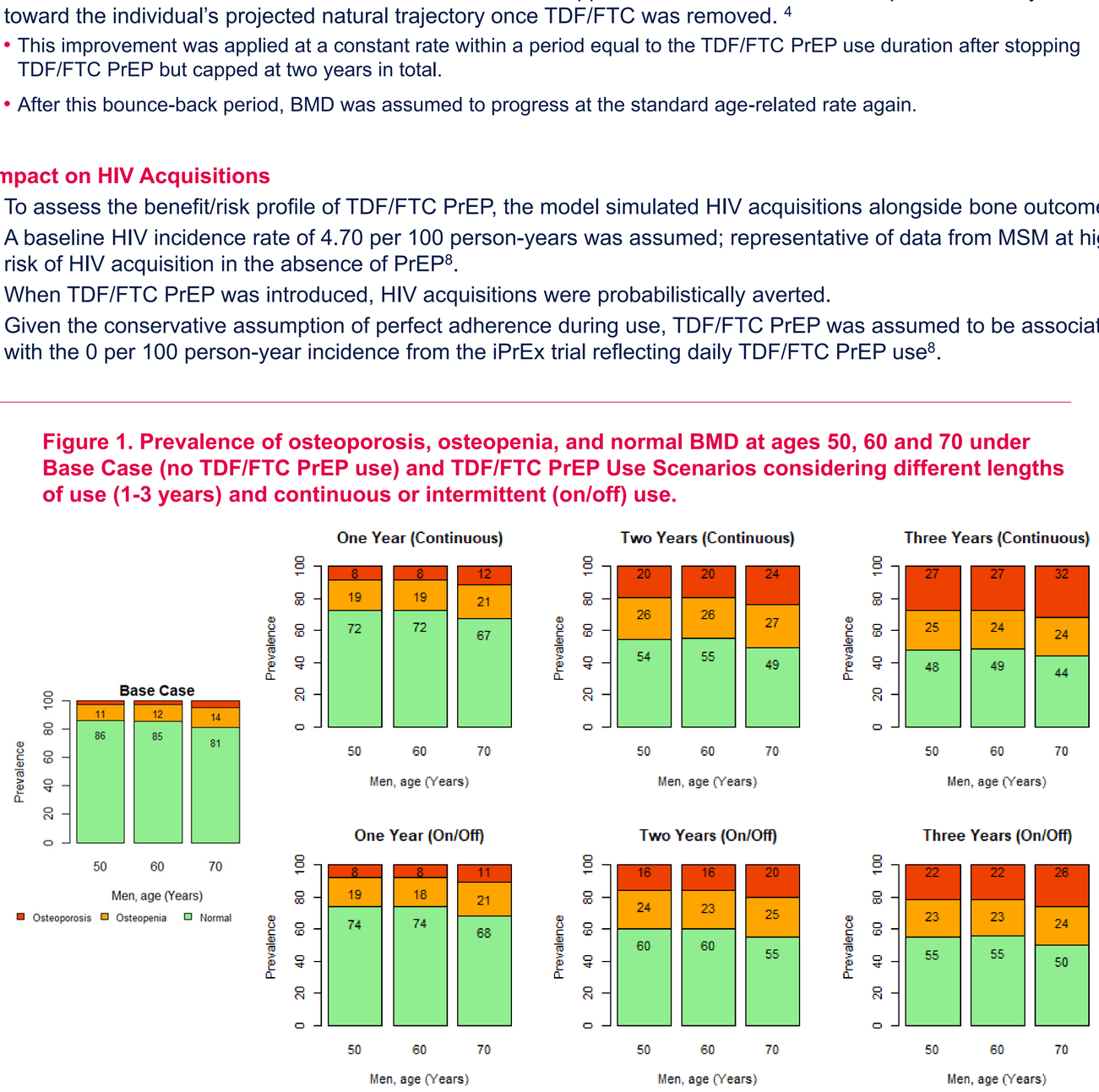
Long-Term Bone Health Outcomes

- Figure 1 presents the prevalence of osteoporosis, osteopenia and normal BMD at age 50, 60 and 70 under different TDF/FTC PrEP use scenarios in adolescent MSM.
- Compared to the modelled scenario with no TDF/FTC PrEP use in adolescence (Base Case in Figure 1), daily dosing led to higher osteoporosis prevalence later in life (e.g., 3 years of continuous use led to a 27% increase in osteoporosis prevalence by age 70 in the modelled population).
- Intermittent use did not entirely prevent long-term bone loss (e.g., 3 years on/off use led to a 21% increase in osteoporosis prevalence by age 70 in the modelled population)

HIV Acquisitions Averted

- One year of continuous TDF/FTC PrEP use (ages 15–16) led to a 32.2% reduction in HIV incidence between the ages 15-18, two years a 65.5% reduction in HIV incidence, and three years averted essentially 100% of HIV acquisitions over the 15-18 age range due to the daily dosing assumed.

Figure 1. Prevalence of osteoporosis, osteopenia, and normal BMD at ages 50, 60 and 70 under Base Case (no TDF/FTC PrEP use) and TDF/FTC PrEP Use Scenarios considering different lengths of use (1-3 years) and continuous or intermittent (on/off) use.



Conclusions

- Effective PrEP options are needed for adolescent MSM who may be at high risk of HIV acquisition. At the same time, long-term consequences for bone health should be considered with TDF/FTC use.
- Periods of high adherence to TDF/FTC protect against HIV acquisition but could lead to BMD loss that may be only partially reversible and could result in lower lifetime BMD trajectory and higher risk of osteopenia and osteoporosis in later life.
- This suggests the need for complementary interventions to minimize the impact on BMD or alternative PrEP options such as CAB-LA. In the HPTN 083 trial, which enrolled MSM and transgender women, a bone sub-study found that participants on CAB-LA actually had slight increases in BMD (+0.5% to +1.5%) over 2 years, whereas those on TDF/FTC had small declines (–0.5% to –1%)[9].

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