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Prevalence of renal and bone risk factors among individuals prescribed oral pre-exposure prophylaxis for HIV ☆

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ABSTRACT

Objectives: The only available oral pre-exposure prophylaxis (PrEP) regimens approved in the United States to prevent HIV infection during the period covered by this study were emtricitabine/tenofovir alafenamide (F/TAF) and emtricitabine/tenofovir disoproxil fumarate (F/TDF). Both agents have similar efficacy, however F/TAF exhibits improved bone and renal health safety endpoints over F/TDF. In 2021, the United States Preventive Services Task Force recommended individuals have access to the most medically appropriate PrEP regimen. To understand the impact of these guidelines, the prevalence of risk factors to renal and bone health was evaluated among individuals prescribed oral PrEP.

Methods: This prevalence study utilized the electronic health records of people prescribed oral PrEP between January 1, 2015 and February 29, 2020. Renal and bone risk factors (age, comorbidities, medication, renal function, and body mass index) were identified using International Classification of Diseases (ICD) and National Drug Code (NDC) codes.

Results: Among 40 621 individuals prescribed oral PrEP, 62% had ≥1 renal risk factor and 68% had ≥1 bone risk factor. Comorbidities were the most frequent (37%) class of renal risk factors. Concomitant medications were the most prominent (46%) class of bone-related risk factors.

Conclusions: The high prevalence of risk factors suggests the importance of their consideration when choosing the most appropriate regimen for individuals who may benefit from PrEP.

1. Introduction

In 2019, the number of individuals with HIV exceeded one million in the United States, with 37.7 million individuals with HIV worldwide [1,2]. The prevention of HIV transmission is an important public health goal. Pre-exposure prophylaxis (PrEP) with antiretroviral drugs has been recommended by the Centers for Disease Control and Prevention in the United States for HIV prevention among individuals at high risk of acquiring HIV [2–4]. At the time of this study, emtricitabine/tenofovir disoproxil fumarate (F/TDF) and emtricitabine/tenofovir alafenamide (F/TAF) were the two oral medications approved by the United States Food and Drug Administration for HIV prevention. F/TDF and F/TAF have both been shown to be highly effective in preventing HIV [5–11] and well-tolerated [11–13] in both clinical trials and real-world studies. For example, the ongoing DISCOVER Trial, started September 13, 2016, has demonstrated that F/TAF had noninferior efficacy compared to F/TDF through 96 weeks of follow-up [11]. Among the several choices of PrEP regimens, F/TDF and F/TAF are the two most utilized currently.

There are, however, important differences between F/TDF and F/TAF in their bone and renal safety profiles. F/TAF has demonstrated improved bone mineral density (BMD) and renal biomarker safety endpoints compared with F/TDF: significant differences were found for hip and spine BMD, β2-microglobulin to creatinine ratio, retinol-binding protein to creatinine ratio, quantitative proteinuria at 48 weeks, serum creatinine, and creatinine clearance [14]. Evidence from real-world data

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shows that F/TDF impacts both renal function and BMD among users, with mixed evidence of recovery after discontinuation of the PrEP regimen [15–17].

The updated United States Preventive Services Task Force (USPSTF) recommendations state that individuals should have access to the PrEP medication that is medically appropriate for them, as determined by the individual's healthcare provider [18]. To assist clinicians in deciding between F/TAF and F/TDF, an algorithm was developed by Fields and Tung for identifying renal and bone risk factors, and choosing which PrEP medication should be prescribed [19]. There are limited real-world data on the prevalence of these risk factors among individuals prescribed oral PrEP, and understanding the prevalence of renal and bone risk factors within a population of individuals prescribed oral PrEP may help inform the scope and applicability of this algorithm in clinical practice, especially in the decision to prescribe F/TAF versus F/TDF [18]. To address this knowledge gap, the present study evaluated the prevalence of the same risk factors for renal and bone conditions included in the Fields and Tung algorithm, among individuals newly prescribed oral PrEP, using retrospective real-world evidence derived from an electronic health record (EHR) database in the United States.

2. Methods

2.1. Study population and study design

This retrospective observational prevalence study analyzed patient-level EHR data (from January 1, 2015 through February 29, 2020) for individuals prescribed oral PrEP (including pharmacy and medical claims data) in the Veradigm Health Insights Database, which consists of United States-based Allscripts ambulatory hosted and on-premise EHR data. F/TDF was approved for PrEP in individuals weighing ≥35 kg in July 2012 [20], while F/TAF was approved for PrEP in individuals weighing ≥35 kg in October 2019 [21]; this study considered any PrEP prescription, regardless of regimen, and regimens were not directly compared.

The first prescription record for PrEP that included F/TDF or F/TAF was designated as the index date for each included individual. To be included, individuals were required to be ≥16 years of age on their index date. To limit the study to individuals who were prescribed F/TDF and F/TAF for HIV PrEP indications, individuals were excluded if there was evidence of any of the following at 6 months pre-index date or 3 months post-index date: antiretroviral or anti-chronic hepatitis-specific treatment, or any indication of current or historical diagnosis of HIV, chronic hepatitis B, opportunistic infection, or contaminated needlestick and/or post-exposure prophylaxis (PEP). Further details are included in Figure 1 and **Appendix** Table A3.

Because Veradigm is an EHR database, insurance eligibility was not available. Instead, individuals were required to have had any observed healthcare activity in the database for at least 6 months pre- or at least 3 months post-index date (e.g., an office visit or pharmacy prescription), to ensure that exclusion criteria could be evaluated. A 3-month post-index inclusion period was selected to avoid the exclusion of younger, relatively healthy individuals for whom the initiation of PrEP might be their first engagement with the health system, relative to the study period.

Included data for individuals prescribed oral PrEP were assessed until one of the following occurred: discovery of any of the five exclusion criteria more than 3 months after the index date; end of the study period; or end of data availability (defined as the last date of observed activity in the EHR data; i.e., the last observed prescription, laboratory record, inpatient visit, or outpatient visit).

2.2. Study objectives and outcomes

The primary objective of this study was to identify individuals newly prescribed oral PrEP within the Veradigm database population between July 1, 2015 (allowing for the 6-month look-back period to January 1, 2015) and February 29, 2020, to assess their demographics and the prevalence of existing renal- and bone-related risk factors (irrespective of the PrEP regimen prescribed). Risk factors included in the present study were identified through prior work that developed an algorithm as a medical-decision tool to aid clinicians in assessing clinical and individual characteristics that may predispose individuals to, or are evidence of existing renal and bone conditions [19]. Included risk factors were categorized by age-, comorbidity-, concomitant medication-, and clinical-related measures (Table 1) and were assessed over the entire study from January 2015 through February 2020. This study assessed the prevalence of risk factors in a population prescribed oral PrEP, as informed by the prior decision-making tool, and did not attempt to weight the relative clinical impact of different risk factors.

Table 1
Risk factors

Renal risk factors	Bone risk factors
Age-related risk factors	
Age >40 years at index date (functional decline)	Age <25 years at index date (rapid bone growth)
	Age >50 years at index date (osteoporosis)
Comorbidity-related risk factors	
Chronic kidney disease	Hypogonadism
Acute kidney injury	Diabetes mellitus
Focal segmental glomerulosclerosis	Hypothyroidism, hyperthyroidism, or hyperparathyroidism
Hydronephrosis	Fracture
Pyelonephritis	Psoriasis
Acute tubular necrosis	Osteopenia/osteoporosis
Renal tubular acidosis	Rheumatoid arthritis
Acute interstitial nephritis	Ankylosing spondylitis
Diffuse cortical necrosis	Gastric bypass surgery
Renal papillary necrosis	Ulcerative colitis
Hypertension	Crohn's disease
Eating disorders	Growth hormone deficiency
Vitamin D deficiency	Hemochromatosis
Sickle cell disease	Celiac disease
Tobacco abuse	Multiple sclerosis
Methamphetamine abuse	Hypercoagulable states
Cocaine abuse	Systemic lupus erythematosus
Opioid abuse	Idiopathic thrombocytopenic purpura
Marijuana abuse	Primary biliary cirrhosis
Alcohol abuse	Primary sclerosing cholangitis
	Monoclonal gammopathy of uncertain significance
	Beta thalassemia major
	Multiple myeloma
	Acromegaly
	Graft-versus-host disease
	Systemic macrocytosis
	Tobacco abuse
	Alcohol abuse
	Methamphetamine abuse
Medication-related risk factors	
Chronic NSAID use	Selective serotonin reuptake inhibitors
Atypical antipsychotics	Anti-epileptics
Tricyclic antidepressants	Proton pump inhibitors
Lithium	Corticosteroids
Haloperidol	Statins
	Opioids
	H2 blockers
	Barbiturates
Clinical-related risk factors	
Impaired renal function (eGFR <90 ml/min)	Underweight or obese (BMI <18.5 or ≥30.0 kg/m^2)

BMI, body mass index; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drugs.

2.3. Age-related risk factors

Age at index date was considered an individual risk factor. Age >40 years was considered a risk factor for suboptimal renal function. While

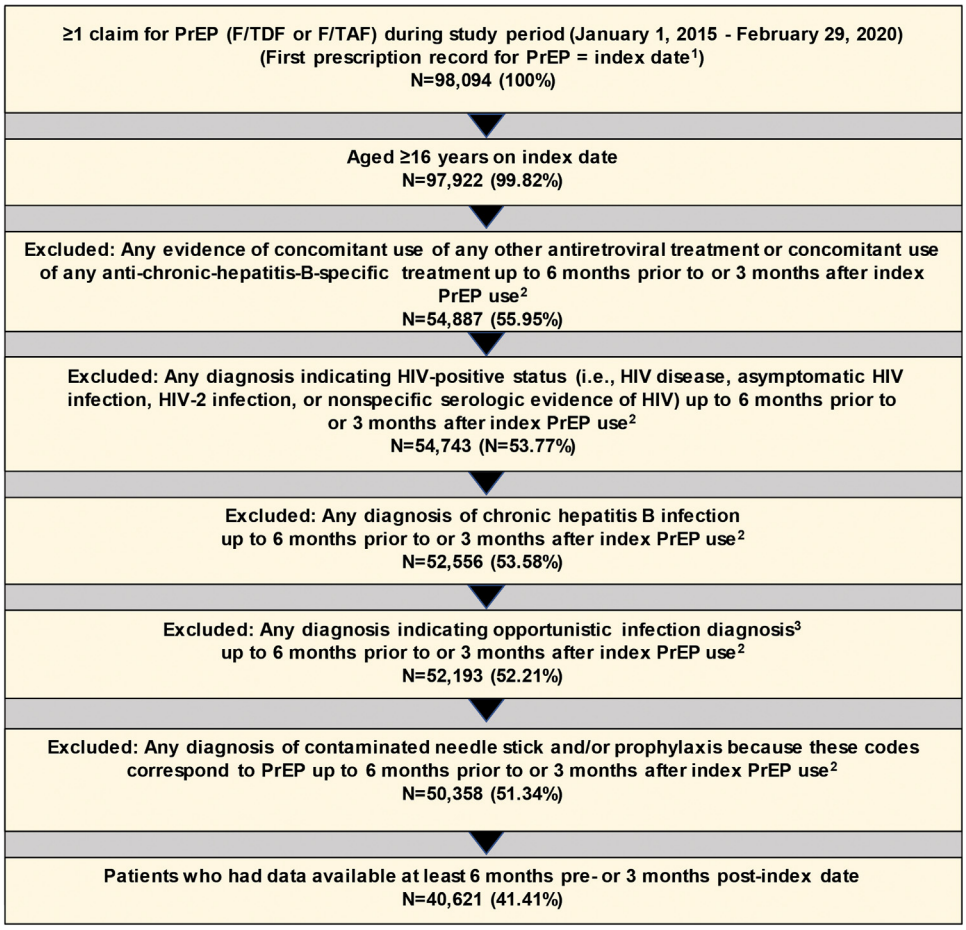

Figure 1. Flow chart of patient data inclusion for analysis.
[1]NDC codes for F/TDF and F/TAF in the EHR were used to identify all individuals who received PrEP (**Appendix** Table A7).
[2]The list of the ICD-9 and ICD-10 codes to identify the conditions applied in the exclusion criteria can be found in **Appendix** A3. (Exclusion criteria adapted from the following reference: Mera R, Ng LK, Magnuson D, Campos A, Silva M, Rawling M. Characteristics of F/TDF for pre-exposure prophylaxis users in the United States (January 2012–September 2013). HIV Drug Therapy in the Americas; Rio de Janeiro, Brazil; May 8–10, 2014.)
[3]Including candidiasis of bronchi, trachea, esophagus, or lungs, toxoplasmosis, coccidioidomycosis, cryptococcosis, cryptosporidiosis, CMV retinitis, Kaposi's sarcoma, *Mycobacterium avium* complex, *Pneumocystisjirovecil* pneumonia.
Abbreviations: CMV, cytomegalovirus; EHR, electronic health record; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; ICD, International Classification of Diseases; NDC, National Drug Code; PrEP, pre-exposure prophylaxis.

chronic kidney disease is more prevalent in the elderly, physiological declines in kidney function can begin as early as 30–40 years of age depending on many factors [19]. For bone health impact, age was stratified as <25 years or >50 years of age. In the United States, a large proportion of individuals 50 years of age have osteoporosis or low bone mass [22]. Bone health is also an important consideration in younger individuals; bones grow rapidly during adolescence until they reach peak mass, typically by 30 years of age, and any factor that reduces peak bone mass during this period can increase the risk of fractures later in life [23].

2.4. Comorbidity-related risk factors

Comorbidities that may predispose individuals to, or are evidence of existing renal and bone conditions were enumerated within the included sample. Chronic kidney disease, acute kidney injury, focal segmental glomerulosclerosis, hydronephrosis, pyelonephritis, acute tubular necrosis, renal tubular acidosis, acute interstitial nephritis, diffuse cortical necrosis, and renal papillary necrosis were considered evidence of active conditions that represent renal risk factors [19]. In addition, tobacco use, hypertension, eating disorders, vitamin D deficiency, sickle cell disease, and methamphetamine, cocaine, opioid, marijuana, and alcohol abuse have all been shown to have negative effects on renal health [19,24–26]. Tobacco, alcohol, and methamphetamine use also have demonstrated negative effects on bone health [27,28]. Comorbidities that were considered to either predispose individuals to, or be evidence of existing bone conditions included hypogonadism, diabetes mellitus, hypothyroidism, fracture, psoriasis, osteopenia/osteoporosis, rheumatoid arthritis, ankylosing spondylitis, gastric bypass surgery, ulcerative colitis, Crohn's disease, hyperthyroidism, growth hormone deficiency, hemochromatosis, celiac disease, multiple sclerosis, hypercoagulable states, systemic lupus erythematosus, hyperparathyroidism, idiopathic thrombocytopenic purpura, chronic liver diseases (primary biliary cirrhosis and primary sclerosing cholangitis), monoclonal gammopathy of uncertain significance, beta thalassemia major, multiple myeloma, acromegaly, graft-versus-host disease, and systemic macrocytosis [19]. These comorbidities were identified in the EHR using International Classification of Diseases ninth and tenth revision codes (ICD-9 and ICD-10) (**Appendix** Tables A4–A8).

2.5. Medication-related risk factors

Commonly prescribed medications that are risk factors for renal and bone impairments were enumerated within the included sample. Many first-line mental health agents can increase the risk of renal dysfunction [29]. Concomitant medications such as corticosteroids, antidepressants, and proton pump inhibitors can increase the risk of bone problems [30–32]. Specific medications considered risk factors for renal impairment included chronic non-steroidal anti-inflammatory drug (NSAID) use, atypical antipsychotics, tricyclic antidepressants, lithium, and haloperidol. Specific medications considered risk factors for bone problems included selective serotonin reuptake inhibitors, anti-epileptics, proton pump inhibitors, corticosteroids, statins, methamphetamines, chronic opioids, H2 blockers, and barbiturates. Chronic use was defined as at least two different prescription records that were more than 30 days apart (See **Appendix** Tables A7 and A8 for lists of these medications).

2.6. Clinical-related risk factors

To identify active renal impairment, the estimated glomerular filtration rate (eGFR; ml/min/1.73m^2) was either extracted directly from the

available laboratory records or calculated based on demographics and creatinine measures, using the record closest to the index date. A measured or calculated eGFR <90 ml/min was used to categorize impaired renal function. If both eGFR and creatinine measures were available on a given date, the eGFR laboratory record was used. In the rare case that multiple creatinine records were available on a single day, the average value was used to calculate the eGFR value. Creatinine records were converted to eGFR using the formula recommended by the National Institute of Diabetes and Digestive and Kidney Diseases, which includes race as a factor [33]. Because the EHR dataset does not include information on race, eGFR in the primary analysis was estimated assuming that the race was non-Black [34,35], and a sensitivity analysis assuming all Black was conducted to assess the potential impact of assuming non-Black race in the eGFR calculations. eGFR was assessed using only eGFR laboratory records and using both creatinine and laboratory records, with only the eGFR laboratory records being used to assess risk factors overall.

Being underweight or obese are risk factors for bone problems [36,37]. To assess this, body mass index (BMI; kg/m^2) was determined and categorized as follows: underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obese (≥30.0) [38,39].

3. Results

3.1. Demographics

A total of 98 094 individuals were identified with ≥1 prescription record for F/TDF or F/TAF during the study period. After applying the exclusion criteria to restrict the sample to individuals who were prescribed F/TDF or F/TAF for PrEP, a total of 40 621 (41.4%) individuals were included in the analysis (Figure 1). The average age for included individuals was 38 years, with a standard deviation (SD) of 12.3 years, and 90.2% of the cohort was male. The most common age groups were 31–40 years (28.8%), 26–30 years (19.1%), and 41–50 years (18.4%; Table 2); 14.8% were <25 years old and 18.9% were >50 years old. The geographic regions of the study population included the South (31.4%), West (32.8%), North Central (11.9%), and the Northeast (23.1%) of the United States. The medical management of oral PrEP was performed mostly by primary care providers: internal medicine (23.6%), family medicine (16.7%), and nurse practitioners (13.8%; Table 2).

The prevalence of renal and bone risk factors was assessed over the entire study period for all individuals with available data. On average, individuals prescribed oral PrEP had 14.2 months of pre-index and 17.2 months of post-index data available. Over half had at least 6 months of pre-index data (53.7%) and at least 12 months of post-index data (53.8%). Individuals were observable until the end of data availability (70.3%) or the end of the study period (23.9%), with the remaining 5.8% experiencing a clinical event that was covered by the exclusion criteria at least 3 months after their index date (individuals with such an event within 3 months of their index date were excluded from the study; Table 3).

3.2. Risk factor overview

Approximately four of five individuals prescribed oral PrEP had at least one renal or bone risk factor (81.4%), with 62.2% at risk for renal conditions and 68.0% at risk for bone conditions. Nearly half (48.8%) had risk factors for both renal and bone conditions (Figure 2). The most common types of risk factors were age-related (affecting 48.8% of individuals prescribed oral PrEP), medication-related (48.3%), and comorbidity-related (44.8%), with clinical-related risk factors being less common (11.5%). After excluding age-related risk factors, most individuals prescribed oral PrEP still had at least one renal or bone risk factor (68.0%), with 46.0% having at least one renal risk factor and 55.8% at least one bone risk factor.

Table 2
Demographic and clinical characteristics at index date

	Overall PrEP users (N = 40 621)	
	n or mean	% or SD
PrEP medication on index date		
F/TAF (regardless of F/TDF use)	1689	4.16%
F/TDF (regardless of F/TAF use)	39 108	96.28%
Both F/TAF and F/TDF	176	0.43%
Age at index date (years)	38	12.31
Range (minimum–maximum)	16–93	
Age group at index date		
16–20 years	1011	2.49%
21–25 years	5003	12.32%
26–30 years	7751	19.08%
31–40 years	11 691	28.78%
41–50 years	7487	18.43%
51–55 years	3423	8.43%
56–64 years	3239	7.97%
65+ years	1016	2.50%
Sex		
Male	36 640	90.20%
Female	3548	8.73%
Transgender	275	0.68%
Unknown	158	0.39%
Region		
Northeast	9364	23.05%
North Central	4825	11.88%
South	12 745	31.38%
West	13 309	32.76%
Other/unknown	189	0.93%
Provider		
Internal medicine	9600	23.63%
Nurse practitioner	5590	13.76%
Family medicine	6787	16.71%
General practice	1729	4.26%
Physician assistant	1295	3.19%
Others	7854	19.33%
Unknown	8041	19.80%
PrEP users with smoking status available (n = 7666)		
Never smoker	4537	59.18%
Former smoker	910	11.87%
Current smoker	1983	25.87%
Unknown	236	3.08%
PrEP users age with BMI reported[a]	40 093	98.70%
PrEP users with BMI available, age >20 years[a]	13 169	32.85%
BMI (kg/m^2)	27.28	4.59
Range (minimum–maximum)	15.60–46.90	
BMI group		
Underweight (<18.5)	51	0.39%
Normal (18.5–24.9)	4549	34.54%
Overweight (25.0–29.9)	5214	39.59%
Obese (≥30)	3355	25.48%

BMI, body mass index; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; PrEP, pre-exposure prophylaxis; SD, standard deviation.

[a] The closest BMI value to the index date during the baseline period was used.

3.3. Renal risk factors

The majority of individuals prescribed oral PrEP had at least one renal risk factor (62.2%), with age-related (37.3%) and comorbidity-related (36.8%) risk factors being most common; medication-related (14.5%) and clinical-related (7.4%) risk factors were also common (see **Appendix** Table A1).

The commonly observed renal comorbidity-related risk factors were substance use disorder (17.6%), hypertension (17.0%), smoking/tobacco use (11.2%), vitamin D deficiency (10.8%), and alcoholism (4.2%). Chronic NSAID use (8.2%, defined as ≥2 different prescription records of NSAID that are more than 30 days apart) and atypical antipsychotics (5.8%) were the most common medication-related renal risk factors. eGFR laboratory measurements were available for 15.6%

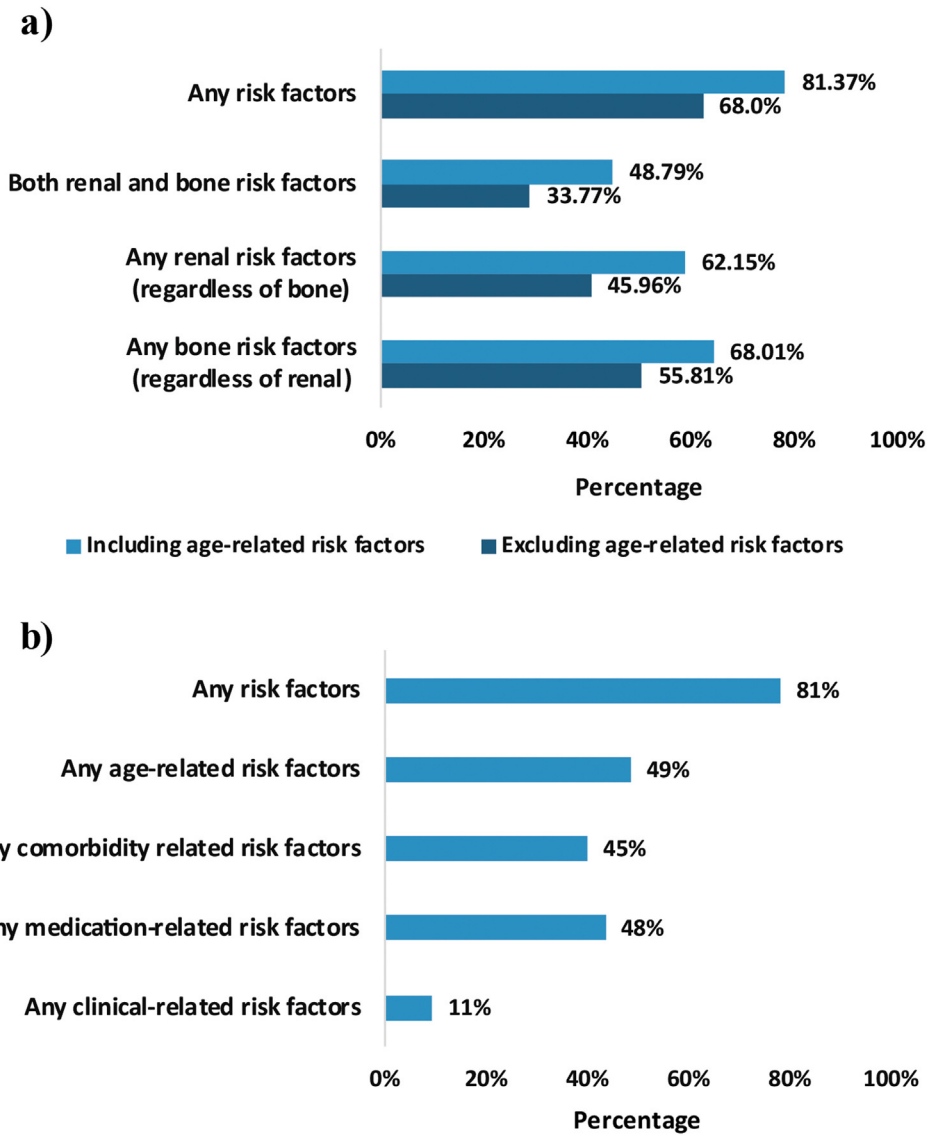

Figure 2. Relationship of risk factors with age, comorbidities, and medications: (a) F/TDF; (b) F/TAF.

of individuals prescribed oral PrEP. Of these, impaired renal function was identified in 47.4% (7.4% of individuals prescribed oral PrEP overall), defined as an eGFR of <90 ml/min (corresponding to stage 2: mild chronic kidney disease or worse) (see Figure 3a for the key renal risk factors and **Appendix** Table A1 for the full list).

3.4. Bone risk factors

The majority of individuals prescribed oral PrEP had at least one bone risk factor (68.0%), with medication-related (46.0%) and age-related (30.4%) risk factors being most common. Individuals prescribed oral PrEP were also affected by comorbidity-related (24.1%) and clinical-related (5.3%) risk factors.

The most frequently observed medication-related bone risk factors included selective serotonin reuptake inhibitors (16.7%), anti-epileptics (13.7%), proton pump inhibitors (13.4%), corticosteroids (12.6%), statins (10.3%), and methamphetamines (7.4%). Hypogonadism (9.3%) and diabetes mellitus (5.5%) were the most often reported comorbidity-related risk factors. There were 5.3% of individuals prescribed oral PrEP who were underweight (0.1%) or obese (5.2%) during the observation period (see Figure 3b for the key bone risk factors and **Appendix** Table A2 for the full list).

4. Discussion

The results of the present study demonstrate that the majority of individuals prescribed oral PrEP had at least one risk factor for bone or renal impairment, with 81% having any risk factor, 68% having bone health risk factors, 62% having renal health risk factors, and 49% having both renal and bone risk factors.

The most prevalent renal risk factors were age (37%) and comorbidities (37%), while the identification of medication-related renal risk factors was more limited (15%). The two most prevalent bone risk factors in this cohort were medication- and age-related, with 68% of individuals prescribed oral PrEP having at least one bone risk factor; over 90% of the included cohort were also identified as male. Often considered a concern for women, men also experience negative health effects with BMD loss, which can lead to an increased risk of fractures and osteoporosis [40]. The lifetime risk of osteoporotic fractures (10–25%) has also been rising in men as life expectancy has increased [40], highlighting the importance of age as a consideration for the choice of oral PrEP regimen.

Close to 15% of included individuals were <25 years old. Fractures later in life are associated with peak bone mass achieved during a person's mid-20s [23]. While there is some evidence that eGFR levels can re-

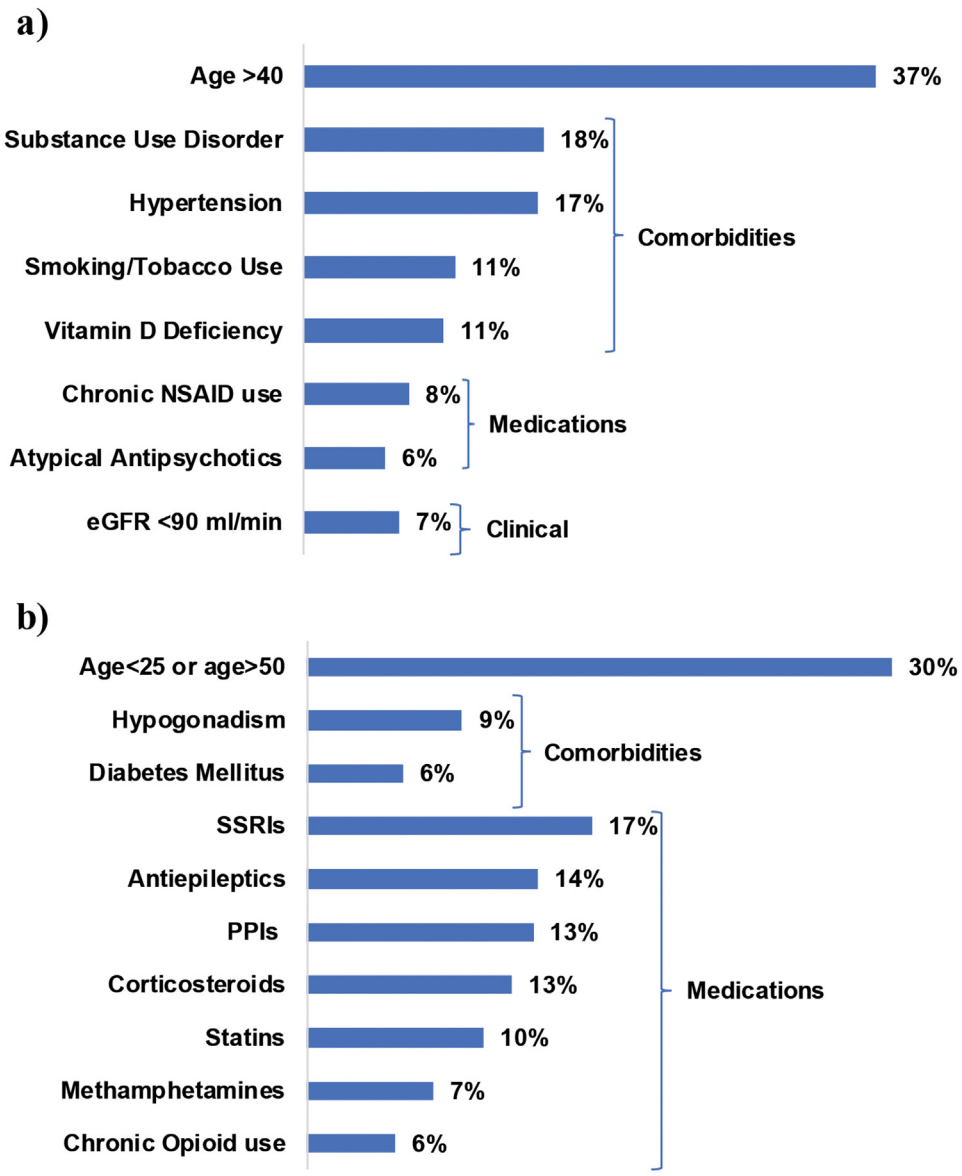

Figure 3. Key renal and bone risk factors. Included renal (a) and bone (b) risk factors are restricted to the risk factors that affected ≥5% of the population; see **Appendix** Table A1 for a full list of renal risk factors and **Appendix** Table A2 for a full list of bone risk factors. Abbreviations: eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug; PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors.

cover to baseline levels within 18 months of discontinuing F/TDF [15], there is mixed evidence on whether BMD *z*-scores fully recover after discontinuation of F/TDF. The results of one study following cohorts aged 15–22 years old suggest that *z*-scores do not recover to baseline levels 48 weeks after discontinuation of F/TDF [16]. An earlier study found that participants recovered to baseline BMD levels by 1 year post F/TDF discontinuation (all ages), but it may have been underpowered to detect differences between age groups [17]. Age as a risk factor was a significant contributor to the overall prevalence of renal (37%) and bone (30%) impairment risk factors in this population. Given the uncertainty around BMD and eGFR of recovery after discontinuation of F/TDF, the prevalence of risk factors excluding age as a factor was also assessed. When age was excluded, the prevalence of risk factors remained high for both renal (46%) and bone (56%) problems.

The clinical importance of existing risk factors for each individual is determined by the clinician on an individual basis. Not all of the included risk factors may be strong predictors of clinical outcomes, and the presence of any one risk factor may not mandate the use of F/TAF or F/TDF; rather the presence of risk factors should be considered as part of a complete assessment of the best option for each individual. Findings from the current prevalence analysis support increased awareness and consideration of renal and bone risk factors when considering the most appropriate regimen for individuals who may benefit from PrEP, especially in light of updated USPSTF recommendations.

4.1. Limitations

All data may not be recorded in the EHR, making records incomplete for diagnoses, laboratory results, medication use, and/or prescriptions. Outcomes like bone density scans are either not common, or data on results are not readily available in EHR datasets, perhaps leading to an underestimate of the prevalence of bone risk factors. Similarly, eGFR data could only be retrieved or calculated from the EHR dataset for 15.6% of individuals prescribed oral PrEP, perhaps leading to an underestimation of the prevalence of active renal impairment. Furthermore, the EHR provide data on medications prescribed, but not on medication use. Over-the-counter medications or medications provided as samples by the prescribing providers are not recorded; thus, for common over-the-counter medications like NSAIDs or proton pump inhibitors, this study may provide an underestimate of the true prevalence of chronic use. Conversely, the clinical relevance of each risk factor must be considered on an individual basis (such as a fracture) and may be determined by a clinician

Table 3
Observation time and reason for censoring

	Overall PrEP users (N = 50 358)	
	n or mean	% or SD
Pre-index data available (months)	14.18	16.48
Range (minimum–maximum)	0–61	
Pre-index data available (months)		
<1 month	13 257	32.64%
≥1 and <3 months	2932	7.22%
≥3 and <6 months	2634	6.48%
≥6 months	21 798	53.66%
Post-index data available (months)	17.16	14.89
Range (minimum–maximum)	0–61	
Post-index data available (months)		
<1 month	3047	7.50%
≥1 and <3 months	2202	5.42%
≥3 and <6 months	5732	14.11%
≥6 and <12 months	7768	19.12%
≥12 months	21 872	53.84%
Reason for end of observation		
End of data availability	26 855	70.26%
End of study period[a]	10 840	23.93%
Due to an exclusion criterion	2926	5.81%
HIV medication	40	0.08%
Use of a third antiretroviral agent	899	2.21%
Any diagnosis indicating HIV-positive status	724	1.78%
Chronic hepatitis B virus infection	64	0.16%
Opportunistic infection	315	0.78%
Needlestick and/or occupational PEP	1016	2.50%

PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; SD, standard deviation.

[a] PrEP users were considered to have data until the end of the study period if their last activity date was within 30 days of the end of the study period.

to be clinically insignificant in choosing the most appropriate PrEP regimen. Thus, the prevalence of clinically relevant risk factors may be overestimated in the current study. Another possible limitation is that this was a cross-sectional study, and it was not possible to analyze the time spent on PrEP and the development of adverse renal/bone outcomes, nor to assess recovery after discontinuation of PrEP. BMI was considered an independent risk factor for bone health in this study, but any limitations of BMI as a measure [41,42] were unlikely to impact the findings of this study. In addition, certain information that may influence study outcomes, such as race and clinical disease-specific parameters, is not readily available in the dataset; race specifically can affect BMD measures and calculations of eGFR from creatinine levels. The potential for bias due to this limitation, however, was demonstrated to be minimal, because the sensitivity analysis conducted that assumed all individuals were Black race instead of non-Black showed minor differences in the estimate prevalence (10% vs 9%: **Appendix** Table A1).

4.2. Conclusions

PrEP is an important strategy to reduce HIV infection among populations at risk for acquiring HIV, with F/TDF and F/TAF currently being the only two approved oral options in the United States. Even as different types of PrEP regimens become available, oral PrEP will continue to be a major tool for HIV prevention, and understanding the populations for which the respective regimens are most appropriate will be important for clinical practice. The results of this prevalence analysis showed that renal and bone risk factors were present in most individuals who were prescribed oral PrEP between 2015 and 2019 in a United States sample. These risk factors are important for clinicians to consider when choosing the most appropriate PrEP regimen for individuals at risk of acquiring HIV given the differences in F/TDF and F/TAF safety profiles, and consistency with updated USPSTF recommendations to ensure access to PrEP medications that are medically appropriate for individuals who can benefit from PrEP. Increased personalization of health care is critical for addressing specific needs of the diverse populations that may benefit from PrEP—an important tool for fighting the HIV pandemic.

Conflict of interest

Joshua Gruber, Jamaal Clue, and Helena Díaz Cuervo were employees of Gilead Sciences at the time of the work. Sheldon D. Fields received consultancy fees from Gilead Sciences. Gabriel Gomez Rey is a paid employee of STATinMED Research, which is a paid consultant to Gilead Sciences.

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Ethical approval

The core study described herein did not involve the collection, use, or transmittal of individual identifiable data. The security of the data meets the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The study protocol was reviewed and determined to be exempt from the Office for Human Research Protections' (OHRP's) Regulations for the Protection of Human Subjects (45 CFR 46) under the following category: Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. This study was performed in accordance with the Declaration of Helsinki of 1964 and its later amendments.

Data availability

The datasets analyzed during the current study are available in the Veradigm Health Insights Database repository at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021752s061lbl.pdf.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.01.004.

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