Drug Saf (2018) 41:843–848
https://doi.org/10.1007/s40264-018-0665-z

SHORT COMMUNICATION

Osteoporosis-Related Fractures in HIV-Infected Patients Receiving Long-Term Tenofovir Disoproxil Fumarate: An Observational Cohort Study

Ayami Komatsu[1] · Atsushi Ikeda[1] · Akio Kikuchi[1] · Chiaki Minami[1] · Motomu Tan[1] · Shuzo Matsushita[2]

Published online: 5 April 2018

Abstract

Introduction Patients with HIV infection may have a higher prevalence of osteoporosis and osteopenia, as well as an increased risk of bone fracture compared with non-HIV-infected individuals. Antiretroviral therapy is thought to be one of factors associated to osteoporosis-related bone fractures.

Objective The aim of this study was to assess the effects of long-term exposure to tenofovir disoproxil fumarate (TDF) on the cumulative risk of osteoporosis-related bone fractures in Japanese patients with HIV infection.

Design This observational cohort study comprised a joint HIV-related drug survey of patients treated with TDF between April 2004 and March 2013.

Methods Thirty-five healthcare facilities in Japan participated in the survey. The incidence of osteoporosis-related fractures was extracted from all adverse events (AEs) using standardized Medical Dictionary for Regulatory Activities queries, and used to calculate the fracture rate per 10,000 patient-years (PY). Kaplan–Meier analysis was used to estimate the cumulative probability of fracture during the study period.

Results A total of 3251 patients who received TDF or TDF/emtricitabine between April 2004 and March 2013 were analyzed in this study; 93.5% of patients were male. The fracture rate was 13.5 per 10,000 PY in males and 42.2 per 10,000 PY in females. The mean age for male patients with osteoporosis-related fracture was 43.2 years, whereas it was 65.7 years in female patients. The cumulative probability of osteoporosis-related fracture increased after $\geq$ 5 years of TDF exposure. The rate of hip fracture (95% confidence interval) was 7.2 (3.1–14.2) per 10,000 PY.

Conclusions Among HIV-infected patients in Japan, treatment with TDF for $\geq$ 5 years increases the risk of bone fractures in younger men, in addition to that seen in older post-menopausal women.

Key Points

Long-term use of tenofovir disoproxil fumarate (TDF) in HIV-infected patients increases the risk of fractures.

All patients who had hip fracture were men with a mean age of 42.5 years.

Experts are encouraged to consider the long-term effects of TDF therapy in patients with HIV before initiating treatment.

✉ Ayami Komatsu
ayami.komatsu@jt.com

✉ Shuzo Matsushita
shuzo@kumamoto-u.ac.jp

[1] Pharmaceutical Division, Drug Safety and Risk Management Department, Japan Tobacco Inc., Tokyo, Japan

[2] Center for AIDS Research, Kumamoto University, Kumamoto, Japan

1 Introduction

Patients with HIV infection may have a higher prevalence of osteoporosis and osteopenia, as well as an increased risk of bone fracture compared with non-HIV-infected

individuals [1, 2]. Multiple factors are thought to cause decreases in bone mineral density (BMD), including the effects of antiretroviral therapy (ART), inflammatory cytokines, and HIV-1 proteins on osteoblasts and bone turnover [3, 4]. A 2013 meta-analysis indicated that HIV infection is associated with a modest increase in the risk of all fractures and fragility fractures [1]. Most of the studies included in this analysis did not show an independent effect of the ART drug class or exposure on the risk of fractures, which suggests that the role of ART in incident fractures is not clearly established.

Studies in rhesus monkeys and humans have indicated that bone fractures associated with ART are due to losses in BMD [5–7]. In particular, the antiretroviral drug tenofovir disoproxil fumarate (TDF) is associated with decreased BMD and increased bone turnover markers, which leads to osteoporosis-related bone fractures [6, 8].

TDF and a TDF/emtricitabine (FTC) combination were approved in Japan for the treatment of HIV-1 infection in 2004 and 2005, respectively. In a global post-marketing study of the safety of TDF over 4 years, the incidence of bone abnormalities and fractures was low [9]. However, a registry study has indicated that cumulative exposure to TDF was an independent risk factor for osteoporosis-related fractures [10].

As the prevalence of HIV and AIDS in Japan is relatively low, with a total of 16,903 cases of HIV infection and 7658 cases of AIDS being reported by the end of 2014 according to the Annual Report on AIDS Trends [11], joint HIV-related drug (HRD) surveys are often used for post-marketing surveillance in Japan [12, 13]. We conducted a post-marketing observational cohort study using a joint HRD survey of TDF safety data in Japanese patients with HIV infection over 8 years to assess the effects of long-term exposure on the cumulative risk of osteoporosis-related bone fractures.

2 Methods

2.1 Data Source

The joint HRD survey was approved by the Pharmaceuticals and Medical Devices Agency of Japan in conjunction with drug manufacturers to collect safety data. The HRD survey has been conducted since Aug 1997. Thirty-five healthcare facilities from different regions of Japan participated in the survey, and collected data were anonymized at a data center (CMIC-PMS Co., Ltd). Patients who had initiated treatment with an HRD were registered by physicians on the first business day of the next fiscal year (Japanese fiscal year starts from April). Data collection continued until the medication was stopped. The survey was conducted in accordance with the Good Post-Marketing Study Practice regulations issued by the Ministry of Health, Labour and Welfare of Japan.

2.2 Observational data

The following patient information was recorded: age, gender, race, ART drugs, general complications, concomitant drugs, hepatitis C status, baseline $CD4^+$ count and HIV viral load, duration of TDF therapy, and adverse events (AEs), including the seriousness, outcome, and causality of AEs as determined by the treating physician. An AE was defined as any unfavorable or unintended sign, symptom, or disease that occurred during treatment.

2.3 Assessments and Definitions

Osteoporosis-related fractures were extracted from all AEs reported between April 2004 and March 2013 using standardized Medical Dictionary for Regulatory Activities queries. All kidney-related AEs were included in concomitant renal dysfunction to assess the influence of drug-induced renal dysfunction on fractures.

2.4 Statistical Analysis

All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc. Cary, NC, USA). Patient-years (PY) of follow-up were calculated from the date of first TDF administration to the first occurrence of osteoporosis-related fracture, the end of administration, or the end of follow-up (whichever happened first). The fracture rate was calculated as the number of fractures per 10,000 PY, with 95% confidence intervals (CI) based on the Poisson distribution. The cumulative probability of osteoporosis-related fracture during the study period was estimated by a Kaplan–Meier analysis. Multivariate logistic regression analysis was used to evaluate the effects of opioid use, comorbid diabetes mellitus and co-infection with hepatitis C virus (HCV) on the risk of osteoporosis-related fracture. Odds ratios (OR) and 95% CI were calculated.

3 Results

3.1 Study Population

A total of 3251 patients treated with TDF or TDF/FTC between April 2004 and March 2013 were analyzed in this study; 987 patients received TDF between April 2004 and March 2012, and 2645 patients received TDF/FTC between April 2005 and March 2013; 381 patients were switched

from TDF to TDF/FTC or vice versa during the study period.

Most of the patient population (3040 of 3251; 93.5%) was male. The mean age was 40.0 years for male patients and 41.2 years for female patients, and the mean duration of TDF treatment was 1246.3 days.

3.2 Osteoporosis-Related Fractures

Overall, 17 (0.52%) patients were diagnosed with osteoporosis-related fractures during the study period. Of these patients, 14 (82.4%) were male. The fracture rate was 42.2 per 10,000 PY in female patients and 13.5 per 10,000 PY in males (Table 1). Among the female patients with osteoporosis-related fractures ($n = 3$), the mean age was 65.7 years and the mean duration of TDF before fracture onset was 123 days. In male patients, the mean age was 43.2 years and the mean duration of TDF was 1437.7 days.

Among patients with osteoporosis-related fractures, the TDF treatment duration prior to fracture onset ranged from 61 to 2965 days, the baseline $CD4^+$ count ranged from 7 to 749 cells/μL (mean 277.9 cells/μL), and all patients had received concomitant ART; protease inhibitor (PI) use was recorded in 11 (64.7%) patients.

The cumulative probability of osteoporosis-related fractures, as estimated by Kaplan–Meier analysis (Fig. 1), indicated that the cumulative probability of osteoporosis-related fracture increased after ≥ 5 years of TDF exposure.

3.3 Prevalence of Hip Fracture

Overall, hip fracture occurred in eight patients (0.25%) (Table 1), all of whom were male with a mean age of 42.5 years. The hip fracture rate (95% CI) was 7.2 (3.1–14.2) per 10,000 PY, and the age distributions were 37.5% ($n = 3$) aged < 40 years, 37.5% ($n = 3$) aged 40–49 years, and 25.0% ($n = 2$) aged 50–59 years. No hip fractures were reported in female patients.

3.4 Risk Factor Analysis

In the entire study cohort ($n = 3251$), 16 patients were reported to use opioids as concomitant medications. However, none of these patients experienced osteoporosis-related bone fractures, therefore, multivariate logistic regression analysis of the effects of opioid use on the risk of osteoporosis-related bone fractures could not be performed.

Nevertheless, multivariate analyses of the effects of comorbid diabetes and co-infection with HCV were carried out. Co-infection with HCV was associated with a statistically significant increase in the risk of osteoporosis-

Table 1 Incidence of osteoporosis-related fractures and hip fractures between 1 April 2004 and 31 March 2013 in HIV-infected patients treated with tenofovir disoproxil fumarate

	Osteoporosis-related fractures				Hip fractures				Non-hip fractures			
	Event	No. at risk	Total PY	Fractures/10,000 PY (95% CI)	Event	No. at risk	Total PY	Fractures/10,000 PY (95% CI)	Event	No. at risk	Total PY	Fractures/10,000 PY (95% CI)
All patients	17	3251	11063.1	15.4 (9.0–24.6)	8	3251	11083.9	7.2 (3.1–14.2)	13	3251	11065.7	11.7 (6.3–20.1)
Females	3	211	710.5	42.2 (8.7–123.4)	0	211	726.4	0.0	4	211	709.3	56.4 (15.4–144.4)
Aged < 40 y	0	114	392.3	0.0	0	114	392.3	0.0	0	114	392.3	0.0
Aged ≥ 40 y	0	53	178.0	0.0	0	53	178.0	0.0	0	53	178.0	0.0
Aged ≥ 50 y	1	24	70.4	142.1 (3.6–791.9)	0	24	72.0	0.0	1	24	70.4	142.1 (3.6–791.9)
Aged ≥ 60 y	2	20	69.9	286.1 (34.6–1033.5)	0	20	84.2	0.0	3	20	68.7	436.7 (90.1–1276.2)
Males	14	3040	10352.6	13.5 (7.4–22.7)	8	3040	10357.4	7.7 (3.3–15.2)	9	3040	10356.4	8.7 (4.0–16.5)
Aged < 40 y	4	1659	5635.9	7.1 (1.9–18.2)	3	1659	5636.6	5.3 (1.1–15.6)	2	1659	5638.2	3.5 (0.4–12.8)
Aged ≥ 40 y	7	805	2780.3	25.2 (10.1–51.9)	3	805	2783.8	10.8 (2.2–31.5)	5	805	2780.7	18.0 (5.8–42.0)
Aged ≥ 50 y	3	395	1382.0	21.7 (4.5–63.4)	2	395	1382.6	14.5 (1.8–52.3)	2	395	1383.1	14.5 (1.8–52.2)
Aged ≥ 60 y	0	181	554.4	0.0	0	181	554.4	0.0	0	181	554.4	0.0

CI confidence interval, *PY* patient years, *y* years

related fracture (OR 5.178; 95% CI 1.732–15.483), whereas no significant association was found with the presence of comorbid diabetes (OR 2.130; 95% CI 0.452–10.046).

None of the patients who experienced osteoporosis-related bone fractures had concomitant renal dysfunction, whereas it was present in 1.2% of patients who did not experience such fractures (38/3234).

4 Discussion

This study was conducted to assess the effects of long-term exposure to TDF on the cumulative risk of osteoporosis-related bone fractures in Japanese patients with HIV infection. To our knowledge, this is the first long-term, observational cohort study to assess the effect of TDF exposure on the cumulative risk of osteoporosis-related fractures in Japanese patients with HIV infection. The results of this study indicated that the overall incidence of osteoporosis-related fractures in this patient population was low, and the rate of fractures was three-fold higher in females than in males, with female patients being approximately 20 years older than males at fracture onset. These findings are consistent with the corresponding statistics for the general population, where osteoporosis is strongly associated with older age and female gender [14]. In a previous cohort study conducted in Japanese patients, the risk for osteoporosis of the lumbar spine was significantly increased in women of advanced age ($p < 0.001$), while the prevalence of osteoporosis in men was low (0–7.4%) regardless of age [15]. Of note, there were no cases of osteoporosis in men aged < 49 years [15].

In the present study, the risk of fractures was increased in relatively young Japanese men with HIV infection. This finding is different from what is known about fractures in the general population, especially with regard to the mean age of hip fracture, which in the present study was 42.5 years. A previous study reported that in the general population in Japan, the incidence of hip fracture was markedly higher in older men and women [16].

In addition to ART, several other factors are known to affect the risk of fractures, such as tobacco and alcohol consumption, opioid use, malnutrition, comorbid diabetes, and co-infection with HCV. However, in the present study it was difficult to estimate their effect due to the low number of patients who experienced fractures. It should be noted that there were few cases of HIV infection via the intravenous route in Japan [17], and therefore, the impact of drug addiction on the risk of fractures should be negligible [17]. In addition, none of the patients who experienced osteoporosis-related bone fractures reported use of an opioid as concomitant medication; therefore, analysis of the effects of opioid use also could not be performed. Analysis of the effects of tobacco and alcohol consumption, as well as of body mass index, on the risk of osteoporosis-related bone fractures could not be performed because the necessary data were not included in the HRD survey. In the present study, co-infection with HCV was found to be associated with a statistically significant increase in the risk of osteoporosis-related fracture. Infection with HCV is a known risk factor for osteoporosis [18]. It should be noted, however, that patients who experienced a fracture and had concomitant HCV infection in the present study ($n = 5$) were all men with a mean age of 38.2 years. Therefore, this is the same demographic that was identified as being at an increased risk of osteoporosis-related fracture (relatively young men).

The results of this study indicate that, among females, older women have the highest incidence of osteoporosis-related bone fractures, while among males, relatively young men are most affected. The major difference between the two groups was found in the mean duration of TDF exposure at the onset of fracture, which was 123 days in women and 1437.7 days in men. Therefore, the duration of TDF exposure is likely to be one of the main risk factors for osteoporosis-related bone fracture in patients with HIV infection.

Current guidelines for the management of patients with HIV infection recommend BMD screening for osteoporosis in postmenopausal women and men over 50 years old [19, 20]. A multicenter cohort study in HIV-infected men highlighted the importance of screening for osteoporosis in HIV-positive men over the age of 50 [21]. Contrary to guideline recommendations, the results of the present study suggested that relatively young men may also be at risk of bone fracture if they have been exposed to TDF for longer than 5 years. As men between the ages of 20 and 40 constitute the majority of new HIV cases in Japan [17], clinicians should consider the risk of osteoporosis-related bone fracture in HIV-infected patients who have been receiving treatment for extended periods of time, even if those patients are relatively young men. The number of patients on TDF or one of its combination drugs has dramatically increased in low- and middle-income countries over the past decade. Special attention should be paid to the risk of osteoporosis in young men with HIV infection in those countries, as bone fractures can have a serious impact on their families and communities.

An ART combination containing tenofovir alafenamide (TAF) was approved in the US and Japan in 2016, and TAF has shown less renal and bone toxicity than the equivalent TDF-containing combination product in the US [22]. It will be interesting to compare the incidence of osteoporosis-related bone fracture between the two treatments. However, if the duration of exposure to TDF is a major factor

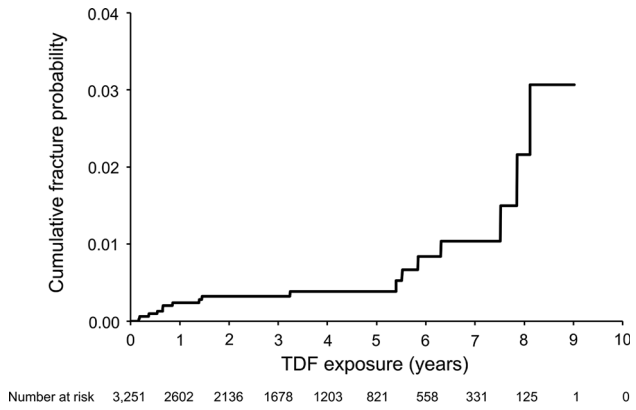

Fig. 1 Kaplan–Meier analysis of the cumulative probability of osteoporosis-related fracture in HIV-infected patients taking tenofovir disoproxil fumarate (TDF)

affecting the incidence of fractures, then patients who had taken TDF for a long time before switching to TAF should continue to be monitored.

This study was limited by a lack of comparison between the incidences of osteoporosis-related fractures in TDF- and non-TDF-treated patients. Lack of information on other risk factors, such as BMI or alcohol and tobacco use, is another limitation of this study. These limitations were because the HRD survey only permitted collection of TDF-related data. Our study also enrolled a limited number of patients aged > 65 years, making it difficult to reach a clear conclusion regarding the risk of bone fractures in older patients. In addition, the incidence of bone fractures after 2011 may be affected by reporting bias, as the potential relationship between TDF and bone fractures has been more widely known since then and physician knowledge of this association may cause an increase in the reporting of fractures.

5 Conclusions

This longitudinal study of 3251 HIV-infected patients in Japan suggests an association between osteoporosis-related fractures and the duration of TDF administration. Patients with a longer duration of TDF exposure have an increased risk of bone fracture, particularly in men aged < 60 years. If the duration of TDF administration is ≥ 5 years, the possibility of bone fracture must be considered, regardless of patient age and gender. When making decisions regarding HIV infection-related issues, experts need to consider the risk of osteoporosis-related fracture with longer-term administration of TDF.

Acknowledgements The authors would like to thank Yoshiko Okamoto, PhD, of Springer Healthcare Communications who wrote the outline of this manuscript, and Sarah Greig, PhD, of Springer Healthcare Communications who wrote the first draft. This medical writing assistance was funded by Japan Tobacco Inc.

Author Contributions AK and AI were responsible for the study design and conception; AK and CM were responsible for acquisition of data; AK, AI, MT, and SM were responsible for analysis and interpretation of data; all authors contributed to reviewing drafts of the manuscript, and approved the final version for publication.

Compliance with Ethical Standards

Funding This study was fully supported by Japan Tobacco Inc.

Conflicts of interest Ayami Komatsu, Atsushi Ikeda, Akio Kikuchi, Chiaki Minami and Motomu Tan are full-time employee of Japan Tobacco Inc. Shuzo Matsushita has received grants and personal fees from Japan Tobacco Inc., and personal fees from Bayer Yakuhin Ltd, MSD K.K., Janssen Pharmaceuticals K.K., Torii Pharmaceutical Co. Ltd, Shire Japan K.K., Bioverativ Japan Ltd, and Novo Nordisk Pharmaceutical Ltd.

Ethical approval The survey was conducted in accordance with the Good Post-Marketing Study Practice (GPSP) regulations issued by the Ministry of Health, Labour and Welfare of Japan.

References

1. Shiau S, Broun EC, Arpadi SM, et al. Incident fractures in HIV-infected individuals: a systematic review and meta-analysis. AIDS. 2013;27:1949–57. https://doi.org/10.1097/QAD.0b013e328361d241.
2. Triant VA, Brown TT, Lee H, et al. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. J Clin Endocrinol Metab. 2008;93:3499–504. https://doi.org/10.1210/jc.2008-0828.
3. Battalora L, Buchacz K, Armon C, et al. Low bone mineral density and risk of incident fracture in HIV-infected adults. Antivir Ther. 2016;21:45–54. https://doi.org/10.3851/imp2979.
4. Young B, Dao CN, Buchacz K, et al. Increased rates of bone fracture among HIV-infected persons in the HIV Outpatient Study (HOPS) compared with the US general population, 2000–2006. Clin Infect Dis. 2011;52:1061–8. https://doi.org/10.1093/cid/ciq242.
5. Castillo AB, Tarantal AF, Watnik MR, et al. Tenofovir treatment at 30 mg/kg/day can inhibit cortical bone mineralization in growing rhesus monkeys (*Macaca mulatta*). J Orthop Res. 2002;20:1185–9. https://doi.org/10.1016/S0736-0266(02)00074-8.
6. Güerri-Fernández R, Molina-Morant D, Villar-García J, et al. Bone density, microarchitecture, and tissue quality after long-term treatment with tenofovir/emtricitabine or abacavir/lamivudine. J Acquir Immune Defic Syndr. 2017;75:322–7. https://doi.org/10.1097/qai.0000000000001396.
7. Tinago W, Cotter AG, Sabin CA, et al. Predictors of longitudinal change in bone mineral density in a cohort of HIV-positive and

negative patients. AIDS. 2017;31:643–52. https://doi.org/10.1097/qad.0000000000001372.
8. Negredo E, Diez-Perez A, Bonjoch A, et al. Switching from tenofovir to abacavir in HIV-1-infected patients with low bone mineral density: changes in bone turnover markers and circulating sclerostin levels. J Antimicrob Chemother. 2015;70:2104–7. https://doi.org/10.1093/jac/dkv063.
9. Nelson MR, Katlama C, Montaner JS, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. AIDS. 2007;21:1273–81. https://doi.org/10.1097/QAD.0b013e3280b07b33.
10. Bedimo R, Maalouf NM, Zhang S, et al. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS. 2012;26:825–31. https://doi.org/10.1097/QAD.0b013e32835192ae.
11. Joint United Nations Programme on HIV/AIDS. Report to UNAIDS—HIV/AIDS trends in Japan. 2016. http://www.unaids.org/sites/default/files/country/documents/JPN_narrative_report_2016.pdf.
12. Kurita T, Kitaichi T, Nagao T, et al. Safety analysis of Epzicom® (lamivudine/abacavir sulfate) in post-marketing surveillance in Japan. Pharmacoepidemiol Drug Saf. 2014;23:372–81. https://doi.org/10.1002/pds.3588.
13. Kurita T, Kitaichi T, Nagao T, et al. Safety analysis of Ziagen® (abacavir sulfate) in postmarketing surveillance in Japan. Pharmacoepidemiol Drug Saf. 2014;23:361–71. https://doi.org/10.1002/pds.3589.
14. Ray NF, Chan JK, Thamer M, et al. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res. 1997;12:24–35. https://doi.org/10.1359/jbmr.1997.12.1.24.
15. Yoshimura N, Muraki S, Oka H, et al. Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab. 2009;27:620–8. https://doi.org/10.1007/s00774-009-0080-8.
16. Orimo H, Yaegashi Y, Hosoi T, et al. Hip fracture incidence in Japan: estimates of new patients in 2012 and 25-year trends. Osteoporos Int. 2016;27:1777–84. https://doi.org/10.1007/s00198-015-3464-8.
17. National Institute of Infectious Diseases. HIV/AIDS in Japan, 2016. Ministry of Health, Labour and Welfare of Japan. 2017. https://www0.niid.go.jp/niid/idsc/iasr/38/451e.pdf. Accessed 8 Feb 2018.
18. Biver E, Calmy A, Rizzoli R. Bone health in HIV and hepatitis B or C infections. Ther Adv Musculoskelet Dis. 2017;9:22–34. https://doi.org/10.1177/1759720x16671927.
19. Aberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2013;58:e1–34.
20. Guidelines Version 8. European AIDS Clinical Society (EACS) http://www.eacsociety.org/files/guidelines_8_0-english_web.pdf. Accessed Oct 2015.
21. Gonciulea A, Wang R, Althoff KN, et al. An increased rate of fracture occurs a decade earlier in HIV+ compared with HIV− men. AIDS. 2017;31:1435–43.
22. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385:2606–15. https://doi.org/10.1016/s0140-6736(15)60616-x.