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Original Article

Comparative pharmacokinetics between tenofovir disoproxil phosphate and tenofovir disoproxil fumarate in healthy subjects

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Conflict of Interest
The authors and reviewers are nothing to declare.

ABSTRACT

Tenofovir is the representative treatment for human immunodeficiency virus and hepatitis B virus infection. This study was conducted to assess the pharmacokinetics (PKs) and safety characteristics after a single administration of tenofovir disoproxil phosphate compared to tenofovir disoproxil fumarate in healthy male subjects. An open-label, randomized, single administration, two-treatment, two-sequence crossover study was conducted in 37 healthy volunteers. Serial blood samples were collected up to 72 hours. Non-compartmental analysis was used to calculate the PK parameters. The 90% confidence intervals (90% CIs) of the geometric mean ratio (GMR) were calculated for comparing tenofovir disoproxil phosphate to tenofovir disoproxil fumarate. Safety assessments were performed including clinical laboratory tests, adverse events, etc. during the study. The GMR and 90% CIs were 1.0514 (0.9527–1.1603) for C_{max} and 1.0375 (0.9516–1.1311) for AUC_{last}, respectively, and both fell within the conventional bioequivalence range of 0.8–1.25. Both tenofovir salt forms were tolerable. This study demonstrated that tenofovir disoproxil phosphate (292 mg) was bioequivalent to tenofovir disoproxil fumarate (300 mg).

Keywords: Tenofovir; Phosphate; Fumarate; Bioequivalence; Comparative Pharmacokinetics

INTRODUCTION

The death toll in the United States from human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections have decreased according to the statistics of the US Centers for Disease Control and Prevention [1,2]. However, there are still HIV and HBV patients. HIV patients were estimated at 1.7 million individuals in the world in 2019 [3], and the World Health Organization (WHO) estimated that 257 million people were living with HBV infection [4]. Both of them could cause chronic diseases, cancer and even death, and HIV and HBV patients cannot recover completely from these infections [5]. Recently, many kinds of combination therapies have been developed for treating HIV or HBV [6-8].

Author Contributions

Conceptualization: Kim E, Lee S[2], Yu KS; Project administration: Moon SJ, Yu KS; Visualization: Lee S[1]; Writing - original draft: Lee S[1]; Writing - review & editing: Kim E, Jung J, Lee S[2], Yu KS.

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Tenofovir is a first-line medication for HIV or HBV infection as an acyclic nucleotide reverse-transcriptase inhibitor approved by the Food and Drug Administration [9,10]. Unlike other nucleoside analogue drugs, tenofovir has shown activity in both lymphoid cells and macrophages [11,12]. According to a previous study, viral DNA from leukocytes, lymph nodes, and plasma was eradicated after a monotherapy of inoculating tenofovir for 24 hours [11,13]. Tenofovir is not a substrate, inducer or inhibitor of CYP450 [9,14], and 70 to 80% of unchanged form is eliminated by renal excretion through glomerular filtration and active tubular secretion [9]. Tenofovir has high solubility and low permeability and thus is classified by the biopharmaceutics classification system as class III [15]. Tenofovir has low bioavailability due to the high charged phosphate group when orally administered [16,17]. To overcome these characteristics, a prodrug of tenofovir was developed as a salt form of tenofovir disoproxil. This prodrug is transformed into tenofovir and intracellularly metabolized into tenofovir diphosphate which subsequently inhibits HIV replication [9]. In an *in vitro* study, tenofovir disoproxil fumarate was stable at pH 1.2, which is the stomach environment, and moderately stable at pH 6.8 which is the intestine environment [16].

The tenofovir disoproxil phosphate, which is being currently developed as an alternative to tenofovir disoproxil fumarate, has shown improvements in the aqueous stability of tenofovir [18]. The bioequivalence study with rats and beagle dogs also showed no difference comparing the tenofovir disoproxil salt forms in the pharmacokinetic (PK) results such as the AUCs and C_{max} [18]. Generally, developing novel salt forms has advantages such as improved solubility and dissolution rate [19]. In addition, from a long-term perspective, cost reduction, improved accessibility to the drug by the patients, and clinical benefits by developing these salt forms of the drugs are also expected [20]. For example, tenofovir disoproxil orotate, which has a reduced manufacturing cost, was developed to provide patients with a more cost-effective treatment [21]. Tenofovir disoproxil phosphate will be a useful substitute for the currently marketed tenofovir disoproxil fumarate if its PK properties and safety are similar to tenofovir disoproxil fumarate, and it is expected to have advantages in terms of its stability and low cost [18].

The objective of this study was to assess the PKs and safety characteristics after a single administration of tenofovir disoproxil phosphate compared to those of tenofovir disoproxil fumarate in healthy male subjects.

METHODS

Subjects and study design

The protocol of this study was reviewed and approved by the Seoul National University Hospital Institutional Review Board (IRB) (clinicaltrials.gov No.: NCT02545829). This study was conducted according to the Declaration of Helsinki (Fortaleza, Brazil) [22] and the International Conference on Harmonisation guideline [23]. All subjects provided written consent prior to the study.

An open-label, randomized, single administration, two-treatment, two-sequence crossover study was conducted to compare the PKs and safety between tenofovir disoproxil phosphate (292 mg, Hanmi Pharm. Co., Ltd., Seoul, Korea) and tenofovir disoproxil fumarate (Viread® tablet 300 mg, Gilead Sciences Inc., Foster City, CA, USA). Both salt forms contained 245 mg of tenofovir disoproxil [9]. The wash-out period was 7 days considering a half-life of

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approximately 20 hours. Under fasting condition, the randomized subjects were administered tenofovir disoproxil phosphate or tenofovir disoproxil fumarate with 150 mL of water.

Demographic assessment was evaluated as a randomized set (n = 38). The study participants were healthy males 19 to 50 years old, body weight between 55 to 90 kg, and body mass index (BMI) between 18 to 27 kg/m^2. Subjects were excluded if their blood AST and ALT exceeded 1.5 times the normal upper range limit. Subjects with genetic problems such as galactose intolerance, lactose deficiency, or glucose-galactose malabsorption were also excluded. And those who were hypersensitive or had a clinically significant history of hypersensitivity to tenofovir disoproxil and other drugs such as aspirin, antibiotics, etc. were excluded.

PK assessments

Serum tenofovir was collected at serial timepoints as follows: pre-dosing, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, and 72 hours after dosing. The serum tenofovir concentration was analyzed by ultraperformance liquid chromatography tandem mass spectrometry (UPLC-MS/MS, Waters ACQUITY UPLC™ System). The total injection volume of serum tenofovir was 10 μL and the flow rate was 0.4 mL/min to be analyzed by the UPLC-MS/MS. Injection wash solution was made into weak to strong which were 90:10:0 to 90:10:0.1 (Acetonitrile: Distilled water: Formic acid, v/v/v). And the cone gas flow of nitrogen was 50L/hr and the desolvation gas flow of nitrogen was 700 L/hr, respectively. The following PK parameters were calculated by non-compartmental analysis using the Phoenix® Certara® (Pharsight, CA, USA) software: Area under the serum concentration-time curve from zero to the last quantifiable time point (AUC_{last}), AUC from zero to infinity (AUC_{inf}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F) and apparent volume of distribution (V_z/F) of tenofovir. The AUCs were calculated using the linear up log down trapezoidal method. $t_{1/2}$ was calculated as ln(2)/terminal elimination rate(λ_z). CL/F was calculated as Dose/(λ_z • AUC_{inf}). And V_z/F was calculated as Dose/AUC_{inf}. The time to maximal plasma concentration (T_{max}) and the maximum observed serum concentration (C_{max}) of tenofovir were determined from the observed serum concentration-time profiles. Subjects who completed the PK sampling were included in the PK assessment.

Safety assessments

Clinical laboratory tests (chemistry, urinalysis, blood coagulation and hematology), adverse events (AEs), physical examination, 12-lead electrocardiograms (12-lead ECGs) and vital sign measurements were performed throughout the study. All AEs were classified by treatment groups and were coded by the Medical Dictionary for Regulatory Activities (MedDRA® version 18.0). Subjects who were administered the drug at least once were included in the safety assessment.

Statistical analysis

The sample size was calculated as thirty-two subjects who would demonstrate a bioequivalence based on an intra-subject variability of 26.1% (C_{max}) [9] with a significance level of 0.05. Anticipating a 15% dropout rate, a total of thirty-eight subjects were planned to be enrolled in this study.

A linear mixed effect model including period, sequence, and treatment as the fixed effect, and the subject within the sequence as the random effect was used to compare the exposure of the two salt forms of tenofovir. The 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) of tenofovir disoproxil phosphate to tenofovir disoproxil fumarate for the C_{max}

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and AUCs were calculated for statistical comparison between the two salt forms of tenofovir disoproxil using SAS® (version 9.4, SAS Institute, Cary, NC, USA). The two forms of tenofovir disoproxil were assessed to be bioequivalent if the 90% CIs of the PK parameters were within the conventional bioequivalence range of 0.8–1.25.

RESULTS

Study dispositions and demographics

A total of forty-seven subjects were screened, and nine subjects were excluded from this study due to several reasons (**Fig. 1**). A total of thirty-eight subjects were randomized, and one subject withdrew his consent after the first study period. The thirty-eight subjects were analyzed for safety assessment. A total of thirty-seven subjects completed this study, and they were included in the PK analysis. Overall, for the thirty-eight subjects who enrolled in this study, the mean ± standard deviation (SD) for age, weight, height, and BMI was 28.08 ± 4.37 years, 69.98 ± 6.81 kg, 1.75 ± 0.05 m, and 22.76 ± 1.78 kg/m^2, respectively. Demographics such as age, weight, height and BMI were similar between the two sequence groups (**Table 1**).

PKs

The mean serum concentration-time profile was similar between the two salt forms of tenofovir (**Fig. 2**). The median T_{max} of the two treatment groups was equal to 0.75 hours.

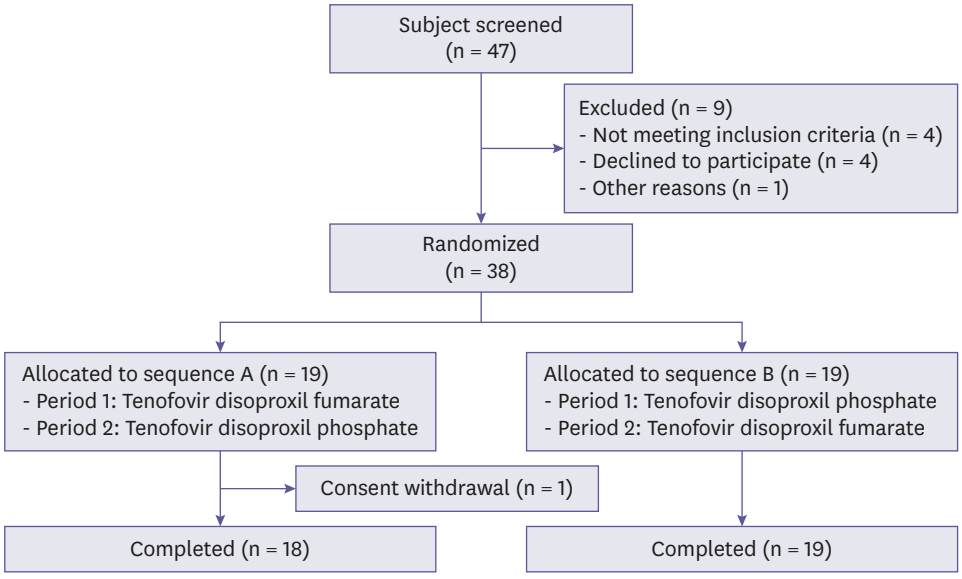

Figure 1. Disposition of subjects.

Table 1. Demographic characteristics of the subjects

Parameters	Sequence A (n = 19)	Sequence B (n = 19)
Age (yr)	27.16 ± 4.02	29.00 ± 4.62
Height (m)	1.75 ± 0.06	1.75 ± 0.05
Weight (kg)	69.34 ± 6.13	70.63 ± 7.54
BMI (kg/m^2)	22.53 ± 1.57	22.99 ± 1.99

Data expressed as arithmetic mean ± standard deviation. BMI was calculated as Weight (kg)/Height (m^2). Sequence A was Tenofovir disoproxil fumarate to Tenofovir disoproxil phosphate. Sequence B was Tenofovir disoproxil phosphate to Tenofovir disoproxil fumarate.
BMI, body mass index.

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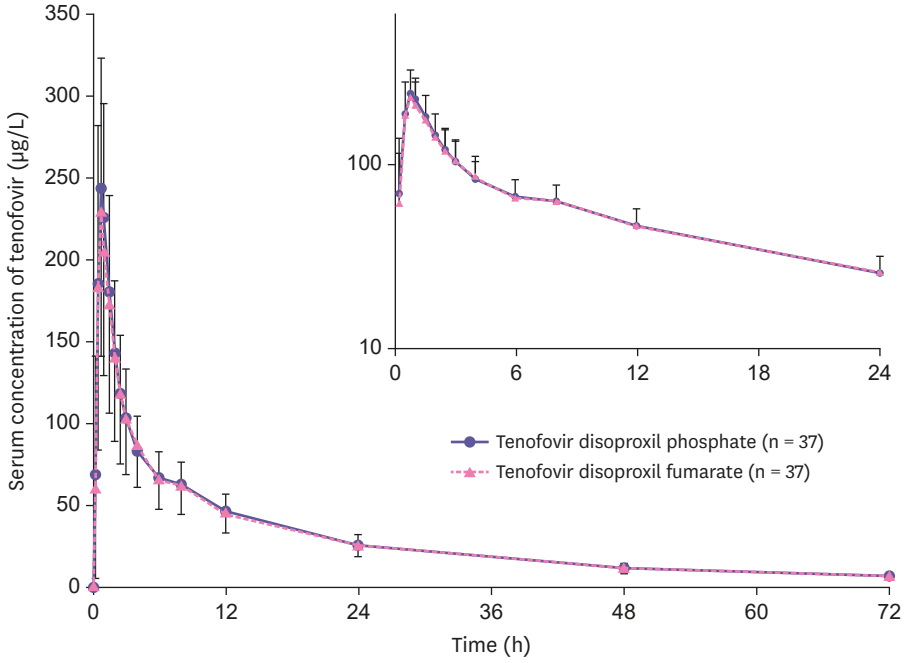

Figure 2. Serum concentration-time profiles for tenofovir after a single administration tenofovir disoproxil phosphate and tenofovir disoproxil fumarate with linear scale. The inset plot shows the profile in semi-log scale.

After reaching the T_{max}, it declined in a biphasic manner (**Fig. 2**). Both tenofovir disoproxil phosphate and tenofovir disoproxil fumarate showed a similar elimination profile with $t_{1/2}$ of about 20 hours (**Table 2**). The GMRs (90% CIs), which is the tenofovir disoproxil phosphate to tenofovir disoproxil fumarate ratio of the C_{max} and AUC_{last}, were 1.0514 (0.9527–1.1603) and 1.0375 (0.9516–1.1311), respectively, and both were within the conventional bioequivalence range of 0.8–1.25.

Safety

Among the thirty-eight subjects, all AEs were mild, and there were no serious AEs. There were no clinically significant changes in the clinical laboratory tests (chemistry, urinalysis, blood coagulation and hematology), AEs, physical examination, 12-lead ECG, and vital signs during this study.

Table 2. Pharmacokinetic parameters of tenofovir disoproxil phosphate (292 mg) and tenofovir disoproxil fumarate (300 mg)

Pharmacokinetic parameters	Tenofovir disoproxil phosphate (n = 37)	Tenofovir disoproxil fumarate (n = 37)	Geometric mean ratio (90% CI)
T_{max} (h)	0.75 [0.25–2.00]	0.75 [0.50–2.50]	-
C_{max} (μg/L)	275.41 ± 77.90	265.41 ± 83.08	1.0514 (0.9527–1.1603)
AUC_{last} (h·μg/L)	2,019.24 ± 553.38	1,982.69 ± 593.32	1.0375 (0.9516–1.1311)
AUC_{inf} (h·μg/L)	2,238.50 ± 584.73	2,207.63 ± 613.99	1.0266 (0.9568–1.1015)
$t_{1/2}$ (h)	20.33 ± 4.17	20.24 ± 4.31	-
CL/F (L/h)	140.02 ± 39.82	152.66 ± 72.34	-
V_z/F (L)	3,956.57 ± 827.02	4,223.37 ± 1,331.52	-

Data expressed as arithmetic mean ± standard deviation except for T_{max} which is expressed median [min–max], '-' indicates data are not shown. Geometric mean ratio calculations of phosphate to fumarate based on log-transformed data.

CI, confidence interval; T_{max}, time of maximum observed concentration; C_{max}, maximum observed concentration; AUC_{last}, area under the serum concentration-time curve to the last quantifiable concentration; AUC_{inf}, area under the serum concentration-time curve from time 0 to infinity; $t_{1/2}$, elimination half-life; CL/F, apparent clearance; V_z/F, apparent volume of distribution.

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Table 3. Adverse drug reactions occurred after a single administration of tenofovir disoproxil phosphate (292 mg) and tenofovir disoproxil fumarate (300 mg)

Adverse events	Tenofovir disoproxil phosphate (n = 38)	Tenofovir disoproxil fumarate (n = 37)	Total (n = 38)
Total	2 (5.26) [3]	2 (5.41) [4]	4 (10.53) [7]
Dyspepsia	0 (0.00) [0]	1 (2.70) [1]	1 (2.63) [1]
Diarrhoea	1 (2.63) [1]	0 (0.00) [0]	1 (2.63) [1]
Headache	1 (2.63) [1]	2 (5.41) [2]	3 (7.89) [3]
Ocular discomfort	0 (0.00) [0]	1 (2.70) [1]	1 (2.63) [1]
Myalgia	1 (2.63) [1]	0 (0.00) [0]	1 (2.63) [1]

Percentages are based on the subjects within each treatment group. Data are presented as number (%) [case].

There were four subjects (10.53%) with seven cases of adverse drug reactions (ADRs). After the administration of tenofovir disoproxil phosphate, two subjects (5.41%) reported four cases of ADRs which were dyspepsia, headache, and ocular discomfort. Similarly, two subjects (5.26%) reported three cases of ADRs after the administration of tenofovir disoproxil fumarate such as diarrhoea, headache, and myalgia (**Table 3**). Headache and diarrhea are well-known AEs from a previous study [9]. All the subjects recovered from the AEs without sequelae during the study period.

DISCUSSION

Comparing between tenofovir disoproxil phosphate (300 mg) and tenofovir disoproxil fumarate (292 mg), we evaluated the PKs and safety after a single oral administration, and it showed similar PK profiles in healthy volunteers. The GMRs and their 90% CIs for both the C_{max} and AUCs (AUC_{last} and AUC_{inf}) between the two salt forms of tenofovir disoproxil were within the conventional bioequivalence range of 0.8 to 1.25. All the AEs were mild, and the subjects recovered without sequelae. Tenofovir disoproxil phosphate can be developed as an alternative to tenofovir disoproxil fumarate based on these results. It is expected that the new salt form of tenofovir disoproxil can be provided to HIV or HBV patients, which can improve the access to the medication, and the clinical benefits from a long-term perspective [20].

The study design including the number of subjects, sampling points, and washout periods was appropriate in this study. According to the results of this study, the maximum intra-subject variability of the PK parameters was calculated as 25.4%. Therefore, for the sample size, the number of subjects considering this intra-subject variability was calculated to be thirty-six subjects with a statistical significance 0.05 [24]. The calculated sample size was almost the same as the number of subjects obtained using the intra CV (%) in a previous study [9]. The number of subjects was appropriate which was enough to compare the PKs between tenofovir disoproxil fumarate and tenofovir disoproxil phosphate. According to the results of this study, the half-life of the tenofovir disoproxil phosphate was approximately 20 hours. The blood samples were collected up to 72 hours, and the wash-out period was 7 days, all of which were over three times the half-life recommended by guidance [25].

There were approximately twofold to threefold differences between some subjects comparing the tenofovir C_{max} and AUC_{last} as shown in **Fig. 3**. Tenofovir highly interacts with the apical proximal-tubule efflux transporters [26]. It can be assumed that individual variances are partly due to the variability in the expression of multi-drug resistance protein (MRP), which has a higher ability to transport tenofovir compared to p-glycoprotein (P-gp) [26]. Although there may have been differences in MRP expression between the individuals, considering

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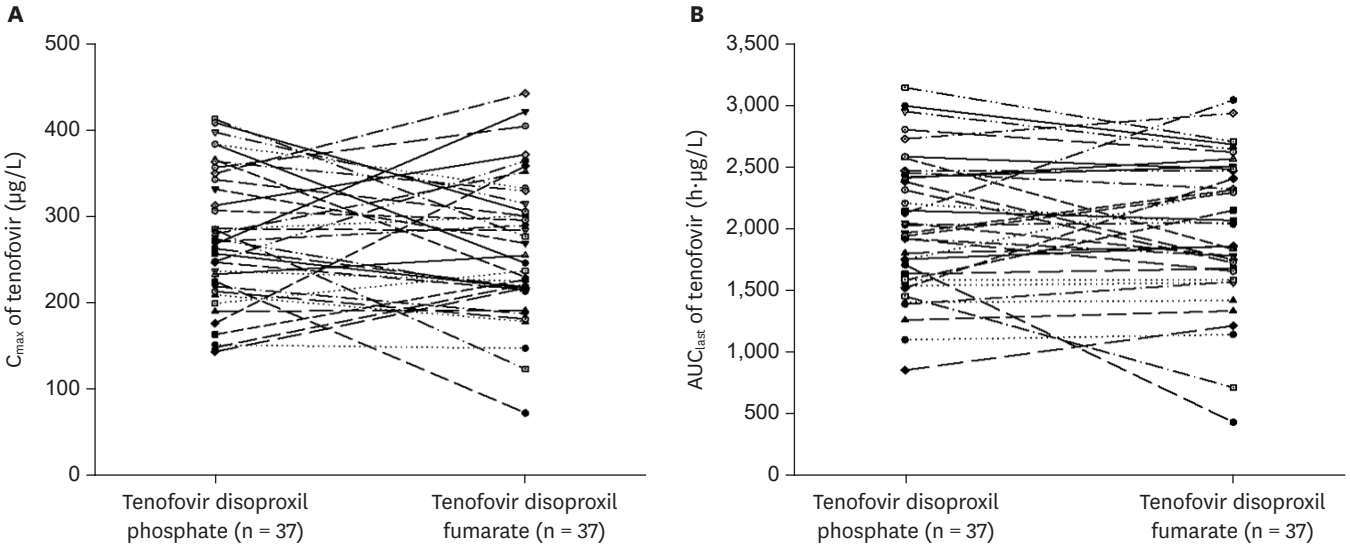

Figure 3. Individual (A) C_{max} and (B) AUC_{last} of tenofovir after a single administration of tenofovir disoproxil phosphate and tenofovir disoproxil fumarate.
C_{max}, maximum observed concentration; AUC_{last}, area under the serum concentration-time curve to the last quantifiable concentration.

the two-way crossover design and well controlled subject conditions of this study, these individual differences did not act as a confounding factor in the study results.

In conclusion, this study demonstrated that tenofovir disoproxil phosphate showed similar PK characteristics compared to tenofovir disoproxil fumarate. Additionally, both tenofovir salt forms were tolerable.

REFERENCES

1. Centers for Disease Control and Prevention. National progress report 2025 goal: reduce reported rate of hepatitis B-related deaths by ≥20%. https://www.cdc.gov/hepatitis/policy/NationalProgressReport-HepB-ReduceDeaths.htm. Accessed January 2021.
2. Centers for Disease Control and Prevention. Diagnose and treat to save lives: decreasing deaths among people with HIV. https://www.cdc.gov/hiv/statistics/deaths/index.html. Accessed January 2021.
3. HIV.gov. The global HIV/AIDS epidemic. https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics. Accessed January 2021.
4. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015.
5. Kourtis AP, Bulterys M, Hu DJ, Jamieson DJ. HIV-HBV coinfection--a global challenge. N Engl J Med 2012;366:1749-1752.
PUBMED | CROSSREF
6. Soriano V, Barreiro P, Cachay E, Kottilil S, Fernandez-Montero JV, de Mendoza C. Advances in hepatitis B therapeutics. Ther Adv Infect Dis 2020;7:2049936120965027.
PUBMED | CROSSREF
7. Asselah T, Loureiro D, Boyer N, Mansouri A. Targets and future direct-acting antiviral approaches to achieve hepatitis B virus cure. Lancet Gastroenterol Hepatol 2019;4:883-892.
PUBMED | CROSSREF
8. Soriano V, Barreiro P, Benitez L, Peña JM, de Mendoza C. New antivirals for the treatment of chronic hepatitis B. Expert Opin Investig Drugs 2017;26:843-851.
PUBMED | CROSSREF
9. Kearney BP, Flaherty JF, Shah J. Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. Clin Pharmacokinet 2004;43:595-612.
PUBMED | CROSSREF

10. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. Clin Infect Dis 2005;40:1194-1198.
PUBMED | CROSSREF

11. Squires K, Pozniak AL, Pierone G Jr, Steinhart CR, Berger D, Bellos NC, et al. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. Ann Intern Med 2003;139:313-320.
PUBMED | CROSSREF

12. Robbins BL, Srinivas RV, Kim C, Bischofberger N, Fridland A. Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the acyclic nucleoside phosphonate 9-R-(2-phosphonomethoxypropyl)adenine (PMPA), Bis(isopropyloxymethylcarbonyl)PMPA. Antimicrob Agents Chemother 1998;42:612-617.
PUBMED | CROSSREF

13. Tsai CC, Follis KE, Sabo A, Beck TW, Grant RF, Bischofberger N, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. Science 1995;270:1197-1199.
PUBMED | CROSSREF

14. Nekvindová J, Masek V, Veinlichová A, Anzenbacherová E, Anzenbacher P, Zídek Z, et al. Inhibition of human liver microsomal cytochrome P450 activities by adefovir and tenofovir. Xenobiotica 2006;36:1165-1177.
PUBMED | CROSSREF

15. Gilead Science. Clinical pharmacology and biopharmaceutics reviews. Foster City, CA: Gilead Science; 2011.

16. Watkins ME, Wring S, Randolph R, Park S, Powell K, Lutz L, et al. Development of a novel formulation that improves preclinical bioavailability of tenofovir disoproxil fumarate. J Pharm Sci 2017;106:906-919.
PUBMED | CROSSREF

17. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Veterinary Medicine. Bioanalytical method validation guidance for industry. Washington, D.C.: U.S. Department of Health and Human Services; 2001.

18. Cho JH, Choi HG. Development of novel tenofovir disoproxil phosphate salt with stability enhancement and bioequivalence to the commercial tenofovir disoproxil fumarate salt in rats and beagle dogs. Int J Pharm 2020;576:118957.
PUBMED | CROSSREF

19. Serajuddin AT. Salt formation to improve drug solubility. Adv Drug Deliv Rev 2007;59:603-616.
PUBMED | CROSSREF

20. Sheppard A. Generic medicines: essential contributors to the long-term health of society. London: IMS Health; 2010, 16.

21. Kim YK, Choi MJ, Oh TY, Yu KS, Lee S. A comparative pharmacokinetic and tolerability analysis of the novel orotic acid salt form of tenofovir disoproxil and the fumaric acid salt form in healthy subjects. Drug Des Devel Ther 2017;11:3171-3177.
PUBMED | CROSSREF

22. Association WMWorld Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-2194.
PUBMED | CROSSREF

23. Branch SK. Guidelines from the international conference on harmonisation (ICH). J Pharm Biomed Anal 2005;38:798-805.
PUBMED | CROSSREF

24. Chow SC, Wang H. On sample size calculation in bioequivalence trials. J Pharmacokinet Pharmacodyn 2001;28:155-169.
PUBMED | CROSSREF

25. Ministry of Food and Drug Safety (KR). Guidance document for bioequivalence studies updated in 2020. Cheongju: Ministry of Food and Drug Safety; 2020.

26. Ray AS, Cihlar T, Robinson KL, Tong L, Vela JE, Fuller MD, et al. Mechanism of active renal tubular efflux of tenofovir. Antimicrob Agents Chemother 2006;50:3297-3304.
PUBMED | CROSSREF