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Short Communication

Pharmacokinetics and dose-range finding toxicity of a novel anti-HIV active integrase inhibitor

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ABSTRACT

Integration of viral DNA into human chromosomal DNA catalyzed by HIV integrase represents the "point of no return" in HIV infection. For this reason, HIV integrase is considered a crucial target in the development of new anti-HIV therapeutic agents. We have discovered a novel HIV integrase inhibitor **1**, that exhibits potent antiviral activity and a favorable metabolism profile. This paper reports on the pharmacokinetics and toxicokinetics of compound **1** and the relevance of these findings with respect to further development of this integrase-targeted antiviral agent. Oral administration of compound **1** in Sprague Dawley rats revealed rapid absorption. Drug exposure increased with increasing drug concentration, indicative of appropriate dose-dependence correlation. Compound **1** exhibited suitable plasma half-life, extensive extravascular distribution and acceptable bioavailability. Toxicity studies revealed no compound-related clinical pathology findings. There were no changes in erythropoietic, white blood cell or platelet parameters in male and female rats. There was no test-article related change in other clinical chemistry parameters. In addition, there were no detectable levels of bilirubin in the urine and there were no treatment-related effects on urobilinogen or other urinalysis parameters. The preclinical studies also revealed that the no observed adverse effect level and the maximum tolerated dose were both high (>500 mg/kg/day). The broad and significant antiviral activity and favorable metabolism profile of this integrase inhibitor, when combined with the *in vivo* pharmacokinetic and toxicokinetic data and their pharmacological relevance, provide compelling and critical support for its further development as an anti-HIV therapeutic agent.

While progress in the global therapeutic response to HIV/AIDS has been demonstrable, much still remains to be done in many worldwide communities (Trono et al., 2010; UNAIDS Global Report, 2013; Richman et al., 2009; Este and Cihlar, 2010). HIV integrase (Mr 32,000) is a significant target in the discovery and development of anti-HIV therapeutic agents because virus-induced helper T-cell death is suggested as being triggered by viral integration (Cooper et al., 2013). This viral enzyme is essential for HIV replication (Frankel and Young, 1998; Krishnan and Engelman, 2012). Integration of HIV DNA into the host genome requires several steps, including the strand transfer of processed viral cDNA ends into host chromosomal DNA (Frankel and Young, 1998; Haren et al., 1999; Hare et al., 2010).

Research on integrase as a HIV/AIDS therapeutic target has produced three FDA-approved drugs, raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) (Sato et al., 2006, 2009; Evering and Markowitz, 2007; Shimura et al., 2008; Summa et al., 2008; Min et al., 2010, 2011; Katlama and Murphy, 2012). However, there is extensive cross-resistance between RAL and EVG (McColl et al., 2007; Shimura et al., 2008; Goethals et al., 2008). EVG has shown selection of N155H, Q148H/R/K, and G140A/C/S mutations, which are also typical for RAL. Major RAL-associated mutations not selective for EVG were Y143C/R/H (Metifiot et al., 2011). EVG exhibits other resistance mutations like T66I and T66R (Goethals et al., 2008; Shimura et al., 2008; Dicker et al., 2008). Accessory mutations of T66I have not been associated with RAL (McColl and Chen, 2010). DTG demonstrated efficacy against most viral clones that were resistant to RAL and EVG (Canducci et al., 2011; Katlama and Murphy, 2012). Viruses that carry E138K, G140S, or Q148H mutations were not as susceptible to DTG. Integrase mutations T124S/S153F, T124A/S153Y, L101I/T124A/S153F, and S153Y persisted throughout serial passaging of DTG (Katlama and Murphy, 2012; Quashie et al., 2012).

Our search for a HIV-1 integrase inhibitor (Nair and Chi, 2007; Nair et al., 2006; Pommier et al., 2005; Taktakishvili et al., 2000)

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that would possess significant anti-HIV efficacy and a favorable profile with respect to resistance and drug–drug interactions (Dye and Williams, 2010; Russell et al., 2010), led us to structure–activity studies on inhibitors of the strand transfer step of HIV-1 integrase (Seo et al., 2011). A novel anti-HIV active integrase inhibitor **1** emerged from these studies (Fig. 1). Compound **1** displayed significant *in vitro* activity against a broad set of HIV-1 subtypes (Keele et al., 2006), as well as against HIV-2 and SIV, and with very low cell cytotoxicity (Okello et al., 2013a). In addition, this compound exhibited a positive drug susceptibility profile against some key clinically-relevant integrase mutations (Fig. 2).

Preclinical pharmacokinetic and toxicokinetic parameters in rats are critical in antiviral drug development because they provide useful initial *in vivo* information on drug passage and disposition. Of particular significance are data associated with drug exposure, systemic distribution and clearance, drug half-life, percent of drug that reaches circulation, toxic side effects, and initial information on dosing (Szczech, 1996). This communication focuses on preclinical studies of integrase inhibitor **1**, the statistical analyses and interpretation of the resulting data, and an insight into the antiviral significance of these findings.

Pharmacokinetics studies (Methods in Supplementary Section) involving iv administration of compound **1** in Sprague Dawley rats at 10 mg/kg dose showed that the mean plasma concentration at the first time-point (C_p) to be 6,403 ng/ml, with a corresponding AUC_{inf} of 3,737 h ng/ml (Table 1). In pharmacological terms, the C_p data show that the drug concentration is about 150-fold of the average EC_{90} (83 nM) for antiviral activity against main Group M subtypes A, B, C and F. Even at the $t_{1/2}$ (6.1 h), the drug concentration is significantly higher than the EC_{90}.

In the po dose groups, the maximal plasma concentration (C_{max}) in Sprague Dawley (SD) rats was rapidly reached (Fig. 3). Plasma AUC increased significantly over the entire dose range with increasing drug concentration, suggesting that neither absorption nor first-pass metabolism appeared to be saturable (Table 1). The plasma drug concentration after 8 h with a po dose of 30 mg/kg was still considerably higher than the average EC_{90} of compound **1** against key HIV subtypes A, B, C and F. The $t_{1/2}$ ranged from 3.2 to 4.6 h. By comparison, the $t_{1/2}$ for raltegravir in rats at po doses of 40–120 mg/kg was $\leqslant$1.6 h (Merck, 2007). The plasma mean residence time (MRT) for compound **1** ranged from 4.1 to 7.3 h in the po dose groups with a clearance rate (Cl) of 2675 ml/h/kg. The Cl rate was close to that observed for raltegravir of 2298 ml/h/kg in rats (Laufer et al., 2009). The apparent volume of distribution (V) of compound **1** was 12.4 L/kg for the 30 mg/kg po dose and was higher than the data for raltegravir (Merck, 2007). Oral bioavailability (F) for the 30 mg/kg dose was 19.2%, which is lower than that observed for raltegravir 32% (Merck, 2007) and elvitegravir (30–35%) (Gilead, 2011). With respect to dose conversion, the human dose equivalent (CDER, 2005), of the 30 mg/kg po dose of

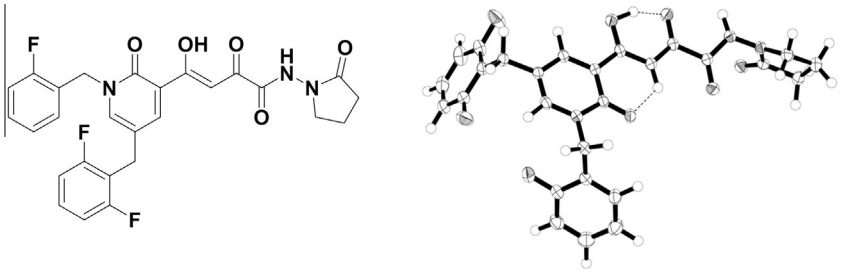

Fig. 1. Integrase inhibitor **1** (left) and its X-ray crystallographic structure (right) depicting its preferred tautomeric form, conformation and intramolecular hydrogen bonding (Bacsa et al., 2013; Okello et al., 2013b).

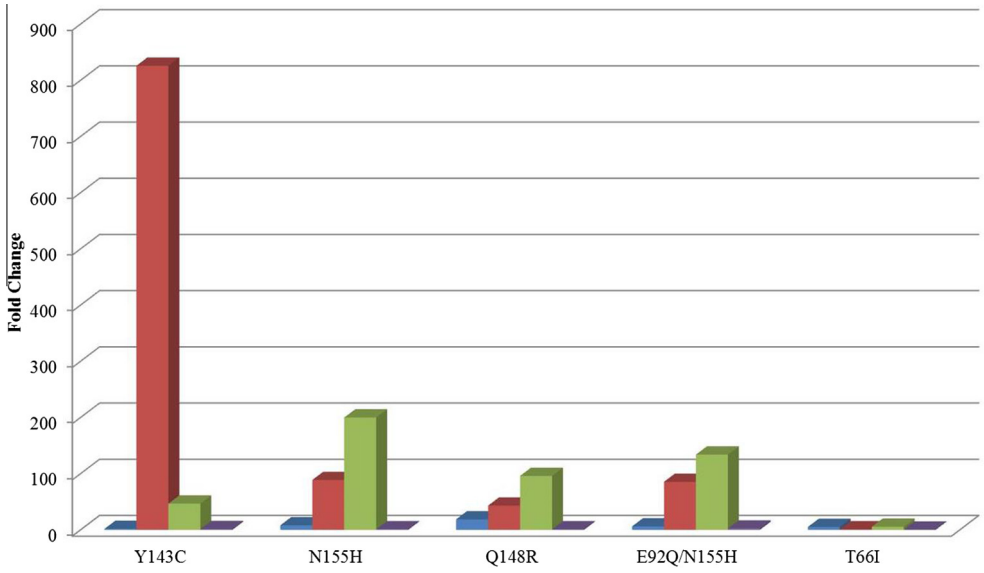

Fig. 2. Fold change, relative to wild type, in drug susceptibility in MT-4 cells against resistant viruses with some key clinical mutations in integrase: compound **1** – blue; raltegravir – red; elvitegravir – green; dolutegravir – purple. The EC_{50} against Wild-Type HIV-1 NL4-3 were 63.5, 6.54, 0.82 nM for compound **1**, raltegravir and elvitegravir, respectively (Okello et al., 2013a) and 0.71 nM for dolutegravir (Kobayashi et al., 2011). CPE inhibition assays in MT-4 cells (Adachi et al., 1986) were used to generate the antiviral data.

Table 1
Pharmacokinetic parameters of compound **1** after iv and po administration in Sprague Dawley rats.

Dose (mg/kg)	Route	C_p[a] or C_{max} (ng/ml)	T_{max} (h)	AUC_{last} (h ng/ml)	AUC_{inf} (h ng/ml)	$t_{1/2}$ (hr)	MRT_{last} (h)	Cl (ml/h/kg)	V (L/kg)	F (%)
10	i.v	6403.3 (837.6)	0.08 (0)	3645.4 (713.8)	3737 (721.1)	6.1 (2.1)	2.2 (0.3)	2751.2 (586.1)	22.9 (4.4)	NA[b]
30	po	463.7 (60.7)	1 (0.9)	2073.8 (778.8)	2148.2 (765.2)	3.2 (1.1)	4.1 (0.9)	2675.9 (0)	12.4 (4.3)	19.2 (6.9)
100	po	416.7 (118)	2.7 (1.2)	4273.2 (279.9)	4442.2 (150.5)	4.5 (1.4)	7.3 (1.7)	2675.9 (0)	17.5 (5.5)	11.9 (0.4)
300	po	958 (187.3)	5.33 (2.3)	7809.2 (1969.8)	8062.9 (1842.4)	4.6 (1.7)	6.7 (1.1)	2675.9 (0)	17.7 (6.4)	7.2 (1.6)

Data are given as the mean with SD in brackets from three animal experiments in each case.
[a] C_p for iv group; C_{max} for po groups.
[b] NA – not applicable for iv route.

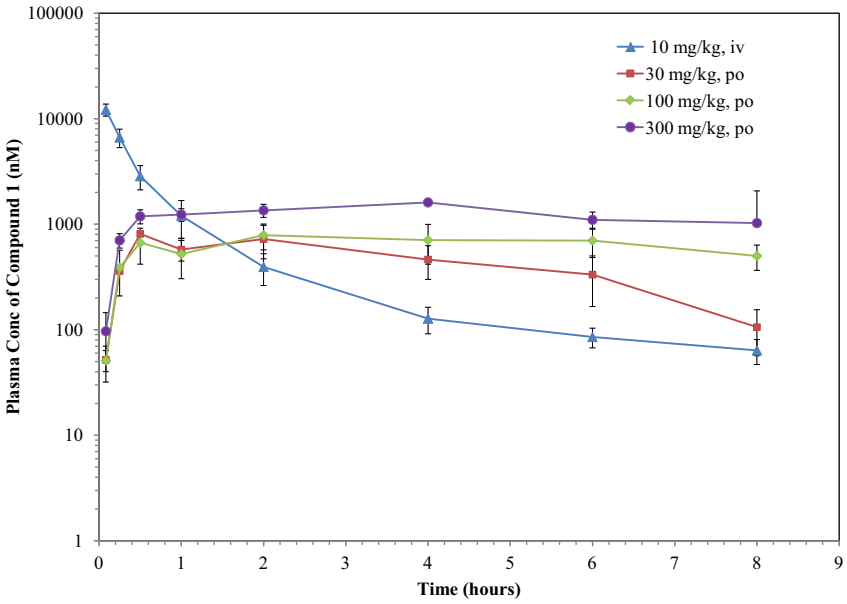

Fig. 3. Plasma concentration of compound **1** in male Sprague Dawley rats after iv and po dose administration of 10, 30, 100 and 300 mg/kg after a single dose in each case. The dosing volume was 5 ml/kg for iv and 10 ml/kg for po.

compound **1** from rats to humans, is 294 mg for a single dose for a human weighing 60 kg.

The objective of the dose-range finding toxicity study was to determine toxic side effects, to identify potential target organs of toxicity, and to determine a no observed adverse effect level (NOAEL) of orally administered compound **1** to adult male and female SD rats (Methods in Supplementary Section). The study was intended to provide preliminary information on the suitability of a proposed safe human dosing. All rats survived until scheduled necropsies. There were no treatment-related effects on body weight at any dose levels tested. The conclusions from these studies were that there were no compound-related clinical pathology findings. There were no statistically significant changes ($p \leqslant 0.01$) in erythropoietic, white blood cell or platelet parameters in male and female rats (Supplementary Tables S1 and S2).

With respect to clinical chemistry parameters (Supplementary Tables S3 and S4), there was no test-article related noteworthy change in these parameters ($p \leqslant 0.01$). Significantly, there were no detectable levels of bilirubin in the urine. Also, there were no treatment-related effects on urobilinogen or other urinalysis parameters (Supplementary Tables S3 and S4). This observation is important because some approved HIV-1 inhibitors such as atazanavir or indinavir affect bilirubin levels in human subjects by inhibiting the bilirubin glucuronidation isoform, UGT1A1. This inhibition leads to the development of hyperbilirubinemia (Michaud et al., 2012; Zucker et al., 2001; Goldsmith and Perry, 2003). Unconjugated bilirubin is highly bound to albumin and can lead to toxicities if the bilirubin/albumin molar ratio exceeds 1:1 (Zhang et al., 2005). We had noted in our earlier studies the lack of UGT substrate activity of compound **1** (Okello et al., 2013a). In contrast, raltegravir, elvitegravir and dolutegravir are substrates and depend on UGTs for clearance. Combination therapies involving drugs such as atazanavir or indinavir with these approved integrase inhibitors could prove challenging as the inhibition of UGT1A1 by atazanavir or indinavir could lead to accumulation of these drugs with potential toxic drug plasma levels, and would also produce low clearance of bilirubin with accompanying consequences.

Oral administration of compound **1** for 7 consecutive days at doses up to 500 mg/kg/day was well tolerated in rats and produced no adverse treatment-related findings. For instance, the liver function tests to determine the levels of certain marker enzymes, such as ALT and AST, indicated no treatment-related hepatotoxicity (Supplementary Tables S3 and S4). Interestingly, all FDA-approved NRTIs, NNRTIs and PIs are associated with hepatotoxicity (Carr et al., 2001; Sharma, 2011). The NOAEL of compound **1** was determined to be greater than 500 mg/kg/day, which provides a significant exposure margin in antiviral therapeutic applications. Dolutegravir had an NOAEL in adult rats of 50 mg/kg/day (Rhodes et al., 2012) and raltegravir showed an NOAEL of 120 mg/kg/day (Merck, 2007), although the dosage and study durations were somewhat different from our studies. The maximum tolerated dose (MTD) for compound **1** is also considered to be greater than 500 mg/kg/day.

The results described in this report provide support that our novel, anti-HIV active integrase inhibitor **1** has additional

compelling properties for its further development. Pharmacokinetic studies in rats revealed rapid absorption, a suitable plasma half-life and acceptable bioavailability. Drug exposure increased significantly with increasing drug concentration, indicative of appropriate dose-dependence correlation. The compound exhibited significant extravascular tissue distribution. Serum and urine bilirubin and urobilinogen levels were not affected. There were no adverse treatment-related findings from clinical pathology or clinical chemistry parameters. The preclinical studies also revealed that the NOAEL and MTD parameters were both convincingly high, providing further evidence that there is low potential for toxicity of this antiviral compound with oral administration. Finally, the broad and significant *in vitro* antiviral activity and favorable metabolism profile of this integrase inhibitor, when combined with the *in vivo* pharmacokinetic and toxicokinetic data and their statistical analysis and pharmacological relevance, provide compelling and critical support for further development of this compound as anti-HIV therapeutic agent.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.antiviral.2014.05.001.

References

Adachi, A., Gendelman, H.E., Koenig, S., Folks, T., Willey, R., Rabson, A., Martin, M.A., 1986. Production of acquired immunodeficiency syndrome-associated retrovirus in human and nonhuman cells transfected with an infectious molecular clone. J. Virol. 59, 284–291.

Bacsa, J., Okello, M., Singh, P., Nair, V., 2013. Solid-state tautomeric structure and invariom refinement of a novel and potent HIV integrase inhibitor. Acta Crystallogr. C 69, 285–288.

Canducci, F., Ceresola, E.R., Boeri, E., Spagnuolo, V., Cossarini, F., Castagna, A., Lazzarin, A., Clementi, M., 2011. Cross-resistance profile of the novel integrase inhibitor dolutegravir (S/GSK1349572) using clonal viral variants selected in patients failing raltegravir. J. Infect. Dis. 204, 1811–1815.

Carr, A., Morey, A., Mallon, P., Williams, D., Thorburn, D.R., 2001. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidaemia. Lancet 357, 1412–1414.

Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA) and U.S. Health and Human Services (HHS), 2005. Guidance for Industry "Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers," Report, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078932.pdf> (accessed on 06/03/2013).

Cooper, A., Garcia, M., Petrovas, C., Yamamoto, T., Koup, R.A., Nabel, G.J., 2013. HIV-1 causes CD4 cell death through DNA-dependent protein kinase during viral integration. Nature, doi:10. 1038/nature12274.

Dicker, I.B., Terry, B., Lin, Z.Y., Li, Z.F., Bollini, S., Samanta, H.K., Gali, V., Walker, M.A., Krystal, M.R., 2008. Biochemical analysis of HIV-1 integrase variants resistant to strand transfer inhibitors. J. Biol. Chem. 283, 23599–23609.

Dye, C., Williams, B.G., 2010. The population dynamics and control of tuberculosis. Science 328, 856–861.

Este, J.A., Cihlar, T., 2010. Current status and challenges of antiretroviral research and therapy. Antivir. Res. 85, 25–33.

Evering, T.H., Markowitz, M., 2007. Raltegravir (MK-0518): an integrase inhibitor for the treatment of HIV-1. Drug Today 43, 865–877.

Frankel, A.D., Young, J.A.T., 1998. HIV-1: fifteen proteins and an RNA. Annu. Rev. Biochem. 67, 1–25.

Gilead Sciences, Inc., 2011. FDA Pharmacology/Toxicology NDA Review and Evaluation. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF. (NDA 203-100) October 27. (Reference ID: 3152844).

Goethals, O., Clayton, R., Van Ginderen, M., Vereycken, I., Wagemans, E., Geluykens, P., Dockx, K., Strijbos, R., Smits, V., Vos, A., Meersseman, G., Jochmans, D., Vermeire, K., Schols, D., Hallenberger, S., Hertogs, K., 2008. Resistance mutations in human immunodeficiency virus Type 1 integrase selected with elvitegravir confer reduced susceptibility to a wide range of integrase inhibitors. J. Virol. 82, 10366–10374.

Goldsmith, D.R., Perry, C.M., 2003. Atazanavir. Drugs 63, 1679–1693.

Hare, S., Gupta, S.S., Valkov, E., Engelman, A., Cherepanov, P., 2010. Retroviral intasome assembly and inhibition of DNA strand transfer. Nature 464, 232–236.

Haren, L., Ton-Hoang, B., Chandler, M., 1999. Integrating DNA: transposases and retroviral integrases. Annu. Rev. Microbiol. 53, 245–281.

Katlama, C., Murphy, R., 2012. Dolutegravir for the treatment of HIV. Expert Opin. Invest. Drugs 21, 523–530.

Keele, B.F., Van Heuverswyn, F., Li, Y.Y., Bailes, E., Takehisa, J., Santiago, M.L., Bibollet-Ruche, F., Chen, Y.L., Wain, L.V., Liegeois, F., Loul, S., Ngole, E.M., Bienvenue, Y., Delaporte, E., Brookfield, J.F.Y., Sharp, P.M., Shaw, G.M., Peeters, M., Hahn, B.H., 2006. Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. Science 313, 523–526.

Kobayashi, M., Yoshinaga, T., Seki, T., Wakasa-Morimoto, C., Brown, K.W., Ferris, R., Foster, S.A., Hazen, R.J., Miki, S., Suyama-Kagitani, A., Kawauchi-Miki, S., Taishi, T., Kawasuji, T., Johns, B.A., Underwood, M.R., Garvey, E.P., Sato, A., Fujiwara, T., 2011. *In vitro* antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob. Agents Chemother. 55, 813–821.

Krishnan, L., Engelman, A., 2012. Retroviral integrase proteins and HIV-1 DNA integration. J. Biol. Chem. 287, 40858–40866.

Laufer, R., Paz, O.G., Di Marco, A., Bonelli, F., Monteagudo, E., Summa, V., Rowley, M., 2009. Quantitative prediction of human clearance guiding the development of raltegravir (MK-0518, Isentress) and related HIV integrase inhibitors. Drug Metab. Dispos. 37, 873–883.

McColl, D.J., Chen, X.W., 2010. Strand transfer inhibitors of HIV-1 integrase: bringing IN new era of antiretroviral therapy. Antivir. Res. 85, 101–118.

McColl, D.J., Fransen, S., Gupta, S., Parkin, N., Margot, N., Chuck, S., Cheng, A.K., Miller, M.D., 2007. Resistance and cross-resistance to first generation integrase inhibitors: insights from a Phase II study of elvitegravir (GS-9137). Antivir. Ther. 12, S11–S11.

Merck Research Laboratories. Briefing Document, 2007. FDA Antiviral Drug Advisory Committee Meeting. ISENTRESS (Raltegravir) for Treatment of HIV (NDA 22-145). September 5, <http://www.fda.gov/ohrms/dockets/ac/07>.

Metifiot, M., Vandegraaff, N., Maddali, K., Naumova, A., Zhang, X.M., Rhodes, D., Marchand, C., Pommier, Y., 2011. Elvitegravir overcomes resistance to raltegravir induced by integrase mutation Y143. AIDS 25, 1175–1178.

Michaud, V., Bar-Magen, T., Turgeon, J., Flockhart, D., Desta, Z., Wainberg, M.A., 2012. The dual role of pharmacogenetics in HIV treatment: mutations and polymorphisms regulating antiretroviral drug resistance and disposition. Pharmacol. Rev. 64, 803–833.

Min, S., Sloan, L., DeJesus, E., Hawkins, T., McCurdy, L., Song, I., Stroder, R., Chen, S., Underwood, M., Fujiwara, T., Piscitelli, S., Lalezari, J., 2011. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. AIDS 25, 1737–1745.

Min, S., Song, I., Borland, J., Chen, S.G., Lou, Y., Fujiwara, T., Piscitelli, S.C., 2010. Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers. Antimicrob. Agents Chemother. 54, 254–258.

Nair, V., Chi, G., 2007. HIV integrase inhibitors as therapeutic agents in AIDS. Rev. Med. Virol. 17, 277–295.

Nair, V., Chi, G., Ptak, R., Neamati, N., 2006. HIV integrase inhibitors with nucleobase scaffolds: discovery of a highly potent anti-HIV agent. J. Med. Chem. 49, 445–447.

Okello, M.O., Mishra, S., Nishonov, M., Mankowski, M.K., Russell, J.D., Wei, J.Y., Hogan, P.A., Ptak, R.G., Nair, V., 2013a. A novel anti-HIV active integrase inhibitor with a favorable in vitro cytochrome P450 and uridine 5′-diphosphoglucuronosyltransferase metabolism profile. Antivir. Res. 98, 365–372.

Okello, M., Nishonov, M., Singh, P., Mishra, S., Mangu, N., Seo, B., Gund, M., Nair, V., 2013b. Approaches to the synthesis of a novel, anti-HIV active integrase inhibitor. Org. Biomol. Chem. 11, 7852–7858.

Pommier, Y., Johnson, A.A., Marchand, C., 2005. Integrase inhibitors to treat HIV/AIDS. Nat. Rev. Drug Discov. 4, 236–248.

Quashie, P.K., Mesplede, T., Han, Y.S., Oliveira, M., Singhroy, D.N., Fujiwara, T., Underwood, M.R., Wainberg, M.A., 2012. Characterization of the R263K mutation in HIV-1 integrase that confers low-level resistance to the second-generation integrase strand transfer inhibitor dolutegravir. J. Virol. 86, 2696–2705.

Rhodes, M., Laffan, S., Genell, C., Gower, J., Maier, C., Fukushima, T., Nichols, G., Bassiri, A.E., 2012. Assessing a theoretical Risk of dolutegravir-induced developmental immunotoxicity in juvenile rats. Toxicol. Sci. 130, 70–81.

Richman, D.D., Margolis, D.M., Delaney, M., Greene, W.C., Hazuda, D., Pomerantz, R.J., 2009. The challenge of finding a cure for HIV infection. Science 323, 1304–1307.

Russell, D.G., Barry, C.E., Flynn, J.L., 2010. Tuberculosis: what we don't know can, and does, hurt us. Science 328, 852–856.

Sato, M., Kawakami, H., Motomura, T., Aramaki, H., Matsuda, T., Yamashita, M., Ito, Y., Matsuzaki, Y., Yamataka, K., Ikeda, S., Shinkai, H., 2009. Quinolone carboxylic

acids as a novel monoketo acid class of human immunodeficiency virus Type 1 integrase inhibitors. J. Med. Chem. 52, 4869–4882.
Sato, M., Motomura, T., Aramaki, H., Matsuda, T., Yamashita, M., Ito, Y., Kawakami, H., Matsuzaki, Y., Watanabe, W., Yamataka, K., Ikeda, S., Kodama, E., Matsuoka, M., Shinkai, H., 2006. Novel HIV-1 integrase inhibitors derived from quinolone antibiotics. J. Med. Chem. 49, 1506–1508.
Seo, B.I., Uchil, V.R., Okello, M., Mishra, S., Ma, X.H., Nishonov, M., Shu, Q.N., Chi, G.C., Nair, V., 2011. Discovery of a potent HIV integrase inhibitor that leads to a prodrug with significant anti-HIV activity. ACS Med. Chem. Lett. 2, 877–881.
Sharma, B., 2011. Anti-HIV-1 drug toxicity and management strategies. Neurobehav. HIV Med. 3, 27–40.
Shimura, K., Kodama, E., Sakagami, Y., Matsuzaki, Y., Watanabe, W., Yamataka, K., Watanabe, Y., Ohata, Y., Doi, S., Sato, M., Kano, M., Ikeda, S., Matsuoka, M., 2008. Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). J. Virol. 82, 764–774.
Summa, V., Petrocchi, A., Bonelli, F., Crescenzi, B., Donghi, M., Ferrara, M., Fiore, F., Gardelli, C., Paz, O.G., Hazuda, D.J., Jones, P., Kinzel, O., Laufer, R., Monteagudo, E., Muraglia, E., Nizi, E., Orvieto, F., Pace, P., Pescatore, G., Scarpelli, R., Stillmock, K., Witmer, M.V., Rowley, M., 2008. Discovery of raltegravir, a potent, selective orally bioavailable HIV-integrase inhibitor for the treatment of HIV-AIDS infection. J. Med. Chem. 51, 5843–5855.
Szczech, G.M., 1996. Preclinical development of antiviral drugs. Clin. Infect. Dis. 22, 355–360.
Taktakishvili, M., Neamati, N., Pommier, Y., Pal, S., Nair, V., 2000. Recognition and inhibition of HIV integrase by novel dinucleotides. J. Am. Chem. Soc. 122, 5671–5677.
Trono, D., Van Lint, C., Rouzioux, C., Verdin, E., Barre-Sinoussi, F., Chun, T.W., Chomont, N., 2010. HIV persistence and the prospect of long-term drug-free remissions for HIV-infected individuals. Science 329, 174–180.
UNAIDS 2013 Global report: UNAIDS report on the global AIDS epidemic. <http://www.unaids.org/en/resources/campaigns/globalreport2013/index.html>.
Zhang, D.L., Chando, T.J., Everett, D.W., Patten, C.J., Dehal, S.S., Humphreys, W.G., 2005. In vitro inhibition of UDP glucuronosyltransferases by atazanavir and other HIV protease inhibitors and the relationship of this property to in vivo bilirubin glucuronidation. Drug Metab. Dispos. 33, 1729–1739.
Zucker, S.D., Qin, X.F., Rouster, S.D., Yu, F., Green, R.M., Keshavan, P., Feinberg, J., Sherman, K.E., 2001. Mechanism of indinavir-induced hyperbilirubinemia. Proc. Natl. Acad. Sci. U.S.A. 98, 12671–12676.

Glossary

HIV: human immunodeficiency virus
AIDS: acquired immunodeficiency syndrome
PAR: peak area ratio
C_p: plasma concentration at the first time-point
AUC_{inf}: area under the curve up to infinity
$t_{1/2}$: terminal elimination half-life
Cl: total clearance rate
V: apparent volume of distribution
C_{max}: maximal plasma concentration
F: oral bioavailability
iv: intravenous
po: oral
HCT: hematocrit
HOB: hemoglobin
RBC: red blood cell count
RDW: red blood cell distribution width
WBC: white blood cell count
WBC: differential and absolute counts
ANS: total neutrophil
ANB: banded neutrophil
PNS: percentage neutrophil
PNB: percentage banded neutrophil
ALY: total lymphocyte
PLY: percent lymphocyte
AMO: total monocyte
PMO: percent monocyte
AEO: total eosinophil
PEA: percent eosinophil
ABA: total basophil percent basophil
MCH: mean corpuscular hemoglobin
MCV: mean corpuscular volume
MCC: mean corpuscular hemoglobin concentration
PLC: platelet count
MPV: mean platelet volume
REA (absolute) and RET (percent): reticulocyte count
TBI: total bilirubin, (direct bilirubin, indirect bilirubin)
CRE: creatinine
SOD: sodium
POT: potassium
CHL: chloride
CHO: cholesterol
TRI: triglycerides
GLU: glucose
BUN: blood urea nitrogen
AST: aspartate aminotransferase
ALT: alanine aminotransferase
ALP: alkaline phosphatase
CAL: calcium
PHO: phosphorus
TPR: protein, total
ALB: albumin
AGR: albumin/globulin ratio
GLO: globulin
PBMC: peripheral blood mononuclear cells
NRTIs: nucleoside reverse transcriptase inhibitors
NNRTIs: non-nucleoside reverse transcriptase inhibitors
PIs: protease inhibitors
CPE: cytopathic effect