Dolutegravir Pharmacokinetics in the Genital Tract and Colorectum of HIV-Negative Men After Single and Multiple Dosing

Benjamin N. Greener, PharmD, MS,* Kristine B. Patterson, MD,† Heather M. A. Prince, PA-C,† Craig S. Sykes, MS,* Jessica L. Adams, PharmD,* Julie B. Dumond, PharmD, MS,* Nicholas J. Shaheen, MD,† Ryan D. Madanick, MD,† Evan S. Dellon, MD,† Myron S. Cohen, MD,† and Angela D. M. Kashuba, BScPhm, PharmD, DABCP**†

INTRODUCTION

Dolutegravir (DTG) is an integrase strand transfer inhibitor currently in phase 3 clinical development for HIV-1 treatment. DTG has potent antiviral activity, a predictable pharmacokinetic (PK) profile in blood plasma (BP) with low intersubject variability [% coefficient of variation (CV) 9–4] compared with raltegravir, and is well tolerated.1–4 DTG is primarily metabolized by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) with a minor route via cytochrome P450 3A (CYP3A) and is also a P-glycoprotein substrate. The 12–15 hours elimination half-life supports once-daily dosing and allows for sustained antiretroviral (ARV) activity without the need for PK boosting.1,2 The recent SPRING-2 study demonstrated noninferiority to raltegravir: 88% and 85% of patients, respectively, achieved HIV-1 RNA <50 copies per milliliter at 48 weeks.4

The exposure–response relationship for ARV agents, including DTG and other integrase inhibitors, is best described by trough concentrations at 24 hours (C24h).2,5 Maintenance of DTG concentrations above the protein-adjusted concentration required for 90% viral inhibition (PA-IC90) across the dosing interval has been used to assess the activity. DTG at a dose of 50 mg achieves a steady state

**Corresponding author:
Angela D. M. Kashuba, BScPhm, PharmD, DABCP, 3318 Kerr Hall CB#7569, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7569 (e-mail: akashuba@unc.edu).

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From the *University of North Carolina at Chapel Hill Eshelman School of Pharmacy; and †University of North Carolina at Chapel Hill School of Medicine, The University of North Carolina, Chapel Hill, NC.

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B.N.G.—subject recruitment and study visit conduct, pharmacokinetic and statistical data analysis, and primary author of manuscript. K.B.P.—study visit conduct, clinical study safety officer, critical review of manuscript. H.M.A.P.—subject recruitment and study visit conduct, critical review of manuscript. C.S.S.—analytical data analysis, critical review of manuscript. J.L.A.—study visit conduct, pharmacokinetic and statistical data analysis, critical review of manuscript. J.B.D.—pharmacokinetic and statistical data analysis, critical review of manuscript. E.S.D.—study visit conduct, critical review of manuscript. R.D.M.—study visit conduct, critical review of manuscript. N.J.S.—study visit conduct, critical review of manuscript. M.S.C.—study design, critical review of manuscript. A.D.M.K.—study design, analytical and pharmacokinetic data analysis, funding, critical review of manuscript.

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Correspondence to: Angela D. M. Kashuba, BScPhm, PharmD, DABCP, 3318 Kerr Hall CB#7569, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7569 (e-mail: akashuba@unc.edu).

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that is approximately 13-fold greater than the PA-IC\textsubscript{90} of 64 ng/mL for wild-type virus.\textsuperscript{1}

The purpose of this study is to describe first-dose and steady state PKs of DTG in seminal fluid (SF), colorectal tissue (RT), and rectal mucosal fluid (RF) compared with BP in HIV-1–negative men. Although current ARV regimens can decrease BP HIV RNA to <50 copies per milliliter, the risk of HIV-1 transmission remains, as viral shedding in the male genital tract and colorectum may still occur.\textsuperscript{6–12} Although a low HIV-1 plasma viral load reduces the risk of heterosexual transmission events, less is known regarding the risk associated with incomplete viral suppression at local sites of transmission.\textsuperscript{13,14} PK requirements to prevent local transmission have not yet been elucidated; however, drugs that achieve high exposure at sites of transmission are expected to make ideal candidates for preexposure prophylaxis and treatment as prevention applications by conferring better protection.\textsuperscript{15} Understanding the PK behavior of DTG in multiple male biological compartments will inform its role in preventing local viral replication in HIV-infected men and its potential in protecting mucosal surfaces against HIV infection. This is the first study of male genital tract and RT ARV PKs to be performed before market approval.

**METHODS**

**Study Design**

This single-center, open-label, prospective PK study evaluated 12 healthy adult men between December 2011 and May 2012. The sample size was chosen to generate PK data adequate for understanding penetration of DTG into the gastrointestinal and genital tracts. Subjects received 50 mg oral DTG once daily for 8 days with intensive PK sampling visits after a single dose and at steady state. PK sampling was performed after 7 and 8 doses to allow appropriate SF volumes to be collected and to accommodate procurement of RT. Visits were conducted at the University of North Carolina at Chapel Hill (UNC) in the Clinical and Translational Research Center (CTRC). The study was approved by the UNC Biomedical Institutional Review Board, operated under FDA IND #113,425, and was registered with the NIH clinical trial registry (NCT01459315). DTG tablets were provided by Viiv Healthcare (Research Triangle Park, NC). All participants provided written informed consent before beginning study procedures.

**Subject Selection**

Screening procedures were initiated within 42 days of administration of DTG. Screening procedures consisted of a complete medical history and physical examination, 12-lead electrocardiogram with cardiology interpretation, and comprehensive laboratory studies (complete blood count with differential, liver function tests, serum chemistries, urinalysis, and urine toxicology). Subjects were screened for active hepatitis B and hepatitis C, HIV, syphilis, gonorrhea, chlamydia, and herpes simplex virus 2(HSV-2). Subjects were eligible to participate if they were natural born men between 18 and 49 years of age, inclusive at the date of screening, and had a body mass index 18–30 kg/m\textsuperscript{2} with total body weight >50 kg. Subjects were required to have fully intact genital and gastrointestinal tracts, have no known medication allergies, and not have participated in another drug research study within the previous 4 months. Subjects were excluded for any clinically significant abnormal laboratory value, physical examination finding or clinical condition that would interfere with study activities including disorders of the gastrointestinal tract or genital tract. Subjects were required to stop all prescription and nonprescription medications 7 days before and herbal supplements 14 days before study enrollment, and medications could not be restarted until study completion. Subjects were limited to consumption of less than 14 alcoholic beverages per week and acetaminophen at doses of ≤1 g/d.

Subjects abstained from sexual activity or use of intrarectal products from 72 hours before dosing until follow-up. Subjects abstained from alcohol, Seville oranges, and grapefruit juice for 7 days before administration of DTG. Additionally, subjects were required to fast for 8 hours before DTG administration at PK sampling visits and adhere to a low fiber diet 3 days prior and a clear liquid diet 12 hours before biopsy procedures. Subjects were sequentially assigned to SF and RF collection and RT biopsy times at screening.

**Safety Assessments**

Vital signs and clinical laboratory testing, including a complete lipid panel, serum chemistries, and complete blood count (CBC) with differential, were performed at every visit. Subjects underwent adverse event (AE) assessment on each PK visit day and daily by telephone between inpatient visits. AEs were captured by subject self-reporting and completion of a standardized assessment form. All AEs and laboratory values were graded by the study physician according to the National Institutes of Health Division of Allergy and Infectious Disease (DAIDS) grading criteria.\textsuperscript{16} Subjects were followed until all AEs resolved.

**Sample Collection and Processing**

Subjects were admitted to the UNC CTRC at least 2 hours before their 50 mg DTG dose on day 1 and on day 7. BP was collected in 3 mL K\textsubscript{2}EDTA tubes (BD Diagnostics, Franklin Lakes, NJ) predose and at 1, 2, 3, 4, 5, 6, 8, 12, 18, and 24 hours postdose on days 1, 7, and 8. RF and SF were self-collected predose and at 2 time points per subject on day 1 and at 3 time points per subject on both days 7 and 8 (1, 3, 6, 12, 18, or 24 hours postdose). RF was self-collected by subjects following instruction via insertion of a Dacron swab approximately 1–2 inches into the rectum for 1–2 minutes. For SF collections, participants were provided with self-care instructions, lubricant, visual aids, and a private room and then given 30 minutes to procure a sample in a sterile container by masturbation. RT was collected at a single time point per subject (1, 3, 6, 12, 18, or 24 hours postdose) on day 1 and on day 7 or 8. Nontargeted endoscopic cold biopsies were taken by flexible sigmoidoscopy (N.I.S., R.D.M., E.S.D.) at approximately 10 cm from the anal verge using a spiral approach with 2.8 mm Radial Jaw 4 Large Capacity Biopsy Forceps (Boston Scientific, Natick, MA). Ten pinch biopsies were taken at each procedure. Subjects were considered evaluable if they were able to provide all RT and 80% of
BP, SF, and RF samples, excluding predose samples but including 24-hour samples.

K$_2$EDTA tubes were stored on ice and processed within 1 hour of collection by centrifugation at 3000 rpm at 4°C for 10 minutes. BP was transferred to 2-mL cryovials and frozen at −80°C until analysis. RF was frozen immediately in 15-mL conical tubes after collection at −80°C. SF was left to liquefy at room temperature for approximately 1 hour and then transferred to 15-mL conical tubes and centrifuged at 5000 rpm at 4°C for 15 minutes. Seminal plasma was then transferred to 2-mL cryovials and frozen at −80°C. RT was flash frozen in liquid nitrogen and stored at −80°C.

DTG Quantification

Quantification of drug concentrations in all matrices was completed using LC-MS/MS methods validated by the UNC Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core. DTG in BP was extracted from calibration standards, quality control samples, and study samples using protein precipitation followed by LC-MS/MS analysis. Dolutegravir-$d_{15}$N (DTG-IS) was used as an internal standard. Thirty microliters of plasma was mixed with 600 μL of acetonitrile containing the internal standard. After the vortex and centrifugation steps, the supernatant was diluted with 50:50 methanol:water before LC-MS/MS analysis. DTG was eluted from a Varian (Agilent, Santa Clara, CA) Pursuit Diplein (2.1 × 50 mm, 3 μm particle size) analytical column. Data were collected using a Sciex Analyst Chromatography Software on an AB Sciex API 5000 triple quadrupole mass spectrometer (AB Sciex, Foster City, CA). Calibration curves were obtained by using a 1/concentration$^2$ weighted linear regression of analyte:internal standard peak area ratio vs. concentration. The calibration range of this assay was 20–20,000 ng/mL. All calibrators and quality control samples were within 15% of the nominal value for both within-day and between-day runs. Within-day and between-day precisions were <15%. Recoveries of DTG and its internal standard seen with this methodology were approximately 100%.

DTG was quantified in SF by similar methodology. Thirty microliters of seminal plasma was mixed with 270 μL of acetonitrile containing the internal standard. After vortex and centrifugation steps, the supernatant was diluted with 50:50 methanol:water and analyzed by LC-MS/MS using the same method as described for BP. The calibration range of the assay was 1–1000 ng/mL. All calibrators and quality control samples were within 15% of the nominal value for both within-day and between-day runs. Within-day and between-day precisions were <15%. Recoveries of DTG and its internal standard seen with this methodology were approximately 100%.

To extract DTG from RT samples, the tissue samples were homogenized in 1 mL of 80:20 water:acetonitrile. A portion of the resulting homogenate was extracted by protein precipitation with acetonitrile containing DTG-IS. After vortex and centrifugation steps, a portion of the supernatant was diluted with water. DTG was detected on an LC-MS/MS system using the same method as described for BP. During method validation, calibration standards were prepared in human vaginal tissue homogenate. Quality control (QC) samples were prepared in human vaginal and rectal tissue homogenates. Method validation results showed that calibration standards prepared in vaginal tissue homogenate could be used successfully to quantitate DTG in rectal tissue samples. For sample analysis, calibration standards and QC samples were prepared in human vaginal tissue homogenate. The dynamic range of the assay was 0.2–200 ng/mL homogenate. The recoveries of DTG and its internal standard were >80% in RT. All calibrators and quality control samples were within 15% of the nominal value with precision values <15%. Human saliva was used as a surrogate matrix for analysis of RF. Calibration standards and QC samples were prepared by adding human saliva and fortified at various concentrations with DTG onto clean swabs to mimic the composition of the study samples. DTG was initially extracted from swabs with 2 mL acetonitrile. A portion of the extract was then mixed with DTG-IS. After vortex and centrifugation steps, samples were transferred to a 96-well plate for LC-MS/MS analysis using the same method as described for BP. Samples above the calibration range of 0.075–75 ng DTG per swab were diluted 20-fold and reanalyzed. All calibrators and quality control samples were within 15% of the nominal value for both within-day and between-day runs. Within-day and between-day precisions were <15%. Recoveries of DTG and its internal standard seen with this methodology were >90%.

PK and Statistical Analysis

Noncompartmental analysis was performed using Phoenix WinNonlin v6.3 (Certara L.P., St. Louis, MO). Actual times were used in all PK analyses. Area under the concentration–time curves from 0 to 24 hours (AUC$_{0–24}$ hours) was calculated using the trapezoidal rule with linear up/log down interpolation. PK estimates were determined at PK1 for SF and at both PK1 and PK2 for RT using the geometric mean of concentrations at each time point. As DTG concentrations in some RF samples were below the limit of detection, composite AUC for RF at PK1 was calculated using median concentrations at each time point. Because RTs from 2 subjects were collected at each time point after single and multiple dosing, composite profiles were used for PK analysis. Spearman rank correlations between RF and RT were calculated using SAS 9.3 (SAS Institute Inc; Cary, NC). PK parameters are separated by day and by matrix. Below the limit of detection concentrations were imputed as 0 and concentrations below the limit of quantification were imputed as half the lower limit of quantification. Accumulation ratios were calculated from the geometric mean AUC$_{0–24}$ hours ratio of PK2:PK1. Data are presented as median (25th–75th percentile) unless otherwise noted.

RESULTS

Demographics

Fourteen participants were enrolled, and 12 completed the study. The median age of the 12 evaluable participants was 25.5 (21–44) years. Participants had a median (range) body mass index of 25.0 (20.4–31.1) and weight of 78.5 (58.2–107) kg at screening. Seven participants were African American, and 5 were whites. One participant identified his ethnicity as Hispanic or Latino. Fourteen subjects were...
enrolled and evaluated for safety. Two participants were not able to complete all protocol procedures.

**Plasma Concentrations**

Single- and multiple-dose PKs of DTG in all matrices are presented in Table 1. DTG achieved BP exposure in men, consistent with previous reports. After a single dose, BP DTG median [interquartile ratio (IQR)] \(\text{AUC}_{0-24\text{ h}}\) was 31.335 \((24.949–39.971)\ ng/mL\), with a median (IQR) \(t_{1/2}\) (calculated within the 24-hour dosing interval) of 12.2 hours (11.2–14.2 hours). The observed median (IQR) DTG \(C_{24\ h}\) was 704 \((580–874)\ ng/mL\), which is approximately 11-fold higher than the PA-IC\(_{90}\) of 64 ng/mL. PK parameters after 7 and 8 days of DTG dosing were comparable, with DTG achieving median (IQR) \(\text{AUC}_{0-24\text{ h}}\) accumulation ratios of 1.6 (1.5–1.9) and 1.3 (1.0–1.6), respectively. Because of the PK differences observed between the days, a BP median profile was used for comparison with other matrices. On day 8, median (IQR) \(\text{AUC}_{0-24\text{ h}}\) was 41.320 \((28.092–47.219)\ ng/mL\) with a median (IQR) \(t_{1/2}\) of 14.2 (12.0–16.1) hours. On day 8, median (IQR) BP DTG \(C_{24\ h}\) was 954 \((554–1093)\ ng/mL\) and remained approximately 15-fold above the PA-IC\(_{90}\) of 64 ng/mL. DTG achieved a \(C_{\text{max}}\) of 2285 \((1790–2743)\ ng/mL\) after a single dose and 2945 \((2120–3400)\ ng/mL\) after 8 doses. Median (IQR) BP \(T_{\text{max}}\) were 4 (2–5) and 2.5 (1–3) hours after single and 8 doses, respectively. Intersubject variability in \(C_{\text{max}}, C_{24\ h}\), and \(\text{AUC}_{0-24\text{ h}}\) ranged from 24 to 43 %CV.

**SF Concentrations**

A composite concentration vs. time profile was generated based on the geometric mean concentrations of sparse samples after a single dose of DTG. SF reached a maximum concentration (range) of 139.7 \((85.2–254)\ ng/mL\) at 11.8 hours postdose with a \(t_{1/2}\) of 7.7 hours. The observed day 1 SF DTG \(\text{AUC}_{0-24\text{ h}}\) was 2017.7 ng/mL, representing approximately 6.6% BP exposure. SF DTG \(C_{24\ h}\) ranged from 33 to 83.4 ng/mL. The observed median (IQR) trough concentration in SF was 41.5 \((34.2–73.8)\ ng/mL\). Single-dose concentration vs. time profiles for all matrices are presented in Figure 1.

Using a composite analysis of SF collections over days 7 and 8 of dosing, the median (IQR) \(\text{AUC}_{0-24\text{ h}}\) was 3229 \((2439–4376)\ ng/mL\). This resulted in a median (IQR) accumulation ratio of 1.6 (1.2–2.2) over 7–8 days and DTG seminal penetration that was 6.8% \((5.5%–8.7%)\) of BP. Peak concentration of 243.5 \((189.5–322.5)\ ng/mL\) was reached after 3.5 (2.8–5.8) hours. Median \(C_{24\ h}\) was 57.9 \((47.6–93.9)\ ng/mL\). SF concentrations reached a \(C_{\text{max}}\) of 243.5 \((189.5–322.5)\ ng/mL\) after 3.5 (3–6) hours. Concentration vs. time profiles for all matrices after multiple doses are shown in Figure 2.

**RF Concentrations**

In RF, a peak concentration of 17.0 ng per swab occurred at approximately 24 hours after a single dose. \(\text{AUC}_{0-24\text{ h}}\) was 91.9 ng per swab. No terminal elimination phase was observed. In the multiple dose composite profile, a median (IQR) peak concentration of 26.5 \((8.0–289)\ ng/mL\) occurred in RF at 12.1 \((6.1–12.1)\) hours. Median (IQR) RF \(\text{AUC}_{0-24\text{ h}}\) was 300.0 \((73.6–3160)\ ng h per swab) and a terminal elimination phase was only quantifiable for 3 subjects. There was no detectable correlation (Spearman rho = 0.43, \(P = 0.17\)) between RF concentrations and RT concentrations collected within an 1-hour window across days 7 and 8. RF exposures were low relative to RT with RF:RT \(\text{AUC}_{0-24\text{ h}}\) ratios of 0.018 and 0.047 after single and repeat dosing.

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**TABLE 1. PKs of DTG in BP, SF, RF, and RT After Single and Multiple Doses**

<table>
<thead>
<tr>
<th>Matrix</th>
<th>(t_{1/2}) (h)</th>
<th>(T_{\text{max}}) (h)</th>
<th>(C_{\text{max}}) (ng/mL, Swab or g)</th>
<th>(C_{24\ h}) (ng/mL, Swab or g)</th>
<th>(\text{AUC}_{0-24\text{ h}}) (ng h/mL, Swab or g)</th>
<th>(\text{AUC}_{0-\text{inf}}) (ng h/mL, Swab or g)</th>
<th>Matrix:BP</th>
<th>(\text{AUC}_{0-24\text{ h}}) Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single dose</td>
<td>12.2</td>
<td>4 (2–5)</td>
<td>2285</td>
<td>704</td>
<td>31,335</td>
<td>44,902</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(11.2–14.2)</td>
<td></td>
<td>((1790–2743))</td>
<td>((580–874)) ((24,948–39,970))</td>
<td>((37,253–58,911))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple doses</td>
<td>14.1</td>
<td>2.5 (1–3)</td>
<td>2945</td>
<td>954</td>
<td>41,320</td>
<td>60,553</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(12.0–16.1)</td>
<td></td>
<td>((2120–3400))</td>
<td>((554–1093)) ((28,092–47,219))</td>
<td>((37,785–70,036))</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SF</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Single dose</td>
<td>7.7</td>
<td>12</td>
<td>140</td>
<td>46.6</td>
<td>2018</td>
<td>2445</td>
<td>0.07</td>
<td></td>
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<tr>
<td></td>
<td>(8.5–14.8)</td>
<td></td>
<td>((190–323))</td>
<td>((47.6–94.0)) ((2439–4376))</td>
<td>((4210–6377)) ((3567–6377))</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Multiple doses</td>
<td>11.5</td>
<td>3.5 (3–6)</td>
<td>244</td>
<td>57.9</td>
<td>3229</td>
<td>4210</td>
<td>0.07 (33)</td>
<td></td>
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<tr>
<td>RF</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Single dose</td>
<td>—</td>
<td>24</td>
<td>17.0</td>
<td>17.0</td>
<td>91.9</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>((8.0–289))</td>
<td>((0.9–88.9)) ((73.6–3160))</td>
<td>((73.6–3160)) ((73.6–3160))</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Multiple doses</td>
<td>—</td>
<td>12 (6–12)</td>
<td>26.5</td>
<td>8.6</td>
<td>300.0</td>
<td>—</td>
<td>—</td>
<td></td>
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<td>RT</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single dose</td>
<td>4.2</td>
<td>6</td>
<td>373</td>
<td>114</td>
<td>5281</td>
<td>5890</td>
<td>0.17</td>
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<tr>
<td></td>
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<td></td>
<td>((8.0–289))</td>
<td>((0.9–88.9)) ((73.6–3160))</td>
<td>((73.6–3160)) ((73.6–3160))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple doses</td>
<td>8.4</td>
<td>4</td>
<td>418</td>
<td>139</td>
<td>7596</td>
<td>9617</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

Parameter estimates are presented as median (IQR) or point estimates for parameters generated from composite profiles. BP multiple dose estimates were calculated from concentrations after the last dose. Matrix:BP ratios are presented as the geometric mean \(\text{AUC}_{0-24\text{ h}}\) ratio (%CV) for SF after multiple doses or geometric mean \(\text{AUC}_{0-24\text{ h}}\) ratio for RT and a single dose of SF.
RT Concentrations

DTG penetration in RT was higher than that observed for either SF or RF. RT AUC$_{0-24}$ hours were 5281 ng/g tissue on day 1 and 7596 ng/g tissue on days 7–8, resulting in RT penetration of 17% compared with BP after both single and multiple dosing. DTG was detected in RT at 1 hour after a single dose and maintained concentrations above the PA-IC$_{90}$ over the entire dosing interval. C$_{24 \text{h}}$ was 114.5 ng/g tissue on day 1 and 139.1 ng/g tissue over days 7–8. DTG accumulated in RT after multiple doses with an accumulation ratio of 1.4.

Safety

AE data include 14 subjects who received one or more doses of DTG. No serious AEs were reported during this study, and all AEs were ≥DAIDS grade 2. Two subjects were discontinued for reasons considered unrelated to study drug by the study physician. One subject with a history of generalized anxiety disorder experienced a panic attack of moderate severity during the second PK visit. Study staff was unable to maintain peripheral intravenous access during the first PK visit in another. Nonserious AEs included headaches (4 subjects) that were considered possibly related to study drug by the investigators. One case of vascular access site soreness was reported and considered to be unrelated to study drug. A single subject experienced transient muscle tightness, and the relation to study drug was unknown. No laboratory abnormalities equal to or greater than DAIDS severity grade 2 were observed.

DISCUSSION

DTG PKs in BP are consistent with published results, with a relatively long terminal elimination half-life and trough concentrations ranging from 6- to 34-fold above the PA-IC$_{90}$ in all subjects.$^{1,2}$ Differences in exposure were observed between days 7 and 8 of dosing. The higher exposure on day 7 was likely a food effect, as diet was unrestricted during home dosing on days 2–6 with likely higher fat content than those given in the research unit. Consistent with this observation, DTG exposures increase from 33% to 66% when taken with food depending on fat content of the meal.$^{17}$

DTG SF median trough concentrations are below the PA-IC$_{90}$ after single and multiple doses. Additionally, SF exposure is only ∼7% of that observed in BP. These low exposures are predicted by the high plasma protein binding of DTG and are similar to results for drugs in other therapeutic classes.$^{15}$ The low genital tract penetration is consistent with the SF to BP penetration ratios of other highly protein-bound ARVs, including enfuvirtide (0%), lopinavir (5%), nelfinavir (5%), ritonavir (3%), saquinavir (3%), and efavirenz (3%). Protein binding in SF is typically lower than in BP, resulting in a higher proportion of available free drug. DTG protein binding in SF was not quantified in this study. Using extremes of SF protein binding in currently documented (8.9%–97%), free median trough DTG concentrations could theoretically range from 1.2 to 37.8 ng/mL after a single dose and from 1.7 to 52.7 ng/mL after multiple doses.$^{18,19}$ DTG trough concentrations would therefore be >6-fold above the in vitro IC$_{50}$ of 0.21 ng/mL after a single dose. Despite the low SF concentrations, distribution to this matrix was rapid and drug was quantifiable in all subjects at 1 hour postdose.

Self-collected RF swabs are unlikely to be a useful surrogate for RT concentrations in future trials. Self-collected swabs of RF were obtained in an effort to identify a substitute for directly obtaining tissue through rectal biopsies. However,
the large intersubject variability in RF DTG exposure is likely because of the variation in self-collection by individual subjects and the lack of a weight or volume correction. Swabs were not corrected for weight or volume because of expected contamination by fecal material and because of the practicality of how these may be collected outside an academic research center.

Although DTG distributes rapidly into RT, the overall exposure is 17% of that observed in BP and lower than the other ARVs ranging from 2.7 (daranavir) to 231 (raltegra-

vir).18,20 Despite the low exposure, DTG concentrations in RT remain above the PA-IC90 across dosing intervals after single and multiple doses and trough concentrations remain approximately 2-fold higher than the PA-IC90.

CONCLUSIONS

The BP PKs of single and multiple doses of DTG in this investigation were similar to previous reports.1,2 Although DTG rapidly distributes to sites of transmission, DTG exposure in SF and rectal tissue was considerably lower than BP and other ARVs. After multiple doses, DTG accumulates in vulnerable fluid and tissue and maintains concentrations above the PA-IC90 in rectal tissue but only 36% of SF samples. Further studies are warranted to determine the implications of these findings on prevention.

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REFERENCES


