Amdoxovir (AMDX) inhibits HIV-1 containing the M184V/I mutation and is rapidly absorbed and deaminated to its active metabolite, β-d-dioxolane guanosine (DXG). DXG is synergistic with zidovudine (ZDV) in HIV-1-infected primary human lymphocytes. A recent in silico pharmacokinetic (PK)/enzyme kinetic study suggested that ZDV at 200 mg twice a day (b.i.d.) may reduce toxicity without compromising efficacy relative to the standard 300-mg b.i.d. dose. Therefore, an intense PK clinical study was conducted using AMDX/placebo, with or without ZDV, in 24 subjects randomized to receive oral AMDX at 500 mg b.i.d., AMDX at 500 mg plus ZDV at 200 or 300 mg b.i.d., or ZDV at 200 or 300 mg b.i.d. for 10 days. Full plasma PK profiles were collected on days 1 and 10, and complete urine sampling was performed on day 9. Plasma and urine concentrations of AMDX, DXG, ZDV, and ZDV-5'-O-glucuronide (GZDV) were measured using a validated liquid chromatography-tandem mass spectrometry method. Data were analyzed using noncompartmental methods, and multiple comparisons were performed on the log-transformed parameters, at steady state. Coadministration of AMDX with ZDV did not significantly change either of the plasma PK parameters or percent recovery in the urine of AMDX, DXG, or ZDV/GZDV. Larger studies with AMDX/ZDV, with a longer duration, are warranted.

Lack of Pharmacokinetic Interaction between Amdoxovir and Reduced- and Standard-Dose Zidovudine in HIV-1-Infected Individuals
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Nucleoside reverse transcriptase inhibitors (NRTI) remain the backbone of current HIV therapy, in which they are combined with protease inhibitors (PI), nonnucleoside reverse transcriptase inhibitors (NNRTI), integrase inhibitors, or entry/fusion inhibitors (11, 12, 32, 42). Since existing combinatorial regimens cannot eradicate infection due to the compartmentalization of the virus and its latent properties, chronic therapy will remain the standard of care for the foreseeable future (44, 45). Highly active antiretroviral therapy (HAART) regimens have limitations, primarily due to toxicities and/or the emergence of drug-resistant HIV strains (39). Therefore, the development of safe and effective drug combinations that can not only inhibit both wild-type and resistant strains of HIV-1 but also prevent or retard future resistance development needs to be a continued focus in HIV drug development. Amdoxovir (AMDX) is a guanosine nucleoside analogue being developed for the treatment of HIV-1 infections (23, 31, 47). AMDX is in advanced phase 2 clinical development under a U.S. Food and Drug Administration Investigational New Drug Application and has been administrated safely to over 200 persons in seven human phase I/II trials (23, 31, 36, 47, 50). AMDX is a prodrug which undergoes rapid oral absorption in humans and other species and is deaminated by the ubiquitous enzyme adenosine deaminase to 9-(β-d-1,3-dioxolan-4-yl)guanine (DXG) (4, 16, 35). DXG is phosphorylated to its active triphosphate form, DXG-triphosphate (DXG-TP), which is a potent inhibitor of wild-type and drug-resistant forms of HIV-1 (16, 33) and a modest inhibitor of hepatitis B virus in human hepatocytes (5, 43, 51). Drug-resistant HIV mutants susceptible to DXG include viruses containing M184V/I and thymidine analog mutations (TAMs) (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) and the 69SS double insert (24, 25, 33). The decay half-life of the active metabolite DXG-TP was ~16 h in activated primary human lymphocytes and ~9 h (or 27 h if including a 48-h time point) in humans, suggesting that twice a day (b.i.d.) dosing should provide adequate therapeutic coverage (26, 30). Cellular toxicity studies suggested that AMDX and DXG did not affect the levels of mitochondrial DNA in human hepatoma cells (HepG2 cells) treated for 14 days at 10 μM, and there was no increase in lactic acid production in these cells (9). Resistance in vitro develops slowly and is associated with a K65R or L74V mutation (20, 38, 49). Viruses containing the K65R mutation show moderate cross-resistance to zalcitabine, didanosine, adefovir, and lamivudine (3TC) but increased sensitivity to zidovudine (ZDV) (38). An in vitro study demonstrated that ZDV alone selected for a mixture of K70K/R mutations at week 25 and that AMDX alone selected for a mixture of K65R and L74V mutations at week 20. However, when AMDX and ZDV were used in combination in HIV-infected primary human lymphocytes, no drug-resistant mutations were detected through week 28 (40). Therefore, the inclusion of ZDV in combination with AMDX may prevent or delay the emergence of these mutations. Coincubation of ZDV and DXG with phytohemagglutinin (PHA)-stimulated human peripheral blood mononuclear (PBM) cells did not result in...
decreased phosphorylation of either NRTI at physiologically relevant concentrations (26).

ZDV is a commonly used NRTI in many HAART regimens (3, 10, 17), and the single-dose plasma pharmacokinetics (PK) of ZDV following intravenous and oral administration in HIV-infected individuals is well described (1, 14, 22, 37, 52). ZDV treatment is limited by toxic side effects, including nausea and malaise, as well as serious bone marrow cytotoxicities, such as anemia and neutropenia (6, 41, 46). The bone marrow cytotoxicities of ZDV are believed to be associated with mitochondrial damage and correlate with ZDV-monophosphate (ZDVM P) levels (48). The current approved dose for ZDV is 300 mg b.i.d. However, Barry et al. demonstrated that a reduced dose of ZDV, 100 mg three times a day (t.i.d.), produced similar cellular levels of ZDV-TP, which mediates antiviral effects, while significantly decreasing ZDV plasma concentrations and intracellular levels of ZDV-MP (2). The Thai national guidelines for the management of HIV recommend that the ZDV dose be reduced from 300 to 200 mg b.i.d. for patients weighing less than 60 kg, which has resulted in fewer side effects and improved long-term tolerability without evidence of reduced efficacy (7, 8, 34). A PK and enzyme kinetic simulation study was conducted by superimposing the population PK of ZDV (37, 52) over the distribution of enzyme kinetic parameters derived from a population of treatment-naïve HIV-1-positive subjects (28, 29) to test the hypothesis that thymidine kinase (TMPK), the rate-limiting enzyme of ZDV phosphorylation, may be oversaturated at clinical doses (19, 27). The in silico study suggested that the current ZDV dose could be lowered from 300 to 200 mg b.i.d. for subjects with body weights more typical of Western populations to reduce toxicities while maintaining adequate ZDV-TP concentrations. However, lowering the dose further was predicted to produce a more steep decrease in ZDV-TP levels.

A proof-of-concept clinical study was performed in which 24 HIV-1-infected subjects not currently receiving antiretroviral therapy were randomized to receive either AMDX at 500 mg b.i.d., ZDV at 200 or 300 mg b.i.d., or AMDX at 500 mg plus ZDV at 200 or 300 mg b.i.d. for 10 days, with full PK profiles collected on day 1 (first dose), day 10 (steady state), and predose on day 5 and with urine collection at days 9 to 10 to determine drug-drug interactions between ZDV and AMDX/DXG as a prelude to a larger phase II study.

### MATERIALS AND METHODS

**Materials.** AMDX, DXG, and ZDV reference standards were obtained from RFS Pharma, LLC; 5′-O-glucuronicide of ZDV (GZDV) was obtained from Toronto Research Chemicals, Toronto, Canada; 2′,3′-Diaminopurine-2′-deoxyriboside (DPRD) and 2′-deoxyadenosine (2′-dA) were obtained from Sigma. Deoxycoformycin (DCF) was purchased from Waterstone Technology (Carmel, IN). Solvents for high-performance liquid chromatography (HPLC) analyses were obtained from Fischer Scientific (Fair Lawn, NJ).

**Clinical samples.** The study protocol was approved by the following ethics committees in Argentina: Facultad de Medicina, Universidad de Buenos Aires, Comité Independiente de Etica en Investigación (CIEI-FM-UBA), and Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT). Written informed consent was obtained from all subjects.

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Measurement of ADA activity in plasma. Adenosine deaminase (ADA) levels in the plasmas of subjects were measured using a commercially available assay kit from Diazyme Laboratories, Poway, CA.

PK and statistical analyses. Noncompartmental PK analysis was performed on plasma concentrations of AMDX, DXG, and ZDV on day 1 (first dose) and day 10 (steady state), using Kinetica (version 5.0; Thermo Fisher Scientific Inc., Waltham, MA) and assuming extravascular drug input. Statistical analysis of percent recovery of AMDX, DXG, ZDV, and GZDV in the urine at steady state was also performed. Areas under the concentration-time curve between doses ($AUC_{\text{day } 10}/AUC_{\text{day } 1}$) were used to calculate relative drug accumulation ($AUC_{\text{day } 10}/AUC_{\text{day } 1}$). Oral clearance ($CL/F$) on day 1 was measured, noting that $AUC_{\text{day } 10}/AUC_{\text{day } 1}$ is theoretically equivalent to $AUC_{\text{day } 1}$, assuming a steady state. Maximum concentration of drug in serum ($C_{\text{max}}$) were reported as actual values. Since NRTI are used for the chronic treatment of HIV-1, detailed statistical analysis was performed on the PK parameters measured at steady state (day 10). Normal probability plots and Shapiro-Wilk tests for normality were performed on the nontransformed and natural log-transformed parameters, using the univariate procedure of SAS (version 9.2; SAS, Cary, NC). $P$ values of $<0.05$ were considered statistically significant. The steady-state PK parameters of ZDV (Table 3) included $C_{\text{max}}$, $AUC_{\text{day } 10}/AUC_{\text{day } 1}$, $t_{1/2}$, $CL/F$, $AUC_{\text{day } 10}/AUC_{\text{day } 1}$, and the percentage of the ZDV dose recovered in urine in one dose interval, as GZDV and ZDV ($\% \text{GZDV}_{\text{urine in day 10}}$ and $\% \text{ZDV}_{\text{urine in day 10}}$, respectively), $C_{\text{max}}$ and $AUC$ parameters for ZDV were normalized to dose to allow comparisons to be performed relative to the pooled ZDV monotherapy cohorts ($n = 4$) and groups receiving ZDV with AMDX. Correlations between ADA activity in plasma and $C_{\text{max}}$ and $AUC$ were assessed by linear regression.

RESULTS

PK of AMDX and DXG. Plasma concentrations of AMDX and DXG on day 1 (first dose) and day 10 (steady state) (mean ± standard deviation [SD]) versus time were plotted for each cohort (Fig. 1A and B, respectively). AMDX was rapidly absorbed and deaminated to DXG following oral administration on both days. Plasma concentrations of AMDX were similar between day 1 and steady state. No correlation was noted between plasma concentrations and $C_{\text{max}}$ of either AMDX or DXG and ADA levels in plasma ($r^2 < 0.2$) (data not shown).

### TABLE 2. Geometric means (% CV) and statistical analysis of pharmacokinetic parameters for DXG administered as AMDX on day 10

<table>
<thead>
<tr>
<th>Group or comparison</th>
<th>Median $t_{\text{max}}$ (h)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$AUC_{\text{day } 10}/AUC_{\text{day } 1}$</th>
<th>$t_{1/2}$ (h)</th>
<th>$AUC_{\text{ratio}}$ (day 10/day 1)</th>
<th>$% \text{DXG}_{\text{urine in day 10}}$</th>
<th>$% \text{AMDX}_{\text{urine in day 10}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (AMDX; $n = 6$)</td>
<td>1.3</td>
<td>1.454 (44.4)</td>
<td>0.88 (19.0)</td>
<td>17.6 (46.8)</td>
<td>1.18 (28.8)</td>
<td>253 (8.3)</td>
<td>1.1 (136)</td>
</tr>
<tr>
<td>2 (AMDX + ZDV at 200 mg; $n = 6$)</td>
<td>1.5</td>
<td>1.312 (41.6)</td>
<td>0.95 (44.8)</td>
<td>14.7 (46.0)</td>
<td>0.91 (34)</td>
<td>26.2 (26.2)</td>
<td>3.6 (64.7)</td>
</tr>
<tr>
<td>3 (AMDX + ZDV at 300 mg; $n = 6$)</td>
<td>1.8</td>
<td>1.938 (56.9)</td>
<td>0.85 (39.0)</td>
<td>14.8 (43.6)</td>
<td>1.39 (59.3)</td>
<td>27.7 (21.3)</td>
<td>3.85 (66.5)</td>
</tr>
</tbody>
</table>

Multiple comparisons of ratios of geometric means ($P$ values in Tukey-Kramer modified $t$ test)

<table>
<thead>
<tr>
<th>$P$ values in Tukey-Kramer modified $t$ test</th>
<th>1 vs 2</th>
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<th>2 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.75 (0.38)</td>
<td>1.48 (0.13)</td>
<td>0.60 (0.08)</td>
</tr>
<tr>
<td>2</td>
<td>1.18 (0.92)</td>
<td>1.10 (0.87)</td>
<td>0.78 (0.49)</td>
</tr>
<tr>
<td>3</td>
<td>0.673 (0.54)</td>
<td>0.74 (0.21)</td>
<td>1.30 (0.39)</td>
</tr>
</tbody>
</table>

### TABLE 3. Geometric means (% CV) and statistical analysis of pharmacokinetic parameters for ZDV on day 10

<table>
<thead>
<tr>
<th>Group or comparison</th>
<th>Median $t_{\text{max}}$ (h)</th>
<th>$C_{\text{max}}$ (ng/ml/mg)</th>
<th>$AUC$ (ng·h/ml/mg)</th>
<th>$CL/F$ (l/h/kg)</th>
<th>$t_{1/2}$ (h)</th>
<th>$AUC_{\text{ratio}}$ (day 10/day 1)</th>
<th>$% \text{ZDV}_{\text{urine in day 10}}$</th>
<th>$% \text{GZDV}_{\text{urine in day 10}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (ZDV; $n = 4$)</td>
<td>0.5</td>
<td>7.58 (59.6)</td>
<td>9.62 (42.6)</td>
<td>1.39 (40.2)</td>
<td>2.2 (30.2)</td>
<td>1.21 (7.6)</td>
<td>61.15 (19.1)</td>
<td>6.24 (36.3)</td>
</tr>
<tr>
<td>2 (ZDV at 200 mg + AMDX; $n = 6$)</td>
<td>0.5</td>
<td>4.34 (101)</td>
<td>6.51 (29.9)</td>
<td>2.34 (34.4)</td>
<td>2.5 (24.5)</td>
<td>1.04 (29.4)</td>
<td>61.87 (23.0)</td>
<td>5.88 (54.4)</td>
</tr>
<tr>
<td>3 (ZDV at 300 mg + AMDX; $n = 6$)</td>
<td>0.5</td>
<td>6.74 (43.8)</td>
<td>8.77 (17.3)</td>
<td>1.80 (30.9)</td>
<td>2.4 (13.1)</td>
<td>0.86 (33.4)</td>
<td>62.89 (17.2)</td>
<td>6.74 (43.8)</td>
</tr>
</tbody>
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Multiple comparisons of ratios of geometric means ($P$ values in Tukey-Kramer modified $t$ test)

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</table>
The noncompartmental parameters (geometric means and %CV) of AMDX and DXG for subjects taking AMDX with and without ZDV, together with the respective P values summarizing Tukey’s paired comparison t tests of each parameter, are reported in Tables 1 and 2, respectively. The \( T_{\text{max}} \) values for AMDX and DXG were similar on days 1 and 10 and were generally between 1 and 3 h (Fig. 1 and 2). The geometric mean plasma \( C_{\text{max}} \) of DXG ranged from 1,272 to 1,398, compared to 514 to 892 ng/ml for AMDX, on day 1 and from 1,315 to 1,908 versus 499 to 714 ng/ml, respectively, on day 10. The intersubject variability in \( C_{\text{max}} \) between cohorts at steady state was from 33.7 to 52.9% and from 14.1 to 44.4% for AMDX and DXG, respectively. AMDX declined more rapidly than DXG, with the geometric mean \( t_{1/2} \) ranging from 1.3 to 1.6 h and from 2.5 to 2.9 h for AMDX and DXG, respectively, on day 1. A much longer \( t_{1/2} \) of decay was noted between 12 and 48 h for DXG (day 10), with geometric mean values ranging from 14.7 to 17.6 h. The corresponding geometric mean percentage of dose recovered in urine in one dose interval was 25.3 to 27.7% as DXG and 1.1 to 3.9% as AMDX. No significant differences were detected in the plasma or urine PK parameters for AMDX and DXG (\( P > 0.05 \)) between cohorts receiving AMDX.

**PK of ZDV.** Plasma concentrations of ZDV on day 1 and at steady state (mean ± SD) versus time were plotted (log-linear scale) for each cohort (Fig. 2A and B, respectively). ZDV was rapidly absorbed and demonstrated a median \( T_{\text{max}} \) of 0.5 to 0.75 h postdosing for all regimens. The noncompartmental PK parameters of ZDV are summarized in Table 3, together with the

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*FIG. 1. Plasma concentrations (ng/ml; mean ± SD) of AMDX (open symbols) and DXG (closed symbols) by cohort following the administration of 500 mg of AMDX b.i.d. following the initial dose on day 1 (A) and following the day 10 dose (B). Subjects received AMDX alone (○) or with ZDV at 200 mg (△) or 300 mg (□) b.i.d.*
respective \( P \) values summarizing Tukey's paired comparison \( t \) tests of each parameter between cohorts. The geometric mean \( C_{\text{max}} \) on day 1 ranged from 4.34 to 7.58 ng/ml per mg of dose. ZDV was eliminated with a geometric mean \( t_{1/2} \) ranging from 2.2 to 2.5 h on day 10. The resulting geometric mean AUC_{12 h/mg} on day 10 for the various cohorts ranged from 6.5 to 7.6. AUC_{\text{GZDV}} accounted for 97.5 and 100% of AUC_{\text{total}} for ZDV on days 1 and 10, respectively. The geometric mean ratios of AUC_{12 h} on day 10 to that on day 1 ranged from 0.86 to 1.21, suggesting limited dose accumulation, as expected due to the relatively short \( t_{1/2} \) of ZDV. The geometric mean percentages of dose recovered in urine in one dose interval at steady state, as GZDV and ZDV, were 61 to 63% and 5.9 to 6.7%, respectively, between cohorts.

**DISCUSSION**

The feasibility of developing an AMDX and ZDV coformulation is currently being explored, since this combination demonstrates synergy *in vitro* and at least additivity *in vivo* (36) against HIV-1 and prevents the selection of K65R mutation/TAMs in primary human lymphocytes (40). A previous simulation study suggested that the ZDV dose may be reduced from 300 mg b.i.d. to 200 mg b.i.d. to limit toxicity without compromising cellular levels of ZDV-TP, which is responsible for ZDV efficacy (27). Drug-drug interactions are often problematic and particularly important in the management of HIV-1 infection (13). There is no *a priori* reason to expect a drug interaction between AMDX and ZDV, since they use

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**FIG. 2.** Plasma concentrations (ng/ml; mean \( \pm \) SD) of ZDV on day 1 (A) and at steady state (B) by cohort. ●, ZDV at 200 mg \( (n = 2) \); ■, ZDV at 300 mg \( (n = 2) \); ▲, ZDV at 200 mg plus AMDX at 500 mg b.i.d. \( (n = 6) \); ▼, ZDV at 300 mg plus AMDX at 500 mg b.i.d. \( (n = 6) \).
different phosphorylation pathways (thymidine kinase and 5’-nucleotidase, respectively). However, it was important to confirm the lack of interaction prior to performing larger studies. Additionally, PK assessment of ZDV at a reduced dose compared to the standard dose, alone and in combination with AMDX, was also appropriate in this context. Therefore, it was prudent to perform a proof-of-concept study to assess whether any clinically significant PK interactions occur between ZDV and AMDX or its metabolite, DXG.

The first-dose and steady-state PK of AMDX/DXG were similar to those reported in a previous study in which PK measurements were performed on days 1 and 15, using the same dose of AMDX for 15 days, in treatment-naive and experienced subjects (47). The lack of correlation between ADA levels in the plasma and C_{max} of AMDX and DXG was expected, since ADA is not confined to blood cells (e.g., erythrocytes) but is also expressed at high levels in the GI tract and liver (35). Therefore, deamination of AMDX to DXG could also occur before it reaches the systemic circulation. The C_{max} of AMDX and DXG was reached within 1 to 2 h following dosing, suggesting rapid oral absorption and conversion of AMDX to DXG in vivo by adenosine deaminase. The variability in AMDX concentrations tended to be higher at early sampling time points (0.5 h), probably due to different absorption and conversion rates of AMDX to DXG. The intersubject variability of DXG plasma concentrations was relatively small compared to that for AMDX. Since DXG triphosphate is the active form of the drug and AMDX is essentially nontoxic at clinically relevant concentrations, AMDX is an acceptable prodrug of DXG. Concentrations of DXG were higher and declined slower than those of AMDX, and they exhibited a long t_{1/2} on day 10 which was evident only after 12 h postdosing, indicative of multieponential decay in plasma.

The PK of ZDV demonstrated similar interindividual variability and parameters to those in previously reported studies (1, 2, 37, 52). Plasma concentrations were similar on days 1 and 10, as expected, due to the relatively short t_{1/2} of ZDV in plasma. Multiple comparisons using analysis of variance (ANOVA) failed to detect any significant differences in plasma or urine noncompartmental PK parameters at steady state (including C_{max}, CL/F, and % recovered in urine as AMDX or DXG) for AMDX/DXG when AMDX was administered alone or with ZDV at 200 or 300 mg b.i.d. (Tables 1 and 2).

In this clinical study, ZDV at 200 and 300 mg b.i.d. and placebo produced mean changes in VL from baseline of −0.69, −0.55, and +0.10 log_{10}, respectively (36), which were similar to those for previous monotherapy trials with ZDV at 300 mg b.i.d. (15). AMDX monotherapy at 500 mg b.i.d. produced a VL change of −1.09 log_{10}, which was similar to what was observed with treatment-naive subjects in a previous monotherapy study (47). AMDX with ZDV at 200 and 300 mg b.i.d. produced VL changes of −1.69 and −2.00 log_{10}, respectively. AMDX with 200 mg of ZDV was significantly more potent than monotherapy with AMDX (P = 0.021), but the difference in mean log_{10} VL decline between AMDX regimens with 200 and 300 mg ZDV b.i.d. was not statistically significant. These results suggest an additive or synergistic activity between AMDX and ZDV. There was also a decrease in the variability in VL in subjects taking ZDV with AMDX compared to those taking AMDX alone, which could have resulted from the complementary resistance patterns of these NRTI (36).

In summary, there were no significant PK drug-drug interactions between ZDV and either AMDX or DXG in plasma or in the urine during coadministration of AMDX and ZDV. This PK study, together with associated antiviral and tolerability data (36), suggests that the combination of ZDV with AMDX warrants further study and that dose reduction strategies for ZDV might be beneficial in maintaining efficacy and limiting toxicity (41). Longer and larger studies with coformulated AMDX-ZDV are warranted to confirm and extend the results of the current study.

ACKNOWLEDGMENTS

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R. F. Schinazi is the founder and major shareholder of RFS Pharma, LLC, and the inventor of AMDX and may receive royalties from future sales of AMDX. RFS Pharma provided no funding to Emory University/VA/AMC.

REFERENCES


