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Interindividual Variability in Pharmacokinetics of Generic Nucleoside Reverse Transcriptase Inhibitors in TB/HIV Co-infected Ghanaian Patients: *UGT2B7*1C* is Associated with Faster Zidovudine Clearance and Glucuronidation

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Abstract

There are limited data on the pharmacokinetics of generic nucleoside reverse transcriptase inhibitors (NRTIs) in native African populations, where they are commonly used. We characterized the pharmacokinetics of lamivudine (n=27), zidovudine (n=16) and stavudine (n=11) in HIV/TB co-infected Ghanaians, and evaluated associations between zidovudine metabolism and UDP-glucuronosyltransferase (UGT) 2B7 polymorphisms. Lamivudine, zidovudine, and stavudine apparent oral clearance (CL/F) values [mean±SD (CV%)] were 7.3±2.8 (39%), 31.9±33.6 (106%), and 16.4±5.8 (35%) mL/min/kg, respectively, whereas half-life values were 4.2±1.9 (46%), 8.1±7.9 (98%), and 1.5±1.0 (65%) hr, respectively. Zidovudine CL/F was 196% higher ($P=0.004$) in *UGT2B7*1c* (c.735A>G) carriers versus non-carriers. This was confirmed using human liver bank samples (n=52), which showed 48% higher ($P=0.020$) zidovudine glucuronidation and 33% higher ($P=0.015$) UGT2B7 protein in *UGT2B7*1c* carriers versus non-carriers. In conclusion, generic NRTI pharmacokinetics in HIV/TB co-infected Ghanaians are similar to other populations, while the *UGT2B7*1c* polymorphism may explain in part relatively high interindividual variability in zidovudine clearance.

Keywords

NRTIs; pharmacokinetics; UGT2B7; rifampin; interindividual variability

INTRODUCTION

Antiretroviral combination regimens of dual nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase

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Conflict of Interest:

All authors report no conflict of interest.

inhibitor (NNRTI) are preferentially used in treatment-naïve human immunodeficiency virus (HIV) infected patients to achieve maximum durable anti-viral activity.^{1, 2} The dual-NRTI backbone drugs differ substantially in pharmacokinetic properties, potency and durability of virologic suppression, incidence and type of short-and long-term toxicities, propensity to select for resistance mutations, dosing convenience and drug-drug interaction potential.¹ The newer once-daily fixed-dose combinations of tenofovir/emtricitabine or lamivudine/abacavir are the preferred choices in industrialized countries because of dosing convenience and lower incidence of short-and long-term toxicities.^{1, 2} However, in resource poor settings, low cost generic forms of lamivudine in combination with zidovudine or co-administered with stavudine are the predominant dual-NRTI backbone.³

The pharmacokinetics of the antiretroviral drugs may depend on genetic polymorphisms of drug metabolizing enzymes or transporters, biological factors (such as age, gender, body weight, or disease state), drug-drug interactions and/or drug formulation.^{4–7} While the pharmacokinetics of the NRTIs have been well established for the brand formulations in HIV-infected populations in industrialized countries,^{7–10} there is limited data on the pharmacokinetics of the generic equivalents in African populations. The pharmacokinetics of generic tablets of the fixed-dose combination of lamivudine/stavudine/nevirapine and brand-name separate formulations of lamivudine, stavudine and nevirapine have been evaluated in HIV-infected patients in sub-Saharan Africa.^{11, 12} Although plasma levels of lamivudine were found to be similar for the generic and brand-name formulations in those studies, one of the studies,¹¹ found lower stavudine concentrations, and the other study¹² found higher stavudine peak concentrations for generic compared with non-generic formulations.

In HIV-infected patients with TB coinfection who require rifampin-containing therapy, the World Health Organization recommends efavirenz with lamivudine/zidovudine or lamivudine/stavudine as the first-line antiretroviral regimen.³ While the pharmacokinetics of efavirenz has been studied in this population because of the concern of drug-drug interactions,^{13, 14} to our knowledge, there are no pharmacokinetic data for the generic NRTIs components in HIV/TB co-infected individuals on TB therapy. Apart from possible impairment of drug absorption resulting from the effects of advanced HIV disease and TB infection,^{15, 16} co-administered rifampin has the propensity to enhance drug clearance mechanisms involving cytochrome P450, uridine diphosphate (UDP)-glucuronosyltransferase (UGT), and drug transporters which may result in detrimental drug-drug interactions.¹⁷ Rifampin co-administration was previously associated with an average of 47 – 50% reduction in zidovudine area under the curve in asymptomatic HIV-infected patients.^{5, 6} Significant rifampin-induced drug-drug interactions are not expected with the other NRTIs as these drugs are not metabolized by hepatic CYP enzymes and are not considered substrates of the rifampin-inducible P-glycoprotein transporter. Zidovudine and lamivudine are known to be substrates for the efflux transporter multidrug resistance protein 4 (MRP4), and over expression of this transporter is associated with impaired intracellular accumulation of the monophosphates.¹⁸ However, in one small study, rifampin did not appear to have any significant effect on the expression of MRP4.¹⁹

Zidovudine undergoes extensive first-pass extraction and is eliminated primarily through hepatic glucuronidation by UGT2B7.²⁰ The large interindividual variation in zidovudine kinetics as well as the variability in the ability to glucuronidate zidovudine would indicate that there may be functional polymorphisms of UGT2B7 that affect zidovudine disposition.^{21, 22} Although several polymorphisms in the *UGT2B7* gene have been identified that could potentially impact zidovudine pharmacokinetics,^{23, 24} as far as we are aware this hypothesis has not been evaluated as yet.

In this study, we determined the pharmacokinetics of lamivudine, zidovudine and stavudine in a cohort of 27 HIV/TB co-infected Ghanaian patients receiving generic preparations of either

lamivudine/zidovudine (fixed dose combination) or lamivudine and stavudine during concurrent rifampin-containing TB therapy. In addition to comparing our results to published data for sub-Saharan black African HIV-infected patients who were not receiving rifampin-containing TB therapy, we compared lamivudine pharmacokinetics between drug formulations. We also evaluated the association between two common *UGT2B7* polymorphisms (c.735A>G, a marker for the *UGT2B7**1c allele and c.802C>T, a marker for the *UGT2B7**2 allele) and zidovudine pharmacokinetics in the 16 patients that received this drug. These pharmacogenetic results were replicated using a retrospective analysis of large bank of human livers that were phenotyped for zidovudine glucuronidation activity as well as *UGT2B7* protein and mRNA content.

METHODS

Study patients

HIV/TB co-infected patients aged 18 years or older, with CD4 cell count ≤ 250 cells/ μ l on TB therapy were enrolled. The anti-tuberculosis regimen consisted of isoniazid 5 mg/kg (max, 300 mg), rifampin 10 mg/kg (max 600 mg), pyrazinamide 25 mg/kg (max 2 gm) and ethambutol 15 mg/kg (max 2 gm) daily. All patients were also on trimethoprim-sulfamethoxazole at the time of initiating HAART and at the time of pharmacokinetic sampling. Antiretroviral therapy consisted of efavirenz 600 mg daily plus lamivudine 150 mg and zidovudine 300 mg (duovir®, Cipla, Goa, India) twice daily, or lamivudine 150 mg (Strides Arcolab, Bangalore, India) and stavudine 40 mg (Strides Arcolab, Bangalore, India) twice a daily. For patients with body weight < 50 kilograms, stavudine dose was 30 mg daily. The median duration of TB therapy to initiation of HAART was 35 (range, 14 – 70) days. Patients were instructed to switch their evening efavirenz administration to mornings three days prior to admission to the hospital for sampling. On the day of pharmacokinetic testing, all drugs including efavirenz were co-administered in the morning. The Institutional Review Boards of the University of Ghana Medical School, and The Miriam Hospital approved the study. A signed consent was obtained from all patients prior to enrolment.

Clinical monitoring and pharmacokinetic sampling

Study participants were evaluated at study entry and baseline liver function tests, CD4 cell count and HIV RNA were done prior to starting HAART. No patients discontinued study medications due to clinical or laboratory toxicity and one patient died prior to pharmacokinetic testing. To determine the steady-state pharmacokinetics of the antiretroviral drugs in a rifampin-induced state, sampling for drug concentrations were performed on day 14 of concurrent HIV and TB therapy. Blood samples were obtained at times 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after observed administration of anti-tuberculous and antiretroviral drugs. Seven to 10 milliliters of blood were collected in heparinized plastic tubes, and centrifuged at 3000 g for 10 minutes. Plasma was separated, transferred into labeled 1.2 mL cryovials, and frozen at -70°C until shipping to the United States. The frozen plasma samples were shipped on dry ice for analysis and were received in good condition. Plasma samples were stored at -70°C until drug concentration assay.

Analytical and pharmacokinetic analysis

Drug concentrations in blood plasma were measured simultaneously using a validated high-performance liquid chromatography (HPLC)/UV method.²⁵ The method was validated over the range of 10–10,000 ng/ml for all three analytes. Assay accuracy estimates determined at three different concentrations ranged from 97.2 to 105%, while within- and between-day precision measures ranged from 0.5 to 5.1% and 0.5 to 5.6%, respectively. Pharmacokinetic parameters, including the area under the concentration-time curve for the dose interval ($\text{AUC}_{0-12\text{h}}$), were estimated using WinNonlin (version 5.2, Pharsight, Inc. Mountain View,

California, USA). For drug concentration measurements below the lower limit of detection at 12 hours, AUC was computed from time 0 – the last time that drug concentration was measurable ($0-T_{last}$). For these computations, concentration measurements below the lower limit of detection were imputed as zero and those below the lower limit of quantitation (LLQ) were imputed as 50% LLQ. Weighting was applied during HPLC/UV analysis of samples, but no weighting was used for the noncompartmental pharmacokinetic analysis. Drug concentration measurements were performed at the University of North Carolina Center for AIDS Research (CFAR) Clinical Pharmacology and Analytical Chemistry Core, which is CLIA certified, and participates in quarterly national and international external proficiency testing.

Zidovudine glucuronidation, UGT2B7 protein and mRNA content

Demographic details of the 52 human liver bank samples used to prepare matched microsomes, DNA and RNA have been published previously.²⁶ Briefly, donors included 48 men and 14 women, and were primarily white American, but also included 3 African-Americans and 2 Hispanics. Mean ($\pm$ SD) donor age was 40 ($\pm$ 20) years. The human liver microsome (HLM) zidovudine glucuronidation activities and UGT2B7 protein content measurements used for analysis here have been reported in detail previously²³, while UGT2B7 and GAPDH mRNA contents have not been reported previously. Enzyme activities were expressed as nanomoles per minute per milligram of microsomal protein, while UGT2B7 specific protein content measured by immunoblotting was expressed relative to the liver with the lowest UGT2B7 content. Total RNA was also extracted from these same liver samples with Trizol reagent (Invitrogen) and used to measure UGT2B7 and GAPDH mRNA content with a branched DNA signal amplification assay. Capture well plates were from Bayer Diagnostics (QuantiGene, Bayer Diagnostics, East Walpole, Massachusetts, USA), while UGT2B7 and GAPDH specific probe sets were from XenoTech LLC (Kansa City, Kansas, USA). The assay technique was similar to that we have previously described for CYP2B6 mRNA content quantification.²⁶ Luminescence from the capture wells was measured using a luminescence counter (Wallace Trilux, #1450 Microbeta, PerkinElmer Life Sciences, Boston, Massachusetts, USA). UGT2B7 mRNA data were normalized to GAPDH data and expressed relative to the liver with the lowest value. Determinations were made in quadruplicate on 4 separate days and results averaged. Inter-assay variability averaged 29% (Spearman correlation coefficient = 0.91).

UGT2B7 genotyping

Genomic DNA was isolated from blood spots collected from patients onto Whatman FTA Classic Cards (Whatman International Ltd, Kent, United Kingdom) according to the manufacturer's protocol. Genomic DNA was also isolated from the human liver bank tissues using DNAzol reagent and stored at -80°C until use. Genotypes for the *UGT2B7* exon 2 SNPs c.802C>T (H268Y; *UGT2B7**2; rs7439366) and c.735A>G (*UGT2B7**1c; rs28365062) were determined by genomic PCR amplification and direct sequencing of exon 2 as we have previously described with minor modifications.²³ Primers included forward PRI-122, 5'-TTA TGA TTA TGA GCA TAC TGA TGC-3' and reverse PRI-123, 5'-TAC TTG CAC ATA TTC TAT CTT TTG-3'. The PCR method (GeneAmp9600, Applied Biosystems, FosterCity, CA) used an initial denaturation at 94°C for 4min, then 40 cycles of 94°C for 30s, 62°C for 30s, and 72°C for 30s, followed by 72°C for 15min. The 829-bp PCR product was treated with ExoSapit (USB Corporation, Cleveland, OH) and cycle sequenced (ABI Prism 3100, Applied Biosystems) using PRI-123. *UGT2B7**1a, *UGT2B7**2, and *UGT2B7**1c alleles (according to the UGT Allele Nomenclature Committee recommendation <http://www.ugtalleles.ulaval.ca>) were inferred from the SNP genotype data.

Statistical analysis

All analytic statistical analyses were performed using Sigmaplot 11 software (Systat, San Jose, CA). This software automatically assesses data for normality of distribution and equal variance to ensure appropriateness of parametric statistical testing methods, and if necessary, nonparametric tests are used instead. All data were summarized as mean and standard deviation (SD). Univariate analyses of effects of patient demographics on mean CL/F of each drug were assessed by unpaired t-test (gender, and alcohol use) or by linear regression (for age, body weight and body mass index, baseline CD4 cell count and HIV RNA level). A backward stepwise regression analysis containing the above patient factors was performed to identify independent variables associated with CL/F of each drug. Possible effects of *UGT2B7* allele carrier status on patient pharmacokinetic parameters and human liver zidovudine glucuronidation rate, *UGT2B7* protein and mRNA content were evaluated using Student's unpaired t-test or by Mann-Whitney rank sum test (if data showed non-normal distribution and/or unequal group variance). The effect of *UGT2B7* diplotype on zidovudine glucuronidation activities was assessed by ANOVA with post-hoc pair-wise multiple comparisons by Student-Newman-Kuels test. A *P* value of less than 0.05 was considered significant. Genotype frequencies were tested for consistency with expected Hardy-Weinberg equilibrium by Chi-squared test. Differences in allele frequencies between patient and liver bank samples were also assessed by Chi-squared test.

RESULTS

Patient characteristics

Twenty-seven HIV/TB co-infected Ghanaian patients were studied. All patients were black, had a mean ($\pm$ SD) CD4 cell count of 101 ($\pm$ 80) cells/ μ L, and included 20 males and 7 females. The mean ($\pm$ SD) age was 40.2 ($\pm$ 7.6) years, body weight was 56.1 ($\pm$ 9.7) kg and body mass index (BMI) was 19.0 ($\pm$ 3.1) kg/m².

Lamivudine, zidovudine and stavudine pharmacokinetics

The mean steady-state plasma drug concentration-time profiles of each drug for all patients are shown in Figure 1. Derived pharmacokinetic parameters are given in Table 1. All drugs were rapidly absorbed with a mean C_{max} achieved between 1 and 3 hours of administration (Figure 1). Lamivudine and zidovudine plasma concentrations were quantifiable (> 10 ng/mL) in most patients prior to dosing and at 12 hour post-dosing (Figures 1). In contrast, stavudine plasma concentrations were below the limit of quantitation for all patients prior to dosing and but one patient at 12 hour post-dosing.

The coefficients of variation for zidovudine pharmacokinetic parameters were consistently higher by as much as 2-fold compared with lamivudine and stavudine pharmacokinetic parameters (Table 1). The greatest difference was observed for body weight normalized CL/F values with a CV of 106% for zidovudine compared with 39% and 35% for lamivudine and stavudine, respectively.

Average lamivudine concentrations were consistently higher in patients who received lamivudine with stavudine as separate preparations as compared to those who received the fixed-dose co-formulated lamivudine/zidovudine tablets at each timed point (data not shown). This difference was reflected by mean lamivudine AUC and C_{max} values, which were 26% ($P=0.031$, unpaired t-test), and 41% ($P=0.025$, unpaired t-test) higher, respectively in those patients that received lamivudine with stavudine compared to the lamivudine/zidovudine preparation. Although mean body weight normalized CL/F was 12% lower in the patients that received lamivudine with stavudine, this difference did not achieved statistical significance ($P>0.05$, unpaired t-test). Lamivudine T_{max} and half-life were also not different between these

preparations ($P > 0.05$, unpaired t-test). However, there were significant differences in mean body weight (49.7 vs. 60.5 kg, $P = 0.003$, unpaired t-test), and BMI (16.9 vs. 20.4 kg/m², $P = 0.002$, unpaired t-test) between the patients that received lamivudine with stavudine compared with the lamivudine/zidovudine preparation, respectively.

Possible effects of age and body mass index (BMI) on body weight normalized CL/F of each drug were evaluated by linear regression, while sex effects were evaluated by unpaired t-test. Stavudine CL/F was somewhat higher in females ($n=3$) than in males ($n=8$) with mean ($\pm$ SD) values of 23.0 ± 6.7 and 14.0 ± 3.1 mL/min/kg, respectively ($P = 0.014$, unpaired t-test). Lamivudine CL/F normalized for body weight appeared to decline modestly with increasing age of the patients in both univariate and multivariate analysis ($P = 0.021$) (Figure 2). Sex did not appear to influence the clearance of lamivudine or zidovudine ($P > 0.05$, unpaired t-test), and BMI was not associated with clearance of any of the drugs evaluated ($R^2 < 0.30$, $P > 0.05$, linear regression).

Effect of UGT2B7 polymorphisms on zidovudine pharmacokinetics and metabolism

The *UGT2B7* exon 2 SNPs c.802C>T and c.735A>G were genotyped in the 16 patients from the pharmacokinetic study who had received zidovudine, and also in 52 of the liver bank samples that we had previously assayed for zidovudine glucuronidation activity, *UGT2B7* protein and mRNA content.^{23, 24} Derived genotype frequencies of the *UGT2B7* exon 2 SNPs c.802CC, CT and TT genotype were 62.5% ($n = 10$), 31.3% ($n = 5$) and 6.3% ($n = 1$), respectively in the 16 HIV/TB co-infected Ghanaian patients and 23.1% ($n = 12$), 42.3% ($n = 22$) and 34.6% ($n = 18$) respectively among the 52 liver samples. The genotype frequencies of the *UGT2B7* exon 2 SNPs c.735AA, AG, GG were 50.0% ($n = 8$), 37.5% ($n = 6$) and 12.5% ($n = 2$), respectively in the HIV/TB co-infected Ghanaian patients and 76.9% ($n = 40$), 21.2% ($n = 11$) and 1.9% ($n = 1$) respectively among the liver samples. The distributions of SNP genotypes were consistent with those predicted by the Hardy-Weinberg equilibrium for both patient and liver samples ($P > 0.05$).

In addition to c.802C>T being nonsynonymous (H268Y), both SNPs were chosen for this analysis because they allowed discrimination of the 3 most common *UGT2B7* alleles that have been identified to date.^{27, 28} Alleles were inferred for each patient and liver sample based on the SNP genotypes, and were either *UGT2B7**2 (c.802C>T), *UGT2B7**1c (c.735A>G) or *UGT2B7**1a (i.e. reference sequence by exclusion). These allele designations had been approved previously by the UGT Allele Nomenclature Committee (available at <http://www.ugtalleles.ulaval.ca>).

UGT2B7 allele frequencies differed somewhat between the Ghanaian patients and the (primarily white American) liver bank samples. The frequency of *UGT2B7**2 in the Ghanaian patients (0.19) was about half that of the human liver bank samples (0.38) ($X^2 = 9.9$; $P = 0.002$). In contrast, the frequency of *UGT2B7**1c in the Ghanaian patients (0.25) was over double that of the human liver bank samples (0.12) ($X^2 = 5.6$; $P = 0.017$). However, the frequency of the reference allele *UGT2B7**1a was similar in the Ghanaian patients (0.55) compared with the human liver bank samples (0.50) ($X^2 = 1.8$; $P = 0.18$).

We next evaluated the possible effects of these *UGT2B7* alleles on zidovudine pharmacokinetics. As shown in Table 2, carriers of either *UGT2B7**1a or *UGT2B7**2 did not have significant differences as compared with non-carriers for any of the zidovudine pharmacokinetic parameters evaluated. However, carriers of *UGT2B7**1c appeared to have higher zidovudine concentrations at each sampling point (Figure 3A). The carriers of *UGT2B7**1c had 57% lower mean AUC ($P = 0.029$, unpaired t-test), 196% higher mean CL/F ($P = 0.004$, unpaired t-test) (Figure 3B), and 67% shorter mean elimination half-life ($P = 0.030$, unpaired t-test) compared with non-carriers.

We then sought to confirm these findings using the human liver bank samples. As shown in Table 3 and Figure 4, *UGT2B7**1c carriers showed 48% higher mean zidovudine glucuronidation activity ($P = 0.020$, unpaired t-test) and 33% higher mean microsomal *UGT2B7* protein content ($P = 0.015$, unpaired t-test) compared with non-carriers. These effects of *UGT2B7**1c on zidovudine glucuronidation and *UGT2B7* protein were also observed when the 3 livers from non-white donors were excluded from the analysis (data not shown). Although mean *UGT2B7* mRNA content was somewhat lower in *UGT2B7**1c carriers compared non-carriers, this difference was not statistically significant ($P > 0.05$, unpaired t-test). Neither *UGT2B7**1a nor *UGT2B7**2 carriers were associated with altered zidovudine glucuronidation activity, microsomal *UGT2B7* protein content or *UGT2B7* mRNA content ($P > 0.05$, unpaired t-test) (Table 3).

Finally, we explored the possible effect of *UGT2B7* diplotype on zidovudine glucuronidation, *UGT2B7* protein and *UGT2B7* mRNA content to determine whether particular diplotypes (rather than simple variant carrier status) might explain the observed liver phenotype. As shown in figure 5, although the ANOVA indicated significant effects of diplotype on zidovudine glucuronidation activity ($P = 0.045$), with higher mean activities in *UGT2B7**1c carriers, post-hoc pairwise comparisons by Student-Newman Kuels method did not identify individual groups that were significantly different from each other. Importantly, no differences were observed between *UGT2B7**1a/*1a, *1a/*2, and *2/*2 groups suggesting that the *2 allele is not likely to have effects on activity independent of any *1c allele effect. Similar analyses of effects on diplotype on *UGT2B7* protein and mRNA content by ANOVA were not significant ($P > 0.05$, data not shown).

DISCUSSION

In this study, we determined the pharmacokinetic parameters of three commonly used generic NRTIs in HIV/TB co-infected patients who were also receiving 4-drug anti-tuberculosis therapy in resource-limited settings. To our knowledge, this is the first study to describe the steady-state pharmacokinetic profiles of generic lamivudine, zidovudine and stavudine in patients with TB/HIV coinfection on concurrent therapy. Our study is also the first to identify a significant pharmacogenetic relationship between a common *UGT2B7* allele and zidovudine clearance in human patients and also zidovudine glucuronidation in human liver.

To date, published studies of the pharmacokinetics of generic antiretroviral agents in resource-limited settings have not included patients taking known inducers or inhibitors of cytochrome P450 enzymes and drug transporters.^{11, 12, 29} Consequently, it is not known if these patients would achieve similar bioavailability of these drugs. We found the steady-state plasma AUC of lamivudine to be 0.98 times and 1.1 times that reported for generic and brand-name lamivudine (respectively) in HIV-infected Ugandan patients who were given lamivudine/stavudine/nevirapine (Triomune®, Cipla, Goa, India) and the patented versions of the drugs (Epivir®, GlaxoSmithKline, Research Triangle Park, NC, USA; Zerit®, Bristol Myers Squibb, Princeton, NJ, USA; Viramune®, Boehringer Ingelman, Columbus, OH, USA).¹¹ Furthermore, the steady-state plasma AUC of stavudine was 1.5 and 1.3 times that reported for generic and brand-name stavudine (respectively) in the above-mentioned study.¹¹ We were not able to identify published studies that have evaluated zidovudine pharmacokinetics in HIV-infected black Africans. However the zidovudine AUC in our patients was 0.78 and 0.84 of values reported for generic and brand name zidovudine (respectively) in HIV-negative Indian women.²⁹ These comparisons to published data suggest that lamivudine and stavudine concentrations in the TB/HIV co-infected patients in present study were at least similar to (or perhaps slightly higher than, in the case of stavudine) other patients that were not taking TB medications. The 14 to 21% lower zidovudine AUC in our patients is consistent with induction of zidovudine clearance by rifampin, though it is lower than the 47 – 50% reduction previously

reported.^{5, 6} The apparent minimal effect of rifampin on zidovudine AUC in our study could be due to population differences between our patients and the historical controls and/or the effect of concurrent medications such as trimethoprim/sulfamethoxazole. Trimethoprim with or without sulfamethoxazole has been shown to decrease zidovudine renal clearance,^{30, 31} and could have in part minimized the induction effect of rifampin in our study population.

We observed high variability in zidovudine clearance (over 100% coefficient of variation) relative to the clearance of stavudine and lamivudine. The mechanism underlying this high variability of zidovudine is not well understood but may involve polymorphisms in genes encoding proteins involved in zidovudine disposition, including *UGT2B7*. In previous work using our human liver bank, we determined that the most common *UGT2B7* nonsynonymous SNP (c.802C>T, *UGT2B7**2) was not associated with altered zidovudine glucuronidation or *UGT2B7* protein expression.²³ These findings were independently confirmed in a more recent study of human liver bank samples by Peterkin et al.³² *UGT2B7* gene re-sequencing by several groups have identified other polymorphisms, many of them in linkage disequilibrium within discrete haplotype blocks.^{27, 28} Consequently in addition to *UGT2B7**2, we also assayed for the common SNP c.735A>G (defining the *UGT2B7**1c allele) and showed higher *in vivo* clearance and also faster hepatic glucuronidation of zidovudine in individuals carrying this allele. Such similar results in two clearly distinct populations (i.e. HIV-infected Ghanaian patients and white American liver donors) suggest that these genotype-phenotype associations are unlikely to have occurred simply by chance. Rather, it implies that the c.735A>G SNP, or perhaps another variant in significant linkage disequilibrium with this SNP (in both white and black populations), may provide a mechanistic explanation for enhanced *UGT2B7* gene expression.

An important and novel finding of this study is that c.735A>G (*UGT2B7**1c) was significantly associated with higher zidovudine glucuronidation activity as well as *UGT2B7* protein content in a human liver bank, confirming the *in vivo* association between *UGT2B7**1c and zidovudine clearance. This association is also confirmed in part by a recent study by Innocenti *et al* that showed about 45% faster 3-hydroxy-glucuronidation of morphine (another *UGT2B7* substrate) in human livers that carried the intron 1 SNP (IVS1 +985A>G).²⁴ This latter SNP is in significant linkage disequilibrium with c.735A>G and also the exon 4 SNP (c.1062C>T). Although they did not measure hepatic *UGT2B7* protein content, they did evaluate *UGT2B7* mRNA content and splicing. Similar to our findings with zidovudine, they also found no effect of *UGT2B7**2 on morphine 3-glucuronidation or on *UGT2B7* mRNA expression.²⁴ However, in contrast to our study, where *UGT2B7* mRNA levels were unchanged, they found higher *UGT2B7* mRNA expression in carriers of the intron 1 SNP. This discrepancy may relate to the mechanism by which these noncoding SNPs may alter gene expression through alteration of mRNA splicing regulatory elements, as was proposed by Innocenti *et al*.²⁴ Several splice variants of *UGT2B7* have been observed, and it is possible that our mRNA assay differed from Innocenti's assay in the splice forms quantified.²⁴ For example, our mRNA assay may have quantified total *UGT2B7* mRNA forms including those that were aberrantly spliced and predicted to result in truncated *UGT2B7* protein.

Polymorphisms in other genes associated with zidovudine disposition such as those encoding drug transporters have the potential to explain the variability in zidovudine clearance observed in this study and warrant future evaluation. A trend ($P=0.06$) for elevated peripheral blood mononuclear cell zidovudine triphosphate levels was observed in carriers of the *ABCC4* (MRP4) c.3724G>A variant.⁴

The clinical relevance of the association between *UGT2B7* genetic variation and zidovudine metabolism and disposition is as yet unclear. Zidovudine like all NRTIs require intracellular phosphorylation to form the active triphosphate moieties that exert clinical effect.³³ While

zidovudine pharmacologic variability affects treatment response,³⁴ no relationship between plasma zidovudine concentrations and clinic effect has been demonstrated. However, percent change in CD4 cell count and rate of decline in HIV RNA in plasma during zidovudine-containing therapy were related to intracellular concentrations of zidovudine triphosphate.^{35, 36} Furthermore, a higher total intracellular concentration of the phosphorylated moieties of zidovudine was associated with increased probability of reduced hemoglobin levels.³⁷ As the relationship between zidovudine plasma exposure and intracellular triphosphate concentrations is currently not predictable, further studies are needed to define the influence of *UGT2B7*1c* carriers status on intracellular concentrations of zidovudine-triphosphate, as well as clinical effect (efficacy and toxicity).

We also investigated potential patient factors that may influence the pharmacokinetic profile of each of the drugs evaluated. Except for a possible small effect of sex on stavudine CL/F normalized for body weight and age on lamivudine CL/F normalized for body weight, patient demographics did not appear to influence drug exposure in our population. However, these results should be interpreted with caution, as the study was not powered sufficiently to detect relatively small differences. The effect of sex on stavudine clearance is not known as few studies have explored the influence of sex on the disposition of antiretrovirals,³⁸ and the largest and most comprehensive previous pharmacokinetic study of 81 patients included only 7 women.⁸ The observed influence of age on lamivudine CL/F needs to be validated in a larger population. Though, it has been shown that children younger than 12 years old tend to have higher values for lamivudine CL/F than children aged 12 – 18 years old, age has not been shown to influence lamivudine CL/F in adults.³⁹

There are no known interactions between lamivudine and zidovudine or stavudine.^{40, 41} The lower AUC of lamivudine observed in the patients who received the co-formulated tablets lamivudine/zidovudine compared to the separate lamivudine tablets given with stavudine could be due to the significant differences in body weight or BMI between the two groups. Clearance and half-life of lamivudine did not differ between the two groups to suggest differences in elimination of the drug.

We recognize that our study had some limitations. The size of the study population was small and so failure to find significant relationships between pharmacokinetic parameters of some of these drugs and patient factors such as age, sex, BMI does not exclude the existence of significant relationships. Comparison of drug exposure in our study patients to historical controls rather than an appropriate control that did not receive rifampin-containing TB therapy does not allow us to exclude the effect of population differences. The differences in lamivudine exposure between patients who received lamivudine/zidovudine and lamivudine/stavudine should also be interpreted with caution as it may be due to differences in disease state, as patients who had hemoglobin < 8g/dL were preferentially given stavudine. Rifampin is known to induce the activity of UGT2B7,^{5, 6} and trimethoprim has been shown to decrease renal clearance of zidovudine by 58% during coadministration but had no influence on the ratio of zidovudine glucuronide to zidovudine.^{30, 31} Although, these patients were on several concurrent medications including rifampin and trimethoprim-sulfamethoxazole, we do not think the concurrent medications confounded the relationship between UGT2B7 polymorphism and zidovudine metabolism as all patients received these medications at the time of initiation of HAART and at the time of PK testing.

Despite the above limitations, this pilot study provides important pharmacokinetic data on commonly used generic NRTIs in HIV/TB co-infected patients receiving concurrent TB therapy, and identifies a novel association between *UGT2B7* genetic variation and zidovudine metabolism and disposition. The influence of *UGT2B7*1c* carriers status on intracellular concentrations of zidovudine and its metabolites, as well as clinical effect (efficacy and toxicity)

needs to be investigated as it may have implications for individualized therapy or dosing of zidovudine.

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Figure 1.

Mean steady-state plasma concentration-time profiles of lamivudine, zidovudine and stavudine in HIV/TB co-infected patients during concurrent HIV and TB therapy. Of the 27 total patients studied, 16 patients received the lamivudine with zidovudine (fixed dose combination) and 11 patients received lamivudine with stavudine. Error bars indicate standard error of the mean.

Figure 2.

Relationship between apparent oral clearance of lamivudine normalized for body weight and the age of HIV/TB co-infected patients receiving lamivudine, with zidovudine or stavudine. All the patients received efavirenz, 4-drug TB therapy, as well as trimethoprim-sulfamethoxazole.

Figure 3. Effect of *UGT2B7**1c allele on mean ($\pm$ SE) zidovudine concentration-time profile (**A**) and body weight normalized apparent oral clearance (**B**). Differences between carrier and non-carrier groups were evaluated by Mann-Whitney rank sum test. Horizontal bars represents median.

Figure 4.

Effect of *UGT2B7**1c allele on glucuronidation of zidovudine (A), relative UGT2B7 protein content in human liver microsomes (B) and relative mRNA (C). Differences between carrier and non-carrier groups were evaluated by unpaired t-test (protein and mRNA), or by Mann-Whitney rank sum test (zidovudine glucuronidation).

Zidovudine glucuronidation activity

Figure 5.

Effect of *UGT2B7* genotype on liver zidovudine glucuronidation activity. Bars represent mean $\pm$ SD values and group differences were evaluated by ANOVA.

Table 1

Plasma pharmacokinetic parameters for lamivudine, zidovudine, and stavudine in 27 Ghanaian HIV/TB co-infected patients. All patients also received efavirenz and rifampin-containing TB therapy. Values represent mean $\pm$ SD (coefficient of variation).

Parameter	Lamivudine (n=27)	Zidovudine (n=16)	Stavudine (n=11)
C _{max} (ng/mL)	1095 $\pm$ 506 (46%)	1092 $\pm$ 811 (74%)	310 $\pm$ 173 (56%)
T _{max} (h)	2.3 $\pm$ 1.5 (66%)	1.6 $\pm$ 1.1 (70%)	2.6 $\pm$ 1.6 (63%)
Half life (h)	4.2 $\pm$ 1.9 (46%)	8.1 $\pm$ 7.9 (98%)	1.5 $\pm$ 1.0 (65%)
AUC (ng/mL*h)	5843 $\pm$ 2580 (44%)	3368 $\pm$ 2747 (82%)	865 $\pm$ 223 (26%)
CL/F (mL/min/kg)	7.3 $\pm$ 2.8 (40%)	31.9 $\pm$ 33.6 (106%)	16.4 $\pm$ 5.8 (35%)
Vd/F (L/kg)	2.6 $\pm$ 1.5	9.9 $\pm$ 4.7	1.7 $\pm$ 0.7

C_{max}, peak concentration; T_{max}, time to peak concentration; h, hour; AUC, area under curve; CL/F, apparent oral clearance normalized for body weight; Vd/F, volume of distribution normalized for body weight.

Table 2

Effect of *UGT2B7* allele on mean $\pm$ SD zidovudine pharmacokinetic parameters measured in 16 HIV/TB co-infected patients who were also receiving lamivudine and rifampin-containing therapy.

Parameter	UGT2B7*1a non-carriers	UGT2B7*1a carriers	P value ^a
Number of patients	5	11	
C _{max} (ng/mL)	830 $\pm$ 224	1310 $\pm$ 909	0.271
T _{max} (h)	1.5 $\pm$ 0.6	1.6 $\pm$ 1.3	0.884
Half-life (h)	5.3 $\pm$ 7.2	9.4 $\pm$ 8.3	0.247 ^b
AUC (ng/mL*h)	2945 $\pm$ 1739	3867 $\pm$ 3061	0.552 ^b
CL/F (mL/min/kg)	38.3 $\pm$ 28.6	28.9 $\pm$ 36.5	0.365
Vd/F (L/kg)	8.5 $\pm$ 5.9	10.5 $\pm$ 4.2	0.453
	UGT2B7*1c non-carriers	UGT2B7*1c carriers	
Number of patients	8	8	
C _{max} (ng/mL)	1302 $\pm$ 968	1018 $\pm$ 550	0.842 ^b
T _{max} (h)	1.4 $\pm$ 1.2	1.8 $\pm$ 1.1	0.274 ^b
Half-life (h)	12.2 $\pm$ 9.0	4.0 $\pm$ 4.0	0.030^b
AUC (ng/mL*h)	4997 $\pm$ 3187	2160 $\pm$ 879	0.029
CL/F (mL/min/kg)	16.1 $\pm$ 19.8	47.6 $\pm$ 38.2	0.004^b
Vd/F (L/kg)	10.3 $\pm$ 5.4	9.4 $\pm$ 4.2	0.727
	UGT2B7*2 non-carriers	UGT2B7*2 carriers	
Number of patients	10	6	
C _{max} (ng/mL)	1283 $\pm$ 963	956 $\pm$ 319	0.444
T _{max} (h)	1.8 $\pm$ 1.3	1.3 $\pm$ 0.7	0.634 ^b
Half-life (h)	6.7 $\pm$ 8.0	10.5 $\pm$ 8.1	0.369
AUC (ng/mL*h)	3553 $\pm$ 3346	3623 $\pm$ 1262	0.293 ^b
CL/F (mL/min/kg)	41.0 $\pm$ 39.5	16.7 $\pm$ 11.6	0.168
Vd/F (L/kg)	10.2 $\pm$ 5.1	9.3 $\pm$ 4.2	0.728

^a Group differences were evaluated by unpaired t-test or by

^b rank sum test if data were not normally distributed or showed unequal variance.

C_{max}, peak concentration; T_{max}, time to peak concentration; h, hour; AUC, area under curve; CL/F, apparent oral clearance normalized for body weight; Vd/F, volume of distribution normalized for body weight.

Table 3

Effect of *UGT2B7* allele on mean $\pm$ SD zidovudine glucuronidation activity and relative *UGT2B7* protein and mRNA content measured in 52 human liver bank samples.

Parameter	UGT2B7*1a non-carriers	UGT2B7*1a carriers	P value ^a
Number of livers	45	7	
Zidovudine glucuronidation (nmoles/min/mg protein)	0.059 $\pm$ 0.027	0.054 $\pm$ 0.025	0.646
UGT2B7 protein (relative to lowest)	7.75 $\pm$ 2.86	7.25 $\pm$ 4.10	0.864 ^b
UGT2B7 mRNA (relative to lowest)	3.73 $\pm$ 2.25	3.56 $\pm$ 2.03	0.969 ^b
	UGT2B7*1c non-carriers	UGT2B7*1c carriers	
Number of livers	40	12	
Zidovudine glucuronidation (nmoles/min/mg protein)	0.052 $\pm$ 0.022	0.077 $\pm$ 0.032	0.020^b
UGT2B7 protein (relative to lowest)	7.14 $\pm$ 3.00	9.51 $\pm$ 2.32	0.015
UGT2B7 mRNA (relative to lowest)	3.75 $\pm$ 2.03	3.61 $\pm$ 2.77	0.863
	UGT2B7*2 non-carriers	UGT2B7*2 carriers	
Number of livers	12	40	
Zidovudine glucuronidation (nmoles/min/mg protein)	0.066 $\pm$ 0.032	0.056 $\pm$ 0.024	0.238
UGT2B7 protein (relative to lowest)	8.62 $\pm$ 3.73	7.40 $\pm$ 2.75	0.160 ^b
UGT2B7 mRNA (relative to lowest)	2.91 $\pm$ 1.63	3.97 $\pm$ 2.32	0.188

^a Group differences were evaluated by unpaired t-test or by

^b rank sum test if data were not normally distributed or showed unequal variance.