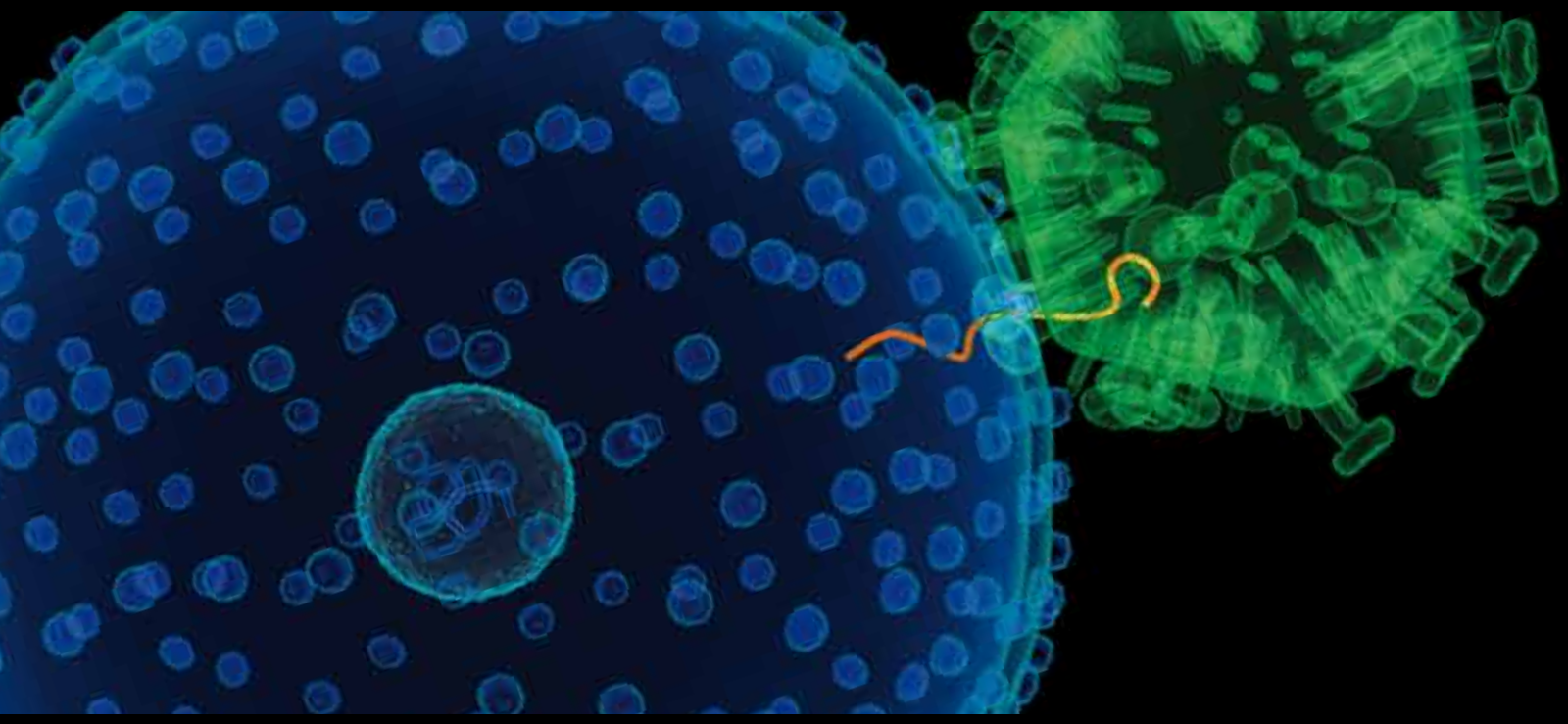
AIDS Research and Treatment

Global HIV/AIDS Clinical and Translational Pharmacology

Guest Editors: Gene D. Morse, Gary Maartens, Charles Chiedza Maponga, and Qing Ma



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Editorial Board

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Editorial

Global HIV/AIDS Clinical and Translational Pharmacology

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The continued development of diagnostic and therapeutic advances for HIV has transformed this once rapidly fatal infection into a chronic disease with an extended lifespan. Initially these benefits were only available to patients in resource-rich countries (RRCs), but since 2003 there has been a global effort through donors and access pricing to provide antiretroviral access to the millions of HIV-infected individuals in resource-limited countries (RLCs) [1–4]. Current combination antiretroviral therapy (cART) achieves viral suppression in a majority of adherent patients [5]. Viral load tests with greater sensitivity have led our appreciation of continued low-level viremia in apparently "suppressed" patients cART while assays that detect latent tissue reservoirs with integrated viral DNA have provided new insight into treatment goals, the source of viral rebound when treatment is interrupted, and the lack of further benefit from treatment intensification [6–11]. A sustained chronic inflammatory state thought to arise in part from translocation of gut microbial products, even during suppressive cART, has led to new mechanistic understanding of chronic ART effects on end organs [12, 13]. These advances have led to new research efforts to augment suppression with pharmacologic strategies to purge the latent viral reservoirs and reduce translocation of intestinal microbial products, to reduce end-organ disease including cardiovascular, neurologic, renal, and bone. The presence of opportunistic infections such as tuberculosis and coinfections including malaria and viral hepatitis (HCV, HBV), as well as cancer, creates additional diagnostic and therapeutic challenges [14].

Clinical and translational pharmacology researchers have made important contributions to our understanding of the complex relationship between antiretroviral pharmacokinetics, pharmacodynamics, and pharmacogenomics [15–27]. As cART regimens are optimized their use in patients with comorbidities is complicated by pharmacologic challenges that include maintaining medication adherence, preventing and managing drug-drug interactions, identifying optimal doses for malnourished patients, drug toxicity monitoring, and pharmacogenomic testing. Each of these areas contributes to the goal of maximizing ART exposure while minimizing risk factors that lead to complications of chronic cART and concurrent medication use. As a result of efforts to treat as many HIV-infected individuals as possible, the requirement for medications for comorbid diseases, the challenge to conducting relevant clinical pharmacology research as quickly as possible is considerable [28]. Ongoing research in the areas of preexposure prevention with oral ART or vaginal or rectal microbicides, and "treatment as prevention" to reduce new HIV infections, along with nanomedicine strategies, pediatric cART dosing, pregnancy, and geriatric considerations also include therapeutic drug monitoring and novel clinical pharmacology components [29–41].

In this special issue, some of these challenges are addressed. With varied global dietary patterns as well as nutritional status, M. Lamorde et al. report on their investigation of "*Effect of food on the steady-state pharmacokinetics of tenofovir, and emtricitabine plus efavirenz in Ugandan adults.*" Other important patient factors are addressed

by T. Kakuda et al. in their study of the "*Pharmacokinetics and pharmacodynamics of darunavir and etravirine in HIV-1-infected, treatment-experienced patients in the gender, race, and clinical experience trial.*" T. Mudzviti et al. have examined "*The impact of herbal drug use on adverse drug reaction profiles of patients on antiretroviral therapy in Zimbabwe*" and A. Reda et al. investigated the "*Determinants of adherence to antiretroviral therapy among HIV-infected patients in Africa.*" With regard to coinfections, F. Fehintola et al. studied "*nevirapine-based antiretroviral therapy impacts artesunate and dihydroartemisinin disposition in HIV-infected Nigerian adults.*" W. WirachMaek-a-nantawat et al. have provided a review *of "Challenges in providing treatment and care for viral hepatitis among individuals co-infected with HIV in resource-limited settings.*" Lastly, in a comprehensive review article K. Dooley et al. have reported on "*TB and HIV therapeutics: pharmacology research priorities.*"

In summary, this issue provides some excellent examples of research groups that are leading the way while additional planning and capacity building proceed. The need to conduct clinical pharmacology research is essential and will require expanding research facilities with instrumentation and training for the next generation of researchers in this field. The conduct of this comprehensive research agenda will be facilitated through planning of a global, translational pharmacology research effort that includes academic, industrial, regulatory, and community partnerships in RRCs and RLCs. The need for human and laboratory capacity building integrated with a comprehensive clinical pharmacology quality assurance program is significant and should be further integrated with research planning and implementation on a global scale. This approach is likely to accelerate the use of new treatments in countries that are most impacted by HIV and other infectious diseases within the global community. The Fogarty International Center at the National Institutes of Health in the United States, along with other international research funders like the Wellcome Trust and the European and Developing Countries Clinical Trials Partnership, is training current and future global health scientists. The mechanism for building new research centers with state of the art instrumentation remains a challenge to meeting clinical pharmacology research needs around the world. Development of a plan to address these needs is the focus of an annual workshop at the International AIDS Conference and has provided a forum for discussion, needs assessment, and strategic planning to advance this effort.

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Review Article

TB and HIV Therapeutics: Pharmacology Research Priorities

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An unprecedented number of investigational drugs are in the development pipeline for the treatment of tuberculosis. Among patients with tuberculosis, co-infection with HIV is common, and concurrent treatment of tuberculosis and HIV is now the standard of care. To ensure that combinations of anti-tuberculosis drugs and antiretrovirals are safe and are tested at doses most likely to be effective, selected pharmacokinetic studies based on knowledge of their metabolic pathways and their capacity to induce or inhibit metabolizing enzymes of companion drugs must be conducted. Drug interaction studies should be followed up by evaluations in larger populations to evaluate safety and pharmacodynamics more fully. Involving patients with HIV in trials of TB drugs early in development enhances the knowledge gained from the trials and will ensure that promising new tuberculosis treatments are available to patients with HIV as early as possible. In this review, we summarize current and planned pharmacokinetic and drug interaction studies involving investigational and licensed tuberculosis drugs and antiretrovirals and suggest priorities for tuberculosis-HIV pharmacokinetic, pharmacodynamic, and drug-drug interaction studies for the future. Priority studies for children and pregnant women with HIV and tuberculosis co-infection are briefly discussed.

1. Introduction

The spread of HIV has fueled the tuberculosis (TB) epidemic, and in less-developed countries, TB is the most common cause of death in HIV-infected individuals, accounting for 22% (350,000) of HIV-related deaths globally [1]. In 2010, 1.1 million of the 8.8 million incident cases of TB worldwide were among people living with HIV [2]. For patients with HIV and TB, there is now strong evidence that treating both diseases concurrently rather than waiting until TB treatment is complete to start antiretroviral (ARV) drugs decreases mortality [3–6]. For this reason, cotreatment is now the standard of care for most patients. Treatment of drug-sensitive TB still requires 6 months of multidrug therapy, but strategies to shorten the treatment duration are being explored and must be tested among patients with and without HIV infection. The coepidemics of TB and HIV have also fostered the global emergence of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB. As such, there is an urgent need for new TB drugs and drug combinations as well as improved approaches to the treatment of TB, particularly in the context of HIV infection. While the current pipeline of new drugs for TB is more robust than it has ever been, advanced planning and active fostering of pharmacokinetic (PK) and pharmacokinetic interaction (PKI) studies with other antimicrobials and ARV drugs are critical to accelerating development and access of new drugs for populations affected by HIV coinfection. These studies are needed to explore the pharmacologic compatibility and tolerability of future combination drug regimens for HIV-TB-coinfected populations. While some PKI studies can be conducted initially among healthy HIV-seronegative volunteers, especially when metabolic drug interactions are expected to result in the need for dose adjustments, it is essential that follow-up studies be conducted among patients with HIV and/or TB so that variability in PK and pharmacokinetic/pharmacodynamic (PK/PD) relationships can be fully explored.

Many of the potential drug interactions between anti-tuberculosis drugs (both current and in development) and ARV drugs have yet to be evaluated. Current dosing strategies, in these instances, are often based on suboptimal data and/or expert opinion. Furthermore, the need for such data is amplified when applied to special populations, such as,

pregnant women and children, as their dosing guidelines are often based on limited data even when HIV coinfection is not a pertinent factor. The first step in addressing these priorities is the design and implementation of early phase clinical trials, including PK and PKI studies that will inform later-phase treatment trials and allow for inclusion of HIV-infected patients taking ARVs in clinical trials of TB regimens. Early consideration and planning of key studies needed in this regard are required to avoid delay in the successful implementation of key treatment strategies for both drug-sensitive and drug-resistant TB in populations living with HIV.

2. Studies of FDA-Approved TB Drugs with ARVs

2.1. Rifampin and Rifabutin. Rifamycin antibiotics are an essential part of multidrug regimens for the treatment of drug-sensitive TB. Up to now, no regimen has been identified that effectively treats TB for six months or fewer that does not include a rifamycin throughout treatment [7, 8]. Rifampin (RMP), though, is a promiscuous inducer of drug metabolizing enzymes and drug transporters, and rifamycins reduce concentrations of companion drugs, including ARVs, that are metabolized by cytochrome (CYP) P450 or Phase II enzymes [9]. While efavirenz (EFV-)based antiretroviral therapy (ART) can be used safely together with standard RMP-containing TB regimens in adults, [10, 11] drug-drug interactions between nevirapine (NVP) and RMP are more significant and can potentially lead to clinically significant decreases in NVP plasma concentrations and HIV treatment failure [12]. Also, the effects of RMP on EFV concentrations may depend on a patient's *CYP2B6* metabolizer status; among extensive EFV metabolizers, RMP appears to reduce EFV concentrations, while EFV concentrations are increased among slow EFV metabolizers [13, 14]. Furthermore, there are few options for patients who are resistant to or intolerant of nonnucleoside reverse transcriptase inhibitors (NNRTIs). RMP decreases the plasma concentration of protease inhibitors (PIs) to subtherapeutic levels when the PIs are given at standard doses [15–18]. Coadministration of the PI at higher doses or super-boosting the PI with higher doses of ritonavir (RTV, or r) may result in unacceptably high rates of liver toxicity [18–21]. To complicate things further, risk of toxicity with double-dose or super-boosted PIs varies by patient population (healthy volunteers, children, or adults) and the PI used, as well as other factors, such as preexisting hepatic disease, HIV status, use of companion drugs, such as, isoniazid, and age.

Although rifabutin (RBT) is a less potent inducer of cytochrome P450 enzymes and is less likely to reduce concentrations of coadministered PIs, it is not yet widely available in developing countries, though access is rapidly expanding [22]. Further, RBT (and its main metabolite) are substrates of CYP3A, [23] leading to bidirectional drug interactions with PIs. For example, giving RTV, a potent inhibitor of CYP3A, together with RBT increases concentrations of RBT and its 25-O-desacetylrifabutin metabolite substantially [24]. This is concerning because rifabutin-induced uveitis is thought to be dose dependent. Though it is clear that RBT dose must be reduced when RBT is given together with RTV-boosted PIs, the optimal dose and dosing frequency has not been determined experimentally. Reducing the dose from 300 mg daily (standard dose) to 150 mg thrice weekly so that RBT can be given together with PIs may be associated with subtherapeutic levels of RBT, [7] especially in HIV-infected persons, leading to increased risk of treatment failure and development of drug resistance [8]. Reducing the dose to 150 mg but giving it once daily with RTV-boosted PIs results in therapeutic or supratherapeutic RBT concentrations, reducing the risk of TB treatment failure, but the associated risk of toxicities, such as, uveitis or neutropenia related to elevated parent drug and metabolite exposures is unknown.

Better strategies for cotreating HIV and TB in patients with NNRTI resistance/intolerance are urgently needed. There are 3 potential strategies that can address these issues with currently available anti-TB drug regimens.

(1) *Optimize the Dose of RBT and Use PI-Based HAART*. This approach requires determination of the best dose of RBT when used in combination with various PI-based ARV regimens. The French Agence Nationale de Recherche sur le SIDA (ANRS) recently sponsored a study to evaluate the pharmacokinetics of RBT combined with antiretroviral therapy (EFV, NVP, or lopinavir (LPV)/r) in patients with TB-HIV coinfection in South Africa (RBT 450 mg once daily (QD) versus RBT 600 mg QD with EFV; RBT 300 mg QD versus RBT 450 mg QD with NVP; RBT 150 mg three times per week (TPW) versus RBT 150 mg QD with LPV/r) (NCT00640887, results awaiting publication) and is currently sponsoring a study of RBT 150 mg TPW versus QD and LPV/r in Vietnam (NCT00651066). Another current study being performed at the Harriet Shezi Children's Clinic in South Africa will evaluate the dosing, safety, and pharmacokinetic profile of RBT in children receiving concomitant treatment with LPV/r and RBT (NCT01259219). Lastly, ACTG 5290 is a trial sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID) and performed by the AIDS Clinical Trials Group (ACTG) that will evaluate RBT 150 mg QD when given with standard dose LPV/r with or without raltegravir (RAL) versus a RMP-based TB treatment with double-dose LPV/r (all as part of multidrug TB and HIV treatment) among HIV-infected participants with TB. In this study, the PK of RBT will be evaluated, and safety and treatment efficacy data will be collected. Following an initial stage to obtain PK and safety data, the doses of RBT and LPV/r may be adjusted prior to proceeding to the second stage of the study.

(2) *Keep RMP and Give PI-Based HAART but Increase the Dose of the PI or Its Pharmacoenhancer*. This approach requires determination of the optimal dose of the PI of interest along with its paired pharmacoenhancer (usually RTV). In a small group of patients with HIV in South Africa taking LPV/r at standard doses,

a gradual stepwise increase in LPV/r dose from 400/100 mg to 800/200 mg when RMP was added was relatively well tolerated with less hepatotoxicity than has been seen in studies in healthy HIV-seronegative volunteers, but this strategy remains to be tested in a larger cohort [25]. The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) is currently evaluating the PK and safety of two different doses of LPV/r in HIV-TB-coinfected patients receiving RMP-containing antituberculosis therapy (NCT01138202). Another study by the Oswaldo Cruz Foundation and Abbot Pharmaceuticals is evaluating the pharmacological interaction of LPV/r and RMP (A06-295) (NCT00771498). Lastly, as noted above, ACTG 5290 will also address this question with an arm that tests the antiviral efficacy and safety of double-dose LPV/r + RMP. Besides these studies, trials to determine the optimal dose of other PIs such as darunavir (DRV) are needed. No PKI studies involving cobicistat, a novel pharmacoenhancer, with a coadministered PI and RMP have been conducted.

(3) *Keep RMP and Use an Integrase Inhibitor instead of or in Combination with a PI*. This strategy requires evaluation of the antiviral effectiveness of this approach among coinfected patients. RAL is metabolized by UDP-glucuronosyltransferase (UGT) 1A1, an enzyme that is induced by rifamycins. Initial PK studies among healthy volunteers demonstrated that giving RAL at twice the standard dose (800 mg twice daily) with RFP resulted in similar overall RAL exposures as RAL given at 400 mg twice daily alone, but trough concentrations were diminished [26]. Though low trough concentrations of RAL when the drug is given once daily are associated with virologic failure [27, 28], the clinical significance of reductions in trough concentrations when RAL is given twice daily is unknown. In the REFLATE trial, ANRS is evaluating higher doses of RAL together with an NRTI backbone among patients taking RMP-based TB treatment (NCT00822315). Clinically relevant results, including virologic suppression and immunologic response, will help guide recommendations for this possible combination. One study evaluating the effect of thrice weekly RMP on RAL concentrations is being planned, and this will contribute to our knowledge about the relationship between RMP dosing frequency and induction of metabolizing enzymes (NCT01424826). Intermittent dosing of RMP, though, is not recommended for patients with HIV and low CD4+ lymphocyte counts. A Phase 1 study evaluating the effect of RMP on dolutegravir, a new-generation integrase inhibitor, in healthy HIV-seronegative volunteers has shown promising results, but TB-HIV regimens including RMP and dolutegravir must be tested in patients to ensure HIV treatment efficacy with this strategy (NCT01231542).

Three studies evaluating the treatment-shortening potential of higher-dose RMP are in development, sponsored by the Division of Microbiology and Infectious Diseases (DMID) at NIH and the European and Developing Countries Clinical Trials Partnership (EDCTP) (HighRIF NCT00760149; HR1 NCT01392911; HIRIF NCT01408914). Should higher-dose RMP prove effective for shortening the duration of treatment needed for drug-sensitive TB, then evaluation of the relationship between RMP dose and induction of the enzymes that play a major role in biotransformation of ARVs, such as CYP3A, CYP2B6, and UGT1A1 should be explored.

2.2. Rifapentine. Approved by the Food and Drug Administration (FDA) for the treatment of TB in 1998, rifapentine (RPT) is the most recently licensed TB drug and is the newest of the rifamycins. In mouse studies, RPT has potent activity, and substitution of RMP with RPT allows for shortening of treatment duration for drug-sensitive TB when given as part of a multidrug regimen. However, the currently approved dosing regimen (600 mg twice weekly during the intensive phase of TB treatment and 600 mg once weekly during the continuation phase of TB treatment) has been associated with treatment failure and development of rifamycin resistance in some populations, including those with advanced HIV [29]. Some feel that intermittent dosing of isoniazid, which has a short half life, and RPT, which has a longer half life, results in "PK mismatch," leading to periods of effective monotherapy which promote the emergence of rifamycin resistance, and this issue remains hotly debated and is of considerable clinical importance [30–32]. One multicenter randomized controlled trial (RIFAQUIN) is evaluating RPT given together with moxifloxacin, two drugs with similar half lives, once or twice weekly during the continuation phase of TB treatment (http://www.edctp.org/). Total treatment duration will be four months (two months of daily moxifloxacin, rifampin, pyrazinamide, and ethambutol followed by two months of once- or twice-weekly moxifloxacin and RPT).

Three studies to determine the optimal daily dose of RPT as part of multidrug treatment for TB are currently enrolling, including a study evaluating RPT doses up to 20 mg/kg daily (TBTC Study 29X) given together with standard companion drugs (isoniazid (INH), pyrazinamide, and ethambutol), one study evaluating daily RPT doses of 450 and 600 mg (with standard companion drugs), and another testing substitution of moxifloxacin for INH and substitution of RPT at a dose of 300–450 mg daily for RMP, (NCT00728507, NCT00814671, NCT00694629). An ACTG study of different dosing strategies to maximize drug exposure, including divided dosing and different meal types is also in the planning stages. Thus, the optimal dosing frequency, dose, and companion drugs for RPT for the treatment of active TB are under active investigation.

RPT induces P450 metabolizing enzymes and Phase II enzymes, similar to its analogue, RMP. The risk of drug interactions when RPT is given together with ARVs that are P450 substrates or are metabolized by Phase II enzymes is high. A study of the effect of daily versus once weekly RPT on RAL in healthy individuals by the Tuberculosis Clinical Trials Consortium (TBTC) has recently been completed, and results are expected soon (NCT00809718). In this study,

as well as the RIFAQUIN study, the relationship between RPT dosing intermittency and the induction of the Phase II enzymes that metabolize RAL and moxifloxacin, respectively, is being explored. Other PKI studies with ARVs that require consideration are studies of daily RPT once the optimized dose is determined plus EFV, NVP, and key PIs, such as, RTV-boosted LPV and DRV. A recent study evaluating CYP3A induction by RPT using oral midazolam as a probe drug revealed that RPT may have greater induction effects than RMP at clinically relevant doses, so recommendations for dose adjustments based on RMP drug-drug interaction studies may not be readily extrapolated to RPT [33]. ACTG 5279 is a trial evaluating the efficacy of one month of daily RPT (dosed at 450 or 600 mg, depending on weight) + INH versus 9 months of daily INH for the treatment of latent TB infection (LTBI) in HIV-infected individuals (NCT01404312). This trial includes an evaluation of the drug-drug interaction between RPT and NNRTIs.

A recent, large, randomized clinical trial showed that directly observed therapy with RPT and INH, each given once weekly for twelve weeks, was noninferior to INH given daily for nine months for the treatment of LTBI [34]. The relationship between dosing frequency and induction of P450 enzymes by RPT has not been tested, so PKI studies involving RPT dosed weekly and key ARVs are warranted to ensure that this 12-week LTBI treatment is safe for patients with HIV taking ARVs and does not compromise the efficacy of their HIV treatment.

2.3. Isoniazid. Lastly, given the growing practice of treating LTBI in HIV-infected individuals with INH in developing countries, the effects of INH on the kinetics of companion ARVs, namely, EFV and LPV/r, should be evaluated. INH is a potent inhibitor of CYP2C19 and CYP3A metabolizing enzymes [35], and while the inducing effects of RMP overpower the inhibitory effects of INH when used together, the effects of INH in the absence of RMP have not been well delineated.

3. HIV-TB PKI Studies of Select TB Drugs in the Pipeline

The current pipeline of new TB drugs represents the most robust portfolio of new drugs in development in the history of TB research. Many of these drugs have advanced to Phase 2 studies and offer the potential for increasingly efficacious TB regimens for both drug-sensitive and drug-resistant disease. Though they represent the future of TB treatment strategies, some of them have or are expected to have clinically significant interactions with current TB drugs and HIV treatment regimens. Thoughtfully selected, appropriately timed PKI studies are essential to ensure that these new regimens will benefit HIV-infected populations as well as those uninfected with HIV.

3.1. Bedaquiline (Formerly TMC-207) (Janssen for MDR TB, TB Alliance for Drug-Sensitive TB). Bedaquiline is a first-in-class diarylquinoline that inhibits bacterial ATP synthase and is proven to have potent activity against MDR TB in randomized, placebo-controlled clinical trials [36, 37]. Bedaquiline has a long terminal half life of over five months, complicating PKI studies and is a CYP3A substrate with moderate to high-risk of drug-drug interactions with CYP3A4 inducers or inhibitors. Its concentrations are reduced by about 50% when given with RMP or RPT, [38] and the effect of RBT on bedaquiline PK is being evaluated in a currently enrolling trial (NCT01341184). Several studies evaluating drug-drug interactions with high-priority ARV drugs have already been completed. Results from a study evaluating the safety and PKI of single-dose bedaquiline with steady-state EFV revealed a good safety profile with bedaquiline concentrations only modestly reduced [39]. Analyses to estimate steady state concentrations of bedaquiline and its M2 metabolite using nonlinear mixed effects modeling is in progress to ensure that accumulation of bedaquiline's M2 metabolite is not a concern [40]. Coadministration of NVP with bedaquiline was well tolerated among patients with HIV on NVP-based ART and did not influence the bedaquiline area under the time-concentration curve (AUC) and reduced the maximum concentration (Cmax) by only 20% [41]. Evaluation of the effect of LPV/r on single doses (400 mg) of bedaquiline revealed that coadministration had no effect on the Cmax of bedaquiline, and the AUC was increased by only 22% [42]. The PK parameter that correlates best with treatment response and PK targets for bedaquiline have not been determined, so it is unclear what reductions in bedaquiline concentrations would be clinically relevant. If bedaquiline is tested in RMP-containing regimens for drug-sensitive TB, the combined inductive effects of RMP and EFV would need to be evaluated before enrolling participants taking EFV-based ART. Higher doses of bedaquiline in this setting could only be used if metabolite concentrations were in an acceptable range.

Lastly, given that the PKI studies to date were conducted in healthy volunteers receiving single doses of bedaquiline and that steady-state concentrations of bedaquiline are difficult to predict from single-dose data given the triphasic elimination of the drug and its exceedingly long terminal half-life, longer term studies involving multiple doses of the drug in patients with TB and HIV will be essential for furthering our understanding of the PK and pharmacodynamics (PDs) associated with this drug and the effects of ARVs on bedaquiline PK.

3.2. Nitroimidazoles-PA-824 (TB Alliance) and Delamanid (Formerly OPC-67683) (Otsuka). PA-824 (TB Alliance) and delamanid (Otsuka) are drugs in the nitroimidazole class with activity against both metabolically active and nonreplicating *M. tuberculosis,* including drug-sensitive and drug-resistant strains [43]. Delamanid is not metabolized by human liver microsomes and does not induce P450 enzymes, so it poses relatively low metabolic drug interaction risk. PA-824 is a weak competitive inhibitor of CYP 3A, 2C8, 2C9, and 2C19, and it is 20% metabolized by 3A4, so its drug interaction liability is, likewise, low. A study evaluating the effects of EFV and LPV/r on PA-824 concentrations (and vice versa) is currently being planned by the ACTG

in collaboration with the TB Alliance. In the ACTG study, evaluation of the effects of RMP on PA-824 PK will also be assessed. Given the potential importance of these drugs in future TB drug combinations, additional studies evaluating drug interactions with other new TB drugs or ARVs may be necessary if overlapping toxicities or interactions affecting absorption are suspected. For example, a combination of PA-824, moxifloxacin, and pyrazinamide showed superior activity to standard TB treatment in mouse models and in a two-week early bactericidal activity (EBA) study in humans [44, 45]. Though no metabolic drug interaction is expected based on the metabolic pathways of the three drugs, a drug interaction study evaluating the combined effect of PA-824 and moxifloxacin on the QT interval is under development.

3.3. SQ109 (Sequella). SQ109 is a [1,2]-ethylenediamine-based drug with structural similarities to ethambutol (EMB) but is ten times more active than EMB in preclinical models [46]. The mechanism of action involves disruption of cell wall assembly but is distinct from that of ethambutol [47]. *In vitro* studies suggest synergy between SQ109 and RMP or INH, [48] and EDCTP-supported clinical trials evaluating SQ109 alone and in combination with other TB drugs are underway (NCT01218217). SQ109 has a terminal half life of 40–50 hours, (Personal Communication, Gary Horwith, Sequella) and *in vitro* experiments suggest that SQ109 is metabolized by CYP2D6 and 2C19, [49] so there is moderate drug-drug interaction risk for this compound when given together with drugs that induce or inhibit those enzymes. A PKI study involving SQ109 and RMP has not, to our knowledge, been done and is of the highest priority especially if synergy between the two drugs is expected from preclinical models and will be tested clinically. Given its potential use for both drug-sensitive and drug-resistant TB disease, a PKI study with SQ109 and a PI/r combination represents an important consideration once a dose going forward is established, especially given that drug interactions with RTV can be highly unpredictable. Additionally, given the frequent use of fluconazole in the HIV population and fluconazole's strong inhibition of 2C19, a PKI study of SQ109 with fluconazole is likely to provide clinically significant information if concentration-dependent toxicities are expected or seen in Phase 2 studies.

3.4. Oxazolidinones–Sutezolid (Formerly PNU-100480) (Pfizer) and AZD5847 (AstraZeneca). Sutezolid (formerly PNU-100480, Pfizer) and AZD5847 (AstraZeneca) are new oxazolidinones in phase 2 development for TB [50]. Sutezolid is largely metabolized by flavin monooxygenases to sulfoxide and sulfone derivatives [51]. The sulfoxide metabolite is present in plasma at five to seven times the concentration of the parent drug and may contribute significantly to the drug's activity. CYP3A4 is responsible for about 30% of sutezolid's metabolism. Neither the parent drug nor the metabolites appear to be inhibitors or inducers of CYP3A4. The dose going forward is not known for sutezolid or for The EBA study of AZD5847 is planned for the future, and results from the EBA study of sutezolid are expected soon (NCT01225640, NCT01516203). Once the doses to be tested in later-phase studies are determined, then drug interaction studies can be considered. However, these would need to be carefully designed and take into consideration the fact that sutezolid's major metabolite circulates at higher concentration and may be more active than the parent drug.

4. Special Populations

Though the large burden of TB among pediatric populations is widely recognized, children represent a historically understudied population in TB research. Given that efficacy trials in adult TB patients depend on production and culture of sputum samples during treatment and young children cannot produce sputum samples for testing, dosing recommendations for TB drugs for children are generally based on PK studies rather than efficacy trials. New compounds that have demonstrated efficacy for which a dose has been selected in adults should immediately be tested in children, beginning in adolescents, and then proceeding to progressively younger groups of children. The importance of this is illustrated by the example of INH and RMP. When given to children at the same mg/kg dose as adults, concentrations are much lower, and children were treated with suboptimal doses of these drugs for decades. Only recently were the doses recommended by the World Health Organization increased to reflect these age-related differences in drug disposition [52]. A pediatric dose finding study of bedaquiline among children with MDR-TB is under development by the NIAID-funded International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) network with support from Janssen. Similar dose finding studies are required for all of the new TB drugs in the pipeline as well as many currently existing TB drugs. Development of formulations that can be used in young children is a high priority for all promising investigational TB drugs.

The magnitude and variability of drug interactions may be expected to be different in pediatric populations than in adults, as expression of key metabolizing enzymes changes as children develop [53], and responses to drugs that inhibit or induce metabolizing enzymes may also vary with age. Therefore, dose adjustments for ARVs when taken together with rifamycins do not necessarily follow from adult recommendations and should be tested specifically in children to ensure adequate drug exposures. For example, while double-dose ritonavir-boosted LPV may result in adequate LPV concentrations in adults taking RMP, the same is not true among children [25, 54]. Similarly, NVP concentrations in young children are substantially reduced by RMP coadministration [55]. Determining the optimal doses of RTV and LPV to give children who are also taking RMP for TB remains a high priority, particularly among very young children for whom EFV dosing recommendations have not been established and is under active investigation [54, 56, 57]. RBT is not available in a pediatric formulation, so substitution of RMP with RBT is not currently an option.

HIV/TB drug interactions in pregnant women and the impact of these interactions on prevention of mother-to-child transmission also deserve attention. Up to now, there

Table 1: High priority TB-HIV PK or PK/PD studies.

FDA approved TB drugs with ARVs
Rifampicin (RMP)
(i) Evaluation of double-dose LPV/r (800/200 twice daily) among HIV/TB co-infected adults taking RMP-containing TB treatment with focus on HIV viral suppression and hepatotoxicity
(ii) Evaluation of super-boosted LPV (1 : 1 LPV/r ratio with weight-based dosing) among HIV/TB co-infected children receiving RMP-containing TB treatment with focus on LPV PK and HIV viral suppression
(iii) Evaluation of EFV at 600 mg versus 800 mg daily among patients with HIV/TB co-infection taking RMP-containing TB treatment who weigh more than 50 kg
(iv) Evaluation of EFV or higher-dose LPV/r among pregnant women with HIV/TB co-infection taking RMP-containing TB treatment
(v) Evaluation of double-dose RAL (800 mg twice daily) among HIV/TB co-infected patients taking RMP-containing TB treatment
(vi) Determination of dose of DRV/r likely to achieve target DRV concentrations among subjects taking RMP
(vii) Evaluation of higher-dose dolutegravir (50 mg twice daily) among HIV/TB co-infected patients taking RMP-containing TB treatment
Rifapentine (RPT)
(i) Drug interaction studies involving RPT at the optimized dose for TB treatment and key HIV drugs, namely EFV, NVP, and ritonavir-boosted PIs
(ii) Drug interaction studies with weekly RPT used for LTBI treatment and key ARVs including EFV, NVP, and ritonavir-boosted PIs among patients with HIV receiving ART
(iii) Dose-finding PK study in infants and pediatric formulations
Rifabutin (RBT)
(i) Evaluation of RBT at a dose of 150 mg daily among HIV-TB co-infected patients taking LPV/r-based ART with a focus on RBT-related toxicities and HIV viral load suppression
(ii) RBT formulations for children
Isoniazid (INH)
(i) Studies of the effects of INH (alone) as treatment for LTBI on the kinetics of EFV and LPV/r
Select Tb Drugs In The Pipeline
AZD5847
(i) PKI studies as appropriate once the dose to be tested in later-phase studies is determined and information regarding its metabolism and capacity to induce or inhibit P450 enzymes are publicly available
Bedaquiline (TMC207)
(i) PK/PD studies among patients with TB/HIV co-infection taking bedaquiline-containing TB treatment and ART that includes EFV or NVP (multiple dose study)
(ii) Dose-finding PK study in children with MDR-TB
(iii) PKI with combined use of RMP and EFV with bedaquiline
Delamanid (OPC-67683)
(i) No specific drug interaction studies currently recommended given low risk of metabolic drug interactions
PA-824
(i) Drug interaction studies with RMP, EFV, and LPV/r with necessity of further studies to be determined by results of these trials of PA-824 given with a potent inducer (RMP) or potent inhibitor (ritonavir)
Sutezolid (PNU-100480)
(i) Drug interaction study with RMP and perhaps key ARVs once dose to be tested in later-phase studies is determined, with measurement of parent drug and active metabolites
(ii) Dose-finding PK study in children
SQ109
(i) PKI study with RMP once the dose of SQ-109 to be tested in later-phase studies is determined

have been no published data on the combined effects of pregnancy and RMP on ARV concentrations and efficacy of HIV treatment. For women with HIV and TB who cannot receive EFV because of potential teratogenic effects early in pregnancy and for whom NVP is contraindicated because of CD4 count higher than 250 cells/mm^3, options are limited. The safety, PK, and efficacy of higher dose LPV/r or RAL when given with RMP-containing TB treatment have not been tested in pregnant women.

5. Conclusion

The coepidemics of TB and HIV represent a deadly marriage of global significance. Advances in the treatment of drug-sensitive and drug-resistant TB, though, are likely in the near future given the increased number of drugs in the development pipeline and promising results in preclinical and early clinical studies of regimens involving existing and investigational drugs. To ensure that patients with HIV can fully benefit from new and currently available TB regimens, studies evaluating the safety, pharmacokinetics, and efficacy of coadministered antiretrovirals and antituberculosis drugs must be undertaken, particularly when metabolic drug interactions or overlapping toxicities are likely (Table 1). Consideration and advanced planning of the most pertinent studies should begin early in the course of drug development with guidance from preclinical studies and should be done before phase IIb trials of multidrug TB regimens. While Phase I studies using crossover designs may be employed for drugs with shorter half lives, for drugs with longer half lives or time-dependent kinetics, nesting PKI studies in Phase IIa treatment trials will be the most informative strategy. For drugs whose concentrations are highly dependent on environmental and host factors, including, genetics, PKI studies must be conducted in the relevant populations, including in high-burden settings, rather than extrapolating results from trials conducted among a small subset of participants, such as, healthy volunteers. Advocacy together with funding support from industry, government, and public-private sources will be needed to ensure that PKI involving investigational TB drugs and relevant ARVs is conducted, particularly when interactions are predicted and dose adjustment strategies must be explored. PK studies to find the age-appropriate dose of investigational agents for children should be conducted as soon as a dose going forward in adults is determined, with special attention to drug formulation. Finally, sparse PK sampling in all large clinical trials of new TB drugs or regimens will help define the PK/PD parameters that correlate best with treatment response and determine PK targets to ensure optimized dosing. Concurrent treatment of HIV and TB saves lives, and careful assessment of the pharmacology of coadministered antiretrovirals and antituberculosis drugs will help ensure that new or improved TB regimens will benefit those patients who need them most.

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Research Article

Prevalence and Risk Factors Associated with Precancerous Cervical Cancer Lesions among HIV-Infected Women in Resource-Limited Settings

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Objective. To assess the prevalence and identified associated risk factors for precancerous cervical cancer lesions among HIV-infected women in resource-limited settings in Kenya. *Methods*. HIV-infected women attending the ART clinic at the Nazareth Hospital ART clinic between June 2009 and September 2010. Multivariate logistic regression model with odds ratios and 95% confidence intervals (CI) were estimated after controlling for important covariates. *Result*. A total of 715 women were screened for cervical cancer. The median age of the participants was 40 years (range 18–69 years). The prevalence of precancerous lesions (CINI, CINII, CIN III, ICC) was 191 (26.7%). After controlling for other variables in logistic regression analysis, cervical precancerous lesions were associated with not being on ART therapy; whereby non-ART were 2.21 times more likely to have precancerous lesions than ART patients [(aOR) = 2.21, 95% CI (1.28–3.83)]. *Conclusion*. The prevalence of precancerous cervical lesions was lower than other similar settings. It is recommended that cancer screening of HIV-infected women should be an established practice. Availability and accessibility of these services can be done through their integration into HIV. Prompt initiation of HAART through an early enrollment into care has an impact on reducing the prevalence and progression of cervical precancerous lesions.

1. Background

Cervical cancer is the second most common malignancy and accounts for the greatest number of deaths from cancer in women worldwide [1]. Human immunodeficiency virus (HIV) infection also represents a tremendous health burden worldwide. Cervical cancer was made an acquired immunodeficiency syndrome (AIDS-) defining illness in 1993 [2]. In 2005, there were almost 260,000 deaths from cervical cancer and more than 500,000 new cases worldwide. Women in developing countries are at greater risk of death from cervical cancer primarily because few have access to the screening and treatment services that have greatly reduced mortality in the industrialized world over the past four decades. About 75% of women in industrialized countries has been screened for cervical cancer in the previous five years, compared to less than 5% in developing countries [3]. According to WHO (1986), it has been estimated that only about 5% of women in developing countries has been screened for cervical dysplasia in the past 5 years, compared with 40% to 50% of women in developed countries [4]. Research findings suggest that HIV-induced immunodeficiency predisposes to cervical intraepithelial neoplasia (CIN) or cervical carcinoma by facilitating the expression of a causal agent [5–8]. The public health importance of assessing the interaction between HIV and HPV infection with respect to cervical disease is suggested by increased rates of dysplasia persistence and recurrence among HIV-positive women and shorter survival for women with HIV infection and cervical cancer [9].

HIV-positive women have a higher prevalence and incidence of cervical precancerous lesions than HIV negative women. HIV-positive women have a 2-fold to 4-fold greater rate of HPV infection than HIV-negative women. The prevalence of HPV among HIV-positive women is associated strongly with CD4 counts and HIV viral load (VL) [10, 11]. Highly active antiretroviral therapy (HAART) has been shown to decrease HIV viral loads, increase CD4 cell counts, and decrease most opportunistic infections. Since the introduction of HAART there has been a decline in certain malignancies in HIV-infected individuals [12, 13]. However, studies on the impact of HAART on the natural history of cervical squamous intraepithelial lesions (SILs) have produced inconsistent results [14, 15]. In HIV-infected women, there is an increased risk of HPV infection and squamous intraepithelial lesions (SIL), the precursor of cervical cancer [16, 17]. There is still limited evidence for understanding the natural history and epidemiology of HPV-induced cervical cancer in HIV-infected women. Therefore this study may assist policy makers to develop guidelines for prevention and treatment strategies for cervical cancer among HIV-infected women which is largely based on limited evidence, or in the case of resource limited settings, which currently are completely lacking. The objective of the study was to assess prevalence and associated risk factors for precancerous cervical lesions in HIV-infected women within resource-limited settings in Kenya.

2. Methods

The study site was a faith-based hospital offering comprehensive care and treatment to approximately 4,000 HIV-infected patients. The study site was located in Central Kenya, Kiambu district which has a HIV prevalence of 4%. The study population constituted eligible women attending the ART treatment clinics. None of the patients had evidence of Kaposi sarcoma or non-Hodgkin lymphoma. Eligibility criteria included being aged 18–69 years and having no current or past history of cervical disease. Women, eighteen years and older, who were on followup for their HIV-positive status, were screened for cervical cancer using the Visual Inspection with Lugol's Iodine (VILI) technique.

Data on sociodemographic status, sexual behavior, history of a sexually transmitted infection (STI), obstetrics, and gynecology history (parity) was obtained from patient medical records as part of the routine quality improvement activities; CD4 count data and HAART status were also extracted from clinical records. Clients were referred to the clinician where a pelvic examination was conducted using a sterile speculum examination. Visual inspection with lugol's iodine (VILI) was used as the screening technique. A positive VILI test necessitated a cervical biopsy; this was preserved in a sterile container using formalin as the fixative and the biopsies were then taken for histology.

The histology result upon biopsy would turn out to be either negative for intraepithelial lesion (IEL), active/chronic cervicitis, precancerous lesions (CIN I, CIN II, or CIN III/CIS), or cervical cancer (squamous cell or adenocarcinoma) which was either differentiated (well, moderately, poorly differentiated) cervical cancer. The cervical cancer clients were clinically staged using the 1986 International Federation of Gynecology and Obstetrics (FIGO) architectural staging system [18].

Their participation in the screening in no way affected access to, or provision of, comprehensive HIV/AIDS care as this was a standard of care at the clinic.

2.1. Statistical Analysis. Statistical analysis was carried out using STATA 11 (StataCorp LP, College Station, TX, USA). Descriptive statistics (medians and proportions) were used to characterize the variables. Bivariate (unadjusted) analysis was performed to identify factors significantly associated with the precancerous lesions. Odds ratios (OR), 95% confidence intervals (CI) and two-tailed P values were calculated. Statistical tests used were the Chi-square and Fischer's exact tests for proportions, median test, and Wilcoxon rank test for continuous variables. Variables found to be statistically significant ($P < 0.05$) on unadjusted analysis were included in a multivariate logistic regression model through a combination of forward and backward stepwise methods.

3. Result

3.1. Sociodemographic Characteristics of the Study Participants. All the 715 HIV-positive women attending the clinic between June 2009 and December 2010 were included for this study. The median age of the participants was 40 years (range 18–69 years). About 589 (85.5%) were in the reproductive age group (15–49) years. Regarding the parity, 555 (94%) have ≥1 child. About 645 (90.3%) were ever married and 53 (7.4%) were single (Table 1).

3.2. Clinical and Reproductive Characteristics. The majority of participants were in WHO stage III 316 (44%) and 210 (29.2%) in WHO stage IV (Table 1). Concerning the baseline CD4 count, 273 (97.5%) ART clients and 7 (2.5%) preART cases were below 200/mm3 while 245 (71.9%) ART and 96 (28.1%) of Pre-aRT cases were above 200/mm3. About 90 (91.8%) Pre-ART and 8 (8.2%) ART of the study cases were below 200 in their current CD4 count and 488 (82.9%) ART and 100 (17.1%) Pre-ART cases were ≥200 in their current CD4 (Table 2). The median and mean baseline CD4 cell count were 228.0/mm3 and 251/mm3 (range 1–1547.0/mm3). The median and mean current CD4 cell count were 438.0/mm3 and 458/mm3 (range 5–1547.0/mm3). About 578 (84.3%) women with HIV infection were on antiretroviral therapy (ART). About 642 (92.6%) of the HIV-infected women were in followup period of ≥1 year. About 610 (85.4%) of the participants did not have any history of abortion and 104 (14.6%) had history of abortion at least once in life time. The prevalence of precancerous lesions (CIN I, CIN II, CIN III, and ICC) was 191 (26.7%) (Table 1).

3.3. Factors Associated with Precancerous Cervical Cancer Lesions in HIV-Infected Women. In the bivariate analysis (Table 3), only two variables are found to be associated

Table 1: Sociodemographic, clinical, and reproductive characteristics of HIV+ women screened for cervical cancer at Nazareth Hospital.

Variables	Sample size (n)	Percentage (%)	Mean (SD)
HAART status ($n = 686$)			
Yes	108	15.7	—
No	578	84.3	—
Presence of precancerous lesions ($n = 715$)			
Negative	524	73.3	—
Positive	191	26.7	—
Marital status ($n = 714$)			
Deceased	10	1.4	—
Married	645	90.3	—
Separated	6	0.8	—
Single	53	7.5	—
Age ($n = 689$)			40 (8.72)
<29	57	8.27	—
30–39	302	43.83	—
40–49	230	33.38	—
50–59	77	11.18	—
60–69	23	3.34	—
Baseline CD4 ($n = 621$)			250 (189)
<200	280	45.0	—
>200	341	55.0	—
Current CD4 ($n = 686$)			458 (236)
<200	98	14.2	—
>200	588	85.8	—
WHO staging ($n = 692$)			
Stage 1	80	11.6	—
Stage 2	88	12.7	—
Stage 3	316	45.7	—
Stage 4	208	30.0	—
History of abortion ($n = 714$)			
None	610	85.4	—
≥1	104	14.6	—
Parity ($n = 591$)			2.81 (1.95)
0	36	6.0	—
1-2	264	44.6	—
>2	291	49.4	—
Duration of followup in care ($n = 693$)			2.62 (1.54)
<1 year	51	7.4	—
1–3 years	443	63.9	—
4–6 years	199	28.7	—
Histology results ($n = 191$)			
Normal	112	58.6	
CIN 1	35	18.3	
CIN 2	20	10.5	
CIN 3	17	8.9	
ICC	7	3.7	

Note: SD stands for standard deviation.

Table 2: CD4 and ART characteristics of HIV+ women screened for cervical cancer in Nazareth Hospital.

CD4 count	on ART	
	No	Yes
Baseline CD4 count ($n = 568$)		
<200	7 (2.5)	273 (97.5)
≥200	96 (28.1)	245 (71.9)
Current CD4 count ($n = 686$)		
<200	8 (8.2)	90 (91.8)
≥200	100 (17.1)	488 (82.9)

with precancerous lesions. Those women whose current CD4 count was less than 200 were 1.6 times more likely to have precancerous lesions than those patients above 200 current CD4 count [crude odds ratios (cOR) = 1.61, 95% CI (1.02–2.53)]. Non-ART patients were 2.2 times more likely to have precancerous cervical lesions than those patients on ART [crude odds ratios (cOR) = 2.23, 95% CI (1.29–3.86)]. In multivariate analysis after controlling other variables, only non-ART patients were 2.21 times more likely to have precancerous lesions than patients on ART patient [adjusted odds ratios (aOR) = 2.21, 95% CI (1.28–3.83)].

4. Discussion

According to the World Health Organization (WHO), invasive cervical cancer (ICC) is the second most common cancer in women worldwide and is more frequent in low-income countries [19]. Recent guidelines recommend that, following two initial normal Pap-smears at a 6-month interval, all HIV-positive women should undergo annual cervical cytologic examination. In addition, it is recommended that all immunosuppressed women with atypical squamous cells undergo colposcopy [20]. In our study the prevalence of precancerous lesions was 26.7% (191). In other studies among HIV-infected women in Lusaka, Zambia was 79% prevalence of high-grade squamous intraepithelial lesions (HSIL) of the cervix [21] and the high prevalence of HPV-DNA in Zambia study (97.2% for any HPV and 90.3% for any HR-HPV) [22]. In Guinea, overall human papillomavirus prevalence was 50.8% (78.5% and 47.9% among women with and without cervical abnormalities, resp.) [23]. A recent meta-analysis shows that the HPV prevalence was 56.6% in Africa, 31.1% in Asia, 32.4% in Europe, 31.4% in North America, and 57.3% in South/Central America [24]. Although the mechanism by which HIV increases risk of cervical cancer is not completely understood, studies suggest that HIV-induced immunosuppression leads to an inability to control the expression of HPV and the production of HPV oncoproteins E6 and E7 [25, 26] and the risk appears to be associated with increased HPV persistence that may result from immunosuppression related to HIV. Furthermore, the risk is greater in women with CD4 counts less than 200 cells per microliter and in those with high plasma HIV RNA levels [27]. Studies have shown that HIV-1 infection is associated with an increased rate of HPV infection, mainly restricted to HR-HPV types which are the cause of invasive cancer of the cervix [28–30]. Several studies conducted in sub-Saharan Africa indicate that among African women, being HIV infected was associated with a high risk of presenting squamous intraepithelial lesions of the cervix, with ORs ranging from 4.4 to 17 depending on the grade of the lesion and other factors [28, 30–33]. Yet, many case-referent studies conducted in Uganda, Rwanda, and Côte d'Ivoire failed to demonstrate any significant association between HIV and ICC, with ORs ranging from 1.1 to 1.6 [34–37]. Case-referent studies in South Africa also found a significant association with ORs of 1.6 and 1.6 [38, 39]. In another case-referent study conducted in Kenya, HIV-positive women were also more likely to be HPV infected compared to HIV-negative women (OR = 3.1) [40]. A cross-sectional study determined the prevalence of HPV infection, HIV infection, and cervical cytological abnormalities in Ugandan women presenting to a sexually transmitted infection clinic [41] and found 49 cases of HPV infection among 106 women with cervical swabs adequate for HPV testing (46.2%). Similarly, a study realized in Zambia among 145 HIV-infected women of which 93.8% had abnormal Pap smears [22]. In other study of women initiating ARV therapy recorded an exceptionally high prevalence of cervical abnormalities (66%) [42]. This finding has implications for future interventions in the implementation of prophylactic HPV vaccines to be the part of care and support programme for HIV-infected women.

In our study those women whose current CD4 count was less than 200 were 1.6 times more likely to have precancerous cervical cancer lesions than those patients with a current CD4 count above 200. However, regarding the effect of immune function, previous studies have consistently demonstrated that the amount of CD4 cell count is a significant predictor for having or developing CIN [43–45]. Given the low CD4 counts in our study population, severe immunosuppression is the most likely explanation for the high prevalence of cervical abnormalities and precancerous cervical lesions detected.

In HIV infection, lower CD4 counts have been associated with a higher prevalence of HPV infection [5, 46] and persistent shedding of HPV DNA [47, 48]. HPV viral load increases with immune suppression, likely accounting for greater facility of HPV DNA detection [46]. In this study there was a positive association between having a CD4 count of <200. This suggests that as the CD4 count declines, vigilant followup of the anogenital tract, particularly with cervical cytological and/or histological screening, is warranted [49].

In our analysis non-ART patients were 2.21 times more likely to have CIN infection than ART patients. Similar findings have been documented in other studies. As HIV-infected women continue to live longer with ART support, albeit in a moderately immunosuppressed state, they may be at increased risk for CIN and invasive cervical cancer [11, 50]. However, studies on the impact of HAART on the natural history of cervical squamous intraepithelial lesions have produced inconsistent results [14, 15]. Antiretroviral therapy (ART) for PLHIV provides a golden opportunity to increase cervical screening through the integration of ART services with frequent screening of women for cervical cancer

Table 3: Unadjusted and adjusted odds ratios of the multilevel logistic regression estimates for factors associated with precancerous cervical cancer lesions among HIV+ at Nazareth Hospital.

Characteristics	Cervical cancer screening		*P* value	Unadjusted/cOR	Adjusted/aOR	*P* value
	Negative	Positive				
Current CD4 count			*0.038*			
<200	78 (72.2)	30 (27.8)		1.61 (1.02–2.53)		
≥200	431 (87.5)	147 (81.3)		1.00		
On HAART			*0.003*			*0.005*
Yes	91 (84.2)	17 (15.8)		1.00	1.00	
No	404 (69.8)	174 (30.2)		2.23 (1.29–3.86)	2.21 (1.28–3.83)	

[21, 50]. Starting HAART has an impact on reducing the incidence and progression and facilitating the regression of CIN infection and cervical abnormalities.

The study should be interpreted in light of the strength and limitations. Major strengths of our study include the large number of women, high participation, and reliance on cost-effective, simple, timely VILI testing. The Limitations include but not limited to the lack of information on some of the variables that can predict cervical cancer in HIV-infected women like the use of oral contraceptives or estrogens, information on sexual behavior, and smoking [49] and the cross-sectional nature of this study allows the possibility for confounding so it is difficult to reach any causality. This may hence hinder the generalizability of our findings.

5. Conclusion

In this study, the prevalence of CIN was 26.7 percent (191) which is lower than other findings reported in Africa. Those patients who were not on antiretroviral therapy were more likely to have CIN diagnosis than who were on antiretroviral therapy. Therefore regular screening of HIV-infected women is of paramount importance. Starting ART acts as leverage for cancer screening and majority of ART patients are likely not to progress to cervical cancer as demonstrated by this study. Conducting well-designed prospective cohort study to study natural history of cervical neoplasia among HIV-infected women in developing country settings is warranted.

Conflict of Interests

All authors declare that they have no conflict of interests associated with the publication of this paper.

Authors' Contribution

W. Mbuthia, F. Odhiambo, G. Kiiru, S. Ojoo, and S. Agbor assisted in the collection of data and technical aspects of the paper. P. Memiah Conceived and designed the study and collected data in the field, performed analysis, interpretation of data, and critical review of the paper. W. Mbuthia, F. Odhiambo, P. Memiah participated in design and helped to draft the paper. S. Biadgilign assisted with the design, interpretation of data, draft, and critical review of the paper. All authors approved and read the final paper. All authors participated in critical appraisal of the paper.

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Review Article

Challenges in Providing Treatment and Care for Viral Hepatitis among Individuals Co-Infected with HIV in Resource-Limited Settings

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Hepatitis B and C infections are prevalent among HIV-infected individuals with different epidemiologic profiles, modes of transmission, natural histories, and treatments. Southeast Asian countries are classified as "highly prevalent zones," with a rate of hepatitis B and C coinfection in people living with HIV/AIDS of approximately 3.2–11%. Majority of hepatitis B coinfection is of genotype C. Most of the patients infected with hepatitis C in Thailand have genotype 3 which is significantly related to intravenous drug use whereas, in Vietnam, it is genotype 6. The options for antiretroviral drugs are limited and rely on global funds and research facilities. Only HBV treatment is available for free through the national health scheme. Screening tests for HBV and HCV prior to commencing antiretroviral treatment are low. Insufficient concern on hepatitis-virus-related liver malignancy and long-term hepatic morbidities is noted. Cost-effective HCV treatment can be incorporated into the national health program for those who need it by utilizing data obtained from clinical research studies. For example, patients infected with HCV genotype 2/3 with a certain IL-28B polymorphism can be treated with a shorter course of interferon and ribavirin which can also help reduce costs.

1. Introduction

Most countries in Southeast Asia currently have limited resources in providing universal coverage for HIV treatment and care. Since the start of the global AIDS epidemic, Thailand has become the only country within this region with a high prevalence of HIV infection (>1%). In 2009, the HIV prevalence has decreased to 2.3 million because of the HIV prevention campaigns. These HIV prevention campaigns focused on promoting the use of condoms among commercial sex workers and their clients which achieved >90–95% success in preventing HIV transmission. Another campaign known as the prevention of mother-to-child transmission (PMTCT) was also successful. However, in recent years, the rates of new HIV infection have increased among hard-to-reach groups such as the men having sex with men (MSM), injection drug users (IDUs), and adolescents. It has been shown that only 20–30% of sexually active young people used condoms consistently. Furthermore, these HIV-infected high risk groups have sexually transmitted hepatitis infection, especially HCV.

Antiretroviral drugs are provided through the national health schemes and international funding agencies such as the Global Fund and PEPFAR. These antiretroviral therapy (ART) programs provide financial support for ARV protocol development, professional health care training, drug supply chain management, formation of a laboratory network, monitoring and evaluation, and other needs requested by the multisector and various people living with HIV/AIDS (PLWHA) groups. The program has scaled up but mostly lacks local leadership, comprehensive training, and coordination to achieve and sustain the success of the program. Furthermore, patients coinfected with hepatitis are currently being ignored. Screening and treatment for hepatitis coinfection should be included in the national policy to reduce problems in the future.

2. Epidemiology of HBV and HCV Coinfection

It has been documented that HBV infection in the general population is high (>8%) in many countries from the Southeast Asia region [1–4]. Reports showing lower infection rates of 3.2–6% from Brunei Darussalam, Indonesia, Philippines, and Thailand [5–9] are based on cases infected through vertical transmission. In tertiary care settings, HBV infection in HIV-infected population was approximately 8.7–11% [10–14]. MSMs and IDUs are at a higher risk of being infected with HBV and HIV. However, the infection rate of HBV in PLWHA is not that much different compared to the general population of which majority are infected perinatally. The most common HBV genotypes are C [15–17] and B [18, 19] followed by A. The most common genotypes found among migrants living in Thailand are C (86%) and B (11.6%) [20]. The prevalences of HBsAg among migrants from Cambodia, Laos, and Myanmar living in Thailand were 10.8%, 6.9%, and 9.7%, respectively [20]. In the last 10 years, chronic perinatal infection has decreased when the national program expanded its immunization protocol to include HBV vaccination in all children. Even though the HBV subtypes of the surface antigen [15, 18, 21] reported are *adr* and *adw*, this is not clinically significant because the HBV vaccine of either *adw* or *ayw* subtype can yield anti-*a* which is protective against crossinfection with other HBsAg subtypes as well [22].

In contrast to HBV, HCV co-infection is moderately high in PLWHA, especially among IDUs and MSMs. If HIV prevalence in IDUs is high, eventually HCV co-infection will become a major problem as currently seen in Thailand and Vietnam [23]. Among PLWHA, it has been estimated that approximately 5–40% have contacted HIV from injecting drugs. In Thailand and Vietnam, at least 50% of IDUs are living with HIV/AIDS, and about 90–95% have also contracted HCV. The estimated prevalence of HCV/HIV co-infection is 7.2–10.1% [10, 11, 14, 24, 25]. Unlike Thailand and Vietnam, in the Philippines, 83–89% of IDUs are infected with HCV whereas only 0.34% are infected with HIV. Hence, the prevalence of HCV/HIV co-infection is low [26]. Factors such as males [10, 27] and IDUs are at higher risk of becoming infected with HCV and HIV. Among the general population, the most common genotypes of HCV in Thailand, Vietnam, and Indonesia are 3a (70%), 6a (32.5%), and 1b (47.3%), respectively [25, 28, 29]. However, in HIV-infected individuals, genotype 1 is increasingly found [27]. The prevalence of HIV-HBV-HCV triple infection is rare (0.4%) but can be found among IDUs and MSMs [11]. The predominant HCV genotypes detected in migrants from Cambodia, Laos, and Myanmar living in Thailand were 1a, 1b, 3, and 6, respectively. However, this data may not accurately reflect the real HCV genotypes among these groups of people because few samples were collected from that study [30].

3. Approach in Diagnosing HBV or HCV among HIV-Infected Patients

Many individuals infected with HBV at birth or during early childhood and subsequently infected with HIV have asymptomatic HBV chronic infection with or without aminotransaminase elevation. Patients who develop acute hepatitis B during their adulthood will have abrupt and progressive jaundice with GI symptoms such as nausea, abdominal pain, flatulence, and bloated abdomen. The general symptoms include fatigue, dizziness, weight loss, or anorexia. The liver is usually not enlarged, and the cutaneous stigmata of chronic liver disease is not detected unless the disease has progressed to decompensated cirrhosis. Cirrhosis is more common in patients with lower levels of ALT and CD4 compared to those monoinfected with HBV [31, 32]. HIV-HBV co-infected men are much more likely to die of liver-related causes compared to monoinfected HBV patients [33]. The risk of HCC is somewhat increased in HIV-infected individuals with low CD4 counts [34]. Patients with genotype C have exhibited earlier progression of cirrhosis and HCC than those with genotype B [17].

Similarly, patients co-infected with HCV and HIV have asymptomatic acute HCV infection. It is also possible that many IDUs co-infected with HCV and HIV may not have reported their symptoms, and this may not necessary reflect an accurate account of HCV infection among these groups of people. Usually, in non-IDUs, acute hepatitis C is detected in PLWHAs currently on treatment and diagnosed with sexually transmitted infections (e.g., syphilis, gonorrhea) because of elevated enzyme levels. HIV positive individuals with acute HCV infection can develop chronic HCV infection. In contrast to HBV, in HCV co-infected patients, disease progression to liver cirrhosis and hepatocellular carcinoma (HCC) occurs very quickly and may exist prior to HCV treatment. As a result of this, physicians need to closely monitor these patients, even those that have sustained viral response to HCV treatment. Routine HBV and HCV screening are not routinely performed at tertiary care setting. Many HIV patients with undetectable HIV RNA and elevated liver enzymes are screened for hepatitis and eventually found to be co-infected with HBV [14, 35].

Currently, the national guidelines for antiretroviral therapy in HIV-infected adults and adolescents in most countries recommend HIV-infected persons to be screened for HBV before initiating ART. The reason for this is because this will help guide physicians in designing the patient's HAART regimen which should contain at least 2 antiretroviral drugs with activity against both HIV and HBV, that is, tenofovir plus lamivudine or tenofovir plus emtricitabine. The viral hepatitis serology is widely available but not routinely used to screen those patients most at risk such as IDUs and MSMs. Tests for HBs antigen are recommended to all HIV-infected patients, but recently, in actual practice, 55–69% of HIV-infected adults were tested for hepatitis [12, 13, 36]. Asymptomatic chronic infected cases are not unmasked and may continue to transmit the viruses through contaminated blood and genital secretions. If HIV-infected people are aware of the effects of HBV and the accessibility of HBV treatment, then the rate of HBV screening prior to ART may improve. The results of HBV serologic profiles are interpreted as mono-HBV infection (see Table 1). However, isolated positive core antibodies are more frequently (20–30%) found in co-infected patients [37] compared

Table 1: Findings and interpretations of HBV serologic markers.

HBs Ag	Anti-HBs	Anti-HBc	Hbe Ag	Interpretation
+	−	−	+	Chronic replicative phase or acute infection
+	−	+	−	Chronic nonreplicative/carrier (DNA neg) Flare up (DNA positive)
+	−	−	−	Precore mutants
−	−	+	−	Isolated core antibody Recovery from acute infection Occult infection (DNA positive)
−	+	−	−	Previously immunized with HBV vaccine

to those monoinfected with HBV, especially in advanced immunocompromised [38], HCV co-infected cases [39–41], or IDUs. The clinical significance of having a positive anti-HBc antibody is not well understood, but there is more evidence indicating that people with this serologic finding has an occult infection with frequent hepatic flares [42] and potential of transmitting the infection [43–46]. In certain cases, some may have undetectable HBV DNA with isolated core antibody [47, 48].

Since HBV/HIV co-infection is common, it is highly recommended that in every HIV-infected individuals, serologic screening tests for hepatitis B should include HBs Ag, anti-HBs, and anti-HBc antibody. If all 3 serologic tests are negative, then it is highly recommended that the patients get a hepatitis B vaccine to prevent infection. If an isolated core antibody is detected, then a confirmatory HBV-DNA or complete liver function workup is needed to help guide the patients' long-term care management. It is not conclusive whether HIV-infected individuals with isolated core antibody should get a Hepatitis B vaccine. The vaccination may have a primary or an amnestic response [37]. If HBs antigen is positive, then it is important to assess whether the patient also has HBe Ag, anti-HBe antibody, HBV-DNA and liver enzymes to rule out viral replication, liver complications and whether treatment is needed.

Majority of patients presenting acute HBV infection will have elevated levels of liver enzymes (ALT > AST with >10 times ULN). However, as for those currently infected with HBV or have tested positive for HBs antigen, it is difficult to differentiate whether they are HBV carriers or have chronic infection with low or nonreplicative phase. In healthy carriers, HBV-DNA may not be detectable because of transient viremia and therefore would require retesting. HBV-DNA is somewhat useful but is too expensive for some countries with limited resources. Certain places may not have access to machines to detect HBV-DNA, and some patients may not be able to afford such diagnostic tests. In order to detect and differentiate chronic active HBV patients from positive serostatus for HBe Ag, physicians would need the patients' medical history, risk behaviors or predisposing factors, and physical findings such as stigmata of chronic liver.

Liver enzymes can be used as a surrogate marker for detecting hepatic necroinflammation, but its elevation may also indicate a hepatic flare from any causes including the virus itself. Serum aminotransferase levels are less reliable in determining whether the patient would need therapy or not. Serum aminotransferase levels can be lower in patients co-infected with HIV and HBV or within normal range in some patients with significant hepatic fibrosis. Even though liver pathology can specifically detect fibrosis and necroinflammation by using a scoring system; however, its procedure is invasive, time-consuming and may not be sensitive if there is bias in the way the samples are collected or assessed. Assessing the extent of the underlying liver damage is important because it will affect the prognosis of the infection as well as the choices for treatment. Another noninvasive test known as the hepatic elastography (Fibroscan) can be used to measure the liver's stiffness or evaluate hepatic fibrosis. The results from the Fibroscan can guide treatment and care but may not be possible in resource-limited settings. Some of the limitations of the fibroscan are its inability to accurately predict the degree of injury seen on a liver biopsy or subsequent clinical events. Close monitoring is necessary to detect early cases.

In regards to HCV co-infection, the national guidelines recommend to screen for anti-HCV antibody before initiating ART in HIV-infected adults exhibiting symptoms or those with risk factors such as intravenous drug use. The treatment cost for HCV is extremely expensive and is not covered by the national health schemes. Patients with HCV who need treatment must pay for their own treatment. Aside from that, the national health schemes do not provide free diagnostic tests for HCV genotype and HCVRNA load. At the present, in majority of the countries, there is insufficient epidemiological data on HIV/HCV co-infection. Hence this may be one of the reasons why the national health schemes will not offer free HCV testing in HIV-infected individuals. According to the physicians who have done anti-HCV tests in their HIV-infected patients, there is a high prevalence of HCV co-infection. This result indicates that an appointed committee should include HCV tests in the national guidelines for HIV-infected patients.

It is possible to use tests to detect for anti-HCV antibody to screen those groups at risk for acquiring the infection. However, it is important to note that anti-HCV seroconversion occurs much slower in HIV-infected patients, and it is still possible to have anti-HCV negative results despite ongoing viral replication for a year [49]. Currently, HCV antibody tests cost around 6–9 USD. In a resource-limited setting, this cost is affordable yet it is not included in the national health care program. This test can be used to screen and diagnose HCV in HIV-infected patients even though

it may not be perfect. It can be used in clinical settings or as requested. In most of the cases, there are no or very little clinical symptoms as seen in people with acute HCV infection. Therefore, acute HCV infection is defined as having detectable HCV-RNA in the first 6 months after infection. Transaminase levels can also be used to accurately detect acute HCV infection. Elevated levels of alanine transaminase (ALT) are more sensitive in detecting acute HCV when compared to anti-HCV antibody tests. Tests to detect HCV-RNA are used to determine the virus's replicative state. Hence results from HCV-RNA tests can detect early infection better than the antibody tests and are usually used to exclude false positive results obtained from the serologic tests when the patients have disclosed not having any risk behaviors. Sometimes it is also used to determine whether the result from the serology test is a false positive or not. Past resolved HCV infection may yield false positive results in the serology test. HIV positive individuals who need to start antiviral treatment should be screened for HCV by using the HCV-RNA tests and monitored regularly [50]. Chronic hepatitis C infection is defined as having ongoing viral replication for more than 6 months. Without the patient's past hepatitis C test results, it is difficult to determine the HCV status of the patient based only on the patient's history, current physical and laboratory examinations. It is very difficult to distinguish between acute and chronic infection because flares during chronic hepatitis C may mimic acute infection.

Genotyping should be done in every case who will need HCV treatment because this will help guide the physician in determining the length of treatment, predict treatment response and prognosis of HCV (see Figure 1). However, if genotyping tests are not available, then physicians from resource-limited setting can use regional epidemiological data to determine the subtype of HCV. As for those patients not on HCV treatment due to no indication, treatment intolerability or failure and drug availability, it is important to continue to monitor and assess the progression of the disease. Liver enzymes should regularly be checked every 3 months and repeated if there are significant elevations. The degree of histologic injury is a better predictor of subsequent clinical events than is the degree of elevated serum aminotransferase levels, genotype, or viral load. The result of the Fibroscan can support the physician's decision to start or defer treatment with a higher level of confidence. CD4 cell count appears to be a good predictor for spontaneous clearance [51]. Antiretroviral treatment may help to control HCV if HCV treatment is not provided. Thrombocytopenia and reversed albumin/globulin ratio can be detected in cases with progressive liver cirrhosis in patients with hepatitis C. Also, serological markers correlated with stages of liver fibrosis can be used with indices obtained from routine blood tests to determine the function of the liver (e.g., APRI (aspartate aminotransferase [AST]-to-platelet ratio index) and Fib-4 (age, AST, platelets, and ALT level)). Alpha fetoprotein (AFP), a tumor marker for hepatocarcinoma, can help interpret liver images whereas pathology can confirm the stage of the disease. Screening for hepatocarcinoma should include ultrasound of the liver and serum AFP should be performed every 6 months for all chronic hepatitis B and C patients with cirrhosis. However, according to the systematic reviews, AFP is not considered sensitive (73.5%) [52, 53] and has no existing correlations in hepatocarcinoma [54]. This serves as a warning sign that more needs to be done to prevent the transmission of the virus as well as increase the community's awareness of comorbidity among hepatitis co-infected patients.

In conclusion, routine screening using serologic tests for hepatitis B and C is beneficial for the patient to determine when to start treatment or those who cannot afford such care to closely monitor the disease progression and complications. The use of stavudine, didanosine, and nevirapine, which are unfriendly to the liver, should be used with caution because it can lead to liver toxicities. For public health concerns, this will also help reduce the risk of transmission if treatment is provided and reduce risk behaviors. As for those at risk of acquiring hepatitis such as immunocompromised patients, physicians can recommend HBV vaccinations. It is highly recommended that in resource-limited settings where there is a high prevalence of hepatitis, HBV and HCV should be screened in HIV-infected patients prior to ART.

4. Management of Coinfected Patients

Recently, the international HIV treatment guidelines 2011 recommend that antiretroviral therapy should be started in all HBV/HIV co-infected adolescents and adults who require treatment for chronic active hepatitis B irrespective of their CD4 cell counts. According to these new guidelines, all HIV-infected individuals with CD4 $\leq$ 350 cells/μL are required to start antiretroviral therapy regardless of symptoms. However, in the middle of 2011, there is evidence that this is not implemented throughout the region. Therefore, it is important to assess the treatment rates in cases with CD4 of 200–350 cell/μL to ensure treatment coverage and care among these people in order to reduce opportunistic infections in severely immunocompromised patients. Some nucleoside/nucleotide analogs for HIV treatment are effective to both HIV and HBV and therefore can be used to treat HIV/HBV co-infected patients. Furthermore, the results from the study on Tenofovir in HBV Coinfection (TICO) which was conducted in Thailand showed that a combination of tenofovir and emtricitabine or lamivudine was better than using only tenofovir [55, 56]. There was an increased loss of HBeAg when a longer follow-up period was implemented to assess HBV treatment outcome. Hepatic flares were observed in 19–25% of the patients without any severe complications. Interestingly, long-term use of tenofovir in HIV/HBV co-infected patients may prevent disease progression to end-stage liver disease in the Thai population, by slowing or reversing liver fibrosis. Currently, the Thai national guideline recommends using tenofovir with either lamivudine or emtricitabine for any HBV co-infected individuals regardless of their baseline CD4+ T-cell count. Since HBV treatment is cheap (approximately 55 USD/mo. for tenofovir plus lamivudine and 70 USD/mo. for tenofovir plus emtricitabine), this is covered by the national health scheme. However, the cost for monitoring HBV-DNA is not included in the national AIDS

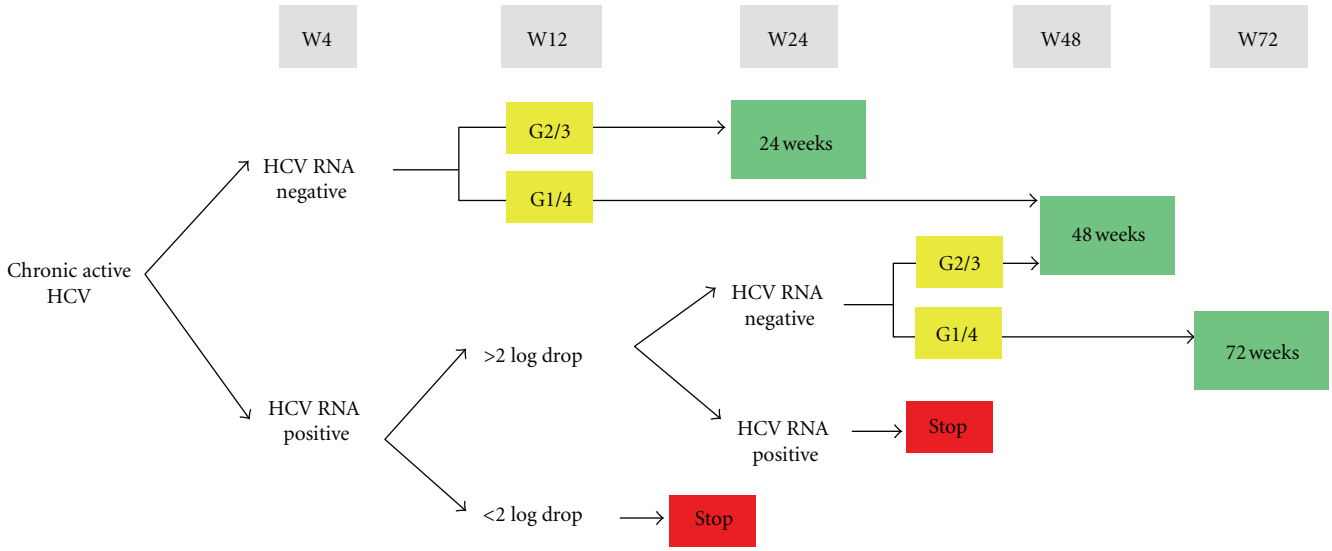

Figure 1: Treatment scheme for HCV coinfection guided by genotype and HCV-RNA load assessment at baseline, wks 4, 12, and 24 [48, 72].*Patients having baseline HCV-RNA load <400,000 IU/mL with minimal fibrosis.

program, and the patients have to pay for this by themselves. Other nucleoside analogs such as adefovir, telbivudine, and entecavir are also not included because the government has decided that these drugs are not essential for the mass treatment of HBV. Moreover, it is still unclear which HBV drugs should be used for the preferred regimen in pregnant women, and infants born to HBV co-infected mothers.

The situation is even worse for those co-infected with HIV and HCV. The current national treatment guideline recommends pegylated interferon α2a or 2b plus ribavirin (Figure 1). Pegylated interferon and ribavirin are not on WHO and Asian national essential medicines lists for all HCV patients and hence are not freely provided through the national health schemes. As for other low and middle-income countries, many patients cannot afford pegylated interferon and ribavirin due to its costs. Currently, patented pegylated interferon from Roche (Pegasys) and Merck (PegIntron) is packaged and sold with generic ribavirin. Because of these patents, hepatitis C treatment remains to be expensive. For a 48-week treatment course, it costs approximately $26,000–30,000 USD. Thus, most health care systems cannot provide treatment for HCV and will refuse to offer treatment to majority of patients with HCV. This price does not include other related investigations such as HCV genotyping and HCVRNA as well as treatment for unexpected complications. HCV RNA should be assessed before commencing treatment and used to assess the efficacy of the treatment regimen. The most common adverse events are neuropsychiatric symptoms and marrow toxicity which can add to the cost of treatment and contribute to premature treatment termination. Therefore, in order to minimize adverse effects, antiretroviral therapy needs to be adjusted. Concomitant use of zidovudine is contraindicated due to its effect on the bone marrow; bone marrow suppression is worsened by the use of zidovudine. The use of didanosine is also not recommended during HCV therapy due to increased risks of hepatic decompensation. Problems are further exacerbated if the patient is co-infected with HCV and HIV and receiving treatment concomitantly. It is not possible for all HCV/HIV co-infected patients to get HCV treatment because it is very expensive and has several intolerable side effects. Patients on ART also suffer from pill burdens and side effects of antiretroviral drugs.

As a result of this, images of the liver by using ultrasound, levels of serum aminotransaminase, and α-fetoprotein are regularly monitored in HCV co-infected patients (see Table 2 for summary). Liver biopsy is rarely done to avoid complications and risks for contamination, especially in HIV-infected treatment-naïve patients. Most Thai patients with HCV infection have genotype 3, the type which responds well to treatment, allowing physicians to reduce the treatment duration to 12–16 weeks in those achieving rapid virological response (RVR); this is based on the findings that 82% of patients were successfully treated for HCV which is comparable to a 24-week treatment course [57] and is still also cost-effective if retreating the cases with relapses for 24 weeks [58]. During treatment, RVR measured at week 4 is a strong predictor of sustained virological response (SVR) [59]. Because of this, short-course treatment for 24 weeks is recommended to the patients infected with genotype 2/3, and a shorter treatment course (12–16 weeks) may be an option for patients unable to tolerate treatment with close RVR monitoring. The response-guided therapy aims to optimize treatment outcomes without compromising SVR rates [60].

IL28B gene polymorphisms modulate early virological response to peginterferon/ribavirin treatment and is associated with SVR in patients infected with genotype 2/3 HCV who did not achieve RVR [61]. The favorable CC genotype, as compared to either the CT or TT genotypes, has been associated with a 3-fold increase in the rate for spontaneous clearance of HCV [62] and 2-3 folds higher rate of SVR

Table 2: Summary of diagnostic criteria and treatment currently in use as well as its perspectives in management.

Stage of disease	Diagnostic criteria	Current treatment practices	Perspectives in management
Chronic hepatitis B coinfection	(i) HBsAg+ >6 mos (ii) Serum HBV DNA >2,000 IU/mL (10^4 copies/mL) (iii) Persistent or intermittent ALT/AST elevation (iv) Liver biopsy (done in some) showing chronic hepatitis with moderate or severe necroinflammation	Tenofovir plus lamivudine or tenofovir plus emtricitabine	(i) HBV-DNA assessment for treatment outcome (ii) Add adefovir or entecavir if no virologic suppression or suspected resistance (iii) Close monitoring of cirrhosis and hepatocellular carcinoma (iv) Hepatitis B vaccination for susceptible partner
Inactive HBsAg carrier state among PLWHA	(i) HBsAg+ >6 mos (ii) HBeAg−, anti-HBe+ (iii) Serum HBV DNA <2,000 IU/mL (10^4 copies/mL) (iv) Persistently normal ALT/AST levels (v) Liver biopsy (unfortunately not done in clinical practice as recommended) confirms absence of significant hepatitis	Due to limited options of antiretroviral regimen, lamivudine is used as part of HAART in majority of cases that need HIV treatment	(i) Misleading term/new term "chronic low replicative hepatitis B" can be used (ii) Lamivudine/emtricitabine preserved for combination treatment for HBV infection if indicated (iii) Need to closely F/U: LFT. α-FP and ultrasound regularly at least q 6–12 mos for cirrhotic patients (iv) Hepatitis B vaccination for susceptible partner
Occult hepatitis B coinfection or isolated core antibody	(i) Presence of anti-HBc +/− anti-HBs (ii) HBsAg− (iii) Undetectable serum HBV DNA (very low levels may be detected by sensitive PCR assays) or serum HBV DNA <2,000 IU/mL (10^4 copies/mL) (iv) Normal ALT levels	Due to limited options of antiretroviral regimen, lamivudine is used as part of HAART in majority of cases that need HIV treatment	(i) Lamivudine/emtricitabine preserved for combination treatment for future HBV infection if occult infection suspected (ii) LFT q 6 mos if ALT/AST elevated, further assessment for HBe Ag and HBV-DNA (iii) Hepatitis B vaccination for susceptible partner (iv) It is not clear whether Hepatitis B revaccination is needed or not
Chronic hepatitis C coinfection	(i) Anti-HCV+ and HCV-RNA+ (ii) Normal ALT levels or ALT elevation (iii) Liver biopsy showing fibrosis (or Fibroscan >7.5 kPa)	No treatment in most cases For those who can afford treatment: PegIFNα2a or 2b plus ribavirin 800 mg/D, duration of treatment guided by genotype: 3,6 for 24 wks; 1 for 48 wks	(i) Selected cases with good prognostic factors can access treatment comprising PegIFN plus RBV (ii) Genotyping and HCV-RNA for assessing EVR, RVR, and SVR (iii) Lower dose of PegIFN (iv) Shorter treatment duration (v) Need F/U: LFT, α-FP and ultrasound q 6–12 mos for cirrhotic patients (vi) Close monitoring of cirrhosis and HCC (vii) Harm reduction to reduce transmission

in HCV genotype 1 chronically infected individuals treated with combination pegylated interferon/ribavirin therapy [63]. In contrast to HCV genotype 1 patients, despite the faster initial viral response in the patients carrying C/C, SVR rates of mono-HCV genotype 3 infection were not different compared to the patients carrying T-allele [64, 65]. Quantitative evaluation of interferon-γ-inducible protein-10 (IP-10) may add on the predictive value of IL28B polymorphisms for HCV treatment responses [66]. The clinical outcomes of an earlier viral decline and a shorter course treatment in CC patients infected with HIV/HCV genotype 2/3 are warranted. Nonetheless, access to treatment in Thailand is still hindered by the costs of the medications. Furthermore, drug toxicities may contribute to incomplete treatment for HCV among HIV-infected individuals. In order to sustain the effectiveness of HCV treatment, evidence base information on epidemiology and IL28B polymorphism in specific population can be used to minimize the duration of treatment but may compromise the cost instead. Therefore, policy makers need to strongly reconsider integrating optimized treatment regimen for HCV co-infection into the national program for the future.

5. Prevention Programs

After successful integration of the national expanded program on immunization (EPI) on HBV immunization, coverage of the vaccinations has increased in most countries up to 80% as seen by the results from many studies on incidence reduction of HBV and hepatocellular carcinoma in the young age group [68–72]. Due to the high prevalence of HBV infection in the region, HBV serology screening prior to vaccination in high risk groups is not necessary, for example, MSMs, IDUs, and health care workers (HCWs).

Many adults, including health care workers (HCWs), cannot reimburse for HBV vaccinations. Currently, the guideline recommendation for HBV treatment and care for HCWs is not well defined. If people are aware of the complications and prognosis of chronic hepatitis, this may encourage people to have HBV serology screening and HBV vaccinations in adults older than 30 years old. For postexposure prophylaxis, hepatitis B immunoglobulin (HBIG) is required in cases that have been exposed to blood from HBV-infected individuals and are not immune to HBV according to the postexposure HBV screening test. Occupational risks can be prevented if high risk groups such as HCWs and health-related students have been immunized. This preventive policy targeting professional health care workers (i.e., hospitals and clinics) at risk of acquiring HBV infection should be integrated into the national health care system. Currently, HBV immunization is recommended to all HIV-infected patients who are susceptible and have achieved immunological success after antiretroviral therapy. However, it is important to conduct a serologic test for HBV to confirm the person's immune status before vaccination because low CD4 levels or the use of NNRTI may affect the response to the vaccine [67]. It has been shown that in HIV-infected individuals, the immune response of generating HBs antibodies was 71.4% which was much lower compared to healthy HIV seronegative individuals. However, no adverse event has been detected.

Since HCV vaccines are not available for the prevention of the disease, hence it is essential for all high risk groups, including MSMs and IDUs, to continuously receive updated information on HCV transmission and outcomes to reduce their behavior risk of blood-to-blood contamination. Lack of free access to clean injecting equipment for IDUs may not be a critical issue because syringes and needles are available cheaply in drug stores. However, due to social stigmatization, discrimination, and illegal issues, IDUs are afraid to access clean needles and syringes resulting in higher rates of HIV and HCV infection. Even though the Needle and Syringe Program, a harm reduction effort, is successful in Australia in preventing HCV and HIV infection among IDUs, but such a program is difficult to launch in resource-limited setting with a conservative society. Hence, continuing education and health promotion are required to provide correct information to the community to change their perception as a preventive strategy. HIV/HCV co-infection among IDUs is a public health emergency that is currently being ignored by the policy makers. The need for proper policy and advocacy are needed and should be presented through health promotion campaigns in collaboration with working groups and peer educators to successfully implement and launch harm reduction programs properly. Community advocates and appropriate waste disposal need to be worked out before rolling out the harm reduction programs. Regular HCV screening for high risk groups, especially HCWs and patients with chronic renal failure on hemodialysis, is necessary. Voluntarily unpaid donor blood must be routinely screened for HBV and HCV serology at every blood bank unit throughout the region as currently being performed by the Red Cross blood banks.

6. Perspectives on Hepatitis B and C Coinfection among HIV-Infected Patients for Testing and Treatment

Since HBV co-infection is more chronic, therefore the national guidelines have recommended sufficient and early screening to initiate proper treatment and care. Despite this, there are still problems for those patients who have developed resistance and have limited selection of drugs to choose from and/or intolerability. It will be a continued struggle to provide alternative treatment and other drug choices for these patients. Hepatitis B vaccination should be implemented at all levels of the population, especially high risk groups and health care workers; HBV vaccination is an urgent and necessary action that should be in place in order to reduce HBV infection. The strategic plan must cover adults older than 30 years old who may become infected and transmit the virus to others via the sexual route. Hepatitis B is preventable and immunization is better than acquiring the virus. The cost of the immunization program is incomparable to the people's quality of life. Recently 2 new protease inhibitors, boceprevir and telaprevir, were approved by the US FDA in May 2011 and by the European Medicine Agency (EMA) in August and September 2011, respectively, for HCV treatment. The drugs can increase the efficacy and RVR when used as a triple drug therapy (with pegylated interferon and ribavirin) in HCV patients with genotype 1 [73–77], but the cost is 2-3 times higher than the standard treatment. For these new drugs, the US FDA is concerned about the adverse events such as suicidal tendencies and lack of efficacy in certain groups of people; boceprevir has been shown to cause rash and gout whereas telaprevir has been associated with TB. Both boceprevir and telaprevir can cause anemia in HCV patients. However, it should be noted that anemia is a common laboratory abnormality among patients infected with both HIV and HCV due to treatment; physicians will need to reduce the dose of their HCV medications in patients with anemia [78]. Aside from additional drug toxicities, evidence-based information from monoinfected HCV clinical trials on shorter triple drug treatment, pharmacokinetics guided optimized dose of new drugs, and potential drug-drug interactions warrant further investigations in Asian population living with HIV/AIDS. HCV Direct-Acting Antivirals (DAAs), new polymerase and protease inhibitors that are under clinical investigations with or without interferon, provide HCV patients with more treatment options. Quad therapy (2 different protease inhibitors plus pegylated interferon and ribavirin) is another option that will become available in the future regardless of the cost of the drugs. To improve tolerability and treatment coverage, the interferon-free DAA-based combination therapy may be an alternative choice for some people [79].

HCV infection is a curable disease and the international clinical guidelines already have provided recommendations for screening, diagnostics, and treatment for HCV/HIV co-infected patients. Yet majority of the patients, especially IDUs co-infected with HIV and HCV, still have problems in getting the proper treatment and care. The social stigma around drug use pervades many aspects of the society,

creating huge barriers that IDUs face when seeking health care. The barriers in the health care setting, including prejudice and stigmatization, are worse than HIV monoinfection because the medical service providers and policy makers have insufficient experience in dealing with co-infected patients resulting in limited care and financial support. Physicians may refuse treatment to IDUs because of their perceptions that these patients have poor adherence to treatment. In fact, treatment adherence among IDUs substantially increased when they have access to health and social services with harm reduction support and mental health care. A challenge can be met through educating medical staff and providing support for patients. Access to treatment and healthcare should be abrogated by national policymakers when it comes to treating HCV in HIV co-infected patients. The main economic benefit to treating people with HCV is that it will lower the cost and amount of medical care needed for HCV in the long term, including treatment for severe liver disease and HCV-related liver malignancy. Moreover, it is absolutely impossible to put a price on the patient's quality of life as it is priceless and invaluable. Successful treatment can also prevent new HCV infections.

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Clinical Study

Pharmacokinetics and Pharmacodynamics of Darunavir and Etravirine in HIV-1–Infected, Treatment-Experienced Patients in the Gender, Race, and Clinical Experience (GRACE) Trial

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Objectives. Evaluation of pharmacokinetics and pharmacodynamics of darunavir and etravirine among HIV-1–infected, treatment-experienced adults from GRACE, by sex and race. *Methods*. Patients received darunavir/ritonavir 600/100mg twice daily plus other antiretrovirals, which could include etravirine 200mg twice daily. Population pharmacokinetics for darunavir and etravirine were determined over 48 weeks and relationships assessed with virologic response and safety. Rich sampling for darunavir, etravirine, and ritonavir was collected in a substudy at weeks 4, 24, and 48. *Results*. Pharmacokinetics were estimated in 376 patients for darunavir and 190 patients for etravirine. Median darunavir AUC_{12h} and C_{0h} were 60,642ng·h/mL and 3624ng/mL, respectively; and for etravirine were 4183ng · h/mL and 280ng/mL, respectively. There were no differences in darunavir or etravirine AUC_{12h} or C_{0h} by sex or race. Age, body weight, or use of etravirine did not affect darunavir exposure. No relationships were seen between darunavir pharmacokinetics and efficacy or safety. Patients with etravirine exposure in the lowest quartile generally had lower response rates. Rich sampling showed no time-dependent relationship for darunavir, etravirine, or ritonavir exposure over 48 weeks. *Conclusions*. Population pharmacokinetics showed no relevant differences in darunavir or etravirine exposure by assessed covariates. Lower etravirine exposures were associated with lower response rates.

1. Introduction

Differences in antiretroviral pharmacokinetic parameters between women and men, caused by variables such as body weight, plasma volume, and cytochrome P450 activity, could lead to different drug concentrations and toxicity profiles between sexes [1–3]. Previous pharmacokinetic data from the antiretroviral therapy with TMC114 examined in naïve subjects (ARTEMIS) and TMC114/r in treatment-experienced patients naïve to lopinavir (TITAN) trials, which studied 343 treatment-naïve and 298 treatment-experienced patients receiving darunavir/ritonavir, respectively, have demonstrated small, nonclinically relevant differences in darunavir pharmacokinetic parameters between women and men and across races [4, 5]. The once-daily darunavir in treatment-experienced patients (ODIN) trial, which studied 294 patients receiving once-daily darunavir versus 296 patients receiving twice-daily darunavir, found that women had higher exposures than men, and Asian patients had lower exposure than white patients; however, these differences were not considered clinically significant [6]. Data from the pooled TMC125 to demonstrate undetectable viral load in patients experienced with antiretroviral therapy (DUET)-1 and DUET-2 trials, which compared treatment with etravirine ($n = 599$)

versus placebo ($n = 604$) in treatment-experienced patients, did not demonstrate any sex or racial differences in etravirine pharmacokinetic parameters [7]. These trials, however, were not specifically designed to investigate sex-based or race-based differences in darunavir or etravirine pharmacokinetics.

The gender, race, and clinical experience (GRACE) study was specifically designed to assess sex-based and race-based differences in the pharmacokinetics, efficacy, and safety of darunavir/ritonavir-based therapy in treatment-experienced, HIV-1–infected patients by enrolling a high proportion of women and people of color [8]. This paper presents the darunavir, ritonavir, and etravirine pharmacokinetic data from GRACE by sex and race, and the relationship of darunavir and etravirine pharmacokinetics with efficacy and safety, collected over 48 weeks. The relationship between extrinsic and intrinsic covariates with darunavir pharmacokinetics is also investigated.

2. Materials and Methods

2.1. Study Design and Treatment. GRACE was a 48-week, open-label, Phase IIIb study conducted at 65 study sites across the United States, Canada, and Puerto Rico. Treatment-experienced adults with HIV-1 RNA ≥1000 copies/mL received darunavir 600 mg coadministered with ritonavir 100 mg twice daily with other antiretrovirals, which could include etravirine 200 mg twice daily. The choice of additional antiretrovirals was based on resistance testing (virco®TY-PE HIV-1). During enrollment, the virco®TYPE HIV-1 resistance test used did not include etravirine, which resulted in some patients with reduced susceptibility to etravirine receiving the drug. Subsequently, at the time of data analysis, baseline samples were reanalyzed using an updated version of the virco®TYPE HIV-1 resistance test interpretation, which included etravirine. The data referenced in this paper are those obtained from the updated analysis. Women who were pregnant were excluded from the study. Other inclusion/exclusion criteria and study visits have been described previously [8]. Human experimentation guidelines of the United States Department of Health and Human Services and the Declaration of Helsinki were followed in the conduct of this clinical research; the research protocol was reviewed and approved by institutional review boards for all 65 study sites; written informed consent was provided by all participants prior to study initiation. Details of the study design were registered at clinicaltrials.gov (ID: NCT00381303).

2.2. Pharmacokinetic Analysis. Sparse sampling for the determination of darunavir and etravirine (if applicable) pharmacokinetic parameters was performed at Weeks 4, 8, 24, and 48. Two samples were taken at Weeks 4 and 24, one immediately before intake of medication and one at least an hour after intake of medication. At Weeks 8 and 48, the samples could be taken at any time after intake of medication. Pharmacokinetics were considered evaluable if the sample had measurable darunavir and ritonavir or etravirine (if applicable) concentrations, and if the time of last intake or administration was known. Previously developed population pharmacokinetic models [7, 9] were applied to the sparse sampling data to derive empirical Bayesian estimates of darunavir and etravirine area under the plasma concentration–time curve (AUC_{12h}) and trough concentration (C_{0h}).

In a subset of consenting patients from the pharmacokinetic substudy, intensive blood sampling for darunavir, ritonavir, and etravirine (if applicable) was conducted over 12 hours; samples were collected before dose and 1, 2, 3, 4, 6, 9, and 12 hours after dose at Weeks 4, 24, and 48. Ritonavir concentrations were determined to assess adherence to that medication. Patients were required to have fasted for 10 hours before arrival at the testing site. A standardized breakfast was served at the facility, and medications were administered within 30 minutes of the meal. In order to be included in the intensive pharmacokinetic sampling, patients had to volunteer and already participate at a study site that was involved in the intensive pharmacokinetic analysis.

Plasma concentrations of darunavir, ritonavir, and etravirine in the main study and substudy were determined using a previously validated liquid chromatography–tandem mass spectrometry method; the lower limit of quantification was 10.0 ng/mL, 5.0 ng/mL, and 2.0 ng/mL for darunavir, ritonavir, and etravirine, respectively [10].

Relationships between darunavir and etravirine pharmacokinetics (Bayesian estimated AUC_{12h} and C_{0h}) and virologic efficacy at Week 48, measured by change in $\log_{10}$ viral load (VL) from baseline and the proportion of patients achieving a VL less than 50 copies/mL, were assessed using analysis of covariance models. The impact of extrinsic and intrinsic covariates (use of etravirine [relationship with darunavir pharmacokinetics only] and use of tenofovir disoproxil fumarate [TDF], age, sex, race, body weight, and hepatitis B coinfection status) on darunavir and etravirine pharmacokinetics was explored graphically, using descriptive statistics and by analysis of covariance. Tenofovir disoproxil fumarate was included in the covariate analysis due to previous evaluations suggesting a drug-drug interaction with etravirine [11]. Relationships between darunavir and etravirine pharmacokinetics and safety (rash-, cardiac-, gastrointestinal-, liver-, lipid-, glucose-, psychiatric-, and nervous system–associated adverse events), including laboratory assessments, were investigated and are presented using descriptive statistics. Week 48 pharmacokinetic data were used to evaluate all relationships with efficacy, covariates, and safety.

3. Results

3.1. Patient Populations and Baseline Characteristics. GRACE enrolled a total of 429 patients, of whom 66.9% were women, 61.5% were black, 22.4% were Hispanic, and 15.2% were white. In the intent–to–treat time–to–loss of virologic response analysis of the overall population, 53.4% of patients achieved virologic response (HIV-RNA <50 copies/mL) after 48 weeks; women had a lower response compared with men (50.9% [confidence interval (CI) range: 45.1%–56.7%] and

58.5% [50.3%–66.6%], resp.), and black patients had a lower response rate compared with Hispanic and white patients (48.5% [42.5%–54.5%], 61.5% [51.7%–71.2%], and 60.0% [48.1%–71.9%], resp.) [8, 12]. Patients who received etravirine had slightly higher response rates than did the overall population. In the intent–to–treat time–to–loss of virologic response analysis of the etravirine population, 59.4% of patients achieved virologic response; women had a slightly lower response rate compared with men (58.0% [49.1%–66.9%] and 61.4% [51.2%–71.5%], resp.), and black patients had a lower response rate compared with Hispanic or white patients (55.6% [47.2%–64.1%], 69.4% [54.4%–84.5%], and 61.8% [45.4%–78.1%], resp.) [12, 13].

Of the 429 patients in the overall GRACE population, evaluable pharmacokinetic data from sparse sampling were available for 376 patients (Table 1). Among these patients, 66% ($n = 248$) were women, 60% ($n = 226$) were black, 22% ($n = 84$) were Hispanic, 17% ($n = 62$) were white, and 1% ($n = 4$) were Asian or other. In total, 37 patients—including 25 women, 12 men, 25 black patients, 10 Hispanic patients, and 2 white patients—underwent intensive pharmacokinetic sampling.

Of the 207 patients who received etravirine in addition to darunavir (Table 1), evaluable pharmacokinetic data from sparse sampling were available for 190 patients. These patients included 108 (57%) women, 122 (64%) black, 33 (17%) Hispanic, 31 (16%) white, and 4 (2%) Asian or other patients. Of the patients who received etravirine, 16 underwent intensive pharmacokinetic sampling, including 8 women, 11 black, 4 Hispanic, and 1 white patient.

Table 1: Baseline demographics and disease characteristics for the pharmacokinetic population (overall and etravirine populations).

Parameter	Overall $N = 376$	Etravirine subgroup $n = 190$
Sex, *n* (%)		
Male	128 (34.0)	82 (43.2)
Female	248 (66.0)	108 (56.8)
Race, *n* (%)		
Black	226 (60.1)	122 (64.2)
Hispanic	84 (22.3)	33 (17.4)
White	62 (16.5)	31 (16.3)
Asian/other	4 (1.1)	4 (2.1)
Median (range) age, years	43.0 (19.0, 78.0)	45.0 (19.0, 78.0)
Mean (SE) weight, kg	76.7 (1.03)	76.8 (1.50)
Mean (SE) BMI, kg/m^2	27.3 (0.35)[a]	27.0 (0.50)
Mean (SE) duration of HIV infection, years	11.3 (0.29)[a]	12.5 (0.38)[b]
Mean (SE) HIV-1 RNA, $\log_{10}$ copies/mL	4.64 (0.044)	4.60 (0.067)
Median (range) CD4$^+$ count, cells/mm^3	203 (2, 1125)	186 (1, 1125)
CDC Class C, *n* (%)	148 (39.4)	87 (45.8)
Median (range) darunavir, fold change[c]	0.6 (0.3, 607.9)[d]	0.6 (0.3, 607.9)
Median (range) etravirine, fold change[c]	1.3 (0.3, 93.8)[d]	1.4 (0.3, 93.8)
Prior use of ≥2 PIs, *n* (%)	228 (60.6)	135 (71.1)

[a] $n = 375$. [b] $n = 189$. [c] virco® TYPE HIV-1 resistance analysis; patients were considered susceptible to darunavir if the fold change was <3.4 and to etravirine if the fold change was <3.2. [d] $n = 374$; 2 patients, one Hispanic and one white (both women), did not have resistance testing at baseline. SE: standard error; BMI: body mass index; CDC: United States Center for Disease Control and Prevention; PI: protease inhibitor.

3.2. Pharmacokinetics

3.2.1. Population Pharmacokinetic Analyses over 48 Weeks. Among the 429 patients enrolled in this trial, 222 did not receive etravirine and 207 received at least one dose of etravirine. Based on pharmacokinetic data available for 376 patients, including both recipients and nonrecipients of etravirine, the median (range) darunavir AUC_{12h} and C_{0h} were 60,642 (26,117–128,790) ng·h/mL and 3624 (931–9570) ng/mL, respectively. Based on pharmacokinetic data available for 187 patients who did not receive etravirine, the median (range) darunavir AUC_{12h} and C_{0h} were 58,933 (26,117–128,790) ng·h/mL and 3489 (1036–9570) ng/mL, respectively. Based on pharmacokinetic data available for 189 patients who received etravirine, the median (range) darunavir AUC_{12h} and C_{0h} were 62,626 (30,960–109,410) ng·h/mL and 3806 (931–7473) ng/mL, respectively. In those patients who received etravirine, the median (range) etravirine AUC_{12h} and C_{0h} were 4183 (212–27,960) ng·h/mL and 280 (4–2211) ng/mL, respectively. Analysis of darunavir and etravirine pharmacokinetics by sex and race showed no clinically relevant difference in AUC_{12h} or C_{0h} between sexes or across races. Based on univariate analysis, hepatitis B co-infection status, age, body weight, or use of etravirine or TDF did not affect darunavir AUC_{12h} or C_{0h} (Table 2).

Patients with TDF in their background regimen had lower median etravirine exposure (AUC_{12h}, 3998 ng·h/mL; C_{0h}, 258 ng/mL) compared with those without TDF (AUC_{12h}, 5051 ng·h/mL; C_{0h}, 329 ng/mL), and patients with hepatitis B co-infection demonstrated a trend toward higher median etravirine exposures (AUC_{12h}, 5504 ng·h/mL; C_{0h}, 382 ng/mL) compared with those without co-infection (AUC_{12h}, 4141 ng·h/mL; C_{0h}, 278 ng/mL). We further analyzed several of these covariates using an analysis of covariance (Table 3). Only age and female sex were statistically correlated with higher darunavir exposure; older age was also correlated with higher etravirine exposure. However, none of these associations were considered clinically relevant as evidenced by univariate analysis.

3.2.2. Intensive Pharmacokinetic Analyses Over 48 Weeks. Intensive pharmacokinetic sampling showed no time-dependent relationship for darunavir, ritonavir, or etravirine exposure over 48 weeks; darunavir and etravirine intensive pharmacokinetic results were generally similar to the population pharmacokinetic results (Table 4). Mean plasma concentration–time profiles for darunavir were higher in women than in men, with an AUC_{12h} approximately 18%, 33%, and 14% higher in women than in men at Weeks 4, 24, and

Table 2: Population pharmacokinetics at Week 48 (univariate analysis).

	Darunavir			Etravirine		
	n	AUC_{12h} Median (range) Ng·h/mL	C_{0h} Median (range) ng/mL	n	AUC_{12h} Median (range) ng·h/mL	C_{0h} Median (range) ng/mL
Overall population	376	60,642 (26,117–128,790)	3624 (931–9570)	190	4183 (212–27,960)	280 (4–2211)
Age, years						
≤30	39	58,309 (33,050–128,790)	3317 (1145–9570)	17	3476 (568–5261)	212 (5–331)
>30 to ≤50	260	59,955 (26,117–105,130)	3584 (931–6841)	128	4348 (212–27,960)	286 (4–2211)
>50 to ≤65	68	64,337 (40,299–120,880)	3957 (2215–8906)	38	4366 (295–11,684)	291 (11–890)
>65	9	63,978 (38,171–84,295)	3916 (1879–5869)	7	7484 (2213–17,921)	541 (126–1392)
Weight at baseline, kg						
≤62.33	94	61,005 (32,271–128,790)	3665 (1169–9570)	46	3675 (295–17,921)	226 (11–1392)
>62.33 to ≤73.94	96	58,367 (29,888–93,408)	3489 (931–6081)	48	3824 (1004–20,495)	250 (42–1605)
>73.94 to ≤87.09	92	63,942 (34,692–105,130)	3903 (1568–6502)	52	4960 (212–27,960)	332 (4–2211)
>87.09	94	61,090 (26,117–100,710)	3561 (1258–6943)	44	4638 (1319–18,977)	314 (60–1487)
Hepatitis B co-infection status						
No	362	60,831 (26,117–128,790)	3618 (931–9570)	184	4141 (212–27,960)	278 (4–2211)
Yes	14	57,936 (37,506–97,125)	3718 (1640–6784)	6	5504 (3751–11,684)	382 (241–890)
Use of TDF						
No	58	61,443 (38,104–109,410)	3489 (1169–7473)	45	5051 (295–17,921)	329 (11–1392)
Yes	318	60,601 (26,117–128,790)	3627 (931–9570)	145	3998 (212–27,960)	258 (4–2211)
Use of etravirine						
No	187	58,933 (26,117–128,790)	3489 (1036–9570)	NA	NA	NA
Yes	189	62,626 (30,960–109,410)	3806 (931–7473)	NA	NA	NA

AUC_{12h}: area under the plasma concentration–time curve over 12 hours; C_{0h}: trough concentration; TDF: tenofovir disoproxil fumarate; NA: not applicable.

Table 3: Relationship of selected covariates with darunavir or etravirine pharmacokinetic parameters at Week 48—analysis of covariance.

	Darunavir				Etravirine			
Covariate	Relationship to AUC_{12h}, estimate (SE)	Relationship to AUC_{12h}, adjusted P value	Relationship to C_{0h}, estimate (SE)	Relationship to C_{0h}, adjusted P value	Relationship to AUC_{12h}, estimate (SE)	Relationship to AUC_{12h}, adjusted P value	Relationship to C_{0h}, estimate (SE)	Relationship to C_{0h}, adjusted P value
Sex	0.028 (0.011)	0.011	0.050 (0.016)	0.002	−0.035 (0.049)	0.479	−0.049 (0.063)	0.432
Race[a]		0.246		0.115		0.808		0.843
Asian	–0.099 (0.096)		−0.136 (0.143)		0.369 (0.331)		0.452 (0.422)	
Black	–0.002 (0.068)		0.017 (0.101)		0.116 (0.236)		0.155 (0.301)	
Hispanic	0.004 (0.069)		0.041 (0.103)		0.148 (0.242)		0.183 (0.308)	
White	0.023 (0.069)		0.058 (0.103)		0.130 (0.240)		0.184 (0.306)	
Other	0.000		0.000		0.000		0.000	
Age,[b] years	0.001 (0.001)	0.005	0.003 (0.001)	<0.001	0.005 (0.002)	0.029	0.007 (0.003)	0.023
Weight,[b] kg	0.000 (0.000)	0.839	0.000 (0.000)	0.784	0.002 (0.001)	0.179	0.002 (0.002)	0.149
Use of TDF	–0.019 (0.014)	0.168	–0.038 (0.021)	0.072	NE	NE	NE	NE
Use of etravirine	–0.024 (0.028)	0.389	–0.032 (0.042)	0.450	NA	NA	NA	NA

[a]Five-way comparison: white, black, Hispanic, Asian, and other. [b]Modeled as continuous linear variables. AUC_{12h}: area under the plasma concentration–time curve over 12 hours; SE: standard error; C_{0h}: trough concentration; TDF: tenofovir disoproxil fumarate; NE: not evaluated; NA: not applicable.

48, respectively. Ritonavir AUC_{12h} was approximately 44% higher in women at Weeks 4 and 24 and 8% lower in women than in men at Week 48. Mean plasma concentration–time profiles for both darunavir and ritonavir slightly differed when comparing black and Hispanic patients. For darunavir, higher concentrations were observed for black patients at Weeks 4 and 48 than for Hispanic patients. When the intensive pharmacokinetic data for etravirine were broken down by sex or race, the sample sizes were too small to draw any definitive conclusions (Table 4).

3.2.3. Relationship between Pharmacokinetics (Sparse Sampling) and Efficacy. When the relationships between darunavir population pharmacokinetics and efficacy parameters were investigated, no relationships were observed between darunavir AUC_{12h} or C_{0h} values and the change in $\log_{10}$ VL from baseline to Week 48, or the proportion of patients achieving less than 50 copies/mL by Week 48 in the overall nonvirologic failure–censored population, which censored patients who discontinued for reasons other than virologic failure (Figure 1(a)). Furthermore, consistent with the above results, no relationship between darunavir Week 48 pharmacokinetics and change in VL or virologic response was seen by sex or race.

When the relationships between etravirine pharmacokinetics and efficacy parameters in the nonvirologic failure–censored population were investigated, patients with AUC_{12h} or C_{0h} in the lowest quartile at Week 48 had the smallest change in $\log_{10}$ VL from baseline to Week 48 (Figure 1(b)). These patients in the lowest quartile of AUC_{12h} or C_{0h} at Week 48 also demonstrated the lowest virologic response rates, compared with the other pharmacokinetic quartiles (Figure 1(b)).

3.2.4. Relationship between Pharmacokinetics and Safety. When the relationships between darunavir and etravirine pharmacokinetic parameters and safety in the overall population were investigated, no apparent relationships were observed between darunavir or etravirine AUC_{12h} or C_{0h} and the incidence of rash-, cardiac-, gastrointestinal-, liver-, lipid-, glucose-, nervous system disorder–, or psychiatric disorder–associated adverse events (data not shown). Similarly, no relationships were seen between darunavir pharmacokinetics and safety parameters by sex or race (data not shown).

4. Discussion

Sex and race did not appear to substantially affect darunavir or etravirine exposure. Similar darunavir exposures have been observed in treatment-experienced patients from the performance of TMC114/r when evaluated in treatment- experienced patients with PI resistance (POWER 1, 2, and 3 and TITAN trials [4, 14]). Likewise, previous studies of etravirine pharmacokinetics have yielded median values similar to those seen here [7]. Furthermore, the ranges of darunavir and etravirine exposure observed in this study were numerically similar to those from previous studies [4, 7].

Although this study was not specifically powered to compare the effects of covariates on pharmacokinetics, all groups (e.g., women versus men) were well represented, allowing for meaningful comparisons. This study demonstrated that the pharmacokinetic exposure (i.e., AUC_{12h} and C_{0h}) to darunavir was not substantially influenced by sex, race, age, body weight, hepatitis B co-infection status, or use of etravirine or TDF, similar to results from other studies of darunavir/ritonavir in treatment-experienced, HIV-infected patients [4, 5, 7, 10, 15]. Trials of other HIV protease inhibitors (PIs) have demonstrated an influence of various covariates on pharmacokinetic parameters. For instance, 2 studies have demonstrated significant differences in exposure of saquinavir and indinavir between women and men [16, 17]. In contrast to the darunavir pharmacokinetic results, patients using TDF or with hepatitis B co-infection demonstrated trends toward lower and higher etravirine exposure, respectively. Similar results were obtained in the DUET trials and were not deemed clinically relevant [7]. The effect of TDF use was as expected, based on a known drug-drug interaction [11], and it should be noted that use of TDF did not affect clinical outcomes in this trial [8].

Although no clinically relevant sex-based differences in population pharmacokinetic parameters were seen during this trial, an analysis of covariance (which showed statistical differences and intensive pharmacokinetic sampling in a subset of patients), did suggest a trend toward higher darunavir and ritonavir exposure in women compared with men. Similar results were seen in TITAN, which suggested that women had slightly higher darunavir exposures than men (~15% higher) and that black patients had slightly higher darunavir exposures than white patients (~8% higher); these differences were not considered clinically relevant. The trend toward increased darunavir exposure in women, observed in this trial and in TITAN, may be due to several factors, including, but not limited to, physiologic differences in protein binding, gastric motility, sex hormones, and/or α_1-acid glycoprotein (AAG) levels [18]. Elevated AAG levels have been linked to increased PI binding and, therefore, exposure [19, 20]. Indeed, at baseline, women in the pharmacokinetic substudy of the GRACE trial had AAG levels approximately 12% higher than those of men [21]. Recently, a post hoc analysis of the GRACE pharmacokinetic Week 4 substudy investigated the relationship of plasma estrone sulfate (E3S), a sex hormone, with darunavir and ritonavir pharmacokinetics [22]. In this case, no differences were seen in the plasma concentrations of E3S between women and men in the substudy. Additionally, although E3S and darunavir were both substrates for the hepatic uptake transporter SLCO1B1, no relationship was seen between plasma concentrations of E3S and the pharmacokinetics of darunavir or ritonavir. In the current study, it is possible that unidentified differences in baseline physiology between the populations undergoing sparse ($n = 376$) or intensive ($n = 37$) pharmacokinetic sampling may also account for the fact that no sex-based difference was seen in the former population, in contrast to the small differences seen in the latter population. Although the sample sizes were too small to draw any definitive conclusions for the etravirine intensive pharmacokinetic

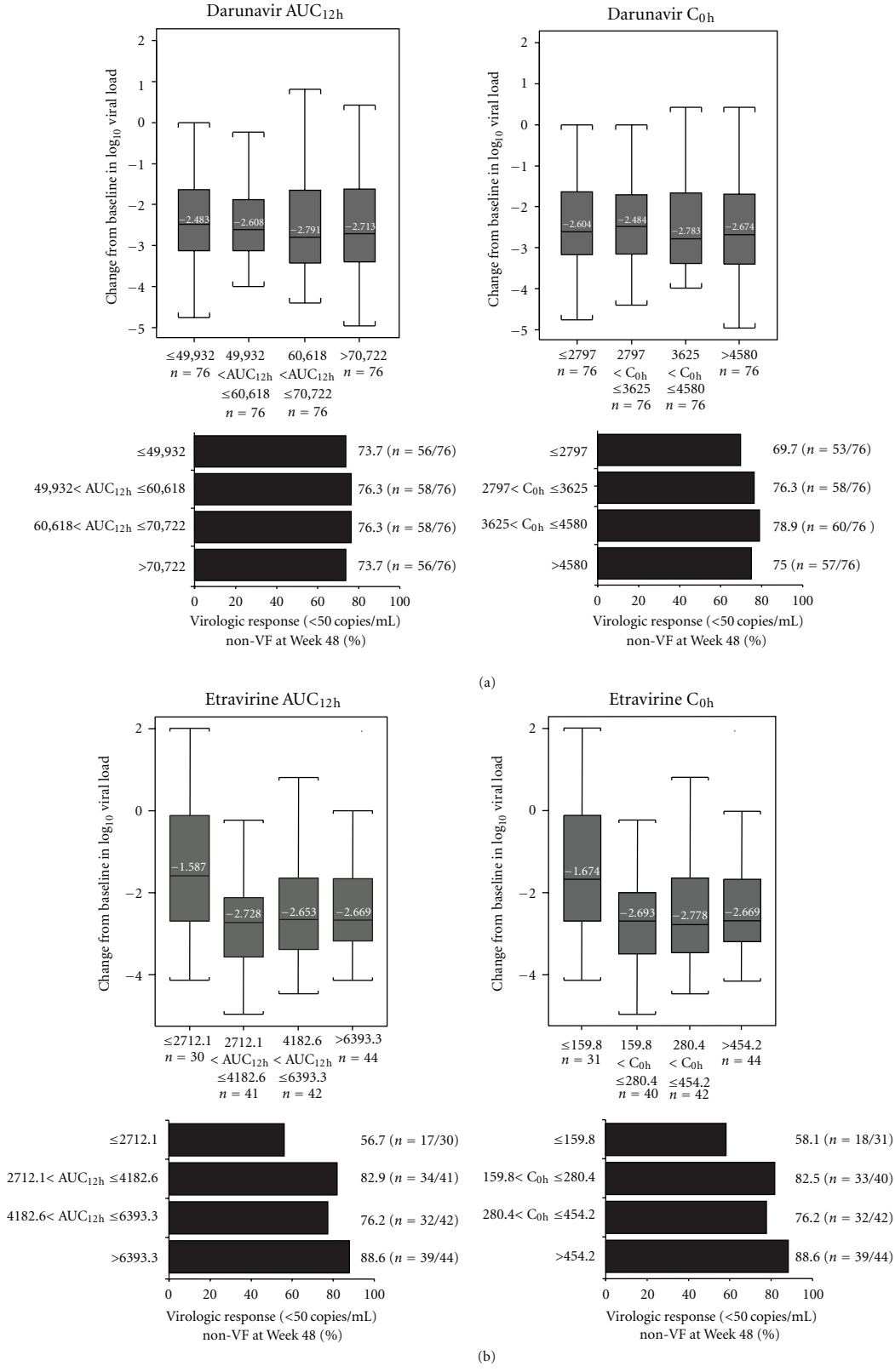

FIGURE 1: Change in $\log_{10}$ viral load from baseline to Week 48 (nonvirologic failure censored) and virologic response by quartile ranges of (a) darunavir AUC_{12h} and C_{0h} (sparse pharmacokinetic sampling; $n = 376$) and (b) etravirine AUC_{12h} and C_{0h} (sparse pharmacokinetic sampling; $n = 190$). In Figures 1(a) and 1(b), the numbers within the boxplots represent the median values, the boxes represent the 25th and 75th percentiles, and the whiskers represent the highest and lowest value within 1.5 interquartile range. AUC_{12h}: area under the plasma concentration–time curve over 12 hours; C_{0h}: trough concentration; DRV: darunavir; non-VF: nonvirologic failure censored population; ETR: etravirine.

Table 4: Pharmacokinetics of darunavir, ritonavir, and etravirine (intense pharmacokinetic sampling).

	Week 4				Week 24				Week 48			
Mean ± SD	AUC_{12h}, ng·h/mL	*n*	C_{0h}, ng/mL	*n*	AUC_{12h}, ng·h/mL	*n*	C_{0h}, ng/mL	*n*	AUC_{12h}, ng·h/mL	*n*	C_{0h}, ng/mL	*n*
Darunavir												
Overall	62,360 ± 25,020	32	3559 ± 2385	26	62,230 ± 27,420	22	5042 ± 2080	20	56,320 ± 22,440	21	3388 ± 2078	21
Men												
Overall	55,570 ± 21,220	10	3863 ± 2402	8	51,510 ± 30,260	8	4765 ± 2240	6	52,040 ± 25,010	9	3406 ± 2134	9
Black	59,410 ± 26,060	6	4445 ± 3006	4	57,690 ± 36,900	5	5175 ± 2771	4	61,300 ± 28,130	4	3836 ± 2268	5
Hispanic	48,110 ± 14,160	3	3280 ± 1875	4	41,210 ± 15,070	3	3945 ± 134	2	35,630 ± 11,440	4	1973 ± 1444	3
White	54, 910	1	—	—	—	—	—	—	80, 630	1	5550	1
Women												
Overall	65,440 ± 26,450	22	3424 ± 2434	18	68,360 ± 24,710	14	5160 ± 2085	14	59,540 ± 20,850	12	3375 ± 2131	12
Black	66,290 ± 29,930	16	3050 ± 2540	14	63,500 ± 22,080	11	5723 ± 1876	10	61,950 ± 23,570	9	3418 ± 2127	8
Hispanic	61,980 ± 17,070	5	4877 ± 1968	3	86,170 ± 30,410	3	3753 ± 2139	4	52,290 ± 7973	3	3290 ± 2465	4
White	69,090	1	4310	1	—	—	—	—	—	—	—	—
Ritonavir												
Overall	5722 ± 3788	32	235 ± 223	26	6473 ± 4561	22	402 ± 326	20	5340 ± 2788	21	281 ± 187	21
Men												
Overall	4399 ± 1876	10	276 ± 227	8	5047 ± 3409	8	296 ± 158	6	5611 ± 3480	9	318 ± 198	9
Black	5060 ± 1676	6	342 ± 260	4	6216 ± 3917	5	343 ± 143	4	7633 ± 3297	4	358 ± 171	5
Hispanic	3625 ± 2290	3	210 ± 204	4	3099 ± 941	3	201 ± 192	2	2833 ± 1620	4	180 ± 202	3
White	2755	1	—	—	—	—	—	—	8639	1	537	1
Women												
Overall	6324 ± 4297	22	217 ± 225	18	7287 ± 5038	14	448 ± 371	14	5136 ± 2286	12	252 ± 182	12
Black	5951 ± 4701	16	146 ± 149	14	7091 ± 5577	11	471 ± 436	10	4773 ± 2354	9	209 ± 136	8
Hispanic	6825 ± 3191	5	457 ± 354	3	8007 ± 2919	3	390 ± 144	4	6226 ± 2048	3	339 ± 251	4
White	9782	1	491	1	—	—	—	—	—	—	—	—
Etravirine												
Overall	6980 ± 4205	16	455 ± 238	14	5495 ± 3232	10	460 ± 319	13	5520 ± 2756	9	375 ± 215	12
Men												
Overall	6636 ± 5720	8	409 ± 305	6	4020 ± 1673	4	410 ± 351	6	5694 ± 3729	5	382 ± 278	6
Black	5919 ± 5840	4	563 ± 392	3	2805 ± 888	2	265 ± 209	2	2027	1	312 ± 338	2
Hispanic	4165 ± 583	3	255 ± 88	3	5235 ± 1306	2	276 ± 14	3	4819 ± 383	3	273 ± 73	3
White	16,910	1	—	—	—	—	1100	1	11, 990	1	846	1

Table 4: Continued.

	Week 4				Week 24				Week 48			
Mean ± SD	AUC_{12h}, ng·h/mL	*n*	C_{0h}, ng/mL	*n*	AUC_{12h}, ng·h/mL	*n*	C_{0h}, ng/mL	*n*	AUC_{12h}, ng·h/mL	*n*	C_{0h}, ng/mL	*n*
Women												
Overall	7323 ± 2212	8	490 ± 188	8	6479 ± 3771	6	503 ± 311	7	5304 ± 1265	4	369 ± 156	6
Black	7381 ± 2383	7	465 ± 187	7	5902 ± 3910	5	456 ± 313	6	5304 ± 1265	4	392 ± 162	5
Hispanic	6918	1	670	1	9362	1	783	1	—	—	253	1

SD: standard deviation; AUC_{12h}: area under the plasma concentration–time curve over 12 hours; C_{0h}: trough concentration.

data by sex or race, results did seem consistent with the population pharmacokinetic results of this and other trials [7].

Intensive pharmacokinetic sampling showed no time-dependent relationship for darunavir, ritonavir, or etravirine. As observed in other studies of darunavir/ritonavir in treatment-naïve and treatment-experienced patients [4, 14, 23], no relevant relationships between darunavir pharmacokinetic parameters and the safety or efficacy of darunavir/ritonavir-based therapy were observed at Week 48 in the overall population, by sex or by race. Week 48 was chosen for these comparisons because we wanted to investigate the correlation between steady-state drug exposure and response or VL over the course of the study. Although no significant sex-based difference in virologic response rates was observed in the GRACE study, black patients did have lower response rates than white or Hispanic patients [8, 12]. Based on the results of this study, however, this lower response rate is not due to differences in pharmacokinetic profiles between racial groups. Even though there was no significant relationship seen between darunavir pharmacokinetic parameters and safety, it is possible that the slightly higher ritonavir exposure in women may contribute to the small sex-based differences in adverse events reported in the GRACE study; women reported slightly higher rates of nausea and vomiting, whereas men had higher rates of diarrhea [8].

A relationship between etravirine pharmacokinetic parameters and efficacy was observed in this study. Patients with etravirine AUC_{12h} or C_{0h} in the lowest quartile ($\leq$2712 ng·h/mL or $\leq$160 ng/mL, resp.) had the smallest change in $\log_{10}$ VL from baseline to Week 48 and the lowest response rates, compared with the other pharmacokinetic quartiles. The response rates of patients in the lowest quartile of etravirine AUC_{12h} were similar in the GRACE and DUET trials (56.7% and 59.0%, resp.; nonvirologic-censored populations; data on file). GRACE was a single-armed study, so it is difficult to determine whether having low pharmacokinetic etravirine exposure itself or a factor contributing to low pharmacokinetic etravirine exposure, such as nonadherence, is contributing to the lower response rates in this group. No relevant relationship between etravirine pharmacokinetic parameters and the safety of etravirine was seen in this study.

Pharmacokinetic results from GRACE demonstrated that darunavir and etravirine exposures are not substantially affected by sex and race, and that the darunavir C_{0h} was above the protein-binding corrected median effective concentration (EC_{50}) value for PI-resistant virus for all patients. These results suggest that darunavir/ritonavir and etravirine therapy are effective in treatment-experienced men and women and across races. Furthermore, no relevant relationship was seen between darunavir pharmacokinetic parameters and a range of extrinsic and intrinsic covariates, or the efficacy or safety of darunavir/ritonavir-based therapy. The response rate obtained by those patients with the lowest etravirine exposures in this study was substantially higher than the response rate of patients in DUET who received no etravirine [24], suggesting that etravirine use may still be beneficial to treatment-experienced patients with lower etravirine exposure. It should be noted that this study was conducted using darunavir/ritonavir 600/100 mg twice daily, which was the approved dose for treatment-experienced patients at the time of the study. Since then, darunavir/ritonavir 800/100 mg once daily has been approved for treatment-experienced patients with no darunavir resistance-associated mutations, based upon results from the ODIN trial [6, 25]. Further pharmacokinetic analyses will therefore be needed for this newly approved dose.

5. Conclusion

These findings support the results from the overall GRACE trial, which showed that darunavir/ritonavir-based therapy is generally safe and effective and that etravirine use is associated with improved outcomes [8, 13], and suggest that darunavir/ritonavir and etravirine may be administered without dose adjustment in both sexes and across races.

Disclosures

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Research Article

The Impact of Herbal Drug Use on Adverse Drug Reaction Profiles of Patients on Antiretroviral Therapy in Zimbabwe

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Background. The main objective was to determine the impact of herbal drug use on adverse drug reactions in patients on antiretroviral therapy (ART). *Methodology*. Patients receiving first-line ART from the national roll-out program participated in this cross-sectional study. Participants were interviewed and a data collection sheet was used to collect information from the corresponding medical record. *Results*. The majority (98.2%) of participants were using at least one herbal drug together with ART. The most common herbal remedies used were *Allium Sativum* (72.7%), *Bidens pilosa* (66.0%), *Eucalyptus globulus* (52.3%), *Moringa oleifera* (44.1%), *Lippia javanica* (36.3%), and *Peltoforum africanum* (34.3%). Two indigenous herbs, *Musakavakadzi* (OR = 0.25; 95% CI 0.076–0.828) and *Peltoforum africanum* (OR = 0.495; 95% CI 0.292–0.839) reduced the occurrence of adverse drug events. *Conclusions*. The use of herbal drugs is high in the HIV-infected population and there is need for pharmacovigilance programs to recognize the role they play in altering ADR profiles.

1. Introduction

Several challenges exist in resource-limited settings between balancing the cost and toxicity that occurs during antiretroviral therapy (ART). Most HIV-infected patients in resource-limited settings receive a first-line triple combination of lamivudine, nevirapine, and stavudine or zidovudine [1]. Typical examples of ART in these settings include the World Health Organization prequalified fixed-dose combinations of stavudine/lamivudine/nevirapine (D4T/3TC/NVP) and zidovudine/lamivudine/nevirapine (AZT/3TC/NVP), which are being widely promoted in highly active antiretroviral therapy (HAART) "scale-up" programs.

ART is associated with a variety of adverse drug reactions (ADRs) that can hamper treatment adherence. Particularly, there is concern about the risk for peripheral neuropathy with use of stavudine, especially among patients with lower CD4 cell counts [2] and the risk of rash (including Stevens Johnson syndrome), hypersensitivity, and life-threatening hepatotoxicity with use of nevirapine, especially among women and those with higher CD4 cell counts at initiation of therapy [3–5]. In Sub-Saharan Africa, different incidence rates have been identified for ADRs associated with ART. The most commonly evaluated regimen in Sub-Saharan Africa is the D4T/3TC/NVP combination and this has been associated with various rates of ADRs in different settings [6–13].

Traditional herbal remedies have been used to treat many ailments in Zimbabwe for many years before the introduction of orthodox medicines. The advent of HIV/AIDS in Zimbabwe increased the popularity and use of herbal remedies because antiretroviral drugs were not available at that time [14]. Studies in South Africa have shown that herbal remedies are good supplements to antiretroviral therapy because of their immune boosting properties [15]. A study in western Uganda found that 38% of HIV-positive patients used traditional medicines and antiretroviral drugs at the

same time for the management of HIV infection [16]. The major reasons for use of traditional medicines were perceived additional efficacy, improvement in quality of life, and a feeling of control over the disease. The majority of traditional medicines currently being used by patients have not been thoroughly researched. The impact of coadministration of traditional herbal medicine with orthodox medicine has not yet been fully evaluated and consequently there is a lack of data which pertains to this subject. Patients are currently taking herbal medicines with orthodox medicines without the knowledge of how this affects them.

Research is required to determine factors which affect occurrence of ADRs associated with ART. Identification of patients at different levels of risk may identify subgroups requiring different monitoring intensities. An evaluation of the potential of the most widely used herbal remedies to interact with antiretroviral drugs may be helpful in improving the clinical outcome of patients on ART. It would enable risk identification and assessment, and if necessary, execution of risk reduction strategies. In view of the above, the objective of this study was to determine the impact of coadministration of herbal therapy with ART on ADRs.

2. Materials and Methods

2.1. Study Site and Population. The study was carried out at the Family Care Centre (FCC) ART clinic in Harare, Zimbabwe. The FCC is part of Parirenyatwa Hospital, which is a major public referral and teaching medical facility. The FCC is integrated into the outpatient department where patients receive antiretroviral drugs and treatments for opportunistic infections for free. The results reported are for patients who had been on first-line or alternate-first-line ART for at least 24 weeks. Inclusion criteria were a documented HIV infection in patients aged 18 years and older on first-line or alternate-first-line HAART for at least 24 weeks. THM use was defined as a daily use of any plant-based extract for a period of at least 24 weeks.

2.2. Antiretroviral Drug Treatment. The first line treatment available through the government roll-out programme consisted of a triple fixed dose combination of nevirapine 200 mg, stavudine 30 mg, and lamivudine 150 mg twice daily. Alternate-first-line therapy was available for patients who did not tolerate stavudine and consisted of nevirapine 200 mg, zidovudine 300 mg, and lamivudine 150 mg twice daily. For patients concomitantly taking antituberculosis therapy, efavirenz (EFV) 600 mg once daily at night was prescribed instead of nevirapine as per the national guidelines. ADRs were documented after commencement of ARVs.

2.3. Data Collection and Statistical Analysis. Eligible patients gave written consent before being enrolled into the study. The FCC pharmacist and peer counselor, who were not members of the regular ART clinic staff, conducted patient interviews. Patient data that was collected included age, gender, ethnicity, type of ART regimen, comorbidities, and herbal medicine use. Interviews took place in either the local language or English, depending on the participant's preference. Data on ADRs was extracted from the ART patient files. Potential herbal formulations that could influence ADRs were identified using multivariate linear regression and logistic regression analysis. An *a prioiri* significance level of $\alpha = 0.05$ was used for analyses. A logistic regression model was used to test whether herbal therapy use affected the occurrence of ADRs. Three regression models, 1 multiple linear regression model and 2 logistic regression models, were run to identify predictors of ADRs. Data analysis was carried out using the Statistical Analysis System (SAS Version 9.2, Cary, North Carolina, USA).

Table 1: Demographic and clinical characteristics of study patients. Unless specified, figures represent frequencies and percentages.

Characteristic	*N*	%
Age (mean ± SD)	40.8	9.2
Gender		
Male	137	35.3
Female	251	64.7
Comorbidities		
Diabetes mellitus	5	1.3
Hypertension	67	17.3
Anaemia	34	8.8
Asthma	21	5.4
Epilespy	4	1.0
Malaria	155	40.0
Tuberculosis	131	33.8
Shingles	125	32.2
ARV regimen		
AZT/3TC/EFV	10	2.6
AZT/3TC/NVP	36	9.3
D4T/3TC/EFV	12	3.1
D4T/3TC/NVP	330	85.1
Number of herbs per patient (mean ± SD)	7.9	4.4

3. Results

3.1. Patient Characteristics. A total of 388 patients were interviewed, and of these, 381 were found to be taking at least 1 herbal drug. Table 1 shows the demographic and clinical characteristics of the study patients. The average age of the patients was 40.8 ± 9.2 years and the majority were female (64.7%). The majority (85.1%) of the patients were on the twice daily regimen of a fixed-dose combination of 30 mg of D4T, 150 mg of 3TC, 200 mg of NVP. The most common comorbidities were malaria (40.0%), tuberculosis (33.8%), shingles (32.2%), and hypertension (17.3%).

3.2. Herbal Drug Use. Table 2 shows the frequency of use of herbal remedies. The majority of patients (98.2%) were on at least one indigenous herbal remedy together with their ART regimen. The most common herbal remedies were *Allium Sativum* (72.7%), *Bidens pilosa* (66.0%), *Eucalyptus globulus* (52.3%), *Moringa oleifera* (44.1%), *Lippia javanica* (36.3%), and *Peltoforum africanum* (34.3%). The results from the

Table 2: Frequencies of herbal use in study population.

Characteristic	*N*	%
Hypoxis hemerocallidea	41	10.6
Dicoma anomala	103	26.6
Aloe vera	108	27.8
Moringa oleifera	171	44.1
Murunguyane†	62	16.0
Musakavakadzi†	13	3.4
Musosote†	15	3.9
Bidens pilosa	256	66.0
Lippia javanica	141	36.3
Peltoforum africanum	133	34.3
Ngoka 11†	30	7.7
Symphytum officinale	41	10.6
Eucalyptus globules	203	52.3
Allium Sativum	282	72.7

†Scientific names could not be identified for these formulations

Table 3: Prevalence of adverse drug reactions in the study patients.

ADR type and severity	*N*	%
ADR prevalence	273	70.4
ADR severity ($N = 273$)		
Grade 1	161	41.5
Grade 2	96	24.7
Grade 3	15	3.9
Grade 4	1	0.3
Type of ADRs		
Peripheral neuropathy	162	41.8
Skin rash	101	26.0
Lipodystrophy	13	3.4
GI symptoms	28	7.2

logistic regression yielded that there was no association between the comorbidities and the severity of the adverse drug reactions. The overall multiple regression model for analyzing the data and interpreting the results was significant for this data analysis (Wald's P value = 0.0055).

A one-way ANOVA test revealed a statistically significant difference in the average number of herbs each patient was using and the type of ARV regimen ($F = 6.40$; df = 3, 384; $P = 0.0003$). A post hoc analysis revealed that patients on AZT/3TC/EFV were using fewer herbs (mean = 4.0) compared to those using other regimens.

Logistic regression was used to identify potential predictors of ADRs, controlling for other variables. There was a statistically significant association between two herbal medicines and the occurrence of ADRs. Patients who used the indigenous herb, *Musakavakadzi,* were 75 percent less likely to develop ADRs compared to patients who did not use the herb (OR = 0.25; 95% CI: 0.076–0.828; $P = 0.023$). Similarly, patients who used *Peltoforum africanum* were less likely to develop adverse drug events compared to patients who did not use the herb (OR = 0.495; 95% CI: 0.292–0.839; $P = 0.0091$).

3.3. Prevalence of Adverse Drug Reactions. Table 3 shows the frequency of ADRs reported by patients. A large proportion of patients experienced at least one ADR during ART treatment (70.4%). The most common ADRs were peripheral neuropathy (41.8%) and skin rash (26.0%). Peripheral neuropathy was mainly reported by patients on regimens that included D4T (93.0%). Skin rash was mainly observed with the NVP-based regimens (88.0%). The other reported ADRs were lipodystrophy, abdominal pain and gastrointestinal symptoms (nausea, vomiting, or heartburn).

4. Discussion

The impact of herbal medicine use on the ADR profiles of the first-line regimens used in Zimbabwe was examined. One of the reasons that patients use herbals is to try and alleviate the discomforts caused by antiretroviral ADRs. A relationship was observed between the type of antiretroviral regimen received and the total number of herbs used. Those patients who were on the regimen containing AZT/3TC/EFV used fewer herbal therapies when compared to the other regimens. One possible reason for this could be the decreased rates of ADRs that are associated with this regimen which decreases the need for herbal use for managing toxicity. Another important finding was the relationship that *Musakavakadzi* and *Peltoforum africanum* had with the rates of ADRs. These herbal remedies were associated with decreased prevalence of ADRs, indicating that these herbals might offer some protection to the patients. It is important to note that 98.2 percent of patients were taking at least one herbal remedy and with such a high rate of herbal use there is a need to increase research in herbal remedies that have the potential to influence treatment outcomes.

This study observed a high prevalence (70.2%) of ADRs in patients receiving ART. Of note is the high prevalence of peripheral neuropathy (41.8%) and skin rashes (26.0%). Skin rash occurrences due to ART were comparable to those that were observed in other studies [6–10]. Even though the rates in Zimbabwe are within other reported rates, the prevalence of skin rash is relatively higher. Lipodystrophy rates were lower when compared to studies that were conducted elsewhere [8, 9, 11]. Similarly, GI symptoms and abdominal pain rates were comparable to those found in other studies conducted elsewhere [6, 8, 10].

In light of this high rate of concomitant use of herbal therapy and ART, there is a potential of altered ART pharmacokinetics. Some herbal formulations have been identified as having pharmacokinetic interactions with ARVs. Leaf extracts of *Moringa oleifera* have been established as having *in vitro* CYP3A4 inhibitory activity [17]. Extracts of other plants such as Sutherlandia and grapefruit juice have been found to also inhibit CYP3A4 [18]. ART in a resource-limited setting where herbal use is high needs to make provision for intensifying the monitoring of herbal medicine use and the potential effects it can have on therapy [19].

Identification of specific herbal medicines that influence ADRs forms a key step in developing further studies that

will aim to explore the mechanism of action through which they elicit their action. Unfortunately, because of the limited laboratory support, the study could only record ADRs that were clinically apparent. Future studies need to be carried out that will identify more factors predisposing HIV-positive patients to toxicities caused by ART.

5. Conclusion

The study observed a high prevalence of concomitant use of herbal medicines with ART. There was a correlation between 2 herbal preparations (*Musakavakadzi* and *Peltoforum africanum*) and a low incidence of ADRs. There is a need to develop pharmacovigilance programs that accommodate herbal medicines as factors that influence ADR prevalence.

Ethical Approval

The study was approved by the University of Zimbabwe and Parirenyatwa Hospital's Joint Research Ethics Committee (JREC, Harare, Zimbabwe). The study was also approved by the Medical Research Council of Zimbabwe. Written informed consent was obtained from all patients at enrolment.

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Research Article

Nevirapine-Based Antiretroviral Therapy Impacts Artesunate and Dihydroartemisinin Disposition in HIV-Infected Nigerian Adults

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Background. Nevirapine- (NVP-) based antiretroviral therapy (ART) and artesunate-amodiaquine are frequently coprescribed in areas of HIV and malaria endemicity. We explored the impact of this practice on artesunate and dihydroartemisinin pharmacokinetics. *Methods*. We conducted a parallel-group pharmacokinetic comparison between HIV-infected patients receiving NVP-based ART ($n = 10$) and ART-naive controls ($n = 11$). Artesunate-amodiaquine 200/600 mg was given daily for three days. Measurement of drug concentrations occurred between 0 and 96 hours after the final dose. Pharmacokinetic parameters were determined using noncompartmental analysis. *Results*. Comparing the NVP group to controls, clearance of artesunate was reduced 50% (1950 versus 2995 L/h; $P = 0.03$), resulting in a 45% increase in the AUC_{0-96} (105 versus 69 ug*hr/L; $P = 0.02$). The half-life of dihydroartemisinin was shorter in the NVP group (1.6 versuss 3.2 h; $P = 0.004$), but other dihydroartemisinin pharmacokinetic parameters were unchanged. A lower conversion of artesunate to dihydroartemisinin was observed in the NVP group (dihydroartemisinin: artesunate $AUC_{0-96} = 5.6$ versuss 8.5 in NVP and control groups, respectively, $P = 0.008$). *Conclusion*. Although NVP-containing ART impacted some pharmacokinetic parameters of artesunate and dihydroartemisinin, overall exposure was similar or better in the NVP group.

1. Introduction

Malaria remains a disease of public health importance with an estimated 169–294 million cases in 2009, resulting in approximately 781,000 deaths [1]. Sub-Saharan Africa not only carries a high burden of the morbidity and mortality associated with malaria but also a disproportionate burden of HIV disease. An estimated 33.3 million people are living

with HIV throughout the world, with more than 65% living in sub-Saharan Africa, contributing 72% of the global HIV/AIDS-related mortality in 2009 [2]. HIV and malaria comorbidity is common given the overlapping geographic areas affected by both diseases [3, 4]. The safe and effective treatment of these common coinfections is a public health priority.

As part of efforts to combat drug resistance, the World Health Organization (WHO) first recommended the use of artemisinin-based combination therapy (ACT) for malaria in 2006 [5] and upheld this recommendation in the 2010 guidelines [6]. Based on this recommendation, artesunate-amodiaquine is one of two regimens endorsed in the Nigeria Malaria Treatment Policy since 2005 while the other is artemether-lumefantrine [7]. Both regimens are used at all levels of care in Nigeria, from home management to tertiary care facilities. Artemisinin resistance has emerged since the initial 2006 WHO malaria treatment guidelines [5, 6], emphasizing the need for vigilant use of these essential medications.

Many HIV-infected patients receiving combination antiretroviral therapy (ART) will inevitably require concomitant use of an ACT in many regions of the world. The complex pharmacology of both ACTs and antiretroviral drugs lends concern to the safe and effective use of these agents in combination. Artesunate is primarily metabolized via esterase-mediated hydrolysis, but also by the cytochrome p450 (CYP) 2A6 isoenzyme, to the active metabolite dihydroartemisinin (DHA) [8]. DHA is subsequently metabolized via uridine diphosphate glucuronosyltransferases (UGTs) 1A9 and 2B7, and excreted in the bile [9]. Generally, both artesunate and DHA are moderately to highly protein bound with an elimination half-life of less than one hour, although DHA has a marginally longer half-life than artesunate [10–12]. Artesunate and DHA both possess antimalarial activity, with DHA being the more potent of the two. Therefore, any drug interaction assessment of artesunate must consider both artesunate and DHA.

Nevirapine (NVP), a nonnucleoside reverse transcriptase inhibitor (NNRTI), is a component of most first-line ART regimens in sub-Saharan Africa. NVP is metabolized via CYP 3A4 and CYP 2B6 and induces its own metabolism via induction of CYP 3A4 and perhaps 2B6 [13–15]. The potential for pharmacokinetic interactions between ACT and NVP has not been fully explored. Unfavourable pharmacokinetic drug interactions may lead to supratherapeutic antimalarial or antiretroviral concentrations, resulting in toxicity or, conversely, subtherapeutic concentrations resulting in treatment failure or drug resistance. There is also the potential for positive pharmacologic interactions, which may be beneficial to patients with malaria and HIV co-infection. In either instance, there is an urgent need to investigate the potential drug interactions resulting from the coadministration of NVP and ACT. Therefore, the primary objective of this study was to explore the pharmacokinetic interactions between NVP and artesunate taken in combination with amodiaquine in asymptomatic HIV-infected Nigerian adults by evaluating the disposition kinetics of artesunate and DHA in the presence and absence of steady-state NVP.

2. Materials and Methods

Patient recruitment, care, and follow up took place at the University College Hospital, Ibadan, Nigeria. The University of Ibadan/University College Hospital Institutional Review Board approved this study, and all patients provided written, informed consent. Eligible subjects had confirmed HIV-1 infection, were over 18 years of age, and had adequate renal and hepatic function, defined as serum creatinine <1.5 mg/dL and alanine transaminase and aspartate transaminase <1.5 times the upper limit of normal, respectively. Subjects were recruited into two groups: (1) NVP group and (2) control group. Subjects in the NVP group were on the same ART, consisting of lamivudine (3TC) 150 mg, zidovudine (AZT) 300 mg, and NVP 200 mg taken twice a day for a minimum period of 8 weeks prior to study enrolment, while all patients in the control group were not yet receiving antiretroviral therapy. Pregnant women, patients with known intolerance to study drugs, and patients who used artemisinin derivatives or other drugs known to induce or inhibit the CYP enzyme system in the preceding four weeks were excluded from the study. All the participants were in a good state of health, with leukocyte, haemoglobin, and hematocrit values within normal limits, no gastrointestinal symptoms or other physical complaints as judged by their primary physician. Patients remained on their current ART (NVP group) or were ART-free (control group) for the duration of the study.

A comprehensive history was obtained from individuals who met the inclusion criteria, including duration of HIV infection, drug history, and past medical history. Targeted physical examination included pulse, blood pressure, weight and height measurements. A capillary blood sample was collected via finger prick for malaria screening; however the results of the screening did not preclude study participation and one patient in each study group was found to be positive for malaria. In addition, about 10 mls of venous blood was drawn to determine baseline renal and hepatic function as well as pretreatment artesunate pharmacokinetics. These pretreatment samples were used to confirm no patients had detectable artesunate concentrations at the time of initiating the study, but were not used in the pharmacokinetic analysis. Subsequently, each participant received oral artesunate 200 mg and amodiaquine 600 mg daily for three days. Samples for the determination of artesunate plasma concentrations were collected according to the following schedule: predose (0 h) on the third day, and 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 48 h, 72 h, and 96 h after the 3rd and last dose of artesunate-amodiaquine. All the samples were immediately centrifuged, separated, stored in a -80°C freezer, and were later batch shipped on dry ice to the Clinical Pharmacology Laboratory at the Mahidol-Oxford Tropical Medicine Research Unit in Thailand for artesunate and DHA quantification. A repeat sample to assess renal and liver functions was taken on day 7 of the study, or 96 h following the last dose of the artesunate-amodiaquine.

2.1. Artesunate and Dihydroartemisinin Quantification. The plasma concentrations of artesunate and DHA were determined using solid-phase extraction and liquid chromatography-tandem mass spectrometry on an API 5000 triple-quadruple mass spectrometer (Applied Biosystems/MDS SCIEX, Foster City, CA) with a TurboV ionization source operated in the positive ion mode [16]. Stable isotope-labeled artesunate and stable isotope-labeled DHA were used as internal standards. Total assay coefficients of variation during analysis of all batches for artesunate and DHA were <6% at all quality control levels (5.87, 117, 1880 ng/mL for DHA, and 2.90, 51.7, 546 ng/mL for artesunate). The lower limits of quantification (LLOQ) for artesunate and DHA were set at 1.2 and 2.0 ng/mL, respectively.

2.2. Pharmacokinetic and Statistical Analyses. Demographic data were compared between the group on NVP and the control group using epi-info version 6. Proportions were compared using χ^2 with Yates' correction or Fisher's exact tests. Normally distributed, continuous data were compared by Student's t-test for independent groups. Standard non-compartmental methods were used to estimate pharmacokinetic parameters. These parameters included the area under the concentration-time curve (AUC_{0-96}), maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), elimination half-life ($T_{1/2}$), apparent distribution volume (Vd/F), and apparent oral clearance (CL_{ss}/F), where F is the oral bioavailability. The maximum plasma concentration (C_{max}) and T_{max} were estimated by inspection of the raw data. Continuous variables were presented as the mean (standard deviation) for subjects who participated in the study in each group, except that the discontinuous variable, T_{max}, was given as median (range). The Kruskal-Wallis test was used to determine P values for all parameters except T_{max}, where the Wilcoxon test was used, and the ratio of DHA to artesunate AUC_{0-96} where the Mann Whitney U test was most appropriate.

3. Results

3.1. Demographic and Clinical Characteristics. A total of 21 adult Nigerians consented and completed the study per protocol: 10 participants were included in the NVP group (7 (70%) female), while the other 11 constituted the control group (8 (73%) female). The NVP group was relatively older than the control group (mean (SD): 39.7 (13.5) versus 35.8 (6.4) years, respectively, $P = 0.008$), but the mean body mass index was similar between groups (23.2 (2.9) versus 22.8 (4.6) kg/m^2; $P = 0.6$). The NVP group received NVP containing ART for a mean duration of 1.65 years with shortest duration of exposure being 6 months; thus all participants in the NVP group were at steady-state NVP exposure. The mean CD4 counts for the NVP and control groups were 415 (229) cells/mm^3 and 438 (219) cells/mm^3, respectively ($P = 0.82$). None of the participants smoked or consumed heavy alcohol. Artesunate-amodiaquine was well tolerated in all participants, with the only reported side effect being moderate-to-severe weakness: 2/10 (20%) in the NVP group, 1/11 (9%) in the control group, $P = 0.93$.

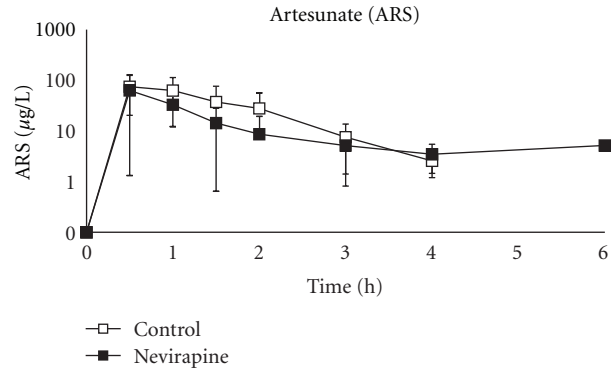

Figure 1: Mean plasma concentration versus time profile of artesunate (0–6 hours).

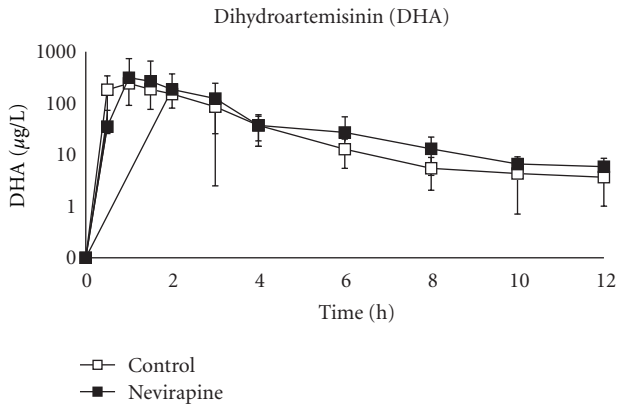

Figure 2: Mean plasma concentration versus time profile of dihydroartemisinin (0–12 hours).

Four individuals in the control group discontinued the study protocol due to weakness, vomiting, diarrhoea, dizziness, and anorexia. No individual in the NVP group experienced treatment-limiting adverse effects.

3.2. Pharmacokinetic Parameters. Pharmacokinetic parameters of artesunate and DHA are presented in Table 1 and Figure 1. For artesunate, the Vd/F of the NVP group was 75% smaller than that of the control group, while the Cl/F was reduced by 50% in the NVP group ($P = 0.01$ and $P = 0.03$, respectively). These changes resulted in a trend toward a lower $T_{1/2}$ in the NVP group ($P = 0.06$), owing to the Vd/F and Cl/F, while the slower Cl/F in the NPV-group resulted in a 45% increase in the artesunate AUC_{0-96} ($P = 0.02$). No statistically significant differences were seen with other artesunate parameters.

The DHA pharmacokinetic parameters are presented in Table 1 and Figure 2. While the Vd/F of DHA in patients on NVP was 55% lower than control patients ($P = 0.04$), the Cl/F of DHA was not different between groups ($P = 0.53$). This resulted in an overall shorter $T_{1/2}$ in the NVP group ($P = 0.004$), but no significant change in the overall exposure to DHA ($P = 0.19$). The ratio of DHA to artesunate, based on a comparison of AUC_{0-96}, was markedly lower in the NVP

Table 1: Comparison of pharmacokinetic parameters of artesunate and dihydroartemisinin.

Artesunate	Nevirapine Group, $n = 10$ Mean (SD)	Control Group, $n = 11$ Mean (SD)	P-value
C_{max} (μg/mL)	108 (42)	71 (57)	0.15
T_{max} (h)*	1.0 (0.5–2.0)*	1.0 (0.5–1.5)*	0.67
Cl/F (L/h)	1950 (543)	2995 (1180)	0.03
Vd/F (L)	1162 (856)	4525 (3535)	0.01
$T_{1/2}$ (h)	0.4 (0.3)	1.1 (0.9)	0.06
$AUC_{0–96}$ ($\mu g * L/h$)	105 (31)	69 (26)	0.02
Dihydroartemisinin	Mean (SD)	Mean (SD)	
C_{max} (μg/ml)	298 (107)	507 (429)	0.15
T_{max} (h)*	1.0 (0.5–3.0)*	1.5 (0.5–6.0)*	0.11
Cl/F (L/h)	1130 (425)	980 (616)	0.53
Vd/F (L)	2405 (1077)	4338 (2518)	0.04
$T_{1/2}$ (h)	1.6 (0.8)	3.2 (1.4)	0.004
$AUC_{0–96}$ ($\mu g * L/h$)	603 (218)	883 (607)	0.19

* Presented as median (range).

group compared to the control group; (median (intraquartile range)) 5.6 (4.4–6.6) versus 8.5 (7.2–18.5), $P = 0.008$.

4. Discussion

To our knowledge, this study represents the first investigation of the disposition kinetics of artesunate and DHA in HIV-infected adults with and without NVP containing ART. Overall, despite a shorter $T_{1/2}$ for both artesunate and DHA, we found an increase in overall exposure ($AUC_{0–96}$) of artesunate in patients receiving NVP compared to those not on ART (105 versus 69 ug $*$ L/hr; respectively; $P = 0.02$) and no difference in the overall exposure to DHA. While the clinical relevance of these results remains unclear, it is noteworthy that the half-life of DHA was significantly shorter when given with NVP, and the conversion of artesunate to DHA was lower in the NVP group. It is possible that a negative impact of NVP on the disposition kinetics of artesunate and DHA may be detected in larger studies. This demands an observant approach to malaria therapy in individuals on NVP containing ART until further investigation into the impact of this interaction can be performed.

Given the metabolic pathways of artesunate (hydrolysis and CYP2A6) and DHA (UGT 1A9 and 2B7), the observed impact on artesunate and DHA pharmacokinetics is unexpected. Nevirapine is well known for decreasing exposure to coadministered medications due to induction of the CYP3A4 and 2B6 isoenzymes [13–15]. Interestingly, one other ACT-nevirapine interaction study described an *in vivo* pharmacokinetic interaction where NVP both increased and decreased exposure to the coadministered ACT [17]. Kredo and colleagues described the interaction between NVP and artemether-lumefantrine in HIV-infected subjects in South Africa in which lumefantrine Day 7 concentrations and $AUC_{0–inf}$ were increased in patients on NVP compared to HIV-infected controls [17]. These directional changes seen with the lumefantrine parameters when combined with NVP are similar to our artesunate results, despite different metabolic pathways of the two antimalarial agents. Contrary to our artemisinin pharmacokinetic results, Kredo and colleagues found that the artemether and DHA $AUC_{0–inf}$ were lower in the NVP group compared to controls [17]. Notably, different CYP enzyme pathways metabolize artesunate (CYP2A6) and artemether (CYP3A4), which may account for the difference in artemisinin pharmacokinetic findings observed in our study of artesunate compared to the results of artemether plus NVP. Although the current study was not designed to evaluate the mechanism of this interaction, our observation of a lower conversion of artesunate to DHA in the NVP group (DHA: artesunate $AUC_{0–96} = 5.6$ versus 8.5 in NVP and control groups, respectively, $P = 0.008$) is noteworthy. Further investigation into the underlying mechanism of this unexpected change is warranted.

The rate of malaria parasite clearance has been associated with the overall exposure to both parent drug and DHA for other artemisinins [18]; hence reduction in the blood concentrations of either or both components may negatively impact on the antimalarial activity of the artemisinin therapy. Reassuringly, our findings suggest that although the $T_{1/2}$ was shorter, the overall exposure of both artesunate and DHA was similar compared to our control group and indeed higher for artesunate. Artesunate is generally a well-tolerated medication, particularly in comparison to other nonartemisinin antimalarial medications [19]. Dizziness, nausea, vomiting, and anorexia have been reported in patients with malaria who were treated with artemisinin monotherapy [19]. However, these toxicities were typically transient and resolved after 1-2 days, raising some question as to the relationship of the toxicity to the medication versus the underlying infectious process. Given the relative safety of artesunate, the observed increase in drug exposure would not be expected to cause additional toxicity; however vigilance for excess toxicity may be warranted.

Artesunate and DHA are known to have wide interpatient variability in their pharmacokinetic parameters, and artesunate and DHA exposure are both decreased by the co-administration of amodiaquine [20]. Additionally, the pharmacology of these agents is known to be different between patients with acute malaria and healthy volunteers. DHA total exposure was shown to be approximately 2-fold higher in patients with active malaria than healthy volunteers (4,024 versus 1,763 nmol $*$ h/L) [21]. Additionally, the protein binding of DHA may change during acute malaria infection related to plasma pH and circulating α-1-acid glycoprotein [22]. Complicating the evaluation of these important drug interactions further, differences in antiretroviral pharmacokinetics and pharmacodynamics exist between healthy volunteers and HIV infected patients [22, 23]; therefore, it is conceivable that HIV-infection may impact antimalarial drug concentrations as well.

There are some limitations in the present study that must be considered. In addition to noncompartmental analysis of artesunate and DHA, a comodelling approach that combines the parent and metabolite is currently underway to more fully describe the pharmacokinetic implications of chronic NVP therapy on artesunate and DHA. The pharmacokinetics of concurrent amodiaquine will be also described to fully understand the impact of NVP on antimalarial treatment with artesunate-amodiaquine. Although we have accommodated for the potential impact of HIV infection on the pharmacokinetics of artesunate and DHA by evaluating this interaction in an HIV-infected population, the pharmacokinetic impact of this interaction may be different in patients with acute malarial infection.

5. Conclusions

In summary, in HIV-infected patients receiving NVP-containing ART, standard multidose therapy with artesunate-amodiaquine resulted in higher overall exposure to artesunate and similar overall exposure to DHA, compared to HIV-infected patients not yet receiving ART. However, the conversion of artesunate to DHA was impaired in patients receiving NVP, and the $T_{1/2}$ of DHA was shorter, both raising potential concern for the overall impact of NVP on the efficacy of artesunate. The impact of NVP on the amodiaquine component of the antimalarial therapy will provide additional insight into the safety and efficacy of combining artesunate-amodiaquine and NVP.

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Review Article

Determinants of Adherence to Antiretroviral Therapy among HIV-Infected Patients in Africa

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Background. There are only a few comprehensive studies of adherence to ART and its challenges in Africa. This paper aims to assess the evidence on the challenges and prospects of ART adherence in sub-Saharan Africa. *Methods*. The authors reviewed original and review articles involving HIV-positive individuals that measured adherence to ART and its predictors in the past decade. *Findings*. Against expectations, sub-Saharan Africa patients have similar or higher adherence levels compared to those of developed countries. The challenges to ART adherence include factors related to patients and their families, socioeconomic factors, medication, and healthcare systems. *Conclusion*. Despite good adherence and program-related findings, antiretroviral treatment is challenged by a range of hierarchical and interrelated factors. There is substantial room for improvement of ART programs in sub-Sahara African countries.

1. Introduction

Acquired immune deficiency syndrome (AIDS) is one of the most destructive epidemics the world has ever witnessed. Presently an estimated 33.4 million people are living with HIV worldwide, nearly two-thirds of these live in sub-Saharan Africa [1].

Antiretroviral therapy (ART) has shown to delay progression to AIDS, resulting in a greater and more sustained virologic and immunologic response [2] and improve survival [3]. In sub-Saharan Africa, there has been a dramatic increase in the number of HIV/AIDS patients on antiretroviral treatment from just 100,000 persons in 2003 to 3.9 million in 2009 involving close to 40% of those in need of the treatment [4]. Two sub-Saharan Africa countries, Botswana and Rwanda, have achieved universal access target (treatment coverage of 80% or more of patients in need) at the end of 2009 [4], while countries such as Ethiopia, Zambia, Namibia, and Senegal are moving closer to the same target having covered 50–80% of patients in need of treatment [4].

According to recent studies, ART regimens require 70–90% adherence in order to be effective [5]. However, sustaining adherence to antiretroviral therapy (ART) over the long term requires accurate and consistent monitoring, and this is a particular challenge for countries in sub-Saharan Africa [5]. It is further challenged by various social and clinical obstacles [5] where inadequate suppression of viral replication by ART are resulting due to poor adherence to therapy, low potency of the antiretroviral regimens, viral resistance to antiretroviral medications, and pharmacokinetic interactions [6] causing inadequate drug delivery [5, 7]. The transmissibility of the antiretroviral resistant viruses from person to person further compounds the problem as a clinical and public health challenge [8, 9].

Adherence is defined as taking medications or interventions correctly according to prescription. There are different methods for assessing adherence and the level of adherence is specific not only to places and patient groups but also to the method of adherence measurement used [10]. They include direct methods such as biologic markers and body fluid assays, or indirect methods such as self-report, interview, pill counts, pharmacy records, computerized medication caps, and viral load monitoring. While a combination of these methods may be employed, patient self-report is the most widely used [11] given its ease of implementation and use of already existing resources. Studies have also

indicated that self-reports correlate well with both viral load and clinical outcomes [12, 13]. Use of computerized medication caps and monitoring of surrogate markers seems reliable and less prone to respondent bias. However, the advanced technology, high cost, and logistic requirements have precluded their wider application in sub-Saharan Africa [14]. In developing countries, pharmacy refill reports and self-reports are commonly implemented for adults [5, 15], while caregiver reports are employed for children [11, 16, 17]. Currently, there are no gold standard methods for measuring adherence [5].

There are only very few studies that investigate adherence to ART in sub-Saharan Africa. The aim of this paper is to assess the challenges of adherence to ART and to identify the factors that contribute to poor adherence.

1.1. Current Estimates of Adherence. Studies indicate that despite earlier fears of poor medication adherence [6, 18], patients in developing countries are able to achieve adherence levels similar to or higher than those of patients in developed countries [19]. For instance, a review by Vreeman and colleagues indicated that the majority of the studies in developing countries report adherence levels of more than 75% (range 45–100%) [11], while in developed countries the majority report less than 75% (range 20–100%) [17]. Another systematic review by Mills and colleagues obtained a pooled estimate of adequate adherence by sub-Saharan Africa patients of 77% (95% confidence interval, 68–85%; based on a total of 12,116 patients), whereas the figure for North American patients was 55% (95% confidence interval 49–62%; based on a total of 17,573 patients) [20]. The same study concluded that adherence is a concern in North America.

1.2. Patient- and Family-Related Challenges. With regard to children, if the mother (or other caregiver) is infected, then she is struggling with her own illness, psychosocial factors, medication regimens, and most often financial burden due to expenses incurred on her own therapy, child's therapy, and associated cost of medical treatment [21, 22]. All of these produce negative influences on adherence. Empirical evidence increasingly suggest that user fees in some centers for antiretroviral therapy (ART) and HIV/AIDS care decrease adherence [23, 24]. These factors on top of the caregivers' and patients' experience, knowledge and beliefs on ART [25], reduce the caregiver's ability to provide proper care to the child, thereby affecting the necessary adherence over time [26–31]. Furthermore, factors such as age (especially infancy and adolescence have a negative effect) [19], refusal of treatment, knowledge of HIV status, clinical stage, and depressive symptoms, male gender, and changes in health status (improvement as well as deterioration) have also been identified as important factors which affect adherence to HAART (highly active antiretroviral treatment) in pediatric patients [22, 27–30, 32]. Denial and fear of HIV status, misinformation, and misconceptions about HIV (for instance beliefs that ART cures HIV [16]), low availability, accessibility, and acceptance of therapy are some of the obstacles among HIV-infected adolescents.

It is known that mothers tend to hide HIV infection status from their children and disclosure is often delayed until adolescence [33]. Reddi and colleagues show that only 7.9% children had been made aware of their own HIV infection status in their study in South Africa [34]. Disclosure of HIV infection status is a critical step and has obvious implications for adherence. Starting the disclosure process as early as 8-9 years of age and combining it with specific support, as suggested (http://www.hivatis.org) may result in increased adherence in children. There are similar reports that indicate lack of disclosure as predictors of poor adherence in adults [35]. Self-perceived family support and/or the family's and the household's knowledge of the patient's HIV infection status are considered important predictors of adherence [36].

1.3. Stigma- and Discrimination-Related Challenges. Stigma, on top of the general knowledge of the population about HIV/AIDS and ART treatment, is an important determinant of adherence in the settings of sub-Saharan countries according to studies conducted recently [17, 37–39].

Social or family stigmatization and fear of the consequences of revealing HIV infection status to sexual partners are closely related to poor adherence [40]. Family plays a crucial role in any kind of treatment in children [41] or adults [42]. Major issues related to family or caregiver that influence adherence include presence of anxiety; depression [37, 43, 44]; active substance abuse [37]; the presence of HIV infection in another family member; fear of disclosure of HIV positivity to the family; family disruptions; belonging to racial minorities or other vulnerable groups of the population.

Family and community members can both play a positive and negative roles in ART treatment initiation and adherence [42, 45]. For instance, the stigma associated with HIV infection or AIDS may be more severe than that of other illnesses, creating barriers to treatment initiation and support for adherence that might otherwise be available [42, 46]. On the positive side, family members and friends can play the role of treatment partners and provide much needed support [39, 42, 47].

Patients need to be encouraged by health care workers to disclose their status. However, studies of interventions to facilitate disclosure are lacking. Social institutions like the church, nongovernmental organizations (NGOs), and food aid services play a crucial role in issues ranging from creating awareness about the illness, mobilizing support, facilitating treatment, and promoting adherence [16, 42, 48]. For instance, in an evaluation program about the impact of family nutritional support during the first year of antiretroviral treatment in the west Africa region, family nutritional support for persons living with HIV initiating antiretroviral treatment showed a positive impact after six months [49].

1.4. Substance- Abuse-Related Challenges. Drug abuse and alcohol consumption are factors that further threaten proper adherences to ART. Studies have consistently shown that

active alcohol use and substance abuse makes it more difficult for patients to adhere to treatment [50–53]. For instance, in Botswana nearly 40 percent of the patients surveyed admitted missing a dose because of alcohol consumption [46]. Similar studies also indicate that alcohol is highly related to reduced adherence [54]. A systematic review in 2009 found that HIV/AIDS patients that used alcohol are 50–60% more likely to adhere less to their prescribed medications [55].

1.5. Socioeconomic Challenges. The patterns of infection have been shown to vary globally depending on the social and economic conditions of the country affected, with poverty having a significant role as a social determinant of HIV/AIDS and the spread of the virus as well as access and adherence to ART treatment [42, 56].

Common reasons reported for missed doses include financial trouble [38, 57] that prevent caregivers of children or adult patients from collecting medication on time [42], distance barrier or lack of transportation facilities to the ART clinic [37, 46], vomiting of medication without redosing, incorrect dosing by a caregiver, missed clinic appointments and pharmacy collections, confusion between multiple caregivers, and self-discontinuation or refusal by children [34, 58, 59]. Furthermore, patients' beliefs that medications need to be taken with food leads them to avoid taking medications whenever food is unavailable, interfering with adherence [42, 60]. Sometimes patients are forced to choose between paying for transportation to the ART facility and using the money for food [42, 57, 61]. Studies in Uganda and Tanzania reported that transportation costs are considered serious obstacles to taking ART [62, 63]. This has implications not only for day-to-day adherence but also losses to follow up [64]. Determinants of ART adherence for HIV-infected persons in sub-Saharan Africa were examined with ethnographic research methods at HIV treatment sites in Jos, Nigeria, Dar es Salaam, Tanzania, and Mbarara, Uganda. The findings indicate that individuals taking ART routinely overcome economic obstacles to ART adherence through a number of deliberate strategies aimed at prioritizing adherence: borrowing and "begging" transport funds, making "impossible choices" to allocate resources in favor of treatment, and "doing without" [65].

1.6. Medication-Related Challenges. Good adherence (i.e., more than 95%) was associated with beliefs regarding the positive impact of the medications on participants' quality of life. Characteristics of the commercially available drug formulations such as taste, palatability, size of pills, availability of liquid formulations, and adverse effects (e.g., metabolic complications, lipodystrophy) can significantly affect adherence. Furthermore, the complicated regimen [66] to be followed, such as the need for daily administration, dietary restriction, drug interactions, frequency of dosing, dosage, and therefore pill burden or amount of liquid, also influence child's adherence to therapy [26, 28, 31, 32, 56]. The above-mentioned medication-related factors are crucial in determining children's adherence to ART.

Chesney [27] reported that factors associated with nonadherence included housing instability and length of treatment with antiretroviral therapy. According to a report by Van Dyke et al. [67], the main reasons mentioned by patients for nonadherence were taste (16%) and child refusal (16%) for ritonavir, and taste (9%) and interference of medication schedule with lifestyle (10%) for nelfinavir [67]. Side effects are also usually associated with irregular medication intake or stopping medication altogether.

1.7. Health-Care- and Systems-Related Challenges. Structural factors not directly related to patient or medications can also influence adherence. Some researchers have even contended that these could be the most important barriers to ART adherence in resource limited settings [5]. Limited availability and accessibility of antiretroviral medications and healthcare facilities for diagnosis and treatment of HIV/AIDs, out-of-pocket payments, high cost of ART and other health services, presence of healthcare providers experienced in ART provision, patient-nurse and other provider relationships, health care providers' beliefs, waiting time and opening hours [16, 42, 59, 68–70], availability of counseling services, and social, economic, or psychological support for people living in both developing as well as developed countries can influence adherence positively or negatively [28]. Ensuring the privacy of ART clinics and waiting areas need to be given special emphasis as authors of this paper and others documented [16, 42]. For instance, Skovdal and colleagues reported about patients who refused to leave consultation rooms citing to nurses Mr. so and so is outside [42].

Adherence support and clinic policies are also important predictors of adherence [37] as well as lack of adherence monitoring mechanisms [10]. A recent study from South Africa indicates that improving adherence is cost effective and helps to reduce health care costs especially those of hospital care [71].

1.8. Interventions to Improve Adherence. Continuous monitoring of both adherence and correlating it with clinical outcomes will create an interactive feedback mechanism that could lead to optimal clinical states and improved quality of life for patients. There are needs for further research and development in the area of ART adherence, adherence support, and patient behavior.

Diagnosing and treating health problems such as depression, reducing substance abuse, improving patient and provider relationship, counseling and enhancing family, and community support mechanisms are shown to improve adherence, as well as intervening on modifiable barriers to adherence before starting ART [72, 73]. A meta-analysis by Amico and colleagues indicated that adherence interventions may be efficacious when targeted at individuals who are identified or anticipated to have poor adherence [74].

The few investigations of interventions indicate that electronic reminders, pill organizers, medication-event monitoring systems (MEMS) to record dosing behavior, use of internet, educations services, use of phones [75], and so forth can also enhance adherence. However, most of these technologies have not had thorough scientific evaluation and their efficacy and cost effectiveness may not be as high as

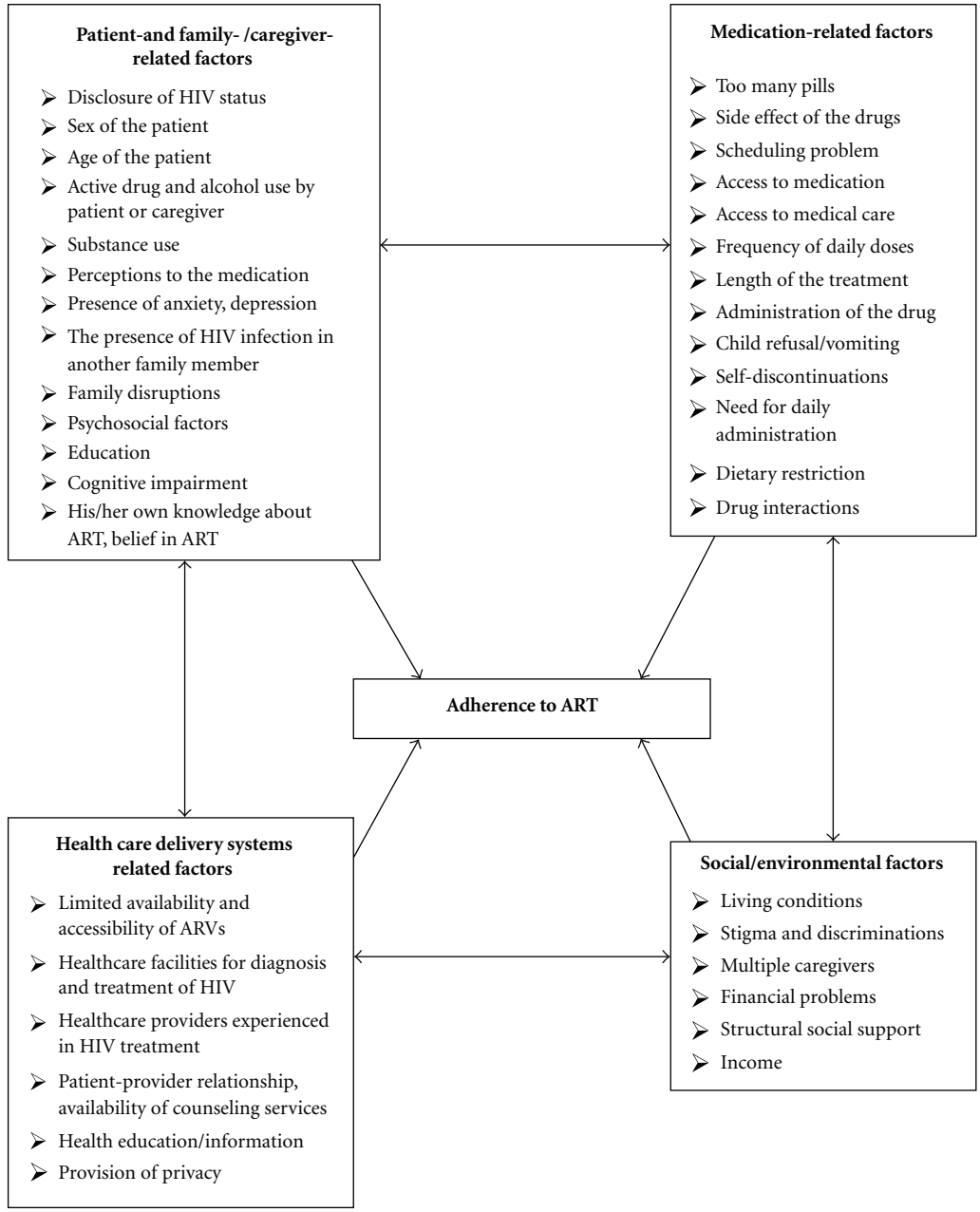

Figure 1: Identified factors for the challenges of adherence to ART.

expectations [5, 72, 76]. Cell phone message reminders and web-based interventions require patient resources and literacy which could create obstacles to their applicability in sub-Saharan Africa. A recent systematic review published by the Cochrane Database of Systematic Reviews reached similar conclusions. It cited diverse methodological problems and issues of study quality, among others as problems underlying the scant evidence on adherence improvement interventions and called for standardized and methodologically rigorous trials of interventions to improve and measure adherence to antiretroviral treatment [77].

2. Discussion

African HIV/AIDS patients have similar or higher adherence levels compared to those of developed countries. The challenges of adherence to ART identified include factors related to patients and their families, socioeconomic factors, medication, and healthcare systems as summarized in Figure 1. This has implications for interventions to improve ART adherence and therefore the program needs to address these interrelated and multidimensional factors [78, 79]. In other words, ensuring adherence to treatment

and retention requires an understanding of the multiple barriers that patients face and developing interventions that overcome these barriers. Long-term maintenance of adherence requires the integration of these interventions into sustainable programs that ensure a reliable supply of drugs, patient education, and ongoing support [80].

Low adherence to treatment has been associated with higher hospitalization rates, productivity loss, disease progression, and death in both high-income and resource-limited settings [35]. It is clear that adherence problems can constitute a significant barrier to ART programs in African countries or elsewhere. Without regulated access to ART, rapid emergence of drug-resistant viral strains and individual treatment failure is a potential threat and could curtail future treatment options and leading to the transmission of drug resistant strains of HIV [18]. We have identified that in order to increase adherence to the appropriate level there needs to be concerted efforts to evaluate and conduct operational research on ART service provision. These include use of new monitoring mechanisms, infrastructure, staffing, training of counselors, community support systems, and suitable drug formulations [78]. But currently there are several research gaps such as lack of capacity to survey the level of drug resistance in sub-Saharan Africa and testing of new tools for monitoring adherence.

This paper mainly focused on studies conducted on African HIV/AIDS patients. As a result, the predictors of ART adherence identified in the review may not necessarily be applicable to countries outside the region. Furthermore, currently there is no gold standard for measuring adherence. Because of this, most of the studies included used the most common forms of adherence assessment—patient recall and pill count—which have recognized biases. These include over reporting, recall, and social desirability bias [81–83]. We measured influential factors for short-term to medium-term adherence and that our conclusions on these factors may not necessarily be extrapolated to losses to follow up or retention to ART programs.

Health system barriers affect adherence, especially a regular and timely supply of medication to patients. An unreliable supply of medications can severely reduce patient adherence rates. In the majority of the sub-Sahara Africa countries they are manifested by weak procurement and supply management systems that lead to frequent shortages of ART and other essential inputs. In a survey of 91 low- and middle-income countries in 2008, 34% had experienced at least one stock out of a required ART medication [4].

In the future, it is possible that the encouraging trend of increased access to ART access may be further scaled up if governments and donors continue their commitment to the program. However, it is important that national governments take an increasing role in the program in order to make it sustainable. These include channeling of funds and policy commitments toward evaluation and improvement of the program. These also call for scale up of efforts to prevent the virus. In addition, policy measures to improve the socioeconomic status and empowerment of their citizens in general are very important.

3. Conclusion and Recommendations

There is a relatively modest level of adherence to antiretroviral treatment among HIV/AIDS patients in sub-Saharan Africa. However, it is challenged by a range of hierarchical and intricately related factors and there is substantial room for improvement of the ART programs in the region. Vulnerable groups such as children and adolescents need special attention by health workers and policy makers. There is also a need for adherence indicators and interventions that are applicable in the setting of developing countries.

Authors' Contribution

Both authors have contributed equally to the manuscript. S. Biadgilign came up with the topic of the paper and involved in writing it. A. Reda developed the idea and involved in writing substantially. Both authors have reviewed and approved the final draft of the paper.

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Clinical Study

Effect of Food on the Steady-State Pharmacokinetics of Tenofovir and Emtricitabine plus Efavirenz in Ugandan Adults

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We investigated the effect of food on the steady-state pharmacokinetics of a proprietary fixed-dose combination (FDC) tablet containing tenofovir disoproxil fumarate (TDF)/emtricitabine/efavirenz. Fifteen Ugandan HIV-1 patients at steady-state dosing with TDF/emtricitabine/efavirenz were admitted for 24-hour intensive pharmacokinetic sampling after dosing in the fasting state. Blood sampling was repeated seven days later with TDF/emtricitabine/efavirenz administered with food (19 g fat). Drug concentrations in plasma were determined by liquid chromatography and tandem mass spectrometry. Geometric mean ratios (GMRs) and confidence intervals (CIs) of parameters were calculated (reference, fasting). For efavirenz, GMRs (90% CIs) for C_{max}, AUC_{0-24}, and C_{24} were 1.47 (1.24–1.75), 1.13 (1.03–1.23), and 1.01 (0.91–1.11), respectively. Corresponding GMRs were 1.04 (0.84–1.27), 1.19 (1.10–1.29), and 0.99 (0.82–1.19) for tenofovir, 0.83 (0.76–0.92), 0.87 (0.78–0.97), and 0.91 (0.73–1.14) for emtricitabine. Stable patients may take the FDC without meal restrictions. The FDC should be taken without food by patients experiencing central nervous system toxicities.

1. Introduction

Food intake around the time of drug dosing may alter the bioavailability of orally administered drugs, and food effects can vary from drug to drug [1]. For fixed-dose combinations (FDCs), food intake may have an unbalanced impact on the component drugs and consensus must be achieved on the meal condition which results in optimal drug exposure for the overall regimen. Tenofovir disoproxil fumarate (TDF) and emtricitabine plus efavirenz is recommended for first-line treatment of HIV-1-infected adults [2–4]. These drugs were released as a single FDC tablet in 2006 following demonstration of bioequivalence between the FDC and the individual dosage forms [5].

Prior to the release of the FDC formulation, manufacturers of individual formulations had issued divergent guidance on food intake during drug dosing. In a single-dose study, a high-fat meal increased exposure (area under the curve, AUC) of TDF by 40% leading to a recommendation to dose TDF along with a meal [6]. Similarly, a high-fat meal increased AUC and maximal concentrations (C_{max}) of efavirenz by 28% and 79%, respectively. In this instance, the manufacturer recommended that efavirenz be administered without food because elevated efavirenz concentrations

may lead to an increased frequency of adverse events [7]. Emtricitabine exposures were unaffected by food intake; therefore, the manufacturer recommended that it could be taken without regard to food [8].

Currently, the manufacturers of the FDC recommend that the tablet be administered without food. However, the new tablet formulation has not been formally evaluated in the presence of food [9]. Ugandan antiretroviral guidelines prefer drugs that are administered without food restrictions [4]. In Uganda, certain patients may prefer to dose their drugs with food because they believe that all antiretroviral drugs must be taken with food to prevent side effects [10]. Although this belief is unfounded, regimens which must be administered without food may be less acceptable to this group of patients.

In order to determine if the FDC can be administered with food, the current study compared the steady-state pharmacokinetics of tenofovir, emtricitabine, and efavirenz during administration of a proprietary FDC containing TDF and emtricitabine plus efavirenz in the fasting state or with a moderate-fat meal in HIV-1-infected Ugandan adults.

Western meals used in food effect studies can greatly differ from meals consumed in African settings, and pharmacokinetic data are scarce in African patients receiving local meals. Therefore, the present study was conducted using a local Ugandan meal.

2. Methods

2.1. Ethics and Regulatory Approval. Ethics committee approval was granted by the Joint Clinical Research Centre (JCRC) Institutional Review Board (Study code: JAFS). The trial was registered with the UNCST (HS553) and on http://www.pactr.org/ (PACTR2009120001702102).

2.2. Study Design. HIV-1-infected patients receiving TDF and emtricitabine plus efavirenz (Atripla, Bristol Myers Squibb & Gilead Sciences LLC) one tablet daily for greater than one month were recruited into this open-label, two-phase, single-sequence, cross-over pharmacokinetic study.

2.3. Patients. The study was conducted at JCRC Mengo, Kampala. Patients were enrolled if they provided written informed consent, were between 18 and 65 years of age, and had no recent use of medications (including traditional medicines) known to interfere with cytochrome P450 (CYP) metabolism. Patients were excluded if they were anaemic (serum haemoglobin < 10 g/dL), had significant derangement in renal function (serum creatinine > 3.4 mg/dL) or hepatic function (serum alanine transaminase > 5 times the upper limit of normal), or if they had severe intercurrent illnesses, vomiting, or diarrhoea or were unable to adhere to the prescribed meal sequence of the study. Women were excluded if they were pregnant.

2.4. Pharmacokinetic Sampling. Enrolled patients attended two 24-hour intensive pharmacokinetic sampling visits scheduled one week apart (day 1 and day 8). Patients taking their antiretroviral drugs at night were switched to morning dosing of a minimum of 3 days before the first sampling visit. On the morning of Day 1 (fasting), one FDC tablet of TDF and emtricitabine plus efavirenz (300 mg/200 mg/600 mg, resp.) was administered to patients after an overnight fast. Blood samples were collected before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing. Breakfast was provided 3-4 hours post-dosing (see below for details). At each time point, 4 mL of venous blood was collected into ethylenediaminetetraacetic-acid-containing tubes, and samples were transferred to the JCRC laboratory within 1 hour of collection. Blood samples were centrifuged at 1500 g for 10 minutes to obtain plasma. Plasma obtained during centrifugation was transferred into 2 mL cryovials and stored at −70°C pending sample shipment. After collection of the blood sample at the 24-hour time-point, patients were allowed home and scheduled for a repeat pharmacokinetic evaluation one week later.

On Day 8 patients were readmitted after an overnight fast and given a standardized moderate fat Ugandan meal. The meal contained 650 Kcal and was composed of approximately 19 g of fat. The meal contents included matooke (local bananas, cooked vegetables, oil and meat, and tea with milk). Meals were started and completed within the 30 minutes prior to the scheduled time of TDF and emtricitabine plus efavirenz dosing. Blood sampling and plasma processing were conducted as in Day 1.

2.5. Determination of Tenofovir, Emtricitabine, and Efavirenz. The laboratory phase was conducted at the Department of Molecular and Clinical Pharmacology, University of Liverpool. Plasma samples were pretreated at 58°C for 40 minutes to inactivate HIV-1 and other pathogens. Tenofovir and emtricitabine were isolated from plasma by protein precipitation and solid-phase extraction, and concentrations were determined using a triple quadrupole liquid chromatography with tandem mass spectrometry (LC-MS/MS). Analytes were resolved on a phenomenex Synergi Polar C_{18} reverse phase 4 μ (150 × 2 mm) column. The lower limit of quantification (LLOQ) for tenofovir was 5.4 ng/mL, accuracy ranged from 86.0 to 95.1%, and imprecision was below 16.5%. The LLOQ for emtricitabine was 6.8 ng/mL, accuracy ranged from 95.5 to 101.0%, and imprecision was below 11.3%.

Efavirenz was isolated from plasma by protein precipitation, and the concentration was determined using LC-MS/MS. Hexobarbital was used as the internal standard. The analytic column was an Atlantis C_{18} reverse phase 3 μ (50 × 2.1 mm) LC column. The LLOQ for efavirenz was 8.5 ng/mL. Assay accuracy ranged from 93.2 to 101.8%, and imprecision was below 7.5%.

The laboratory participates in an external quality control program for antiretroviral drugs/(http://www.kkgt.nl/)

2.6. Safety Assessments. Reported adverse events were recorded at pharmacokinetic sampling visits.

2.7. Data Analysis. Patient demographic parameters are presented as summary statistics (medians, interquartile ranges).

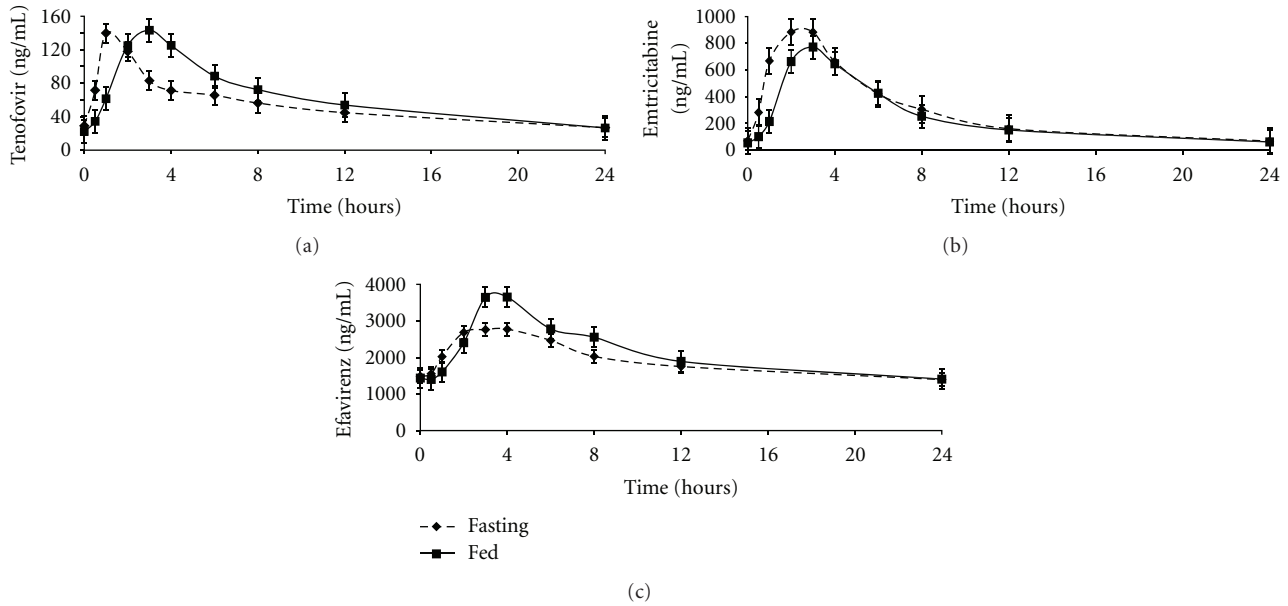

Figure 1: 24-hour plasma-concentration-time profiles of (a) tenofovir, (b) emtricitabine, and (c) efavirenz when administered in the fed and fasting states. Error bars, standard error.

Pharmacokinetic parameters including maximal concentrations (C_{max}), time to C_{max} (T_{max}), and concentrations 24 hours after dosing (C_{24}) were obtained from the data. The AUC over 24 hours (AUC_{0-24}) and half-life ($t_{1/2}$) were calculated by noncompartmental methods (WinNonlin Version5.2, Pharsight, MountainView, CA, USA). Values for T_{max} are presented as medians and interquartile ranges.

Geometric means (GMs) and ratios (GMRs) were calculated for AUC_{0-24}, C_{max}, and C_{24}. The fasting state (Day 1) was used as the reference based on the manufacturer's recommendation to dose the FDC without food. Absence of a food effect was assumed if the 90% CI for GMR between fed and fasting treatments was not contained in the equivalence limits of 80–125% for either AUC_{0-24} or C_{max}. Tenofovir and emtricitabine $t_{1/2}$ was presented as harmonic means and 90% CI. The 24-hour dosing interval is inadequate to characterise efavirenz $t_{1/2}$, and these results are not presented. Efavirenz plasma concentrations 12 hours after dosing (C_{12}) were evaluated using the suggested therapeutic range of 1,000–4,000 ng/mL based on a study in which efavirenz samples were collected between 8 and 20 hours after dosing [11].

3. Results

3.1. Patients. Demographic characteristics of patients at screening are shown in Table 1. Of the 15 patients enrolled, 11 were male. At enrolment, patients were on treatment with the TDF and emtricitabine plus efavirenz FDC for a median (interquartile range) of 413 (210–600) days. Fourteen patients were receiving cotrimoxazole prophylaxis while one patient was on dapsone. All 15 patients completed the study.

3.2. Pharmacokinetics. Figure 1 shows 24-hour plasma-concentration-time profiles for tenofovir, emtricitabine, and efavirenz under fed and fasting dosing conditions. Plasma pharmacokinetic parameters and comparisons for these three drugs are presented in Table 2. Figure 2 displays individual AUC_{0-24}, C_{max}, and C_{24} of the study drugs when administered under fasting and fed conditions.

Table 1: Patient characteristics at screening.

Parameter	Median (interquartile range)
Age (years)	43 (40–50)
Weight (kg)	74 (69–80)
Height (m)	1.70 (1.68–1.75)
CD4 (cells/μL)	355 (312–419)
Hb (g/dL)	14.9 (13.1–15.3)
Alanine transaminase (IU/L)	25 (17–32)
Aspartate transaminase (IU/L)	23 (20–27)
Blood urea nitrogen (mg/dL)	10 (8–13)
Creatinine (mg/dL)	0.87 (0.78–0.94)

Median (interquartile range) tenofovir T_{max} was 2.0 (1.5–3.0) hours in the fasting state and 3.0 (2.0-3.0) hours with food. Tenofovir AUC_{0-24} was significantly increased by 19% in the presence of food while other parameters were not significantly altered by food intake. In the fasting and fed states, CVs for AUC_{0-24} was 48% and 43%; C_{max} was 65% and 74%; C_{24} was 57% and 41%, respectively. Other parameters were not significantly altered by the presence of food. On Day 1 and Day 8, $t_{1/2}$ was 10.3 (9.8–12.1) and 8.9 (8.4–10.4) hours, respectively.

For emtricitabine, T_{max} was 1.0 (1.0-2.0) hours in the fasting state and 3.0 (2.0–3.5) hours with food. Emtricitabine C_{max} and AUC_{0-24} were significantly lower with food (17% and 13%, resp.) while C_{24} was unchanged. In the fasting and

Table 2: Pharmacokinetic parameters and comparisons during tenofovir and emtricitabine plus efavirenz administration in the fasting (Day 1) and fed (Day 8) states.

	Parameter	GM (95% CI)		GMR (90% CI)
		Fasting*	Fed	Fed/Fasting
Tenofovir	C_{max} (ng/mL)	169 (137–255)	175 (136–275)	*1.04* (0.84–1.27)
	AUC_{0-24} (ng·h/mL)	1316 (1117–1748)	1568 (1369–2032)	**1.19 (1.10–1.29)**
	C_{24} (ng/mL)	27 (23–39)	27 (23–34)	*0.99* (0.82–1.19)
	$CL/F_{(0-24)}$ (L/h)	186 (168–231)	156 (139–198)	*0.84* (0.78–0.91)
Emtricitabine	C_{max} (ng/mL)	1043 (935–1233)	870 (789–1016)	**0.83 (0.76–0.92)**
	AUC_{0-24} (ng·h/mL)	7029 (6300–8313)	6115 (5642–6846)	**0.87 (0.78–0.97)**
	C_{24} (ng/mL)	67 (57–92)	61 (53–81)	*0.91* (0.73–1.14)
	$CL/F_{(0-24)}$ (L/h)	28 (26–33)	33 (30–37)	*0.89* (0.80–0.99)
Efavirenz	C_{max} (ng/mL)	3128 (2678–4203)	4611 (3961–6037)	**1.47 (1.24–1.75)**
	AUC_{0-24} (ng·h/mL)	46299 (37411–69475)	52194 (41827–76643)	*1.13 (1.03–1.23)*
	C_{24} (ng/mL)	1395 (1082–2335)	1408 (1073–2448)	*1.01 (0.91–1.11)*
	$CL/F_{(0-24)}$ (L/h)	13 (11.6–17.3)	12 (10.5–14.4)	**0.89 (0.81–0.97)**

GM: geometric means; GMR: geometric mean ratio; CI: confidence intervals, C_{max}: maximum concentration; C_{24}: concentration 24 hours after dosing; AUC_{0-24}: area under the concentration-time curve; CL/F: clearance.
*reference.

fed states, CVs for AUC_{0-24} were 48% and 43%; C_{max} was 65% and 74%; C_{24} was 57% and 41%, respectively. On Day 1 and Day 8, $t_{1/2}$ was 6.1 (5.8–6.8) and 4.8 (4.5–5.7) hours, respectively.

For efavirenz, T_{max} was 3.0 (2.0–4.0) hours in the fasting state and 3.0 (3.0–6.0) hours with food. Efavirenz AUC_{0-24} and C_{max} were significantly increased in the fed state by 13% and 47%, respectively, while efavirenz C_{24} was identical under both meal conditions. High inter-individual variability was observed for C_{24} (80% and 85%) in the fasting and fed states, respectively. For these two meal conditions, CV for AUC_{0-24} was 66% and 64% and C_{max} was 48% and 45%, respectively. Two individual patients (number 05 and number 10) had unusually high efavirenz concentrations. For these two patients, efavirenz AUC_{0-24} ranged from 119,178 to155,895 ng·h/mL on both sampling visits (Figure 2(c)). These patients were the only two patients with C_{12} values above 4000 ng/mL. Their respective C_{12} were 4,968 ng/mL and 6067 ng/mL without food and 6,300 and 5936 ng/mL with food. The C_{24} measured below 1,000 ng/mL in five patients in the fasting state and four patients in the fed state.

3.3. Safety. No study-related adverse events were reported.

4. Discussion

Efavirenz trough concentrations were similar under both meal conditions; however, peak concentrations were increased by 47% during administration with a moderate-fat Ugandan meal. However, food did not alter the proportion of patients with efavirenz concentrations above the threshold of 4,000 ng/mL 12 hours after dosing. In 2001, Marzolini et al. reported an approximately 2.5-fold increase in the frequency of sustained central nervous system (CNS) toxicity among patients with efavirenz concentrations above 4,000 ng/mL versus patients with concentrations between 1,000 and 4,000 ng/mL [11]. However, this threshold was not confirmed in a larger analysis which found a correlation between symptoms and plasma levels only in the first week of treatment [12], instead single-nucleotide polymorphisms of drug-metabolizing enzymes were shown to be more predictive of efavirenz pharmacokinetics and clinical outcomes.

Efavirenz is primarily metabolised by hepatic CYP2B6 [7]. In the ACTG A5097s study, a gene-dose effect for efavirenz pharmacokinetics was observed among patients with CYP2B6 polymorphisms with three-fold-higher efavirenz exposure among *CYP2B6* 516T/T homozygotes as compared to G/G homozygotes, and with intermediate values for G/T heterozygotes [13]. A subsequent analysis revealed that the composite *CYP2B6* 516 G → T and 983 T → C genotype best predicted efavirenz pharmacokinetics, suggesting a slow-metaboliser genotype for efavirenz. Among Caucasians, this genotype was associated with a first CNS adverse event ($P = 0.04$). Surprisingly, among Black patients (in whom slow-metaboliser genotypes are more frequent), no association was found [14]. Instead, Black patients with the slow-metaboliser genotype had a lower incidence of virologic failure than other races ($P = 0.02$) [14]. The authors of that study postulated that higher efavirenz concentrations among patients with the slow-metaboliser genotype could permit continued suppression of HIV-1 during episodes of treatment interruption [14].

Therefore, the clinical relevance of the moderately increased efavirenz concentrations observed with food in the current study is a balance between the risk of increased toxicity (at the onset of therapy) and the potential benefit of higher efavirenz exposures leading to a lower incidence of virologic failure, based on the assumption that dosing efavirenz with food would have analogous effects to those seen among Blacks with the slow-metaboliser genotype in the ACTG study.

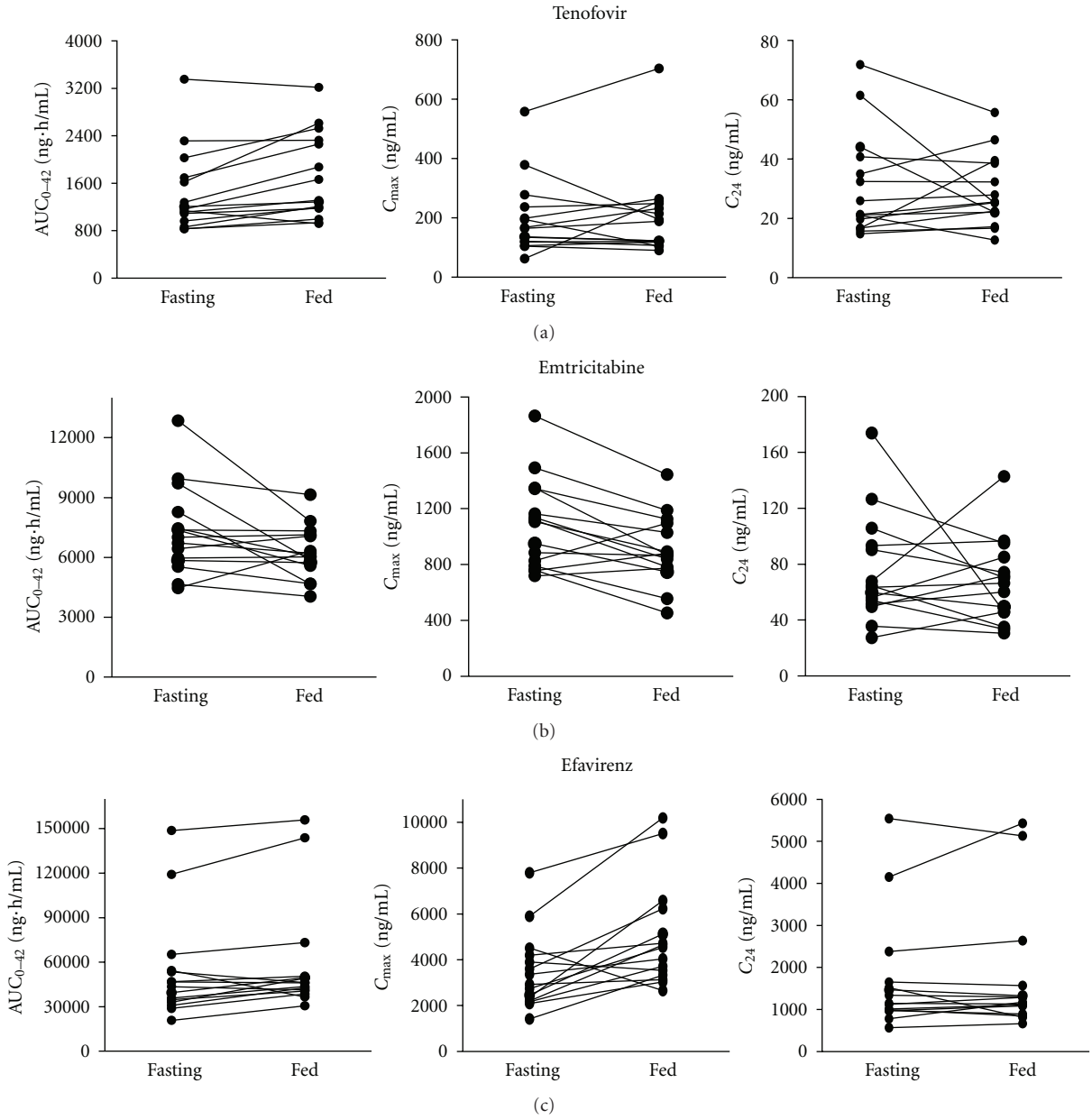

Figure 2: Individual pharmacokinetic parameters for (a) tenofovir and (b) emtricitabine when administered in the fed and fasting states. (c) Individual pharmacokinetic parameters for efavirenz when administered in the fed and fasting states.

In the present study, only two patients had efavirenz concentrations in the expected range for patients with the *CYP2B6* 516TT genotype. For other patients, food modestly increased exposure, but absolute concentrations did not attain values of the two patients under either meal condition. Although the genotype of those two patients is not known, one can postulate that genetic influence on efavirenz metabolism plays a more significant role than food on efavirenz pharmacokinetics and efavirenz-related toxicity.

Although the patients in the current study reported no adverse events, formal psychometric testing was not conducted and mild changes in CNS function cannot be completely ruled out. Importantly, these patients had received efavirenz-based therapy for a minimum of seven months prior to enrolment. Since efavirenz-related CNS toxicity tends to resolve within the first few weeks of treatment [7], the safety findings of the current study may not be representative of safety outcomes among patients initiating efavirenz-based regimens. Nevertheless, the findings from the current study suggest that stable patients may administer efavirenz-containing regimens without meal restrictions.

For tenofovir, peak concentrations were unaffected by food intake while tenofovir exposure was marginally increased by food. Emtricitabine exposure and peak concentrations were only mildly reduced (13% and 17%, resp.) by a meal. Tenofovir is a nucleotide reverse transcriptase

inhibitor which undergoes intracellular phosphorylation in two steps to its active diphosphate anabolite. Like tenofovir, emtricitabine undergoes intracellular phosphorylation. However, emtricitabine undergoes phosphorylation in three steps to its active triphosphate. For these two drugs, mild and transient changes in plasma concentrations are unlikely to be of clinical relevance as drug effect is not only dependent on absorption and elimination but also on the rate and extent of intracellular phosphorylation [15]. Consequently, TDF and emtricitabine may be taken with or without food.

In general, for lipophilic drugs, absorption is improved by food, particularly food containing fat [16]. Efavirenz is lipophilic, and enhanced absorption with fat is expected. The diester derivative of tenofovir (TDF) was specifically developed to improve the lipophilicity of tenofovir and enhance oral bioavailability [17, 18]; thus, enhanced absorption with fat would also be expected. The increases in tenofovir exposure seen in the current study were of lesser magnitude than those reported with single-dose TDF which may relate to less fat being used in the present study than the single-dose study which had 50% of the calories of a 700–1,000 Kcal meal derived from fat [6]. In contrast to TDF and efavirenz, emtricitabine is an acidic hydrophilic molecule [19]. Fat may interfere with emtricitabine dissolution, and food may delay dissolution of the tablet by reducing gastric pH, resulting in lower emtricitabine exposures with food.

In conclusion, a fat-containing meal moderately increased efavirenz steady-state peak concentrations. In contrast, pharmacokinetic parameters of tenofovir and emtricitabine were mildly affected by food, and those changes do not appear clinically significant. Since efavirenz-related central nervous system toxicity may be concentration dependent, patients experiencing these toxicities should take the FDC tablet without food. However, for patients without toxicities, the FDC can be taken without regard to meals.

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