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Can TDM Improve Pharmacotherapy of HIV Infection in Adolescents?

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Abstract

Currently, therapeutic drug monitoring (TDM) of antiretroviral therapy (ART) is not performed in the US as part of routine clinical care of an HIV-infected adolescent patient. TDM is recommended to rule out subtherapeutic drug concentrations and to differentiate between malabsorption, drug interactions, poor adherence, or increased drug metabolism or clearance as possible causes of decreased drug exposure. The use of TDM is also considered to assist in finding the optimal dose of a drug in patients in patients whose virus has shown a reduced susceptibility to that drug.

The dosing of antiretroviral (ARV) drugs in adolescent patients with HIV infection depends on the chronological age, weight, height and the stage of sexual maturation. Due to the limited data on the pharmacokinetics (PK) of ART during puberty the transition of a dosing regimen from higher pediatric (weight and surface-based) to adult (fixed) range is not well defined. Developmental PK differences contribute to high variability in pediatric and adolescent patients and an increased frequency of suboptimal ARV exposure than in adults. Individualized, concentration-targeted optimal dosing of ARV medications can be beneficial to patients for whom only limited dosing guidelines are available.

This manuscript describes 3 cases of the application of TDM in treatment experienced adolescent patients whose ART was optimized using of ARV TDM. TDM of ARV drugs is useful in managing

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the pharmacotherapy of HIV in adolescent patients and is well received by the adolescent patients with HIV and their families. Among others, the benefits of TDM provide evidence for adherence interventions and create grounds for enhanced education of the adolescent patient and involved adult caregivers about ART. Finally, TDM in adolescents provides valuable information about the clinical pharmacology of ART during puberty.

Keywords

HIV; pharmacotherapy; TDM; adolescents; efavirenz

INTRODUCTION

Currently, therapeutic drug monitoring (TDM) of antiretroviral therapy (ART) is not routine in the clinical care of HIV-infected adolescents in the United States. Nonetheless, in the recently updated Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection TDM is considered to be useful in a pediatric patient with ART failure.(1) TDM is recommended to rule out subtherapeutic drug concentrations and to differentiate between malabsorption, drug interactions, poor adherence, or increased drug metabolism or clearance as possible causes of decreased drug exposure. The use of TDM is also considered to assist in finding the optimal dose of a drug in a patient whose virus has shown a reduced susceptibility to that drug.(2,3)

The dosing of antiretroviral (ARV) drugs in an adolescent patient with HIV infection depends on the chronological age, weight, height and the stage of sexual maturation.(4) Due to the limited data on the pharmacokinetics (PK) of ART during puberty, the transition of a dosing regimen from higher pediatric (weight and surface-based) to adult (fixed) range is not well defined. Developmental PK differences contribute to high variability in pediatric and adolescent patients and a greater frequency of suboptimal ARV exposure than in adults.(5–8) While multiple adherence barriers represent one of the major challenges to the successful ART of pediatric HIV infection, the information on failed ART or increased resistance in the HIV-infected adolescents is very limited.(9,10) Equally limited are the data on the short and long term effect of potentially toxic ARV exposures during growth and development in early childhood and puberty.

In the absence of TDM, HIV-infected adolescents and young adults are placed at a significant risk of developing resistance from subtherapeutic drug exposure or toxicity from supratherapeutic dosing.(5) This manuscript describes 3 cases of the application of TDM in treatment-experienced HIV-infected adolescent patients whose therapy was ultimately optimized through the use of ARV TDM.

PATIENTS AND METHODS

All patients were adolescents with perinatally acquired HIV-1 infection receiving care at the large (>300 patients) metropolitan pediatric HIV program at Children's National Medical Center (CNMC), Washington, DC. TDM of ART has been routinely implemented into clinical practice within the program at CNMC since 2002. In addition, in the period between 2004 and 2008 the program conducted a study on the optimization of ART in children and adolescents with HIV-infection which involved the evaluation of CYP450 and MDR1 genotypes, extensive (up to 12 hours) pharmacokinetic (PK) studies and intense TDM follow up.(11) The research protocol, parental consent and assent documents (for children older than 7 years of age) were approved by the Institutional Review Board. All subjects in this study were on uninterrupted, PI-based ART for at least 4 weeks prior to study entry. Blood samples for ARV drugs measurement were obtained during routine clinical visits (for random TDM samples) and

during admission to the General Clinical Research Center (GCRC) for an extensive PK study after an observed dose. The subjects were administered their standard prescribed dose under direct observation with a standard light snack. Plasma and paired saliva samples were obtained before and at 0.5, 1, 2, 4, 8, 12 hours after the observed intake of ARV for the 12 hours PK study or on the alternative schedule for a shortened PK (<12 hours) study.

The ARV plasma and saliva concentrations of all ARV drugs except tenofovir (TDF) were measured in the laboratory at CNMC, which is an accredited member of the of the International Quality Control Program for Therapeutic Drug Monitoring in HIV infection (University Medical Center Nijmegen, The Netherlands).(12,13) A published tandem-mass spectrometric method with an Applied Biosystems/Sciex API-2000 was used.(14–16) The lower limit of quantification was 10 ng/mL. TDF was measured at the University of Southern California using an API 3+ tandem-mass spectrometer coupled to an Agilent 1100 liquid chromatography system. Samples were extracted using methanol. The lower limit for TDF quantification was 10 ng/mL. For both assays, within-run error was below 7% and between-day error was below 10% for all analytes at the tested concentrations.

Non-compartmental PK techniques were used to analyze individual concentration data. Area under the drug time-concentration curve (AUC) was calculated using the standard trapezoidal approximation, implemented in the freely available statistical package “R” (version 2.10, available at www.r-project.org). Drug clearance (CL) was calculated using the formula $CL = \text{Dose}/AUC_{\infty}$, where AUC_{∞} is the sum of the observed AC up to the last sample time, t , and an extrapolated AUC from time t to infinity. The latter is calculated from the last 2 or 3 observed concentrations in the terminal elimination phase after drug absorption is largely complete. Adult reference values for all drugs included in this report are in Table 1. All plots were generated using R.

CYP2B6 genotypes were determined using PCR amplification followed by allelic discrimination assays based on the use of fluorogenic oligonucleotide probes (TaqMan) and direct sequencing analysis performed on ABI Prism 3130 Genetic Analyzer at the Department of Clinical Chemistry (AKC), Erasmus Medical Centrum, Rotterdam, the Netherlands.

RESULTS

Scenario 1: TDM in a Patient with Treatment Failure

Patient A was a 13 year-old obese African American girl (Tanner Stage IV) with perinatally acquired HIV infection, CDC category B3. Her past medical history was significant for poststreptococcal glomerular nephropathy (resolved), familial obesity, and mild lipodystrophy with slightly elevated cholesterol and triglycerides. Her mother died from AIDS, and the patient was living with her maternal grandmother and two siblings, both of whom were also HIV infected. She has been disclosed about her HIV status since the age of 12 years. She had a history of multiple nucleoside-reverse transcriptase (NRTI) and nelfinavir (NFV) resistance mutations by the age of 11.5 years. At the age of 12 years she was placed on a new regimen of atazanavir (ATV) boosted with low-dose ritonavir (RTV), nevirapine (NVP), abacavir (ABC) and tenofovir (TDF). Throughout the following 12 months a progressive decline in CD4+ cell count and an increase in HIV RNA viral load were observed.

Despite the immunologic and virologic evidence of treatment failure, both the patient and her caregiver consistently reported 100% adherence on joint and separate interviews. However, all random plasma ARV drug concentrations obtained during routine clinic visits were undetectable. The patient enrolled in our optimization of ART study with the CD4+ count of 18% (292 cells/mm³) and HIV RNA of 50,600 copies/mL).(11) During the first 12-hour study visit the patient again reported 100% adherence at home and was observed by staff to take all

5 medications with a glass of water following a light standardized snack. All ARVs (ABC, TDF, ATV, RTV, and NVP) were undetectable in the plasma and paired saliva (TDF not measured in saliva) pre-dose sample and in 6 paired samples obtained over 12 hours after the observed intake. Potential sample processing and laboratory errors were thoroughly investigated and not found. The patient denied the use of herbal preparations or concomitant medications except for the use of Loratidine (Claritin®) on an as-needed basis, which was not administered in the 24 hours prior to study. The findings were discussed with the family and the patient and it was mutually agreed to repeat the 12-hour PK study, which was performed 24 weeks later. During this period the NVP therapy was discontinued due to a newly identified resistance mutation (Y181C).

As previously, during the second 12-hour PK study 100% adherence to ARV medications was reported by the caregiver and the patient. The concentrations of all ARVs were again undetectable in the plasma, while the saliva concentrations of ABC were detectable at 1, 2, 4 and 8 hours (757, 545, 365, 18 ng/ml, respectively). The study and clinical teams, including a treatment adherence specialist, social worker, nutritionist and psychologist, reviewed the results and concluded that the evidence overwhelmingly supported either self-induced emesis or oral retention of the medications without swallowing. With patient and caregiver's agreement, the TDM after an observed intake of the medications followed by 2 hours of close supervision (patient was never left alone by the clinic nurse) was conducted during a routine clinic visit. The plasma concentrations of ABC (2105 ng/ml) and ATV (290 ng/ml) were detectable 2 hrs after observed intake with supervision, and yet RTV concentrations were still undetectable. The results of all PK and TDM studies were discussed with the patient and the caregiver, and they both denied the possibility of the self-induced emesis, while continuing to insist on 100% adherence. The family agreed, however, to a psychology evaluation and additional adherence interventions, which included phone call reminders, pill boxes, partial directly observed therapy (DOT) and financial rewards. During psychological counseling the adolescent girl admitted that she was very concerned with a potential ART-associated increase her obesity and did not like swallowing the pills.

Following a further 24 weeks of counseling and adherence interventions, the positive feedback from the family and team assessments suggested that adherence to the ARV regimen had improved. Based on the low ATV/RTV concentrations at 2 hours post-dose (references are shown in Table 1), the ATV/RTV dose had been increased to 600/200 mg and a third 12-hour PK study was conducted five weeks after ATV/RTV dose adjustment. (Figure 1) While all administered ARVs were measured in plasma, RTV was not detected in plasma or saliva. (Table 2)

Due to persistent virologic failure and concerns for non-adherence to RTV as a separate pill, following the PK study the patient was placed on a new regimen with ABC, TDF and Lopinavir/Ritonavir (LPV/RTV; Kaletra®), and the fourth 12-hour PK study after 10 weeks was performed. (Figure 2) This PK study demonstrated normal PK parameters for all measured ARV medications including RTV. (Table 2) Nonetheless, during routine clinic follow up the undetectable random LPV/RTV plasma concentrations (on 2 separate measurements), small (<1 log) decline in HIV RNA and continued decline in CD4+ cells prompted the arrangement of the full-time DOT with 30 minutes close observation following the dose intake. With DOT the patient maintained a detectable random plasma concentration of LPV (10,760 ng/mL) and achieved undetectable HIV RNA (<400 copies/mL) within 12 weeks.

Unfortunately, after 6 months of vigorous DOT the family grew tired of the effort and the ART intake again became unsupervised, which led to undetectable LPV plasma concentrations and recurrent treatment failure. During our recent discussion of adherence, the patient (now 17 years old) openly admitted that she finds 200 mg Kaletra tablets too difficult to swallow and

was switched to 100 mg tablets. Further considerations are given to the return to DOT, repeat psychological counseling and new classes of ARV drugs.

Scenario 2: TDM in Patients with Excellent Virologic Suppression

Patient B was a 13 year-old African American boy (Tanner Stage III–IV) with perinatally acquired HIV, CDC category B3, and history of excellent adherence. His past medical history included lymphocytic interstitial pneumonitis, herpes zoster, and failure to thrive. At the age of 6 years he was placed on the ART regimen with stavudine (d4T), efavirenz (EFV) and amprenavir (APV), which remained unchanged for more than 7 years. Since the initiation of this regimen, he had maintained an undetectable HIV viral load (<400 copies/ml and later <48 copies/mL) and stable CD4+ cell counts >500 cells/mm³ (25–30%).

Random TDM plasma samples obtained during routine clinic visits demonstrated high concentrations of EFV (21,000 ng/mL) and low concentrations of APV (29 ng/mL). (references are shown in Table 1) The patient enrolled in the optimization of ART study(11) and had the 12-hour PK study. Prior to the release of the results of the PK study, his medical provider increased his EFV dose from 400 mg to 600 mg, based on his weight. Subsequently, when the plasma EFV exposure was found to be high on the first PK study, he underwent a second confirmatory PK study at the higher EFV dose. (Table 3) Despite the extremely high EFV exposure (Figure 3), at no time did the patient demonstrate any evidence of clinical or laboratory toxicity, including sleep patterns, energy levels, liver enzymes, amylase, lipase, and lipids. Nonetheless, concern for possible long-term adverse effects of continued high EFV exposure and a documented *CYP2B6 516 TT* “slow-metabolizer” polymorphism prompted reduction of his EFV dose to 200 mg daily –33% of the recommended dose for his weight. The final, abbreviated PK study on 200 mg EFV once daily is also shown in Figure 3, while the summary of PK values for all three doses of EFV are represented in Table 3. Subsequent random plasma concentrations at 9–11 hours after unobserved 200 mg doses at home ranged between 2,790 to 4,200 ng/mL. In addition to high EFV exposure, at his first PK visit, the patient was found to have negligible concentrations of APV ($C_0=20$ ng/mL; $C_{0.5}=20$ ng/mL; $C_1=25$ ng/mL; $C_2=42$ ng/mL; $C_4=15$ ng/mL; $C_8=11$ ng/mL; $C_{12}<10$ ng/mL). The results of the PK study prompted a change of his ART to lamivudine (3TC) and ABC as Epzicom®, TDF, and EFV at dose discussed above. The patient maintained full virologic suppression (HIV RNA <48 copies) at 52 weeks after the change in EFV dose.

Patient C was a 14 year-old African American male with perinatally acquired HIV, CDC category N-2, and a history of excellent adherence and virologic suppression. From 4 to 12 years of age he was treated with d4T, 3TC and NVP. At the age of 12 years, secondary to the request for once-daily dosing of ART, his regimen was switched to a fixed-dose combination tablet containing 600 mg of EFV, 300 mg of TDF and 200 mg of emtricitabine (FTC) (Atripla®). Three months after starting this new regimen, the patient reported headache and diarrhea, and also complained of a rash, but all symptoms resolved within another three months. No toxicities on laboratory findings including liver enzymes, amylase, lipase, and lipids were detected.

TDM during routine clinic visits revealed high plasma EFV concentrations ranging from 22,400 to 23,400 ng/mL at 10–11 hours after reported intake. (references are shown in Table 1) Interestingly, high random NVP plasma concentrations (up to 15,120 ng/mL) were also found during routine TDM in the past, but were used only as a proof of adherence at that time. Based on these results, the *CYP2B6* genotype was ordered and a 12-hour PK study was conducted in the clinic after unobserved dose intake, which was documented on the phone by the clinic nurse the night before the clinic visit. The EFV plasma concentrations were measured at 12, 14, 16, 20 and 24 hours after the intake and confirmed high EFV exposure (Figure 4), while the patient genotype confirmed *CYP2B6 516 TT* polymorphism. Based on the results of

the pharmacogenetic analysis and PK data, the therapy with fixed-dose TDF/FTC/EFV was discontinued and was replaced with the smaller dose of EFV (200 mg) in combination with TDF/FTC (Epzicom®). Full virologic suppression (HIV RNA <48 copies) was maintained at 52 weeks after the change in EFV dose and two random concentrations measured on different days at 22 and 24 hours after unobserved dose intake at home were 1.8 and 1.3 mg/L, respectively. (references are shown in Table 1)

DISCUSSION

TDM in HIV-infected adolescents has similar indications to adults and is primarily used to monitor the adherence to ART, evaluate the cause of treatment failure and to manage drug-drug interactions. Depending on the availability of a TDM consultant and the acceptance of TDM in clinical practice, the use of ART TDM may extend to optimization of the ARV dose by targeting specific trough concentrations or ratios of trough concentration and viral susceptibility (i.e. inhibitory quotients). Several investigations have demonstrated the benefits of incorporating TDM into the clinical management of HIV infection.(2,3) Very few studies, however, have evaluated the benefits of measuring ARV concentrations in HIV-infected adolescents and young adults.(17) Our cases represent a summary of some of the diverse applications of TDM in the management of the pharmacotherapy of ART in adolescent patients. We have selected three patients, one of whom represented currently accepted clinical indications for the use of TDM, while two others would have not been considered for the application of TDM under current standard of care.

The First Scenario describes a challenging case of an adolescent patient with consistently reported 100% adherence despite the evidence of treatment failure. The high level of adherence was not only stated by the patient, but was also confirmed by the dedicated adult primary caregiver who also provided ART to twin siblings with HIV infection who are 3 years younger than patient A. Both of these siblings have consistently demonstrated high levels of medical adherence, which has been confirmed by TDM and clinical outcome. In addition, patient A had been fully aware of her HIV status since 12 years of age and had regularly participated in the treatment discussions. Despite the fact that some form of non-adherence had been long suspected by the clinical team, none of the involved home and medical providers foresaw her practice of withholding medications in the mouth and spitting them up until documented through TDM. The first and second PK studies confirmed the absence of the ARV drugs in plasma samples after an observed intake. The absence of the ARV saliva concentrations in the first study was likely related to prompt spitting up of the medications after intake. During the second PK study the patient was detained for about 10 minutes by the nurse despite her urge to use the bathroom right after taking the medications, which could be responsible for the detectable concentrations of ABC in saliva. We speculate that the patient either swallowed the medications and induced subsequent emesis, or retained the medications in her mouth without the staff noticing and discarded them after a 10 minute delay. It is plausible that capsule preparations of ATV and RTV were less likely to start dissolving in saliva than ABC tablets, and therefore the detectable concentrations of ABC in saliva were found after holding the medications in the mouth prior to spitting them up (TDF was not measured in saliva).

The results of the first two PK studies prompted more open, evidence-based discussion than previously possible with patient A and family members involved in her care. An assumption of the behaviorally motivated non-adherence without the evidence would have had the potential to disrupt the patient and caregiver liaison with the medical team. Even after psychological counseling, patient A clearly had selective acceptance of ARV drugs, as demonstrated by the repeat PK study with increased dose of ATV/RTV. The only 12- PK study which documented the presence of ATV demonstrated adequate concentrations of ATV with increased dose (ATV/RTV=600mg/200mg) and the absence of RTV in plasma samples. The PK parameters of ATV

perfectly fit the PK of the unboosted ATV and together with absent RTV in plasma, provide strong evidence for continued oral withholding of RTV dose by the patient despite close observation by the medical staff at the GCRC. The therapy with an unboosted ATV regimen is not recommended in treatment-experienced pediatric patients with pre-existing PI mutations, as ATV resistance can develop through mutations associated with resistance to other PIs instead of through the ATV associated I50L mutation.(1) Once placed on a fixed-dose co-formulated boosted PI (Kaletra®), patient A demonstrated normal absorption and PK parameters for RTV.

HIV-infected adolescents face multiple adherence challenges during their transition to adulthood. In addition to palatability issues, pill burden and interference of ART with lifestyle, adolescent patients with HIV experience growing independence, increased peer pressure and fear of stigmatization, increased risk-taking behavior (including substance abuse), denial and fear of HIV infection (particularly after witnessing the death from HIV as in case with our patient A who lost her mother to AIDS), long history of poor adherence and non-disclosure issues in perinatally infected patients, and psychiatric problems (depression, anorexia).(9,18–21) In our recent study, we have shown that adolescents (13–18 yrs old) were significantly less likely to reach undetectable HIV RNA than younger children (<13 yrs old) (OR=0.38; 95% CI: 0.16, 0.89).(22) For every year increase in age, the odds of reaching undetectable VL decreased by 10% after controlling for self-reported adherence and medications refill mechanism. While considered to be ready to assume the responsibility for adherence to an appropriate administration of their ARV medication, many adolescents lack social and financial autonomy, privacy, and mobility, and generally will decrease their adherence to ART. (23) A comprehensive assessment of adherence through multiple indirect methods (self-report, caregiver report, pill count, pharmacy refills) should be incorporated into the management of every adolescent patient with HIV infection. While patient and caregiver reports are the main adherence measurement used in the majority of clinical setting,(20,24) TDM is the only direct measure of verifying the patient compliance as all other methods do not prove the actual intake of ARV drugs.

Studies have shown that it is crucial to take the evolutionary nature of the caregiver's and the child's coping process into account when integrating adherence to ART into children's daily lives.(25) The care team should work continuously and concomitantly on three factors: knowledge, capacity, and motivation. In the case of patient A, TDM has allowed us to identify a cause of non-adherence in a form of a very complex behavioral pattern with selective acceptance of ARV medications. The TDM evidence created grounds for the motivation of the patient and the family and their cooperation with the implementation of DOT. While the adherence problems in this young woman are far from being solved, the success of the previous TDM based interventions allows us to continue our work with her and her family to explore further strategies to increase her ART adherence.

According to the current TDM guidelines the measurement of the ARV drugs concentrations would have not been indicated in the Second Scenario with patients B and C due to the excellent virologic suppression and immunologic status with EFV based ART. Doses that result in excessive plasma drug concentrations are unlikely to be detected unless and until clinical toxicity develops, and without TDM, dose-dependent versus dose-independent toxicity cannot be distinguished. (5) EFV is extensively metabolized by *CYP2B6* with partial involvement of *CYP3A4* and *CYP2A6*.(26–29) The *CYP2B6* *G to T* polymorphism at position 516 has been associated with elevated EFV plasma concentrations and an increase in neurotoxicity in adults and children.(30–33) Most recently the *CYP2B6* 983T>C and *CYP2A6* genotypes have also been reported to affect EFV plasma concentrations.(34–36) High EFV plasma concentrations and successful *CYP2B6* genotype-based EFV dose reduction were demonstrated in adults with the haplotypes *CYP2B6* *6/*6 (516G>T, 785A>G) and *6/*26 (499C>G, 516G>T,

785A>G).(37) Genotype *CYP2B6* based dose reduction has also been proposed in several population PK models.(38,39)

The identification of the high EFV exposure in our patients led to pharmacogenetic evaluation and confirmation of the “slow metabolizer” type of *CYP2B6* polymorphism. Moreover, the lack of dose-proportionality in EFV AUC observed in patient C indicates that at the two higher doses, the PK behavior of EFV could best be described as Michaelis-Menten or zero order elimination. Michaelis-Menten PK occurs when clearance mechanisms become saturated, and a constant amount of drug, rather than a constant fraction, is eliminated per unit time. The implications of Michaelis-Menten PK are that clearance becomes dose-dependent (Table 3) and small changes in dose can result in large changes in plasma concentration, as was observed when the dose was reduced by 50% from 400 mg to 200 mg daily, yet the AUC dropped by more than 90% (Table 3). Note that at all doses, the observed clearance was still well below the referenced adult values (Table 1). To our knowledge this is the first description of Michaelis Menten EFV PK associated with *CYP2B6* “slow metabolizer” polymorphisms.

While the successful dose reduction of EFV has been described in adults and a single report in an adolescent patient, to our knowledge,(40,41) this is the first report of successful reduction of the EFV dose in two African American adolescent pediatric patients based on the *CYP2B6* genotype in combination with PK evaluations. The *CYP 2B6 516 G>T* polymorphism is significantly higher in Sub-Saharan Africans (45.5%) and African Americans (46.7%) as compared to Hispanic (27.3%), European (21.4%) and Asian (17.4%) populations.(42–44) In addition to the *CYP2B6 516 G>T* polymorphisms, the DNA samples for both patients were analyzed for the presence of *CYP 2B6 415>G*, *785A>G*, *983 T>C* and *1459 C>T* polymorphisms. Patient C had *CYP2B6 785GG* polymorphism in addition to the *CYP 516 TT* genotype, suggesting the presence of haplotype *CYP2B6 *6/*6 (516G>T, 785A>G)* associated with “slow metabolizer” profile for EFV.(37) Patient C had also the history of high NVP exposure in the past caused by his *CYP2B6* polymorphism.(45) However, the plasma NVP concentrations were used only for the confirmation of adherence at that time. Interestingly, while both patients and their families recalled that children experienced transient sleep problems shortly after the initiation of EFV therapy, their high EFV exposure did not prompt treatment discontinuation. This is consistent with recently published data on the lack of association between *CYP2B6* genotype and EFV plasma concentrations, and the risk of EFV discontinuations because of neurotoxicity.(46,47) Equally, no other EFV associated toxicities were identified in both patients, particularly in patient B with more than 7 years of high EFV exposure. This patient was placed on the combination ART with EFV co-administered with APV prior to the wide acceptance of boosted fos-APV into pediatric practice. EFV has been reported to decrease the C_{max} , AUC and C_{min} of unboosted APV by approximately 40% in adults, however, this effect of EFV is compensated by the PK booster effect of RTV when APV is combined with RTV.(48) While the treatment with EFV in combination with unboosted APV is not recommended, patient B continued his regimen due to the excellent virologic and immunologic outcome. In reality, his high EFV concentrations produced an APV exposure so negligible, that he can be considered to have been treated with dual (d4T and EFV) therapy for a prolonged period of time (>7 years). We would like to speculate that such a high degree of EFV exposure allowed him to avoid development of the K103N, Y181C and other multi-NNRTI resistance mutations on the ART regimen with a single efficient NRTI backbone.

In summary, our experience suggests that TDM evaluation (when available) should be considered in HIV-infected adolescent patients on ART independently of the degree of virologic suppression and immunologic outcome. We recognize that many of the currently identified barriers to the routine application of TDM in pediatric ART (prolonged time for laboratory processing, difficulties in coordinating sample collections at appropriate times, limited availability of certified laboratories for ARV drug concentrations, lack of third party

reimbursement of costs) were not experienced at our site. The extended PK analyses were provided through grant funding. However, routine TDM measurements during clinic follow up are a well accepted standard of care in our program and we have not encountered difficulties in the reimbursement process. Clearly, through the availability of a dedicated pediatric GCRC and in house laboratory we were able to repeat the studies to eliminate significant limitations of ARV TDM such as high inpatient variability from single drug concentration measurement.(2,49) Finally, we hope that similar reports and randomized controlled studies will help to eliminate the most significant barrier to the successful TDM of ART such as inadequate information on safety and effectiveness of dose adjustment strategies in children and adolescents.

CONCLUSIONS

The physiological and psychosocial changes during puberty create strong grounds for an individualized therapeutic approach to an HIV-infected adolescent. Individualized, concentration-targeted optimal dosing of ARV medications can be beneficial to patients for whom there are limited dosing guidelines. TDM of ARV drugs is useful in managing the pharmacotherapy of HIV in adolescent patients and is well received by the adolescent patients with HIV and their families. Among others, the benefits of TDM provide evidence for adherence interventions and create grounds for enhanced education of the adolescent patient and involved adult caregivers about ART. Finally, TDM in adolescents provides valuable information about the clinical pharmacology of ART during puberty.

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Figure 1. AUC of the standard dose ABC, TDF and high dose ATV/rtv (600mg/200mg) in Patient A

Figure 2. AUC of the standard dose ABC, TDF and LPV/RTV in Patient A

Figure 3. The summary of three 12-hour PK studies with three different doses of efavirenz in Patient B

Figure 4. The summary of the PK parameters with two different doses of efavirenz in Patient C

Table 1

Reference adult PK ARV values

Drug	Dose (mg)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	AUC (ng * h/mL)	CL (L/h)	Ref
Abacavir	300	3090	0.75	18	6080	51	(50,51), PI
Tenofovir	300	326	2.3	41	3020	131 *	(52,53), PI
Efavirenz	600	4072	3-5	1640	58085	10 *	(54), PI
Atazanavir	400	2298	2	120	14874	25	(55), PI
Lopinavir	400	9800	4	5500	92600	6	PI
Ampranavir	1200	7600	1	1480	17700	20	PI
Ritonavir	100	500	4	320	3580	19	(56,57), PI

* Calculated

PI=Package insert; Values for atazanavir are those for unboosted dose, i.e. without ritonavir; Values for lopinavir are when given with ritonavir as co-formulation

Table 2

The PK parameters of ARV medications in Patient A

Drug	Dose (mg)	C _{max} (ng/mL)	T _{max} (h)	AUC _∞ (ng•h/mL)	CL (L/h)
12-hour PK study with increased dose ATV/rtv					
Abacavir	300	2590	1.2	9231	32.5
Tenofovir	300	257	1.2	2313	129.7
Atazanavir	600	2610	4.2	23611	25.4
Ritonavir	200	0	-	0	-
12-hour PK study with standard dose LPV/rtv					
Abacavir	300	1970	1.1	8722	34.4
Tenofovir	300	386	1.1	2013	149.0
Lopinavir	400	18100	8.2	276959	1.4
Ritonavir	100	565	8.2	4190	23.9

Table 3
The PK parameters of three different doses of Efavirenz in Patient B

Drug	Dose (mg)	C _{max} (mg/L)	T _{max} (h)	AUC _∞ (mg•h/L)	CL (L/h)
Efavirenz	200	6.03	2	147	1.4
Efavirenz	400	27.76	0.5	1875	0.2
Efavirenz	600	27.50	0.5	1155	0.5