Clinical pharmacology and pharmacokinetics of antiretrovirals in Asia

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Pharmacokinetics can be used to establish dose response relationships in terms of efficacy and toxicity. Nevertheless the majority of the registered dose in the treatment of HIV are based on data from Caucasian men. It is questionable however if the recommended doses are optimal for all ethnicities and in all circumstances. Several studies suggest that a more population-based approach may benefit different ethnicities. Here we review the pharmacokinetics of commonly used non-nucleoside analog reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) in the Asian setting, for both adults and children. Studies of nevirapine, efavirenz, saquinavir, lopinavir, ritonavir, indinavir and atazanavir have been reported mostly among Thai patients. The data strongly indicated that Thai and most likely Asians have on average a significantly higher exposure to both the drugs classes (NNRTIs and PIs) compared to the Caucasian. In patients with active tuberculosis who are taking rifampicin, the standard dose of either efavirenz or nevirapine was found to be sufficient and efficacious for Asians with average body weight of 60 kg. Lower dose studies of saquinavir, indinavir, lopinavir and atazanavir have shown promising efficacy results, however most are small scale studies. In pregnancy, nevirapine seems an adequate option whereas efavirenz has no PK data during the third trimester. In conclusion, more likely Asians are significantly higher exposed to both NNRTIs and PIs compared to the Caucasians. Further studies on pharmacokinetics, TDM and larger scale clinical trials among Asian populations are warranted to identify suitable low doses of ARVs for inclusion in the clinical practice guidelines of this region.

Keywords: Asia, HIV, NNRTI, pharmacokinetics, protease inhibitors.

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Pharmacokinetics can be used to establish dose response relationships in terms of efficacy and toxicity. For most antiretrovirals (ARVs) from the protease inhibitor (PI) and non-nucleosides reverse transcriptase inhibitors (NNRTI) classes, such a relationship is apparent [1-3]. Therefore, plasma concentrations of these drugs generate a valuable indicator whether the appropriate dose is used for a particular patient population or for an individual patient.

Currently, the great majority of the registered doses in the treatment of HIV are based on data from Caucasian men. These dosages are extrapolated worldwide and, in recent history, no dose adjustment, except for stavudine, has been made. It is questionable, however, if the recommended doses are optimal for all ethnicities and in all circumstances. Several studies suggest that a more population-based approach may benefit different ethnicities. Here, we review the pharmacokinetics of commonly used ARV in the Asian setting, for both adults and children. We will discuss its possible impact on daily clinical practice and the impact from a public health point of view. Moreover, the use of the drugs in pregnancy will be reviewed and discussed. A summary of the most important results is shown in Figs. 1-5.
**Nucliosides reverse transcriptase inhibitors (NRTIs)**

NRTIs are phosphorolysated intracellular and therefore plasma pharmacokinetics correlate poorly with the efficacy and safety of this class of drugs. Although studies in the Asia region have been done, suggesting the dose reduction of ziduvodine, stavudine and didanosine [4-6], those results were not based on pharmacokinetics and will therefore not be discussed in this review.

**Nevirapine**

Nevirapine is a drug with a long elimination half-life and plasma concentration will decline very slowly during the dose intervals and therefore random samples will be representative for the whole day. The minimal effective concentration (Cmin) is established at 3.0 mg/L (www.hivpharmacology.com) and no toxic cutoff is described as for most antiretrovirals. Several studies with Asian subjects have reported nevirapine plasma concentrations. Manosuthi et al. report a mean Cmin of 6.56 mg/L [7] in 70 Thai patients on a regular HAART regimen, similar to other studies where plasma concentrations between 6.4-8.7 mg/L were found [8-10]. Most of the data originate from control groups used to compare the levels of nevirapine when co-administered with rifampicin. The levels of nevirapine, when co-administered with rifampicin, were around 5 mg/L with the great majority above the therapeutic level of 3.0 mg/L. A study of Avihingsanon et al. where 32 patients were randomized to either the standard dose of nevirapine (rifampicin) or a daily dose of 600mg (rifampicin) showed an increase in toxicity for 600mg arm, hypersensitivity in particular, whereas the 48 weeks efficacy data for the two randomized arms looked similar [11]. Based on the limited data, increase of the nevirapine dose during tuberculosis (TB) treatment is not recommended.

Among Caucasian studies, the average plasma concentration of nevirapine standard dose was approximately 4.0 mg/L [2, 12]. Despite these differences, no dose reduction studies in an Asian setting have been conducted that we are aware of. More NNRTI related toxicity in an Asian setting, compared to Caucasians, has been reported, and therefore a dose-finding study, probably with a once daily component included, might be worthwhile [13]. However, other studies report rash and hepatotoxicity at a similar level as for other populations [14].

In children, the GPO-vir® (fixed dose combination of nevirapine, lamuvidine and stavudidine) was studied when tablet cut was applied. The administration of GPO-VIR S30® fixed-dose combination tablets in

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**Fig. 1** Summary of pharmacokinetics studies done with nevirapine in the region of Southeast Asia. The standard dose is administered (200 mg twice daily for adults, weight or body surface area appropriate for pediatrics). RIF = Rifampicin; N = number of subjects in the study. The numbers in superscript indicate the references.
fractions or as a whole tablet to children resulted in appropriate nevirapine exposure and satisfactory virological and immunological benefit [15]. Now, the Thai Governmental Pharmaceutical Organization (GPO) has developed a pediatric fixed-dose combination (nevirapine 30 mg, lamuvidine 50 mg and stadavudine 7 mg) for which the pharmacokinetic data will be presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2009.

Nevirapine in pregnancy

From a pharmacokinetic (PK) point of view, nevirapine seems an adequate option during pregnancy. The plasma levels are not affected by gestation and therefore no dose adjustment is needed [16]. However it is not recommended to initiate it when the CD4 is higher than 250 cells/mm³, especially as pregnancy is an additional risk factor for developing hepatotoxicity [14]. Single dose nevirapine should be avoided and if used, the solely nevirapine exposure-tail should be covered for at least a week with a dual NRTI combination. Nonetheless, due to lack of data and great intervariability in terms of nevirapine clearance, a strong recommendation is hard to make. The safest option after nevirapine single dose is a PI-based HAART regimen for at least 2 weeks.

Efavirenz

Efavirenz is another NNRTI with an even longer half-life than nevirapine. It has been proposed that efavirenz concentration (taken between 8-20 hours after intake) within the range of 1.0 to 4.0 mg/L would be preferable to ensure efficacy and reduce the risk of drug toxicity [1]. It is an often used drug, with less side-effect compared to nevirapine and of special value due to its limited interaction with rifampicin. Although interaction between efavirenz and rifampicin does occur, it is quite well established that no dose increase is necessary for Asian individuals [17, 18].

One study, with a crossover design, was conducted to look into a lower dose of EFV [19]. The 400mg dosages generated a median Cmin of 2.04 mg/L compared to the 2.89 mg/L for the 600 mg dosage (with no patient under the therapeutic level of 1.0 mg/L). It is remarkable that the levels of the last-mentioned studies are lower than the levels of Manosuthi et al. where rifampicin was added. In the study of Marzolini et al. with mainly Caucasians a median of 2.13 mg/L was found. The data of the 400 mg efavirenz dose look promising, although the benefit in terms of toxicity could not be identified due to the study design (i.e., all patients started with 400 mg).

Fig. 2 Summary of pharmacokinetics studies done with efavirenz in the region of Southeast Asia. If not otherwise specified, the standard dose is administered (600 mg once daily for adults, weight or body surface area (BSA) appropriate for pediatrics). RIF = Rifampicin; N = number of subjects in the study. The numbers in superscript indicate the references.
The correlation between EFV plasma levels and the CYP3A 2B6 gene is quite well established [20]. Puthanakit et al. [21] showed that also for Thai children this correlation is apparent. Another objective of the study was to assess the plasma concentration in Thai children as concern was raised in an African and Caucasian cohort that the current recommended dose was not appropriate for children [22, 23]. Based on the study, the concern was not shared for the Asian pediatric population. However, it could also be concluded that reducing the recommended dose in children is not advisable due to the great variability and the current data available.

**Efavirenz in pregnancy**

In pregnancy, efavirenz is contraindicated in the first trimester due to its teratogenicity. However, in the second and third trimester it seems a safe option that might be used for TB co-infected pregnant patients or patients for whom protease inhibitors (PIs) are not available. Due to its limited use in pregnancy, no PK data are available on efavirenz and therapeutic drug monitoring (TDM) should therefore be considered for the third trimester, if available.

**Lopinavir**

Lopinavir/ritonavir fixed dose is currently the most used second line drug in Asia. However, not all countries have access to this fixed dose combination or to both formulations, tablet and soft gel capsule [24]. Generic products may be a solution for better and cheaper access, but quality assurance remains an issue. A study to measure the bioavailability of the generic lopinavir/ritonavir (publication in preparation) and check for quality of consecutive batches has been done in order to guarantee the quality of the product. Preferably, a joint effort should be made to make quality control and quality assurance of generic products an ongoing process.

For both lopinavir and ritonavir, the tablet formulation tends towards a greater bioavailability compared to the soft gel capsule, [25], which may generate opportunities for exploring dose reduction for Asians (or other populations), especially since an earlier pilot study in a double-boosted PI setting showed adequate PK parameters in Thai HIV-infected subjects when lopinavir/ritonavir was used in a 266/66 mg twice daily dose [26]. With the standard dose (400/100 mg twice daily) an AUC of 128 h*mg/L was found, around 30% higher than was reported in the package insert of Abbott where an AUC of 92 h*mg/L was reported [27].

![Fig. 3](image-url)

**Fig. 3** Summary of pharmacokinetics studies done with lopinavir in the region of Southeast Asia. If not otherwise specified, the standard dose is administered (400/100 mg once daily for adults, weight or body surface area (BSA) appropriate for pediatrics). RIF = Rifampicin; N = number of subjects in the study. The numbers in superscript indicate the references.
In the HIVNAT 017 study, 12 hour PK as well as consecutive TDM was done in a (N)NRTI experienced pediatric population [28, 29]. The plasma levels were high compared to the limited data available for Caucasian children [30], and compared to adult plasma levels. Based on these results, a dose reduction study was initiated, designed for children older than two years of age. The subjects were assigned to either the WHO recommended dose or a dose reduced by 30% [31]. With AUCs of 107 h*mg/L for the standard dose and 85 h*mg/L for the dose reduction arm, the PK values were not significantly different, possibly due to the large variation of the plasma concentrations of lopinavir. The efficacy data were similar after 48 weeks, although, with the small sample size, not conclusive. It is interesting to note that children’s doses are based on body surface area or weight and therefore leave out of the equation the variable of weight, which is often used as an argument why Asians need a lower dose than Caucasians, suggesting that other stronger factors may play a dominant role.

**Lopinavir in pregnancy**

In many current mother-to-child transmission (MTCT) guidelines lopinavir is recommended as first choice when NNRTI is contraindicated. However, in several studies lopinavir plasma levels appeared to be severely affected by pregnancy with an over 30% difference in plasma concentration, and pre-post partum. Therefore TDM or even an increase of the dose in the third trimester is recommended [32, 33]. Most of these studies, however, are done with the soft gel capsule and in a non-Asian population. Studies are in progress to assess the pharmacokinetics in the Thai population and the need for dose adjustment in pregnancy.

**Ritonavir**

Ritonavir is not used any more in a therapeutic setting because of its toxic profile and intolerability. However it is still frequently used due to its strong inhibition of the CYP450 3A pathway that prolongs the half-life and increases plasma levels of the co-administered PI. The smallest formulation currently available, in a non-fixed dose combination, is the 100mg capsule. Despite this low dose, data have shown that ritonavir still generates significant toxicities on dyslipidemia and lipodystrophy [34]. Currently, it is not clear what the optimal boosting dose is for the different PIs. Studies show that there is no linear correlation with dose and boosting effect [35]. Exploring a lower than 100 mg dose faces difficulties as the liquid formulation has a poor taste and is hard to dose. In combination with saquinavir, preliminary data showed that boosting with 50 mg (liquid) generates the same saquinavir PK parameters as the 100mg boosting dose [36]. Whether this can be extrapolated to all other protease inhibitors and how “low we can go” with the boosting is a subject for further investigation. A lower dose tablet of ritonavir would be a big step forward especially for the pediatric population.

**Saquinavir**

Although saquinavir is not the most frequently used protease inhibitor in the region, data collected on this particular PI are the most conclusive in terms of its use for the Asian setting. It is an example of how solid data can change the guidelines for a special sub-population. Due to the extensive data generated from saquinavir for both PK and efficacy, saquinavir is now recommended at a 1500 or 1600 mg dose with a boosting dose of 100 mg according to the guidelines [37-39]. One cohort study was done comparing the 1600/100 dose in the UK population to the Thai population which showed in a significant difference in terms of AUC and Cmin [40, 41]. Although levels below therapeutic levels were found in the different studies (<0.1 mg/L), this did not correlate with a higher rate of virological failure [37]. Of note, when used with NNRTIs, it is still recommended to use the standard 1000/100 mg twice daily dose of saquinavir as NNRTIs are shown to reduce the drugs exposure of protease inhibitors.

Saquinavir in children is not registered yet, but seems a safe option for this population. In the double boosted PI setting, the mean Cmin of a total 348 samples from 48 patients was 1.37 mg/L, which is above the therapeutic level of 0.1 mg/L. In the HIVNAT 017, the physicians reduced the dose by 21% based on TDM results over a 96 weeks period [28]. This suggests that lower dose might be adequate [42].
Pregnancy

Thailand participated as a site in a multicentre trial where saquinavir during pregnancy was assessed. Nine Thai subjects enrolled in the study, all achieving undetectable HIV-RNA at time of delivery and adequate PK parameters were recorded. It must be noted that the international standard dose was used with a 1000/100 mg twice daily dosing. The overall conclusion of this study was that saquinavir is a safe and potent drug which does not need dose adjustment during pregnancy.

Indinavir

Indinavir is known as the most toxic protease inhibitor, especially for its nephrotoxicity. It is therefore not currently used in most Asian countries. China, unfortunately, has only indinavir available due to poor accessibility to other PIs. In the past few years, indinavir has been used widely and has shown to be a very potent drug and has been extensively studied in Asians in different settings both boosted and unboosted, and in subjects with renal problems [43, 44]. It seems safe and efficacious to use indinavir in a 400/100 mg setting in the Asian population [45]. Cut-off value for optimal virological efficacy for boosted indinavir Cmin is 0.10 mg/L. Patients with an indinavir > AUC 60 h*mg/L are at increased risk of developing nephrotoxicity.

In another study, efavirenz was co-administered. There the dose of indinavir was 800/100 mg, due to the known interaction between efavirenz and indinavir. In this of study, significant toxicities were reported [46].

Atazanavir

Atazanavir is not widely used due to its high price, but is actually the preferred PI in the developed world due to its safety profile and once-daily dosing. To increase accessibility, dose reduction would be of particular economical interest. A 24 hour PK study of 200/100 mg was done and showed levels comparable to historical data from studies performed in Caucasian subjects on a standard 300/100 mg dose [47-49]. In this study, a significant decrease of bilirubine was achieved after reducing the dose from 300/100mg to 200/100mg. Some small scale efficacy data have been collected for 14 patients for this reduced regime [50]. All had an undetectable viral load with a median follow up of 68 weeks.
Due to concerns of hyperbilirubenia binemia in infants, atazanavir has long not been administered in pregnant women. But recent studies have shown that atazanavir is safe to use for mother and child [51]. The data on pharmacokinetics and pregnancy are somewhat conflicting and a study increasing the dose of atazanavir in the third trimester is underway.

Conclusions

From the data available, we can conclude that there are strong indications that Asians have on average a higher exposure to ARV compared to the Caucasian. Explanations for the higher drug exposure are complex and probably multiple. Although weight is often used as the main explanation, it is debatable. In several studies, weight is not a strong predictor for drug exposure. Moreover, the pediatric data, which is corrected for weight by means of drug administration, show that other reasons should be thought of. Genetics of the metabolic pathway may be another explanation, but hard to prove as it is unlikely that a single polymorphism will be found that can explain most of high levels of certain ARV.

Another conclusion is that too little information is available to make strong recommendations for guidelines or clinical practice. Therapeutic drug monitoring could be a good alternative, but in most settings it is not available. The only drug that is supported with strong data is saquinavir, a drug not frequently used in Asia. For the other ARV, well-powered efficacy data are lacking. Another limitation is that the great majority of the studies are done in the Thai setting, and it is far from certain that we can actually extrapolate all these data to the rest of the region. In order to tackle both sample size and the little diversity of population, a joint effort with other countries should be made to generate adequate data which can convince policy makers as well as clinicians.

Besides the convenience of the patients, the economic perspective is of interest. Big progress has been made in scaling up the access to treatment worldwide. Now, with more patients on treatment, the financial burden will continue to grow and more and more people will be in need of a second line regimen. Reducing the dose by 30%-50% would save an equal amount of money and therefore increase accessibility.

In conclusion, it is more likely Asians have a significantly higher exposure to both NNRTIs and PIs compared to the Caucasian. Further studies on pharmacokinetics, TDM and larger scale clinical trials among Asian populations are warranted to identify suitable low doses of ARVs for adoption in the clinical practice guidelines of this region.

Conflict of interest: none.

Fig. 5 Summary of pharmacokinetics studies done with atazanavir in the region of Southeast Asia. If not otherwise specified, the standard dose is administered (300/100 mg twice daily for adults, weight or body surface area (BSA) appropriate for pediatrics); N= number of subjects in the study.

**Atazanavir in pregnancy**

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