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Do activities of CYP3A, CYP2D6 and P-glycoprotein differ between healthy volunteers and HIV-infected patients?

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Running head: CYP3A, CYP2D6 and P-gp activities in HIV-infected and healthy individuals

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Abstract:

Background
In inflammation and infection, cytochrome P450 enzyme activities are down-regulated. However, information on possible discrepancies in activities of cytochrome P450 (CYP) enzymes and drug-transporters between HIV-infected patients and healthy people is scanty.

Methods
We used midazolam, dextromethorphan, and digoxin as in-vivo phenotyping probes for CYP3A (CYP3A4/5), CYP2D6 and P-glycoprotein activities, respectively, and compared these activities between 12 healthy Caucasians and 30 therapy-naïve HIV-infected patients.

Results
In the patients, the overall CYP3A activity (apparent oral midazolam clearance) was approximately half the activity observed in healthy volunteers (point estimate 0.490, 90% confidence interval CI, 0.377-0.638). The CYP2D6 activity (plasma ratio AUC_dextromethorphan / AUC_dextrophan) was essentially unchanged (point estimate 1.289, 90% CI 0.778-2.136). P-glycoprotein activity was slightly lower in patients (digoxin C_max point estimate 1.304, 90% CI 1.034-1.644).

Conclusions
The overall CYP3A activity was approximately 50% lower in HIV infected patients than in healthy volunteers. The CYP2D6 activity was highly variable, but in average not different, while a marginally lower P-glycoprotein activity was observed in therapy-naïve HIV infected patients.

Key words: CYP3A, CYP2D6, P-gp, HIV patients, clinical trial, clinical pharmacology.
Introduction:

Although many drug metabolism and drug-drug interaction studies are carried out in healthy volunteers and results are carried forward to the treatment of patients, a number of in vitro and animal studies have shown that activities of drug-metabolizing enzymes and drug transporters in infection and inflammation are altered, mainly decreased. These decreases in activities appear to be caused by nitric-oxide mediated inhibition or destabilization of the protein and / or a modulation of expression by pro-inflammatory cytokines directly or via nuclear transcription factors [1-3].

In humans, however, the knowledge about differences in activities of drug-metabolizing enzymes and drug transporters between healthy volunteers and patients is limited [4]. The incentive observation of a lower drug clearance in patients was made with theophylline in children with asthma during acute respiratory illness [5] and later explained by a decrease in cytochrome P450 (CYP) 1A2 enzyme activity. In a study using antipyrine as a probe for “global CYP activity”, critically ill children with sepsis had a twofold reduced antipyrine clearance compared to critically ill children without sepsis [6]. In patients with heart failure, negative correlations were observed between both tumour necrosis factor alpha and interleukin-6 and the activities of CYP1A2 and CYP2C19 [7]. In cancer patients, the CYP3A activity (measured with the erythromycin breath test) was markedly reduced in comparison to healthy volunteers. This observation was interpreted as a result of an inflammatory reaction [8].

In HIV infected patients, only indirect evidence for different enzyme- and transporter-activities exists. For CYP2D6 and the phase-II enzyme N-acetyltransferase 2 (NAT2), comparisons between genotypes and enzyme activities revealed slow metabolism phenotypes in spite of extensive-metabolizer genotypes in 5-17% of HIV-infected patients and patients with AIDS. The quantifications of enzyme activities were carried out with dextromethorphan and caffeine as probes for CYP2D6 and NAT2, respectively [9, 10]. However, using dapsone as NAT2 probe, the genotype-phenotype discordances were not confirmed [11]. Paracetamol sulfation and glucuronidation were not influenced by the state or progression of HIV infection [12].
Only one comparison of differences in CYP2D6 activity between healthy people and therapy-naïve HIV infected patients has been published to date, and no information is available on the differences in activities of the most important cytochrome P450 enzyme, CYP3A, at its two expression sites and of the most important drug-transporter, P-glycoprotein. We therefore investigated the activities of CYP2D6, CYP3A and P-glycoprotein in HIV infected patients and healthy volunteers using a phenotyping cocktail approach with the same probes and the same doses in both groups.
Methods:

Study designs and populations
In this investigation, the results of the antiretroviral treatment-free “reference” periods from two studies on the effects of the combination of lopinavir with low-dose ritonavir on CYP3A, CYP2D6 and P-glycoprotein were compared. The term “CYP3A” is used as an abbreviation for the combined enzyme activities of CYP3A4 and CYP3A5, since they cannot be distinguished with midazolam. Additionally, active CYP3A5, which is present in only few Caucasians, but in the majority of Africans, confers little to midazolam metabolism, and CYP3A5 activity appears to be small in comparison to CYP3A4. In the study which has been previously published [13], 30 therapy-naïve HIV infected patients received twice a phenotyping cocktail, once before the start of an antiretroviral combination therapy regimen containing 400 mg lopinavir + 100 mg ritonavir (3 capsules Kaletra®, Abbott, Wiesbaden, Germany) twice daily, and 14 days thereafter. In the other, unpublished study, 12 healthy volunteers received in a randomized crossover fashion the phenotyping cocktail either alone or together with a single dose of 400 mg lopinavir + 100 mg ritonavir. Both studies were approved by the Ethics Committee of the Medical Faculty of the University of Cologne, and all participants gave written informed consent after ample information had been provided. The studies were carried out in accordance with German laws and international guidelines.

The phenotyping “cocktail” in both studies was identical. It consisted of an oral part which contained 1.5 mg midazolam hydrochloride (CYP3A, Dormicum® V 5 mg/5 ml, Hoffmann-La Roche, Grenzach-Wyhlen, Germany), 30 mg dextromethorphan hydrobromide (CYP2D6, Hustenstiller-ratiopharm®, ratiopharm, Ulm, Germany), and 0.5 mg digoxin (P-glycoprotein, Lanicor®, Hoffmann-La Roche), administered in the morning either alone or together with Kaletra®. Four hours later, 1.0 mg midazolam hydrochloride (hepatic CYP3A, Dormicum®) were given intravenously. Before and until 12 h after the oral part of the cocktail, a total of 22 blood samples were withdrawn, plasma was separated by centrifugation and stored at -80°C until analysis. Genotyping of CYP2D6 (*3, *4, *5, *6 and allele duplications), the CYP3A5*3 polymorphism as well as the quantification of midazolam, dextromethorphan, dextrorphan, and digoxin in plasma were carried out as described earlier [13] without modification.
In the study with healthy volunteers, subjects were hospitalized the evening before the cocktail administration and had to remain fasted until 2 h after the cocktail, when a light breakfast was served. Food and beverage intake was standardized until 12 h after the oral part of the cocktail, when the volunteers left the study ward. All participants were considered healthy based on an extensive pre-study screening examination, they tested negative for HIV and hepatitis B and C, and did not take any drugs, herbal remedies or grapefruit containing food and beverages during the entire course of the study. Smokers of up to 10 cigarettes / day could participate, but smoking was not allowed during the hospitalization period. The conditions for the volunteers were kept as comparable as possible to the conditions for the HIV infected patients in our published study.

Pharmacokinetic and statistical analysis
The calculation of the pharmacokinetic parameters to estimate the activities of hepatic, intestinal, and hepatic + intestinal CYP3A, of CYP2D6 and of P-glycoprotein were carried out as described earlier [13, 14]. Geometric means and geometric coefficients of variation are shown, unless otherwise stated. P-values < 0.05 were considered statistically significant. The quantification of differences between healthy volunteers and HIV-infected patients in enzyme and transporter activities was handled as a bioequivalence problem with parallel groups for the respective probe drugs. Sample size calculations have shown that 12 subjects were sufficient to detect intraindividual differences of at least 30% in the respective enzyme and transporter activities with a level of significance of 0.05 and a power of 80%. A linear mixed effect modelling of the ln-transformed pharmacokinetic parameters was carried out with the status “healthy” or “HIV infected” as a fixed effect factor. Statistically significant differences between the groups were accepted if the 90% confidence intervals around the point estimates of the means of the ratios of \( \frac{\mu_{\text{HIV-infected patients}}}{\mu_{\text{healthy volunteers}}} \) did not include unity. A potentially meaningful difference was assumed if the 90% confidence intervals (CI) were entirely outside the bioequivalence acceptance zone of 0.80 – 1.25. The 90% CI translate to the results of two one-sided tests each on a level of significance of 0.05.

WinNonlin 5.2.1 (Pharsight, Mountain View, CA, USA) was used for these analyses, and graphs were designed using SigmaPlot 11.0 (Systat software, San Jose, CA, USA).
Results:

In the study with healthy volunteers, who received a phenotyping cocktail either alone or together with a single dose of 400 mg lopinavir and 100 mg ritonavir, 12 male Caucasians participated (table 1). CYP2D6 genotyping revealed that one volunteer was a poor metabolizer. All tested volunteers were homozygous CYP3A5*3 carriers. No serious adverse events occurred. A few volunteers showed mild sedation and euphoria, respectively, upon intravenous administration of midazolam. All events subsided without intervention. For the comparisons with HIV-infected patients, results from the period without coadministration of lopinavir / ritonavir were taken. For the group of HIV-infected patients, we used the phenotyping results obtained in 30 patients before any highly active antiretroviral therapy was started. These patients had participated in our previously published study in HIV infected patients [13] which used the same phenotyping cocktail.

The parameters for the activities of CYP3A, CYP2D6 and P-glycoprotein without lopinavir / ritonavir in both healthy volunteers and HIV infected patients and the comparisons between the groups are shown in table 2 and figures 1 - 3. In summary, overall CYP3A activity (apparent oral midazolam clearance) in patients was approximately 50% of the activity in healthy volunteers, but hepatic CYP3A activity (midazolam clearance after i.v. dosing) was essentially not different. The molar metabolic plasma ratio AUC_dextromethorphan / AUC_dextrorphan, which served as parameter for CYP2D6 activity, was essentially unchanged, but although no CYP2D6 poor metabolizers were included, variability was considerable. In patients, P-glycoprotein activity was 22-30% lower than in healthy volunteers (statistically significant change for digoxin C_max, but not for digoxin AUC). Since all healthy volunteers were male Caucasians, we additionally compared the data only from those 20 HIV-infected patients who were male Caucasians to the healthy volunteers’ data (right columns in table 2). In summary, variability increased, but the results for CYP3A and CYP2D6 were essentially unchanged. Only the difference in P-glycoprotein activity between the groups did not reach statistical significance any more.
Discussion:

In this investigation, we directly compared the activities of CYP3A, CYP2D6 and P-glycoprotein between therapy-naïve HIV infected individuals and healthy volunteers. The overall CYP3A activity in HIV infected patients was roughly half of the activity in healthy volunteers. This was mainly attributable to a lower intestinal CYP3A activity, while hepatic CYP3A activity was not significantly lower. The CYP2D6 activity was essentially comparable, but P-glycoprotein activity was decreased by 22-30% in the HIV infected patients. Major advantages of our study are that in both populations, the same dosages and application schemes of the phenotyping probe substrates were used and that sample analysis was carried out with the same methods. Additionally, all participants did not take any drug, herbal remedy, or foodstuff which is known to alter the activities of the proteins studied. Since among the healthy controls, no females (8 in the HIV infected patients) and no Africans (5 HIV positive patients) participated, we carried out a subgroup analysis including only male Caucasians, which essentially corroborated the results. Only the lower P-glycoprotein activity in HIV-infected patients in the entire group did not remain statistically significant in the subgroup comparison. The healthy volunteers were slightly younger than the HIV-infected patients, but age does not have an influence on CYP activities [15]. The other demographic factors were comparable between the groups. Besides the differences in gender and ethnicity between our two studies and the fact that we did not match the healthy controls to the patients, a limitation of this investigation arises from the relatively small sample sizes which limit the robustness of the results. This particularly became visible in the large variabilities in CYP2D6 activity, although genotypically poor metabolizers were excluded.

Data in literature regarding influences of gender and ethnicity on activities of cytochrome P450 enzymes and drug transporters are conflicting. While some authors found an approximately 20% higher CYP3A activity in women [16], others could not substantiate any gender- or ethnicity-related differences in CYP3A or CYP2D6 activity [17-19]. For CYP2D6 activity, it has been shown that genotype-corrected differences observed between Ethiopians and Swedes are mitigated in Ethiopians living in Sweden for a longer time [20], suggesting that other than ethnic factors influence the actual CYP2D6 activity. While a slightly higher hepatic P-glycoprotein activity may be present
in men [21], the more important intestinal P-glycoprotein activity does not appear to be
influenced by gender [22]. Our subgroup analysis also does not suggest major influences
of gender or ethnicity on the activities of CYP3A, CYP2D6, and P-glycoprotein.

The lower activities of CYP3A and P-glycoprotein in HIV-infected patients may be
explained by differences in cytokine profiles, which seem to shift towards a T-helper-
cell 2 like cytokine secretion profile during HIV infection [23]. Different cytokines
differentially regulate the activities of CYP450 enzymes [4], which may explain why
CYP3A activity was much more altered in HIV infected patients than P-glycoprotein
activity or CYP2D6 activity, which was not significantly changed. However, this does
not explain why particularly intestinal CYP3A activity was much lower, while hepatic
CYP3A activity was comparable between the groups. While it may be possible that
differences in absorption caused e.g. by a higher gastric pH in HIV infected patients [24]
may have contributed to this finding, there is also good evidence that lymphoid tissues in
the gut are an important site of HIV replication [25, 26]. This may cause local
differences in enzyme- and transporter-regulating messengers like cytokines or nitric
oxide, which may explain why particularly intestinal CYP3A activity was lower in HIV
infected patients. Further studies will be needed to test these hypotheses.

The phenotyping probes chosen were the best probes available for the assessment of the
activities of CYP3A, CYP2D6, and P-glycoprotein [27]. Midazolam is a validated probe
for CYP3A activity, which is not influenced by P-glycoprotein activity (in contrast to
e.g. erythromycin [28]). The sequential administration of oral and intravenous
midazolam in low doses to assess hepatic and intestinal CYP3A activity separately is
supported by several in vivo interaction studies [27, 29]. In the present two studies, we
further reduced the oral dose to 1.5 mg which did not lead to quantification difficulties
(the lower limit of quantification was 0.31 ng/mL), but reduced the plasma
concentrations before the intravenous application (geometric mean 1.46 ng/mL, CV
79.5%) to a level comparable to the concentrations observed 8 h after the intravenous
application (geometric mean 1.23 ng/mL, CV 96.9%). Our estimates for hepatic,
intestinal and combined hepatic and intestinal CYP3A activity were comparable to
literature [30, 31]. It therefore seems feasible to further reduce midazolam doses for
phenotyping purposes.
Since urinary dextromethorphan-based metrics for CYP2D6 activity are influenced by urinary pH, show a considerable variability and cannot detect smaller changes in CYP2D6 activity [32, 33], it seems advisable to use a plasma-based metric. We chose to use the ratio of full molar AUCs of dextromethorphan over dextrorphan which is considered to appropriately reflect the CYP2D6-mediated fractional clearance of dextromethorphan to dextrorphan. This ratio is also taken as reference for the assessment of appropriateness of phenotyping metrics [33-35]. Since the ways how metabolic ratios are calculated differs between publications, a comparison is difficult, however, ratios above 2 indicate CYP2D6 slow metabolizers [35], and the participants included in the comparison all had ratios well below this threshold. However, the considerable interindividual variability even after the exclusion of poor metabolizers negatively influenced the accuracy of the result, which is reflected in the large 90% confidence interval of the comparison between the populations. A larger study will be necessary to yield more accurate estimations of possible differences.

P-glycoprotein phenotyping methods are not so well developed and validated as CYP probes. However, digoxin pharmacokinetics have been shown to correlate with (intestinal) P-glycoprotein expression and some P-glycoprotein polymorphisms, to reflect induction of P-glycoprotein by rifampicin and inhibition by ritonavir both in patients and healthy volunteers [13, 27, 36-38]. Varying doses and routes of administration of digoxin have been used in other trials so that the suggested phenotyping metric digoxin C_{max} [27] cannot be directly compared between studies.

In a study on the influences of genotypes, disease activity, and concomitant medications on the activity of CYP2D6 in HIV infected patients, a reduction in CYP2D6 activity in patients with active disease was observed, as well as a shift of genotypically CYP2D6 extensive metabolizers towards lower CYP2D6 activities, but these values were not compared to healthy volunteer data [10]. Another comparison of the activities of CYP3A and CYP2D6 has just recently been published [39]. The authors state that hepatic CYP3A- and CYP2D6-activities in patients were approximately 20% and 90% lower, respectively, than in healthy volunteers. Since CYP2D6 poor metabolizers were not excluded from the analyses, since a urine-based CYP2D6 phenotyping method was used
and since 5 of 17 HIV-infected patients were not therapy-naïve, the results may not be directly comparable to our results. For P-glycoprotein, no such information is available.

The present evaluation aimed at identifying differences between HIV-infected patients and healthy people in the absence of any comedication which could influence the enzyme and transporter activities. The clinical situations in which such an influence could be relevant are therefore limited to patients with an untreated HIV infection. When patients receive an antiretroviral therapy regimen, most will receive drugs like ritonavir which is a strong inhibitor of CYP3A, CYP2D6, and P-glycoprotein [13], or efavirenz, an inducer of CYP3A activity [40, 41]. Hence, during antiretroviral therapy, the effects observed here are likely to be overlaid by induction and/or inhibition. On the other hand, pharmacokinetic differences between healthy volunteers and HIV infected patients may be caused by other factors as well: differences in gastric pH [24], decreased gastrointestinal transit time and diarrhoea [42], and differences in protein binding have been described for HIV-infected patients. For example, differences in pharmacokinetics of atazanavir between healthy volunteers and HIV-infected patients [43, 44] are likely not explained by differences in (intestinal) CYP3A activity, since ritonavir coadministration did not alter the presystemic first-pass metabolism of atazanavir, but its (metabolic) elimination. A more probable explanation are higher gastric pH values in the HIV-infected population, since the absorption of atazanavir is highly pH-dependent [44].

We also compared the extents of changes in the activities of CYP3A, CYP2D6, and P-glycoprotein between healthy volunteers after a single dose of ritonavir-boosted lopinavir and patients after chronic intake for at least 2 weeks. The effects observed after a single dose in healthy volunteers differed substantially from the effects seen in HIV infected patients during highly active antiretroviral therapy (data not shown). Therefore, a single dose interaction study with ritonavir-boosted lopinavir in healthy volunteers is not useful to predict effects in patients after chronic administration.

In conclusion, we were able to substantiate a roughly 50% lower overall CYP3A activity in HIV infected patients before the start of any antiretroviral therapy, while CYP2D6 activity was essentially unchanged, but variable, and P-glycoprotein activity showed 20% - 30% lower values.
Acknowledgements:

The study in healthy volunteers was supported by the Köln Fortune program of the Medical Faculty of the University of Cologne. AJ, GF, CW are supported by the German Federal Ministry of Research and Education (BMBF grant 01KI0771). We are much obliged to the HIV infected patients and the healthy volunteers to their participation in the studies. We greatly appreciate the support of Andreas Lazar, Ingrid Fehrenz, Axel Drechsler, Patricia Wieloch, Gregor Zadoyan, Ellen Rund, Gisela Kremer, Farid Abdulrazik, Norbert Schmeisser and Andrea Birtel. Parts of this work have been presented at the 11th congress for Clinical Pharmacology in Germany, Heidelberg, Germany, October 2009, and at the 12th European AIDS Conference, Cologne, Germany, November 2009.
References:


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Legends to tables and figures:

Table 1: Demographic characteristics (absolute numbers or means and ranges)

Table 2: Geometric means, coefficients of variations (CV), point estimates of the ratios of $\mu_{\text{HIV-infected patients}} / \mu_{\text{healthy volunteers}}$ or of $\mu_{\text{HIV-infected male Caucasian patients}} / \mu_{\text{healthy volunteers}}$ and corresponding 90% confidence intervals of the parameters for the activities of CYP3A, CYP2D6, and P-glycoprotein. All data are from periods without comedication. In the CYP2D6 evaluation, participants with no active CYP2D6 allele were excluded.

Figure 1: Individual hepatic CYP3A activity (hepatic midazolam (MID) clearance, upper panel, left side), hepatic + intestinal CYP3A activity (apparent oral MID clearance, upper panel, right side) and intestinal CYP3A activity (intestinal MID availability, lower panel) in 12 healthy volunteers and 30 HIV infected, therapy-naïve patients.

Figure 2: Individual CYP2D6 activity (molar metabolic plasma ratio $\text{AUC}_{\text{dextromethorphan}} / \text{AUC}_{\text{dextrorphan}}$) in 11 healthy volunteers and 24 HIV infected, therapy-naïve patients.

Figure 3: Individual P-glycoprotein activity (digoxin AUC$_{0-12}$, upper panel, and digoxin $C_{\text{max}}$, lower panel) in 12 healthy volunteers and 30 HIV infected, therapy-naïve patients.
Table 1: Demographic characteristics (absolute numbers or means and ranges)

<table>
<thead>
<tr>
<th></th>
<th>Healthy volunteers</th>
<th>HIV infected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>12 males</td>
<td>8 females, 22 males</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>12 Caucasians</td>
<td>5 (3 female, 2 male) Africans, 25 Caucasians</td>
</tr>
<tr>
<td>Smoking status</td>
<td>7 smokers, 5 non-smokers</td>
<td>17 smokers, 13 non-smokers</td>
</tr>
<tr>
<td>Age</td>
<td>32 (18 – 48) years</td>
<td>40 (25 – 60) years</td>
</tr>
<tr>
<td>Body weight</td>
<td>72 (60 – 82) kg</td>
<td>71 (49 – 106) kg</td>
</tr>
<tr>
<td>Body height</td>
<td>180 (171 – 190) cm</td>
<td>174 (156 – 190) cm</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>22.3 (20.2 – 24.9) kg/m²</td>
<td>23.5 (16.4 – 36.7) kg/m²</td>
</tr>
</tbody>
</table>
Table 2: Geometric means, coefficients of variations (CV), point estimates of the ratios of $\mu_{\text{HIV-infected patients}} / \mu_{\text{healthy volunteers}}$ or of $\mu_{\text{HIV-infected male Caucasian patients}} / \mu_{\text{healthy volunteers}}$ and corresponding 90% confidence intervals of the parameters for the activities of CYP3A, CYP2D6, and P-glycoprotein. All data are from periods without comedication. In the CYP2D6 evaluation, participants with no active CYP2D6 allele were excluded.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy volunteers</th>
<th>HIV-infected patients</th>
<th>HIV-infected male Caucasian patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n  Mean  CV</td>
<td>n  Mean  CV</td>
<td>Point estimate 90% confidence interval</td>
</tr>
<tr>
<td>Parameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic CYP3A activity: hepatic MID clearance (L/h)</td>
<td>12  25.5  43.0 %</td>
<td>30  24.4  23.6 %</td>
<td>0.956  0.807 – 1.131</td>
</tr>
<tr>
<td>Overall CYP3A activity: apparent oral MID clearance (L/h)</td>
<td>12  81.3  63.9 %</td>
<td>30  39.9  41.3 %</td>
<td>0.490  0.377 – 0.638</td>
</tr>
<tr>
<td>Intestinal CYP3A activity: intestinal MID availability (-)</td>
<td>12  0.565  19.8 %</td>
<td>30  0.797  25.6 %</td>
<td>1.409  1.229 – 1.616</td>
</tr>
<tr>
<td>Dextromethorphan AUC0-12 (ng/mL*h)</td>
<td>11  6.03  172.6 %</td>
<td>24  10.1  83.8 %</td>
<td>1.671  0.967 – 2.890</td>
</tr>
<tr>
<td>Dextrorphan AUC0-12 (ng/mL*h)</td>
<td>11  16.3  60.2 %</td>
<td>24  21.1  39.3 %</td>
<td>1.297  0.989 – 1.701</td>
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<tr>
<td>CYP2D6 activity: metabolic ratio</td>
<td>11  0.351  115.2 %</td>
<td>24  0.453  90.3 %</td>
<td>1.289  0.778 – 2.136</td>
</tr>
<tr>
<td>P-glycoprotein activity: digoxin AUC0-12 (μg/L*h)</td>
<td>12  4.29  35.2 %</td>
<td>30  5.22  43.1 %</td>
<td>1.216  0.969 – 1.526</td>
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<td>P-glycoprotein activity: digoxin C_max (μg/L)</td>
<td>12  0.98  37.8 %</td>
<td>30  1.28  43.5 %</td>
<td>1.304  1.034 – 1.644</td>
</tr>
</tbody>
</table>

Footnote: MID, midazolam, DEX, dextromethorphan, DOR, dextrophan.
**Figure 1:** Individual hepatic CYP3A activity (hepatic midazolam (MID) clearance, upper panel, left side), hepatic + intestinal CYP3A activity (apparent oral MID clearance, upper panel, right side) and intestinal CYP3A activity (intestinal MID availability, lower panel) in 12 healthy volunteers and 30 HIV infected, therapy-naïve patients.
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