<table>
<thead>
<tr>
<th>P75</th>
<th>Etravirine concentrations in seminal plasma in HIV-infected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tiraboschi, J; Nubio, J; Ferrer, E; Barrera-Castillo, G; Rozas, N;</td>
</tr>
<tr>
<td></td>
<td>Maso-Serna, M; Podzamczer, D* (Barcelona, Spain)</td>
</tr>
<tr>
<td>P76</td>
<td>Lack of correlation between UGT1A1*6, *28 genotypes, and plasma</td>
</tr>
<tr>
<td></td>
<td>raltegravir concentrations in Japanese HIV-1-infected patients</td>
</tr>
<tr>
<td></td>
<td>Takahashi, M*; Hirano, A; Oishi, Y; Sato, M; Yoshino, M; Ikemura,</td>
</tr>
<tr>
<td></td>
<td>K; Shibata, M; Fukushima, N; Amioka, K; Nomura, T; Yokomaku, Y;</td>
</tr>
<tr>
<td></td>
<td>Sugiyama, W (Nagoya, Japan)</td>
</tr>
<tr>
<td>P77</td>
<td>Use of antacid preparations with HAART</td>
</tr>
<tr>
<td></td>
<td>Vekaria, S*; Nelson, M (London, UK)</td>
</tr>
<tr>
<td>P78</td>
<td>Darunavir plasma level in HIV overweight patients</td>
</tr>
<tr>
<td></td>
<td>Poupidard, M*; Boussairi, A; Krause, J; Khudong-Josses, M (Saint</td>
</tr>
<tr>
<td></td>
<td>Denis, France)</td>
</tr>
<tr>
<td>P79</td>
<td>No change of plasma darunavir concentrations by switching from</td>
</tr>
<tr>
<td></td>
<td>ritonavir soft capsule to tablet</td>
</tr>
<tr>
<td></td>
<td>Shibata, M*; Takahashi, M; Fukushima, N; Yamaguchi, F; Nomura, T;</td>
</tr>
<tr>
<td></td>
<td>Yokomaku, Y; Sugiyama, W (Nagoya, Japan)</td>
</tr>
<tr>
<td>P80</td>
<td>Determination of rilpivirine (TMC-278) plasma concentrations by</td>
</tr>
<tr>
<td></td>
<td>the conventional LC-MS method</td>
</tr>
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<td>Shibata, M*; Takahashi, M; Kuwahara, T; Nomura, T; Yokomaku, Y;</td>
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<tr>
<td></td>
<td>Sugiyama, W (Nagoya, Japan)</td>
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<tr>
<td>P81</td>
<td>Interaction of antiretroviral medications with finasteride</td>
</tr>
<tr>
<td></td>
<td>Ward, D* (Washington DC, USA)</td>
</tr>
<tr>
<td>P83</td>
<td>Moderator effect of CYP2B6 genotype in HIV-1 patients with</td>
</tr>
<tr>
<td></td>
<td>tuberculosis treated with rifampicin and efavirenz</td>
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<tr>
<td></td>
<td>De la Calle, C; Sanchez, A; Cordero, M; Iglesias, A; Luna, G*</td>
</tr>
<tr>
<td></td>
<td>(Salamanca, Spain)</td>
</tr>
</tbody>
</table>

*Indicates presenting author.
Etravirine (ETR) concentrations in seminal plasma in HIV-infected patients ("The NESS Study")

Hospital Universitari de Bellvitge, L'Hospitalet, 08907 Barcelona, SPAIN

PURPOSE OF THE STUDY

Good penetration of antiretroviral drugs to the seminal plasma, a suggested surrogate marker of the male genital tract, may be associated with a decrease in viral replication and play an important role in the prevention of sexual transmission of HIV. We present data from a series of HIV-infected ARV-experienced patients receiving etravirine (ETR)-containing regimens, in whom ETR concentrations and viral loads were determined in blood plasma and seminal plasma. The objective was to determine ETR concentrations and HIV-1 viral load (VL) in blood plasma (BP) and seminal plasma (SP) of HIV-infected patients.

PATIENTS AND METHODS

Patients: Ten asymptomatic adult, HIV-infected, ARV pre-treated patients with no clinical evidence of sexually transmitted disease were enrolled. All had been taking etravirine as part of an ARV regimen for at least 4 weeks.

Interventions: Adherence to ARV drugs was assessed using the Simplified Medication Adherence Questionnaire (SMAQ).

In order to determine the lowest blood plasma ETR concentrations, blood and the first semen sample were taken on the same day, approximately 12 h after the previous etravirine dose in patients taking a twice-daily regimen and 24 h after the ETR dose in those taking the drug once a day. HIV-1 viral load was analyzed in both blood and semen sample. Total ETR concentration in blood plasma (BP) and semen plasma (SP) samples was analyzed by a validated liquid chromatography tandem mass spectrometry assay (LC/MS/MS). The samples were analyzed against a plasma curve using a set of quality controls (QC) samples made in plasma and a set of QC samples made in semen. During the extraction process, the matrix was balanced to be 1:1 plasma:semen. The internal standard for the assay was a stable label (D8-etraVirine) and all QC samples showed acceptable bias relative to the nominal concentration. The internal standard showed consistent results throughout the run (Tandem Labs-New Jersey, USA). HIV-1 viral load was quantified with a real-time PCR technique (Abbot Molecular Inc., Des Plaines, IL; limit of detection, 40 copies/mL).

RESULTS

Baseline characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Risk practice</th>
<th>CD4 cel/mm³</th>
<th>HIV Viral Load</th>
<th>Weeks on ETR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>Heterosexual</td>
<td>572</td>
<td>&lt;40</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>Homosexual</td>
<td>712</td>
<td>&lt;40</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>Homosexual</td>
<td>817</td>
<td>&lt;40</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>Homosexual</td>
<td>540</td>
<td>&lt;40</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>Heterosexual</td>
<td>464</td>
<td>&lt;40</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>Homosexual</td>
<td>399</td>
<td>&lt;40</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>IVDU</td>
<td>450</td>
<td>362</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>Heterosexual</td>
<td>728</td>
<td>&lt;40</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td>Homosexual</td>
<td>252</td>
<td>&lt;40</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>IVDU</td>
<td>456</td>
<td>&lt;40</td>
<td>124</td>
</tr>
</tbody>
</table>

Median (range) 45.5 (33-64) 502 (252-817) <40 52 (12-124)

Pharmacokinetic, virological, and therapeutic data

<table>
<thead>
<tr>
<th>Patient</th>
<th>BP (ng/mL)</th>
<th>SP (ng/mL)</th>
<th>SP:BP</th>
<th>VL (copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31.2</td>
<td>375</td>
<td>0.08</td>
<td>&lt;40</td>
</tr>
<tr>
<td>2</td>
<td>57.1</td>
<td>307</td>
<td>0.18</td>
<td>&lt;40</td>
</tr>
<tr>
<td>3</td>
<td>36.8</td>
<td>506</td>
<td>0.07</td>
<td>&lt;40</td>
</tr>
<tr>
<td>4</td>
<td>80.6</td>
<td>399</td>
<td>0.15</td>
<td>&lt;40</td>
</tr>
<tr>
<td>5</td>
<td>68.1</td>
<td>258</td>
<td>0.26</td>
<td>&lt;40</td>
</tr>
<tr>
<td>6</td>
<td>104.0</td>
<td>414</td>
<td>0.25</td>
<td>&lt;40</td>
</tr>
<tr>
<td>7</td>
<td>107.0</td>
<td>491</td>
<td>0.21</td>
<td>&lt;40</td>
</tr>
<tr>
<td>8</td>
<td>65.3</td>
<td>592</td>
<td>0.11</td>
<td>&lt;40</td>
</tr>
<tr>
<td>9</td>
<td>52.2</td>
<td>518</td>
<td>0.1</td>
<td>&lt;40</td>
</tr>
<tr>
<td>10</td>
<td>186.0</td>
<td>751</td>
<td>0.22</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

Median 62.8 452.5 0.16 <40

In this table, semen and plasma concentrations of ETR, seminal plasma: blood plasma ratios as well as viral loads of both compartments are described for the 10 patients included. In addition, ARV drugs administered concomitantly with ETR are shown.

Abbreviations: 3TC, lamivudine; ABC, abacavir; BP, blood plasma; DRV, darunavir/ritonavir; FTC, emtricitabine; LPV, lopinavir/ritonavir; SP, seminal plasma; TDF, tenofovir; VL, viral load

*Patients taking ETR once a day.

In male genital secretions ETR reaches modest concentrations, only 16% of the BP concentration. Nevertheless, they are more than 10 times greater than the wild-type IC(50) range (not adjusted for protein binding). These findings suggest that ETR in combination with other ARV drugs may contribute to suppress viral replication in semen.

CONCLUSIONS

Adapted from Taylor S, Davies S. Antiretroviral drug concentrations in the male genital tract: implications for the sexual transmission of HIV. Curr Opin HIV AIDS. 2010;5:335-43.
Lack of correlation between UGT1A1 *6 and *28 genotypes, and plasma raltegravir concentrations in Japanese HIV-1 infected patients


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[Background]
Raltegravir is one of a new class of antiretroviral agents that work by inhibiting the insertion of viral DNA into the cellular genome, resulting in the prevention of virus replication. Raltegravir is metabolized by glucuronidation via UDP-glucuronosyl-transferase 1A1 (UGT1A1). The genetic polymorphism of UGT1A1 is known to be associated with UGT1A1 activity. In these polymorphisms, *6, *27, *28, and *37 alleles are associated with reduced levels of UGT1A1. In particular the *28[(TA)7TAA] allele accounts for most of the polymorphisms, and the *6, *27, *28, and *37 alleles are associated with reduced concentration seen among white patients. On the other hand, in Asian patients, the *6(IIIG-A) and *27(A166C-A) alleles are more commonly found in comparison with white patients. In this study, we aimed to clarify the contribution of UGT1A1 polymorphisms to plasma raltegravir concentrations in Asian patients. Therefore, we analyzed the UGT1A1 *6, *27, *28, *37 genotypes in Japanese HIV-1 infected patients, and then examined the correlation between each allele and the plasma raltegravir concentrations.

[Results]
A total of 74 Japanese HIV-1 infected patients were examined for their allelic variants of UGT1A1 *6, *27, *28, and plasma raltegravir concentrations. Among the 74 patients, the UGT1A1 genotype in 3 patients was *6 homozygote. Heterozygous variants were found in 20 patients for *6, and in 14 patients for *28, while all of the patients were found to carry wild-type sequences at the position corresponding to the *27 allele. One patient heterozygous for both *6 and *28 was found in this study.

1. Among the 74 patients who were treated with raltegravir-containing regimen, three patients were found to be homozygous for the *6 allele. The *6 homozygote patient had modestly higher plasma raltegravir concentration (0.53 µg/ml) than other patients who were wild type (0.12 µg/ml) or heterozygote (0.16 µg/ml) for the *6 polymorphism (Fig. 1A). Other two UGT1A1*6 homozygote patients had a lower plasma raltegravir concentration (0.03 and 0.05 µg/ml). On the other hand, patients heterozygous for the *6 or *28 allele did not display significantly different plasma raltegravir concentrations when compared to patients homozygous for the respective wild-type allele (Fig. 1A and 1B).

Table 1 shows plasma raltegravir concentrations and patient characteristics for each UGT1A1 genotype in 74 patients. The body weights of the 3 patients with *6 homozygote were lower than those of patients who were wild type or heterozygous for this allele, and this difference was statistically significant. However, the other differences in patient characteristics for each UGT1A1 genotype (*6 and *28) were not significant, indicating that these characteristics did not correlate with the differences in raltegravir concentration seen among UGT1A1 genotypes.

2. Table 1 shows plasma raltegravir concentrations and patient characteristics sorted by the UGT1A1 genotype of the 74 patients. The body weights of the 3 patients with *6 homozygote were lower than those of patients who were wild type or heterozygous for this allele, and this difference was statistically significant. However, the other differences in patient characteristics for each UGT1A1 genotype (*6 and *28) were not significant, indicating that these characteristics did not correlate with the differences in raltegravir concentration seen among UGT1A1 genotypes.

3. Table 2 shows the relationship between UGT1A1 genotype (both *6 and *28) and raltegravir concentration in the 74 patients. Plasma raltegravir concentrations were 0.12 µg/ml (*6-/- *28-/-; n=38), 0.11 µg/ml (*6-/- *28-/+; n=13), 0.16 µg/ml (*6+/*28-/-; n=10), 0.30 µg/ml (*6+/*28+/-; n=1). There were no statistically significant differences in the plasma raltegravir concentrations between patients carrying wild-type alleles and those heterozygous for *6 or *28.

[Conclusions]
In this study, we did not find any patients with *28 homozygosity among our 74 recruited patients. Within our patient sample, there were no statistically significant differences in plasma raltegravir concentrations between patients with wild-type and *28 heterozygous genotypes. Further assessment of the relationship between UGT1A1*6 and *28 genotypes to plasma raltegravir concentrations will require studies additional subjects. UGT1A1*6 and *27 polymorphisms are commonly found among Asians, where the UGT1A1*6 polymorphism is more common than UGT1A1*28. Among our 74 recruited patients, we found 3 patients with *6 homozygote, and another 20 patients with *6 heterozygote. On the other hand, all 74 of our patients carried wild-type sequences at the position corresponding to the *27 allele. In the one patient homozygous for *6, the plasma raltegravir concentration (0.53 µg/ml) was modestly higher than that seen in patients with wild-type alleles (0.12 µg/ml) or *6 heterozygote (0.16 µg/ml). The two patients homozygous for *6 had a lower plasma raltegravir concentration (0.03 and 0.05 µg/ml). Thus, in this study, we examined only a small number of patients with *6 homozygote. In addition, the intra-individual variability in raltegravir concentration is known to be very large. As a result of these limitations, we could not demonstrate any correlation between UGT1A1*6 homozygosity and plasma raltegravir concentration.

Finally, our results indicated that heterozygosity for the reduced-function *6 and *28 alleles appeared to have no significant effect on plasma raltegravir concentrations in Japanese HIV-1-infected patients. Additional clarification of the contribution of UGT1A1*6 and *28 polymorphisms to plasma raltegravir concentrations will require further investigations with larger subject populations.
Use of Antacid Preparations with HAART

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1 Chelsea and Westminster Hospital NHS Foundation Trust, London, UK 2 Imperial College School of Medicine, London, UK

Introduction

Consumption of antacids and ulcer healing preparations can affect the absorption of some antiretrovirals (ARV) due to increases in intra-gastric pH and should therefore be avoided with drugs dependent on gastric pH for absorption. All patients initiating or switching antiretroviral therapy (ART) are routinely counselled and advised on potential interactions including those between ARVs and antacid/ulcer healing medication. The purpose of this study was to determine the awareness for the potential for interactions with ART and to assess the effect of concurrent administration on virological failure.

Method

Questionnaires were given to consecutive patients presenting to the outpatient pharmacy who were stable on antiretroviral therapy (ART) which consisted of either atazanavir (TAZ), darunavir (DRV) or efavirenz (EFV) for more than 1 year. Information was gathered on the awareness of potential interactions between ARVs and antacid/ulcer healing medication and the use of such preparations over the past year. Viral load (VL) data was then observed for each patient and any VL blips (VL>200 copies/ml) in the preceding year recorded.

Results

247 patients were questioned of whom only 30% were aware of interactions between ART and antacids/ulcer healing medication; 38% of patients on TAZ, 31% on DRV and 25% on EFV. 62% of patients receiving ART with TAZ were therefore not aware of the need for caution with co-administration of antacid preparations.

Table 1: Comparison of antacid/PPI interaction awareness and administration between atazanavir, darunavir and efavirenz

<table>
<thead>
<tr>
<th></th>
<th>TAZ</th>
<th>DRV</th>
<th>EFV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>72</td>
<td>76</td>
<td>99</td>
<td>247</td>
</tr>
<tr>
<td>Aware of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>interactions</td>
<td>27</td>
<td>24</td>
<td>25</td>
<td>76</td>
</tr>
<tr>
<td>Prescribed antacid</td>
<td>7</td>
<td>16</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>Bought antacid</td>
<td>19</td>
<td>17</td>
<td>19</td>
<td>55</td>
</tr>
<tr>
<td>Viral blips in last year</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>18</td>
</tr>
</tbody>
</table>

30% (n=76) of patients had been prescribed and/or bought antacid and ulcer healing medication in the previous year whilst on ART.

Table 2: Shows how patients were aware of the interactions between ARV’s and antacids/PPI’s

<table>
<thead>
<tr>
<th>Who informed you about interactions</th>
<th>TAZ</th>
<th>RTV</th>
<th>EFV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Reading</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nurse</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Can’t remember</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3: Viral blips and antacid/PPI use with patients on atazanavir

<table>
<thead>
<tr>
<th></th>
<th>Prescribed/bought antacid</th>
<th>Denies antacid use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>21</td>
<td>51</td>
</tr>
<tr>
<td>One or more viral blips in last year</td>
<td>5 (24%)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

18 out of the 247 patients were recorded as having at least one VL blip in the previous year; 10 on TAZ, 7 on DRV, and 1 on EFV. 8 of these patients had either bought or been prescribed antacids during this time. FIVE of the patients on TAZ had taken antacid/ulcer healing medication.

Conclusion

The majority of patients are unaware of potential interactions between ARVs and antacids. However, few patients developed a positive viral load during the period studied. Of these patients, there was a higher rate of viral blips with patients on atazanavir who had taken antacids and other ulcer healing medication. Patients receiving TAZ were not anymore aware of the potential drug interaction than those receiving other agents. It is therefore essential that information is given to patients at each clinic visit to reinforce interactions between antacids and HAART (highly active antiretroviral therapy). Of the patients who were aware of the interactions with antacids/ulcer healing medication, most patients recalled their doctor as being the source of this information.

Acknowledgments

The authors would like to thank all the people who made this project possible including the staff and patients at the Kobler Clinic, Nkosi Johnson Unit and 56 Dean Street Clinic.

Chelsea and Westminster Hospital NHS Foundation Trust
Plasma concentration of darunavir in overweight HIV infected patients

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3Pharmacoepidemiology department - Synergie Hospital - Saint Denis - France

Background

Darunavir (DRV) is one of the most commonly used boosted protease inhibitors in France. Drug plasma levels are well known for this boosted PI treatment for 800 mg doses twice daily, less evaluated for 800 mg in once daily regimen.

Therapeutic drug monitoring (TDM) could be indicated in some situations (pregnancy, drug-drug interaction...) and is useful in optimizing antiretroviral treatment.

Cases of decrease exposure of efavirenz have been reported in obese patients.1

With an increasing population of HIV infected patients receiving antiretroviral therapy and having overweight problems we decided to conduct TDM on overweight patients receiving DRV/r.

Results

Baseline characteristics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Men (n=46)</th>
<th>Women (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (±SD)</td>
<td>41 (±8)</td>
<td>38 (±7.3)</td>
</tr>
</tbody>
</table>

We included 53 patients, 36 women and 17 men.

Mean age was 41 years old (SD 8.8), women were younger (mean age 38) than men (mean age 46).

The majority of the patients (62%) were from Sub-saharan Africa, 10% were from North Africa, 10% from Caribbean area and 15% were Caucasian.

Fifty percent of the patients were CDC stage A, and 30% stage C.

The median CD4 cells count was: 426 cells/mm³ (297-615). The HIV-1 RNA was < 35 copies/ml for 77% of the patients (n=41), for patients with detectable viral load (n=12), HIV-1 RNA was < 500 copies/ml for 80% (n=10/12).

In average patients were taking antiretroviral for more than 2 years, but with large intervals from 2 weeks to 9 years.

For boosted DRV, mean ARV duration was 11.5 months (± 9).

87% of the patients received DRV/r 800/100 once-daily dosing schedule associated with tenofovir/elvitegravir (72%) or abacavir/lamivudine (17%).

BMI consideration

Thirty patients were overweight : 13 patients had BMI > 30 and 16 patients had BMI between 25 and 30. Women were more often overweight and obese than men.

Adherence

(n=31)

We didn’t find any difference in adherence between patient with BMI above 25 and those with normal BMI. However, adherence was not recorded for 22 patients.

We also split into two groups the patients under or above BMI of 25.

Among the six patients with low plasma DRV concentration no adherence issues was recorded.

Impact on viral load

To investigate the impact on viral load we performed two different analyses, first with 3 groups of BMI: normal, overweight and obese patients. Then we also split into two groups the patients under or above BMI of 25.

We found no clear evidence of virologic failure linked to overweight patients.

Conclusion

In this study, C12h DRV and RTV were lowered respectively by 27 and 57 % in obese patients (BMI> 30) vs patients with BMI <25 kg m² receiving DRV/r 800/100 once a day.

No difference for viral load was found, but our sample size was small.

Based on the results of this small cohort, we propose in obese patients a TDM of DRV (and RTV) and to increase the dose of DRV/r if necessary to 600/100 mg twice a day.

Methods

This monocentric study enrolled HIV infected adults age > 18 years who had been taking DRV/r 600/100 mg BID or 800/100 mg OD as part of a combination ART regimens for a least 2 weeks.

DRV and RTV plasma concentrations (C12h=12 ± 3 hours) were determined using HPLC with photodiode array detection (limit of quantification 0.06 mg/L) with [DRV] Cmin =1.3 mg/L as target level. Ritonavir plasma concentrations were also checked, with [RTV] Cmin < 0.05 mg/L.

CD4 cells count and HIV viral load at time of drugs plasma concentration were also collected.

For each patient, baseline characteristics were registered: sex, age, date of antiretroviral initiation, CDC stage. Weight (W) and height (H) were also measured to calculate body mass index (BMI) with the following formula :

BMI = W(kg) /H² (m).

Weight (W) and height (H) were also measured to calculate body mass index (BMI) with the following formula :

BMI = W(kg) /H² (m).

Impact on viral load

We found no clear evidence of virologic failure linked to overweight patients.
No change of plasma darunavir concentrations by switching from ritonavir soft capsule to tablet

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Introduction

The clinical treatment of patients with human immuno deficiency virus (HIV)-1 infection has been advanced by the success of highly active antiretroviral therapy (ART). The latest treatment guidelines recommend that patients naïve to antiretroviral therapy should be started on one of the three types of combination regimens (Table 1). Selection of each regimen should be individualized based on virologic efficacy, toxicity, pill burden, and dosing frequency. In the three regimens, protease inhibitor-based regimens generally are associated with gastrointestinal symptoms and lipid abnormalities. Therefore, new protease inhibitor, which is more safe and effective, was required to continue effective ART for the treatment of HIV-1. Darunavir, a second-generation inhibitor of the HIV-1 protease with potent activity against resistant virus, was initially approved by the FDA (2006) and the EMA (2007) for the treatment of antiretroviral-experienced adults, and later for naïve adults. Darunavir (ideally given with two other active antiretrovirals) demonstrated superior efficacy and low toxicity compared to other protease inhibitors in highly experienced patients. Darunavir is used with a low boosting dose of ritonavir to improve its clinical efficacy. The boosting dose of ritonavir acts as an inhibitor of CYP3A4, thereby increases darunavir bioavailability. Recently, ritonavir tablet has been on sale in place of ritonavir soft capsule. However, pharmacokinetic study of darunavir by changing ritonavir form is still not clear. In this study, we aimed to compare plasma darunavir concentrations by switching from ritonavir soft capsule to tablet in Japanese HIV-1 infected patients.

TABLE 1. Preferred antiretroviral regimens for antiretroviral therapy-naïve patients

<table>
<thead>
<tr>
<th>Preferred Regimens (3 types of combination regimens)</th>
<th>1. Non-nucleoside reverse transcriptase inhibitor-based regimen</th>
<th>2. Protease inhibitor-based regimens</th>
<th>3. Integrase strand transfer inhibitor-based regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz (EFV) + Tenofovir (TFV) + Emtricitabine (FTC)</td>
<td>Atazanavir (ATV) + Ritonavir (RTV) + Tenofovir (TFV) + Emtricitabine (FTC)</td>
<td>Raltegravir (RAL) + Tenofovir (TFV) + Emtricitabine (FTC)</td>
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Method

We recruited 34 Japanese HIV-1 infected patients (32 males: 2 females) who were treated with darunavir containing regimen at the National Hospital Organization Nagoya Medical Center, Japan. All patients had been administered with 800/100mg darunavir/ritonavir (soft capsule) once daily in combination with other antiretrovirals. For all recruited patients, we switched ritonavir soft capsule to tablet in darunavir containing regimen. At 7 days after switching to ritonavir tablet, we measured plasma darunavir concentrations. Darunavir plasma concentrations were determined by the HPLC method we established. Plasma sampling for each patient was performed at the outpatient HIV clinic. A paired t-test was used to compare their darunavir concentrations by switching from ritonavir soft capsule to tablet. Drug adherence of each patient was confirmed by interview and viral load during darunavir containing therapy. This study was approved by the institutional review board of national Hospital Organization Nagoya Medical Center, and each subject provided written informed consent.

Results

The mean of age, body weight, and duration of antiretroviral therapy for 34 patients were 41.9 (range: 24-62) years, 66.3 (range: 51.4-90.0) kg, and 436 (range: 182-739) days, respectively. The combination of co-administered antiretroviral agents with darunavir/ritonavir was tenofovir/emtricitabine in 32 patients, and abacavir/lamivudine in 2 patients. When ritonavir soft capsule was administered, the mean viral load was 78 copies/ml (range: 40-27700 copies/ml) and mean CD4 cell count was 417 cells/mm³ (range: 118-912 cells/mm³). At 7 days after switching to ritonavir tablet, the mean viral load was 40 copies/ml (range: 40-197 copies/ml) and mean CD4 cell count was 439 cells/mm³ (range: 199-886 cells/mm³). There was no significant difference in viral load, and CD4 cell count by switching to ritonavir tablet. (Fig.1 and Fig.2).

On the other hand, the mean ± SD of darunavir concentration was 3.44±1.78 µg/ml when ritonavir soft capsule was co-administered. After switching to tablet, the mean ± SD of darunavir concentration was 3.30±2.02 µg/ml. Statistical difference was not found in plasma darunavir trough concentration between ritonavir soft capsule and tablet (Fig.3).

Conclusion

After switching from ritonavir soft capsule to tablet, recruited all patients had been sustained an undetectable viral load and CD4 cell count increased slightly. In this study all patients had no severe side effects and could continue darunavir containing regimen. In addition, switching from ritonavir soft capsule to tablet had no significant difference on plasma darunavir concentrations in Japanese HIV-1-infected patients. These result suggest that boosting effect of ritonavir tablet for darunavir is almost similar to that of ritonavir soft capsule.

After switching to tablet, the mean ± SD of darunavir concentration was 3.30±2.02 µg/ml. Statistical difference was not found in plasma darunavir trough concentration between ritonavir soft capsule and tablet (Fig.3).
**Determination of rilpivirine (TMC-278) plasma concentrations by the conventional LC-MS method**

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**Background**

Rilpivirine (TMC-278) is a second-generation NNRTI that is high potent against both wild-type and drug-resistant HIV-1 strains. Consequently, rilpivirine is expected to treat therapy-experienced patients who failed to use current drugs due to the emergence of drug-resistant HIV mutants. Rilpivirine is primarily metabolized by cytochrome P450 (CYP) 3A. Therefore, co-administration of rilpivirine and CYP3A inducer may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine. To avoid these risks, therapeutic drug monitoring of rilpivirine is essential, especially in patients with severe renal or hepatic impairment. In this study, we intended to develop a conventional method for determining plasma rilpivirine concentrations by LC-MS.

**Material & Methods**

**Chemicals and Reagents**

Rilpivirine was supplied by Janssen Pharmaceutica (Turnhoutseweg, Beerse, Belgium) and the internal standard (IS), 6,7-Dimethyl-2,3-di-(2-pyridyl)-quinoxaline, was purchased from Sigma-Aldrich (St Louis, MO, USA). All other chemicals and solvents were of analytical grade.

**Equipment**

A Waters Alliance 2695 HPLC and a Micromass ZQ-2000 MS (Waters Assoc., Milford, MA, USA), controlled with Masslynx version 4.0 software, were used for detection. The analytical column was a SunFire C18 column (3.5 µm, 2.1×50 mm, Waters), protected by a SunFire C8 Guard Column.

**Chromatographic condition**

The mobile phase was a mixture of 0.1 mM EDTA in 0.1% acetic acid (A), 100% acetonitrile (B) and 100% methanol (C). An isocratic mobile phase consisting of A-B-C (65:15:20) was used during the first 2 min of the run, followed by a linear gradient elution consisting of A-B-C (30:50:20) for the next 8 min. The final conditions were maintained for the final 5 min. The flow rate of the mobile phase was 0.2 ml/min, and the column temperature was 40°C.

**Sample Preparation**

Two milliliters of ethyl acetate/n-hexane (50:50, v/v) containing the IS (177.5 ng/ml) and 1.0 ml of 0.2 M ammonium acetate were added to a 500 µl plasma sample prepared from peripheral blood anticoagulated with heparin. The mixture was vortexed for 5 min and then centrifuged at 3,500 g for 5 min. The upper layer was separated and evaporated dry. The dried material was then dissolved in 50 µl of a mobile phase solution. Lastly, 5 µl of the upper solution was injected into the LC-MS system.

**Results**

Figures 1A and B show selected-ion recording chromatograms obtained from a spiked plasma sample containing 143 ng/ml of rilpivirine and 177.5 ng/ml of the IS. Under the described chromatographic conditions, retention times were 6.8 min for rilpivirine and 10.5 min for IS. Figures 1C and D show chromatograms obtained from a blank plasma sample. Assays performed on drug-free human plasma succeeded to show no interfering peaks during the interested intervals of the retention times. Figure 1D is the expanded figure of the baseline part of Fig. 1B. These peaks did not affect the quantification of the IS. There were no interfering peaks affecting quantification of rilpivirine in this chromatogram. Anticoagulants of heparin and EDTA did not hinder the selected-ion recording chromatograms for rilpivirine and the IS. Calibration curves of rilpivirine appeared linear in the concentration range of 18 to 715 ng/ml with a correlation of 0.995. Precision, accuracy, and recovery of our LC-MS method are shown in Table 1. The selected concentration of rilpivirine covers the expected plasma concentrations found in the patients. The relative standard deviation (RSD) calculated for rilpivirine in the inter- and intraday assays ranged from 0.8 to 3.3%, which are similar to values reported by LC-MS/MS method previously. Accuracies ranged from 100.0 to 100.6%. Recoveries from plasma ranged from 82.0 to 88.3%. Figure 2 shows the distribution of plasma rilpivirine concentrations in 22 Japanese HIV-1 infected patients. Rilpivirine plasma concentrations were measured at outpatient clinic. These rilpivirine concentrations were similar to values reported by foreign healthy volunteers.

**Conclusions**

We developed a method for determining plasma rilpivirine concentrations using LC-MS. The principal advantages of our method are rapid liquid-liquid drug extraction from plasma and use of an available IS, a commercial compound. Validation showed our method was successful in measuring plasma rilpivirine with high precision and satisfactory RSD values. The rilpivirine calibration curve was linear at the concentration range of 18 to 715 ng/ml, and the average accuracy ranged from 100.0 to 100.6 %. Both inter- and intraday RSDs for rilpivirine were less than 3.3 %. These results indicate our newly developed method achieves the same level of reproducibility and accuracy as the LC-MS/MS method. As plasma concentrations of rilpivirine are expected in the 67 to 204 ng/ml range when rilpivirine is administered at single dose of 25 mg for healthy volunteers, our method successfully covers this region with good precision and accuracy. In clinical practice, mean rilpivirine plasma concentration at trough was 49 ng/ml. This level compared favourably with trough concentrations of about 50-80 ng/ml seen in ECHO and THRIVE trials. Consequently, our LC-MS method provides a conventional, accurate and precise way to determine rilpivirine in human plasma. This method can be used in routine clinical application for HIV-1 infected patients, and permits management of drug interactions and toxicity for rilpivirine.
Interactions of Antiretroviral Medications with Finasteride
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Background:
Finasteride 1 mg (Propecia) is commonly used for the prevention of hair loss in men. It works by inhibiting the conversion of testosterone (T) to dihydrotestosterone (DHT) by the enzyme 5α-reductase. This treatment has been shown to slow the rate of hair loss in younger men, and is generally well tolerated.

What is not commonly recognized is that finasteride is primarily metabolized by the enzyme cytochrome p450 (CYP) 3A4, so that its levels can be affected by medications that induce or inhibit this enzyme. Many antiretrovirals are potent inducers or inhibitors of CYP 3A4, and may therefore affect the level, and therefore the efficacy of finasteride.

Patients taking medications that induce or inhibit CYP 3A4 may need to adjust their dosage of finasteride. Since finasteride for hair loss is not covered by insurance, and is not inexpensive, proper dosage can be an important consideration.

Methods:
This is a retrospective review of patients in a large HIV-specialty private practice of patients receiving finasteride in addition to various antiretrovirals.

Since serum levels of finasteride are not easily available, the effect of the drug interaction was evaluated by measuring the end effect: serum levels of testosterone and dihydrotestosterone.

Since finasteride 5 mg is available generically in the United States (for the treatment of prostatic hypertrophy) and is significantly less expensive than brand-name Propecia (finasteride 1 mg), most patients in this study actually took one quarter of a 5 mg tablet (approximately 1.25 mg) daily.

The target level of DHT to inhibit hair loss is not well defined; in the clinical trials of finasteride for hair loss efficacy was measured by hair counts, not drug or hormone levels. Since the lower limit of “normal” levels for DHT is 40 pg/dL, a value half of this, <20 pg/ml, was chosen as the target level for the effect of finasteride. A level of <15 pg/ml is probably even preferable. This level is consistent with the level seen in patients on finasteride not on CYP 450 active medications.

Patient Population:
Demographics:
- Age: Mean: 42, Range 28-65
- Sex: 22 Male
- Race: 20 White, 1 Black, 1 Asian
- HIV Risk: 22 Homosexual

P450-Active Concomitant medications:
Inducers: Efavirenz 9, Nevirapine 4, Etravirine 1
Inhibitors: Darunavir/ritonavir 2, Atazanavir/ritonavir 2, Unboosted atazanavir 2, Cobicistat 1

Non-p450 active: Raltegravir: 1, Dolutegravir: 1, Rilpivirine 1

Results:
All 7 patients taking p450 inhibitors had DHT levels less than 15 pg/ml (7.3-14).
Two of these patients switched to taking finasteride 1 mg every-other day. Their levels remained acceptably low at 8.3 and 12 pg/ml.

4 patients on nevirapine had acceptable levels <15 pg/ml (6.5-14).
One patient switched to rilpivirine (which does not inhibit or induce p450). His DHT level was unchanged at 12 pg/ml before and after.

1 patient on etravirine had a level of 27 pg/ml. With increase of the dose to 2 mg/day the DHT came down to 17 pg/ml.
Of the 9 patients on efavirenz, 4 had high levels (20-26 μg/ml) and 5 had low levels (6.9-15 pg/ml). The reason for this dichotomy is uncertain, but may be related to genetic differences in p450 activity.
Two of these patients with low DHT had switched from an unboosted integrase inhibitor to efavirenz. Neither had a significant change in DHT after the switch.
2 efavirenz patients with high levels patients increased their finasteride dose to 2 mg/day and had subsequent reduction of DHT to 14 and 17 pg/ml.

Conclusions / Recommendations:
This is a small observational study, and clearly significantly more data, including formal pharmacokinetic evaluations, are needed in order to make definitive recommendations. This is unlikely to ever happen.

However, CYP p450 inhibitors (ritonavir, atazanavir, cobicistat) appear to significantly increase the effect of finasteride, and a lower dose (0.5 mg/day or 1 mg every other day) is likely to provide sufficient suppression of DHT conversion.

The effect of p450 inducers is more variable, but in some individuals the standard dose of 1 mg finasteride does not sufficiently lower DHT levels.
For patients taking efavirenz or etravirine either checking DHT/T levels, or an empiric increase in dose to 2 mg finasteride/day should be considered. Nevirapine, a less potent p450 inducer, does not appear to have a significant effect on DHT levels.

Monitoring of DHT/T levels, if available, is appropriate for any patient taking finasteride along with CYP 450 inducers or inhibitors.
Efavirenz (EFV) is the preferred nonnucleoside reverse transcriptase inhibitor component of the ARV regimen in HIVTB patients. Concomitant use of EFV with rifampicin (RIF), an important component of firstline tuberculosis treatment, induces various hepatic cytochrome P450 enzymes and is known to decrease EFV plasma concentrations in healthy volunteers and HIV1 patients and EFV plasma concentrations below 1,000 μg/mL have been associated with an increased risk of virological failure. Moreover, previous studies have shown that interindividual variability in EFV plasma concentrations are associated with the presence of allelic variants in CYP2B6 gene. Carriers of the T allele of polymorphism 516 G>T are reported to be associated with slower EFV oral clearance.

**OBJECTIVE**

The aim of our study was to determine the influence of CYP2B6 genotype in EFV levels in HIV patients with TB treated with RF.

**PATIENTS AND METHOD**

Four HIV patients who started ARV treatment concomitantly with TB treatment were analyzed. These patients started a regimen based on EFV at doses higher than standard due to RIF interaction. Viral load, CD4+ cell count and plasma levels of EFV in plasma were measured at each visit, and genotyping for CYP2B6 (516G>T) polymorphism were performed. The self-reported rates of adherence to HAART were very high.

**RESULTS**

Patient 1, who had TT genotype, required progressive dose reduction by toxic levels (Cmin: 20 μg/mL) and effects on the central nervous system. Dose was adjusted to 600 mg qd despite treatment with RIF, and he required even lower doses after completion of TB treatment, 400 mg qd.

Patients 2 and 3, with no mutated genotype (GG) required dose escalation up to 1000 mg qd to achieve minimum recommended EFV concentrations between 1 and 4 μg/mL. All of them achieved virological suppression at six months.

The fourth patient, who had no mutated genotype, required dose increases for several months until dose adjustment. He needed 1600 mg qd during treatment with RIF. He presented virological failure, likely to maintain infratherapeutic levels of EFV for several months.

**CONCLUSIONS**

Our study shows that the variability in EFV pharmacokinetic behaviour justifies the use of therapeutic drug monitoring (TDM) in situations in which there are potential interactions with other drug. Also, it is recommended to know CYP2B6 genotype in patients receiving HIVTB to predict their metabolizing behaviour. TDM in clinical practise continues to be the best tool for optimizing the dosing of EFV.