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Serotonin syndrome following drug–drug interactions and CYP2D6 and CYP2C19 genetic polymorphisms in an HIV-infected patient

Potential pharmacokinetic drug–drug interactions (DDIs) between anti-HIV drugs and antidepressants have been studied mainly in healthy human volunteers. However, it is difficult to demonstrate their clinical significance and, despite known DDI, no guidance on how to adjust antidepressant doses in HIV-infected patients on antiretroviral treatment is available. Some evidence suggests that these patients are at heightened risk of developing serotonin syndrome [1]. We describe the case of a patient who presented a serotonin syndrome resulting from pharmacokinetic DDI between the selective serotonin re-uptake inhibitor escitalopram and recently introduced darunavir/ritonavir combination and proton pump inhibitor (PPI) esomeprazole. This 46-year-old woman, HIV–hepatitis C virus co-infected and with child C cirrhosis, was hospitalized on 12 April 2012 for spontaneous bacterial peritonitis and evaluation of hepatic transplantation. She also suffered from a depressive disorder treated with escitalopram 10 mg b.i.d. for 5 years. She had received various antiretroviral combinations since 1995 due to several toxicities and resistance to multiple agents. Since 25 April, the newly initiated treatment included darunavir 600 mg b.i.d., ritonavir 100 mg b.i.d. and emtricitabine/tenofovir 200/245 mg q.d. Three days earlier, esomeprazole 40 mg q.d. was introduced for symptoms of gastro-esophageal reflux. On 29 April, the patient presents with nausea and confusion. Physical examination shows diaphoresis, mydriasis, myoclonus, deep tendon hyper-reflexia and rigidity. A serotonin syndrome was suspected and escitalopram treatment discontinued. A favorable outcome was observed after 24 h of observation.

Clinical investigations included escitalopram serum level measurements, cytochromes P450 (CYP), 2D6 and 2C19 genotyping [2], and CYP3A4/5, 2D6 and 2C19 phenotyping using a cocktail approach and metabolic ratio calculations [3–5]. Indeed, the formation of S-demethylcitalopram, the lesser active metabolite of escitalopram, is catalyzed predominantly by CYP2C19 and 3A4 and to a lesser extent by CYP2D6 [6], whose activity is known to be modulated by DDI and/or genetic polymorphisms [7].

Twelve hours after the patient received the last dose of escitalopram, the serum level of escitalopram was highly elevated at 695 nmol/l, as compared with expected therapeutic range of 40–250 nmol/l. Serum levels measured up to 5 days after treatment discontinuation allowed calculation of the escitalopram elimination half-life, which was estimated to be 67–69 h in our patient. In comparison to the literature data describing a mean half-life of 27–33 h [8], her half-life was therefore doubled. Escitalopram serum level measured 3 days before the introduction of esomeprazole was in the therapeutic range (52 nmol/l). The serum level measured 5 days later (2 days after the start of esomeprazole and 1 day before the new antiretroviral treatment) was already supratherapeutic (619 nmol/l).

The genotypes and phenotypes of the patient are presented in Table 1. Our patient was heterozygous for *CYP2C19* carrying one *CYP2C19*2*-deficient allele. The measured phenotype showed a decreased CYP2C19 enzyme activity resulting from the presence of the deficient allele in conjunction with CYP2C19 potent inhibition by esomeprazole [9,10]. Concerning *CYP2D6*, our patient was heterozygous for two deficient alleles: *CYP2D6*5*, corresponding to *CYP2D6* deletion, and *CYP2D6*10*, resulting in decreased activity. Therefore, the predicted *CYP2D6* phenotype was a poor metabolizer, which was confirmed *in vivo* by phenotype measurement. Phenotyping of CYP3A4/5 showed a decreased enzyme activity, which is explained by potent and irreversible CYP3A inhibition by both ritonavir [11,12] and darunavir [13].

The unusual response of this patient to therapeutic doses of escitalopram is thus explained by both drug inhibition of CYP2C19 and CYP3A4, as well as *CYP2C19* and

Table 1. Genotype and phenotype results of cytochrome P450.

Isoenzyme	Genotype	Predicted phenotype	Metabolic ratio	Measured phenotype
CYP1A2	NA	NA	0.068	Extensive metabolizer
CYP2C9	**1/*1*	Extensive metabolizer	0.065	Extensive metabolizer
CYP2C19	**1/*2*	Extensive or intermediate metabolizer	5.9	Poor metabolizer
CYP2D6	**5/*10*	Poor metabolizer	0.3	Poor metabolizer
CYP3A4/5	NA	NA	0.9	Reduced activity

NA, not applicable.

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CYP2D6 genetic polymorphisms. The presence of a variant allele could predispose to a pharmacokinetic interaction, as already shown with the warfarine–simvastatine interaction [14].

The serotonin syndrome is a potentially life-threatening adverse drug reaction resulting from an excess serotonergic agonism of central and peripheral serotonergic receptors [15]. The typical clinical features of serotonin syndrome are a triad of neuromuscular hyperactivity (tremor, myoclonus, hyper-reflexia), autonomic hyperactivity (diaphoresis, fever, tachycardia, tachypnea, mydriasis) and altered mental status (agitation, confusion) [16]. Tachycardia, hypertension and hyperthermia were absent in our patient.

In conclusion, as illustrated by the present case, clinically relevant DDIs have become a major issue in HIV patients [17]. Relevant DDIs involve frequently prescribed drugs such as PPI. In our case, recently introduced esomeprazole and darunavir/ritonavir blocked all metabolic pathways involved in escitalopram elimination. CYP450 phenotyping confirmed decreased activities of CYP2C19, CYP2D6 and CYP3A4, resulting in a prolonged (two to three times) elimination half-life of escitalopram and a considerable serum level increase (twelve times). In the absence of routine marker of CYP450 activity, the prescription of CYP2C19 and CYP3A4 substrate antidepressants (e.g. citalopram, imipramine, sertraline) [18] needs to be closely monitored in HIV-infected patients on antiretroviral and PPI treatment.

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Undiagnosed HIV prevalence in France: no evidence against universal HIV screening

Recently, Crémieux *et al.* [1] attempted to estimate undiagnosed HIV prevalence in France using data from a nontargeted screening survey in emergency departments of the metropolitan region of Paris. We would like to raise two points about the conclusion and assumptions of this article.

First, the authors' conclusion does not represent the findings. They estimated undiagnosed HIV prevalence at 0.09% [95% confidence interval (CI): 0.04–0.13%] and concluded that the undiagnosed HIV prevalence was below the 0.10% threshold suggested by health authorities for implementing universal screening. However, as the 95% CI includes the value 0.10%, the difference between the threshold value and their estimated mean of undiagnosed HIV prevalence is not statistically significant. The undiagnosed HIV prevalence would be significantly below the 0.10% threshold if the upper bound of the 95% CI was below 0.10%.

Second, there are inconsistencies in the authors' assumptions. In their most recent article [1], the authors used standardization techniques to estimate the undiagnosed HIV prevalence. These techniques are used to reduce the bias in the sampling frame. However, these techniques do not appear to be justified. In a previous article [2], in which the results from their screening survey were first described, the authors claimed that their sample was representative for the French population and obtained 0.14% [95% CI: 0.08–0.22%] for the undiagnosed HIV prevalence.

The majority of new HIV transmissions are believed to originate from individuals who are unaware of their HIV infection [3]. To reduce the pool of individuals living with undiagnosed HIV infection, many countries plan to revise, or have recently revised, their HIV-screening guidelines [4–7]. Before implementing new screening strategies, it is necessary to obtain estimates on how many people are living with undiagnosed HIV infection. Therefore, providing accurate and reliable estimates of the undiagnosed HIV prevalence is essential. Crémieux *et al.* [1] provide no compelling evidence against the implementation of universal screening in the area the most affected by the HIV epidemic in France. Further studies are needed to evaluate the prevalence of undiagnosed HIV infection in France and whether universal testing should be promoted.

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Undiagnosed HIV prevalence in France: universal HIV screening should definitely be questioned

Supervie and Costagliola [1] comments suggest first that our conclusion is not in accordance with our analysis. Our estimated 0.09% undiagnosed HIV prevalence is below the 0.10% threshold suggested by health authorities for implementing universal screening. We agree that this difference is not statistically significant. However, that value, obtained in the most affected area in France, combined with the fact that undiagnosed infections were

Table 1. Characteristics of patients HIV tested in Emergency Departments and completing questionnaires compared with a reference general population.

Variable	ED-tested patients ($n = 11\,356$)[a]	General population[b] (%)
Sex		(1)[b]
Female	5428 (47.8) [46.9–48.7]	51
Male	5928 (52.2) [51.3–53.1]	49
Country of birth		(1)[b]
France	8666 (76.3) [75.5–77.1]	73.8
Born abroad	2690 (23.7) [22.9–24.5]	26.2
In sub-Saharan Africa	898 (7.9) [7.4–8.4]	6.6
Previous HIV test reported		(1)[b]
No	4860 (42.8) [41.8–43.7]	48.2
Yes in the past 5 years	4508 (39.7) [38.8–40.6]	29.6
Yes more than 5 years ago	1988 (17.5) [16.8–18.2]	22.2
Self-perceived HIV risk versus general population		(2)[b]
More risk	545 (4.8) [4.4–5.2]	4
The same risk	3562 (31.4) [30.5–32.2]	39.4
Less risk	2522 (22.2) [21.4–23.0]	42.2
No risk	2044 (18.0) [17.2–18.7]	14.4
Do not know	2683 (23.6) [22.8–24.5]	–[c]
More than one sexual partner during last 12 months		(3)[b]
Among women	961 (17.7) [16.7–18.8]	13.8
Among men	1334 (22.5) [21.4–23.6]	22.1
Same-sex partner		(3)[b]
Among women	227 (4.2) [3.6–4.7]	4
Among men	268 (4.5) [3.9–5.1]	4.1%

ED, emergency department.
[a]Multiple imputation was used to estimate missing data from the questionnaires. Values are expressed as *n* (%) [95% confidence interval].
[b]Reference data for the metropolitan Paris region population was taken from three sources: French national population census of 2006, Knowledge, Attitudes, Behaviors and Practice relating to AIDS in France (2004), Context of Sexuality in France (2004).
[c]This response was not available in the questionnaire used to obtain the reference data.

only found in high-risk groups,' amply justifies our conclusion that a 'universal testing strategy should be questioned in France'.

A second remark states that, in a previous study [2], we claimed that the Emergency Department (ED) tested population was representative of the French population. That is a misinterpretation. We clearly mentioned that those two populations differed by over-representations of foreign-born people (particularly sub-Saharan Africans), women with more than 1 sexual partner during the last 12 months and more frequent HIV screening among the ED-tested population (see Table 1, p. 14) [2]. Thus, ED-undiagnosed HIV prevalence could not be considered the same as that of the general population. That situation then led us to estimate the general population prevalence with a calibration method [3]. Such a method is not applied to reduce bias in the sampling frame, as Supervie and Costagliola [1] claim, but to decrease the variance of estimators through the use of auxiliary information, which could not initially be taken into account in the design of the survey [4]. Our analysis used socio-demographic data, for example, sex and age from a population census, to perform a poststratification (also called standardization) and included data on sexual orientation and country of birth, which could not be crossed with all the other variables, and thus required a raking ratio method [5].

We thank Supervie and Costagliola [1] for giving us the opportunity to provide more details on the calibration method used, which, along with the management of missing data through multiple imputations allowed us to obtain an accurate and reliable estimate of the undiagnosed-HIV prevalence in the general population.

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Raltegravir in the prevention of mother-to-child transmission of HIV-1: effective transplacental transfer and delayed plasma clearance observed in preterm neonates

HIV infection may be associated with an increased risk of preterm labour [1], and preterm neonates are at an increased risk of acquiring HIV congenitally [2]. Absorption of orally administered drugs in preterm neonates is unpredictable due to gastrointestinal tract immaturity, and parenteral antiretroviral options are also limited [3]. The HIV-1 integrase inhibitor, raltegravir (RGV), has rapid antiretroviral activity with shorter times to achieving virological suppression when used in combination treatments compared with conventional combination antiretroviral therapy (ART) [4,5]. RGV has a favourable pharmacokinetic profile with a terminal elimination half-life of between 7 and 12 h and a time to steady state of approximately 2 days [6]. It is eliminated by glucuronidation in the liver by human UGT1A1 [6] and much of the RGV glucuronide metabolite is eventually excreted in bile (approximately 50%) or in urine (31%) [6].

Although unlicensed in pregnancy, RGV has been used in patients who present late in pregnancy with high HIV-1 viral loads when it is critical to reduce the viral load to undetectable levels before delivery [7]. We have previously demonstrated effective RGV transplacental transfer and persistence of therapeutic drug concentrations in neonates for several days after delivery in mothers with HIV-1 resistant to protease, nucleoside/nucleotide and nonnucleoside inhibitors [8].

We describe three cases of preterm delivery in which RGV was used in the prevention of mother-to-child transmission (PMTCT) of HIV-1. Paired blood samples were taken from the mother and baby as close to delivery as possible and subsequently postpartum. RGV plasma concentrations (RPC) were measured using liquid chromatography with tandem mass spectrometric detection. Maternal HIV-1 viral load was monitored regularly until delivery and neonates were assessed for HIV-1 infection by HIV-1 DNA PCR at 0, 6 and 12 weeks (Roche Taqman 2.0 assay).

Cases are summarized in Table 1. The mother in case 1 was a 24-year-old Rwandan lady who had been diagnosed with HIV-1 infection 10 years previously. She had a long history of poor adherence to ART and was known to have had K103N and M184V resistance mutations previously detected, as well as intolerance to ritonavir at pharmacoenhancing doses. This was her sixth unplanned pregnancy, and all her previous pregnancies had been obstetrically complicated. The mother in case 2 was 32 years old, from Ghana, and in her first pregnancy. She was newly diagnosed with HIV-1, having tested positive through routine antenatal screening, and was having difficulty accepting the diagnosis. She was poorly adherent to ART and her viral load never became undetectable. Her viral load was unknown when she presented at the time of delivery. The mother in case 3 was 32 years old, from Uganda and also in her first pregnancy. She had been diagnosed with HIV-1 3 years previously but had never previously received ART. She was started on combination ART in the second trimester of pregnancy and was fully adherent with a suppressed HIV viral load. All babies received 4 weeks of ART postpartum and have tested HIV negative by DNA PCR to date with no apparent adverse reactions.

Therapeutic RPC ($\geq$15 ng/ml) were achieved in all mothers and in all babies at both sampling times, despite RGV being initiated 22.5 and 14 h prior to delivery in two cases. RPC can remain at therapeutic levels for up to 5 days in preterm neonates, longer than babies born at

Table 1. Summary of cases.

	Case 1		Case 2		Case 3	
Optimized background regimen	Tenofovir, atazanavir		Truvada, atazanavir/ritonavir		Truvada, efavirenz	
Other ART at delivery	IV AZT		Nevirapine + IV AZT		Nevirapine + IV AZT	
Obstetric complications	Preeclampsia, placenta praevia, SGA		SGA		Spontaneous rupture of membranes: multiple fibroids	
VL at RGV initiation	5030		100		<40	
RGV started	22 weeks gestation		14 h before delivery*		22.5 h before delivery	
Mode of delivery	ELSCS		ELSCS		ELSCS	
Gestation at delivery (weeks)	33 + 2		30 + 3		29 + 5	
VL at delivery	<40		55		<40	
Neonatal birthweight (g)	1510		920		1365	
Maternal RPC (ng/ml)	2318		64		300	
Time after maternal dose/after delivery (h)	6/0		3/1		10.5/0	
Neonate RPC (ng/ml)	3781	312	120	67	602	–*
Time after maternal dose /after delivery (h)	7/1	98/92	4/2	65/63	11/0.5	–*

ART, antiretroviral therapy; AZT, zidovudine; ELSCS, Emergency Lower Segment Caesarean Section; RGV, raltegravir; RPC, Raltegravir plasma concentrations; SGA, small for gestational age; VL, HIV-1 Viral load (copies/ml).
*Repeat raltegravir dose omitted due to advanced labour and obstetric complications.

term [8], probably reflecting immature UGT1A1-mediated glucuronidation.

The use of RGV preloading in pregnancy for HIV PMTCT in preterm neonates may thus have added benefits above rapidly reducing maternal viral load by having a similar role to nevirapine [9] or double-dose tenofovir [10] for preloading preterm neonates who cannot take or absorb oral drugs poorly and for whom parenteral options are limited. In this small series, RGV levels in the mothers and neonates who commenced RGV with the aim of preloading the baby were much lower than in the mother who was on established treatment and had presumably reached steady state. The use of a dose of 800 mg should be explored for rapidly preloading premature infants. Larger studies are needed to further characterize the pharmacokinetics of RGV in pregnant women and neonates.

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