

Letters to the Editor

Pharmacokinetic Variability Caused by Gender: Do Women Have Higher Indinavir Exposure Than Men?

To the Editor: The pharmacokinetics of HIV-protease inhibitors are characterized by high interpatient variability. This variability can be explained by many factors, including drug-drug interactions, impaired absorption caused by either presence or absence of food, and patient-related factors. Gender may be one of these factors, as it is well known that large differences can exist in the way men and women metabolize drugs (1,2). So far, little attention has been paid to the possibility of gender being a relevant determinant of interpatient variability of HIV-protease inhibitor pharmacokinetics. For example, the product monograph of indinavir (Crixivan; Merck & Co., Rahway, NJ, U.S.A.) mentions only that no influence of gender has been noted on indinavir pharmacokinetics (3), despite data from pre-clinical research indicating that indinavir displays sex-dependent pharmacokinetics (4). We have reviewed indinavir plasma concentrations in HIV-infected women and compared them with indinavir concentrations in a control group of men.

The Department of Clinical Pharmacy at the University Medical Centre Nijmegen is a national referral center for therapeutic drug monitoring of indinavir in The Netherlands. From our database we selected all female patients who were using indinavir. Other information collected included age, body weight, dose regimen, indication for drug level monitoring, and indinavir plasma concentration. Individual plasma concentrations of patients using 800 mg of indinavir every 8 h were compared with the time-adjusted plasma concentration values in a population of 14 HIV-infected patients (12 male, 2 female) from whom an 8-hour pharmacokinetic curve was recorded after observed intake. The ratio of the individual value versus the population value is called the indinavir concentration ratio (CR). The pharmacokinetic parameters of the population curve (AUC, C_{max} , C_{min}) are comparable with literature data of 800 mg of indinavir (19.1 mg/L per hour, 8.7 mg/L, and 0.13 mg/L, respectively (3)). A control group of 94 men was chosen by randomly selecting indinavir plasma samples that were received at the same day of the samples from the female group. Differences between women and men were tested for significance by Mann-Whitney *U* test or the two-sample proportion test.

A total of 380 samples from 220 female patients was available for analysis. Out of this group, 227 samples came from patients using 800 mg of indinavir every 8 hours. The median CR of indinavir in these samples was 1.18 (interquartile range: 0.65-1.89), with 58.8% of the samples having an indinavir CR >1.00. In the control group of 94 men, 61 samples came from patients using indinavir 800 mg every 8 hours. The median CR of indinavir in these samples was 0.96 (interquartile range: 0.60-1.70) with 47.4% of the samples having an indinavir CR >1.00. The difference in the indinavir CRs between men and women is not significant ($p = .19$), suggesting no

difference in indinavir pharmacokinetics between men and women.

However, some additional comments can be made. First, "intoxication" was noted as an indication for drug level monitoring in 17.4% of the women versus 6.6% of the men ($p = .03$). Second, a dose reduction of indinavir to 600 or 400 mg every 8 hours after a diagnosis of indinavir-related side effects was applied in 9.7% of the female patients versus 1.1% of the male patients ($p < .01$). Finally, the proportion of patients with an indinavir CR >2.0, which has been associated with an increased risk of urologic complaints (5), was higher in women than in men (21.3% vs. 13.1%, $p = .15$).

These data indicate that women, as a group, have roughly similar pharmacokinetic parameters of indinavir compared with men, which is in agreement with the product labeling (3), but that a subgroup of 10% to 20% of the women may have substantially elevated indinavir plasma concentrations. Gender-related differences in pharmacokinetics can be attributed to metabolic variations in cytochrome P450 enzymes, protein binding, and body weight or composition (1). Even though the women in our data set had a lower median body weight than the men (63 vs. 75 kg), no relationship between low body weight and increased indinavir exposure was found.

Recently, similar relationships between gender and pharmacokinetics were reported for verapamil, which, like indinavir, is a cytochrome P450 and P-glycoprotein substrate (6). Elevated drug concentrations result in a higher risk for side effects. Several recent cohort studies have confirmed this higher incidence of side effects in women versus men (7,8). Our data suggest that women who experience indinavir-related toxicity may benefit from dose reduction, under the guidance of therapeutic drug monitoring.

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Multidrug-Resistant HIV-1 RNA and Proviral DNA Variants Harboring New Dipeptide Insertions in the Reverse Transcriptase *pol* Gene

To the Editor: Selection of drug-resistant HIV-1 mutants is a major cause of antiretroviral treatment failure. Resistance to

HIV reverse transcriptase (RT) inhibitors usually results from base-pair (bp) substitutions leading to amino-acid replacements in the RT *pol* gene. The substitution mutation Q151M or insertion-deletion mutations conferring multidrug resistance (MDR) may occur in a minority of cases (1). MDR-related insertions generally consist of two amino-acids following the *pol* 69 RT codon (serine-glycine [S-G], serine-alanine [S-A] and serine-serine [S-S]), and are associated with high phenotypic resistance to various nucleoside RT inhibitor (NRTI) analogs (1-3). Management of patients harboring MDR variants remains challenging (1).

During year 1999, we have prospectively evaluated genotypic resistance mutations of plasma HIV-1 RNA variants in 131 NRTI-experienced patients failing antiretroviral therapy, by using the consensus procedure proposed by the French National Agency for AIDS Research (ANRS), as previously described (4). Three of these plasma viruses (2.3%) exhibited a two amino-acid insertion following the codon 69 (glutamine-glycine [E-S], valine-alanine [V-A] and valine-serine [V-S]) plus aminoacid substitution at codon 70 (K70R), in association with T215Y (patient 1) or T215F (patient 3), M184V (patient 2) or M184I (patient 3) substitutions (Table I). The three patients had a long-term history (median, 33 months) of antiretroviral

TABLE 1. Aminoacid sequences in reverse transcriptase HIV-1 *pol* gene and phenotypic resistance to reverse transcriptase inhibitors of plasma HIV-1 RNA and blood mononuclear cells HIV-1 proviral DNA, in 3 multidrug experienced patients harboring circulating HIV-1 variants with dipeptide insertions in *pol* gene

Patient	Plasma HIV-1 load (log ₁₀ copies per mL)	CD4 ⁺ T cell (per μL)	Antiviral therapy ^a			Aminoacid sequences																Other mutations in RT gene
			RTI	PI		60	61	62	63	64	65	66	67	68	69	70	71	72	73	74		
1	5.6	127	ABC NVP	NFV	HIV RNA	V	F	V ^c	I	K	K	K	D	S	S	E	S	R	W	A98G, K101Q, Y181C, G190A, T215Y A98G, K101Q, Y181C, G190A, T215Y		
					Proviral DNA	V	F	V	I	K	K	K	D	S	S	E	S	R	W			
2	4.2	231	d4T ddI		HIV RNA	V	F	V	I	K	K	K	D	S	S	V	A	R	W	M41L, M184V		
					Proviral DNA	V	F	V	I	K	K	K	D	S	S	V	A	R	W			
3	3.9	456	3TC d4T	NFV	HIV RNA	V	F	V	I	K	K	K	D	S	S	V	S	R	W	M184I, T215F		
					Proviral DNA	V	F	V	I	K	K	K	D	S	T	—	—	R	W		—	
						RVA index for drug ^{b,c}																
Patient	Sample				AZT	3TC	d4T	ddI	ABC	EFV	NVP											
1	HIV RNA/proviral DNA				>301	>619	>550	4	>400	20	>947											
2	HIV RNA/proviral DNA				>3688	>346	14.8	6	9	1	1											
3	2 lines HIV RNA and proviral DNA				>586	>619	322	40	>19	<1	<1											
					ND	ND	ND	ND	ND	ND	ND											

^a Antiretroviral therapy taken at time of resistance genotype determination. ^b Phenotypic results are expressed as RVA index determined for each drug tested: RVA index < 4 indicates phenotypic sensitivity; RVA index between 4 and 10 indicates low level of resistance; RVA index > 10 indicates high level of resistance. ^c Since the same genotypic pattern was observed in the HIV-1 RNA and DNA RT *pol* gene, the RVA indexes for plasma HIV-1 RNA and PBMC HIV-1 DNA were considered similar. ^d In *italics* are shown the aminoacids of consensus HIV-1 RT sequence of the HXB2 reference HIV-1 strain. ^e In **bold** are shown codons harboring mutated aminoacids by reference to the HXB2 H-1 strain. (—) represents aminoacid insertions. ND, not determined; RT, reverse transcriptase; RTI, reverse transcriptase inhibitor; PI, protease inhibitor; RVA, recombinant virus reverse transcriptase inhibitor sensitivity assay; PBMC, peripheral blood mononuclear cells; ABC, abacavir; EFV, efavirenz; NVP, nevirapine; NFV, nelfinavir; d4T, stavudine; ddI, didanosine; 3TC, lamivudine.