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Is There a Drug–Drug Interaction Between Darunavir/Ritonavir and Raltegravir?

To the Editors:

We have read with interest the study by Jackson et al,¹ recently published in your journal, that investigated plasma and intracellular pharmacokinetics of darunavir/ritonavir (800/100 mg once daily) and raltegravir (800 mg once and 400 mg twice daily) alone or coadministered in a group of 24 HIV-infected individuals. The authors' main conclusions were that no remarkable interactions between darunavir/ritonavir and raltegravir were observed. However, although no modification of raltegravir pharmacokinetic (PK) was observed after darunavir/ritonavir intensification, some darunavir PK parameters showed a significant change after raltegravir discontinuation. In particular, in patients taking daruna-

vir/ritonavir 800/100 mg once daily plus raltegravir 400 mg twice daily plus 2 nucleoside reverse transcriptase inhibitors (NRTIs; n = 13, group 1), significantly higher darunavir area under the curve (AUC) and C_{trough} were observed both in plasma (24% and 37% increase, respectively) and in intracellular environment (24% and 45% increase, respectively) after raltegravir removal. Moreover, raltegravir discontinuation led to a significantly higher plasma AUC (14% increase) also in patients taking darunavir/ritonavir 800/100 mg once daily plus raltegravir 800 mg once daily plus 2 NRTIs (n = 11, group 2); no changes in intracellular AUC and plasma or intracellular darunavir C_{trough} were observed in this group, but the smaller number of subjects included could have limited the statistical power to detect such differences. The authors suggested that these changes could be the consequence of the high interindividual PK variability observed in plasma and intracellular darunavir concentrations rather than a true drug–drug interaction.

On the basis of current knowledge, we believe that further evidence is required before drawing this conclusion. The issue of potential PK drug interactions between raltegravir and darunavir is debated and its clarification would be quite important for the management of HIV-infected patients. Given the different metabolic pathways of the 2 drugs,^{2,3} a drug–drug interaction would have not been predictable. However, some recently published articles^{4,5} have provided data in support of an unexpected drug–drug interaction between these 2 drugs. In a previous observational study performed during routine clinical practice,⁴ our research group observed a significantly lower plasma darunavir C_{trough} in patients taking darunavir/ritonavir 600/100 mg twice daily plus raltegravir 400 mg twice daily plus 2 NRTIs when compared with those not receiving raltegravir. In line with this, Cattaneo et al⁵ observed that coadministration of raltegravir was associated with a 40% reduction in darunavir C_{max} and estimated AUC and also a 60% increase in the estimated darunavir clearance compared with patients not receiving raltegravir. Moreover, 2 further studies found lower plasma darunavir concentrations when it

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was coadministered with raltegravir, even if these findings could also be partly related to interactions with other concomitant antiretroviral drugs (tenofovir or enfuvirtide).^{6,7} Taken together, the observations by Jackson et al and by the other aforementioned studies seem to suggest a potential drug–drug interaction between the 2 drugs.

The mechanism at the basis of this interaction remains unclear and needs adequate investigations. Darunavir is primarily metabolized by cytochrome CYP3A4, whereas raltegravir undergoes metabolism through hepatic glucuronidation; as a consequence, an influence of raltegravir on darunavir metabolism would be negligible. However, because darunavir is a substrate of p-glycoprotein and other transporters, drugs that can modulate the activities of these pumps could influence darunavir distribution and affect darunavir plasma and intracellular concentrations. Because recent studies demonstrated that raltegravir is a substrate of p-glycoprotein and a potential inducer of ABCB1,^{8,9} an interaction at this level could be hypothesized and needs to be adequately investigated. Moreover, this mechanism might also explain the unexpected but clearly documented effect of raltegravir on the PK of atazanavir,¹⁰ which is also a substrate of p-glycoprotein, like darunavir and other protease inhibitors.

Because population PK data show that plasma darunavir C_{trough} usually far exceed 0.550 $\mu\text{g/mL}$ (the IC_{50} for protease inhibitor-resistant virus)¹¹ and the reduction in darunavir levels with concomitant raltegravir appears to be modest, the clinical significance of this interaction is probably negligible in the majority of patients taking combined antiretroviral regimens. Several data seem to support this conclusion. A high efficacy of raltegravir combined to darunavir plus an optimized background therapy was demonstrated in clinical trials performed in treatment-experienced patients.¹² Moreover, a previous study showed a higher proportion of treatment-experienced patients with viral load <50 copies per milliliter when raltegravir and darunavir were coadministered, despite lower darunavir plasma levels.⁴ However, in selected clinical circumstances, such potential interaction

should be taken into consideration. In a previous study,⁶ 4 of 14 (28.6%) patients receiving a dual therapy with darunavir/ritonavir 800/100 mg once daily plus raltegravir 400 mg twice daily obtained darunavir plasma trough levels below the threshold of 0.550 $\mu\text{g/mL}$; this could be suboptimal in certain settings, like in naive subjects starting antiretroviral therapy with high viral load that could theoretically require a higher drug concentration. Interestingly, a recent single-arm AIDS Clinical Trials Group study performed in naive subjects starting antiretroviral therapy with darunavir/ritonavir 800/100 mg once daily plus raltegravir 400 mg twice daily showed unexpectedly high rates of virological failure at 48 weeks (26%) with a high rate of development of integrase resistance, particularly in patients with baseline viral load >100,000 copies per milliliter.¹³ Suboptimal adherence could be an explanation for the results of this trial, but the concomitant role of a detrimental drug interaction of raltegravir on darunavir exposure might be an alternative hypothesis. However, the potential clinical significance of a drug–drug interaction between darunavir/ritonavir and raltegravir was not confirmed by a randomized study comparing raltegravir (arm 1) or tenofovir/emtricitabine (arm 2) both in combination with darunavir/ritonavir 800/100 mg once daily in naive subjects: no significant differences in the rates of virological failure were observed between the 2 arms at 24 weeks but 48 weeks results are pending and no PK data are yet available.¹⁴ Moreover, a further large multicenter randomized trial exploring the efficacy of darunavir/ritonavir 800/100 mg once daily plus raltegravir 400 mg twice daily in naive patients is ongoing and its results will provide additional data on clinical efficacy and PK of this drug combination.¹⁵

In conclusion, in our opinion, the possibility of an unexpected drug–drug interaction between darunavir/ritonavir and raltegravir cannot be fully excluded on the basis of currently available results. Indeed, several data suggest that a certain effect of raltegravir on darunavir/ritonavir PK might exist, despite the fact that its mechanism remains to be determined. The clinical significance of this potential interaction in selected set-

tings would be clarified when long-term results of ongoing randomized clinical trials exploring this combination will become available.

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Lack of Association Between Concurrency and HIV Infection: An Artifact of Study Design

To the Editors:

Kasamba et al¹ make a common mistake in studying the association between concurrent partnerships and HIV status: they test for associations that are not predicted by the concurrency hypothesis or not appropriate given their cross-sectional study design. The former is unique to the study of concurrency and the latter reflects a failure to follow general principles of epidemiological inference. The authors have data on both partners (spouses), which is one of the requirements for estimating the impact of concurrency, but they have data on prevalent, not incident, HIV infection.

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TABLE 1. Concurrency and HIV Transmission Risk by HIV Status at Marriage

HIV Status at Marriage		Husband	
		HIV Positive	HIV Negative
Wife	HIV positive	Husband's extraspousal partnerships pose no risk of HIV transmission to wife	Husband's extraspousal partnerships pose no risk of HIV transmission to wife
	HIV negative	Wife's HIV risk linked to husband, not to his extraspousal partners	Husband at risk for acquiring HIV from concurrent extraspousal partner; creates risk of transmission to wife

Although the investigators correctly characterize the risk concurrency poses for partners, their data do not allow accurate estimation of this risk. This compromises every association they test between HIV status (of husband, wife, and couple) and the husband's extraspousal partnerships.

First, with respect to the association between a husband's concurrency in the last year and his HIV status (Tables 2 and 3 in Kasamba et al), the fundamental problem is that the concurrency hypothesis does not predict an association between husband's concurrency and his HIV status. His risk is simply a function of his cumulative number of partners and unprotected coital exposures with each. Whether his partners are concurrent or serial, his risk is the same. However, testing the association of his recent behavior with his prevalent infection is an additional problem.

Second, with respect to the association between the HIV status of the couple and the husband's concurrency, the discrepancy between the timeframes of infection and behavior is the key problem. Recent behavior (in this case, concurrency in the 12 months before the survey) may have nothing to do with a prevalent infection in one or both members of the couple because that infection that may have been contracted many years earlier.

Third, the authors test for an association between the wife's HIV status and the husband's extraspousal partnerships, and conclude "despite the hypothesis that concurrency would lead to a likelihood of transmission to sexual partners, we do not find evidence that women whose husbands report having extra-spousal partnerships are at greater risk of HIV infection." The problem is that the concurrency hypothesis does not predict this association in a cross-

sectional study, and what the hypothesis does predict—increased incidence in the husband, and then the monogamous partner—is not measured by this study. Table 1 illustrates the conditions needed for proper causal inference when using HIV prevalence here: concurrency can only be inferred as *potentially responsible* for the wife's infection when HIV prevalence is observed in a couple that began their partnership concordant negative. Even then, one would need to rule out the possibility that the wife also may have been infected from an extraspousal partnership.

Since the study did not measure the spouses' HIV status at the time of marriage, 3 of the 4 possible conditions in Table 1 confound the observed association between husbands' concurrency and wives' HIV status.

The logic of the causal chain—for a couple that begins concordant negative, the husband's additional partners directly place him at risk of infection, and subsequently place his wife at risk of potential exposure—requires a longitudinal cohort study design if one wants to estimate the individual and population level contributions of concurrency to HIV transmission. With a more appropriate design, one would still want to examine other factors that will influence the impact of one spouse's concurrency on their partner's HIV exposure (eg, whether the spouses are still having sex, the partner's concurrent extraspousal partnerships, condom use, and coital frequency).

The authors note the limitations of their cross-sectional study design in the conclusion, but they do not acknowledge that their study design makes it inappropriate to test these associations, and impossible to draw meaningful conclusions about the relationship between