Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults

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The rise in didanosine concentrations in plasma when given with tenofovir raises concern for a high risk of toxic effects. Recommendations to reduce didanosine dose have been issued, but only for adults weighing more than 60 kg. We reviewed cases of pancreatitis in patients receiving didanosine plus tenofovir, didanosine alone, and tenofovir alone to assess the incidence of and risk factors for pancreatitis. Between Aug 1, 2001, and Nov 30, 2003, five of 185 (2.7%) patients receiving didanosine plus tenofovir, one of 182 (0.5%) on didanosine without tenofovir, and none of 208 on tenofovir alone developed pancreatitis (p=0.016). Co-administration of both drugs versus each of them individually was an independent risk factor for pancreatitis (crude hazard ratio 10.666, 95% CI 1.246–91.294, p=0.031). These results suggest that the risk of pancreatitis is heightened when didanosine and tenofovir are given together.

Simple regimens with few toxic effects are needed to maintain long-term success of antiretroviral treatment. Co-administration of didanosine and tenofovir has gained popularity because both can be taken as single pills, once daily, without food restrictions. An early pharmacokinetic study of the co-administration of these drugs reported a 40% rise in didanosine plasma concentrations, which has raised concern over potential high risk of didanosine toxic effects. However, the clinical significance of this pharmacokinetic effect is not known because intracellular didanosine concentrations do not always correlate with plasma concentrations.

Data from two 24-week placebo-controlled tenofovir trials, which included 197 patients receiving didanosine, have been assessed. Comparisons of toxic effects between groups receiving didanosine plus tenofovir, and didanosine plus placebo, showed no difference in the frequency of pancreatitis. However, cases of severe pancreatitis, with didanosine and tenofovir given together, have been reported. Findings of a pharmacokinetic investigation of reduced daily dose of didanosine in combination with tenofovir (300 mg), showed that didanosine (250 or 200 mg) given with food resulted in didanosine exposures similar to that of didanosine (400 or 250 mg) given alone with no food.

Many clinicians use these results in clinical practice, whereas others continue to use standard didanosine doses. Because we noticed several cases of pancreatitis in HIV-infected patients treated with didanosine plus tenofovir we decided to review cases of pancreatitis in patients receiving didanosine plus tenofovir, didanosine alone, and tenofovir alone to assess the incidence of and risk factors for pancreatitis, and the effect of these treatments on serum lipase and amylase concentrations.

Tenofovir was first used in our HIV clinic in August, 2001. By Nov 30, 2003, 575 patients had received either didanosine plus tenofovir, didanosine alone, or tenofovir alone for at least a week, as part of their antiretroviral regimens (table). Patients treated with didanosine plus tenofovir who weighed more than 60 kg (n=123) received didanosine 400 mg (n=43, 35%), 250 mg (n=78, 63%), or 200 mg (n=2, 2%), and those weighing 60 kg or less (n=62) received didanosine 400 mg (n=5, 8%), 250 mg (n=48, 77%), and 200 mg (n=9, 15%). For those treated with didanosine alone, the dose was adjusted for weight. Five (2.7%) patients given didanosine plus tenofovir, and one (0.5%) given didanosine alone developed pancreatitis after a median follow-up (IQR) of 22 (12–24) weeks. Symptoms were acute and included nausea, vomiting, and abdominal pain. These patients had neither history of previous pancreatitis, nor any apparent predisposing factor, with the exception of stable, mild hypertriglyceridaemia (<4 g/L) in one patient. All six patients with symptomatic pancreatitis were women, without renal impairment, weighing between 47 and 56 kg, and they had been given either 250 mg or 400 mg of didanosine. Other concurrent treatments in patients with pancreatitis included lopinavir plus ritonavir (n=1), lamivudine (2), and...
efavirenz (2) for those treated with didanosine plus tenofovir; and lamivudine plus nevirapine for the patient given didanosine alone. Pancreatobiliary imaging was normal and all patients recovered after stopping antiretroviral treatment. We noted no other didanosine-related clinical complications, such as polyneuropathy or lactic acidosis. Plasma lactate concentration was normal in two of the six patients in whom it was measured.

Baseline characteristics including sex, age, weight, CD4 cell count, plasma HIV-1 RNA, amylase, and lipase were similar in the three treatment groups (data not shown). There were substantial differences between patients with and without pancreatitis in nucleosides used, sex; and baseline weight, CD4 count (cells per \( \mu \text{L} \)), and amylase (table). Since pancreatitis did not develop in men, in patients who weighed more than 60 kg, or those given tenofovir alone, these variables were excluded from the multivariate analysis. Multivariate analysis of baseline values of CD4 cell count, HIV-1 RNA, amylase, and lipase showed that the only independent risk factor for pancreatitis was the number of CD4 cells per \( \mu \text{L} \) (crude hazard ratio 0·992 per unit increase, 95% CI 0·985–0·999, p=0·032). Multivariate analysis including patients taking didanosine alone and tenofovir alone, and grouped together, suggested that didanosine plus tenofovir was an independent factor for development of pancreatitis (crude hazard ratio 10·666, 95% CI 1·246–91·294, p=0·031).

Incidence (cases per 100 person-years, 95% CI) of pancreatitis in the overall population was 0·9 (0·4–2·0), whereas in those patients on didanosine plus tenofovir it was 2·3 (1·0–5·6), in those on didanosine without tenofovir it was 0·5 (0·1–3·3), and in those on tenofovir without didanosine it was 0 (0–1·6). The incidence in women was 4·0 (1·8–8·9), and in men it was 0 (0–0·7). The incidence in people weighing 60 kg or less (n=179) was 2·9 (1·3–6·5), and in those greater than 60 kg (n=396) it was 0 (0–0·8). By didanosine dose, the incidence in patients on didanosine 400 mg daily was 0·4 (0·1–2·9), in those on 250 mg daily it was 2·9 (1·2–6·9), and in those on 200 mg daily it was 0 (0–0·8).

In patients receiving didanosine plus tenofovir, the incidence of pancreatitis in those weighing 60 kg or less...
(n=62) was 7.3 (3.0–17.4), in women (n=37) it was 10.9 (4.5–26.2), and in women weighing 60 kg or less (n=31) it was 13.3 (5.6–32.1).

Although amylase and lipase concentrations remained within normal ranges (<400 U/L and <200 U/L, respectively) in most patients, both enzymes were higher after patients were given didanosine plus tenofovir than with didanosine alone or tenofovir alone (figure). In patients given didanosine plus tenofovir, lipase was paradoxically higher in those who had daily didanosine doses of either 250 mg or 200 mg than in those given 400 mg (figure). Increased concentrations of amylase or lipase, above the normal range, either at baseline or at 3 months were not predictive of clinical pancreatitis.

The present didanosine summary of product characteristics (February, 2003) suggests that appropriate doses for the combination of didanosine and tenofovir, with respect to effectiveness and safety, have not been established. The tenofovir summary of product characteristics was revised in August, 2003, to include a dose recommendation of 250 mg didanosine when co-administered with tenofovir in adults weighing more than 60 kg, although it notes that there are no available data to recommend didanosine dose adjustments for patients weighing less than 60 kg. Our data suggest that didanosine, even at a dose of 250 mg daily, when given with tenofovir is associated with increased risk of pancreatitis, especially in women weighing 60 kg or less.

Conflict of interest statement
E Martinez has received research grants from Abbott, Bristol-Myers Squibb, and Gilead Sciences. J Mallolas has received research grants from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, GlaxoSmithKline, MSD, Roche, and Schering-Plough. J M Miró has received research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Chiron, Gilead Sciences, Pfizer, Roche, and IDIBAPS-Hospital Clinic, Barcelona, Spain. José M Gatell has received research grants from Bristol-Myers Squibb, MSD, GlaxoSmithKline, Gilead Sciences, Tibotec, Roche, and Boehringer-Ingelheim. E Martínez, J Mallolas, J M Miró, and José M Gatell have received honoraria for speaking for and participation in advisory boards. Ana Milinkovic, Elisa de Lazari, Giovanni Ravasi, José I Blanco, Maria Larrousse, and Felipe García have no potential conflicts of interest.

Acknowledgments
This study was supported in part by grants PI02590 from Fondo de Investigaciones Sanitarias and RIS G03/173 from Red Temática Cooperativa de Investigación en SIDA, Ministerio de Sanidad y Consumo, Spain. The funding sources had no role in the study design, data collection, data analysis, data interpretation, and writing of the report.

References

Contributors
E Martínez and A Milinkovic conceived and designed the study, participated in the analysis, and drafted the manuscript; both authors contributed equally to the study. E de Lazari undertook the statistical analyses and participated in manuscript preparation. G Ravasi, J L Blanco, M Larrousse, J Mallolas, F García, and J M Miró contributed to study design and data management. J M Gatell participated in study analyses and manuscript preparation.


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