Minimal Removal of Dolutegravir by Hemodialysis in HIV-Infected Patients

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SUMMARY
Data on dolutegravir removal by hemodialysis are lacking. To study this, we measured dolutegravir plasma concentrations in samples of blood entering and leaving the dialyzer, and resulting dialysate from 5 HIV-infected patients with end-stage renal disease. Median dolutegravir hemodialysis extraction ratio was 7%. Dolutegravir concentrations after the dialysis session remained above the protein-binding-adjusted inhibitory concentration. Our results show minimal dolutegravir removal by hemodialysis with no specific dolutegravir dosage adjustment required in this setting.

BACKGROUND & OBJECTIVE
Chronic kidney disease may be considered epidemic among HIV-infected patients, and the number of patients with end-stage renal disease (ESRD) requiring hemodialysis as renal replacement therapy is increasing.

HIV drugs differ in the extent of their removal from blood by hemodialysis, and specific dosing recommendations may be required. Although no dolutegravir dosage adjustment is necessary for patients with creatinine clearance <30 ml/min, little is known about dolutegravir removal from plasma by hemodialysis.

Our objective was to evaluate the effect of hemodialysis on dolutegravir concentrations in HIV+ patients with ESRD.

METHODS
Single-centre, open-label, pilot study in HIV-infected patients with ESRD undergoing routine hemodialysis.

After enrollment (day 1), dolutegravir (Tivicay, Viiv Healthcare) 50 mg once daily was added to cART for five days. Patients were told to take dolutegravir in the morning, separated from other drugs that could interfere with dolutegravir absorption (e.g., antacids, multivitamins, chelating agents, etc.).

On day 5, dolutegravir concentrations in plasma were determined (LC-MS/MS) in blood samples collected at each patient at the beginning (Cpre) and at the end of a dialysis session (Cpost), as well as in paired samples of blood entering (Cin) and leaving (Cout) the dialyzer, and in resulting dialysate.

The hemodialysis extraction ratio (ER) for dolutegravir was calculated as

\[ ER(\%) = \frac{C_{\text{in}} - C_{\text{out}}}{C_{\text{in}}} \times 100 \]

where \(C_{\text{in}}\) is predialyzer dolutegravir concentration (i.e., blood entering the dialyzer), and \(C_{\text{out}}\) is postdialyzer dolutegravir concentration (i.e., blood leaving the dialyzer).

Due to the high protein binding of dolutegravir, postdialyzer concentrations (Cpost) were corrected for hemococoncentration by a factor F based on total protein (TP) concentration pre- and postdialyzer: \(F = TP_{\text{pre}} / TP_{\text{post}}\).

RESULTS
Five anuric HIV-infected patients (4 men, 1 woman), undergoing routine hemodialysis (n=3) or on-line hemodiafiltration (OL-HDF, n=2) were included in the study.

Median (range) age and body weight were 53.0 (41.3-69.5) years and 77.1 (57.5-91.9) kg, respectively.

The cART regimen included boosted protease inhibitors in three participants, and non-nucleoside reverse transcriptase inhibitors in two. Additionally, four of the patients were receiving raltegravir at enrolment.

Dolutegravir was well tolerated and all participants completed the study. At the start of the dialysis session on day 5, median (range) time after the last dolutegravir dose was 5.9 (5.6-6.4) hours.

Dialysis specifications
- Conventional hemodialysis: Revaclear®400, capillary dialyzer, membrane area 1.8 m², bicarbonate cartridge Bicar® Gambro. Blood flow 300 ml/min. Dialysate flow 500 ml/min. Duration 4h.

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<th>C\text{pre} (mg/l)</th>
<th>C\text{post} (mg/l)</th>
<th>Dialysate C (mg/l)</th>
<th>ER (%)</th>
<th>C\text{pre} (mg/l)</th>
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CONCLUSIONS
The minimal extraction ratio of dolutegravir by hemodialysis coupled with dolutegravir concentrations in plasma far above the protein-binding-adjusted IC50 (0.064 mg/l) in this study support no dolutegravir dose adjustment in HIV-infected patients with ESRD undergoing hemodialysis.

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