

Transplant Drug Interactions and a Word of Caution for the HIV Provider. A Case Report

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Electronic medical record platforms fail to support provider alerts when a drug is discontinued. Protease inhibitors, often boosted by ritonavir or cobicistat, increase the serum concentration of calcineurin inhibitors. This case demonstrates acute liver transplant rejection in an HIV-positive recipient due to a failure to recognize the loss of protease inhibitor interaction with his immunosuppressive regimen.

Keywords. drug interactions; electronic medical records; HIV; transplantation.

Due to improvement in the survival rate of HIV-infected individuals, end-stage organ disease in this population is occurring more frequently. With both improved antiretroviral (ART) and antirejection therapies, organ transplantation has become the standard of care for many patients experiencing organ failure. Specifically, in the United States, more than 1500 solid organ transplantations have been performed in HIV+ recipients since 2007, including more than 300 liver transplants (based on organ procurement and transplantation network (OPTN) data as of October 20, 2017). Outcomes after liver transplantation in the HIV-infected population have been improving [1], in part due to the availability of better ART and viral hepatitis therapies. Despite this, drug interactions between ART and immunosuppressive agents remain challenging. Potential consequences can impact both HIV control and transplant survival. They include increased morbidity from drug toxicity, resurgence of HIV viremia, and inadequately dosed immunosuppression and consequent graft rejection.

We present a case of drug interaction due to a change in ART that led to significant graft rejection and describe strategies to avoid such complications. Health care providers, often assisted

by electronic prescribing tools, are experienced at checking interactions before starting new medications. However, these prescribing technologies are poor at identifying potential complications related to discontinuing medications.

CASE REPORT

A 56-year-old African American man with a 25+-year history of HIV and liver transplantation due to hepatocarcinoma 4 years prior was referred to the Transplant Infectious Diseases service for assistance with his ART regimen.

The patient had been on a stable regimen with atazanavir/ritonavir (ATV/r), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF) with a CD4 count of 402 cells/mm³ and an HIV viral load of <20 copies/mL. His immunosuppressive regimen included prednisone and tacrolimus, with a prior tacrolimus level of 5.8 mcg/L (desired range, 5–6 mcg/L) and no evidence of rejection. He had been followed by an outside HIV provider who had discontinued his ATV/r and started him on dolutegravir (DTG) due to mild hyperbilirubinemia and the desire for improved long-term efficacy with the addition of an integrase inhibitor. Two weeks later, he presented with elevated liver function tests: alkaline phosphatase 335 U/L (prior 87), AST 175 U/L (prior 20), ALT 272 U/L (prior 51); his bilirubin had fallen to 0.9 mg/dl (2.6–3.3 on ATV/r), and tacrolimus level was undetectable. Liver biopsy showed moderate acute cellular rejection. His liver function recovered after an 8-week taper of steroids and adjustment of his tacrolimus; he went from taking 1 mg every other week to 3 mg twice a day with the dolutegravir-based regimen that no longer included protease inhibitors. The electronic medical record (EMR) in the HIV clinic failed to detect the removal of the cytochrome P450 inhibition when ATV/r was discontinued. He continues on FTC/TDF/DTG with excellent viral control.

DISCUSSION

We present a case where withdrawal of a ritonavir-boosted HIV protease inhibitor led to a critical decline of tacrolimus levels in a patient with a liver transplant. Due to failure of the EMR to alert the clinician who modified the ART regimen and lack of communication between the care providers, the patient experienced acute graft rejection. After substantial readjustment of the tacrolimus dose and a steroid taper, fortunately, the patient recovered well.

Ritonavir is a well-known inhibitor of cytochrome p450 3A4 (CYP3A4) and is used to boost other protease inhibitors. The immunosuppressive drugs tacrolimus, cyclosporine, and sirolimus are widely used in solid organ transplants, and all extensively metabolize by CYP3A, so drug-drug interactions are significant [2].

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Patients with HIV who have undergone transplants are at particularly high risk for clinically significant drug interactions [3–5], and HIV providers should be vigilant in reporting any changes to medications, even discontinuations. This remains crucial as long as the patient is on a regimen with high interaction potential and is not limited to the early post-transplant period but is a lifelong commitment. Electronic prescribing tools usually linked to the EMR are now pervasive in HIV clinics. In the United States, more than 85% of office-based physicians use an EMR platform [6], mainly EPIC and Cerner [7]. These platforms fail to support provider warnings when drugs are discontinued. Strategies to avoid errors associated with drug-drug interactions include a thorough assessment of all medication and interactions, open and frequent communication between treatment team members, and ideally limiting prescriptions to 1 pharmacy.

As end organ disease becomes more common, transplantation becomes more prevalent, and transplant outcomes continue to improve, primary HIV providers need to remain actively engaged with transplant programs to minimize pharmaceutical complications due to bidirectional interactions between ART and immunosuppressants. Caution is necessary when new ART drugs are introduced *or withdrawn* from a stable regimen as more frequent monitoring of immunosuppressive drugs, specifically tacrolimus or cyclosporine, might become necessary. In the pretransplant setting, clinicians should strive to modify ART to include regimens that do not include either ritonavir or cobicistat. Providers who are less familiar with ART should have a low threshold for consulting more experienced colleagues.

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