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Successful optimization of antiretroviral regimens in treatment-experienced people living with HIV undergoing liver transplantation

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Abstract

Modern antiretroviral therapy (ART) extends life expectancy for people living with HIV (PLWH). However, most older PLWH (≥50 years) "aged" with HIV and were exposed to historical HIV care practices and older, more toxic ART. In PLWH with exposure to older and multiple ART regimens, the drug interactions between ART frequently used in treatment-experienced persons and commonly used immunosuppressants remain a significant challenge. However, the advent of newer ART classes (eg, integrase non-strand transfer inhibitors) and more advanced HIV genetic resistance testing may allow optimization of ART regimens with minimal drug interactions. Here, we present a case series of three PLWH whose complicated ART interacted (or was at risk for interacting) with their post–liver transplant immunosuppression. After a review of their proviral DNA resistance testing, they successfully transitioned onto safer integrase non-strand transfer inhibitor-containing ART regimens without viral blips or evidence of organ rejection.

Keywords

antiretroviral therapy; drug interaction; HIV; organ transplantation

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AUTHOR CONTRIBUTIONS

Georgina Waldman and Stephen Rawlings contributed equally to the manuscript in the collection of data, analysis, and writing the paper. Janice Kerr Sudaria, Irene Vodkin, Saima Aslam, Cathy Logan, Jennifer Dan, Sanjay Mehta, and Lucas Hill all contributed to data analysis and editing the paper. Maile Young Karris was a senior author and conceived the concept for the paper, contributed to analysis, and reviewed/edited the paper.

CONFLIC T OF INTEREST

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1 | INTRODUCTION

Cases of transplantation of solid organs into people living with HIV (PLWH) have been reported since the beginning of the epidemic.[1] Modern antiretroviral therapy (ART) provides PLWH the opportunity to live near-normal life spans; thus, non–HIV-related organ dysfunction in PLWH (eg, kidney failure, end-stage liver disease) may require solid organ transplantation. In addition, liver transplantation in recent years has also been associated with a survival benefit for HIV-infected liver recipients with a Model for End-Stage Liver Disease (MELD) ≥15.[2] Donors with HIV are now being considered through the HIV Organ Policy Equity (HOPE) Act, with 25 centers currently enrolled to permit HIV-seropositive to HIV-seropositive organ transplantation.[3–5] However, many transplant centers still do not offer organ transplantation to PLWH because of the increased medical complexity of such cases.

Calcineurin inhibitors (CNIs; eg, tacrolimus, cyclosporine) are an integral component of current immunosuppressive regimens for SOT recipients. However, CNIs are subject to many clinically significant drug interactions that require close therapeutic drug monitoring to prevent both toxicity and rejection. This is particularly relevant in patients receiving ART, as many potential drug-drug interactions exist between immunosuppressant drugs and antiretrovirals.[6] Calcineurin inhibitors such as tacrolimus are metabolized by cytokine P450 (CYP450) enzymes 3A4 and 3A5, and are substrates of P-glycoprotein (P-GP).[7,8] These metabolic pathways are commonly the reason for drug interactions; medications may compete for these binding sites or may inhibit or induce medication clearance through these pathways (see Table 1).

Within ART, we can use this effect to our advantage, “boosting” concentrations of antiretrovirals using pharmacokinetic enhancers such as cobicistat and ritonavir to prevent resistance. However, when combining these potent CYP3A4 inhibitors with immunosuppression, it can be difficult to maintain drug levels in the therapeutic range and prevent toxicities such as nephrotoxicity and neurotoxicity (see Table 2).[8] Specifically, interaction of protease inhibitors (PI) with CNIs is well known. This drug-drug interaction is thought to have contributed to several cases of graft rejection, with case reports dating back to the late 1990s.[9–13] Sawinski, et al found a 1.8-fold increased risk of allograft loss in a national survey of renal transplant patients on a PI regimen.[14] The American Society of Transplant (AST) Infectious Disease Community of Practice guidelines recommend caution with use of PI-containing regimens due to these concerns.[15]

Calcineurin inhibitors are not the only immunosuppressants that interact with HIV medications (see Table 2). Sirolimus, an mTOR inhibitor, is also metabolized through the CYP 3A4 enzyme.[16] These drug interactions have added complexity due to the long half-life of mTOR inhibitors, which delays dose titration and clearance of drug if levels become high. In vitro interactions have been noted between mycophenolic acid and some NRTIs, but this has not led to an increase in adverse effects.[16] Several in vitro drug interactions have varying effects on clinical practice. For example, a 35-patient case series of liver and kidney transplants from 2007 describing modifications to immunosuppression reported that patients

on EFV required nearly double their CNI dose to achieve therapeutic troughs, despite EFV having both inducing and inhibiting effects.[17]

Advances in diagnostic technology have allowed clinicians to further understand each patient's peculiar HIV strain and optimize treatment. There are currently two types of available drug resistance testing: phenotypic testing and genotypic testing. Phenotypic testing amplifies DNA segments and inserts them into vector constructs creating pseudovirions that are exposed to ART, resulting in a direct observation of the drugs' impact on the patient-specific virus. Genotypic testing sequences amplified patient viral DNA compared to a wild-type reference sequence. Susceptibility to specific ART is based on known resistance mutations and provides a prediction of response to drug. These tests often cannot be performed in patients with suppressed viral loads, and thus, the proviral DNA resistance testing (AKA archived genotypic testing) was developed. This technology allows amplification of viral RNA and proviral DNA, thereby permitting extrapolation of likely resistance profiles in patients with suppressed viral loads.[18]

Antiretroviral therapy switch has been successful in simplification strategies for non-transplant HIV^+ patients,[19–21] though the myriad drug interactions between commonly used immunosuppressant agents and historical ART regimens can render the prospect of switching ART after transplant daunting. Fortunately, however, recent advances in available ART classes and resistance testing methods may permit clinicians to avoid the most troublesome drug interactions—even in PLWH with extensive historical exposure to multiple classes of ART (Table 3).

Liver transplantation is a unique population within SOT, as patients are often maintained on lower immunosuppression overall compared to other transplanted organs. To add to the literature supporting SOT in PLWH, we describe three cases of successful changes to ART in order to minimize drug interaction with tacrolimus in treatment-experienced PLWH undergoing orthotopic liver transplantation (OLT) between 2014 and 2018.

2 | CASE 1

A 50-year-old man, perinatally infected with hepatitis B virus (HBV), who progressed to chronic HBV infection before acquiring HIV was admitted in 2014 for jaundice, weight loss, and transaminitis after anti-HBV treatment lapse. He presented with acute-on-chronic liver failure in the setting of HBV flare. His HIV regimen at that time was tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) + etravirine (ETR) + raltegravir (RAL) + ritonavir-boosted darunavir (DRV/r). He had extensive treatment experience with regimens that included zidovudine, zalcitabine, abacavir, lamivudine (3TC), stavudine, didanosine, efavirenz, nelfinavir, indinavir, lopinavir/ritonavir, and atazanavir and had been on ART since 1994. He had a prior HIV phenotype in 2002 that demonstrated resistance to all first-generation, non-nucleoside reverse transcriptase inhibitors (NNRTI) with susceptibility to the nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) class. Subsequently, he had an HIV genotype completed in 2005 that demonstrated high-level resistance to 3TC and FTC, and possible resistance to stavudine and tenofovir (K65R, Y115F, M184V in reverse transcriptase) with susceptibility to the NNRTI and PI class.

Due to worsening liver failure during his admission, with a MELD of 45, the patient received a liver transplant. Given his treatment-experienced status, history of resistance, and concerns for archived HIV resistance in minority variants not captured by genotype testing, he was discharged without adjustments to his HIV/HBV medication regimen. Post-transplant issues were minimal except for high pill burden and frequent changes to tacrolimus dosing due to CYP3A4 inhibition from ritonavir. HIV remained suppressed, however, in response to the pill burden, we simplified his DRV/r to the fixed-dose combination of darunavir and cobicistat (DRV/c), but this did not significantly improve the drug interaction with tacrolimus. In fact, over the course of 20 months post-transplant, his dose of tacrolimus had decreased to 0.3 mg every 72 hours with levels still within goal of 5–8 ng/mL. Proviral DNA resistance testing (archive resistance testing) revealed no additional HIV resistance; thus, an effort was made to remove pharmacokinetic inducers and inhibitors of CYP-450 enzyme from his HIV/HBV regimen. We further simplified his regimen to the fixed-dose combination of tenofovir alafenamide, FTC, and rilpivirine (TAF/FTC/RPV) and a second-generation integrase non-strand transfer inhibitor, dolutegravir (DTG). Within days, his tacrolimus dose was increased to 1.5 qAM and 1 mg qPM and more recently is stable at 1 mg twice daily. With this ART change, he has remained virologically suppressed for more than 30 months and has not experienced any episodes of organ rejection (Figure 1a).

3 | CASE 2

The second case is a 64-year-old man with HIV and hepatitis C virus (HCV) cirrhosis complicated by hepatocellular carcinoma (HCC). He was listed for liver transplantation with a MELD of 34. Prior to transplantation, his ART history included monotherapy with indinavir, followed by regimens containing 3TC, ritonavir-boosted atazanavir, abacavir (ABC), and nevirapine (NVP) and resistance testing revealed K65R, K70R, and M184V in reverse transcriptase. Proviral DNA resistance testing (archive resistance testing) did not reveal any additional mutations. His HIV regimen shortly before transplant consisted of the fixed-dose combination of ABC/3TC/DTG + DRV/c. At our institution, the SOT protocol for PLWH requires virologic suppression in the 6 months leading up to transplant. Thus, to preserve his ability to continue on the transplant list, we did not alter this ART regimen. He underwent OLT and due to ART drug interactions required frequent changes to tacrolimus dosing with bi-weekly level monitoring, ultimately resulting in a miniscule dose of 0.4 mg every 72 hours to avoid CNI toxicity. Five months after transplantation, we changed his ART regimen to TAF/FTC/RPV + DTG and his tacrolimus dose stabilized at 1 mg every morning and 0.5 mg every evening. On this regimen, he has maintained virologic suppression for more than 27 months and has not experienced any organ rejection (Figure 1b).

4 | CASE 3

Lastly, a 53-year-old man with HIV, hepatitis B, and HCC presented to clinic in 2015 for discussion of his HIV regimen as part of his liver transplant evaluation. He had been living with HIV for 27 years and had historical exposure to efavirenz, NVP, stavudine, tenofovir, nelfinavir, atazanavir, ABC, and zidovudine. His proviral DNA resistance (archived resistance) test demonstrated the following mutations: NNRTI Y181Y/C in reverse

transcriptase, INSTI V151I in the integrase region, and PI V82V/I in the protease region, and trofile testing revealed CCR5-utilizing HIV. Using his history and resistance testing, we optimized his regimen of TDF/FTC + ETV + DRV/r + DTG to TDF/FTC + DTG + DRV/c. Approximately 1 year before transplant, we changed the TDF/FTC to TAF/FTC given better safety profile and new availability of TAF. The patient was transplanted in 2017 while on TAF/FTC + DTG + DRV/c. At the time of transplant, we discontinued DRV/c due to interactions with tacrolimus, and we increased dolutegravir to twice daily due to the pre-existing INSTI mutation and the concern for minority variant TAMs not captured with resistance testing. His post-transplant course has been uncomplicated for over 16 months now with no viral rebound, episodes of rejection, or unusual difficulties with dosing of immunosuppressants.

5 | DISCUSSION

This case series presents the clinical outcomes of treatment-experienced PLWH who successfully underwent OLT despite initial, significant drug interactions between ART and immunosuppressive agents. PIs remain the backbone of therapy for many PLWH with extensive exposure to multiple classes of ART because of their well-established utility in persons with ART resistance (due to the high genetic barrier to resistance). However, newer classes and generations of ART (specifically the INSTI, DTG) also demonstrate a high genetic barrier to resistance and usefulness in treatment-experienced PLWH.[22] As demonstrated in our cases, replacing protease inhibitors with dolutegravir may be a successful strategy to minimize drug interactions and improve the safety and efficacy of immunosuppressants post-transplant in PLWH. RAL is another INSTI that similarly avoids significant drug interactions; however, this medication has a lower barrier to resistance and often requires twice-daily dosing. Our experience also shows that rilpivirine can be an effective and safe option in patients without significant NNRTI resistance. Although we commonly transitioned the patients to TAF/FTC/RPV + DTG, newer fixed-dose combination ART such as bictegravir/FTC/TAF may also be appropriate. However, bictegravir, unlike DTG, has not yet been extensively evaluated in treatment-experienced PLWH. Similarly, the new NNRTI doravirine may also be useful in the post-transplant setting given its lack of potential drug interactions.

Our experience highlights both the difficulties that can be encountered with this transition in the post-transplant setting and the success with optimization of ART regimen prior to transplantation. The first two cases show the difficulty of switching ART in the post-transplant setting. Once discontinued, the CYP3A4 inhibition continues despite the drug not being present so clinicians should use caution when escalating tacrolimus doses without close monitoring.[23] Previous cases in renal transplant have increased tacrolimus dose tenfold[24,25]; however, our approach on the date of discontinuation was to increase the tacrolimus dose fivefold, then, after close level monitoring (within 3 days), increase consecutively until doses reached nearly 20-fold above baseline approximately 30 days post-conversion (diagrammed in Figure 2). This boosting from PIs lasts for several days due to its inhibition binding coefficient (ki) of <0.09 nmol/L to CYP3A4.[26] In comparison, the antifungal agent voriconazole has a reported ki of 15 nmol/L.[27] The lower the ki, the greater the binding affinity of the medication, resulting in prolonged inhibitory effects.

We understand that there are potential cases that necessitate ongoing PI use (ie, extensive resistance across three classes of ART). In this setting, one could still attempt to manage the interaction with dose adjustment of the affected medication. The AST Infectious Disease Community of Practice has guideline recommendations for close monitoring and titration of tacrolimus in this setting. However, use of these agents comes with the risk of adverse effects of immunosuppression (including significant nephrotoxicity and neurotoxicity) and rejection due to potentially subtherapeutic levels while in the dose-finding stages, as well as difficulty with patient compliance.[28] Encouragingly, Sparkes, et al recently reported data showing reduced renal graft failure rates with PI use at their transplant center.[29] Further research into the close monitoring of tacrolimus in this setting is warranted. Other classes of ART do exist that could also potentially be utilized, including inhibitors of viral fusion (enfuvirtide) and post-attachment (ibalizumab). This highlights the importance of active involvement of Infectious Diseases and Pharmacy Colleagues with HIV knowledge and experience in the pre- and post-transplant management of this complex population.

The increasing life span of PLWH, development of newer classes of ART, higher prevalence of hepatitis B and C infection, and increasing nonalcoholic fatty liver disease in PLWH, along with supportive national policies, will likely lead to more PLWH needing SOT. However, there are still unanswered questions in this field that would benefit from further exploration. It remains unknown whether minority HIV variants not captured by current HIV resistance testing (including genotype resistance testing) will impact virologic response following SOT. Still, it is reassuring that our participants had a mean duration of follow-up of 24 months without evidence of virologic failure and our experience suggests that neither complicated history of ART regimens nor concern for drug-drug interactions between ART and post-transplant immunosuppression should be barriers to SOT.

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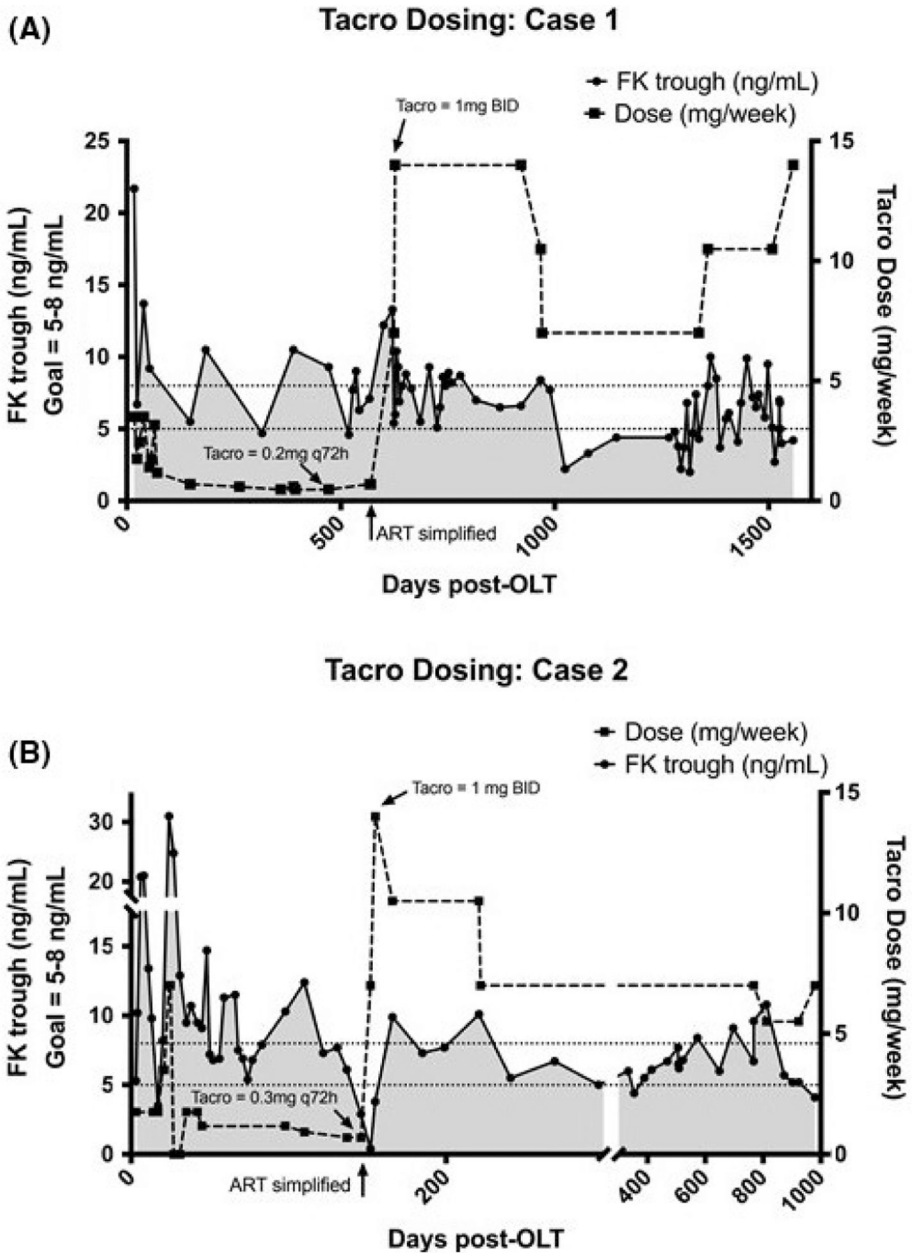

FIGURE 1.

Graph of tacrolimus ("FK") levels over time compared to tacrolimus dose prescribed before and after antiretroviral (ART) simplification in patients described in case 1 (panel A) and case 2 (panel B). Due to variations in lab draw timing and dose consumption, the FK trough was not always able to be determined, so dose adjustments were made per standard clinical practice based on best available information and clinical judgment of the transplant team. For this reason, not every level that may appear to be out of range was acted upon with a change in prescribed dose. Abbreviations: OLT, orthotopic liver transplant; ART, antiretroviral therapy; FK/tacro, tacrolimus; q72 h, every 72 h; BID, twice daily

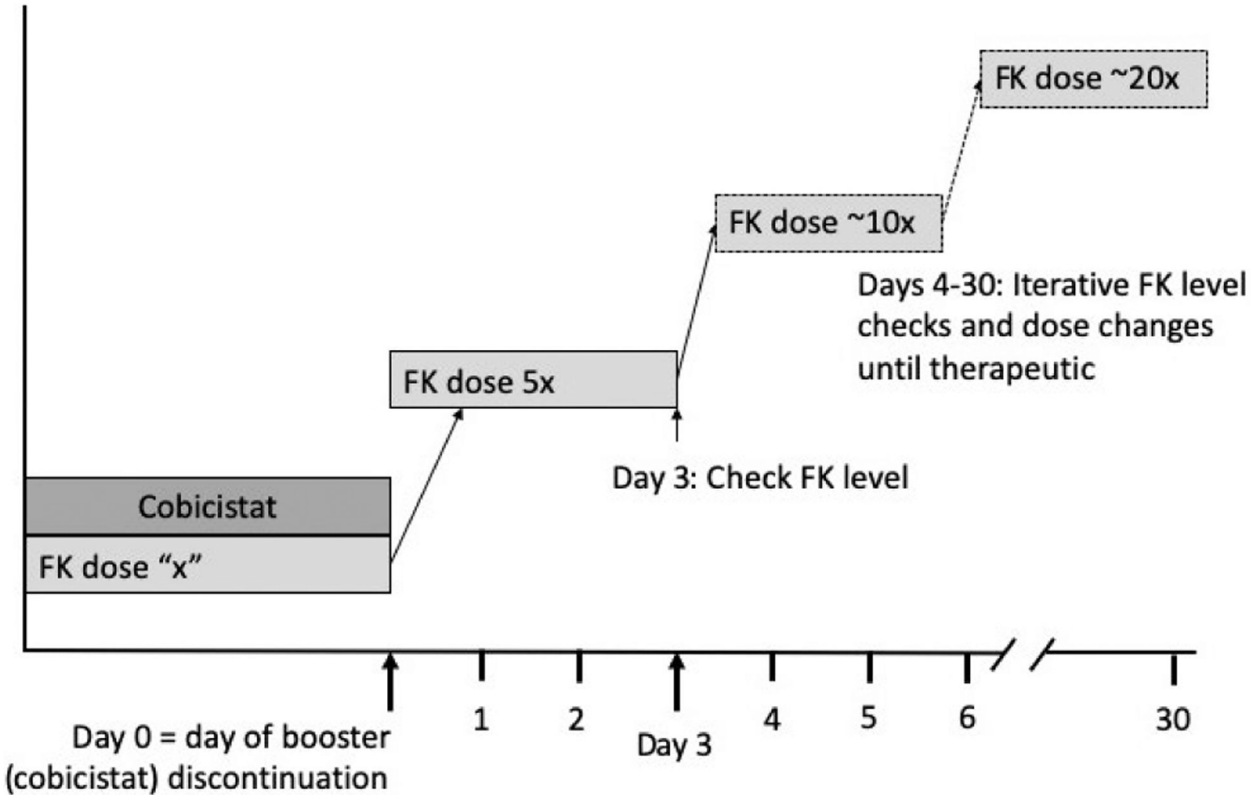

FIGURE 2.

Schematic of tacrolimus dose management after optimization of antiretroviral regimens. Pharmacologic boosting of tacrolimus (FK) persists for several days after discontinuation of cobicistat. Thus, our approach to adjusting FK dosing after cobicistat discontinuation (Day 0) is illustrated here. Briefly, FK dose was quintupled on Day 0; then, an FK level was checked after 3 d. Subsequent adjustments in FK dose were made with close clinical/laboratory monitoring over the ensuing weeks until a stable FK dose was achieved, which was typically, approximately 20-fold higher than the dose when the patient was taking the pharmacologic booster (cobicistat)

TABLE 1

Immunosuppression metabolism. Major metabolic pathways for commonly used immunosuppression medications

	Calcineurin Inhibitors (CNI)				
	Tacrolimus[8]	**Cyclosporine**	**mTOR inhibitors[14]**	**Cell cycle inhibitors**	**Prednisone**
Major metabolic pathways	CYP3A4 CYP3A5	CYP3A4 CYP3A5	CYP3A4 CYP3A5 CYP2C8	Glucuronidation UGT	11-B-hydroxydehydrogenase conversion to active prednisolone CYP3A4
Transporter metabolism (substrates)	P-gP	OATP P-gP	P-gP	None	None

Abbreviations: CYP, cytokine P450-specific pathways; UGT, Uridine 5’-diphospho-glucuronosyltransferase; OATP, organic-anion-transporting poly-peptide; P-gP, P-glycoprotein.

TABLE 2

Immunosuppression and ART drug interactions.* Known drug interactions between antiretroviral medications (by class) and commonly used immunosuppression medications

	Calcineurin inhibitors (CNI)					
	Tacrolimus	**Cyclosporine**[15]	**mTOR inhibitors**	**Mycophenolate mofetil**	**Prednisone**	**Comments**
Nucleoside reverse transcriptase inhibitors (NRTI)[16] • Abacavir (ABC) • Emtricitabine (FTC) • Lamivudine (3TC) • Tenofovir alafenamide (TAF) • Tenofovir disoproxil fumarate (TDF)	↑ TAF due to P-GP	↑ TAF due to P-GP and OATP inhibition	No interaction noted	↑ TAF and MMF due to competition for active tubular secretion	No interaction noted	No dose adjustment of medications required Possible risk of tubular necrosis with TAF and MMF
Non-nucleotide reverse transcriptase inhibitors (NNRTI) • Efavirenz (EFV) • Etravirine (ETR) • Rilpivirine (RPV) • Doravirine (DOR)	All NNRTIs are CYP3A4 substrates, possible competitive inhibition ↓, tacrolimus EFV and ETR ↓, tacrolimus, CYP3A4 inducer	All NNRTIs are CYP3A4 substrates, possible competitive inhibition ↓, cyclosporine	All NNRTIs are CYP3A4 substrates, possible competitive inhibition ↓, mTOR EFV and ETR *I* mTORs, CYP3A4 inducer	Mycophenolate mofetil (MMF) conversion to active mycophenolic acid (MPA) through glucuronidation NNRTIs can affect this pathway	EFV ↓ AUC of active prednisolone through CYP3A4 induction	Monitor immunosuppression with EFV and ETR, may require dose increase RPV and DOR do not cause clinically significant interactions May have altered MPA and prednisolone exposure
Protease Inhibitors (PI) • Atazanavir (ATV) • Darunavir (DRV) • Lopinavir (LPV) • Ritonavir (RTV)	Potent ↑ tacrolimus concentration, CYP3A4 inhibitors	Potent ↑ cyclosporine concentration, CYP3A4 inhibitors	Potent ↑ mTOR concentration, CYP3A4 inhibitors	MMF conversion to active MPA through glucuronidation Pis can affect this pathway	↑ prednisolone exposure	Avoid coadministration to prevent toxic levels of immunosuppression
Pharmacokinetic enhancers • Cobicistat (COBI) • Ritonavir (RTV)	↑ tacrolimus, CYP3A4 inhibitors	↑ cyclosporine, CYP3A4 inhibitors	↑ mTORs, CYP3A4 inhibitors	No interaction noted	↑ prednisolone exposure	Avoid coadministration to prevent toxic levels of immunosuppression
Integrase Inhibitors (INSTI) • Bictegravir (BIC)	DTG and BIC partial CYP3A4 substrates, potential for competitive inhibition	DTG and BIC partial CYP3A4 substrates, potential for competitive inhibition	DTG and BIC partial CYP3A4 substrates, potential for	No interaction noted	Prednisone ↑ DTG concentrations ~11%[17]	No dose adjustment necessary EVG cannot be given without a pharmacokinetic enhancer

	Calcineurin inhibitors (CNI)					
	Tacrolimus	**Cyclosporine**[15]	**mTOR inhibitors**	**Mycophenolate mofetil**	**Prednisone**	**Comments**
• Dolutegravir (DTG) • Raltegravir (RAL) • Elvitegravir (EVG)			competitive inhibition			
Fusion Inhibitor • Enfuvirtide (T20)	No interaction noted	No interaction noted	No interaction noted	No interaction noted	No interaction noted	No dose adjustment necessary
CCR5 Antagonist • Maraviroc (MVC)	CYP3A4 substrates, potential for competitive inhibition	Cyclosporine ↑ MVC, CYP3A4 and P-gP substrate	CYP3A4 substrates, potential for competitive inhibition	No interaction noted	No interaction noted	No dose adjustment necessary
Post-Attachment Inhibitor • Ibalizumab (IBA)	No interaction noted	No interaction noted	No interaction noted	No interaction noted	No interaction noted	No dose adjustment necessary

* Not a comprehensive list, less commonly used agents have been excluded for relevance to current practice.

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TABLE 3

Case summary. Comparison of pertinent details from the described clinical cases

	Case 1	Case 2	Case 3
Organ transplanted	Liver	Liver	Liver
Year of transplant	2014	2016	2017
Estimated year of HIV infection	Before 1994	~1995	1988
Pre-transplant ART regimen	TDF/FTC + ETR + RAL + DRV/r	ABC/3TC/DTG + DRV/c	TAF/FTC + DTG + DRV/c
Post-transplant ART regimen	TAF/FTC/RPV + DTG	TAF/FTC/RPV + DTG	TAF/FTC + DTG (dosed BID)
Tacrolimus dose while on boosted regimen[a]	0.3 mg every 72 h	0.4 mg every 72 h	N/A (regimen simplified at time of transplant)
Tacrolimus dosing after off boosted regimen	1.5 mg QAM/1 mg QPM	1 mg QAM/0.5 mg QPM	

[a]Boosted regimen = protease inhibitor plus a pharmacokinetic enhancer (either cobicistat or ritonavir).