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CASE: HIV+ End-Stage Renal Disease Patient with Immunosuppressive Drug-Drug Interactions Received Successful Transplantation After Ibalizumab Suppressed Switch

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Introduction

TRANSPLANTATION IN HIV+ INDIVIDUALS

- The HOPE Act of 2015[1] allowed organ transplantation between HIV-positive donors and recipients, enabling life-saving transplants for our patients.
- While the current possibility of transplant is welcome, the complexity of managing antiretroviral (ARV) regimens that are limited due to resistance and drug-drug interactions (DDIs) poses significant clinical challenges.
  - The guidance[1] requires that transplant recipients must have undetectable viral load and CD4 cell count >200 cells/mm^3; this may be difficult to achieve for patients with limited treatment options due to drug resistance or comorbidities, including end-stage renal disease (ESRD).
  - Post-transplant, recipients must receive immunosuppressive anti-rejection medications for the rest of their lives, creating the potential for DDIs between the immunosuppressants and ARV regimen.

1. National Institutes of Health (NIH). Federal Register. November 25, 2015. https://www.govinfo.gov/content/pkg/FR-2015-11-25/pdf/2015-30172.pdf

IBALIZUMAB

- Ibalizumab (IBA) was approved in the US in 2018 as the first long-acting antiretroviral and monoclonal antibody for HIV-1 treatment.
- IBA is a CD4-directed post-attachment HIV-1 inhibitor that is indicated, in combination with other ARVs, for the treatment of HIV infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current ARV regimen.
- No significant DDIs have been identified nor are expected between IBA and other medications.

Patient History

DEMOGRAPHICS AND HIV HISTORY

- The patient is a 67-year-old Black male diagnosed with HIV in 2003.
- CD4 nadir <200 cells/mL pre-transplant with the only known opportunistic infection of oral candidiasis.
- He has a history of ARV side effects with tolerability issues.

KEY CLINICAL CHALLENGES

- The patient had ESRD and was hemodialysis-dependent for a number of years requiring transplantation.
- The key challenge was to find a regimen to maintain suppression while eliminating future DDIs between his ARV regimen that is limited by resistance mutations and his immunosuppressive medications.
- Unfortunately, complete historical records from the previous clinic where the patient was followed from 2003 and 2018 have been unable to be recovered. However, the same treating physician has been caring for this patient since 2004 throughout the change in clinics.

Patient History *(cont'd)*

MEDICAL HISTORY

Diagnoses

- Chronic kidney disease
- HIV-1 infection
- Cerebrovascular disease
- Seizure disorder – secondary to CVA in 2002
- Hypertension
- Type 2 Diabetes Mellitus

Physical Exam

- Remarkable for gait disorder from past CVA
- Vision changes from diabetic retinopathy.
- Hypertension is controlled.

Surgical and Procedure History

- Cardiac catheterization – 2021 – no pertinent findings
- Renal transplant (non-familial, cadaver allograft) – 2019
- Arteriovenous fistula placement - 2012
- Lung biopsy – 2011 – negative

Family History

- Mother, father, and sister are all deceased of complications related to diabetes, hypertension, and/or kidney disease.

ARV HISTORY

Table 1: Patient's ARV History Since Diagnosis (New drugs in red)

Timeline	Regimen*	Notes
2003 (Diagnosis)	FOS/r, ddI, 3TC	• Patient recalls only taking this regimen intermittently due to gastrointestinal and neuropathy adverse effects. • Regimen failure.
2006	EFV/TDF/FTC	• Patient recalls taking this regimen more consistently but still intermittently due to CNS adverse effects. • Regimen failure.
2008	DRV/r, RAL, TDF/FTC	• Patient remained suppressed on this regimen until 2018. • Patient did not want to change regimens during this time as he was suppressed. • TDF/FTC was renally dosed in 2011.
2018	ETR, RAL, TDF/FTC	• DRV/r changed to ETR by Transplant ID to avoid boosting DDIs post-transplant.
2019 March	IBA, RAL, TDF/FTC	• ETR changed to IBA by Transplant ID due to lack of DDIs. • DOR was not selected due to lack of data in treatment-experienced patients
2019 June to Current	IBA, DTG, TAF/FTC	• Transplant ID changed RAL to DTG and opted to maintain BID dosing given low-level tenofovir resistance. • TDF/FTC was changed to TAF/FTC.

ARV RESISTANCE DATA

- Due to inability to recover previous treatment records, past resistance tests were unavailable. Given patient's long period of suppression from 2008 to 2018, the only available sequencing pre-transplant was proviral DNA (Table 2).
  - Coreceptor Tropism – Proviral DNA – 8/30/2018 – Assessment – CXCR4 virus
  - Proviral DNA – 10/04/2018

Table 2: Patient's Proviral Testing Results and Assessment

	Mutations	Standford HIVdb Assessment*
NRTIs	D67N, T69N, K70R, M184V, K219E	• **High-level resistance:** ABC, FTC, 3TC • **Intermediate resistance:** AZT, d4T, ddI • **Low-level resistance:** TDF/TAF
NNRTIs	K103R, Y179D, G190A	• **High-level resistance:** EFV, NVP • **Intermediate resistance:** RVP • **Low-level resistance:** ETR • **Susceptible:** DOR
PIs	None detected	N/A
INSTIs	None detected	N/A

*https://hivdb.stanford.edu/hivdb/by-mutations/report/ - Accessed May 6th, 2021

ARV Switch, Kidney Transplantation, and Outcomes

- Ibalizumab was selected for combination with raltegravir, tenofovir disoproxil fumarate, and emtricitabine due to its lack of expected DDIs; pre-transplant, this combination maintained viral suppression successfully.
- Successful kidney transplantation occurred in June 2019 at the University of Miami.
  - His recovery was prolonged by anemia as he refused transfusions.
  - Transient dysphagia required temporary PEG tube placement for enteral nutrition and medications. Ibalizumab infusion was important as other ARV absorption may have been impacted until return to oral intake.
- Post-transplant, raltegravir was changed to dolutegravir; almost 2 years after transplantation, HIV suppression has been maintained (Table 3) and the patient's quality of life has improved dramatically.
- No DDIs were detected between IBA and immunosuppressants. No safety issues have been reported by the patient or treating physicians related to antiretrovirals, ESRD medications pre-transplant or immunosuppressants post-transplant.
- Anemia resolved 2 months post-transplant and other labs were unremarkable during this time period.

*Table 3: Laboratory Values and ARV Regimens Pre- and Post-Transplant**

Date	Viral Load (copies/mL)	CD4 %	CD4 Count (cells/mm^3)	CD8 Count (cells/mm^3)	Creatinine (mg/dL)	eGFR (mL/min/1.73m^2)	ARVs and Immunosuppressants	Hgb A1c
8/23/2018	<20	28	343	-	10.39	5	ETR BID, RAL BID, TDF/FTC BIW	-
2/19/2019	**Ibalizumab Started**							
3/21/2019	<20	28	391	546	7.12	9	IBA q2w, RAL BID, TDF/FTC BIW	-
6/11/2019	**Allographic Renal Transplant, Start of Immunosuppressive Medications**							
7/17/2019	<20	23	80	-	-	-	IBA q2w, DTG BID, TAF/FTC QD, tacrolimus 5mg QD, MMF 1000mg BID, prednisone 5mg QD	-
7/19/2019	-	-	-	-	1.87	43		-
7/31/2019	<20	29	231	-	-	-		-
8/5/2019	-	-	-	-	1.02	90		-
10/11/2019	<20	25	250	-	1.55	-		-
12/12/2019	<20	29	231	-	1.51	56		-
1/28/2020	<20	28	166	-	1.45	56		-
3/23/2020	<20	27	213	-	1.43	59		11.1
6/1/2020	<20	23	263	577	-	-		10.5
10/1/2020	24	-	-	-	-	-		-
3/1/2021	<20	17	108	365	1.44	56		10.3
4/26/2021	<20	30	344	560	1.43	59		9.3

*All values included when available or calculated

3TC, lamivudine; ABC, abacavir; ARVs, antiretrovirals; AZT, zidovudine; BID, twice daily; BIW, twice weekly; CKD, chronic kidney disease; CNS, central nervous system; CVA, cerebrovascular accident; DDIs, drug-drug interactions; D4T, stavudine; ddI, didanosine; DOR, doravirine; DTG, dolutegravir; DRV, darunavir; EFV, efavirenz; eGFR, estimated glomerular filtration rate; ETR, etravirine; FTC, emtricitabine; FOS, fosamprenavir, HIV, human immunodeficiency virus; IBA, ibalizumab; INSTIs, integrase strand transfer inhibitors; MMF, mycophenolate mofetil; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PEG, percutaneous endoscopic gastrostomy; PIs, protease inhibitors; QD, daily; q2w, every two weeks; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 4: Other Concomitant Medications

	Medication	Dosage
Pre-transplant Medications During Hemodialysis (Discontinued or Reduced at Time of Transplant)		
All	Amlodipine besylate	10 mg daily (discontinued)
	Carvedilol	12.5 mg two times daily (reduced)
	Cinacalcet	60 mg daily (discontinued)
	Clonidine	0.1 mg/daily transdermal patch (discontinued)
	Nystatin	500000U every 8 hours (discontinued)
	Sevelamer carbonate	800 mg three times daily (discontinued)
Post-Transplant and Current		
Cardio-vascular/ Neurologic	Apixaban	5 mg daily (to discontinue in June 2021)
	Atorvastatin	20 mg daily
	Carvedilol	6.25 mg two times daily
	Levetiracetam	500 mg two times daily
	Tamsulosin	0.4 mg daily at night
Anti-hyperglycemics	Sitagliptin	100 mg daily
	Insulin glargine	As directed
	Insulin aspart	As directed
Other	Omeprazole	40 mg daily
	Thiamine	100 mg daily
	Folic acid	1 mg daily
	Magnesium oxide	400 mg daily
	Docusate sodium	100 mg daily

Conclusions

- Ibalizumab is the first long-acting antiretroviral and monoclonal antibody approved for the treatment of HIV-1 infection.
- With no expected DDIs or cross-resistance with other ARVs, it became a key option for this patient.
- Pre-transplant, the combination of ibalizumab, emtricitabine/tenofovir disoproxil fumarate and raltegravir maintained viral suppression successfully.
- Post-transplant, raltegravir was changed to dolutegravir and almost 2 years after transplantation, HIV suppression has been maintained.
- Patient reports his quality of life is significantly improved and he is happy with current treatment. He is more active and has had no tolerability or infusion-related issues since February 2019.
- Importantly, this case represents the first known use of ibalizumab in an HIV+ person undergoing kidney transplantation.