INTRODUCTION

Months after the first reports of a previously unknown pathogen isolated from patients with pneumonia in Wuhan, China, coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO). Mediated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 can present with flu-like illness and progress to acute hypoxic respiratory failure. Bilateral infiltrates on chest imaging, lymphopenia, and elevated inflammatory markers have been noted in those with COVID-19-related pneumonia. Increased incidence of severe disease is cited in the elderly and in those with comorbidities including cardiovascular disease, diabetes mellitus, and chronic respiratory disease.

Immunocompromised patients, including solid organ transplant recipients and people living with human immunodeficiency virus (HIV), merit particular attention as altered host immunity may influence both disease severity and duration of viral shedding as is described with several other ribonucleic acid respiratory viruses. Yet immunocompromised status alone, in the absence of other comorbidities, may not necessarily predict severe illness presentations and poorer clinical outcomes as indicated by recent reports of COVID-19-infected solid organ transplant recipients and people living with human immunodeficiency virus (HIV). Such patients may even be spared the robust inflammatory response that precipitates ARDS associated with COVID-19, complicating the management of iatrogenic immunosuppression in this setting. We present a case of an orthotopic liver transplant recipient with well-controlled HIV who successfully recovered from a mild, flu-like illness attributed to SARS-CoV-2.

KEYWORDS
COVID-19, HIV, hydroxychloroquine, immunocompromised, orthotopic liver transplantation
Solid organ transplant recipients living with HIV uniquely demonstrate features of both immune suppression and immune activation, as evidenced by the increased rates of allograft rejection in such patients. Definitive guidance on management strategies for COVID-19 in this specific population is lacking. We hope to contribute to the literature of COVID-19 in immunocompromised patients by describing an orthotopic liver transplant (OLT) recipient with well-controlled HIV who experienced a mild flu-like illness attributed to SARS-CoV-2.

## 2 | CASE REPORT

Our patient is a 32-year-old African American man diagnosed with HIV 10 years prior to presentation with a peak viral load of 107,000 copies/mL and a CD4 + T-cell count of 477 cells/µL. Efavirenz, emtricitabine, and tenofovir disoproxil fumarate were initiated at the time of diagnosis, and the patient rapidly achieved viral suppression. Two years after diagnosis, he suffered progressive liver failure attributed to antiretroviral-induced hepatotoxicity and underwent OLT in 2013. His maintenance immunosuppression consisted of mycophenolate mofetil (MMF), prednisone, and tacrolimus. His antiretroviral therapy (ART) was changed to raltegravir, emtricitabine, and tenofovir disoproxil fumarate post-transplantation. He experienced two episodes of biopsy-proven acute cellular rejection diagnosed two years and four years after OLT, treated with anti-thymocyte globulin.

In March of 2020, five days after returning from a trip to New York City, he developed fatigue, fever, headache, and a dry cough. He presented to the emergency department and was found to have a temperature of 101°F. Nucleic acid amplification testing for influenza A, influenza B, and respiratory syncytial virus (Cepheid Xpert Xpress) performed on nasopharyngeal specimens was negative. Nucleic acid amplification testing for SARS-CoV-2 (Centers for Disease Control and Prevention, USA) performed on nasopharyngeal and oropharyngeal specimens was positive. He had been working at a community health center since his return, but reported no overtly ill contacts in that setting. The patient was initially instructed to engage in supportive care measures at home; however, the development of chest tightness and shortness of breath prompted presentation to the hospital the following day.

He complained of aggravating dry cough, but denied any abdominal symptoms. His vital signs were within normal limits. Pertinent laboratory results are listed in Table 1. Chest X-ray did not demonstrate any infiltrates. Computerized tomography (CT) imaging was not obtained. Given the patient’s immunocompromised status and

|                              | Baseline (4/2019) | Day 2 (Admission) | Day 3 | Day 7 (Discharge) | Day 18 (Follow-Up) |
|------------------------------|-------------------|------------------|-------|------------------|-------------------|
| HIV RNA Viral Load (copies/mL) | Undetectable      | Undetectable     |       | Undetectable     |                   |
| CD4 Absolute Count (cells/µL) | 532               |                  | 1012  |                  |                   |
| CD4 Percentage (%)           | 24                |                  | 33    |                  |                   |
| White Blood Cell Count (cells/µL) | 9230                | 6770             | 5920  | 7410             |                   |
| Absolute Lymphocyte Count (cells/µL) | 2450             | 1220             | 2650  |                  |                   |
| Lymphocyte Percentage (%)    | 26.5              | 18               | 35.8  |                  |                   |
| AST (U/L)                    | 46                | 37               | 38    | 54               | 58                |
| ALT (U/L)                    | 65                | 50               | 48    | 58               | 87                |
| Alkaline Phosphatase (U/L)   | 78                | 63               | 65    | 91               | 99                |
| Total Bilirubin (g/dL)       | 0.5               | 0.7              | 0.5   | 0.6              | 0.4               |
| Creatinine (mg/dL)           | 0.99              | 0.9              | 1.0   | 0.98             | 0.86              |
| Tacrolimus/FK506 (ng/mL)     | 3.5               | 3.7              | 12.2  | 6.7              | 6.9               |
| C-Reactive Protein (mg/dL)   | 1.5               | 0.8              | 2.0   | 0.1              |                   |
| Ferritin (ng/mL)             | 221               |                  |       |                  |                   |
| Interleukin-6 (pg/mL)        | 5                 |                  |       |                  |                   |
concern for symptom progression, he was admitted to the hospital despite his mild illness presentation. MMF was discontinued; prednisone was maintained, and tacrolimus was dosed to target a lower trough of 5-9 ng/mL. Hydroxychloroquine was administered outside of a clinical trial for five days. Antiretroviral therapy was continued. The patient’s respiratory symptoms gradually improved, and he never demonstrated fever or hypoxia. He was discharged home on the sixth day of admission and instructed to maintain isolation for 14 days. Post-discharge laboratory testing demonstrated improved inflammatory markers and lymphopenia. Figure 1 depicts his clinical timeline.

3 | DISCUSSION

We report COVID-19 in an HIV-positive solid organ transplant recipient. His uneventful course may indicate that this uniquely immunocompromised population is not at particular risk for adverse clinical outcomes in the absence of other comorbidities.

Emerging reports about COVID-19-infected solid organ transplant recipients similarly invoke comorbidities as the ultimate drivers of disease severity. A large case series of 90 solid organ transplant recipients in New York City noted no differences between baseline immunosuppression and disease severity.7 Rather, advanced age and comorbidities such as hypertension and the presence of active malignancy were associated with severe illness (need for mechanical ventilation, admission to the intensive care unit, or death). A separate series of 36 kidney transplant recipients from New York City observed 90% of individuals had hypertension or diabetes mellitus related to their original indications for transplant and 40% of individuals suffered severe illness as defined above.10 Both case series report higher mortality as compared to the general population (18% and 28%, respectively, as compared to 1%-5%), attributed to the burden of comorbidities in solid organ transplant recipients. Despite an immunosuppression regimen identical to that of the majority of individuals included in these studies, our patient did not suffer severe illness due to COVID-19 likely because of his youth and lack of comorbidities.

Increased time from transplant and associated induction immunosuppression to COVID-19 diagnosis may not always serve as a protective factor against adverse clinical outcomes. An Italian series of 111 COVID-19-infected long-term liver transplant recipients (defined as those who underwent transplant over a decade prior to COVID-19 diagnosis) reported three deaths (3%) over a 21-day follow-up period.11 All three individuals were men over the age of 65 years, afflicted with obesity, hypertension, hyperlipidemia, and diabetes mellitus. In contrast, three COVID-19-infected short-term liver transplant recipients (defined as those who underwent transplant within the last two years) experienced mild illness. While short-term liver transplant recipients were exposed to augmented immunosuppression including lymphodepleting agents more recently than their long-term counterparts, the short-term liver transplant recipients were significantly younger and healthier overall.11 Our patient was transplanted seven years prior to diagnosis of COVID-19 and last received a lymphodepleting agent for the treatment of acute cellular rejection three years previously. Yet, his age and overall health more closely approximate those of the short-term liver transplant recipients included in this study.

The important role of comorbidities in determining disease severity has been demonstrated in other immunocompromised patient populations. Case series of COVID-19-infected people living with HIV suggest that HIV infection itself, in the absence of acquired immunodeficiency syndrome (AIDS) or other comorbidities, may not necessarily portend to adverse clinical outcomes. A Spanish case series of five COVID-19-infected men living with HIV reported well-controlled HIV infection in four individuals on antiretroviral therapy; one individual was diagnosed with HIV at presentation and demonstrated a viral load of 45,500 copies/mL and CD4 + T-cell count of 13 cells/µL.12 Those with well-controlled HIV infection and no other comorbidities experienced mild illness, while two individuals with comorbidities (hypothyroidism, asthma) and the newly diagnosed HIV-positive individual suffered moderate-to-severe illness.12 Similar to those with well-controlled HIV infection and no other comorbidities, our patient was a young, healthy man who had consistently adhered to antiretroviral therapy since the time of HIV diagnosis and achieved viral suppression. His CD4 + T-cell count, though suppressed by anti-rejection medications post-transplantation, remained above the AIDS threshold. These factors may explain his relatively benign flu-like illness.

COVID-19-infected patients experience three distinct phases of disease: early, pulmonary, and extra-pulmonary.14 Early and localized pulmonary infection are mediated by viral replication and binding
to target receptors on host epithelial cells in the lung, resulting in flu-like illness and respiratory symptoms. A systemic, hyperinflammatory syndrome mediated by host cytokines develops within days to weeks, precipitating respiratory failure and cardiopulmonary collapse in a subset of patients. Immune dysregulation associated with HIV infection raises theoretical concerns about the severity of all of these phases in people living with HIV; reduced helper/inducer T-cell quantity and function may potentiate early respiratory distress and prolonged viral shedding, while immune activation of suppressor/cytotoxic T cells may subsequently trigger a robust cytokine storm. Our patient did not demonstrate manifestations of either immune suppression or immune activation, likely attributable to long-term, successful suppression of HIV viral replication and preserved CD4 + T-cell counts.

Immunosuppressive agents administered to solid organ transplant recipients compromise T-cell immunity responsible for viral recognition and eradication, thus prompting particular concern for the severity of the early and localized pulmonary phases of COVID-19 in this vulnerable patient population. Yet reduction in immunosuppression during the initial management of COVID-19 to facilitate a more appropriate immune response to ongoing viral replication may serve to trigger a later systemic, hyperinflammatory syndrome. Transplant centers worldwide grapple with this paradox, with many ultimately opting to hold antiproliferative agents on the basis of expert opinion. We similarly held our patient’s MMF and reduced his calcineurin inhibitor exposure, just as is often done in the setting of many serious infections. Prednisone was maintained to prevent allograft rejection, adrenal insufficiency, and cytokine storm. While he did not suffer a severe early, pulmonary illness or later systemic, hyperinflammatory syndrome, the impact of our management strategy remains unclear. The role of hydroxychloroquine therapy in this patient’s disease course is also questionable. Early enthusiasm based on biological plausibility and limited data has been dampened by subsequent comparative data sets. The results of ongoing randomized, controlled trials are still awaited.

Several tests of academic interest were not deemed necessary to guide this patient’s management, including a CD4 + T-cell count at the time of COVID-19 diagnosis; a CT scan of the chest, which may have revealed infiltrates not appreciable on chest X-ray; and repeat PCR testing for SARS-CoV-2 after clinical recovery to evaluate duration of nucleic acid detection. Large case series incorporating these data and ongoing randomized clinical trials will better delineate the clinical course and optimal management strategies for COVID-19-infected immunocompromised patients. As we continue to learn about the nature of COVID-19 in this vulnerable population, it is worth noting that not everyone is equivalently susceptible to adverse clinical outcomes. A range of disease manifestations, from flu-like illness to severe respiratory failure and death, occurs in immunocompromised patients and may be predominantly mediated by age and comorbidities. Our patient, a young OLT recipient with well-controlled HIV, successfully recovered from COVID-19. The impact of reduced immunosuppression and early hydroxychloroquine therapy in this setting has yet to be determined.

CONFLICTS OF INTEREST
The authors of this manuscript have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS
Modi, AR contributed drafting article, table, and figure, and approval of article. Koval, CE contributed concept/design, drafting article, critical revision of article, and approval of article. Taeg, AJ contributed approval of article. Modaresi Esfeh, J contributed concept/design, critical revision of article, and approval of article. Eghtesad, B contributed critical revision of article and approval of article. Narayan Menon, KV contributed critical revision of article and approval of article. Quintini, C contributed approval of article. Miller, C contributed approval of article.

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How to cite this article: Modi AR, Koval CE, Taege AJ, et al. Coronavirus disease 2019 in an orthotopic liver transplant recipient living with human immunodeficiency virus. *Transpl Infect Dis*. 2020;22:e13351. https://doi.org/10.1111/tid.13351