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Dolutegravir-based Antiretroviral Therapy in People With HIV With Solid Organ Transplantation: A Single-arm Pilot Clinical Trial (DTG-SOT)

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Background. This study assessed the pharmacokinetic interactions between dolutegravir (DTG)-based antiretroviral therapy (ART) and immunosuppressants in solid organ transplantation (SOT) recipients with HIV and ART safety.

Methods. A phase IV, single-center, open-label, single-arm clinical trial (DTG-SOT, NCT03360682) including adult SOT recipients with HIV conducted between 2017 and 2019. People with HIV with plasma viral load <50 copies/mL during ≥12 months and receiving stable raltegravir-based ART during ≥6 months were switched to tenofovir disoproxil fumarate/emtricitabine or lamivudine/abacavir + DTG and followed up for 48 weeks. Immunosuppressant pharmacokinetic parameters were compared before and 2 weeks after ART switch (primary outcome). Efficacy and safety were analyzed at 48 weeks by intention-to-treat analysis.

Results. Nineteen consecutive participants (median, 57 years; interquartile range, 51–60), mostly liver recipients (63.2%), received DTG/lamivudine/abacavir (63.2%) and DTG + emtricitabine/tenofovir disoproxil fumarate (36.8%). Pharmacokinetic parameters changed, albeit not significantly, before and after ART, for mycophenolic acid (maximum [Cmax] +63%, trough [Cmin] +53%, area under the curve [AUC] +16%; n = 7) and cyclosporine A (Cmax −64%, Cmin +14%, AUC −47%; n = 2), with smaller changes for tacrolimus (Cmax +14%, Cmin −29%, AUC −9%; n = 7). No participants experienced acute rejection or virological failure and CD4+ cell counts and percentages remained unchanged during follow-up. Three (15.8%) discontinued treatment because of adverse events. Estimated glomerular filtration rate decreased ($P = 0.0015$) and creatinine increased ($P = 0.0001$) slightly.

Conclusions. DTG-based ART lacked clinically significant drug–drug interactions with tacrolimus and mycophenolic acid. Switching to DTG-based ART was effective in people with HIV SOT recipients. More studies are needed to evaluate DTG safety in this setting.

Keywords. dolutegravir; drug-drug interactions; HIV infection; immunosuppressants; solid organ transplantation.

Since the introduction of antiretroviral therapy (ART), the outcomes of people with HIV (PHIV) have improved, and non–HIV-related conditions have become more frequent causes of mortality [1]. Because PHIV live longer, end-stage cardiovascular, liver, and kidney disease, among others, have become more frequent in this population [1]. Solid organ transplantation (SOT) is the current standard of care to manage end-stage organ disease, and therefore, the number of PHIV needing SOT is increasingly growing [2–4].

SOT is safe in selected PHIV [5, 6], with comparable outcomes in PHIV and general population with end-stage organ disease who cleared hepatitis C virus coinfection before or after SOT [7]. However, posttransplant management is challenging because of drug–drug interactions between immunosuppressive and antiretroviral agents [8]. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors inhibit and induce, respectively, the cytochrome P450 enzyme CYP3A4, the

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enzyme that metabolizes calcineurin inhibitors (ie, tacrolimus, cyclosporine A) and mTOR inhibitors, requiring frequent monitoring of these immunosuppressants [8, 9]. Moreover, protease inhibitors may interfere with the pharmacokinetics of corticosteroids and mTOR inhibitors, resulting in an increased risk of toxicity or rejection, respectively, in PHIV SOT recipients [10].

Raltegravir (RAL), the first integrase strand transfer inhibitor (INSTI) approved lacks interaction with immunosuppressants and has shown favorable pharmacokinetic profiles and efficacy and safety outcomes in PHIV SOT recipients treated with different immunosuppressants [11]. Consequently, ART regimens based on nonboosted INSTIs, such as RAL, plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) have become the preferred regimen for posttransplant management in this population [12–14]. Because of its low genetic barrier, RAL is typically administered with 2 NRTIs, such as tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) or lamivudine (3TC)/abacavir (ABC). TDF is associated with low, albeit significant, nephrotoxicity, and its concomitant use with calcineurin inhibitors, also associated with nephrotoxicity, may not be suitable [12]. Dolutegravir (DTG) is a second-generation INSTI with a higher genetic barrier and has been approved for treatment-naïve and treatment-experienced PHIV [15, 16]. Its metabolization through UGT1A and lack of induction or inhibition effect on cytochrome P450 or UGT suggests that DTG lacks interaction with immunosuppressants similar to RAL and may be a valuable ART for treating SOT recipients [17, 18].

Therefore, the rationale for switching from RAL to DTG was to move to a more convenient ART regimen while maintaining/improving efficacy and tolerance [18]. However, clinical information on DTG use in PHIV SOT recipients is limited, with only 2 case reports and 1 previous patient series showing that 50% of the 10 PHIV liver transplant recipients switching to DTG-based ART returned to previous ART regimens due to adverse events (AEs) 1 year later [19–21]. Moreover, the interactions between DTG and immunosuppressants in PHIV SOT recipients remain unassessed.

This single-arm, pilot, open-label clinical trial aimed to: (1) assess the interactions between DTG plus 2 NRTIs and immunosuppressant drugs in PHIV SOT recipients and (2) know the safety of DTG-based ART in SOT recipients. Secondary objectives were to assess efficacy and viral resistance in cases of virological failure, changes in CD4+ cell counts and lipid profile, and kidney and liver function.

METHODS

Study Design and Setting

This was a phase IV, single-center, open-label, single-arm clinical trial (DTG-SOT) to assess drug–drug interactions between DTG and immunosuppressants (ie, pharmacokinetics) and safety of a triple DTG-based ART regimen administered during 48 weeks in adult (≥18 years) PHIV SOT recipients. The study was conducted in Hospital Clínic de Barcelona (Barcelona, Spain) between August 2017 and August 2019. Study participants were consecutively recruited during 1 year. Patients with plasma viral load <50 copies/mL during ≥12 months and receiving stable RAL-based ART during ≥6 months were switched to DTG-based ART. Prospective recruitment started with those who switched to DTG-based ART before study inclusion and were followed by those who switched to DTG-based ART upon study inclusion, who were invited to participate in the pharmacokinetics study. Participants were followed-up for 48 weeks (1 year).

The study was performed in accordance with the local national laws (Royal Decree 1090/2015), the guidelines of the International Conference on Harmonization, and the guidelines of the Declaration of Helsinki (Fortaleza, Brazil). All participants signed the informed consent form. The Ethics and Research Committee (Comité de Ética de la Investigación con Medicamentos, CEIm) of the Hospital Clínic de Barcelona approved the study protocol (code HCB/2017/0514). The study protocol was registered at EU Clinical Trials Register (EudraCT: 2017-000469-62) and clinicaltrials.gov (NCT03360682).

Participants

Adult (≥18 years) PHIV SOT recipients (heart, liver, or kidney) on stable RAL-based ART for at least 6 months and plasma viral load (pVL) < 50 copies/mL during at least 12 months (with 2 determinations at least 12 months apart and no pVL >50 copies/mL between them) were included. Participants and donors (if available) were required to be HLA B5701 negative and lack major reverse transcriptase or integrase gene mutations (assessed by proviral DNA sequencing) affecting study drug efficacy. PHIV who stopped ART because of virological failure, and those who required treatment with potent enzyme inducers contraindicated with immunosuppressants that would also have required an increase in the dose of DTG were excluded. Additional exclusion criteria were history or presence of allergy or intolerance to the study drug, active opportunistic infection, neoplasms requiring chemotherapy, pregnancy or breastfeeding or planned pregnancy during the study period, and any other contraindications to study drugs.

Intervention

Patients receiving TDF/FTC or 3TC/ABC plus RAL were switched to DTG plus the 2 same NRTIs. Participants may have switched to DTG plus 2 NRTIs in the previous 48 weeks. The DTG-based treatments administered were 3TC 300 mg/ABC 600 mg/DTG 50 mg (Triumeq), 1 tablet once daily, or FTC 200 mg/TDF 245 mg (Truvada) and DTG 50 mg (Tivicay), 1 tablet once daily each.

Variables and Assessments

Pharmacokinetics (Primary Outcome). To assess interactions between DTG and immunosuppressant drugs, including cyclosporine A (CsA), tacrolimus, and mycophenolic acid (MPA), pharmacokinetic studies before and 2 weeks after the ART switch were performed. Blood samples were extracted at 0, 0.5, 1, 2, 4, 8, 10, and 12 hours after ART and immunosuppressant administration, and plasma concentrations were determined using a liquid chromatography tandem mass spectrometry detector for DTG and a liquid chromatography fluorescence detector for RAL. Concentrations of blood CsA and plasma MPA were analyzed using standard immunoassays (EMIT200, Siemens). Tacrolimus concentrations were analyzed in blood samples by liquid chromatography tandem mass spectrometry or a chemiluminescent microparticle immunoassay (ARCHITECT and 2000 SR, Abbott). We calculated the areas under the concentration-time curve (AUC) (ng/h/mL or µg/h/mL), maximum (Cmax) (ng/mL or µg/mL) and trough concentrations (Cmin) (ng/mL or µg/mL), and Tmax (h).

Efficacy and Secondary Outcomes. Efficacy outcome was evolution of pVL (copies/mL) and was assessed at weeks 0, 4, 12, 24, and 48 after treatment initiation. Virological failure was defined as at least 2 consecutive determinations of pVL >200 copies/mL. Secondary outcomes were evolution of CD4+ cell counts (cells/µL) and evolution of the lipid profile, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides (mg/dL for all), assessed at weeks 0, 12, 24, and 48.

Safety Outcomes. Safety included AEs (clinical safety outcomes) and changes in laboratory parameters assessing kidney and liver function (laboratory safety outcomes). AEs occurring during follow-up (48 weeks) and 28 days after end of study (after end-of-study visit) were recorded and classified according to severity (grades 1–4) and system organ class/preferred term. Kidney function parameters were estimated glomerular filtration rates (eGFR; CKD-EPI, mL/min/1.73 m^2), creatinine (mg/dL), and total protein/creatinine ratio (mg protein/g creatinine); liver function parameters were levels of the liver enzymes aspartate aminotransferase and alanine aminotransferase.

Statistical Analysis

This was a pilot single-arm trial, and, for this reason, a formal sample size calculation was considered unnecessary. The number of individuals required in drug–drug interaction studies ranges between 5 and 10. For the efficacy and safety outcomes, we planned to include 20 participants in the study.

The intention-to-treat (ITT) analysis included all participants who received at least 1 dose of DTG-based ART, and data for all timepoints were considered regardless of treatment discontinuation. The per-protocol analysis considered data from participants who continued in the study at each time point. Given this study's reduced size and pilot nature, data are presented according to the ITT analysis.

Categorical variables were presented as frequencies and percentages, and continuous variables as the median and interquartile range (IQR; Q1, Q3). Changes in pharmacokinetic (PK) parameters before and after switching to DTG-based ART were analyzed using the Wilcoxon signed-rank test. Changes in CD4+ cells, lipid profile, and kidney and liver function parameters were evaluated using a mixed-effects linear regression model fitted using the restricted maximum likelihood method. Values and changes from baseline with 95% confidence intervals (CI) were calculated. Statistical significance was set at a 2-tailed <0.05. All statistical analyses were performed using the Stata version 15 software (StataCorp. 2017. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

Role of the Funding Source

This study was funded by ViiV Healthcare. The funder did not participate in any stage of study development and only revised and approved the final version of the manuscript.

RESULTS

Demographic and Clinical Characteristics of Study Patients

Twenty consecutive PHIV SOT recipients were recruited between August 2017 and August 2018. One patient was a screening failure, resulting in a study population of 19 participants, of which 12 (63.2%) were included in the PK study. Patients had received the transplantation a median (IQR) of 6 years (2–12) before starting the clinical trial. All participants received at least 1 dose of the study treatment (ITT population) and 3 discontinued the treatment before weeks 4, 12, and 24 and were excluded from the per-protocol analysis from these timepoints and onwards (Supplementary Figure 1). Regarding the primary outcome (PK), 12 prospective patients were invited to participate. Two discontinued treatment before the assessment, and 1 had logistic issues and withdrew the consent to participate, resulting in a PK population of nine patients.

Table 1 summarizes the demographic, clinical, and treatment characteristics of study participants, which were similar in prospective patients included in the PK analysis and in those who were not included. Most patients (63.2%) were liver recipients. Regarding study treatments, 12 (63.2%) switched to DTG/3TC/ABC and 7 (36.8%), to DTG + FTC/TDF. Regarding immunosuppressants, SOT recipients received prednisone and calcineurin inhibitors (tacrolimus and CysA) or mTOR inhibitors (everolimus); kidney SOT recipients additionally received MPA. Individual immunosuppressants are described in Table 1. The most frequent comorbidities are summarized in Supplementary Table 1.

Table 1. Demographic, Clinical, and Treatment Characteristics of Study Patients n = 19

	Prospective n = 7[a]	Prospective With PK n = 12[a]	Total n = 19[a]
Demographic			
Sex, n (%)			
Female	2 (28.57)	6 (50.00)	8 (42.11)
Male	5 (71.43)	6 (50.00)	11 (57.89)
Age (y), median (IQR)	54 (48, 57)	58 (52.5, 60.5)	57 (51, 60)
Body mass index (kg/m^2), median (IQR)	26.34 (25.95, 26.72) *n = 2*	25.00 (22.99, 26.47) *n = 5*	25.50 (23.08, 26.60) *n = 12*
Clinical			
SOT recipient, n (%)			
Heart	0 (0.0)	1 (8.33)	1 (5.26)
Liver	7 (100)	5 (41.67)	12 (63.16)
Kidney	0 (0.0)	6 (50.00)	6 (31.58)
CD4 + cells (cells/μL), median (IQR)	417 (371, 598)	786 (422, 924.5)	518 (381, 840)
CD8 + cells (cells/μL), median (IQR)	698 (465, 828) *n = 6*	976.5 (602.5, 1073.5)	834.5 (488, 1067) *n = 18*
pVL <50 copies/mL, n (%)	7 (100)	12 (100)	19 (100)
Laboratory and biochemical parameters, median (IQR)			
Lipids (mg/dL)			
Total cholesterol	162 (85, 171)	186 (174.5, 223.5)	176 (162, 210)
LDL cholesterol	97.5 (84, 105) *n = 4*	100 (99, 124) *n = 9*	100 (95, 110) *n = 13*
HDL cholesterol	44 (39, 62) *n = 4*	50.5 (40, 65)	48.5 (39.5, 65) *n = 16*
Triglycerides	111 (49, 195)	128 (92.5, 200.5)	117 (89, 195)
Glucose (mg/dL)	93 (82, 103)	93.5 (86, 139.5)	93 (84, 120)
Estimated GFR (mL/min/1.73 m^2)	87 (66, 90)	63.5 (48.5, 74.5)	67 (53, 90)
Creatinine (mg/dL)	0.9 (0.77, 1.26)	1.205 (0.915, 1.375)	1.19 (0.85, 1.29)
Total protein/creatinine	81 (78, 154) *n = 5*	145.5 (51.5, 410.5)	99 (52, 302) *n = 17*
Aspartate aminotransferase (U/L)	27 (23, 27)	23 (16, 34)	23 (16, 33)
Alanine aminotransferase (U/L)	19 (11, 30)	21.5 (13.5, 26.5)	21 (11, 27)
Treatments, n (%)			
RAL-based ART			
ABC + 3TC	3 (42.86)	7 (58.33)	10 (52.63)
TAF + FTC	1 (14.28)	4 (33.33)	5 (26.31)
TDF + FTC	3 (42.86)	1 (8.33)	4 (21.05)
Assigned DTG-based ART			
DTG/3TC/ABC	4 (57.14)	8 (66.67)	12 (63.16)
DTG/FTC/TDF	3 (42.86)	4 (33.33)	7 (36.84)
Immunosuppressants			
Prednisone[b]	3 (42.86)	6 (50.00)	9 (47.37)
Cyclosporine A	1 (14.29)	2 (16.67)	3 (15.79)
Mycophenolic acid or mycophenolate mofetil[c]	5 (71.43)	8 (66.67)	13 (68.42)
Tacrolimus[d]	4 (57.14)	8 (66.67)	12 (63.16)
Everolimus	0 (0)	2 (16.67)	2 (10.53)

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; DTG, dolutegravir; FTC, emtricitabine; GFR, glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; ITT, intention to treat; LDL, low-density lipoprotein; N/A, not available; PK, pharmacokinetics; pVL, plasma viral load; RAL, raltegravir; SOT, solid organ transplant; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Total number of patients; in cases of missing data, the number of patients with available data is indicated in italics in the corresponding cell.

[b]Oral or enteric coated table or oral capsule.

[c]Mycophenolic acid: 180- or 360-mg enteric coated tablet; mycophenolate mofetil: 250- or 500-mg oral capsule or tablet.

[d]1 or 5 mg.

Pharmacokinetics

Seven of the 9 participants included in the PK analysis before and after ART switch received tacrolimus and MPA and 2 CsAs. The median (IQR) daily doses of tacrolimus, mycophenolate mofetil, and CsA were 5 (3–5), 720 (500–1000), and 125 (100–150) mg/day, respectively. RAL and DTG were in the normal range (Supplementary Table 2). PK parameters changed for all immunosuppressants before and after

Table 2. Pharmacokinetic Parameters of Immunosuppressants Before and After ART Switch, Median (IQR), n = 9

	Tacrolimus (ng/mL)			Mycophenolic Acid (µg/mL)			Cyclosporine A (ng/mL)		
	Before	After	% Change	Before	After	% Change	Before	After	% Change
n	7	7	…	7	7	…	2	2	…
Cmax (ng or µg/mL)	14.4 (10.8, 18.3)	16.4 (12.1, 18.7)	14	6.3 (3.8, 10.7)	10.3 (5.3, 12.9)	63	825 (686, 964)	299 (120, 478)	−64
Cmin (ng or µg/mL)	6.2 (5.2, 8.9)	4.4 (4.3, 8.5)	−29	1.9 (1.5, 2.5)	2.9 (1.7, 4)	53	86.5 (83, 90)	98.5 (65, 132)	14
Tmax (h)	2 (1, 2)	2 (1, 2)	…	2 (0.5, 4)	1 (0.5, 2)	…	1 (1, 1)	.75 (0.5, 1)	…
AUC (ng or µg·h/mL)	113 (78.6, 166.3)	103 (59.2–171.1)	−9	35.8 (23.7, 43.9)	41.4 (33.9, 47.7)	16	2649.55 (2307.30, 2991.80)	1407.50 (900.10, 1914.90)	−47

ART, antiretroviral therapy; AUC, area under the curve; IQR, interquartile range.

$P > .05$ for all comparisons (Wilcoxon signed-rank test).

the ART switch, especially for MPA (Cmax +63%, Cmin +53%, and AUC 16%) and CsA (Cmax −64%, Cmin +14%, and AUC −47%), but lacked statistical significance ($P > 0.05$ for all comparisons) (Table 2).

Secondary Outcomes: Efficacy of DTG-based ART

No participant experienced virological failure during the study, with pVL remaining at <50 copies/mL. One participant had a pVL blip (103 copies/mL) at week 24.

Secondary Outcomes: Evolution of CD4+ Cell Counts and Lipid Profile

CD4+ cell counts and percentage remained unchanged throughout the study ($P = 0.4193$ and 0.5155, respectively) (Figure 1). Likewise, the lipid profile, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein, cholesterol, and triglycerides remained unchanged ($P = 0.0686$, $P = 0.7384$, $P = 0.1373$, and $P = 0.7476$, respectively) (Supplementary Figure 2).

Safety Outcomes

Fifteen (78.9%) participants experienced 43 AEs during the study and until after the end-of-study visit (Table 3). AEs were mostly not treatment-related (81.4%) and mostly mild or moderate (95.3%). Three (15.8%) experienced 5 AEs that resulted in definite treatment interruption: hyperglycemia with difficult medical control in a patient with diabetes, which occurred during the PK assessment, insomnia plus diarrhea, and tremor plus anxiety. These AEs are described in detail in the Supplementary materials file and Supplementary Figure 3. One participant experienced a serious AE consisting of a cytomegalovirus infection unrelated to treatment. All AEs are summarized in Supplementary Table 3.

Kidney function parameters showed significant changes during the study, with decreased eGFR (−8.7%) ($P = .0015$) and increased creatinine (+8.7%) ($P = .0001$), whereas protein/creatinine ratios remained unchanged ($P = .6379$) (Figure 2). The liver enzymes aspartate aminotransferase and alanine aminotransferase showed no significant changes during the study (Supplementary Figure 4).

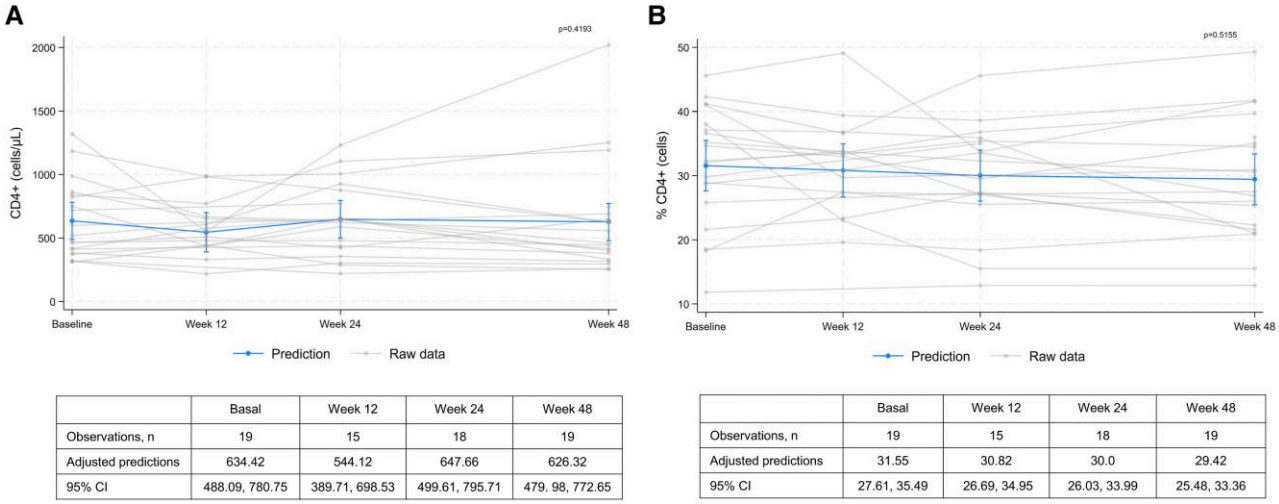
No participants experienced organ rejection during the study.

DISCUSSION

This pilot single-arm clinical trial showed that DTG plus 2 NRTIs lack clinically significant drug–drug interactions with calcineurin inhibitors (tacrolimus) and MPA in PHIV SOT recipients, whereas the sample size for the PK analysis of CsA (n = 2) was insufficient to draw robust conclusions. Participants remained virologically suppressed, and CD4+ cell counts and the lipid profile remained unchanged throughout the 48-week study. Estimated GFR and creatinine showed changes, albeit expected and clinically irrelevant, whereas liver enzymes were unaffected. AEs were mostly mild and moderate and not treatment-related, but 3 (15.8%) participants discontinued treatment because of treatment-related AEs.

To our knowledge, this is the first study assessing PK interactions between DTG-based ART and immunosuppressants in the transplant setting. Although the PK profile of tacrolimus was similar before RAL and after switching to DTG, with no clinically relevant changes, MPA increased after switching to DTG, although changes were not statistically significant and clinically not relevant. Regarding CsA, only 2 patients included in the PK analysis received this immunosuppressant, resulting in a small sample size with insufficient statistical power to draw conclusions. The lack of significant drug–drug interactions observed in this study was expected, given the DTG metabolization through UGT1A and the lack of interferences with CYP3A, similar to RAL [17, 18]. Accordingly, the PK profile of the immunosuppressants was similar in the context of RAL- and DTG-based ART.

However, DTG has additional advantages over RAL, including a higher genetic barrier and a more convenient once-daily administration, which may significantly impact



	Basal	Week 12	Week 24	Week 48
Observations, n	19	15	18	19
Adjusted predictions	634.42	544.12	647.66	626.32
95% CI	488.09, 780.75	389.71, 698.53	499.61, 795.71	479. 98, 772.65

	Basal	Week 12	Week 24	Week 48
Observations, n	19	15	18	19
Adjusted predictions	31.55	30.82	30.0	29.42
95% CI	27.61, 35.49	26.69, 34.95	26.03, 33.99	25.48, 33.36

Figure 1. Evolution of CD4+ cell counts (*A*) and percentages (*B*) in solid organ transplant recipients receiving DTG-based ART throughout the study. The fine lines represent individual values and bold lines the predicted values with the corresponding 95% confidence intervals (CI). Data are shown in the table below each graph. ART, antiretroviral therapy; DTG, dolutegravir.

Table 3. Summary of Adverse Events (AEs) During the Study and the After End-of-study Visit, n = 19

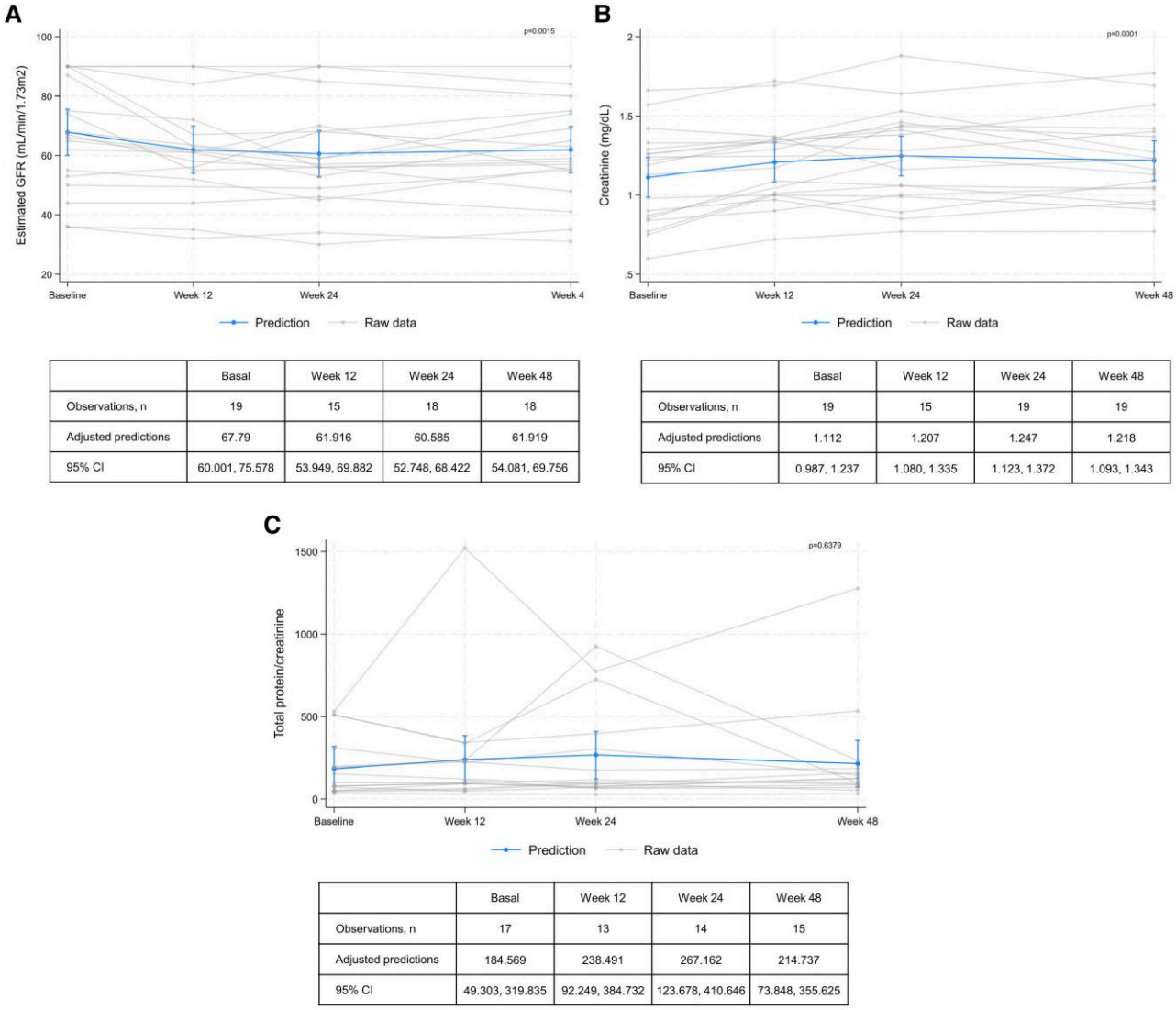
	Prospective n = 7	Prospective With PK n = 12	Total n = 19
Patients with AE, n (%)	5 (71.4)	10 (83.3)	15 (78.9)
Number of AE per patient, median (IQR)	1 (0, 2)	3 (1, 4)	2 (1, 4)
Total number of AEs	n = 14	n = 29	n = 43
AEs leading to definite treatment interruption, n (%)	0	5 (17.24)	5 (11.63)
Relationship with the study treatment, n (%)			
Not related	14 (100)	21 (72.41)	35 (81.40)
Possibly related	0	5 (17.24)	5 (11.63)
Probably related	0	3 (10.34)	3 (6.98)
Severity, n (%)			
Mild	8 (57.14)	16 (55.17)	24 (55.81)
Moderate	6 (42.86)	11 (37.93)	17 (39.53)
Severe	0	2 (6.90)	2 (4.65)
Outcome, n (%)			
Recovered without sequelae	10 (71.43)	17 (58.62)	27 (62.79)
Not recovered/persisting	2 (14.29)	7 (24.14)	9 (20.93)
Unknown	2 (14.29)	5 (17.24)	7 (16.28)
Serious AEs (SAEs), n (%)	1 (7.14)	0	1 (2.33)

AE, adverse event; IQR, interquartile range; ITT, intention to treat; PK; pharmacokinetics.

treatment adherence [22]. In this regard, bictegravir is another second-generation INSTI with similar properties to DTG, such as minimal drug–drug interactions and a high genetic barrier. Bictegravir is available as a single tablet for once-daily dosing, representing another potentially suitable ART option similar to DTG in the SOT setting. However, evidence is still scarce and awaits more studies assessing bictegravir in larger series of SOT recipients [23–25]. Importantly, RAL and DTG levels in SOT recipients receiving immunosuppressants remained similar to those reported in previous studies including healthy volunteers and PHIV [17, 26, 27]. Overall, PK results obtained in this study indicate that DTG may be a suitable option for PHIV SOT recipients, whereas RAL remains an option, although less convenient.

Regarding efficacy, all participants in our study remained virologically suppressed, showing that the regimens based on DTG with 2 NRTIs were highly efficacious in SOT recipients. In a previous retrospective study including 10 liver transplant recipients, participants discontinued DTG-based ART and switched to other ART regimens for reasons different from virological failure, in line with our study's results [19]. In addition to the favorable virological outcomes in all participants, our study showed that the CD4+ cell count and the lipid profile remained unchanged. Overall, these results, consistent with previous trials in treatment-experienced, nontransplanted PHIV, demonstrate the efficacy of DTG-based ART in PHIV SOT recipients [28, 29].

Kidney function is a significant concern in PHIV SOT recipients due to the nephrotoxicity associated with calcineurin inhibitors and NRTIs [12]. In this study, we detected changes in eGFR and creatinine, which were used as surrogate markers of kidney function, similar to previous studies evaluating DTG [19, 30]. These modest alterations are well-known effects of DTG, which inhibits the renal organic cation transporter OCT2 and potentially the multidrug and toxin extrusion transporter MATE1 in renal tubules, thus interfering with creatinine clearance, and do not reflect altered kidney function [31]. Even



	Basal	Week 12	Week 24	Week 48
Observations, n	19	15	18	18
Adjusted predictions	67.79	61.916	60.585	61.919
95% CI	60.001, 75.578	53.949, 69.882	52.748, 68.422	54.081, 69.756

	Basal	Week 12	Week 24	Week 48
Observations, n	19	15	19	19
Adjusted predictions	1.112	1.207	1.247	1.218
95% CI	0.987, 1.237	1.080, 1.335	1.123, 1.372	1.093, 1.343

	Basal	Week 12	Week 24	Week 48
Observations, n	17	13	14	15
Adjusted predictions	184.569	238.491	267.162	214.737
95% CI	49.303, 319.835	92.249, 384.732	123.678, 410.646	73.848, 355.625

Figure 2. Evolution of estimated glomerular filtration rate (GFR) (*A*), creatinine (*B*), and protein/creatinine ratio (*C*) in solid organ transplant recipients receiving DTG-based ART throughout the study. The fine lines represent individual values and bold lines the predicted values with the corresponding 95% confidence intervals (CI). Data are shown in the table below each graph. ART, antiretroviral therapy; DTG, dolutegravir.

though our study population included stable patients who had been transplanted long before switching to DTG-based ART, the increased creatinine levels and decreased eGFR may raise serious concerns after transplantation, leading to DTG-based ART discontinuation as previously reported [19]. Surgeons and care providers should be aware of this mild effect to prevent unnecessary testing and treatment discontinuation. In this regard, other biomarkers, such as cystatin c, may be used to monitor kidney function in PHIV and discriminate acute rejection or renal failure from the DTG effects on creatinine transporters [32].

Despite the lack of severe AEs and treatment-related serious AEs, discontinuation rates (15.8%) were higher than in previous clinical trials including nontransplant recipients, reporting discontinuation rates ranging from 2% to 3% [28, 29]. A previous retrospective, real-world study in 10 liver transplant recipients reported a 50% discontinuation rate from various reasons including, among others, elevated creatinine levels and fluctuating immunosuppressant concentrations [19]. In this trial, the 3 participants discontinued because of AEs likely associated with DTG treatment (hyperglycemia in a patient with diabetes, insomnia plus diarrhea, and tremor plus anxiety). Although uncommon, hyperglycemia has previously been described as a DTG-associated AE in a patient with diabetes mellitus [33]. Despite the lack of safety concerns, these observations suggest increased discontinuation rates in the transplant setting and warrant larger studies to confirm these results.

Results from this study should be interpreted in the context of limitations, mainly associated with its pilot nature and relatively small size. Despite reaching the recommended sample size for PK analyses (n = 5–10) (primary outcome), the uneven distribution of participants across immunosuppressant regimens resulted in only 2 participants receiving CsA and, therefore, insufficient statistical power to draw robust conclusions. To evaluate the efficacy and safety outcomes on a larger population, we included a cohort of consecutive SOT recipients who had switched to DTG-based ART before the trial was initiated. The study population was mostly liver and kidney transplant recipients (18 of 19) and heart transplant recipients were underrepresented (n = 1). Despite these limitations, efficacy was consistent with previous trials assessing DTG in treatment-experienced PHIV individuals [28, 29]. Moreover, to our knowledge, this was the first clinical trial assessing drug–drug interactions (DDI) between DTG and immunosuppressants, providing robust, relevant data, at least for tacrolimus and MPA. In this regard, bictegravir, another second-generation INSTI approved with efficacy and safety profiles like DTG, may be another suitable option besides RAL, but more evidence is needed in SOT recipients [23, 24, 34, 35]. The promising results of DTG-based ART in this pilot trial warrant larger studies, particularly focusing on the CsA PK profile and the discontinuation rates in SOT recipients. Moreover, as DTG becomes more frequently used as an alternative to RAL in PHIV SOT recipients, larger, real-world datasets will become available to evaluate the effectiveness and safety of DTG in this population.

CONCLUSIONS

To our knowledge, this pilot clinical trial provides the first evidence regarding the lack of PK interactions between ART treatment regimens of DTG plus 2 NRTIs and tacrolimus and MPA immunosuppressants in PHIV SOT recipients. The DTG-based treatments were efficacious as reported for DTG in nontransplanted individuals. The higher rate of treatment interruptions due to AEs warrants larger studies to inform treatment recommendations in this population.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. J.M.M., E.d.L., A.R., and A.M. conceived the study protocol. J.M.M. wrote the original draft and performed literature search. J.M.M., D.M., L.B., C.M., A.C., M.B., O.R., J.A., F.C., P.R., M.A.C., E.d.L., A.R., and A.M. performed data collection and statistical analyses. J.M.M., L.B., and E.d.L. accessed and verified data. All authors reviewed the work critically for important intellectual content and approved the final version of the manuscript to be published. All authors confirm that they had full access to all the data in the study and accept responsibility to submit it for publication.

Availability of Data and Materials. Datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Data Sharing Statement. Data will be available upon request to the corresponding author.

Consent for publication. Not applicable.

Patient consent statement. All patients provided written informed consent to participate in the study; the study protocol was approved by the Ethics and Research Committee (Comité de Ética de la Investigación con Medicamento, CEIm) of the Hospital Clínic de Barcelona (code HCB/2017/0514) and by the Spanish Regulatory Authorities and was conducted in accordance with the principles of the Helsinki Declaration and the Spanish Personal Data Protection Law (LOPD 15/1999).

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