ORIGINAL ARTICLE

Safety of Kidney Transplantation from Donors with HIV

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ABSTRACT

BACKGROUND

Kidney transplantation from donors with human immunodeficiency virus (HIV) to recipients with HIV is an emerging practice. It has been performed since 2016 under the U.S. congressional HIV Organ Policy Equity Act and is currently approved for research only. The Department of Health and Human Services is considering expanding the procedure to clinical practice, but data are limited to small case series that did not include donors without HIV as controls.

METHODS

In an observational study conducted at 26 U.S. centers, we compared transplantation of kidneys from deceased donors with HIV and donors without HIV to recipients with HIV. The primary outcome was a safety event (a composite of death from any cause, graft loss, serious adverse event, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection), assessed for noninferiority (margin for the upper bound of the 95% confidence interval, 3.00). Secondary outcomes included overall survival, survival without graft loss, rejection, infection, cancer, and HIV superinfection.

RESULTS

We enrolled 408 transplantation candidates, of whom 198 received a kidney from a deceased donor; 99 received a kidney from a donor with HIV and 99 from a donor without HIV. The adjusted hazard ratio for the composite primary outcome was 1.00 (95% confidence interval [CI], 0.73 to 1.38), which showed noninferiority. The following secondary outcomes were similar whether the donor had HIV or not: overall survival at 1 year (94% vs. 95%) and 3 years (85% vs. 87%), survival without graft loss at 1 year (93% vs. 90%) and 3 years (84% vs. 81%), and rejection at 1 year (13% vs. 21%) and 3 years (21% vs. 24%). The incidence of serious adverse events, infections, surgical or vascular complications, and cancer was similar in the groups. The incidence of HIV breakthrough infection was higher among recipients of kidneys from donors with HIV (incidence rate ratio, 3.14; 95%, CI, 1.02 to 9.63), with one potential HIV superinfection among the 58 recipients in this group with sequence data and no persistent failures of HIV treatment.

CONCLUSIONS

In this observational study of kidney transplantation in persons with HIV, transplantation from donors with HIV appeared to be noninferior to that from donors without HIV. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT03500315.)

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Kidney transplantation provides a survival benefit for persons with human immunodeficiency virus (HIV) and end-stage renal disease,[1] but access is limited by a shortage of available organs. In particular, persons with HIV who are receiving dialysis have a higher risk of death[2,3] and less access to kidney transplantation[4,5] than persons without HIV.

Kidney transplantation from donors with HIV to recipients with HIV is a strategy that addresses the organ shortage and mitigates disparities in mortality among candidates on the waiting list and in transplantation access. Good outcomes from a series in South Africa involving transplantation from donors with HIV to recipients with HIV provided preliminary evidence to support this practice.[6,7] In the United States, transplantation from donors with HIV to recipients with HIV was historically banned; however, after the passage of the HIV Organ Policy Equity (HOPE) Act in 2013[8-10] and the publication of research guidance from the Department of Health and Human Services (HHS) in 2015,[11] the procedure became legal as research only, and implementation of kidney transplantation from donors with HIV to recipients with HIV for research purposes began in 2016.[12]

A HOPE pilot study in the United States that included 25 persons with HIV who received kidney transplants from donors with HIV showed the feasibility of the procedure with encouraging short-term results.[13] However, that study was not designed or powered to determine whether kidney transplantation from donors with HIV to recipients with HIV would be noninferior to kidney transplantation from donors without HIV to recipients with HIV, given the potential risks of donor-derived HIV superinfection, opportunistic infections, and the increased incidence of allograft rejection or dysfunction.[14] Such determination is critical because the HHS secretary is tasked by the HOPE Act with deciding whether kidney transplantation from donors with HIV to recipients with HIV should move from research to clinical practice.[15]

We conducted a multicenter, observational study that was larger than the HOPE pilot study and that was designed to assess whether kidney transplantation from donors with HIV to recipients with HIV would be safe and would be noninferior to transplantation from donors without HIV. In addition, we assessed the risks of HIV breakthrough infection, HIV superinfection, and post-transplantation complications.

METHODS

STUDY DESIGN AND OVERSIGHT

Our observational, noninferiority study compared kidney transplantation from deceased donors with HIV to recipients with HIV with that from deceased donors without HIV to recipients with HIV at 26 transplantation centers in the United States (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The study was designed by the principal investigators and by the project team at the National Institute of Allergy and Infectious Diseases (NIAID), Division of Allergy, Immunology, and Transplantation (DAIT). HHS HOPE Act research criteria were followed.[11] The institutional review board at each center approved the study. All the participants provided written informed consent. The NIAID–DAIT data and safety monitoring board reviewed annually. The protocol (available at NEJM.org) included pausing rules if the incidence of allograft rejection, graft loss, biopsy complications, or HIV breakthrough infection exceeded prespecified thresholds.

Data were managed by the Johns Hopkins Transplant and Oncology Infectious Diseases Clinical Research Center and were analyzed by the investigators and the NIAID–DAIT team. The first author wrote the first draft of the manuscript; all the authors revised the manuscript and approved the final version for submission. The first two authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

This study used data from the Scientific Registry of Transplant Recipients (SRTR), which includes data on all donors, candidates on the waiting list, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, Department of Health and Human Services, oversees the activities of the OPTN and SRTR contractors.

STUDY PARTICIPANTS

Persons with HIV and end-stage renal disease were eligible if they were 18 years of age or older, met local criteria for kidney transplantation,

and consented to consider receiving a kidney from a deceased donor with HIV. Additional criteria included a CD4+ cell count of at least 200 cells per microliter, active antiretroviral therapy, and an HIV RNA level of less than 50 copies per milliliter. Exclusion criteria were an active opportunistic infection, previous progressive multifocal leukoencephalopathy, and central nervous system lymphoma.

INTERVENTION

All the participants provided consent and were eligible to receive a kidney from a donor with or without HIV, whichever was available first. Allocation could not be randomized because of constraints of the national OPTN (e.g., blood type, HLA matching, and geographic location). To account for the potential overenrollment of participants into the group receiving a kidney from a donor without HIV, some participants in this group were randomly assigned to a limited observational group with the use of a balancing rule. Investigators were unaware of the outcomes according to group until study completion.

According to HOPE research criteria, donors with HIV could not have an active opportunistic infection or cancer. There were no criteria for donors with respect to the HIV RNA level or CD4+ cell count; however, investigators had to anticipate and prescribe effective antiretroviral therapy that recipients would receive after transplantation.[11] Donors without HIV were evaluated according to local criteria. As previously described, some donors had false positive tests for HIV.[16] According to OPTN, all donors in the United States are screened for HIV with the use of antibody and nucleic acid testing. Donors without known HIV who had a single positive test for HIV were suspected to have a false positive test but were treated as having HIV during allocation. Subsequently, confirmatory testing was performed by OPTN or the HOPE in Action laboratory, with results available within 7 days or less. All the donors with a suspected false positive test underwent a subsequent negative confirmatory test; accordingly, recipients of kidneys from these donors were assigned to the group whose donors did not have HIV.

MEASUREMENTS AND OUTCOME DEFINITIONS

Participant visits occurred before transplantation; at transplantation; at weeks 1, 2, 3, 4, 13, and 26 after transplantation; and then every 6 months for a minimum of 1 year and for up to 4 years. Data on medications, hospitalizations, infections, and laboratory values were collected at each visit. An allograft biopsy was performed at transplantation, at weeks 26 and 52 after transplantation, and when clinically indicated. Testing for donor-specific antibodies was performed before transplantation, at week 52 after transplantation, and when clinically indicated.

The primary outcome, assessed in a time-to-event analysis, was a safety event, defined as a composite of death from any cause, graft loss, serious adverse event, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection, whichever occurred first. Graft loss was defined as the use of renal-replacement therapy for at least 90 days, graft nephrectomy, or repeat transplantation. Serious adverse events were defined according to the Division of Acquired Immunodeficiency Syndrome Table for Grading the Severity of Adult and Pediatric Adverse Events.[17] HIV breakthrough infection was defined as at least two consecutive measurements of an HIV RNA level of more than 200 copies per milliliter or as one measurement of more than 1000 copies per milliliter. Persistent failure of HIV treatment was defined as an HIV RNA level of more than 1000 copies per milliliter for more than 90 days. Opportunistic infections included acquired immunodeficiency syndrome (AIDS)–defining conditions as defined by the Centers for Disease Control and Prevention (CDC).[18]

Secondary outcomes included overall survival, survival without graft loss, serious adverse events, allograft rejection, graft function, HIV breakthrough infection, persistent failure of HIV treatment, CD4+ cell count, infection, surgical or vascular complications, cancer, and new donor-specific antibodies at week 52 after transplantation. Rejection was categorized as clinically suspected and treated or as biopsy-proven, according to the Banff classification.[19] Graft function was defined as the estimated glomerular filtration rate (eGFR), as assessed by means of the 2021 Chronic Kidney Disease Epidemiology Collaboration equation, a tool that omits race.[20] Infections were defined with the use of CDC definitions for AIDS-defining conditions[18] and Swiss Transplant Cohort Study definitions for other infections.[21] Kaposi's sarcoma–associated herpesvirus infection was considered to be both

an opportunistic infection and cancer. Induction therapy, maintenance immunosuppression, and infection prophylaxis were administered according to local practice (Table S2).

HIV SUPERINFECTION

HIV superinfection was defined as the acquisition of a new, genetically distinct strain of HIV and was evaluated among recipients of kidneys from donors with HIV as previously described.[22] Genomic DNA was extracted from recipient and donor peripheral-blood mononuclear cells. Site-directed next-generation sequencing for HIV reverse transcriptase (*HIV pol*) and glycoprotein 41 (*gp41*) was performed (MiSeq, Illumina). Phylogenetic analyses were conducted to identify genetically distinct viral populations after transplantation, which were considered to be potential HIV superinfections or dual infections.

STATISTICAL ANALYSIS

The primary outcome was adjusted for factors potentially associated with transplantation outcomes, including recipient hepatitis C viremia, treatment with antithymocyte globulin (ATG), and participation in a trial of C-C motif chemokine receptor 5 blockade (ClinicalTrials.gov number, NCT02741323). The hazard ratio for the primary-outcome safety event was compared between the groups with the use of Cox regression analysis in a noninferiority framework; a margin of 3.00 for the upper bound of the 95% confidence interval was selected to indicate noninferiority with respect to a survival benefit of kidney transplantation in persons with HIV.[1] Prespecified sensitivity analyses included the primary outcome with adjustment for age, sex, race, CD4+ cell count, and the duration of renal-replacement therapy; individual components of the composite primary outcome; and opportunistic infections. On the basis of estimated event rates, we calculated that 100 participants per group would provide the study with 96% power to determine noninferiority with respect to the primary outcome, at a two-sided alpha of 0.05.

With respect to secondary outcomes, recurrent events and the proportions of participants with new donor-specific antibodies were quantified with the use of Poisson regression. Multilevel mixed-effects linear regression with a participant-level random intercept was used to analyze the eGFR. No correction was made to account for multiple comparisons. Missing data on longitudinal outcomes were assumed to be missing at random; data for participants who died were censored for longitudinal outcomes.

To ensure completeness, data were linked to the SRTR.[23] All the analyses were two-tailed (alpha, 0.05) and were performed with the use of Stata/MP software, version 17.0 (StataCorp).

RESULTS

RECIPIENT AND DONOR CHARACTERISTICS

From April 2018 through September 2021, a total of 515 persons with HIV consented to participate in the study; 408 participants were eligible for transplantation and put on a waiting list (Fig. S1). Of those participants, 58 were withdrawn from the study and 209 received a transplant, leaving 141 participants on the waiting list; 2 of the 209 participants withdrew on the day of transplantation, and 9 recipients of a kidney from a donor without HIV were randomly assigned to limited observation, which left 198 participants who had received a kidney transplant from a deceased donor (99 participants who had received a kidney from a donor with HIV and 99 who had received a kidney from a donor without HIV) in the analysis group. The characteristics of the recipients and transplantations were similar in the two groups.

There were 146 donors: 64 donors with HIV and 82 without HIV; a total of 27 donors without HIV initially had a false positive test for HIV. The characteristics of the donors were similar in the two groups, except that the donors with HIV were more often Black, had a lower median Kidney Donor Profile Index score, and were more often seropositive for hepatitis B and cytomegalovirus than the donors without HIV (Table 1).

PRIMARY OUTCOME

The median follow-up was 2.2 years (interquartile range, 1.8 to 3.1) among recipients of kidneys from donors with HIV and 2.3 years (interquartile range, 1.5 to 3.2) among recipients of kidneys from donors without HIV. With regard to the composite primary outcome (a composite of death from any cause, graft loss, serious adverse event, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection), the adjusted hazard ratio in the group whose donors had HIV as compared with the

Table 1. Characteristics of Kidney-Transplant Recipients with HIV and Donors, According to Donor HIV Status.*

Characteristic	Donors with HIV	Donors without HIV	Absolute SMD
Recipients			
No. of recipients	99	99	
Median age (IQR) — yr	53 (45–60)	57 (50–63)	0.264
Female sex — no. (%)	16 (16)	19 (19)	0.080
Race or ethnic group — no. (%)†			0.296
Black	72 (73)	69 (70)	
White, non-Hispanic	10 (10)	13 (13)	
Hispanic or Latino	10 (10)	15 (15)	
Other	7 (7)	2 (2)	
Hepatitis C antibody–positive — no. (%)	9 (9)	17 (17)	0.241
Positive hepatitis C nucleic acid test — no./total no. (%)	1/9 (11)	6/17 (35)	0.598
HIV RNA level <200 copies/ml at transplantation — no. (%)‡	98 (99)	98 (99)	0
Median CD4+ cell count (IQR) — cells/μl	511 (375–652)	492 (362–686)	0.021
Antiretroviral therapy — no. (%)			
Containing a protease inhibitor or cobicistat	6 (6)	6 (6)	0
Containing integrase strand transfer inhibitor	98 (99)	95 (96)	0.194
Cause of kidney failure — no. (%)§			0.092
HIV-associated nephropathy	34 (34)	36 (36)	
Diabetes	23 (23)	25 (25)	
Hypertension	20 (20)	17 (17)	
Median duration of renal-replacement therapy (IQR) — yr	4.1 (2.6–6.1)	4.8 (2.6–7.6)	0.359
Induction immunosuppression — no. (%)			0.187
ATG or ATGAM	61 (62)	63 (64)	0.042
Basiliximab	34 (34)	33 (33)	0.021
ATG or ATGAM plus basiliximab	4 (4)	2 (2)	0.118
Maintenance immunosuppression — no. (%)			
Tacrolimus	96 (97)	98 (99)	0.144
Mycophenolate mofetil or mycophenolic acid	96 (97)	95 (96)	0.054
Glucocorticoids	77 (78)	82 (83)	0.127
Participation in CCR5 trial — no. (%)	30 (30)	23 (23)	0.160
Donors			
No. of donors	64	82	
Median age (IQR) — yr	36 (28–45)	40 (30–49)	0.305
Female sex — no. (%)	18 (28)	26 (32)	0.078
Race or ethnic group — no. (%)¶			0.480
Black	25 (39)	17 (21)	
White, non-Hispanic	30 (47)	47 (57)	
Hispanic or Latino	9 (14)	15 (18)	
Other	0	3 (4)	
Median Kidney Donor Profile Index score (IQR)‖	38 (26–54)	53 (35–69)	0.407
Hepatitis C antibody virus–positive — no. (%)	3 (5)	10 (12)	0.273

Table 1. (Continued.)

Characteristic	Donors with HIV	Donors without HIV	Absolute SMD
Hepatitis C RNA detectable — no. (%)	2 (3)	8 (10)	0.273
False positive HIV test — no. (%)	NA	27 (33)	NA

* An unabridged version of this table is shown in Table S3. ATG indicates rabbit antithymocyte globulin, ATGAM equine antithymocyte globulin, CCR5 C-C motif chemokine receptor 5, HIV human immunodeficiency virus, IQR interquartile range, NA not applicable, and SMD standardized mean difference.
† Race and ethnic group of the recipients were determined by the investigator.
‡ One recipient of a kidney from a donor with HIV had an HIV RNA level of 423 copies per milliliter at transplantation, which decreased to less than 20 copies per milliliter 9 days after transplantation. One recipient of a kidney from a donor without HIV had an HIV RNA level of 38,679 copies per milliliter at transplantation, which decreased to less than 40 copies per milliliter 30 days after transplantation.
§ Other causes of kidney failure are listed in Table S3 in the Supplementary Appendix.
¶ Race and ethnic group of the donors were recorded from medical records.
‖ Scores range from 0 to 100, with higher values indicating a greater risk of graft loss.

group whose donors did not have HIV was 1.00 (95% confidence interval [CI], 0.73 to 1.38), which showed noninferiority (Fig. 1A). Results of prespecified sensitivity analyses are shown in Figure 1B.

SECONDARY OUTCOMES

The adjusted incidence rate ratio of opportunistic infections in the group whose donors had HIV as compared with the group whose donors did not have HIV was 1.28 (95% CI, 0.51 to 3.18) (Fig. 1B). Overall survival was 94% among recipients of kidneys from donors with HIV and 95% among recipients of kidneys from donors without HIV at 1 year and was 85% and 87%, respectively, at 3 years (Fig. 2A and Table S4). Survival without graft loss in the two groups was 93% and 90%, respectively, at 1 year and was 84% and 81% at 3 years (Fig. 2B and Table S5).

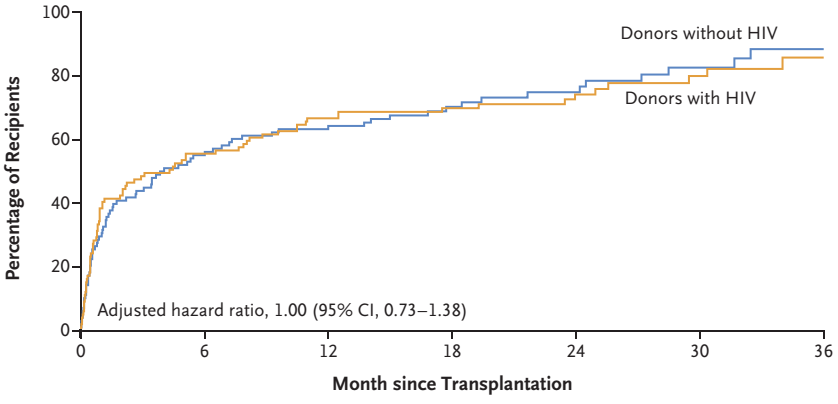
The incidence of rejection was 13% among recipients of kidneys from donors with HIV and 21% among recipients of kidneys from donors without HIV at 1 year, and was 21% and 24%, respectively, at 3 years (Fig. 2C and Table S6). Data on overall survival, survival without graft loss, and rejection in the observational group whose donors did not have HIV are provided in Table S7. The incidence rate ratio for rejection in the group whose donors had HIV as compared with the group whose donors did not have HIV was 0.63 (95% CI, 0.37 to 1.10) (Table 2). The median eGFR was 49 ml per minute per 1.73 m^2 (interquartile range, 37 to 60) among recipients of kidneys from donors with HIV and 48 ml per minute per 1.73 m^2 (interquartile range, 36 to 60) among recipients of kidneys from donors without HIV at 1 year and was 41 ml per minute per 1.73 m^2 (interquartile range, 26 to 60) and 48 ml per minute per 1.73 m^2 (interquartile range, 33 to 69), respectively, at 3 years (Figs. S3 and S4).

The incidence of serious adverse events, infections, infections leading to hospitalization, opportunistic infections, surgical or vascular complications, or cancer did not differ between the two study groups (Table 2 and Tables S8 and S9). There were 19 opportunistic infection events: 11 in the group whose donors had HIV and 8 in the group whose donors did not have HIV. The two most common infections were cytomegalovirus and esophageal candidiasis. A total of 17 HIV-breakthrough infections occurred, with 13 in the group whose donors had HIV and 4 in the group whose donors did not have HIV (incidence rate ratio, 3.14; 95% CI, 1.02 to 9.63) (Table 2 and Table S10). The most common reason for breakthrough infection was nonadherence to antiretroviral therapy (11 of 17 breakthrough infections); in all cases, the HIV RNA level decreased to less than 200 copies per milliliter at a median of 26 days after the HIV-breakthrough infection event.

HIV SUPERINFECTION

Among the 99 recipients of kidneys from donors with HIV, 71 had sequence amplification of *HIV pol*, *gp41*, or both before transplantation and at one time point or more after transplantation.

A Cumulative Incidence of Composite Primary-Outcome Event among Recipients with HIV



No. at Risk							
Donors without HIV	99	44	35	21	14	7	3
Donors with HIV	99	44	33	26	17	9	4

B Adjusted Relative Risks of Primary- and Secondary-Outcome Event among Recipients with HIV

Outcome	Donors with HIV	Donors without HIV	Adjusted Relative Risk (95% CI)
	no. of events/no. of recipients		
Primary outcome: composite safety event	79/99	77/99	1.00 (0.73–1.38)
Composite safety event, with additional adjustment	79/99	77/99	1.05 (0.75–1.47)
Death	12/99	11/99	0.93 (0.39–2.20)
Death or graft loss	14/99	17/99	0.72 (0.34–1.51)
Death, graft loss, or first serious adverse event	74/99	76/99	0.96 (0.68–1.34)
Death, graft loss, first serious adverse event, or first opportunistic infection	75/99	76/99	1.00 (0.71–1.40)
Secondary outcome: opportunistic infection	11/99	8/99	1.28 (0.51–3.18)

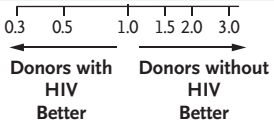


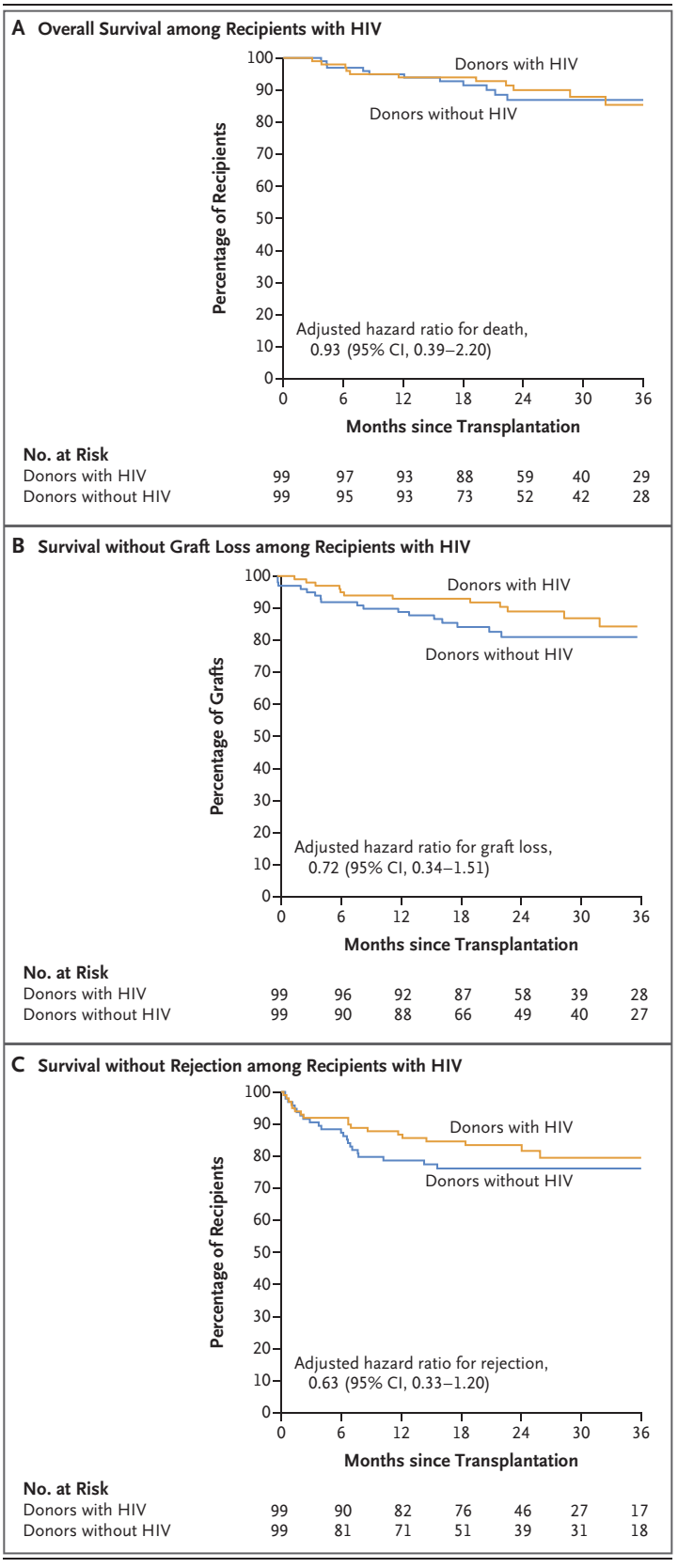
Figure 1. Composite Primary Outcome and Sensitivity Analyses.

Panel A shows the cumulative incidence of a safety event (primary outcome), which was defined as a composite of death from any cause, graft loss, serious adverse event, human immunodeficiency virus (HIV) breakthrough infection, persistent failure of HIV treatment, or opportunistic infection, among kidney-transplant recipients with HIV. Of 99 recipients of a kidney from a donor with HIV, 79 had a primary-outcome event: 71 had a serious adverse event, 6 had HIV breakthrough infection, 1 had an opportunistic infection, and 1 died. Of 99 recipients of a kidney from a donor without HIV, 77 had a primary-outcome event: 70 had a serious adverse event, 3 had graft loss, 2 had HIV breakthrough infection, and 2 had opportunistic infection. The median time without a primary-outcome event was 0.36 years (interquartile range, 0.05 to 2.08) among recipients of kidneys from donors with HIV and 0.34 years (interquartile range, 0.05 to 2.02) among recipients of kidneys from donors without HIV. Panel B shows the adjusted relative risk (hazard ratio is shown for all outcomes except the secondary outcome of opportunistic infection, for which incidence rate ratio is shown) for each outcome in the prespecified sensitivity analyses of the primary outcome with adjustment for age, sex, race, CD4+ cell count, and the duration of renal-replacement therapy; individual components of the composite primary outcome; and opportunistic infections. The shaded area indicates the prespecified noninferiority margin of 3.00. Kaplan–Meier estimates of prespecified components of the primary outcome are shown in Figure S2.

Of these 71 participants, 58 had successful amplification of the same region at both time points, which allowed for longitudinal phylogenetic analysis. In 1 of these 58 participants, a genetically distinct viral population was identified after transplantation (Fig. S5). HIV sequence amplification from donor peripheral-blood mononuclear cells was unsuccessful in this case; therefore, this participant was categorized as having a potential HIV superinfection (Table S11).

Figure 2. Overall Survival, Survival without Graft Loss, and Survival without Rejection.

Shown are the Kaplan–Meier estimates of overall participant survival (Panel A), survival without graft loss (Panel B), and survival without rejection (Panel C). Overall survival was 94% (95% CI, 87 to 97) among recipients of kidneys from donors with HIV and 95% (95% CI, 88 to 98) among recipients of kidneys from donors without HIV at 1 year, and was 85% (95% CI, 74 to 92) and 87% (95% CI, 77 to 93), respectively, at 3 years. Twelve deaths occurred in the group whose donors had HIV and 11 deaths occurred in the group whose donors did not have HIV. Survival without graft loss was 93% (95% CI, 86 to 97) in the group whose donors had HIV and 90% (95% CI, 82 to 94) in the group whose donors did not have HIV at 1 year and was 84% (95% CI, 73 to 91) and 81% (95% CI, 71 to 88), respectively, at 3 years. Rejection occurred in 13% of the participants (95% CI, 8 to 22) who received kidneys from donors with HIV and in 21% of those (95% CI, 14 to 31) who received kidneys from donors without HIV at 1 year and in 21% (95% CI, 13 to 31) and 24% (95% CI, 16 to 34), respectively, at 3 years.



DISCUSSION

In this multicenter, noninferiority, observational study involving transplantation candidates with HIV, we found that kidney transplantation from donors with HIV was noninferior to kidney transplantation from donors without HIV with respect to the primary safety outcome (a composite of death from any cause, graft loss, serious adverse event, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection). No meaningful difference was observed between the two groups in terms of overall survival, survival without graft loss, or rejection. Furthermore, the incidence of serious adverse events, infections, surgical or vascular complications, and cancer was similar in the two groups. The occurrence of HIV breakthrough infection was approximately three times as high in the group whose donors had HIV as in the group whose donors did not have HIV, primarily because of nonadherence to antiretroviral therapy. In all participants with HIV breakthrough infection, viral suppression was regained. A single case of potential HIV superinfection or dual infection occurred, without clinical consequences. Taken together, these outcomes support the expansion of kidney transplantation involving donors and recipients with HIV from research to clinical care.

Table 2. Post-Transplantation Events According to Donor HIV Status.

Outcome	Donors with HIV (N=99)		Donors without HIV (N=99)		Crude Incidence Rate Ratio (95% CI)
	Participants with Event	Total No. of Events	Participants with Event	Total No. of Events	
Serious adverse event — no. (%)	74 (75)	206	76 (77)	222	0.90 (0.74–1.08)
Allograft rejection — no. (%)	18 (18)	21	22 (22)	32	0.63 (0.37–1.10)
Allograft rejection at 1 yr — no. (%)	13 (13)	13	20 (20)	25	0.52 (0.26–1.01)
HIV breakthrough infection — no. (%)	10 (10)	13	4 (4)	4	3.14 (1.02–9.63)
Persistent failure of HIV treatment — no.	0	0	0	0	NA
Any infection — no. (%)	81 (82)	273	71 (72)	229	1.15 (0.97–1.37)
Opportunistic infection — no. (%)	8 (8)	11	7 (7)	8	1.33 (0.53–3.30)
Any infection with hospitalization — no. (%)	43 (43)	94	43 (43)	97	0.94 (0.70–1.24)
Surgical or vascular complication — no. (%)	12 (12)	17	19 (19)	23	0.71 (0.38–1.34)
Cancer — no. (%)	8 (8)	9	6 (6)	6	1.45 (0.52–4.07)
New donor-specific antibodies at 1 yr — no./total no. (%)*	9/67 (13)	9	13/59 (22)	13	0.61 (0.28–1.33)

* A total of 32 recipients of kidneys from donors with HIV and 40 recipients of kidneys from donors without HIV had no donor-specific antibody data either at day 0 or at 1 year.

More than 500 persons with HIV consented to participate in this study, with the age, sex, and race or ethnic group of these participants being generally similar to what has been reported among persons with HIV and end-stage renal disease in the United States (Table S12).[24,25] At the close of the study, 141 participants remained on the kidney transplantation waiting list; most of these participants subsequently enrolled in a follow-up study involving donors and recipients with HIV, highlighting the need for kidney transplantation in persons with HIV.[4,5] Although the annual number of donors with HIV has not yet reached the projected potential number,[9,26-28] it has been increasing over time,[29] and a substantial advantage with respect to wait time exists for recipients who are willing to accept kidneys from donors with HIV.[30]

Overall survival among participants with HIV who received a kidney transplant from a donor with HIV was slightly lower in our study (94% at 1 year) than in the HOPE kidney transplantation pilot study (100% at 1 year).[13] This difference may be due to the coronavirus disease 2019 (Covid-19) pandemic, which occurred after the pilot study; 8 of 23 participants with Covid-19 died during our study. Nonetheless, overall survival among the 99 recipients of kidneys from donors with HIV in our study (94% at 1 year and 85% at 3 years) was similar to survival among the 51 recipients with HIV in South Africa (87% at 1 year and 87% at 3 years)[31] and among the 150 recipients with HIV in the National Institutes of Health (NIH) Transplant Recipient cohort (95% at 1 year and 88% at 3 years),[32] all of whom received kidneys from donors with HIV. Moreover, survival without graft loss in our study (93% at 1 year and 84% at 3 years) was higher than that observed in the South Africa cohort (75% at 1 year and 61% at 3 years)[31] and in the NIH Transplant Recipient cohort (90% at 1 year and 74% at 3 years).[32] These data may reflect improvements in post-transplantation treatment of persons with HIV over time[33] or the effects of curative treatment for hepatitis C virus (HCV), a common coexisting disease among persons with HIV that is associated with lower graft survival.[32,34] In our study, most recipients with HCV were cured before transplantation, with only seven recipients having HCV viremia at transplantation.

In previous studies, rejection was recognized as an increased risk among kidney-transplant recipients with HIV.[32,35] Multiple factors contributing to rejection in these recipients have been proposed, including lower overall exposure to

immunosuppressants owing to interactions with antiretroviral therapy[32,36] or immune dysregulation resulting from HIV. The observed incidence of rejection varies according to type of immunosuppression, with a lower incidence of rejection with the receipt of ATG induction therapy than with non–lymphocyte-depleting therapy,[35,37] and with tacrolimus for maintenance than with cyclosporine.[32,38] In our study, the incidence of rejection among recipients of transplants from donors with HIV (13% at 1 year and 21% at 3 years) was lower than that observed in the HOPE kidney transplantation pilot study (50% at 1 year).[13] One explanation is that 66% of the participants in our study received ATG, as compared with 33% of those in the pilot study. The incidence of rejection was also lower in our study than in the South Africa cohort of donors and recipients with HIV (25% at 1 year and 39% at 3 years).[31] In that cohort, 100% of the recipients were receiving ATG; however, 24% of the recipients were also receiving a protease inhibitor as antiretroviral therapy (which interacts with maintenance immunosuppression), as compared with only 6% of the recipients in our study who were receiving a protease inhibitor or cobicistat. The incidence of rejection was also lower in our study than in the NIH Transplant Recipient cohort of recipients with HIV and donors without HIV (31% at 1 year and 41% at 3 years); in that study, only 32% of the participants received ATG induction therapy, 66% received tacrolimus maintenance, and 42% received protease inhibitors.

The participants in our study had 19 opportunistic infections (11 in the group whose donors had HIV and 8 in the group whose donors did not have HIV), which was a lower incidence than that observed in the HOPE kidney transplantation pilot study.[13] The adjusted incidence rate ratio was 1.28 in the group whose donors had HIV as compared with the group whose donors did not have HIV. Herpesvirus infections, which are more prevalent among donors with HIV than among those without HIV,[29] were the most common infections, followed by esophageal candidiasis. The incidence of infections warranting hospitalization was similar in the two groups.

Donor-derived HIV superinfection is a risk associated with the transplantation of kidneys from donors with HIV to recipients with HIV, which could contribute to HIV breakthrough infection or to persistent failure of HIV treatment. In our study, 17 HIV breakthrough infections occurred. However, in all cases, the HIV RNA level subsequently decreased to less than 200 copies per milliliter without resistance to antiretroviral therapy. According to phylogenetic analysis, one recipient of a kidney from a donor with HIV had a potential HIV superinfection or dual infection without HIV breakthrough infection. In the HOPE kidney transplantation pilot study, no HIV superinfections were detected among 14 donors and recipients with HIV.[22] In the South Africa cohort of donors and recipients with HIV, donor virus was transiently detected in 8 of 24 recipients at the earliest time points after kidney transplantation, with one case of a donor-derived minor variant at 12 weeks after kidney transplantation, which was not sustained.[31] Similarly, in a U.S. case report of kidney transplantation involving donors and recipients with HIV, in-depth viral analysis revealed transient detection of donor HIV sequences in recipient urine and renal cells, but donor HIV was not detected at later time points.[39] These data suggest that HIV superinfection is rare and is without clear clinical ramifications.

Our study has certain limitations. True randomization of organs from donors with and those without HIV was not possible because of OPTN allocation constraints (e.g., blood type, HLA matching, and geographic location). However, participants were equally eligible for a kidney from a donor with or a donor without HIV; group assignment was determined according to whichever organ was available first. Furthermore, the group whose donors did not have HIV served as a control group and included 27 donors who had false positive HIV tests and were treated as having HIV during allocation; recipients of kidneys from these donors represent an ideal counterfactual control group. Immunosuppression and prophylaxis were heterogeneous; however, these factors were balanced between the two groups and reflect real-world practice, which increases the generalizability of our results.

This multicenter, observational study showed that kidney transplantation from donors with HIV to recipients with HIV is noninferior to kidney transplantation from donors without HIV to recipients with HIV.

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APPENDIX

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