**HLA-DQ Mismatches Lead to More Unacceptable Antigens, Greater Sensitization and Increased Disparities, as Demonstrated in Repeat Transplant Candidates**

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**Significance Statement**

HLA-DQ donor-specific antibodies are associated with antibody-mediated rejection and renal graft loss in single-center studies, however HLA-DQ remains largely unaccounted for in kidney allocation. US transplant registries do not include donor-specific antibody data, precluding direct analysis of HLA-DQ mismatches and transplant outcomes. Our innovation in this work was to examine patients in the Scientific Registry of Transplant Recipients relisted after graft failure with unacceptable antigens corresponding to the HLA typing of their previous donor as a proxy for donor-specific antibodies. Mismatched HLA-DQ antigens were the most likely to be designated as unacceptable, especially in African American and Hispanic patients. HLA-DQ unacceptable antigens precipitated sensitization greater than or equal to any other HLA locus. These findings underscore the immunogenicity of HLA-DQ mismatches, which ultimately serves as a barrier to transplantation.

**Abstract**

*Background*

In single-center studies, HLA-DQ mismatches stimulate the most pathogenic donor-specific antibodies, however this cannot be directly confirmed with registry-based analyses.

*Methods*

We evaluated patients in the Scientific Registry of Transplant Recipients who were relisted after renal graft failure with new unacceptable antigens corresponding to the HLA typing of their previous donor (UA-PD) as a proxy for donor-specific antibodies. Linear regression was applied to estimate the effects of HLA mismatches on UA-PD and of UA-PD on calculated panel reactive antibody (cPRA) values for 4,867 kidney recipients from 2010-2021.

*Results*

HLA-DQ mismatches increased the probability of UA-PD by 25.2% in deceased donor recipients and 28.9% in living donor recipients, significantly more than all other HLA loci ($p<0.05$). HLA-DQ UA-PD increased cPRA by 23.5% in deceased donor recipients and 29.0% in living donor recipients, significantly more than all loci except for HLA-A in deceased donor recipients (23.1%). African American deceased donor recipients (29.3%) were more likely to develop HLA-DQ UA-PD than Hispanic (24.0%) and White recipients (21.6%, $p<0.05$). African American (34.1%) and Hispanic (33.0%) living donor recipients were more likely to develop HLA-DQ UA-PD than White recipients (27.6%, $p<0.05$). Models evaluating interactions between HLA-DR/DQ mismatches revealed largely independent effects of HLA-DQ mismatches on HLA-DQ UA-PD.

*Conclusions*

HLA-DQ mismatches had the strongest associations with UA-PD, an effect that was greatest in African American and Hispanic recipients. cPRA increases with HLA-DQ UA-PD were equivalent or larger than any other HLA locus. This suggests a need to consider the effects of HLA-DQ in kidney allocation.

**Introduction**

Kidney transplantation is the most definitive treatment for end-stage renal disease (ESRD) and confers improved longevity and quality of life as compared to dialysis.[1,2] While current US trends have shown improvements in graft survival, more than 20% of deceased donor and 10% of living donor kidneys still fail by five years.[3]

Antibody-mediated rejection (ABMR) is the leading cause of graft loss after kidney transplantation.[4] Correspondingly, donor-specific antibodies (DSA) produced by recipients against mismatched human leukocyte antigens (HLA) are highly predictive of graft failure.[5-7] Although single-center studies have demonstrated that donor HLA-DQ antigens stimulate the most common and pathogenic DSA,[8-11] HLA-DQ matching is not yet considered in many kidney-matching algorithms, including the US Kidney Allocation System.[12]

Registry-based analyses of HLA-DQ matching and kidney transplant outcomes have shown variable results. Early studies found no associations between serologic DQ mismatches and graft outcomes.[13,14] Subsequent analyses demonstrated effects of HLA-DQ mismatches on rejection episodes and biopsy-proven ABMR[15] and on graft loss in living donor recipients and deceased donor recipients with cold ischemic times ≤17h.[16] These registry-based studies have several key limitations. Inclusion of records prior to 2010 risks bias due to higher rates of missing HLA-DQ data and heterogeneous HLA typing methods. The Scientific Registry of Transplant Recipients (SRTR) includes HLA typing only at low resolution with serologic-equivalent (1-field) typing, as opposed to modern high-resolution allele-level (2-field) typing. This prevents rigorous analysis of HLA mismatches as donor/recipient types that appear matched with 1-field coding may truly be mismatched at the allelic level.[17,18] Finally, the SRTR does not record DSA or ABMR, preventing direct study of DQ DSA and transplant outcomes.

Given these limitations, we conceived a novel analysis of SRTR data to assess the effects of HLA-DQ mismatches in kidney transplantation. We identified patients who were relisted after a failed first transplant and used the incidence of new unacceptable antigens corresponding to the HLA typing of their previous donor (UA-PD) as a proxy for DSA. Unacceptable antigens (UA) refer to potential donor antigens analogous to a candidate's existing HLA antibodies and are designated when a candidate is initially listed or relisted and then periodically until transplantation. We propose that the presence of antibodies to the previous donor's antigens at the time of relisting is consistent with those antibodies having played a role in graft failure. We apply these principles to evaluate whether HLA-DQ mismatches have a differential effect on the development of UA-PD and recipient sensitization as compared to other HLA loci.

## Methods

### *Institutional Review Board*

This study was classified as IRB exempt by the institutional review board at Northwestern University prior to data collection and analysis.

### *Study Population*

This study used data from the Scientific Registry of Transplant Recipients. The SRTR data system includes data on all donors, wait-listed candidates and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Adult (≥18 years) patients in the SRTR who received an initial single deceased or living donor kidney transplant between January 1, 2010 and March 2, 2021 were eligible for inclusion in the study if

they were relisted after allograft failure. We limited inclusion to patients with complete donor/recipient HLA typing and recipient UA data. Subjects were excluded if they had broad HLA antigen typing listed to ensure all matching was assessed at the split (private antigen) level, if they had received other transplanted organs, or if they had experienced graft loss within thirty days after transplantation. We further excluded patients who were preemptively listed for re-transplantation to minimize the potential confounding effects of continuing full-dose immunosuppression.

*Data Collection*

Data collected on kidney donors included antigen-level HLA-A/B/C/DR and -DQ typing. Data collected on recipients included age, sex, race/ethnicity, body mass index (BMI), education level, insurance status, cause of ESRD, time on dialysis pre-transplant, dates of graft failure and re-listing, antigen-level HLA-A/B/C/DR and -DQ typing, HLA-A/B/C/DR and -DQ UA data and pre/post-transplant cPRA.

*Outcomes*

The primary outcomes of the study were: 1) the probability of relisting after graft failure with a new UA-PD given a mismatch at an HLA locus and 2) the change in cPRA from the pre-transplant value to the maximal value recorded after graft failure given development of a new UA-PD at an HLA locus. Primary outcomes were stratified by living or deceased donor status of the initial transplant kidney and by recipient race/ethnicity. Secondary analyses evaluated the interactions between the effects of HLA-DR and -DQ on the primary outcomes.

*Statistical Analyses*

Baseline demographics were expressed as percentages or medians with interquartile ranges (IQR). T-tests and one-way analyses of variance (ANOVA) were applied to determine statistical significance of differences in characteristics between groups.

To establish the relationship between HLA mismatches and UA-PD, a multiple linear regression model was created. This model assessed the effect of mismatches at an HLA locus [0-2] on relisting with new UA-PD at that locus, controlling for mismatches at all other HLA loci. The model was applied to the cohort overall and stratified by recipient race/ethnicity classifications. A second regression model was estimated to test for statistical significance of differences between the effect of DQ mismatches on DQ UA-PD versus the effects of other HLA mismatches on corresponding UA-PD. A third regression model assessed for statistical significance of differences in the probabilities of DQ UA-PD between recipients of different race/ethnicity groups.

To determine the effects of HLA-DQ mismatches on recipient sensitization, linear regression was again applied. The outcome was the increase in cPRA from the final pre-transplant value to the maximal value recorded after relisting. Independent variables were the presence of a new UA-PD at each HLA locus. To eliminate potential confounders of sensitization, this model controlled for the effects of UA at each locus not being assessed, HLA mismatches [0-2], pre-transplantation cPRA, time between graft failure and relisting and time between relisting and final follow-up. Results were calculated for the cohort overall and stratified by pre-transplantation cPRA (0%, 1-50%, 51-100%) and recipient race/ethnicity classifications. A second regression model was applied to assess for statistical significance of the differences in cPRA increases for each HLA locus as compared to HLA-DQ. A third regression model assessed the statistical significance of differences in cPRA increases with a new HLA-DQ UA-PD between subjects of different race/ethnicity groups.

To evaluate the interactions between the effects of HLA-DR and HLA-DQ in these analyses, the regression models were augmented to include HLA-DR/DQ interaction terms. In the models assessing the effects of HLA mismatches on relisting with new UA-PD, the interaction term estimates how the change in probability of UA-PD with an additional HLA-DQ mismatch differs between cases without an HLA-DR mismatch and cases with an HLA-DR mismatch. In the models evaluating cPRA changes with new

UA-PD, the interaction term estimates how the change in cPRA with an additional HLA-DQ UA-PD differs between cases without an HLA-DR UA-PD and cases with an HLA-DR UA-PD.

P-values <0.05 were considered statistically significant throughout the study. Calculations were performed in Stata version 17 (StataCorp, College Station, TX, USA).

**Results**

*Study Population*

34,891 patients experienced graft failure during the study period, of whom 28,553 (81.8%) were not relisted (Figure 1). Of the 6,338 (18.2%) patients relisted, 4,867 (76.8%) were included: 3,443 deceased donor recipients (70.7% of included patients) and 1,424 living donor recipients (29.3% of included patients).

*Baseline Characteristics*

Demographics and characteristics related to sensitization are stratified by failed deceased vs. living donor kidney and the presence/absence of new DQ UA-PD in Table 1. Characteristics are further stratified by recipient race/ethnicity in Table S1.

*Probabilities of New Unacceptable Antigens Corresponding to Previous Donor Typing*

Figure 2 depicts the probabilities that recipients would return to the waitlist after graft failure with new UA-PD (0-100.0%). Each additional HLA-DQ mismatch increased the probability of relisting with an HLA-DQ UA-PD by 25.2% in deceased donor recipients and 28.9% in living donor recipients. This probability was significantly greater than with mismatches at all other HLA loci ($p<0.05$).

*Probabilities of New Unacceptable Antigens by Recipient Race/Ethnicity*

The probabilities of relisting with new UA-PD by recipient race/ethnicity are presented in Figure 3. Analyses include African American, Hispanic and White recipients only, as we did not have sufficient subjects to include Asian/Pacific Islander recipients or recipients reporting other races/ethnicities. (See Table 1 for the distribution of the cohort by race/ethnicity).

Figure 3A-C illustrate results for deceased donor recipients. For African American deceased donor recipients, the probability that DQ mismatches would produce UA-PD (29.3%) was significantly greater than any other HLA locus ($p<0.05$). For Hispanic recipients, the probability of DQ UA-PD (24.0%) was only significantly different from HLA-C. In White recipients, the probability of DQ UA-PD (21.6%) was significantly greater than HLA-B, -C and -DR and comparable to HLA-A (22.2%). African American recipients were significantly more likely to be relisted with new DQ UA-PD as compared to Hispanic and White recipients ($p<0.05$). There was no significant difference in the probabilities of DQ UA-PD between Hispanic and White recipients.

Results for living donor recipients are depicted in Figure 3D-F. For African American living donor recipients, DQ mismatches were associated with the greatest probability of UA-PD (34.1%), significantly more than HLA-C. In Hispanic recipients, the probability of DQ UA-PD (33.0%) was significantly greater than all HLA loci except for HLA-A (26.9%). In White recipients, the probability of DQ UA-PD (27.6%) was significantly greater than all other HLA loci ($p<0.05$). Both African American and Hispanic living donor recipients were more likely to be relisted with new DQ UA-PD as compared to White recipients ($p<0.05$). There was no significant difference in the probabilities of DQ UA-PD between African American and Hispanic recipients.

*HLA Unacceptable Antigens and Increases in cPRA*

The fully adjusted analyses assessing cPRA increases with new UA-PD are depicted in Figure 4. Results are presented for deceased and living donor recipients overall and stratified by pre-

transplantation cPRA. The majority of deceased (63.1%) and living donor recipients (72.8%) were unsensitized prior to transplantation (cPRA 0%), comprising an important subgroup as the full impact of cPRA changes is most accurately captured in these patients.

In deceased donor recipients (Figure 4A-D), patients who developed new HLA-DQ UA-PD experienced mean overall cPRA increases of 23.5%, significantly greater than HLA-B, -C and -DR but not HLA-A (23.1%, Figure 4A). In initially unsensitized deceased donor recipients (Figure 4B), the average cPRA increase with a new DQ UA-PD (27.9%) was significantly greater than HLA-B, -C and -DR but not HLA-A (28.3%). In living donor recipients (Figure 4E-H), DQ UA-PD resulted in an average overall cPRA increase of 29.0%, significantly greater than all other HLA loci ($p<0.05$, Figure 4E). In previously unsensitized living donor recipients, DQ UA-PD had a significantly greater effect on cPRA (33.2%) than every other HLA locus ($p<0.05$, Figure 4F).

These effects of UA-PD on cPRA were largely independent of other potential contributors to sensitization such as overall HLA mismatches and the time intervals between graft failure, relisting and final follow-up (Table S2).

*HLA Unacceptable Antigens and Increases in cPRA by Recipient Race/Ethnicity*

The adjusted analyses evaluating cPRA increases with UA-PD are stratified by recipient race/ethnicity in Figure 5 and sub-stratified to evaluate previously unsensitized recipients in Figure 6. As in the cohort overall, the majority of African American, Hispanic and White deceased donor recipients (61.2%, 64.5% and 65.7%, respectively) and living donor recipients (67.6%, 76.0% and 74.2%, respectively) were unsensitized prior to transplantation.

In initially unsensitized deceased donor recipients (Figure 6A-C), African American recipients experienced average cPRA increases of 27.5% with a new DQ UA-PD, significantly greater than HLA-B, -C and -DR but not statistically different from HLA-A (30.6%). For Hispanic recipients, the average increase

in cPRA with a new DQ UA-PD (23.9%) was significantly greater than HLA-DR only. In White recipients, the mean cPRA increase with a new DQ UA-PD (29.9%) was significantly greater than all other HLA loci except for HLA-A (25.6%). There were no significant differences in the magnitudes of cPRA increases with DQ UA-PD between race/ethnicity groups either in the cohort overall or in the subgroup of initially unsensitized recipients.

In initially unsensitized living donor recipients (Figure 6D-F), African American recipients experienced overall mean cPRA increases of 30.4% with a new HLA-DQ UA-PD, significantly greater than all loci except HLA-A (27.6%). The cPRA increases with new DQ UA-PD for Hispanic and White living donor recipients (46.1% and 32.0%, respectively) were greater than the effects of all other HLA loci ($p<0.05$). As in deceased donor recipients, there were no significant differences in cPRA increases with DQ UA-PD between race/ethnicity groups in either the overall cohort or in previously unsensitized recipients

*Interactions of HLA-DR/DQ on Unacceptable Antigen Probabilities and cPRA Increases*

To illustrate the interactions between HLA-DR and -DQ mismatches on the probabilities of UA-PD, we formulated scenarios with example recipients demonstrating how these probabilities change with addition or removal of HLA-DR and/or DQ mismatches (Figure S1). Note that the magnitudes of the coefficients in this model are not directly comparable to those in the initial model without the DR/DQ interaction term (Figure 2). As compared to a deceased donor recipient initially transplanted with no HLA-DR or -DQ mismatches, a simulated recipient with no HLA-DR mismatches and one HLA-DQ mismatch had a 40.2% (95% CI 35.0 – 45.5%) probability of developing an HLA-DQ UA-PD and a 9.5% (95% CI 4.1 – 14.8%) probability of developing an HLA-DR UA-PD (Figure S1A). A simulated recipient with an HLA-DR mismatch and an HLA-DQ mismatch comparatively had a 41.5% (95% CI 36.3 – 46.7%) probability of developing an HLA-DQ UA-PD and a 29.0% (95% CI 23.7 – 34.2%) probability of developing

an HLA-DR UA-PD. An analogous example in living donor recipients is presented in Figure S1B. The output of the models upon which these examples are based is included in Table S3.

Similar scenarios demonstrating how overall cPRA increases vary with addition or removal of HLA-DR and/or -DQ UA-PD at relisting are presented in Figures S2 and S3. These depict hypothetical deceased (Figure S2) and living donor recipients (Figure S3) with pre-transplant cPRA of 0% (Figure S2A, S3A) or 1-50% (Figure S2B, S3B). Changes in cPRA are relative to a recipient who did not develop DR or DQ UA-PD. The output of the models upon which these scenarios are based is included in Table S4. As in Figure S1, note that the magnitudes of the coefficients in these models are not directly comparable to those in the initial model without the DR/DQ interaction term (Figure 4) and that the additive effect of DR and DQ UA-PD can be slightly lower than the individual effects due to the negative interaction term and the uncertainty of each of the estimates.

**Discussion**

We present a novel method utilizing SRTR data to quantify the differential impacts of HLA mismatches on generation of DSA (determined based on the appearance of new UA-PD at relisting) and on the likelihood of receiving an antibody-compatible deceased donor kidney after graft loss (measured as increase in cPRA). We demonstrate that HLA-DQ mismatches are associated with the highest probability of new UA-PD after graft failure, an effect that disproportionately affects African American and Hispanic recipients as compared to White recipients. We show that UA-PD at distinct HLA loci have differential effects on cPRA and that HLA-DQ has an impact greater than or equal to any other HLA locus. While this method does not prove causality, these findings are consistent with the broader literature, based largely on single-center studies using single antigen bead assays, which has shown that HLA-DQ DSA are the most common alloantibodies that develop after kidney transplantation and are strongly associated with ABMR and graft loss.[9,10,19]

The patients in our study who were relisted with new UA-PD after allograft failure, should by definition have developed *de novo* DSA. Other explanations, such as reactivation of quiescent immune responses, cannot entirely be ruled out, but are less likely given that 66% of the cohort had a pre-transplantation cPRA of 0%. Also possible is that these antibodies developed after graft failure following decreases in immunosuppression—a recent prospective multicenter study demonstrated moderate cPRA increases in recipients observed for a median of 1.5 years after kidney transplant failure.[20] We could not directly control for immunosuppression changes after graft loss as the SRTR does not record these data, however our models did not show effects of time elapsed between graft failure, relisting and final follow-up on overall sensitization, as would likely be expected if this were the primary driving factor behind the effects observed in this study[10] (Table S2).

Our analyses found that each HLA-DQ mismatch increased the probability of DQ UA-PD by 25.2% in deceased donor recipients and 28.9% in living donor recipients, an effect significantly greater than all other HLA loci (Figure 2). This suggests that HLA-DQ mismatches have the greatest impact of any HLA locus on graft loss in our cohort, although a causal relationship cannot be definitively proven within limitations of registry data. The significantly smaller probability of HLA-DR UA-PD after DR-mismatched transplantation is a notable finding given the longstanding assumption that, due to high linkage disequilibrium between HLA-DR and DQ, matching at DR implicitly results in DQ matching, rendering explicit DQ matching unnecessary.[21] Our analysis of the interactions between DR and DQ mismatches (Figure S1) goes further in supporting the independent relationship of HLA-DQ mismatches and DQ UA-PD. In these models, the effect of adding an additional DR mismatch to an existing DQ mismatch resulted in only a small absolute increase in the probability of DQ UA-PD proportional to the uncertainty of the estimates.

Overall, HLA-DQ UA-PD were associated with cPRA increases equal to or greater than with UA-PD at any other HLA locus (Figure 4). These effects were largely driven by patients who were

unsensitized (cPRA 0%) prior to transplantation, who comprised 63.1% of deceased donor recipients and 72.8% of living donor recipients. In unsensitized recipients and recipients overall (Figure 4A-B, E-F), UA-PD at HLA-A in deceased donor recipients produced the only cPRA increases not statistically distinguishable from those of HLA-DQ, effects conceivably attributable to the high population frequency of HLA-A2, which is present in close to half (48%) of US donors.[22] Effects of HLA-DQ UA-PD relative to other UA-PD in previously sensitized recipients (cPRA 1-50, 51-100%, Figure 4C-D, G-H) were less consistent, likely due to smaller sample sizes, though notably no effects were significantly greater than those of HLA-DQ. A potential contributor to these observations is that there are only seven DQ serologic specificities, the fewest of any HLA locus[23], meaning that individuals with pre-existing HLA-DQ UA may have proportionally fewer DQ antigens remaining to become unacceptable.

We analyzed the interaction between the effects of HLA-DR and HLA-DQ UA-PD on cPRA increases and demonstrated that the addition of a DR UA-PD to an existing DQ UA-PD resulted in only small changes in overall cPRA proportional to the uncertainty of the estimates (Figures S2-S3). This finding further supports the independent relationship of HLA-DQ UA-PD with recipient sensitization after graft loss. The summation of this observation with the overall findings of our study is that HLA-DQ UA-PD disqualify patients relisted for transplantation from a share of the US donor pool equal to or greater than UA-PD at any other HLA locus. This has implications in deceased donor kidney allocation, particularly in transplantation of younger patients with life expectancy greater than that of their allograft.

Racial/ethnic minority recipients, especially African Americans, are more likely to receive HLA-mismatched kidneys[24,25], to experience graft failure[24] and to return to the waitlist highly sensitized.[19,26] In this work, HLA-DQ mismatches were associated with significantly higher probabilities of UA-PD in African American deceased donor recipients as compared to Hispanic and White recipients and for African American and Hispanic living donor recipients as compared to White recipients (Figure 3).

Although African American and Hispanic recipients in our cohort were more highly sensitized than White recipients after returning to the waitlist (Table S1), we did not find any significant differences in cPRA increases with new DQ UA-PD between race/ethnicity groups (Figures 5, 6). Overall, these results are important in the context of kidney allocation, in which the paradigm has been to de-emphasize HLA matching to increase access for underserved groups.[27,28] Our findings suggest that this strategy may expose recipients to unintended risks of developing DSA and graft loss.

Our race/ethnicity findings come with caveats as illustrated by the demographic breakdown of the cohort (Table S1). After graft failure, African American and Hispanic deceased donor recipients waited an average of 456 and 243 additional days prior to relisting, respectively, as compared to White recipients. Medicaid insurance rates were comparable between African American and White recipients, however the share of Hispanic recipients with Medicaid insurance was 11.0% higher than White recipients, a factor we have previously shown trends with poor health indicators.[29] While we controlled for several potential contributors to sensitization in our models, some of which were relatively well-balanced between race/ethnicity groups (i.e., pre-transplantation cPRA), the potential existence of unidentified differences in care and socioeconomic factors necessitates a degree of caution in interpretation of our results.

Of strengths of this work, we made conservative judgements to only include patients from the era of mandated molecular HLA typing, with no missing HLA data, who were transplanted in a time period with use of consistent immunosuppressive therapies.[30] Despite this, our novel method enabled an analysis 1-2 orders of magnitude larger than previous single-center studies of HLA-DQ mismatches and DSA.

Study limitations include its retrospective design and use of registry data, in which potential confounders may not be recorded. Our analyses were reliant on low-resolution, serologic-equivalent

HLA typing, in which multiple common HLA alleles are indistinguishable within antigenic groups. One hypothesis underlying this work is that certain donor-recipient HLA mismatches are likely more immunogenic than others,[7] however we considered a mismatch-level analysis performed with antigen-level typing likely to implicate entire antigenic groups without identifying true culprit allelic mismatches. Subsequent studies using high-resolution typing should investigate the differential immunogenicity of HLA mismatches and their implications on transplantation equity given allelic distributions across donor and recipient races/ethnicities. Additionally, the resolution of our HLA data did not allow us to specifically delineate or account for cPRA increases attributable to cross-reactive antigens. Our study focuses on individuals relisted for transplant, who may not be representative of all recipients experiencing graft loss. Our race/ethnicity analyses use SRTR classifications which are based on patient self-declaration and do not distinguish between concepts of race and ethnicity.[31] Therefore, overlap may exist between patients classified as Hispanic versus African American and White.

**Conclusions**

This is the first study applying registry data to evaluate the impact of HLA mismatches on generation of DSA and recipient sensitization after renal graft failure. HLA-DQ mismatches have the highest probability of producing unacceptable antigens corresponding to previous donor typing after graft loss and these DQ UA-PD result in cPRA increases greater than or equal to any other HLA locus. The association between DQ mismatches and UA-PD is most pronounced in African American and Hispanic recipients as compared to White recipients. These findings expand the existing literature demonstrating that HLA-DQ alloantibodies are the most pathogenic and suggest a need to consider the effects of HLA-DQ in kidney allocation.

**Author Contributions**

*Conception/Design: D.I., J.D.S., M.W.G., H.C.C., V.K., A.R.T.; Data Acquisition/Analysis: D.I., J.D.S., M.W.G., V.K., A.R.T.; Manuscript Writing: D.I., J.D.S., M.W.G., H.C.C., V.K., A.R.T.; Final Approval: D.I., J.D.S., M.W.G., H.C.C., V.K., A.R.T.*

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**Disclosures**

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**Data Sharing Statement**

The data that support the findings of this study are available from the Scientific Registry of Transplant Recipients (SRTR) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the SRTR.

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**Table Legends**

**Table 1.** Demographics and characteristics related to sensitization stratified by deceased vs. living donor category of the initial failed graft and the presence or absence of a new HLA-DQ UA corresponding to prior donor typing (UA-PD). Asterisks (*) denote statistically significant differences between groups ($p<0.05$).

**Figure Legends**

**Figure 1.** Flowchart defining the subsets of eligible patients included in and excluded from the study.

**Figure 2.** Probabilities (0-100.0%) of relisting after a failed kidney transplant with a new HLA unacceptable antigen corresponding to previous donor typing (UA-PD) for each additional mismatch [0-2] at each HLA locus. The probability of relisting with an HLA-DQ UA-PD was significantly greater than for all other HLA loci in both (A) deceased donor recipients (DQ UA-PD probability of 25.2%) and (B) living donor recipients (DQ UA-PD probability of 28.9%). Asterisk (*) denotes statistically lower probability of an UA-PD for an HLA locus as compared to HLA-DQ ($p<0.05$).

**Figure 3.** Probabilities (0-100.0%) of relisting after a failed deceased donor (A-C) or living donor (D-F) kidney transplant with a new UA-PD for each additional mismatch at each HLA locus. Results are stratified by African American (A, D), White (B, E) and Hispanic (C, F) recipient race/ethnicity. Asterisk (*) denotes statistically significant difference in probability for an HLA locus as compared to HLA-DQ ($p<0.05$). Daggers (‡) indicate statistically significant differences in probability of DQ UA-PD for a race/ethnicity group as compared to DQ UA-PD in African American recipients ($p<0.05$).

**Figure 4.** Average changes in cPRA (0-100%) after development of a new UA-PD at each HLA locus following failed deceased donor (A-D) or living donor (E-H) kidney transplant and relisting. Changes are demonstrated overall (A, E) and stratified by pre-transplantation cPRA of 0% (B, F), 1-50% (C, G) and 51-100% (D, H). Asterisk (*) denotes statistically significantly different cPRA increase with an UA-PD at an HLA locus as compared to HLA-DQ ($p<0.05$).

**Figure 5.** Average changes in cPRA (0-100%) after development of a new UA-PD at each HLA locus following failed kidney transplant and relisting. Results are stratified by receipt of an initial deceased (A-C) or living donor (D-F) kidney and by African American (A, D), White (B, E) and Hispanic (C, F) recipient race/ethnicity. Asterisk (*) denotes statistically significantly different cPRA increase with a UA-PD at an HLA locus as compared to HLA-DQ ($p<0.05$). There were no significant differences in the effects of HLA-DQ UA-PD on cPRA between recipients of different race/ethnicity groups.

**Figure 6.** Average changes in cPRA (0-100%) after development of a new UA-PD at each HLA locus following failed kidney transplant and relisting. Results are for recipients unsensitized (cPRA 0%) prior to transplantation and are further stratified by receipt of an initial deceased (A-C) or living donor (D-F) kidney and by African American (A, D), White (B, E) and Hispanic (C, F) recipient race/ethnicity. Asterisk (*) denotes statistically significantly different cPRA increase with a UA-PD at an HLA locus as compared to HLA-DQ ($p<0.05$). There were no significant differences in the effects of HLA-DQ UA-PD on cPRA between recipients of different race/ethnicity groups.

**Abbreviations**

95% CI: 95% confidence interval

ABMR: Antibody-mediated rejection

ANOVA: Analysis of variance

BMI: Body mass index

CI: Confidence interval

cPRA: Calculated panel reactive antibody [value]

DSA: Donor-specific antibody/antibodies

ESRD: End-stage renal disease

HHRI: Hennepin Healthcare Research Institute

HLA: Human leukocyte antigen

IQR: Interquartile range

IRB: Institutional Review Board

OPTN: Organ Procurement and Transplantation Network

SRTR: Scientific Registry of Transplant Recipients

UA: Unacceptable antigen(s)

UA-PD: [HLA] Unacceptable antigen(s) corresponding to previous donor typing

UNOS: United Network for Organ Sharing