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The Influence of HLA-DP on Kidney Transplantation: A Systematic Review

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Summary

Kidney transplantation is the treatment of choice for chronic kidney failure, and HLA compatibility is crucial for graft outcomes. Although other loci are routinely evaluated, the clinical impact of HLA-DP is not yet fully understood.

This systematic review aimed to evaluate the role of HLA-DP as a predictor of outcomes in kidney transplantation, including rejection, survival and graft loss, development of donor-specific antibodies (DSA), and renal function. The review was conducted according to PRISMA guidelines, including observational studies with adult kidney transplant recipients that analyzed HLA-DP mismatches, DSA presence, expression level, and clinical outcomes. The search was performed in PubMed, Embase, and Lilacs databases, and methodological quality was assessed using the Newcastle-Ottawa scale. Due to the heterogeneity of the data, the results were synthesized by narrative analysis. Seven studies were included. The presence of pre-formed anti-HLA-DP DSA was independently associated with acute antibody-mediated rejection, with a similar impact to that observed for HLA-DR and HLA-DQ. A higher burden of molecular mismatches was related to poorer graft survival and accelerated decline in renal function, even with low-intensity antibodies. It is concluded that HLA-DP has significant clinical relevance in kidney transplant outcomes, reinforcing the need for a more detailed immunological evaluation of this locus.

Keywords: HLA-DP; Graft rejection; Donor-specific antibody; Crossmatch.

Abstract

Kidney transplantation is the treatment of choice for end-stage renal disease, with HLA compatibility being a key determinant of graft outcomes. Although other HLA loci are routinely evaluated, the clinical impact of HLA-DP has not yet been fully elucidated. This systematic review aimed to assess the role of HLA-DP as a predictor of kidney transplant outcomes, including rejection, graft survival and loss, development of donor-specific antibodies (DSAs), and renal function. The review was conducted in accordance with PRISMA guidelines and included observational studies involving adult kidney transplant recipients that evaluated HLA-DP mismatches, DSA presence, expression levels, and clinical outcomes. Literature searches were performed in PubMed, Embase, and Lilacs databases, and methodological quality was assessed using the Newcastle–Ottawa Scale. Due to data heterogeneity, results were synthesized using a narrative approach. Seven studies were included. The presence of preformed anti–HLA-DP DSAs was independently associated with antibody-mediated acute rejection, with an impact comparable to that observed for HLA-DR and HLA-DQ. A higher burden of molecular incompatibilities was associated with poorer graft survival and accelerated decline in renal function, even in the presence of low-intensity antibodies. In conclusion, HLA-DP has significant clinical relevance in kidney transplant outcomes, underscoring the need for more

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detailed immunological assessment of this locus.

Keywords: HLA-DP; Graft rejection; Donor-specific antibody; Crossmatch

1. Introduction

Brazil has the largest public organ donation program in the world - the System.
The National Transplant System (SNT) guarantees the possibility of transplantation for the entire population through the Unified Health System (SUS). The SNT regulates and oversees the organ donation process. ensuring that it occurs equitably and according to the single waiting list. Between the beginning Between 2023 and October 2025, for example, 74,621 organ transplants were performed in the territory. national (BRAZIL, 2025), which highlights the magnitude and organization of this operation, in addition to its essentiality in the treatment of countless patients who depend on organ transplants for survive.

The National Transit System (SNT) is regulated by Consolidation Ordinance No. 4/2017, which brings together the rules for...

The systems and subsystems of the SUS (Brazilian Unified Health System) are defined in Annex I, outlining the structure and operation of the system.

of transplants in the country. The SNT, in coordination with the Organ Notification, Procurement and Distribution Centers (CNCDOs) and authorized transplant teams, is responsible for evaluation of potential donors and recipients, storage, distribution and allocation of organs and tissues. In this structure, the diagnosis of brain death, laboratory compatibility tests A thorough clinical evaluation of the donor is a mandatory step before the donation can be finalized. (BRAZIL, 2017; BRAZIL 2021).

Kidney transplantation is considered the treatment of choice for patients with kidney failure. Chronic kidney disease offers longer survival and a better quality of life compared to... Dependence on hemodialysis for survival. Currently, in the process of organ donation at the centers.

Of all transplants, kidney transplantation is the only one for which HLA is fundamental to achieving the desired outcome (BAHIA, 2025), given that antibody-mediated rejection (ABMR) is the main immunological cause. related to kidney graft loss (DI COCCO et al., 2020). For other organs, HLA is Dosed only to assess the level of immunosuppression needed for continued treatment.

For a candidate to be registered on the national waiting list, current legislation stipulates... performing human leukocyte antigen (HLA) typing, as well as the Reactivity Panel. of Antibodies (PRA) for classes I and II, in order to identify unacceptable antigens and guide the Compatibility between donor and recipient. The order of organ distribution considers, among other things... Factors include blood compatibility, number of HLA incompatibilities, clinical severity, and time frame. in a list, with the chronological criterion used in case of a tie (BRAZIL, 2025; BRAZIL, 2021; (BRAZIL, 2017).

The human leukocyte antigen (HLA) system is encoded by the major complex of Histocompatibility complex (MHC) and comprises a group of genes located in a small segment.

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of chromosome 6, divided into three sub-regions, with two main ones: class I (A, B and C) and class II (DR, DQ, and DP). Within class II, the DP locus contains the DPA1 and DPB1 genes, responsible for to encode the ÿ and ÿ chains of antigens, more specifically, of epitopes. HLA antigens are cell surface glycoproteins involved in regulating the immune response, whose function is to display Peptide fragments of proteins for recognition by antigen-specific T lymphocytes. In In a population, there are several alleles of each MHC gene, which are expressed in a codominant manner. in each individual, which significantly increases the number of HLA molecules available and contributes to immunogenetic variability among humans (BRASIL, 2017; SHIINA et al., 2009; CHOO, 2007; ROCK et al., 2016).

HLA-A antigens and antibodies -B, -C, -DR, and -DQ are widely used in allocation. of solid organs, however HLA-DP typing is not part of the routine testing for donors and receptors (BRAZIL, 2021; BRAZIL 2017). This class II molecule was identified more than 40 years ago. It is years old and is composed of two chains, which are encoded by the polymorphic loci DPA1 and DPB1. As They are not part of routine typing, and little is known about the impact of HLA-DP incompatibilities and anti-HLA-DP antibodies on post-transplant outcomes (SHIINA et al., 2009 and DANIËLS). et al., 2021). Even in cases of donor-specific antibodies (DSAs or AADs) HLA- Although isolated PDs are rare, the meta-analysis performed by Pan et al. (2023), which analyzed data up to 2021, showed that they pose a significant risk in antibody-mediated rejection and recommends- if the addition of HLA-DP typing in pre-transplant testing (PAN et al., 2023). The analysis of this locus This will allow for an assessment of its true potential and whether its presence could signal a possible... Rejection after organ transplantation (SHIINA et al., 2009 and DANIELS et al., 2021).

In the organ donation process, after confirmation of brain death and acceptance by the donor, the organ donor is admitted. In the case of family donation, the first step is to perform HLA typing on the donor. HLA testing of recipients is performed when the patient is to be enrolled on the transplant waiting list. (ERLICH et al., 2001; LITMAN, 2005 and SCHIAVO et al., 2023). In order to reduce immunogenicity In transplanted grafts, the goal is to achieve greater HLA compatibility between donor and recipient. aiming at reducing acute and chronic rejections, it is essential to analyze the presence of Anti-donor antibodies (DSAs). The characterization of DSAs is performed using an antibody panel. of the recipients waiting on the waiting list. The analysis of this panel shows if the potential recipient has antibodies against the donor, which makes transplantation contraindicated. (PAN et al., 2023; ERLICH et al., 2001 and LITMAN, 2005)

Another test performed is the flow cytometry crossmatch (FCXM), developed by Terasaki and Patel, which serves to determine whether or not the recipient is sensitized against the antigens. donor histocompatibility test, and must be negative for the transplant to occur (PATEL et al. al., 1969). Furthermore, virtual cross-checking (VXM) is an important tool used in

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immunology laboratories, as it allows for a specific evaluation of the antibody profile of
The recipient is compared with the HLA antigens of a donor to determine the presence of DSAs.
and predicts the immunological risk of the donor/recipient pair (SCHIAVO et al., 2023). With this, it is possible
to anticipate not only the possibility of a negative FCXM, but also to measure the probability of a
A real positive test. In this way, agility is achieved in the selection of recipients and the following occurs.
facilitating the distribution of organs from national donors (BRAZIL, 2021; PAN et al., 2023;
SCHIAVO et al., 2023; PATEL et al., 1969 and LIWSKI et al., 2017).

The overall objective of the study is to analyze the influence of HLA- allele incompatibility.
DP (mismatch), the presence of pre-formed anti-HLA-DP antibodies (preDSA-DP), and the level of
HLA-DPB1 expression in graft survival, in the occurrence of acute rejection, in
development of de novo donor-specific antibodies (dnDSA) and renal function
estimated by the estimated glomerular filtration rate (eGFR).

2. Method

2.1 Type of study

This study is a systematic literature review conducted in accordance with
the recommendations of the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and
Meta-Analyses) (PAGE et al., 2020). The protocol for this review was previously registered in
International Prospective Register of Systematic Reviews (PROSPERO) platform, under number
CRD420251180360.

2.2 Data source and period

This research aims to analyze, based on available literature, the role of HLA class II PD in
renal graft survival. Furthermore, to search the literature available in the last 20 years for the impact
This HLA index was used in the FCXM results. Therefore, data from the [source missing] were used in this study.
databases: PubMed, Embase and Lilacs, in two separate searches, aiming to cover the
The overall objective in the first [method] is to include cross-checking results in the second. Search strategies
The characteristics of each database are described in Table 1.

Table 1: Databases and search strategies.

Database First	Search Strategy
PubMed	("HLA-DP"[tiab] OR "HLA-DPA1"[tiab] OR "HLA DP"[tiab]) AND ("kidney transplantation"[Mesh] OR "renal transplantation"[tiab] OR "kidney transplant"[tiab] OR "renal graft"[tiab]) AND ("graft survival"[Mesh] OR "graft loss"[tiab] OR "rejection"[tiab] OR "antibody-mediated rejection"[tiab] OR "donor-specific antibody"[tiab] OR "DSA"[tiab])
Embase	('hla-dp':ab,ti OR 'hla-dpb1':ab, ti OR 'hla dpa1':ab, ti OR 'hla dp':ab,ti) AND ('kidney transplantation'/exp OR 'renal transplantation':ab,ti OR 'kidney transplant':ab,ti) AND ('graft survival'/exp OR 'graft loss':ab,ti OR 'rejection':ab,ti OR 'antibody mediated rejection':ab,ti OR 'donor specific antibody':ab,ti OR 'dsa':ab,ti)
Lilacs	("HLA-DP" OR "HLA-DPB1" OR "HLA DP")

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	AND ("kidney transplant" OR "kidney transplant" OR "kidney transplant") AND ("graft survival" OR "rejection" OR "anti-HLA antibodies" OR "DSA" OR "donor-specific antibodies")
Database Second search strategy	
PubMed	(("HLA-DP"[tiab] OR "HLA-DPA1"[tiab] OR "HLA-DPB1"[tiab]) AND ("kidney transplantation"[Mesh] OR "renal transplantation"[tiab] OR "kidney transplant"[tiab] OR "renal graft"[tiab]) AND ("graft survival"[Mesh] OR "graft loss"[tiab] OR "rejection"[tiab] OR "antibody-mediated rejection"[tiab] OR "donor-specific antibody"[tiab] OR "DSA"[tiab]) AND ("crossmatch"[tiab] OR "cross-match"[tiab] OR "flow cytometry"[Mesh] OR "flow cytometry"[tiab]))
Embase	('human leukocyte antigen DP'/exp OR "HLA-DP":ti,ab OR "HLA-DPA1":ti,ab OR "HLA-DPB1":ti,ab) AND ('kidney transplantation'/exp OR "renal transplantation":ti,ab OR "kidney transplant":ti,ab OR "renal graft":ti,ab) AND ('graft survival'/exp OR 'transplant rejection'/exp OR "graft survival":ti,ab OR "graft loss":ti,ab OR "rejection":ti,ab OR "antibody-mediated rejection":ti,ab OR "donor-specific antibody":ti,ab OR "DSA":ti,ab) AND ('crossmatch test'/exp OR 'flow cytometry'/exp OR "crossmatch":ti,ab OR "cross-match":ti,ab OR "flow cytometry":ti,ab)

Source: Authors, 2025.

2.3 Eligibility criteria Studies

evaluating adult kidney transplant recipients (ÿ18 years) will be included.
including first transplants and re-transplants. The restriction to the adult population is justified by
significant immunological, physiological, and therapeutic differences between pediatric patients and
adults (SIMON et al., 2015), which could introduce biases in the analysis of immunological outcomes.
and graft survival.

Observational studies (prospective and retrospective cohort studies, etc.) will be eligible.
registry), case-control studies and randomized clinical trials, as these designs allow
To observe associations between HLA-DP incompatibility and clinical outcomes with greater validity.
external. The focus on analytical designs is justified by their provision of comparative measures of
Risk and outcome are fundamental for estimating the impact of HLA-DP.

Studies that analyzed mismatches in the HLA-DP alleles will be included.
presence of anti-HLA-DP antibodies (pre-formed or de novo), molecular scores and/or markers
DPB1 expression. These parameters reflect different levels of immunological characterization and
They provide a comprehensive view of the influence of HLA-DP on the post-transplant immune response.
and in laboratory results, such as cross-matching by flow cytometry.

Studies should report at least one of the following outcomes of interest: survival
graft failure (in the short, medium, or long term), acute rejection (cellular and/or humoral), development
dnDSA-type antibodies, renal function (estimated by eGFR), or graft loss. The inclusion of
Multiple clinical and laboratory outcomes aim to ensure a more complete analysis of the impact.
HLA-DP incompatibility clinical presentation.

The search will be conducted in two stages, with different time constraints: for the
The main objectives of the review are to consider only studies published in the last 5 years.
in order to guarantee the methodological and technological updating of the analyses, especially in light of
advancements in molecular typing and antibody detection techniques. For the specific purpose of

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to evaluate the impact of HLA-DP presence on flow cytometry crossmatch results,

Studies will be accepted from the date of first publication until 2025, with an attempt to include all evidence.

present.

Full articles published in English or Portuguese will be included, with no country restriction.

or clinical setting. This decision seeks to balance methodological rigor and linguistic comprehensiveness,

allowing the inclusion of evidence from different contexts, provided it has been submitted to scientific evaluation.

Individual case reports and small case series will be excluded, as these designs

They present a high risk of bias and do not allow causal inference. Pediatric studies (<18 years) will be

Studies will be excluded due to the aforementioned immunological differences.

Experimental studies in animals or in vitro, since the focus of this review is the immune response and the

clinical performance in humans.

Studies in which renal recipient data cannot be analyzed will be excluded.

separately, such as multi-organ transplants without discrimination of specific outcomes of

kidney, to avoid misinterpretations of the outcomes. Abstracts of will also be excluded.

conference, paid articles or articles not available in full, since the lack of full access to

This text prevents the evaluation of the methodology, the risk of bias, and the completeness of the results.

Exclusion aims to preserve the quality and transparency of the analysis.

Finally, studies that do not present outcomes of interest, either because they do not... will be excluded.

having evaluated variables related to HLA-DP compatibility, whether by mentioning the

outcomes without presenting quantitative results. This decision avoids the inclusion of studies

descriptive without analytical relevance, ensuring that all evidence considered contributes

effectively to answer the question of revision.

2.4 Variables analyzed

The selection of the variables analyzed was directly guided by the overall objective of the study.

Primary clinical outcomes were evaluated, specifically renal graft survival and...

Renal function measured by the estimated Glomerular Filtration Rate (eGFR). Within the scope of the response

Immunological analysis and its pathophysiological mechanisms focused on the incidence of rejection.

Acute antibody-mediated rejection (ABMR) and T-cell-mediated rejection (TCMR), and in chronic rejection. Finally, for

In characterizing pre- and post-transplant immunological risk, the following parameters were considered.

laboratory results, including cross-matching results and mean intensity values of

Antibody fluorescence (MFI).

2.5 Data processing and analysis

The studies underwent a double screening process for analysis, first by title and then by abstract.

and secondly, by reading the entire text. Finally, seven studies were selected for analysis.

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To assess the methodological quality of the studies, the Newcastle-Ottawa scale was used.

Scale (WELLS, 2025).

3. Results

A sample of seven studies that met the inclusion criteria was formed.

The process of identifying, screening, and selecting studies is described in Figure 1. The studies

The selected studies were published between 2014 and 2024, with 2008 being the latest period studied and

2022 is the earliest. The research was conducted in Germany, Brazil, the United States, and Spain.

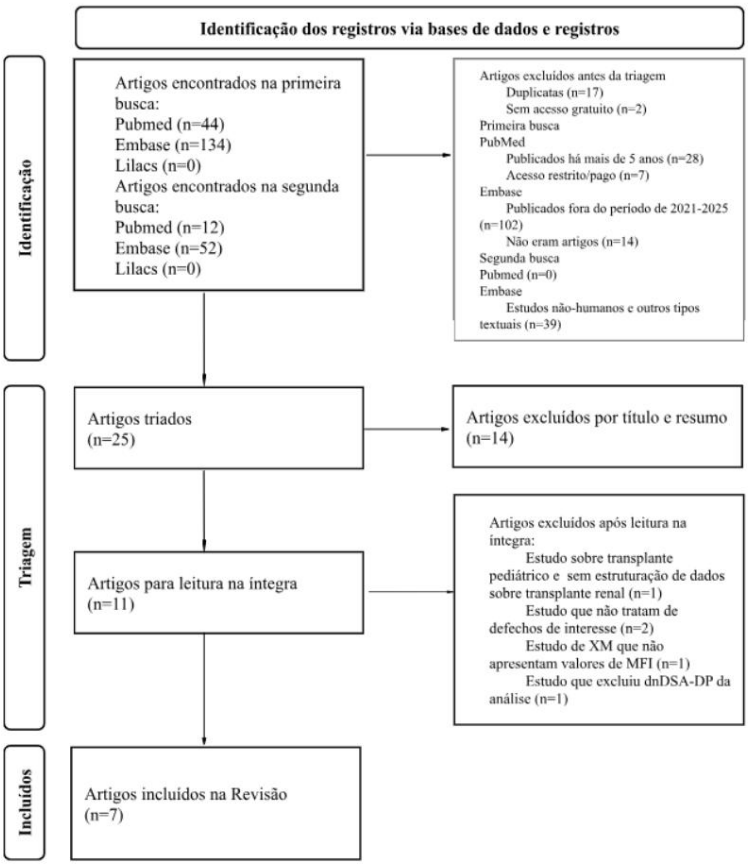
France, United Kingdom, and Switzerland. All are cohort studies, with six being retrospective and one prospective, two

There were five multicenter and five single-center studies. All studies were rated as good quality.

Methodologically, based on the Newcastle-Ottawa Scale and following AHRQ guidelines.

Specifics of the included studies are described in Table 2.

Figure 1: Study selection process according to the PRISMA Diagram (16)



Source: Authors, 2025.

Table 2: Main characteristics of eligible studies.

Authors (Year), Title; Country	Outline	Sample	HLA evaluated	Typing method	Outcomes assessed
Seitz et al. Beads Antibodies, Survival United	Isolated Pre-existing Rejection Mediated by HLA-DP Single Antigen (2022), Kingdom HLA-DP Donor-Specific with DSA HLA-DP Isolated Antibodies, 46 with (CAB/Luminex) Graft, Histology				

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	Associated with Poorer Immune Transplantation; Cohort of Single - Center-Retrospective	Risk Outcomes in Renal Non-Specific HLA-D antibodies (from donor and 27 highly sensitized but with HLA-DP without antibodies in serum)		for detection of (Banff C4d scores, antibodies. MFI MVI, used with CG/glomerulopathy) standardized cut > 2000	
Frinschknecht et al. (2022), The impact of pre-2215 transplants HLA DNA-based HLA-typing (SSO Antibodies, Survival Switzerland)	antibodies on the e1804 negative) Renal Antibodies (rate of decline from the Swiss transplant DQ). study; Single-by-multicenter prospective cohort study of antigen beads	in transplantation – Data (DR, DP, detected	Rejection Mediated 1 (A, B, C) and SSP	by transplant donor-specific (411 DSA positive class 9). of the Graft, Kidney eGFR and eGFR slope). primarily cohort (SAB/ Luminex).	Function outcome of class 2
de Marco et al.	HLA-DPB1 molecular 130 HLA-Mismatches are a risk factor for Factors for cross-test rejection and function in first and last kidney transplant recipients; DSA Retrospective cohort	receptors (2021), Brazil first kidney disease with DBP1. acute pregraft low 5-year negative		DNA based on SSOP (sequence-specific oligonucleotide probe, Luminex)	Acute rejection, DSA and dnDSA and eGFR)
Laboux et al.	Impact of Preformed 183 DSA Donor-Specific Anti-Drug (DP only included) HLA-Cw and Anti-DSA Antibodies with either Acute Antibody-DSA Rejection in Kidney Transplantation; at least one anti-DP (with at least one anti-DPB1) (multicenter cohort), being 91 retrospective	Anti-receptors (2023), France on patients who presented anti-Cw or DSA-Mediated with preDSA-DP; more than half of the patients were retransplant recipients.		Single Antigen ABMR, death-censored Beads graft loss and prophylactic strategies (SAB/Luminex) for antibody detection.	
García-Jiménez et al. (2024), a personalized delisting strategy for HLA Single Antigen with HLA Single Antigen et al. (2024) enable highly class Beads grafting in "deslisted" Spain. successful kidney sensitized, 53 (A, B, C) and (SAB/Luminex, preDSA patient" transplantation in highly sensitized patients with class 2 One Lambda (DR, DP, preformed donor-DSA and 53 non-DQ). specific anti-HLA sensitized Antibodies; Retrospective cohort			1	rejection and survival in Spain, has antibodies.	shown that 159,53 patients
Chen Tang et al. (2021), Analysis of de novo 366 HLA-receptors. donor-specific HLA-DPB1 Germany	DPB1 antibodies in pre- and post- retrospective cohort.	kidney transplantation; single antigen test, and high-resolution HLA-DPB1 typing of the donor and recipient.		dnDSA against HLA-DPB1 donor-specific mismatches at allele level, eplet mismatch level or do graft TerEp mismatch level.	Antibody formation de novo (dnDSA) versus HLA-DPB1 and survival

Baxter-Lowe et Center-Defined 240 patients on HLA-A, - Unacceptable HLA KPD waiting list crossmatch Transplants for DRB1, - patients with DRB3/4/5, acceptable. Causes of Multi-Center Kidney Disease - DQB1 and - crossmatches; DPB1 retrospective cohort)			B, -Bw4/6, Crossmatch in Antigens Facilitate prediction -C, of a -	Not found. Accuracy of Virtual al. (2014), USA Based on cells sensitized in Exchange Program virtual flawed (resulting in a unacceptable in C-XM). Transplant rates for highly sensitized patients. Short-term graft function (mean serum creatinine levels at 6 months and 1 year).	

Source: Studies included in the systematic review.

Regarding the samples, all studies had more than 100 participants, ranging from 114 (SEITZ et al., 2022) to 2215 (FRISCHKNECHT et al., 2022), including first-generation receptors transplantation and retransplantation. Regarding the HLA typing method, it was described in two studies, in which was done by Luminex SSOP in which the patient's DNA is extracted and amplified by PCR. (Polymerase Chain Reaction). The amplified products are then hybridized with a a set of sequence-specific oligonucleotide probes (SSOs) that are linked to Luminex colored microspheres (beads). To identify the presence and formation of antibodies. anti-HLA-DP was performed in four studies by Luminex SAB, in which the patient's serum is incubated with the Luminex single antigen microsphere (SAB) panel, where each one is coated with a specific purified HLA antigen. Five studies performed VXM and five FCXM performed.

Upon analyzing the studies, heterogeneous information was found in the measurement of The results are described in Table 3. However, based on the results and discussion sessions, it is It is possible to categorize the selected studies into four themes: immunogenetic characteristics of HLA-DP and risk rationale; pathogenicity and clinical impact of anti-HLA-DP antibodies: preformed and de novo; accuracy and limitations of FCXM and VXM in HLA-DP; implications for practice Clinical and policy allocation.

Table 3: Narrative summary of the main results in the selected studies.

Author (Year) Main results	
Seitz et al. (2022)	**Rejection:** 65% of patients presented with ABMR. preDSA-DP was an independent risk factor for ABMR (HR 9.58, p=0.012), associated with greater microvascularinflammation and C4d+. **Graft Survival:** 30% graft loss. Associated with lower survival in univariate analysis (p=0.048), but lost significance in multivariate analysis. **dnDSA:** Not evaluated **Renal Function:** No significant difference in eGFR at 3 months, 1 year, and 3 years compared to controls. **MFI and Crossmatch:** Median MFI of 11.009. FCXM positive in 32%, but was not able to predict rejection or graft loss.

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Frinschknecht et al.	**Rejection (ABMR):** The presence of pre-transplant DSA significantly increased the risk of al. (2022) ABMR (p<0.0001). When analyzing specific loci, the risk of ABMR was increased for all, with no statistically significant difference between them (p=0.52 in the comparison between single loci), indicating that isolated HLA-DP carries a risk of rejection comparable to the others. **Graft Survival:** There was a marked decline in graft survival for anti-HLA-DP DSA in the first 6 years, with a survival curve similar to that of HLA-DQ (approx. 70-80% at 6 years for DP), although the overall statistical comparison between single loci resulted in p=0.073. **dnDSA:** Not evaluated. **Renal Function (eGFR slope):** Isolated anti-HLA-DP DSA (as well as DQ and DR) showed a trend of faster decline in renal function compared to the group without DSA and DSA Class I (average annual slopes were visually more negative in the graphs, although the specific p-value for DP vs others is not numerically isolated in the main text; the overall Class II group had p<0.0001 vs without DSA). **MFI and Crossmatch:** Even Class II DSAs (including PD) with an MFI < 1000 were associated with a significantly increased risk of ABMR (p<0.0001). The study used Virtual Crossmatch (vXM) based on an MFI cutoff > 500-1000.
de Marco et al.	**Acute Rejection (TCMR):** Unlike classic allelic mismatch, which showed no association with (2022) In multivariate analysis, molecular mismatches were identified as independent predictors of acute rejection. Significant risk factors included non-permissive TBI (HR 3.01, p=0.008), Epitope MM ÿ 6 (HR 5.08, p<0.001), Eplet MM ÿ 7 (HR 4.26, p=0.001), and AbVer EpMM ÿ 3 (HR 3.38, p=0.01). **Graft Survival:** Not evaluated **dnDSA:** No development of dnDSA-DPB1 was detected in the samples tested after 5 years. **Renal function:** When specifically analyzing Standard Criteria Donor (SCD) transplants, high molecular mismatch burdens were independent risk factors for poor graft function: SAMM ÿ 7 (OR 4.23, p=0.006) and AbVer EpMM ÿ 2 (OR 3.09, p=0.03). **MFI and Cross-Proofing:** Not evaluated
Laboux et al.	**Acute Rejection (aABMR):** The incidence of aABMR at 2 years was 28% in the anti-DSA group (2023) Isolated HLA-DP. The presence of preDSA-DP was associated with an independent increase in the risk of aABMR compared to anti-HLA-Cw (HR 2.25; p=0.015). **Graft Survival:** No significant association was found between the presence of pre-formed anti-HLA-DP DSA and graft loss censored by death in the multivariate analysis (HR 1.10; p=0.786). The probability of graft loss at 5 years was 19.5% in the DP-DSA group. **dnDSA:** The emergence of de novo antibodies (dnDSA) occurred in 12 patients in the DP-DSA group. Only 4 of the 27 aABMR episodes (14.8%) in this group were attributable to the onset of dnDSA. **MFI and Crossmatch:** The mean MFI on the day of transplantation for anti-HLA-DP DSA was 3.855. The MFI value on the day of transplantation was independently associated with the risk of aABMR (HR 1.09 per 1,000 MFI increment; p=0.032). Positive CDC crossmatch was also associated with a higher risk of aABMR (HR 4.59; p=0.045). Interaction analysis showed that this increased risk for HLA-DP was significant specifically for antibodies with MFI < 3,000 (HR 4.69; p=0.033), with no significant difference for MFI > 3,000.
Garcia-Jiménez et al. (2024)	**Acute Rejection (aAMR):** The incidence of antibody-mediated acute rejection was 12% in the group with pre-formed DSA, with anti-HLA-DP antibodies showing the highest MFI values (median of 10,796) and accounting for 50% of all rejection cases in this group11. Patients classified as high risk (MFI > 10,000) had a significantly higher rejection rate of 30% (p=0.0002). **Graft Survival:** Graft survival censored for death at 5 years was 67% in the group with pre-formed DSA, a result statistically comparable to the group of sensitized patients without DSA (p=0.69), but significantly lower than the group of non-sensitized patients (p=0.002). **dnDSA:** The development of de novo antibodies (dnDSA) was significantly more frequent in the group with pre-existing DSA (18%) compared to the control groups (p=0.024). Persistence of pre-formed DSA post-transplant occurred in 46% of recipients, and was associated with higher pre-transplant MFIs (p=0.003). **Renal Function:** No significant differences were observed in graft function (assessed by serum creatinine and eGFR) between the group transplanted with pre-formed DSA and the control groups. **MFI and Crossmatching:** The strategy allowed transplantation with DSAs based on C1q test negativity and MFI stratification. The pre-transplant sum of MFI (SumMFI) was significantly higher in patients who developed aAMR (p=0.049), with HLA-DP showing the highest median MFI in the study.

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Chen Tang et al. (2021)	**Rejection, Renal Function, and Crossmatch:** Not evaluated. **Graft survival:** The classic HLA-DPB1 allelic mismatch did not impact 3-year graft survival (p=0.86). In contrast, an increase in the number of eplet mismatches and TerEp mismatches was significantly associated with worse graft survival (p=0.035 and p=0.022, respectively). Multivariate analysis confirmed that eplet mismatches (HR 1.29, p<0.001) and TerEp mismatches (HR 1.86, p=0.003) were independent risk factors for graft loss. **dnDSA:** The study evaluated the emergence of anti-HLA-DPB1 dnDSA in patients without pre-existing antibodies against the donor. The overall incidence of anti-HLA-DPB1 dnDSA was 9.7% (30 of 310 patients) when analyzed by allelic mismatch. When analyzed by eplet and Terasaki epitope (TerEp) mismatches, the incidence was 5.0% and 7.6%, respectively. There was no significant association between the number of mismatches (whether allelic, eplet, or TerEp) and the risk of developing dnDSA. Furthermore, the donor HLA-DPB1 expression level (based on SNP rs9277534) did not influence the development of dnDSA. However, TerEps #4002 and #4005 proved to be significantly more immunogenic, inducing dnDSA more frequently than expected (p=0.036).
Baxter-Lowe et al. al. (2014)	**Rejection, Survival, dnDSA, and Renal Function:** Not evaluated. **MFI and Crossmatch:** This study evaluated the effectiveness of virtual crossmatching (vXM) in a matched kidney donation (KPD) program. HLA-DPB typing became mandatory for donors after multiple vXM failures were attributed to the presence of anti-HLA-DPB antibodies. In some cases, precise characterization of antibody specificity required high-resolution subtyping of alleles such as HLA-DPB104:01 and HLA-DPB104:02. Despite these advances, vXM remained limited in its ability to predict crossmatch by flow cytometry (FCXM), with failures attributed to cumulative effects of multiple low-intensity DSAs and antibody dynamics. **HLA-DP sensitization:** Approximately 26% of candidates on the National Kidney Registry (NKR) waiting list listed HLA-DP antigens as unacceptable. This sensitization was even more evident among high-risk patients, given that 42% of those with 100% cPRA had anti-HLA-DP antibodies.

Source: Studies included in the systematic review.

4. Discussion

4.1 Immunogenetic characteristics of HLA-DP and risk rationale

HLA-DP molecular mismatch (MM) can be immunogenic because differences in antigen structure (epitopes that are recognized by antibodies or T cells) and by Differences in gene expression, that is, in the amount of DP antigens on the cell surface. A The expression of DPB1, for example, is associated with the rs9277534 polymorphism, in which there is greater The expression of the G allele compared to the A allele is used as a marker of incompatibility. expression. According to de Marco et al. (2022), unlike the DR and DQ loci, HLA-DP presents a weak disequilibrium linkage pattern compared to other class II locs, that is, Apparent compatibilities in DR and DQ do not guarantee compatibility in DP, causing the DP has an independent immunological risk.

de Marco et al. (2022) analyzed the immunological risk associated with HLA-DP resulting from molecular differences between donor and recipient were investigated, and it was found that, in addition to terminal creatinine in the In the donor category, only structural incompatibilities showed an independent association with rejection. acute (HR 2.69-5.08), while simple allelic MM had no significant clinical impact in Adjusted models. In the Brazilian cohort of 130 first-time transplant recipients with FCXM Negative, the findings related to HLA-DPB1 molecular incompatibility are that 17.7% of the patients had acute T-cell mediated rejection (TCMR).

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Regarding kidney function, the same study observed that patients with low kidney function At 5 years of age (5Y-GF ÿ40.3 ml/min/1.73m²) they present the highest rejection rate (25.4% x 10.4% p = 0.03). When donors meet expanded criteria (either > 60 years old, or 50-60 years old with a history of hypertension). and/or serum creatinine >1.5 mg/dl, or death due to cerebrovascular causes) (METZGER et al., 2003) were excluded from the analysis, two molecular MMs (AbVer EpMM and SAMM) were independently associated with low 5Y-GF, this occurs because these factors have a greater influence on loss of renal function compared to molecular MM. Furthermore, Frischknecht et al. (2022) They observed that the risk of isolated HLA-DP DSA is comparable to that of HLA-DR as well. Accelerated decline in renal function (eGFR), solidifying PD as a Class II risk factor. primary.

4.2 Pathogenicity and clinical impact of anti-HLA-DP antibodies: preformed and de novo

When dealing with acute antibody-mediated rejection (ABMR), Frischknecht et al. (2022) They validated that the presence of pre-formed anti-HLA-DP DSAs (preDSA-DP), even in isolation, It poses risks to ABMR comparable to HLA-DR DSAs. This virulence is even more highlighted by Seitz et al. (2022), who found that these antibodies were the only factor. independent associated with acute antibody-mediated rejection (HR= 9.578), with a rate of 65% ABMR in patients with pre-existing isolated DPDSA. Laboux et al. (2023) assessed that preDSA-DP increases the risk of acute antibody-mediated rejection (aABMR) in transplantation. renal rejection compared to anti-HLA-Cw preDSAs (28% vs. 12%), showing that acute rejection is more related to preDSA-DP compared to dnDSA-DP. When creating a multivariate model adjusted, anti-PD preDSA increases the risk of aABMR (HR = 2.25 [1.17–4.31] p = 0.015). García-Jiménez et al. (2024) highlighted that anti-DP antibodies were highly prevalent in the cohort and associated with significant risk, with 50% of aABMR cases having three rejection cases due to anti-DP bias. One case of anti-B, one case of anti-DR, and one case of anti-DQ; among the 11 patients who presented with preDSA. anti-DP, three developed aABMR, resulting in a 27% rejection rate within that subgroup.

Understanding the influence on graft survival, Frischknecht et al. 2022 indicated that isolated HLA-DP DSA presented comparable risks to HLA-DR DSA for the outcome of long-term graft loss. Complementarily, the single-center cohort of Seitz et al. (2022) It was demonstrated that 30% of patients with isolated DSA-DP suffered graft loss during the Monitoring, even in the absence of DSA against HLA-A, B, C, DR, or DQ loci. Tang et al. (2021) observed that, in terms of clinical impact on graft survival, the mismatches of The HLA-DPB1 allele did not have a significant effect, but in contrast, a growing number of Eplet or TerEp HLA-DPB1 mismatches had a significant and deleterious negative impact on Three-year graft survival ($p < 0.001$ and $p = 0.003$, respectively, in the multivariate analysis).

The article by Tang et al. (2021), focused on the analysis of de novo donor-specific antibodies.

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(dnDSA) HLA-DPB1 in 366 kidney transplant recipients, found that neither the HLA- mismatches DPB1 at the allele, eplet, or Terasaki epitope (TerEp) level, nor exposure to high expression of HLA-DPB1 from the donor were significantly associated with the risk of developing dnDSA against The detection of anti-HLA-DPB1 dnDSA (de novo donor-specific antibodies) was considered positive if the patient tested negative for pre-formed antibodies against HLA-DPB1 incompatibility of the donor (i.e., no pre-transplant anti-HLA-DPB1 DSA), but Positive for anti-HLA-DPB1 DSA post-transplant. Some of these patients had non-DSA. additional testing against HLA-DPB1 pre- or post-transplant. However, the frequency of dnDSA against the TerEps 4002 and 4005 were significantly higher than expected, suggesting their possible immunodominance. It is important to note that the study focused primarily on dnDSA, although It is acknowledged that previous literature often failed to distinguish between pre-HLA-DP anti-antibody antibodies. trained and then again.

4.3 Accuracy and limitations of FCXM and VXM in HLA-DP

The work of García-Jiménez et al. (2024) observed that DSAs with higher values of MFIs were those related to HLA-DP, with a median of 10,796 MFI (IQR 2,887-14,589). Although the initial delisting prioritized low MFI (lower MFI) anti-HLACw or anti-DP antibodies at 5,000), the risk assessment of anti-DP antibody proved complex. Laboux et al. (2023), when at the same time as it related the MFI on the day of transplantation to aABMR (HR 1.09 [1.08–1.18] p = (0.032), found no difference between MFI levels triggering rejection. Therefore, Patients with an MFI < 3000 for preDSA-DP are more than four times more likely to develop ABMR compared to preDSA-Cw (HR 4.69 [1.68–13.1] p = 0.033), whereas with MFI > 3000 for preDSA-DP shows no difference in risk. This suggests that HLA-DP has intrinsic pathogenicity and that, even antibodies in smaller quantities can be clinically significant. Furthermore, the analysis of the Swiss cohort by Frischknecht et al. (2022) reinforces the problem. From low MFI to Class II, showing that Class II DSA (group that includes DP), with MFI cumulative levels below 1000 were already associated with a significantly increased risk of ABMR. These findings suggest that VXM algorithms should adopt higher MFI thresholds. conservative (low) levels for Class II DSAs, so as not to underestimate subtle pathogenicity. HLA-DP.

Regarding the results of cross-testing in the Kidney Exchange Program, studied by A. According to Baxter-Lowe et al. (2014), HLA-DPB typing in donors became mandatory after multiple Virtual crossmatch (VXM) failures have been attributed to the presence of anti-HLA-DPB antibodies. In some cases, precise characterization of antibody specificity required high-level subtyping. resolution of alleles such as HLA-DPB104:01 and HLA-DPB104:02. Despite these specific advances Regarding HLA-DP, VXM remains limited in its ability to predict FCXM.

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The main sources of disagreement include virtual crossmatches and errors arising from the effect. cumulative effect of multiple low-intensity DSAs, responsible for 46% of failures, and the dynamics intrinsic to the recipient's antibody repertoire, which accounts for 21% of the discrepancies.

In the study by Seitz et al. (2022), the positivity of the B-Cell Flow Crossmatch (BFXM), a tool considered more sensitive than the Cytotoxicity Crossmatch Complement-dependent (CDC-XM) was unable to predict the risk of ABMR or failure of grafting in patients with isolated anti-DP DSAs, and there was no correlation between the values cumulative MFI and the BFXM result (P = 0.2666). This dissociation highlights a limitation. intrinsic value of routine laboratory tests for stratifying the risk conferred by HLA-DP. García-Jiménez et al. (2024) revealed that, as HLA-DPB1 and DPA1 typing was not mandatory in In the PATHI program (Spanish Program for Access to Transplantation), these alleles were not considered. in VXM, which led to the acceptance of organ donations without prior knowledge of the presence of anti-DP antibodies.

5. Conclusion

HLA-DP confers rejection potential and influences survival as much as the... other HLA alleles that are part of the testing protocol, thus, their inclusion in the research. Testing performed before transplantation is essential to avoid negative outcomes. Given the results, The authors García-Jiménez et al. (2024) concluded that anti-DP preDSAs exhibit pathogenicity. comparable to that of other clinically relevant specificities and that its systematic inclusion in Organ allocation algorithms are essential for a higher transplant success rate. Laboux et al (2023) also linked the presence of anti-DP preDSA with ABMR and reinforce that the presence The presence of antibodies before transplantation is a marker of immunological risk. de Marco et al. (2022) They associated HLA-DPB1 molecular mutations with MRCT and worsening of chronic kidney function, reinforcing the The need to include DP in compatibility protocols.

According to Baxter-Lowe et al. (2014), the HLA-DPB1 locus has been shown to possess important characteristics. Immunogenicity in kidney cross-donation (KPD) programs. In the National Kidney Registry (NKR), approximately 26% of candidates listed HLA-DP antigens as unacceptable. This Sensitization is even more evident among high-risk patients, given that 42% of those with cPRA 100% presented anti-HLA-DP antibodies. They reported that the identification of these patterns led to the revision of testing policies, making HLA-DPB typing mandatory in donors of program.

The large cohort of the Swiss Transplant Cohort Study analyzed by Frischknecht et al. (2022) provides the most compelling longitudinal evidence that isolated HLA-DP DSA should be treated. as a risk factor comparable to DSA DHA-DR for long-term outcomes such as loss

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graft-versus-graft involvement and the decline in renal function. This finding justifies the inclusion of all HLA loci.

(including DP) in the allocation criteria. In a more immediate scenario, clinical practice should be

Adjusted: Seitz et al. (2022) demonstrated that pre-existing and isolated anti-DP DSAs lead to a

The acute ABMR rate is 65%, and graft loss occurs in 30% of cases, requiring these patients to undergo treatment.

They are classified as being at very high immunological risk, requiring more sophisticated management strategies.

aggressive measures, such as desensitization and rigorous post-transplant monitoring, regardless of

other ex vivo tests such as Flow Crossmatch.

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