

NARRATIVE REVIEW

African HLA Diversity and Its Implications for Transfusion, Transplantation, Infectious-Disease Immunity, Vaccination and Pharmacogenomics

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ABSTRACT

The human leukocyte antigen (HLA) system shapes antigen presentation, alloimmune recognition and variation in immune responses. African populations harbour extensive HLA diversity, but remain underrepresented in high-resolution reference datasets and international donor resources, constraining the clinical interpretation and application of this diversity. This review examines the relevance of African HLA variation to transfusion medicine, transplantation, infectious-disease immunity, vaccination and pharmacogenomics. In transfusion practice, HLA alloimmunisation contributes to immune platelet transfusion refractoriness and may complicate the identification of compatible platelet products. In haematopoietic stem-cell and solid-organ transplantation, population-specific HLA frequencies and haplotypes influence donor matching, while HLA antibodies and donor-specific antibodies are important determinants of compatibility and transplant outcomes. African studies of malaria, HIV, tuberculosis and vaccine responses further demonstrate associations between HLA variation and pathogen-specific immunity, disease susceptibility or control, and variation in vaccine-induced antibody responses. Pharmacogenomic studies illustrate an additional clinical application, although evidence for several actionable HLA–drug associations remain limited across many African populations. Collectively, these findings highlight the need for population-resolved HLA datasets linked to clinical and immunological phenotypes. We propose an integrated African HLA framework connecting high-resolution population characterisation with histocompatibility services, antibody testing, HLA-typed platelet and stem-cell donor resources, clinically annotated biobanks, functional immunology, pathogen–HLA–epitope studies and pharmacogenomic evidence. Strengthening these interconnected resources could support safer transfusion, improved transplantation, population-informed vaccine research, pharmacogenomic implementation and the development of emerging cellular therapies in African settings.

Keywords: *HLA; Africa; immunogenetics; transfusion; platelet refractoriness; transplantation; infectious-disease immunity; vaccination; pharmacogenomics*

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INTRODUCTION

HLA Diversity as an Overlooked Component of African Precision Medicine

The human leukocyte antigen (HLA) system lies at the interface between human genetic variation and immune function. Encoded within the major histocompatibility complex (MHC) on chromosome 6, HLA molecules mediate peptide antigen presentation to T lymphocytes: HLA class I molecules primarily present intracellularly derived peptides to CD8⁺ T cells, whereas HLA class II molecules predominantly present extracellularly derived peptides to CD4⁺ T cells. Through these functions, HLA molecules shape thymic selection, the T-cell repertoire and self–non-self discrimination, while HLA class I molecules additionally regulate natural killer (NK)-cell activity through interactions with killer-cell immunoglobulin-like receptors (KIRs). Consequently, HLA variation has important biological and clinical implications for infectious-disease susceptibility and immune control, vaccine-induced immunity, transplantation, transfusion-related alloimmunisation and immune-mediated adverse drug reactions (Tshabalala et al., 2015).

HLA variants are strongly associated with severe cutaneous adverse drug reactions, including Stevens–Johnson syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms, illustrating how HLA variation can be translated into precision-medicine interventions through pharmacogenetic screening. The HLA region is also the most polymorphic region of the human genome, reflecting the combined effects of demographic history and long-standing pathogen-mediated balancing selection. This extraordinary diversity continues to expand as sequencing technologies and high-resolution molecular typing improve. According to IPD-IMGT/HLA Database release 3.65.0 (July 2026), the database contained 46,652 distinct HLA allelic variants (Barker et al., 2026). The continuing expansion of characterized HLA diversity has been facilitated by next-generation and long-read sequencing technologies and the increasing characterization of previously under-represented populations.

Importantly, HLA polymorphism is not merely descriptive genetic diversity; it has direct functional consequences because individuals carrying different HLA alleles differ in the repertoire of peptides that can be presented to T cells. These differences can influence pathogen recognition and immune control, the breadth and magnitude of vaccine responses, susceptibility to immune-mediated disease, the probability of donor–recipient compatibility in transplantation, and the

development of clinically significant alloantibodies following transfusion or pregnancy. These considerations are particularly important in Africa. African populations harbour exceptionally high human genetic diversity as a consequence of deep evolutionary history, extensive population structure, migration, admixture and adaptation to heterogeneous environments and pathogen pressures. However, African populations have historically been underrepresented in genomic and HLA reference resources, creating an important mismatch between underlying biological diversity and the evidence base available to guide precision medicine (Tshabalala et al., 2015).

HLA research illustrates the clinical importance of this diversity for African health systems. High-resolution studies have demonstrated substantial allelic and haplotypic diversity both within and between African populations. In South Africa, high-resolution analysis of HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQA1 and HLA-DQB1 in 3,005 individuals demonstrated extensive HLA diversity and genetic differentiation, while highlighting the continuing under-representation of African populations in global HLA datasets. Earlier work by Paximadis et al. similarly demonstrated marked differences in class I and class II allele and haplotype distributions between Black and White South African populations (Paximadis et al., 2012). More recently, Banjoko et al. (2025) demonstrated substantial class I HLA diversity across Eastern and Southern African populations, including considerable within-country heterogeneity in Kenya, Uganda and Zambia. Importantly, the HLA profiles of these African populations differed substantially from those of African-American and European-American reference populations, underscoring the limitations of extrapolating HLA frequencies from proxy populations and the need for population-specific African reference datasets for immunogenetic research and T-cell vaccine development.

Complementing these findings, Mentzer et al. (2024) developed a high-resolution African HLA reference and imputation resource and demonstrated that HLA variation has measurable functional consequences for vaccine-induced immunity. Notably, variation in HLA-DRB1 expression was associated with vaccine-induced antibody responses, providing evidence that population-specific HLA architecture can influence clinically relevant immune phenotypes (Mentzer et al., 2024).

North African populations display additional patterns reflecting their distinct demographic histories and genetic relationships with Mediterranean and sub-Saharan populations.

In Morocco, HLA-DRB103:01 and HLA-DRB107:01 occur at appreciable frequencies, with HLA-DQB102 and associated HLA-DRB1–HLA-DQB1 haplotypes also commonly represented (Brick et al., 2006; Brick et al., 2015). Tunisian populations similarly exhibit substantial HLA diversity, including HLA-DRB107:01 and HLA-DQB102:01, with variation among subpopulations (Hajjej et al., 2015, 2017).

The clinical significance of this population-specific variation extends across several domains. In transfusion medicine, HLA alloimmunisation is a major cause of immune platelet transfusion refractoriness and may necessitate the selection of HLA-compatible or antibody-compatible platelet products (Panch et al., 2023). Sensitisation acquired through transfusion may also subsequently complicate histocompatibility assessment in transplantation. In infectious disease, African HIV cohorts have demonstrated allele-specific effects of HLA class I variation on viral control, including differential associations involving HLA-B57 and HLA-B81 (Prentice et al., 2013), further illustrating the functional consequences of population-specific HLA variation.

Pharmacogenomic relevance is similarly population dependent. Among 4,016 individuals with HIV from Burkina Faso, Côte d'Ivoire, Gabon and Togo, HLA-B57:01, the principal genetic marker used to predict abacavir hypersensitivity, was detected in only three individuals, corresponding to an overall prevalence of 0.1% (Kolou et al., 2021). This low prevalence illustrates how population-specific allele frequencies may influence the population-level utility of established HLA-guided pharmacogenomic interventions. This evidence shows that African HLA diversity is not a population-genetic characteristic but has clinically relevant implications for infectious-disease immunity, vaccine responsiveness and pharmacogenomics.

Evidence shows that Africa cannot be considered a genetically homogeneous population, as HLA allele and haplotype frequencies vary substantially across and within regions, reflecting demographic history, migration, admixture and pathogen-driven selection (Tshabalala et al., 2015). Such diversity, coupled with persistent underrepresentation in genomic reference resources, limits the transferability of HLA evidence generated elsewhere. This review examines HLA diversity as an underutilised component of African precision medicine, integrating evidence across transplantation, transfusion medicine, infectious diseases, vaccinology and pharmacogenomics.

It further identifies priorities for translating population-specific HLA data into interconnected reference resources, donor registries, clinical immunogenetics infrastructure and functional platforms that support equitable, African-led precision healthcare.

HLA Diversity and the Evolutionary History of African Populations

HLA diversity has been shaped by both demographic history and natural selection, with balancing selection contributing to the maintenance of extensive polymorphism at several classical HLA loci (Meyer & Thomson, 2001; Solberg et al., 2008). Infectious pathogens are considered an important component of this selection because variation in HLA peptide presentation can influence immune recognition of pathogen-derived antigens (Blackwell et al., 2009). Population-level analyses have further associated HLA class I diversity, particularly at HLA-B, with local pathogen richness, supporting a role for pathogen-mediated selection in shaping HLA variation (Prugnolle et al., 2005).

Evidence from African populations provides specific examples of these relationships. In Gambian children, HLA-Bw53 and the class II haplotype DRB11302-DQB10501 were independently associated with protection against severe malaria (Hill et al., 1991). Across African populations, the frequencies of HLA-B53, HLA-B78 and HLA-A*74 were significantly associated with *Plasmodium falciparum* prevalence. High-throughput sequencing further identified the HLA-B alleles as B*53:01:01 and B*78:01 in all but one of the individuals tested, supporting their consideration as candidates for malaria-related pathogen-driven selection (Sanchez-Mazas et al., 2017). HLA associations are also evident in other major infections. In African HIV-1 cohorts from Kenya, Rwanda, Uganda and Zambia, HLA-B*57 and HLA-B*81 showed distinct associations with virological and immunological outcomes. HLA-B*57, predominantly B*57:03, was associated with lower viral load, whereas HLA-B*81, exclusively B*81:01 in the study population, was more strongly associated with preservation of CD4⁺ T-cell counts (Prentice et al., 2013).

Tuberculosis provides further evidence of population-specific HLA associations. In Uganda, HLA-DQB1*03:03 was less frequent among patients with pulmonary tuberculosis than among healthy controls, suggesting a possible protective association (Wamala et al., 2016). Studies in Mali have also identified HLA class I and class II associations with *Mycobacterium tuberculosis* and *M. africanum*, while more recent South African analyses have implicated HLA class II variation in tuberculosis susceptibility (Croock et al., 2025).

These support there is a role for infectious disease in shaping African HLA diversity while showing that individual HLA associations vary by pathogen and population.

HLA Diversity and Blood Transfusion

Blood transfusion is essential for individuals with severe anaemia, haemorrhage, haematological malignancies, sickle cell disease and other cytopenias. While red-cell compatibility depends predominantly on erythrocyte antigens, HLA diversity becomes particularly important in platelet transfusion and leukocyte alloimmunization. Platelets express HLA class I molecules, predominantly HLA-A and HLA-B, and exposure to non-self HLA antigens through transfusion, pregnancy or transplantation can induce HLA alloantibodies (Saris & Pavenski, 2020). In platelet transfusion refractoriness (PTR), recipient HLA alloantibodies can recognize HLA class I antigens on transfused platelets, resulting in accelerated platelet clearance and inadequate post-transfusion platelet increments; affected patients may therefore require HLA-selected or antibody-compatible platelet products (Saris & Pavenski, 2020; Panch et al., 2023). HLA immunogenetics is also relevant to other transfusion-associated complications, including transfusion-related acute lung injury (TRALI). Thus, the clinical relevance of HLA extends beyond compatibility to alloimmunization, platelet transfusion efficacy, donor availability and transfusion-associated adverse events. These consequences are particularly relevant to genetically diverse African populations, where extensive HLA diversity and incomplete population characterization may complicate the development of representative HLA-typed donor resources for precision transfusion medicine.

HLA Antibodies and Transfusion-associated Complications

The clinical relevance of HLA alloimmunisation extends beyond platelet transfusion refractoriness. In antibody-mediated transfusion-related acute lung injury (TRALI), donor-derived antibodies against recipient HLA class I, HLA class II or human neutrophil antigens (HNA) can contribute to leukocyte activation, pulmonary endothelial injury and increased vascular permeability (Curtis & McFarland, 2006; Kao et al., 2003). This differs from platelet transfusion refractoriness, in which recipient alloantibodies mediate the clearance of transfused platelets. Plasma-rich components are therefore particularly relevant to antibody-mediated TRALI (Flesch et al., 2011). Pregnancy is an important source of HLA sensitisation among donors because exposure to paternally derived fetal HLA can induce antibodies that persist after pregnancy.

The frequency of HLA class I and class II antibodies increases with the number of pregnancies (Endres et al., 2010), and haemovigilance investigations have implicated HLA and HNA antibodies from previously pregnant donors in TRALI reactions (Reil et al., 2008).

Experience from the South African COVID-19 convalescent-plasma programme provides an African example. Among 34 previously pregnant donors selected for leukocyte-antibody testing, all had detectable anti-HLA antibodies: 25 had antibodies against both HLA class I and class II, while nine had antibodies against either class I or class II. Anti-HNA antibodies were detected in three donors. All 34 donors were classified as being at high risk for TRALI and were excluded from plasma donation (Glatt et al., 2021). Because this was a selected group of previously pregnant donors rather than an unselected donor population, these findings cannot be used to estimate the prevalence of HLA or HNA antibodies among South African blood donors. They do, however, provide an example of HLA/HNA antibody screening being incorporated into donor selection in an African blood-service setting.

Evidence on TRALI from African settings remains sparse. A systematic review and meta-analysis of acute transfusion reactions in sub-Saharan Africa identified only 11 reported cases of TRALI among the included studies (Twumasi et al., 2026). The small number of reported cases is difficult to interpret in the context of differences in haemovigilance systems, diagnostic capacity and recognition of acute respiratory transfusion reactions across settings. More systematic surveillance and investigation of suspected cases are needed to establish the burden and characteristics of TRALI in African blood services.

HLA Alloimmunization Following Transfusion

HLA alloimmunisation may follow transfusion, pregnancy or transplantation. In transfusion recipients, antibodies directed against HLA class I antigens on platelets can cause immune platelet transfusion refractoriness (PTR), although infection, fever, bleeding, disseminated intravascular coagulation and splenomegaly are more common causes of poor platelet increments (Legler et al., 1997; Saris & Pavenski, 2020). Evidence for transfusion-induced alloimmunisation was established by the Trial to Reduce Alloimmunization to Platelets (TRAP), which randomised 530 previously antibody-negative patients with acute myeloid leukaemia to receive conventional or modified platelet products.

Lymphocytotoxic antibodies developed in 45% of recipients of unmodified platelets compared with 17–21% receiving leukocyte-reduced or ultraviolet-B-treated components, while alloimmune PTR occurred in 13% and 3–5%, respectively (Trial to Reduce Alloimmunization to Platelets Study Group, 1997). Comparable sensitization occurs in chronically transfused haemoglobinopathies. Friedman et al. demonstrated platelet alloimmunization among heavily transfused patients with sickle cell disease (SCD), highlighting its potential relevance when such patients subsequently require intensive platelet support during haematopoietic stem-cell transplantation (Friedman et al., 1996). In a later study of 73 multiply transfused children with SCD, McPherson et al. detected HLA antibodies in 25 (34%); sensitization was more frequent among patients with red-cell alloantibodies than among those without them (53% versus 21%; OR 4.32, 95% CI 1.6–12.1), suggesting that some recipients may exhibit broader alloimmune responsiveness following repeated transfusion exposure (McPherson et al., 2010). Chronic red-cell transfusion can also result in HLA alloimmunisation. Among 60 transfusion-dependent thalassaemia patients, Lo et al. (2005) detected HLA antibodies in 31%, with a further 22% having both HLA and platelet-specific antibodies. In Morocco, HLA antibodies were detected in 50.9% of 53 patients with transfusion-dependent β -thalassaemia major; among sensitised patients, 59.3% had both class I and class II antibodies. Alloimmunisation was associated with female sex and receipt of more than 300 red-cell units (Ouadghiri et al., 2024).

Risk is also influenced by pregnancy, cumulative donor exposure and recipient factors (Mishima et al., 2015; Slichter et al., 2011). Current evidence does not show that African HLA diversity itself increases susceptibility to alloimmunisation. Its clinical importance becomes apparent after sensitisation, when the availability of compatible platelets depends partly on the HLA composition of the donor pool. African prospective studies linking HLA type, transfusion exposure, anti-HLA antibodies and post-transfusion platelet increments are needed to define the burden of immune PTR and inform the development of HLA-typed donor panels.

HLA Alloimmunization and Platelet Transfusion Refractoriness

Platelet transfusion refractoriness (PTR) is defined by repeated inadequate post-transfusion platelet increments, commonly assessed using the corrected count increment (CCI). Most cases are attributable to non-immune factors, including bleeding, infection, fever, disseminated intravascular coagulation and splenomegaly, while HLA class I

antibodies are the principal cause of immune PTR (Saris & Pavenski, 2020; Panch et al., 2024). Recipient anti-HLA antibodies can accelerate the clearance of transfused platelets expressing the corresponding antigens. Investigation of suspected immune PTR should therefore combine serial platelet increments with HLA and, where appropriate, human platelet antigen antibody testing.

Moreover, detection of anti-HLA antibodies alone does not establish immune PTR. In the TRAP cohort, low-level HLA antibodies detected by sensitive solid-phase assays were not consistently associated with transfusion failure, whereas stronger antibody responses were more predictive (Jackman et al., 2013). Confirmed HLA-mediated PTR may be managed using HLA-matched or compatible platelets, antibody-specific prediction or platelet crossmatching (Saris & Pavenski, 2020; Panch et al., 2023, 2024). African studies combining donor–recipient HLA typing, antibody specificity and serial CCI measurements are needed to define the burden of immune PTR and guide locally feasible platelet-selection strategies.

HLA/HNA Antibodies and Transfusion-Related Acute Lung Injury

HLA and human neutrophil antigen (HNA) antibodies are implicated in antibody-mediated transfusion-related acute lung injury (TRALI), characterised by acute hypoxaemia and non-cardiogenic pulmonary oedema during or within 6 hours of transfusion (Bux & Sachs, 2007; Kleinman et al., 2004; Vlaar et al., 2019). Donor anti-HLA or anti-HNA antibodies may react with recipient antigens, causing leukocyte activation and pulmonary endothelial injury. Pregnancy is an important source of donor HLA sensitisation through exposure to paternally derived fetal HLA antigens. In a South African COVID-19 convalescent-plasma programme, previously pregnant donors were screened for HLA and HNA antibodies as part of TRALI risk reduction, and all selected donors tested for anti-HLA antibodies were positive (Glatt et al., 2021). As this was a selected high-risk group, the findings do not represent antibody prevalence among South African blood donors.

TRALI risk reduction includes preferential use of plasma from male or never-pregnant female donors and HLA-antibody screening of previously pregnant donors (Vlaar et al., 2019). Strengthened haemovigilance and further studies of HLA and HNA antibodies among African blood donors are needed to determine their contribution to TRALI in African settings.

Implications of HLA for Haematopoietic Stem-Cell Transplantation

Haematopoietic stem-cell transplantation (HSCT) is a potentially curative therapeutic approach for a broad spectrum of malignant and non-malignant haematological diseases, including acute leukaemias, myelodysplastic syndromes, bone-marrow failure syndromes, immunodeficiencies and haemoglobinopathies, as well as selected congenital and metabolic disorders, solid tumours and autoimmune diseases. The use of HSCT has expanded substantially worldwide where the global registry data documented 93,105 procedures performed by 1,768 transplant teams across 89 countries in 2018, compared with 48,709 procedures in 2007. However, access remains geographically unequal, with transplantation activity strongly associated with national income and healthcare resources (Atsuta et al., 2024).

HLA matching is central to donor selection for allogeneic haematopoietic stem-cell transplantation (HSCT). This is particularly relevant in Africa, where HSCT and high-resolution HLA-typing capacity remain limited despite the substantial burden of transplant-treatable disorders. Allogeneic HSCT offers potentially curative treatment for severe sickle cell disease, particularly with an HLA-matched sibling donor (Rostami et al., 2024), but HSCT remains available in relatively few African countries (Odame & Bazuaye, 2024). Historical data illustrate this access gap: between 2006 and 2013, 29 transplant teams in 12 countries in the combined African/Eastern Mediterranean region reported 2,331 HSCT procedures, representing 3.3% of procedures reported worldwide (Baldomero et al., 2019). More recently, Tanzania established an HSCT programme and performed 11 autologous peripheral-blood stem-cell transplants during its initial implementation phase (Rwezaula et al., 2024).

Donor availability remains a major challenge for allogeneic HSCT because only a minority of patients have an HLA-matched sibling donor. The likelihood of identifying a matched unrelated donor depends on HLA diversity and ancestry representation within donor registries. Analysis of the U.S. National Marrow Donor Program registry estimated an available high-resolution 8/8 HLA-matched adult donor for approximately 75% of white patients of European descent, compared with 16–19% among the Black American groups examined (Gragert et al., 2014). These U.S. estimates should not be interpreted as direct measures of donor availability in African populations, but they demonstrate the effect of HLA diversity and donor representation on matching.

Expansion of African HSCT programmes therefore requires parallel investment in high-resolution HLA typing, histocompatibility services and representative donor resources. Population-resolved HLA datasets and targeted donor recruitment could improve donor-match prediction and support the development of regional registries and alternative-donor transplantation strategies (Gragert et al., 2014; Kollman et al., 2016).

Expansion of allogeneic HSCT in Africa requires investment in high-resolution HLA typing and representative donor resources. HLA diversity and limited donor representation can reduce match probabilities, as illustrated by the 16% likelihood of identifying an 8/8 matched unrelated donor in some Black ancestry groups in the U.S. registry (Gragert et al., 2014). Population-specific HLA data, targeted donor recruitment, regional registries and strengthened histocompatibility services are therefore important for expanding donor access.

HLA Matching Criteria and Clinical Outcomes

High-resolution HLA matching is a key determinant of donor selection and outcomes in unrelated-donor haematopoietic stem-cell transplantation (HSCT).

Landmark evidence established the importance of allele-level matching at HLA-A, -B, -C and -DRB1. In an analysis of 3,857 unrelated-donor transplants, 8/8 matching was associated with 52% one-year overall survival compared with 43% following a 7/8 match, while a single mismatch increased mortality by approximately 25% (Lee et al., 2007). Subsequent evidence demonstrated that the effects of HLA disparity extend beyond survival to clinically important outcomes including acute graft-versus-host disease (GVHD), graft failure and non-relapse mortality, reinforcing high-resolution HLA typing as an integral component of unrelated-donor selection. Donor assessment has subsequently evolved beyond conventional 8/8 matching. Contemporary recommendations incorporate additional immunogenetic characteristics, including HLA-DPB1 permissiveness and donor-specific HLA antibodies, particularly when several otherwise suitable donors are available (Dehn et al., 2019). Importantly, recent large-scale evidence confirms that HLA disparity remains clinically relevant: among 17,292 unrelated-donor transplants, HLA mismatch was associated with increased mortality (HR 1.23), with a stronger effect observed for HLA class-I mismatches at HLA-A, -B and -C (HR 1.29) (Arrieta-Bolaños et al., 2024).

The clinical impact of HLA mismatch is changing with advances in transplantation.

Post-transplant cyclophosphamide (PTCy) reduces alloreactivity, and outcomes after single-locus mismatched unrelated-donor transplantation may approach those of matched unrelated-donor transplantation (Shaffer et al., 2024). This may expand donor options for underrepresented populations, although population-specific HLA data remain important for donor searches and selection of alternative donor strategies.

Establishing African Donor Registries

Despite more than 41 million registered unrelated stem-cell donors worldwide, access remains uneven because donor availability depends on the representation of population-specific HLA haplotypes within registries (Sauter et al., 2025). In South Africa, patients of Black African ancestry have historically been underrepresented in donor registries, often requiring international donor searches (Tshabalala et al., 2018). However, analysis of 56,961 South African potential donors showed comparable intrapopulation matching probabilities in Black South African and White populations and estimated that a registry of one million Black African donors could provide approximately an 80% probability of identifying at least one fully matched donor for a Black African patient (Sauter et al., 2025). These findings support population-informed donor recruitment, high-resolution HLA typing and strengthened regional registry and histocompatibility infrastructure.

Haploidentical Transplantation as a Complementary Strategy

Haploidentical transplantation expands donor options for patients without HLA-matched sibling or unrelated donors, particularly with the use of post-transplant cyclophosphamide (PTCy). In South Africa, a study of 134 patients with haematological malignancies undergoing haploidentical HSCT with PTCy reported 1- and 3-year overall survival of 56% and 37%, respectively (du Toit et al., 2021). Haploidentical HSCT has also expanded donor options for sickle cell disease, although early PTCy-based approaches were affected by graft failure (Bolaños-Meade et al., 2012), with improved engraftment reported following subsequent regimen optimisation (de la Fuente et al., 2019). HLA assessment remains important because donor-specific anti-HLA antibodies are associated with increased graft-failure risk in haploidentical HSCT (Chang et al., 2015; Xie et al., 2021). Thus, expansion of haploidentical HSCT in Africa should be accompanied by HLA typing, donor-specific antibody testing and strengthened histocompatibility services.

Implications for Solid-Organ Transplantation

In solid-organ transplantation, previous pregnancy, transfusion or transplantation may induce anti-HLA antibodies that restrict compatible donor options and increase the risk of antibody-mediated rejection, particularly in kidney transplantation (Alelign et al., 2018; McCaughan & Tinckam, 2018). Large registry studies have demonstrated superior graft survival with increasing HLA compatibility, particularly at HLA-A, -B and -DR, although improvements in immunosuppression have modified the magnitude of individual locus effects over time (Opelz & Döhler, 2007). In 9,209 paediatric kidney recipients, increasing numbers of HLA-A, -B and -DR mismatches were similarly associated with poorer graft survival, demonstrating that histocompatibility remains relevant even in the modern immunosuppression era (Opelz & Döhler, 2010). For African transplant programmes, however, the challenge extends beyond maximizing HLA matching: donor availability, population-specific HLA diversity, sensitization and access to histocompatibility testing must be considered simultaneously. Historical clinical experience from Kenya illustrates the importance of strengthening this infrastructure. Among 15 living-donor kidney recipients followed at Kenyatta National Hospital, most donors were siblings, with one-year graft and patient survival of 93% and 86.6%, respectively (Kayima et al., 1996), while a later study of living-related kidney donation at the same institution documented continuing reliance on family donors and highlighted financial, workforce and transplantation-system constraints (Muturi et al., 2017). These observations support the development of HLA services alongside expanding African living- and deceased-donor transplantation programmes rather than treating histocompatibility as an isolated laboratory function.

HLA Antibodies and Transplant Outcomes

Donor-specific HLA antibodies (DSA) are important determinants of kidney-transplant outcomes. Pre-transplant DSA are associated with poorer graft survival, while de novo DSA may contribute to antibody-mediated injury and graft loss (Caro-Oleas et al., 2012; Wiebe et al., 2012). In 892 deceased-donor kidney recipients with negative cytotoxic crossmatches, pre-transplant DSA were associated with significantly poorer graft survival than either non-donor-specific HLA antibodies or absence of HLA antibodies (Caro-Oleas et al., 2012). South African studies also demonstrate the value of sensitive HLA antibody testing.

Among patients awaiting deceased-donor kidney transplantation, those who received a transplant had lower HLA antibody reactivity than those who remained untransplanted (median 2% versus 8%; $p=0.0006$), supporting the use of single-antigen testing for immunological risk assessment (Worsley & Mayne, 2018). Comparison of complement-dependent cytotoxicity, flow-cytometric and Luminex-based assays further showed differences in the detection of preformed HLA antibodies and supported donor-specific antibody assessment in pre-transplant evaluation (Kwofie et al., 2021). These findings support strengthening HLA typing, antibody testing and crossmatching capacity as transplantation services expand in Africa.

Deceased-Donor Allocation and HLA

Deceased-donor kidney allocation requires HLA compatibility to be considered alongside sensitisation, waiting time and other clinical criteria. Donor-pool composition can affect access to well-matched organs; historically, only 2% of Black recipients compared with 8% of non-Black recipients received zero-HLA-mismatched kidneys in a predominantly non-Black donor pool (Lazda, 1992). More recent UK registry data also demonstrate ethnic differences in the relationship between HLA-DR matching and transplant outcomes (Ali et al., 2026). Thus, African transplantation programmes require locally derived evidence to determine the appropriate role of HLA matching in organ allocation. Population-specific HLA data, donor and recipient typing, and identification of unacceptable antigens could support donor matching and virtual crossmatching. South African experience demonstrates the feasibility of higher-resolution HLA typing for renal transplantation (Gandini et al., 2021). Prospective African studies linking HLA matching and donor-specific antibodies with rejection and graft survival are needed to inform locally appropriate allocation strategies.

Implications for Infectious-Disease Immunity and Vaccine Responses

The clinical importance of HLA diversity extends beyond alloimmunity and transplantation because HLA molecules determine which pathogen-derived peptides are presented to CD4⁺ and CD8⁺ T cells, thereby influencing immunodominance, pathogen control, immune escape and vaccine-induced immunity. Evidence from African populations provides particularly compelling examples. In Gambian children, HLA-Bw53 and the DRB11302-DQB10501 haplotype were independently associated with protection against severe malaria, providing early evidence that HLA variation can influence infectious-disease outcomes in African populations (Hill et al., 1991; PMID: 1865923).

Similar associations have been reported in HIV infection. Among 538 recent HIV-1 seroconverters from African cohorts, HLA-B*57 and HLA-B*81 showed distinct associations with virological and immunological control (Prentice et al., 2013). Studies of HIV-1 subtype C infection in southern Africa further showed that closely related HLA-B*57 variants can differ in epitope presentation, viral selection pressure and their association with viraemic control (Kloverpris et al., 2012). HLA associations have also been reported in tuberculosis. In South Africa, Salie et al. (2015) identified HLA class I alleles associated with pulmonary tuberculosis in a case-control study of 408 cases and 351 controls. More recent ancestry-aware analysis of an admixed South African population identified an association within the HLA-DPB1 region, highlighting the importance of population structure in studies of HLA-associated tuberculosis susceptibility (Croock et al., 2025).

The relevance of HLA diversity to vaccination was demonstrated by Mentzer et al. (2024), who analysed 2,499 infants from Uganda, Burkina Faso and South Africa and identified HLA associations with antibody responses to five of eight vaccine antigens. HLA-DR/DQ variation explained up to 10% of variation in antibody responses, and the genetic architecture of pertussis responses differed between African- and European-ancestry cohorts. The study also generated an African HLA imputation resource using high-resolution HLA data from 1,702 individuals representing 11 African-ancestry populations.

Population-specific HLA data may therefore improve vaccine-response studies, epitope selection and assessment of HLA-restricted immunity. However, HLA associations should not be generalised across African populations because allele and haplotype frequencies vary considerably. Studies combining HLA typing with functional immune measurements and clinical outcomes are needed to define population-specific vaccine responses and protective immunity.

HLA-Restricted Pathogen Immunity

HLA polymorphism influences susceptibility to infection and pathogen control by determining the pathogen-derived peptides presented to T cells. These associations vary by pathogen, viral strain and population genetic background, as demonstrated in several African populations. In Gambian children, HLA-Bw53 and the DRB11302-DQB10501 haplotype were associated with protection against severe *Plasmodium falciparum* malaria (Hill et al., 1991). This provided early evidence that HLA variation can influence clinically important infectious-disease outcomes in African populations.

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Implications for Infectious-Disease Immunity and Vaccine Responses

The clinical importance of HLA diversity extends beyond alloimmunity and transplantation because HLA molecules determine which pathogen-derived peptides are presented to CD4⁺ and CD8⁺ T cells, thereby influencing immunodominance, pathogen control, immune escape and vaccine-induced immunity. Evidence from African populations provides particularly compelling examples. In Gambian children, HLA-Bw53 and the DRB11302-DQB10501 haplotype were independently associated with protection against severe malaria, providing early evidence that HLA variation can influence infectious-disease outcomes in African populations (Hill et al., 1991; PMID: 1865923).

Similar associations have been reported in HIV infection. Among 538 recent HIV-1 seroconverters from African cohorts, HLA-B*57 and HLA-B*81 showed distinct associations with virological and immunological control (Prentice et al., 2013). Studies of HIV-1 subtype C infection in southern Africa further showed that closely related HLA-B*57 variants can differ in epitope presentation, viral selection pressure and their association with viraemic control (Kloverpris et al., 2012). HLA associations have also been reported in tuberculosis. In South Africa, Salie et al. (2015) identified HLA class I alleles associated with pulmonary tuberculosis in a case-control study of 408 cases and 351 controls. More recent ancestry-aware analysis of an admixed South African population identified an association within the HLA-DPB1 region, highlighting the importance of population structure in studies of HLA-associated tuberculosis susceptibility (Croock et al., 2025).

The relevance of HLA diversity to vaccination was demonstrated by Mentzer et al. (2024), who analysed 2,499 infants from Uganda, Burkina Faso and South Africa and identified HLA associations with antibody responses to five of eight vaccine antigens. HLA-DR/DQ variation explained up to 10% of variation in antibody responses, and the genetic architecture of pertussis responses differed between African- and European-ancestry cohorts. The study also generated an African HLA imputation resource using high-resolution HLA data from 1,702 individuals representing 11 African-ancestry populations.

Population-specific HLA data may therefore improve vaccine-response studies, epitope selection and assessment of HLA-restricted immunity. However, HLA associations should not be generalised across African populations because allele and haplotype frequencies vary considerably. Studies combining HLA typing with functional immune measurements and clinical outcomes are needed to define population-specific vaccine responses and protective immunity.

HLA-Restricted Pathogen Immunity

HLA polymorphism influences susceptibility to infection and pathogen control by determining the pathogen-derived peptides presented to T cells. These associations vary by pathogen, viral strain and population genetic background, as demonstrated in several African populations. In Gambian children, HLA-Bw53 and the DRB11302-DQB10501 haplotype were associated with protection against severe *Plasmodium falciparum* malaria (Hill et al., 1991). This provided early evidence that HLA variation can influence clinically important infectious-disease outcomes in African populations.

HIV-1 provides further evidence of HLA-associated differences in pathogen control. HLA-B*57 and HLA-B*27 have been associated with favourable HIV outcomes, whereas some HLA-B*35 alleles have been associated with more rapid disease progression; however, these effects vary across populations and viral subtypes (Goulder et al., 2001; Kiepiela et al., 2007). In African cohorts, HLA-B*57 and HLA-B*81 showed distinct associations with virological and immunological outcomes among 538 recent HIV-1 seroconverters (Prentice et al., 2013). Mechanistic studies in South Africa further demonstrated viral adaptation under HLA-B*81:01-restricted immune pressure, while HLA-associated Gag mutations can alter viral replication capacity (Ntale et al., 2012; Wright et al., 2012). In a KwaZulu-Natal cohort, Gag-specific CD8⁺ T-cell responses were associated with lower viraemia, whereas responses to Env and accessory or regulatory proteins were associated with higher viraemia, demonstrating that the antigenic target of the response is relevant to viral control (Kiepiela et al., 2007). More recently, HLA-A*23 was associated with lower odds of acute retroviral syndrome during primary HIV-1 infection in cohorts from Kenya, Rwanda, Uganda and Zambia (Lindquist et al., 2024).

HLA class II variation is also relevant to infections requiring effective CD4⁺ T-cell responses. In a two-stage Gambian study, HLA-DRB1*1302 was more frequent among individuals who cleared HBV than among those with persistent infection, with the association observed in both children and adults (Thursz et al., 1995). The original study identified the RFLP-defined 25-1 pattern as corresponding to two haplotypes, DRB11302-DRB30301-DQA10102-DQB10501 and DRB11302-DRB30301-DQA10102-DQB10604, and concluded that the association was most likely attributable to HLA-DRB1*1302. Subsequent peptide-binding studies provided functional evidence that HLA-DR molecules differ in their capacity to present HBV-derived peptides to CD4⁺ T cells, providing a possible mechanistic basis for HLA class II associations with HBV immunity (Godkin et al., 2005).

HLA class I and II variation has also been associated with spontaneous hepatitis C virus clearance, although much of this evidence derives from non-African cohorts; these associations should therefore not be assumed to have identical effects in African populations without population-specific validation.

Tuberculosis provides another increasingly important African example. HLA class II variation has been associated with susceptibility to *Mycobacterium tuberculosis*, but ancestry and

population structure can substantially affect detectable associations. Recent work in an admixed South African population identified an HLA-DPB1-region signal associated with TB susceptibility and traced the signal to KhoeSan local ancestry, reinforcing both the contribution of HLA class II variation to TB susceptibility and the importance of ancestry-aware analysis in genetically diverse African populations (Croock et al., 2025). Such findings caution against treating African populations as a homogeneous genetic group and demonstrate why HLA associations identified in one population require validation in others. Evidence for SARS-CoV-2 illustrates an additional need for caution when interpreting emerging HLA associations. Augusto et al. identified a strong association between HLA-B*15:01 and asymptomatic SARS-CoV-2 infection in two cohorts and demonstrated cross-reactive, polyfunctional memory T cells recognizing conserved seasonal-coronavirus and SARS-CoV-2 peptides, suggesting pre-existing HLA-restricted immunity (Augusto et al., 2023). However, this association was not replicated across independent cohorts, emphasizing the need for population-level validation before specific HLA alleles are considered reliable predictors of clinical outcomes (Marchal et al., 2024). The priority for African HLA research should extend beyond allele-based disease-risk stratification toward identifying reproducible HLA-peptide-T-cell relationships that confer functional protection. Integrating high-resolution HLA typing with pathogen sequencing, epitope prediction and mapping, functional CD4⁺/CD8⁺ T-cell assays and longitudinal outcomes could identify protective epitopes and HLA-driven immune escape. Population-resolved evidence could subsequently guide vaccine antigen and epitope selection, immune-monitoring reagents and population-coverage assessment, providing clinically actionable translation of African HLA diversity.

Vaccine Responsiveness

Vaccine responsiveness provides compelling evidence that HLA variation influences clinically relevant immune phenotypes in African populations. Mentzer et al. analysed 2,499 infants from Uganda, Burkina Faso and South Africa, identifying HLA associations with antibody responses to five of eight vaccine antigens, including pertussis, diphtheria and hepatitis B. HLA-DR/DQ variation explained up to 10% of antibody-response variance, while HLA-DRB1 expression was associated with pertussis vaccine responses (Mentzer et al., 2024). Importantly, response architecture differed between African- and European-ancestry cohorts, highlighting limited cross-population transferability.

Earlier studies provide complementary evidence: HLA-DRB1*03, *07 and *14 were enriched among hepatitis B vaccine non-responders while HLA class I and II variants influenced measles vaccine antibody responses (Ovsyannikova et al., 2012). However, these predominantly non-African studies provide mechanistic evidence rather than population-specific estimates for African populations. Mentzer et al. generated high-resolution HLA data from 1,702 individuals across 11 African-ancestry populations, developing an African HLA imputation resource and demonstrating that HLA-DRB1 expression, beyond peptide-binding specificity, may contribute to vaccine responsiveness (Mentzer et al., 2024). Banjoko et al. (2025) demonstrated substantial HLA class I diversity across African populations, including Kenya, supporting the use of population-specific HLA data in T-cell vaccine research. Integrating HLA typing with epitope selection, immune-response measurements and clinical outcomes could improve the evaluation of vaccine responses across diverse African populations (Banjoko et al., 2025)..

Implications for Pharmacogenomics and Drug Hypersensitivity

HLA variation is associated with several immune-mediated adverse drug reactions, including HLA-B*57:01 with abacavir hypersensitivity,

HLA-B*15:02 with carbamazepine-induced severe cutaneous adverse reactions and HLA-B*58:01 with allopurinol hypersensitivity (White et al., 2017). Because the frequencies of these alleles vary among populations, the clinical utility of HLA-guided prescribing is population dependent. This is particularly relevant in Africa, where pharmacogenomic evidence remains limited and population-specific HLA data are needed to evaluate established HLA-drug associations. In a study of 4,016 individuals with HIV from Burkina Faso, Côte d'Ivoire, Gabon and Togo, HLA-B*57:01 was identified in only three individuals, corresponding to an overall prevalence of 0.1% (Kolou et al., 2021).

HLA-Associated Drug Hypersensitivity

HLA-associated drug hypersensitivity demonstrates how population HLA diversity can inform precision medicine. Established associations include HLA-B*57:01 with abacavir hypersensitivity, HLA-B*15:02 and HLA-A*31:01 with carbamazepine hypersensitivity, and HLA-B*58:01 with allopurinol-associated severe cutaneous adverse reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Because allele frequencies vary substantially among populations, the predictive value and cost-effectiveness of pre-treatment testing may also vary, requiring population-specific

implementation strategies (Zhou & Lauschke, 2022). Carbamazepine provides a particularly clear example of population specificity. HLA-B*15:02 is strongly associated with carbamazepine-induced SJS/TEN, particularly in several Asian populations, whereas HLA-A*31:01 has been associated with a broader spectrum of carbamazepine hypersensitivity reactions (McCormack et al., 2011). An updated meta-analysis involving 46 case-control studies and 8,431 participants found markedly increased odds of carbamazepine-induced SJS/TEN among HLA-B*15:02 carriers (OR 26.01; 95% CI 15.88–42.60), while also demonstrating population heterogeneity (Biswas et al., 2022). More recent reviews similarly emphasise that the frequency and predictive performance of HLA-B*15:02, and consequently the utility of pre-treatment testing, vary among populations (Zhu et al., 2024). Abacavir provides an informative African example. The association between HLA-B*57:01 and abacavir hypersensitivity has led to the use of HLA-B*57:01 testing before treatment. However, the frequency of **HLA-B*57:01** varies considerably among populations. Among 4,016 people living with HIV from Burkina Faso, Côte d'Ivoire, Gabon and Togo, HLA-B*57:01 was detected in only three participants, corresponding to an overall prevalence of approximately 0.1% (Kolou et al., 2021). The authors therefore questioned the cost-effectiveness of routine HLA-B*57:01 screening for preventing abacavir hypersensitivity in the four countries studied, while cautioning that their findings should not be generalised to all West and Central African populations. More recently, Adechina et al. (2024) detected no HLA-B*57:01 carriers among 110 people living with HIV in Benin.

Conversely, a severe abacavir hypersensitivity reaction has been reported clinically in a Kenyan patient, illustrating that low population frequency does not mean absence of individual risk and highlighting the challenge of translating population frequencies into clinical testing policies (Koech et al., 2022). HLA-B*58:01 is strongly associated with allopurinol-induced severe cutaneous adverse reactions (SCARs). However, evidence remains limited for North African and sub-Saharan African populations, highlighting the need for population-specific data on HLA-B*58:01 frequency and allopurinol-associated clinical outcomes before broader implementation of HLA-guided screening across Africa (Pham et al., 2025).

Implementing Pharmacogenomic Screening

Implementing HLA-based pharmacogenomic screening in African health systems requires moving beyond identifying strong HLA-drug associations towards establishing their clinical utility within specific populations.

The value of screening depends on local risk-allele frequencies, patterns of drug exposure, incidence and severity of adverse reactions, predictive performance, availability of alternative therapies and cost-effectiveness. This is particularly important given Africa's substantial genetic diversity and persistent underrepresentation in pharmacogenomic studies, which limit direct extrapolation of evidence generated in other populations (Twesigomwe et al., 2025). Implementation should therefore be guided by population-resolved evidence. Priority HLA–drug pairs should be evaluated according to allele frequency, medicine utilization, adverse-event burden, positive and negative predictive values, number needed to genotype, turnaround time and testing costs. Important barriers include limited genotyping and sequencing capacity, insufficient population-specific evidence, financial constraints and gaps in implementation frameworks (Twesigomwe et al., 2025). Validated PCR- or sequencing-based HLA assays should consequently be accompanied by clinical guidelines defining when testing is indicated and how results should inform prescribing. Thus, translation into routine care will additionally require integration of HLA results into electronic health records and clinical decision-support systems, enabling clinically actionable genotypes to inform future prescribing (Hicks et al., 2016). Strengthened pharmacovigilance is equally important for linking HLA variants prospectively with severe adverse drug reactions and evaluating clinical outcomes (Stegmann et al., 2022). Workforce development for laboratory scientists, pharmacists and clinicians will also be essential (B Tata et al., 2020). Existing HLA infrastructure supporting transplantation, transfusion medicine and immunogenetics could provide shared technical capacity. Ultimately, population-informed pharmacogenomic panels prioritizing locally relevant HLA–drug pairs could translate African HLA diversity into safer prescribing and equitable precision medicine.

Towards Integrated African HLA Infrastructure

Clinical and research applications of HLA require shared capacity for high-resolution typing, antibody testing, histocompatibility assessment and population immunogenetics. As illustrated in Figure 1, an integrated African HLA framework could link population-specific HLA resources with transfusion medicine, transplantation, infectious-disease immunology, vaccination, pharmacogenomics and emerging cellular therapies. This framework would be supported by representative donor resources, biobanks, interoperable datasets, quality-assured laboratories, workforce development and African-led governance.

Population-Resolved HLA Reference Resources

High-resolution HLA reference data are needed to capture the substantial variation within and between African populations. Banjoko et al. (2025) demonstrated marked class I HLA diversity across Eastern and Southern African populations, including considerable within-country diversity in Kenya, Uganda and Zambia. Mentzer et al. (2024) similarly generated high-resolution HLA data from 1,702 individuals representing 11 African-ancestry populations and developed an African HLA imputation resource. Such datasets can support donor matching, population genetic studies, vaccine research and pharmacogenomics.

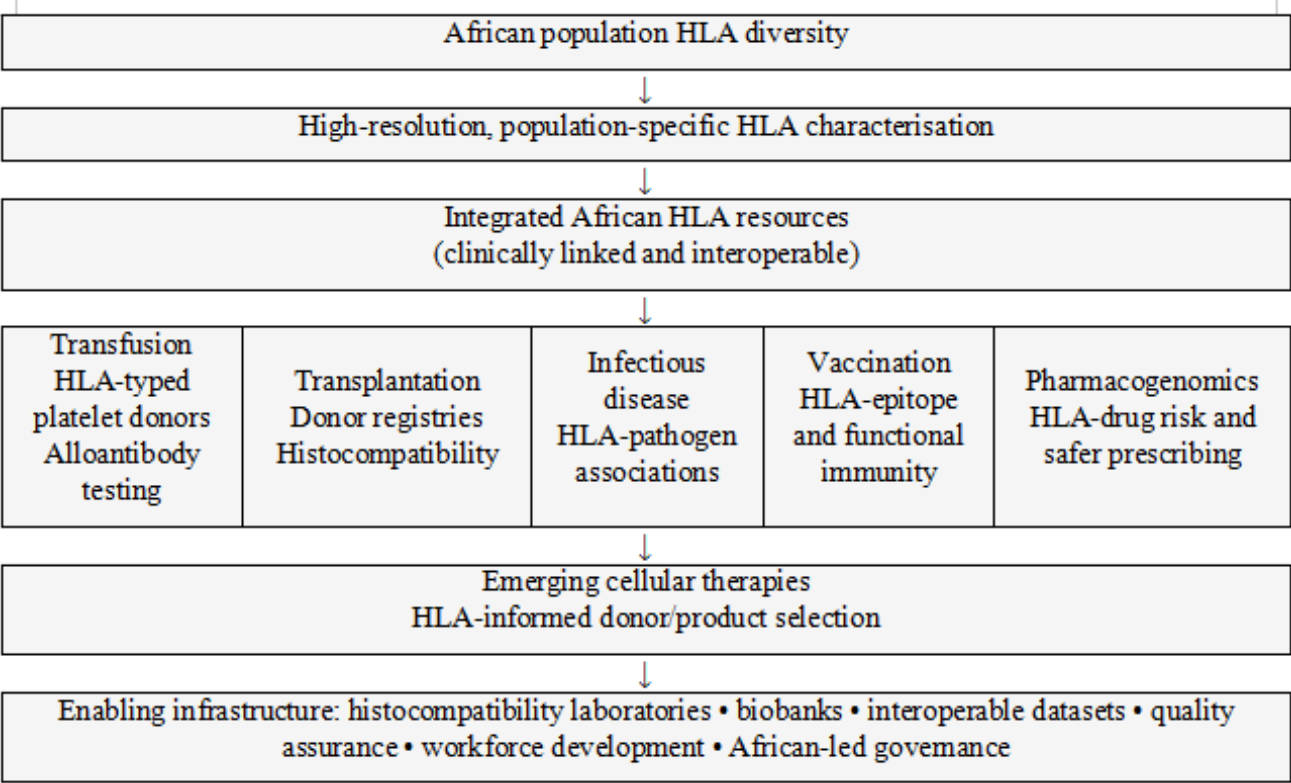
Donor Resources and Histocompatibility Services

Population HLA data should inform donor recruitment and clinical histocompatibility services. African HSCT registries require representative donor recruitment, high-resolution HLA typing and interoperable data systems, as illustrated by experience from the South African Bone Marrow Registry (Tshabalala et al., 2018). HLA-typed blood-donor panels could similarly support patients with HLA-mediated platelet refractoriness. These services require quality-assured laboratories capable of HLA typing, anti-HLA antibody testing, donor-specific antibody assessment and crossmatching, supported by proficiency testing and trained personnel.

Functional Immunology, Vaccines and Cellular Therapies

HLA population data should also be linked to functional immune phenotypes. Mentzer et al. (2024) demonstrated associations between HLA variation, HLA-DRB1 expression and vaccine antibody responses, while Banjoko et al. (2025) highlighted the relevance of African class I HLA diversity to T-cell vaccine research. HLA-informed resources may also support virus-specific T-cell therapies. Withers et al. (2018) showed that a bank generated from carefully selected donors could provide a suitably HLA-matched virus-specific T-cell product for more than 90% of HSCT recipients in their transplant population. Similar approaches in Africa would require locally representative HLA and epitope data.

Figure 1: *Integrated Framework for Translating African HLA Diversity into Clinical and Research Applications.*



Population-specific, high-resolution HLA characterisation provides the foundation for interconnected applications in transfusion medicine, haematopoietic stem-cell and solid-organ transplantation, infectious-disease immunology, vaccination, pharmacogenomics and emerging cellular therapies. Translation across these areas depends on HLA typing and antibody testing, representative donor resources, clinically annotated biobanks and interoperable datasets, supported by quality-assured laboratory infrastructure, workforce development and African-led data governance. The framework illustrates how coordinated HLA resources can support population-informed research and clinical practice across diverse African populations.

Pharmacogenomics and Sustainable Implementation

HLA infrastructure could also support pharmacogenomic testing for clinically relevant HLA–drug associations, including those involving abacavir, carbamazepine and allopurinol where supported by local evidence. Implementation should consider population allele frequencies, clinical validity, medicine use and health-system capacity. Sustainable African HLA infrastructure will require interoperable data systems, laboratory quality assurance, workforce development and African leadership in data generation, governance and clinical translation.

CONCLUSION

African HLA diversity should be recognized as clinically actionable immunogenetic variation rather than solely a feature of population genetics. Its consequences extend across transfusion, transplantation, infectious diseases, vaccination and pharmacogenomics, yet translation requires representative, clinically linked HLA resources. Priority actions include high-resolution characterization of diverse African populations; development of population-informed platelet and stem-cell donor resources; strengthened histocompatibility laboratories and antibody testing; integration of HLA data with functional immunology, pathogen–epitope mapping and vaccine studies; and evaluation of clinically relevant HLA–drug associations using local evidence such as in Table 1.

These efforts should be supported by interoperable datasets, quality-assurance systems, workforce development and African-led governance. Thus, the objective is not to define a single continental HLA profile, but to develop locally representative, interconnected systems that reflect Africa’s immunogenetic diversity, disease burden and clinical priorities. Such infrastructure could translate HLA diversity into a practical resource for safer transfusion, improved transplantation, precision vaccination, pharmacogenomics and emerging cellular therapies.

LITERATURE SEARCH

Relevant literature was identified through searches of PubMed, Scopus, and Web of Science. Search terms included HLA, human leukocyte antigen, HLA

diversity, Africa, individual African countries, transfusion, platelet refractoriness, transplantation, infectious disease, vaccination, pharmacogenomics, and drug hypersensitivity. Searches also included combinations of these terms with specific infectious diseases discussed in this review. Primary research articles involving African populations were prioritised, particularly studies reporting population-specific HLA allele and haplotype frequencies, clinically relevant HLA associations, and recent advances in HLA immunogenetics. Seminal studies were included where they provided historical context or established key mechanistic or clinical concepts. Reference lists of relevant articles and reviews were also screened to identify additional studies relevant to the scope of this narrative review.

Table 1: Selected Clinically Relevant HLA Associations Reported in African Populations.

Domain	HLA allele / haplotype	Population / cohort	Phenotype / exposure	Direction / interpretation	Effect estimate / quantitative finding	Evidence type	Reference
Malaria	HLA-Bw53; HLA-DRB1*13:02–HLA-DQB1*05:01	Gambian children	Severe Plasmodium falciparum malaria	Both markers were associated with protection against severe malaria.	Independent protective associations were reported. For the class II haplotype, the reduction in disease incidence was described as comparable in magnitude to the sickle-cell haemoglobin variant;	Case–control association	Hill et al., 1991; PMID 1865923

HIV-1	HLA-B*44; HLA-B*57	Sub-Saharan African seroconverters (n=134)	Peak and set-point HIV-1 viral load	Both HLA-B groups were associated with more favourable viral control.	Peak viral load: HLA-B*44 $\beta = -1.08 \pm 0.26 \log_{10}$ and HLA-B*57 $\beta = -0.83 \pm 0.27 \log_{10}$ (both $P < 0.005$); both were also favourable for set-point viral load ($P \leq 0.03$).	Prospective seroconverter cohort	Tang et al., 2011; PMID 21715491
HIV-1	HLA-B*57 (predominantly HLA-B*57:03); HLA-B*81 (HLA-B*81:01 in this cohort)	Kenya, Rwanda, Uganda and Zambia; 538 recent seroconverters plus 292 participants of unknown infection duration	Pre-ART viral load and CD4+ T-cell count	HLA-B*57 was associated primarily with lower viral load, whereas HLA-B*81 was associated with higher CD4+ T-cell counts despite limited effect on set-point viral load.	HLA-B*57: lower viral load in multiple models ($P \leq 0.03$), without an early CD4 advantage ($P \geq 0.37$). HLA-B*81: set-point viral-load effect $P > 0.18$; higher CD4 counts during early/chronic infection $P = 0.01$.	Prospective and cross-sectional cohort analysis	Prentice et al., 2013; PMID 23365442

HIV-1	Seroconversion: favourable HLA-A*01, HLA-C*06:02, HLA-C*07:01; susceptible HLA-A*23:01, HLA-B*07:02, HLA-B*42:01. Progression: favourable HLA-A*74:01, HLA-B*14, HLA-B*57:03; adverse HLA-B*07:02, HLA-B*15:10, HLA-B*53:01.	Pumwani Sex Worker Cohort, Kenya (>1,000 women typed)	HIV-1 seroconversion and subsequent disease progression	Distinct HLA profiles were associated with lower or higher likelihood of seroconversion and with slower or faster CD4 decline.	Seroconversion: favourable group OR 0.503 (95% CI 0.320–0.790), P=0.00001; susceptible group OR 2.059 (95% CI 1.290–3.285), P=0.002. Progression associations: A*74:01 P=0.04/0.006; B*14 P=0.003/0.003; B*57:03 P=0.012/0.038; B*07:02 P=0.020; B*15:10 P=0.022; B*53:01 P=0.007.	Longitudinal cohort / genetic association	Peterson et al., 2013; PMID 23330720
HIV-1	HLA-A*30:02–HLA-B*45:01	Pumwani Sex Worker Cohort, Kenya (595 HIV-positive; 176 HIV-negative)	Progression to AIDS / CD4 <200 cells/mm ³	Associated with faster disease progression and retained significance after false-discovery-rate correction.	Log-rank P=0.0008; LR=11.183; FDR=0.013.	Haplotype survival analysis	Luo et al., 2014; PMID 24992306

Tuberculosis	HLA-DQB1*03:03	Uganda; HIV-negative pulmonary-TB cases (n=43) and genetically related household controls (n=42)	Pulmonary tuberculosis due to <i>M. tuberculosis</i>	Lower frequency among cases, consistent with a potential protective/resistance association.	10% in controls versus 0% in cases; P=0.003; corrected P=0.018.	Case-control association	Wamala et al., 2016; PMID 26803588
Tuberculosis	Multiple HLA-A, HLA-B and HLA-DRB1 alleles; HLA-DRB1*03:01 associated with both pathogen groups	Mali; active pulmonary TB due to <i>M. africanum</i> or <i>M. tuberculosis</i> versus controls	Pathogen-specific tuberculosis susceptibility patterns	Differential HLA allele distributions were observed according to infecting <i>Mycobacterium</i> species.	Several HLA-B alleles were associated with <i>M. africanum</i> (40–45%) and <i>M. tuberculosis</i> (75%), and several HLA-A alleles with both groups (65–70%);	Prospective genetic association / pathogen-stratified analysis	Tientcheu et al., 2018; PMID 30516034

Vaccination	HLA class II HLA-DR/HLA-DQ variation; HLA-DRB1 expression	Uganda (n=1,391), Burkina Faso (n=353) and South Africa (n=755)	Antibody responses to routine infant vaccines	HLA variation was associated with vaccine-antibody responses, with heterogeneity across populations and antigens.	Associations were identified for 5 of 8 tested antigens; fine-mapped HLA-DR/DQ variants explained up to 10% of antibody-response variance.	Multi-cohort genetic association / fine-mapping	Mentzer et al., 2024; PMID 38740997
Pharmacogenomics	HLA-Bw53; HLA-DRB1*13:02–HLA-DQB1*05:01	Tunisia; carbamazepine-DRESS cases (n=7) and tolerant controls (n=25)	Carbamazepine-induced DRESS	Strong risk association in a small pilot study.	4/7 cases (57.14%) versus 1/25 controls (4%); OR 32 (95% CI 2.6–389.2); P=0.004.	Case–control pharmacogenetic association	Ksouda et al., 2017; PMID 29125944
Pharmacogenomics	HLA-B*44; HLA-B*57	Burkina Faso, Côte d’Ivoire, Gabon and Togo; adults with HIV-1 (n=4,016)	Abacavir pharmacogenomic implementation	Very low prevalence of the established abacavir-hypersensitivity risk allele; this study did not estimate local hypersensitivity risk.	3/4,016 participants; prevalence 0.1% (95% CI 0.0–0.2%);	Cross-sectional allele-frequency / implementation study	Kolou et al., 2021; PMID 34294032

The table summarises representative HLA associations with infectious diseases, vaccine responses and pharmacogenomic phenotypes reported in African study populations. It presents the HLA allele or haplotype, population and study cohort, clinical phenotype or exposure, direction of association, quantitative effect estimates where available, study design and primary reference. Related HLA associations reported within the same study or cohort are consolidated to minimise repetition while retaining allele-specific findings. HLA nomenclature and allelic resolution are presented as reported in the primary studies. The Quantitative estimates reflect the analytical approaches used in the individual studies and are not directly comparable across different study designs. HLA-Bw53 is retained to reflect the terminology used in the original Gambian malaria study. For HLA-B57:01 and abacavir, the African study reports allele prevalence rather than an African-specific estimate of hypersensitivity risk.

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