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REVIEW

The Duffy antigen: A narrative review of testing, epidemiology, neutrophil counts and clinical consequences

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Summary
The null variant of the Duffy antigen is a non-pathological mutation that is partially protective against *Plasmodium vivax* and results in a lower absolute neutrophil count (ANC) in peripheral blood without increasing the risk of infection. Healthcare practices, clinical trials eligibility and medication dosing are often influenced by the definition of neutropenia. In many regions, however, neutropenia has been defined by the ANC distribution of Duffy-positive individuals, which may be unsuitable for decision-making in Duffy null individuals. This review describes the association between Duffy status, *Plasmodium vivax* exposure, racial or ethnic groupings and ANC. We outline biological and iatrogenic associations between Duffy antigen status and health outcomes and recommend changes to healthcare practices required to ensure equity for Duffy null individuals.

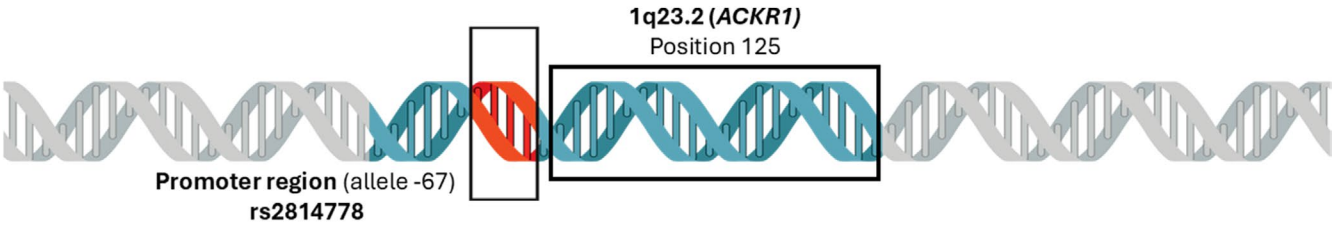
KEYWORDS
blood groups, chronic neutropenia, clinical haematology, general haematology, neutropenia, red cell antigens

SUMMARY

The null variant of the Duffy antigen is a non-pathological mutation that is partially protective against *Plasmodium vivax* and results in a lower absolute neutrophil count (ANC) without increasing the risk of infection. In many regions, neutropenia has been defined by the ANC distribution of Duffy-positive individuals, which may be unsuitable for decision-making in Duffy null individuals. This review describes the association between Duffy status, *Plasmodium vivax* exposure, racial or ethnic groupings and ANC. We outline biological and iatrogenic associations between Duffy antigen status and health outcomes, and we recommend changes to health practices required for equitable care for Duffy null individuals.

DUFFY ANTIGEN STRUCTURE AND TESTING

The Duffy antigen is a chemokine receptor expressed in many tissues including endothelial cells of the blood vessels, Purkinje cells in the cerebellum, lung alveoli, thyroid and spleen.[1] The Duffy antigen is also found on erythrocytes and is recognised as a minor blood group.[2,3] It is encoded by the atypical chemokine receptor 1 (*ACKR1*; previously the Duffy antigen receptor for chemokines [*DARC*]) gene.[2,4] There are rare mutations in *ACKR1* that result in a lack of expression of the Duffy antigen on all tissues.[5] However, the focus of this review is on a common single nucleotide polymorphism (SNP) T to C substitution at rs2814778 in *ACKR1* that impairs the promoter activity in erythroid cells by disrupting a binding site for the GATA1 erythroid transcription factor.[6] Individuals who are homozygous for the rs2814778 CC SNP do not express the Duffy protein on their red blood cells and are described as 'Duffy null'.[7,8] The other possible genotypes at the GATA1 binding site at rs2814778 (e.g. CT, TC, TT), which each leads to Duffy protein expression on erythrocytes, are collectively described as 'Duffy non-null' or 'Duffy-positive' phenotypes.[7,8] The association between Duffy phenotype, genotypes and nomenclature is described in Figure 1.



Phenotype	All possible genotypes	Genotype at promoter region (-67 allele; rs2814778)	Nomenclature
Fy(a-b-)	*Fy*amorph+Fy*amorph* *FyB*^{ES} *+FyB*^{ES}	*FyB*^{ES} *+FyB*^{ES}	Duffy null
Fy(a-b+)	*Fyb + Fyb* (homozygous for A at position 125) *Fyb +Fy*amorph* *Fyb + FyB*^{ES}	*Fyb + FyB*^{ES} (one Duffy B allele and one Duffy B allele with GATA mutation)	Duffy non-null Duffy B positive
Fy(a+b-)	*Fya + Fya* (homozygous for G at position 125) *Fya +Fy*amorph* *Fya + FyB*^{ES}	*Fya + FyB*^{ES}	Duffy non-null Duffy A positive
Fy(a+b+)	*Fya +Fyb*	N/A	Duffy non-null Duffy A/B positive

FIGURE 1 Relationships between Duffy phenotype, genotype and nomenclature. This schematic outlines the relationship between Duffy phenotype by serology, possible genotypes and the nomenclature commonly used to describe Duffy status. The focus of this review and the most common SNP occur at the promoter region (rs2814778) and result in a lack of expression of the Duffy antigen on erythrocytes only. Other genotypes that can result in the Duffy null phenotype by serology are not discussed in this review.

Assessing Duffy status can occur via two methods: serological phenotyping and genotyping. Genotyping provides allele-specific information for red blood cell antigens. The most popular automated genotyping platforms utilise multiplex polymerase chain reaction (PCR), a process which amplifies multiple gene loci simultaneously using several primer pairs. These platforms are ideal for detecting blood group alleles that are differentiated by SNPs, such as those of the Duffy blood group.[9] The three genotypes that result in the lack of expression of the Duffy antigen on erythrocytes (*Fy*amorph*, homozygous *Fy*B*^{ES} [−67T>C] and heterozygous *Fy*B*^{ES}/*Fy*X*) can be distinguished via genotyping (Figure 1). *Fy*amorph* and heterozygous *Fy*B*^{ES}/*Fy*X* are relatively rare, and the relationship with expected ANC is understudied. Homozygous *Fy*B*^{ES} (−67T>C) is the genotype most extensively linked with lower ANC and the focus of this review. It is by far the most common genotype found among individuals of African or Middle Eastern ancestry who serologically phenotype as Duffy null.[10]

Serological phenotyping is a manual process that requires approximately 1 h of trained technician time to identify antigens present on the red blood cell surface using antibody reagents.[10] In most healthcare systems, serological phenotyping is more widely available, has a faster turnaround time and incurs a lower cost than genotyping. However, serological phenotyping is unable to distinguish between the different Duffy null genotypes, which will all appear serologically Duffy null (Figure 1).[10] Given that the overwhelming majority of serologically Duffy null individuals in Africa, the Middle East, Europe and North America have the homozygous *Fy*B*^{ES} (−67T>C) genotype, serological testing alone is clinically adequate to identify individuals who are likely to have lower baseline ANC. However, identification of the homozygous *Fy*B*^{ES} (−67T>C) genotype (rather than *Fy*amorph*) in a serologically Duffy null person can be beneficial in chronically transfused individuals. Homozygous *Fy*B*^{ES} (−67T>C) individuals express Duffy antigen on tissues other than erythrocytes and thus can receive Duffy B (Fyb)-positive units (most of the blood supply) without concern for Duffy B alloimmunisation.

DUFFY ANTIGEN ROLE AND EPIDEMIOLOGY

The Duffy antigen is a chemokine receptor that regulates leucocyte trafficking, binds inflammatory chemokines to internalise them for lysosomal degradation and influences the tissue microenvironment for antitumour immunity.[11,12] The antigen is also thought to act both as a sink and a reservoir for cytokines, providing a buffering function.[13] However, the relationship between the Duffy antigen and chemokine homeostasis as well as its association with inflammation and disease has been incompletely elucidated.

The Duffy null variant likely arose from and has been sustained by selective evolutionary pressure. Duffy antigens are utilised by the parasite *Plasmodium vivax* to enter

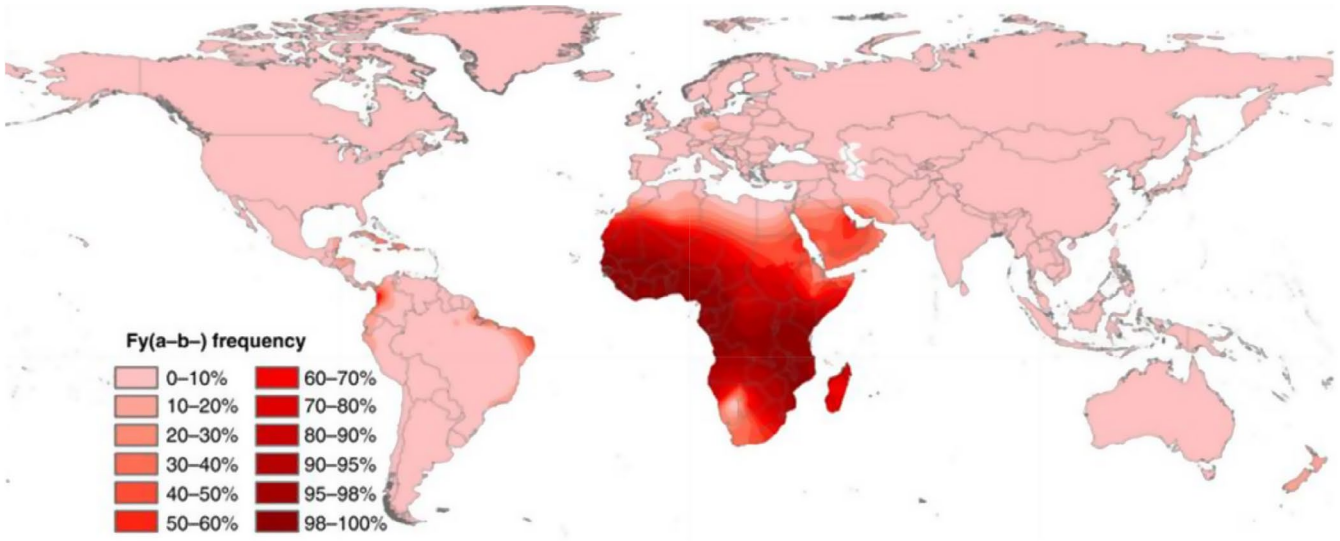


FIGURE 2 Prevalence of the Duffy null (Fy[a–b–]) phenotype. Prevalence of the Duffy null phenotype varies globally with >80% frequency in areas of Sub-Saharan Africa and >50% in areas of the Arabian Peninsula. Figure reproduced from Howes et al.[18] with permission.

erythrocytes.[14,15] Multiple studies have shown that people with the Duffy null variant are less susceptible to *P. vivax* parasitaemia and consequent clinical infection.[14,16,17] There is a 2- to 22-time higher infection rate with *P. vivax* among those who are Duffy non-null compared to Duffy null, with parasite positivity rates 10–50 times higher in febrile Duffy non-null patients than febrile Duffy null patients.[17] The magnitude of this protection is imprecise, but a meta-analysis estimates that Duffy null individuals have approximately half the odds of *P. vivax* infection compared to Duffy non-null individuals.[16]

The distribution of the Duffy null variant is most prevalent in areas where *P. vivax* is endemic—Sub-Saharan Africa and the Arabian Peninsula.[18] Worldwide prevalence of the Duffy null phenotype is shown in Figure 2. In some parts of West Africa, Duffy null prevalence approaches 100%.[18] In contrast, this SNP is seen in <1% of the population with genetic ancestry from Europe or regions of Asia (including populations identifying as Tamil, Punjabi, Vietnamese, Telugu, Gujarati, Finnish, Han Chinese, Bengali or White British).[18–20] People of African descent who now live in the Caribbean and in the United States have an assortment of Duffy genotypes, likely due to the transatlantic slave trade and subsequent genetic admixture with indigenous and colonial populations with European ancestry.[8,21] The Fya antigen is seen in 66% of White Americans, 10% of Black Americans and 99% of Asian Americans while the Fyb antigen is seen in 83% of White Americans, 23% of Black Americans and 18.5% of Asian Americans.[3] Given the co-dominant inheritance pattern, this results in approximately 66% of people who identify as Black or African American with the Duffy null variant (Fy[a–b–]) in the United States.[3,8] In the United Kingdom, around 83% of people who identify as Black African or Caribbean have the Duffy null variant.[19]

HISTORY AND CURRENT UNDERSTANDING OF DUFFY STATUS, RACE AND ETHNICITY, AND ABSOLUTE NEUTROPHIL COUNTS

Given the strong association between Duffy status and ancestral malarial exposure, Duffy status is associated but not synonymous with socially constructed categories of race and ethnicity. We provide definitions of race, ethnicity and ancestry in Figure 3.[22] We emphasise that racial and ethnic groupings are social constructions rather than biological classifications, and they are complicated, limited proxies for human genetics.[23]

The first publications describing lower neutrophil counts in healthy Black Americans than in White Americans living and working in the same conditions were reported in the 1940s.[24] This observation was later confirmed in studies from the 1960s and 1970s.[25–27] A similar observation was described in other racial and ethnic groups such as Israeli Jews of Yemenite origin, Arab Jordanians, Jews of Ethiopian descent and Black Bedouins.[27] Reflecting the racialised perspectives of the time, one study observed that 'all ethnic groups thus far reported have tanned or dark skin. The significance of this common feature has still to be elucidated[27]'. This association of a healthy person with lower ANC was labelled 'benign ethnic (or familial) neutropenia (or leukopenia)'.[26,27]

In the early 2000s, the association between the rs2814778 SNP and absolute neutrophil counts (ANC) was elucidated.[28,29] The Duffy null variant (rs2814778 CC) is closely associated with lower ANC,[21,28–30] and the diagnosis of 'benign ethnic neutropenia' was found to be closely associated with rs2814778 CC ($p = 4.09 \times 10^{-53}$).[30] These studies underscore that when the

Race: A social-political system of classifying individuals based on physical characteristics (e.g. "African American" or "White").
Ethnicity: A social-political system of classifying individuals based on both physical characteristics alongside other forms of shared identity, such as language, religion or dietary practices (e.g. "Hispanic" or "South Asian")
Genetic ancestry: A biologically-based system of classifying individuals based on genomic variation, mostly through single nucleotide polymorphisms. The results of such analysis may be referred to as "genetic ancestry" or a closely related concept of "genetically-inferred ethnicity".
Benign ethnic neutropenia: A diagnostic label developed in the 20th century based on the observation that lower neutrophil counts are often seen in individuals of from particular ethnic groupings. This observation is explained by Duffy status. We consider this label to be inaccurate and superseded.
Duffy associated neutrophil count (DANC): A descriptive label that foregrounds a *variation* in neutrophil count based on Duffy null status, rather than an abnormality.
ACKR1/DARC-associated neutropenia (ADAN): An alternative descriptive label that links ACKR1 status with neutrophil counts, though the label still designates "neutropenia", normalising Duffy positive individuals.

FIGURE 3 Definitions used in this review. Definitions for race, ethnicity and ancestry are adapted from Lu et al.[22] These terms do not have universally agreed definitions, but these are provided to demonstrate that they are not interchangeable concepts. Race, ethnicity and genetic ancestry relate to one another in complex ways, and these systems of categorisations are situated within historical contexts.

Duffy null variant is accounted for, there is no independent association between race or ethnicity and ANC.

As neutrophils are critical for maintaining health and controlling infection, there is reasonable concern that people with the Duffy null variant may be at higher risk for infection. However, neutrophil function is not impaired in Duffy null individuals, including proteolytic activity within the phagosome, reactive oxygen species production and neutrophil extracellular trap (NET) formation.[31] Normal neutrophil activity is also supported by clinical evidence. One study showed that children with 'benign ethnic neutropenia' ($n=37$) had a clinical course comparable to other healthy children despite significantly lower median ANC.[32] Additionally, a study in adults across the UK Biobank ($n=7450$) and a Danish cohort ($n=283$) showed that Duffy null participants did not have a higher incidence of bacterial or viral infection.[19] A recent study from the All of Us Biobank, Vanderbilt University Medical Center's Biobank and the Million Veteran Program similarly showed no associations between the Duffy null genotype and sepsis, pneumonia, abscesses, diarrhoea or any other infectious disease categories.[33]

'Benign ethnic neutropenia' and similar terminology served a historical purpose when the link between Duffy status and circulating neutrophils was not established, but this terminology is now outdated and considered pejorative.[34] In a Brazilian study, the Duffy null variant (Fy[a–b–]) had substantially stronger diagnostic utility supporting health in a person with ANC $<1.5\times10^9$/L than self-identified race or ethnicity.[35] Furthermore, the term 'benign ethnic neutropenia' reinforces existing power imbalances and centres White as normal.[36] Two alternative terms are now preferred: Duffy null-associated neutrophil count (DANC) or ACKR1/DARC-associated neutropenia (ADAN) (Figure 3).[7,8,36,37] Both terms highlight the importance of individuals' Duffy phenotype, rather than race or ethnicity, on ANC.

DUFFY STATUS AND EXPECTED ABSOLUTE NEUTROPHIL COUNTS

The precise mechanism linking erythrocyte Duffy null variants to ANC remains unclear. Individuals with the Duffy null variant have normal bone marrow morphology and maturation patterns and robust responses to neutrophilic stimuli.[38–40] For example, there seems to be a more robust response to physiologic and exogenous granulocyte colony-stimulating factor among people who are likely Duffy null compared to Duffy non-null.[41–44] It is likely that different chemokine regulation in Duffy null individuals changes the localisation of neutrophils.[12,13,45] In one study, participants with the Duffy null variant showed activated cytokine profiles impacting leucocyte migration and cell mobilisation pathways.[30] Additionally, individuals with the Duffy null exhibit altered haematopoiesis, leading to phenotypically distinct neutrophils that readily leave the circulation and specifically localise to the spleen.[46] Current data support the model that there are sufficient levels of mature total body neutrophils, but their localisation and/or response to cytokines may be different from neutrophils in Duffy-positive individuals.

Recent studies have quantified the expected differences in ANC by Duffy status. There is no significant difference in ANC between Duffy non-null people with Fy(a+b+), Fy(a–b+) or Fy(a+b–) phenotypes.[21,33] However, there is a significant difference in ANC between those with the Duffy null variant compared to Duffy non-null phenotypes (Figure 4).[8,19,33] In one prospective study, median ANC for healthy Duffy null adults was reported as 2.820×10^9/L (interquartile range [IQR]: $2.088–3.490\times10^9$/L) vs. 5.005×10^9/L (IQR: $3.675–5.828\times10^9$/L) among Duffy non-null adults.[8] Two independent studies have reported 23.8% and 21.1% of healthy Duffy null participants had an ANC $<2.0\times10^9$/L vs. 0% and 1.59%

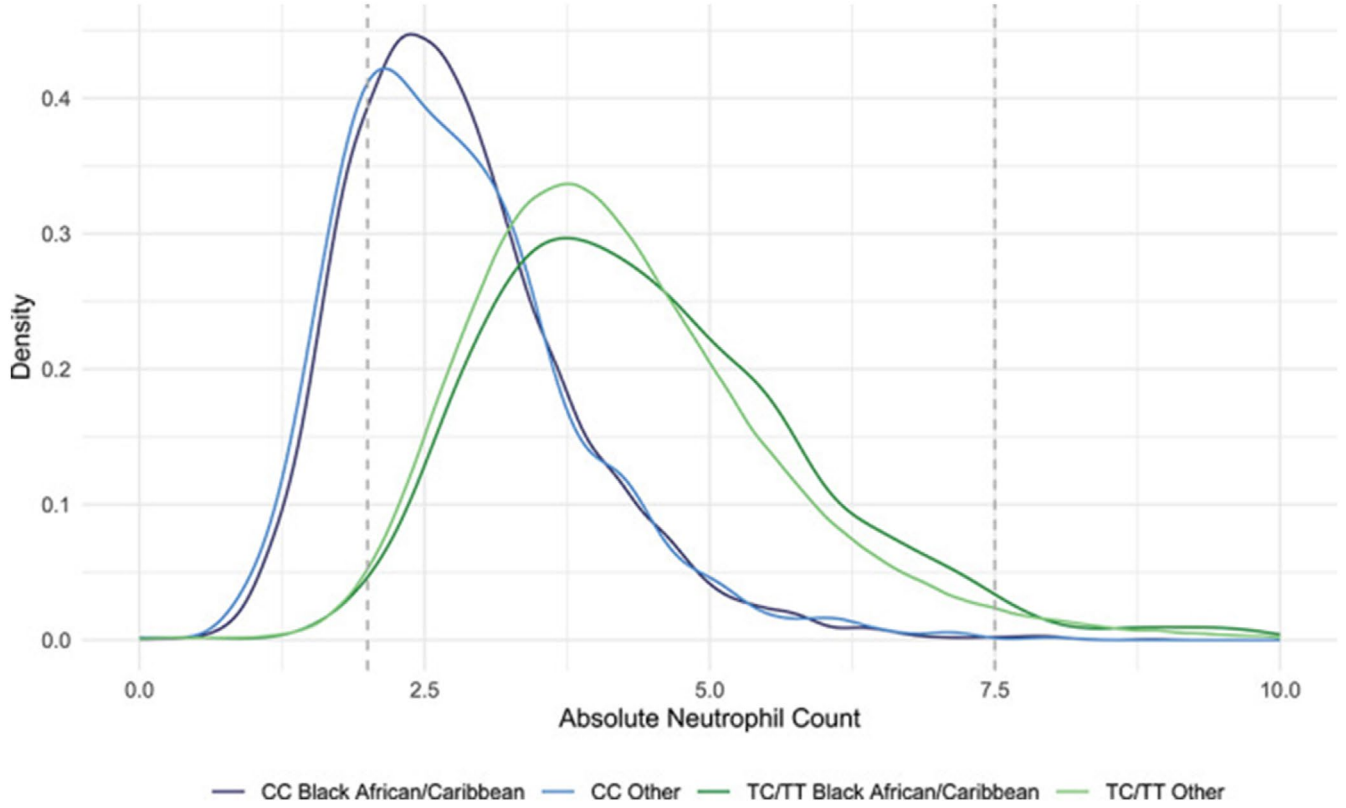


FIGURE 4 Absolute neutrophil counts (ANCs) by race and Duffy genotype. A UK biobank study reports a mean ANC of 2.82×10^9/L (SD = 1.02) in Duffy null adults versus 4.43×10^9/L (standard deviation [SD] = 1.41) in Duffy non-null adults. There is a significant difference in ANC by Duffy status. There is no significant difference in ANC by race among those who are Duffy null nor Duffy non-null. Reproduced with permission.

of Duffy non-null participants respectively.[8,19] Another large biobank study reported that 9.22% of Duffy null participants had an ANC $<1.5 \times 10^9$/L compared to 2.51% of Duffy non-null participants.[33] Importantly, the healthy Duffy null participants in these studies do not have pathological 'neutropenia'; rather the expected ANC is approximately 1.5–2.5×10^9/L lower in individuals with the Duffy null variant compared to Duffy non-null people.

Additionally, a single-centre study in the United States reported no significant difference in Duffy non-null ANC and institutional reference intervals ($p = 0.64$), but a significant difference in Duffy null ANC and the institutional reference interval ($p < 0.001$).[7,8] Across the world, healthy Duffy null adults have ANC below current ANC reference intervals in their respective healthcare systems: 27.9% in Namibia, 50.7% in Saudi Arabia and 21.7% in the United States.[47] A similar pattern to a lesser degree is seen for white blood cell counts (WBC), likely driven by lower ANC.[47] In paediatrics, ANC among healthy Duffy null children referred for neutropenia evaluation may be as low as 0.1×10^9/L in children 3 years old or younger and as low as 0.5×10^9/L in children 12 years old or older.[48]

Given these differences in ANC, Duffy null-specific ANC reference intervals are crucial. Reference intervals are intended to represent health for the entire community, but they are often derived from convenience samples that may not accurately represent the population. The first publication of a Duffy null-specific ANC reference interval came from healthy primary care patients self-identifying as Black or African American from a single centre in the north-eastern United States, reporting a reference interval of 1.21–5.14×10^9/L (compared to Duffy status agnostic reference interval of 1.92–7.60×10^9/L).[7] Efforts to replicate this globally have also been pursued, with Duffy null ANC reference intervals of 0.82–6.37×10^9/L (Namibia), 1.09–5.10×10^9/L (Saudi Arabia) and 1.30–5.16×10^9/L (UK) reported.[47]

CLINICAL CONSEQUENCES OF DUFFY-AGNOSTIC DECISION-MAKING

Neutropenia is commonly defined as ANC $<1.5 \times 10^9$/L, but this definition is inaccurate for many Duffy null individuals and likely compromises care as most current clinical practices are agnostic to Duffy status. We outline recognised clinical ramifications below but acknowledge that other unrecognised implications are likely to exist. These ramifications raise ethical concerns about current practices with respect to health equity, obligations by practitioners and the healthcare system writ large and optimal clinical research practices; these concerns are not addressed directly but indirectly through our suggestions on how to advance care for those with the Duffy null phenotype.

Investigation of unexpected neutrophil counts

Duffy null individuals are commonly misclassified as pathologically 'neutropenic'.[7,8,47] This can lead to unnecessary referrals to haematology, diverting personnel and care delivery capacity while causing emotional distress and potential financial consequences for patients. One study in paediatrics found that 64.8% of referrals for neutropenia (average ANC 1.10×10^9/L) were assessed as 'benign ethnic neutropenia', of which 77.7% of cases were confirmed as having the Duffy null variant.[49]

There is also evidence of excessive bone marrow biopsy procedures performed on Duffy null individuals. In one study of patients undergoing bone marrow biopsy for neutropenia in the United States, there was no pathology identified in 95% of Black patients (compared to 68% of White patients) and a final diagnosis of 'clinically insignificant' neutropenia was given to 60% of Black patients (compared to 9% of White patients).[50] Another study reported that among patients who underwent bone marrow biopsy for isolated leucopenia, 97% ($n = 34$) had the Duffy null variant and 94% ($n = 33$) had a normal bone marrow biopsy.[51] After assessing for signs or symptoms of pathology such as other cytopenias, progressively declining ANC or constitutional symptoms, clinicians can differentiate an isolated lower ANC in a person with Duffy null as consistent with DANC rather than pathology and avoid unnecessary referrals or additional testing.

Clinical Trials

Eligibility criteria for clinical trials may inadvertently exclude participation due to ANC thresholds within the expected Duffy null ANC reference interval. These criteria can contribute to the underrepresentation of people from African and Middle Eastern ancestry and limit the generalisability of results. A recent study assessed the frequency of trial eligibility criteria that could exclude otherwise healthy Duffy null individuals. Across 289 phase 3 oncology clinical trials, 76.5% had criteria that could exclude individuals with an ANC within the expected range for Duffy null individuals.[52] Notably, such exclusions were seen in 50% of clinical trials testing hormonal therapies alone, in which substantial myelosuppression would not be expected.[52]

Many paediatric oncology clinical trials also require ANC $>1.5 \times 10^9$/L for inclusion, especially in industry sponsored trials.[53] A study of myeloma patients who were ineligible for clinical trials found that Black patients had a higher (24%) rate of ineligibility than White patients (17%)—most commonly due to a failure to meet haematological eligibility criteria.[54] Although Duffy status was not measured in this study, the authors note that differential rates of 'benign neutropenia' was a likely reason for their findings.[54] Similar restrictions have been reported in infectious disease clinical trials. For example, a paediatric rotavirus trial in South Africa found that 28% of healthy infants who were otherwise eligible for the study were excluded on the basis of low neutrophil counts.[55]

Furthermore, the Common Terminology Criteria for Adverse Events (CTCAE) is used widely across clinical trials. However, it defines 'low neutrophil counts' within the Duffy null expected interval as a grade 1 or grade 2 criteria. As trial protocols commonly mandate dose holds, modifications or discontinuations for grade 3 neutropenia, Duffy null individuals who begin the trial already categorised as having grade 1 or 2 neutropenia may be subject to unnecessary dose adjustments.[56] For example, a South African paediatric rotavirus vaccine study was temporarily stopped on the basis of neutropenia 'safety events' until the triallists switched to an AE criteria framework which better accounted for variations in baseline neutrophil counts.[55] This is not only important for the clinical trial and the patients participating in it, but these data impact post-approval medication prescribing guidelines.

Classification of neutrophil counts in assessing remission or response to treatment

Current remission criteria or definitions of response to treatment based on ANC may not be appropriate for people with the Duffy null phenotype. The International Workshop on Chronic Lymphocytic Leukemia (CLL) criteria require ANC above 1.5×10^9/L without growth factor support to be assessed as 'complete remission'.[56] Response assessment criteria for other haematological malignancies include ANC and may perform differently in Duffy null individuals.[56] For example, chimeric antigen receptor T-cell (CAR-T) therapy, neutrophil recovery has been used to predict survival and infective morbidity. However, a recent study showed that Duffy null individuals receiving CAR-T cells had delayed neutrophil recovery, but no difference in severe infection or death compared to those who were Duffy non-null.[57]

Medication prescribing guidelines, safety and monitoring

Duffy-related neutrophil variation impacts therapeutic prescribing through prescribing guidance (e.g. regulatory labels) that mandate dose reduction, delay or discontinuation based on Duffy-agnostic ANC thresholds. Examples are outlined below and summarised in Table 1. While some therapeutic classes have been investigated, neutrophil-based prescribing criteria likely impact additional prescribing guidelines that have not yet been assessed. Currently, there is a lack of data on the optimal approach for dosing, monitoring and modifying therapies for individuals with Duffy null variant.

Systemic anti-cancer therapy (SACT)

Dose intensity for systemic anti-cancer therapy (SACT) regimens is an important predictor of survival.[58] An analysis of

TABLE 1 Summary of medication prescribing guidelines, safety and monitoring.

Medication	Indication	Examples of prescribing guidance	Evidence of impact on Duffy null individuals
Palbociclib (CDK 4/6 inhibitor)[59]	Breast Cancer	*FDA*: Hold for ANC $<1.0\times10^9$/L *PALINA trial protocol*: Dose reduction in patients with ANC $<1.5\times10^9$/L	55.6% of Duffy null patients versus 7.7% of non-null patients received dose reductions No differences in rates of febrile neutropenia
Mercaptopurine (6-MP)[60]	Acute lymphoblastic leukaemia (ALL)	*FDA*: Adjust for 'excessive myelosuppression' *Example of institutional protocols*: Targeted to WBC of 1.5 to 3.5×10^9/L If ANC $<0.75\times10^9$/L, reduce 6-MP by 50% If ANC $<0.5\times10^9$/L, hold 6-MP and restart when ANC $>0.75\times10^9$/L	Duffy null children with ALL received lower intensity dosages relative to the target daily dose of 75 mg/m^2 (0.83 vs. 0.94; $p=0.013$)
Hydroxyurea[61–65]	Sickle cell disease	*FDA*: Hold if ANC $<2.0\times10^9$/L *British Society of Haematology*: Hold if ANC $<1.0\times10^9$/L	No clear impact of Duffy status on drug initiation or dosage
Azathioprine[60]	Autoimmune disease	*EMC*: At the first signs of an abnormal fall in blood counts, treatment should be interrupted *Example of institutional protocol*: Hold or discontinue for WBC $<3\times10^9$/L	Threefold higher discontinuation rate in Duffy null individuals versus non-null individuals (controlling for race and metaboliser status)
Clozapine[19,66]	Schizophrenia	*EMC*: ANC $>2.0\times10^9$/L to commence. Discontinue if ANC $>1.5\times10^9$/L	20-fold risk of clozapine discontinuation in Duffy null vs. Duffy non-null patients

Note: Examples of medications with prescribing guidance based on absolute neutrophil counts or white blood cell counts, and implications for Duffy null individuals.
Abbreviations: ANC, absolute neutrophil count; EMC, Electronic medicines compendium (UK); FDA, Food and Drugs Administration (US); WBC, white blood cell.

patients receiving palbociclib for breast cancer found that Duffy null participants had higher rates of neutropenia (ANC $<1.0\times10^9$/L; 72% vs. 23%), more frequent dose reductions (55% vs. 8%), lower dose intensity and reduced clinical benefit. Despite their lower neutrophil counts, no episodes of febrile neutropenia were observed in the Duffy null group.[60]

Another study assessed prescribing guidelines for first-line solid tumour chemotherapy regimens. Prescribing guidelines mandated SACT dose reductions, delays or discontinuations in 53.5% of regimens on the basis of neutrophil counts within the expected Duffy null range.[52] A single-centre study of patients with multiple myeloma showed that Duffy null patients were more likely to have baseline ANC $<1.8\times10^9$/L (34% vs. 10%) and neutropenia during treatment (85% vs. 48%), but no Duffy null patients experienced febrile neutropenia (0/52) compared to 8% (7/84) of Duffy non-null patients.[61] Additionally, in a cohort of African American children with acute lymphoblastic leukaemia treated with mercaptopurine (6-MP), Duffy null children had lower dose intensity relative to the target daily dose of 75 mg/m^2 compared to Duffy non-null children (0.83 vs. 0.94; $p=0.013$).[62] These data suggest that ANC-based dose modification criteria are widespread in SACT prescribing and are likely inappropriate for people with the Duffy null variant, resulting in reduced clinical benefit through lower relative dose intensity without the benefit of preventing excess clinical toxicity.

Hydroxyurea (hydroxycarbamide)

Hydroxyurea is commonly used in patients with sickle cell disease (SCD), and the maximum tolerated dose is predominantly determined based on ANC. SCD is an umbrella term encompassing people with HbSS, HbSC, and other forms. Patients with SCD have baseline elevated ANC compared to healthy controls. There is a difference in baseline ANC by Duffy status among patients with SCD, but the effect is weaker, and the ANC values are significantly higher than in healthy controls.[63,64] One small study in adult patients showed that Duffy null patients were less likely to initiate hydroxyurea (49% vs. 72%, $p=0.002$).[65] However, multiple paediatric studies showed no difference in hydroxyurea initiation, remaining on medication for >1 year, nor prescribed doses by Duffy status.[63,66,67]

Azathioprine

Azathioprine is used to treat many autoimmune diseases, and prescribing guidelines recommend stopping the medication if WBC drops below 3×10^9/L.[62] One study reported that azathioprine discontinuation rates for haematopoietic toxicity were significantly higher for Duffy null patients (hazard ratio [HR] = 2.92, $p=0.001$), which remained significant when adjusted by race (HR = 2.61, $p=0.047$). There was no difference in discontinuation of azathioprine between White and Black Duffy non-null patients (HR = 0.96, 95% confidence interval [CI]: 0.30–2.99, $p=0.94$).[62] Additionally, weight-adjusted final azathioprine dose was lower in those with the Duffy null genotype compared to Duffy non-null.

Clozapine

Clozapine is the preferred medication for treatment-resistant schizophrenia, but use can be limited by neutropenia. One study found that 19.81% ($n=83$) of Duffy null individuals had ANC $<1.5\times10^9$/L during treatment with clozapine compared to 1.74% ($n=2$) Duffy non-null individuals.[19] A systematic review found that patients with ANC $<1.5\times10^9$/L

(described as 'benign ethnic neutropenia') had no difference in the frequency, severity or outcome of infections compared to other patients taking clozapine.[68]

The ANC threshold for those with 'benign ethnic neutropenia' used in the United States Risk Evaluation and Mitigation Strategy (REMS) for clozapine was changed based on these studies. This decision reduced treatment interruptions during the first year of treatment.[69] Recently, a trial of clozapine in people of African descent with schizophrenia (Duffy null: 100% Nigeria site, 65% US sites) reported only one case of ANC $<0.5\times10^9$/L (0.36%) over 1467.6 person-months of clozapine exposure with no difference in infection risk by Duffy status (7.5% vs. 8.0%; $p=0.91$).[70]

BIOLOGICAL DIFFERENCES ASSOCIATED WITH THE DUFFY NULL VARIANT AND THEIR CLINICAL IMPLICATIONS

This section examines emerging evidence on biological differences in disease incidence and natural history in individuals based on Duffy status. The literature focuses on differences attributed to inherent biology rather than clinical decision-making. However, individuals with the Duffy null phenotype also face the iatrogenic risks and other systemic inequities. As a result, the mechanisms linking Duffy status to clinical outcomes are frequently more entangled than these studies suggest (Figure 5).

Human immunodeficiency virus (HIV)

While there is no evidence of generalised increase in the risk of infection for Duffy null individuals, there are conflicting reports of associations between Duffy status and HIV acquisition and progression. A study of 142 Black women in South Africa reported a threefold higher HIV seroconversion rate in Duffy null women compared to other women in the study.[71] However, within a cohort of HIV-positive African Americans, the clinical progression of HIV was slower in Duffy null individuals.[72] Notably, however, other studies have not found an increased susceptibility of Duffy null individuals to HIV seroconversion or a slower course of disease progression.[31,73]

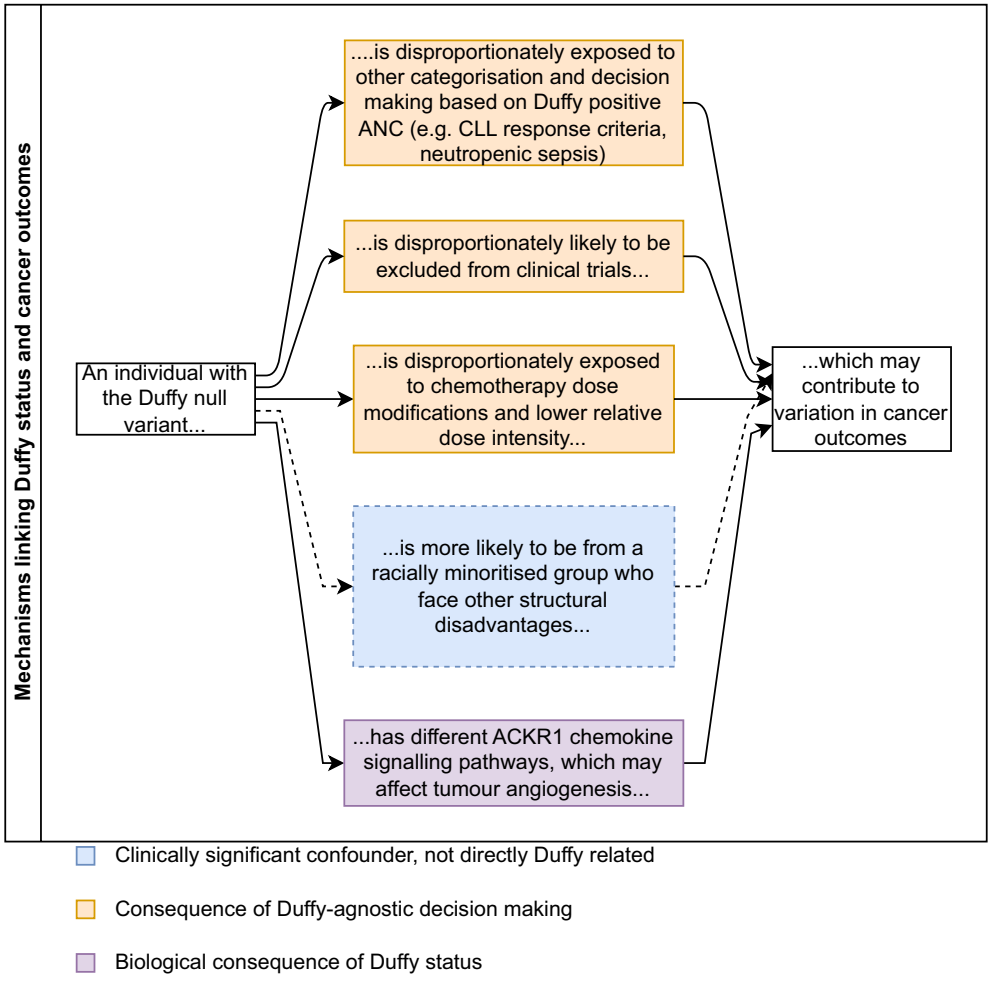


FIGURE 5 Mechanisms linking Duffy status to variation in cancer outcomes. The Duffy null variant can result in differences attributed to inherent biology, structural racism and clinical decision-making. These different mechanisms are illustrated for cancer but are likely present in other clinical contexts.

Cancer

Several studies have reported associations between Duffy status and breast cancer incidence or aggressiveness. A study in China assessed patients undergoing breast biopsy, reporting that individuals with the Duffy null variant were at significantly higher risk of a cancer diagnosis, axillary spread and inferior 5-year survival compared to Duffy-positive counterparts.[74] However, this study did not report demographic information of participants, and as Duffy null individuals were likely from a racially minoritised group (the variant is rare in China), Duffy status may be a confounding variable rather than a driver of this association. Another study found that African American women with the Duffy null variant are at threefold higher risk of triple-negative breast cancer (odds ratio, 3.8) compared to African American women who were Duffy positive.[75] Mouse studies show a protective effect of *ACKR1* expression through inhibition of angiogenesis of breast cancer cells, indicating that people with the Duffy null variant may have higher risks of breast cancer tumorigenesis and metastasis.[76]

There are few data in other cancers. A small study of 33 patients with endometrial cancer reported an association between the Duffy null variant and more aggressive endometrial cancer subtypes, as well as reduced survival.[77] Conversely, another study reported a lower rate of progression from Barrett's oesophagus to oesophageal cancer in those with the Duffy null genotype.[78] Although Duffy status has not been directly studied in the setting of prostate cancer in humans, a lower neutrophil count at the time of biopsy in African American patients (likely a proxy for Duffy null status) was associated with a higher tumour grade in one report.[79] Additionally, mouse models of prostate cancer show tumours from *ACKR1*-deficient mice having greater concentrations of angiogenic chemokines and increased rates of cancer cell growth.[80] The association between *ACKR1* expression, tumour angiogenesis and cancer aggressiveness (both histological differentiation and spread) has also been replicated in histological studies of colorectal cancer.[81] Collectively, these studies suggest a potential link between inherited Duffy status and susceptibility to some forms of cancer and their progression.

Sickle cell disease

The Duffy null variant is present in 72%–78% of people living with sickle cell disease (SCD) in the United States and 89% in the United Kingdom.[63,65,67,82] Several studies have assessed clinical outcomes in SCD by Duffy status. To date, few associations have been seen, and their clinical relevance is unclear. Duffy null status was associated with a slightly lower prevalence of leg ulcers[82] and a higher rate of proteinuria in SCD patients, compared to Duffy non-null counterparts.[65] Other studies in adults and children with SCD have not replicated these findings, nor found associations with risks of any other SCD complications.[66,67,83,84] At present, there is no clear impact of Duffy status on SCD severity.

Other associations of Duffy status with disease

A recent phenome-wide association study examined associations between the Duffy null variant and various clinical conditions across the All of Us Biobank, the Vanderbilt University Medical Center's Biobank and the Million Veteran Program. There were no associations of the Duffy null variant with any infectious disease, neoplasms, mental health issues, pregnancy complications or injuries, nor any metabolic, endocrine, haematopoietic, neurological, circulatory, respiratory, digestive, genitourinary, dermatological, musculoskeletal or congenital disorders.[33] Conversely, one small study ($n = 132$) in African American patients with acute lung injury showed that patients with the Duffy null genotype had inferior outcomes compared with individuals who are Duffy non-null.[85] The replicability and potential mechanisms of this association remain unclear.

PARTNERING WITH LABORATORY MEDICINE TO IMPLEMENT DUFFY NULL-SPECIFIC PRACTICES

Partnering with laboratory medicine is necessary to increase Duffy testing orderability, capacity and interpretation as well as connecting Duffy status to appropriate interpretation of the ANC reference interval.

First, a simplified process for ordering Duffy antigen typing will facilitate identification of individuals who are Duffy null. Most institutions have no specific ordering mechanism to assess Duffy status and rely on unintuitive methods such as adding a comment to a blood type and antibody screen order or calling the blood bank to request testing. A specific 'Duffy antigen typing' test name or ordering code added to the local clinical laboratory catalogue would be intuitive for most clinicians to use and provides clear communication to the transfusion laboratory about the desired testing. Additionally, a specific test would generate a dedicated result report with informative comments about the Duffy phenotype and associated expected variations in ANC to assist interpretation.

Additionally, the development of Duffy null-specific ANC reference ranges by processes defined by the Clinical Laboratory Standards Institute may represent the most significant step towards eliminating care disparities for individuals with DANC.[86,87] De novo reference ranges require measurement of ANCs in 120 healthy Duffy null individuals per physiologic group (i.e. paediatrics and adults) with the central 95th percentile of these measures defining a new reference interval.[86] Alternatively, laboratories may adapt published Duffy null-specific ANC reference ranges by a simpler validation process which requires assessment of at least 20 samples.[7,87] There is currently an effort underway through

the Doris Duke Foundation and the American Society of Hematology in partnership with institutions throughout the United States to verify Duffy null-specific adult ANC reference intervals as well as develop Duffy null-specific paediatric ANC reference intervals. These data will add to existing published reference intervals and are expected to be available by 2026.

After developing or validating Duffy null-specific ANC reference intervals, these intervals must be appropriately communicated to other clinicians. The simplest method to raise the possibility of DANC is an informative comment outlining the expected ANC reference interval for those with the Duffy null phenotype on all ANC result reports (Supporting Information).[7] A suggestion to obtain Duffy antigen testing could also be added. Pitfalls of this strategy could include misinterpretation of the comment leading to diagnostic failures or notification fatigue. Laboratories could also work with hospital information technology experts to build infrastructure to report two separate ANC reference intervals tailored to Duffy status (analogous to separate haemoglobin reference intervals for males and females). However, this is currently limited as very few individuals have had Duffy antigen testing. Efforts to build capacity are underway such as the development of ICD-10 codes of the four major Duffy phenotypes (Supporting Information). Duffy antigen testing could be routinely added to early childhood blood testing or initial blood group testing, especially for high-prevalence groups, to increase awareness of Duffy status. The cost-effectiveness of these strategies to increase the utility of Duffy null-specific ANC reference intervals will vary across different regions and patient populations based on both the local prevalence of the null variant and blood bank laboratory capability.[88] Increased connectivity between electronic health record or laboratory information systems could reduce redundant Duffy typing and enable smaller transfusion services to benefit from testing performed at larger hospitals.

Successful integration of new Duffy-specific antigen testing codes, laboratory workflows, interpretation guides and reference intervals into clinical practice will depend on clear and deliberate communication between laboratory and clinical partners.[89] Awareness campaigns could include emails, conference announcements and educational sessions. Efforts should be customised to each healthcare system to maximise dissemination and uptake. Interval reassessment of the ease of use and value of these tools to all stakeholders will be critical to evaluate impact and identify opportunities to improve orderability and interpretation of results.

CALL TO ACTION AND RESEARCH PRIORITIES

The Duffy null variant sits at the intersection of evolutionary biology, malarial epidemiology, socio-political groupings of race and ethnicity, chemokine signalling pathways, laboratory medicine and healthcare delivery. Beyond reducing *P. vivax* susceptibility[15,17] and a likely increase in triple negative breast cancer incidence,[75] the direct biological consequences of the Duffy null variant remain underexplored. However, the iatrogenic impacts of Duffy-agnostic ANC interpretation on clinical practices are seen across invasive and non-invasive investigations of 'neutropenia', clinical trial access, medication dosing and remission criteria.

Duffy null is a common variant that has been understudied and under-recognised for decades. Given the evidence now available, continuing to overlook Duffy-related ANC variation in clinical practice constitutes a form of structural racism.[34,36,56] We suggest a list of implementation and research priorities in Table 2. Given the widespread use of ANC in clinical decision-making, there are likely other iatrogenic sequelae which have not yet been identified. Current practices and decision-making that rely on ANC must be re-evaluated, and future research should strongly consider reporting outcomes by Duffy status to facilitate equitable care.

TABLE 2 Implementation and research priorities to account for Duffy-associated variation.

Implementation priorities
- Avoid references to 'benign ethnic neutropenia' and use the terminology Duffy null-associated neutrophil count or ACKR1/DARC-associated neutropenia instead; - Make *ACKR1* genotyping or Duffy phenotyping available and easily orderable across healthcare systems; - Increase ease of locating and interpreting results of Duffy antigen typing in the electronic healthcare record; - Develop and implement Duffy null and Duffy non-null reference intervals for ANC and white blood cell counts; - Re-evaluate clinical trial ANC eligibility and dose modification criteria to be minimally restrictive, tailored to toxicities observed in early phase trials and personalised for Duffy null and Duffy non-null patients; - Update remission criteria and risk scores to reflect known differences in ANC by Duffy status; - Reconsider definition of neutropenia CTCAE to better represent people with the Duffy null phenotype.
Research priorities
- Further elucidate the mechanism of lower ANC in those with the rs2814778 CC genotype; - Determine Duffy null-specific ANC reference intervals in healthy children; - Examine the correlation between ANC and febrile neutropenia or risk of infection in people who are Duffy null; - Establish safe parameters for medication dosing by ANC among patients who have the Duffy null variant to increase access and efficacy; - Understand the association of Duffy status and disease outcomes, severity or complications in conditions like HIV or sickle cell disease; - Understand the relationship and mechanism between the Duffy null phenotype and incidence or aggressiveness of some cancers.

Note: A suggested list of current implementation and research priorities to address gaps in care and knowledge for people with the Duffy null variant.

Abbreviations: ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; HIV, human immunodeficiency virus.

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LEM and SPH conceptualised the manuscript. SPH, JJ, AH and LEM wrote and edited the manuscript. All author have approved the final version of this manuscript.

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PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Permission obtained for Figure 2 (Licence: 5991520669195; full permissions attached). Figure 4 is open access.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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