The development of an effective vaccine against HIV is desperately needed. The successive failures of HIV vaccine efficacy trials in recent decades have shown the difficulty of inducing an appropriate protective immune response to fight HIV. Different correlates of antibody parameters associated with a decreased risk of HIV-1 acquisition have been identified. However, these parameters are difficult to reproduce and improve, possibly because they have an intricate and combined action. Here, we describe the numerous antibody (Ab) functions associated with HIV-1 protection and report the interrelated parameters regulating their complex functions.

Indeed, besides neutralizing and Fc-mediated activity, additional factors such as Ab type, concentration and kinetics of induction, and Fc-receptor expression and binding capacity also influence the protective effect conferred by Abs. As these parameters were described to be associated with ethnicity, age and sex, these additional factors must be considered for the development of an effective immune response. Therefore, future vaccine designs need to consider these multifaceted Ab functions together with the demographic attributes of the patient populations.

**INTRODUCTION**

According to World Health Organization (WHO) data from 2020, 37.7 million people are living with HIV-1/AIDS and 68% of them are Africans [1]. In contrast to western Europe and America, where subtype B is predominant, subtype A is largely distributed in Eastern Europe and Central Asia and subtype C in East Asia. Africa shows the highest HIV-1 diversity with subtypes A and D in eastern Africa, C in southern Africa, A, G, CRF02_AG, and CRF06_cpx in western Africa, and B and CRF02_AG in northern Africa [2–4]. To fight against and end the HIV-1 pandemic, an efficient protective vaccine is needed. However, due to the high diversity of HIV-1 subtypes, vaccines need to induce antibodies (Abs) with broad inhibitory activity, i.e., antibodies able to inhibit numerous HIV-1 variants. This requirement is considered as one of the main limitations for the development of an efficient HIV vaccine [5, 6].

Over more than three decades, several HIV-1 vaccine trials have been conducted all over the world [7]. However, in HIV-1 vaccine history, only the RV144 phase III trial performed in Thailand showed a statistically significant decreased risk for HIV-1 acquisition at 42 months (31.2%) [8]. Interestingly, analysis of immune correlates for risk showed that Abs binding to the V1V2 region of gp120 correlated with a decreased risk for infection [9]. The IgG1 and IgG3 subclasses mediating antibody-dependent cell-mediated cytotoxicity (ADCC) seem to play a predominant role in protection against HIV-1 acquisition [10]. Moreover, the concentration of plasma envelope (Env)-specific IgA Abs was found to be directly correlated with a higher risk for HIV acquisition [10, 11]. These correlates of risk highlight the predominant role of isotypes and Fc-mediated functions in addition to the previously known protective role of neutralizing antibodies (NAb). Knowledge of these new factors opens windows of opportunities for innovations in inducing a broad inhibitory humoral immune response to fight HIV and introduces new parameters to be considered, such as Fc domain/Fc receptor (FcR) interactions [12–17].

**ANTIBODIES AND THE PLEIOTROPIC FUNCTION OF THE HUMORAL RESPONSE**

**Induction of HIV-specific Abs of various isotypes**

The B cells of the immune system produce Abs that are classified into five major immunoglobulin (Ig) classes or isotypes: IgM, IgG, IgA, IgD, and IgE [18]. IgG is further divided into four subclasses (Fig. 1A) that are diversely distributed according to ethnicity, sex and age, with IgG1, IgG2, IgG3, and IgG4 representing 60–72%, 20–31%, 5–10%, and <4% of total IgG, respectively [19]. IgG subclass prevalence has been reported to change over time following the course of disease and symptoms [20]. Following HIV-1 infection, the adaptive immune response predominantly induces IgG1, IgG3 and IgA [21]. In the RV144 vaccine trial, high levels of HIV-1-specific IgG3 and low Env-specific IgA correlated with a decreased risk of HIV-1 infection [10]. The various Ab isotypes and subclasses bind differently to Fc receptors at the surface of immune cells, including dendritic cells and mainly macrophages.
Fig. 1 Antibodies and FcR-mediated functions. A IgG subclasses. B Fc gamma receptors (FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, FcγRIIIb), their main function, polymorphisms, and distribution on immune cells. C FcγR binding affinities of IgG subclasses. CDC complement dependent cytotoxicity, ADCC antibody-dependent cellular cytotoxicity, ADCP antibody-dependent cellular phagocytosis, Mo Monocyte, Mϕ Macrophage, DC Dendritic cell, MC Mast cell, Neu Neutrophil, Bas Basophil, Eos Eosinophil, NK Natural killer cell, BC B cell, PLT Platelet.
against HIV acquisition [23, 25]. Considering these data, immuno-
models demonstrate their high potential for conferring protection
passive injection of broadly NAbs in nonhuman primate (NHP)
Fab domain to the infectious agent (Fig. 1B) [23, 24]. Studies of the
inhibiting any effect leading to infection via the binding of their
NAbs protect cells from pathogens or infectious particles by
functions
Two main antibody functions observed in HIV-infected
patients and in vaccine trials: neutralization and Fc-mediated
functions
NAbs protect cells from pathogens or infectious particles by
inhibiting any effect leading to infection via the binding of their
Fab domain to the infectious agent (Fig. 1B) [23, 24]. Studies of the
passive injection of broadly NAbs in nonhuman primate (NHP)
models demonstrate their high potential for conferring protection
against HIV acquisition [23, 25]. Considering these data, immuno-
gens aiming to induce the production of these NAbs were
developed [23, 26]. Many vaccines have been designed to induce
Abs targeting the envelope glycoproteins of the virus, mainly
gp120 or gp160 [26–28]. However, these vaccines failed to induce
broadly NAbs. Indeed, the production of broadly NAbs is
extremely difficult to induce due to the need for an extensive
maturation process [29, 30].

The success of the RV144 vaccine trial supported the develop-
ment of new vaccine designs for the induction of Abs with
additional functions, namely Fc-mediated Ab functions [31, 32]. It
has been proposed that several Fc-mediated mechanisms,
including ADCC, antibody-dependent cellular phagocytosis
(ADCP), antibody-dependent complement deposition (ADCD),
aggregation and immune activation, participate in HIV infection
(Figs. 1B, 2) [14, 33–37]. In addition, viruses can be directly
opsonized by phagocytosis via Ab and FcR binding. The virus is
then destroyed, and digested peptides can be retrieved by
antigen-presenting cells for T cell activation (Fig. 2) [17, 34, 38, 39].
If the virus escapes this lysis process, opsonized virus entry may
also lead to increased infection by a process called antibody-
dependent enhancement (ADE) [40]. This ADE function should
of course be avoided [41–43]. All these different Fc-mediated
mechanisms involve the binding of the Fc domain of the Ab to
the Fc receptor present on immune cells. The Fc-mediated
functions of Abs are therefore also directly interconnected with
FcR expression at the surface of immune cells [44, 45].

MODULATING FCR EXPRESSION AT THE SURFACE OF IMMUNE CELLS
FcRs are cell surface glycoproteins that bind to the Fc domain of
Abs. This binding varies according to the isotype and subclass of
the Ab but also according to the type of FcR (Fig. 1B, C) [44–46].
These FcRs are differentially expressed on most immune cells,
including natural killer (NK) cells, monocytes, macrophages,
eosinophils, dendritic cells, B cells and even some T cells
[17, 46]. There are three family classes of FcRs (I, II, and III), each
of which comprises a different number of proteins: FcγRI, FcγRIIa,
FcγRIIb, FcγRIIIa and FcγRIIIb (Fig. 1B) [18]. All human FcγRs
except FcγRIIIb signal through an immunoreceptor tyrosine-based
activating motif (ITAM), whereas FcγRIIIb delivers inhibitory signals
through an immunoreceptor tyrosine-based inhibitory motif (ITIM)
[4, 46]. The diversity of human FcγRII and III is further increased by
single nucleotide polymorphisms (SNPs) in their extracellular
domains, the most studied of which are H131R in FcγRII coding
gene FCGR2A, 126C>T in FCGR2C, F158V in FCGR3A, and NA1/2 in
FCGR3B (Fig. 1C). FcγRIIC has an unusual structure and is
generated by an unequal crossover between FcγRIIA and FcγRIIB.
FCGR2C signals through the ITAM similarly to FCGR2A. FcγRIIC
(126C>T), rs114945036 presumably lead to an open reading frame
with an atypical FcR protein sequence.

Importantly, the different FcR polymorphisms of the host
need to be considered when analyzing FcR-mediated functions of
Abs. FcyR SNPs will impact both on the the binding to the
complementary Fc portion of the Abs and on the expression or
activation state of the cells [46] (Fig. 1B). Increasing evidence
suggests that FcyR SNPs impair receptor expression on DCs,
in which turn influences the risk for HIV infection and vaccine
efficacy [15, 16, 47]. Interestingly, a combination of polymor-
phisms may also influence FcR expression, such as the combina-
tion of rs1801274 and rs10800309 in the FcγRIIIA coding gene
FCGR2A, which affects the expression level of FcR on immature
dendritic cells [48]. FcγRIIA polymorphism appears to modify
NK cell activation and, as a consequence, ADCC activity [49].
| Vaccine trial | Year | Location | Target population | Vaccine | Ab function | Fc receptor | FcR | Polymorphism | Association with risk of infection | Vaccine efficacy | Ref. |
|--------------|------|----------|-------------------|---------|--------------|-------------|-----|--------------|----------------------------------|-----------------|------|
| VaxSyn       | 1987 | Canada   | 72 adults         | Recombinant envelope glycoprotein subunit (gp160) of HIV | Low Tier 1 | NFD | – | – | – | No | [66, 67] |
| HIVAC-1e     | 1988 | USA      | 35 male adults    | Recombinant vaccinia virus designed to express HIV gp160 | N/F | ADE | – | – | – | No | [68, 69] |
| Vax004       | 1998–2002 | North America | 5417 MSM and 300 women | AIDSVAX B/E gp120 with alum | Tier 1 | ADCC ADCP | FcGR2A rs1801274 | ↓ | No | [37, 50, 52, 77, 84] |
| Vax003       | 1999–2003 | Thailand | 2545 men and women IDUs | AIDSVAX B/E gp20 with alum | Tier 1 | ADCC | – | – | – | No | [77, 83, 84] |
| STEP/HVTN502 | 2004–2007 | North America, Caribbean South America, and Australia | 3000 MSM and heterosexual men and women | MRKAd5 HIV-1 gag/pol/nef tivalent vaccine | Low Tier 1 | NFD | – | – | – | 1.4 increased risk of infection | [70, 71, 74, 75] |
| Phambili/ HVTN503 | 2003–2007 | South Africa | 801 adults | rAd5 (gag/pol/nef) | Low Tier 1 | NFD | – | – | – | 1.7 increased risk of infection | [72, 73] |
| RV144        | 2003–2009 | Thailand | 16,402 community-risk men and women | ALVAC-HIV (vCP1521) and AIDSVAX B/E vaccine | Low Tier 1 | ADCC ADCP | FcGR2C rs114945036 | ↓ | 3.1% decreased risk of infection | [8, 10, 51, 54, 82, 83, 85, 86] |
| HVTN505      | 2009–2013 | USA | 2504 men or transgender women who have sex with men | Three vaccinations with DNA encoding HIV clade B gag, pol and nef as well as env from HIV clades A, B and C followed by an Ad5 vector-based vaccine encoding clade B gag and pol as well as env from clades A, B and C | Low Tier 1 | ADCC ADCP | FcGR2A rs2165088 | ↓ | No | [54, 81, 87] |
| HVTN305      | 2012–2017 | Thailand | 162 women and men | ALVAC-HIV and AIDSVAX B/E vaccine | Low Tier 1 | ADCC ADCP | – | – | – | No | [86, 88] |
| HVTN306      | 2013–2020 | Thailand | 360 men and women aged 20–40 years old | ALVAC-HIV and AIDSVAX B/E vaccine | Low Tier 1 | ADCC ADCP | – | – | – | No | [89, 90] |
| HVTN097      | 2012–2013 | South Africa | 100 black Africans (men and women) aged 18–40 years old | ALVAC-HIV (vCP1521) and AIDSVAX B/E vaccine | Low Tier 1 | ADCC ADCP | – | – | – | No | [91] |
| HVTN100      | 2015–2018 | South Africa | 252 men and women | ALVAC-HIV (vCP2438) and bivalent subtype C gp120/MF59 | Low Tier 1 | ADCC ADCP | – | – | – | No | [92–94] |
Specific polymorphisms at the FCGR2A (encoding Arg or His at position 131) and FCGR3A (encoding Phe or Val at position 158) gene loci have been associated with an HIV vaccine benefit [50]. The rs396991 SNP leads to an increased binding capacity of Abs for FcγRIIIA, which is the main receptor involved in ADCC, suggesting that the vaccine efficacy may be related to an increased efficacy of this function. More recently, Li et al. described that a tag SNP (rs114945036) in FCGR2C (126C>T, presumably leading to a stop codon or an open reading frame) was significantly associated with protection against infection with a subtype AE HIV-1 strain in the RV144 vaccine clinical trial [51]. The direct effect of this SNP is not well documented. Authors propose that it may lead to an alternative splicing, bypassing the FCGR2C-Stop codon to encode a product with an atypical FcR protein sequence, thereby modifying FcR expression or accessibility on cells [51].

Overall, the interplay between IgG subclasses, multiple FcRs and polymorphisms thereof contribute to the complexity of the Fc-mediated response [15, 46]. As a consequence, numerous studies have analyzed the association between FcR genes or their polymorphisms and the evolution of HIV disease or vaccine protection (Table 1) [50–55].

### EFFECT OF ETHNICITY, SEX, AND AGE ON FC-MEDIATED AB RESPONSE TO HIV

Several studies have shown that serum Ig concentrations vary according to ethnicity, sex, and age. Total IgG and IgA levels increase with age and reach the adult concentration at ~10 years of age. Thereafter, the levels of serum IgG were found to be significantly reduced with age, and the level of IgA was found to be maintained. Total IgG and IgA concentrations are higher in Black populations than in White populations [19, 56, 57]. A similar result of higher total IgG levels in HIV-infected Africans than in Caucasians and Hispanics was also found [57–60]. Notably, all these studies comparing Ab profiles according to ethnicity were performed in individuals living in the same country. The difference in Ab responses in Africans living in Africa and Caucasians living in Europe or the USA needs to be investigated to integrate the effect of geographic origin in these studies.

In addition, age-related differences in clonal expansion with decreased IgA levels and skew toward IgG2 were observed after influenza vaccination [61, 62].

These results illustrate the importance of Ab classes in vaccine studies. This difference in Ab isotypes and concentrations according to ethnicity, age and sex may directly impact FcR functions and influence the efficacy of Ab induction in HIV-vaccinated individuals.

The demonstration of the role of Fc-mediated function also brings into question the importance of FcR features. The frequencies of SNPs of FcR genes differ significantly between ethnic groups [63–65]. These differences may strongly modify the association found between FcR polymorphisms and HIV-1 protection or disease outcome. In Kawasaki disease for example, the association with the FCGR2C-ORF haplotype becomes evident only when Asians, in whom FCGR2C-ORF is a nearly absent haplotype, are excluded from the cohort [64].

Overall, analyzing Fc-mediated Ab functions without considering ethnicity, sex, and age is hazardous. These factors need to be considered for genotype/phenotype association studies, as well as for the analysis of FcR involvement in HIV vaccine trials.

### FCR AND AB FUNCTIONS IN VACCINE TRIALS

During the past three decades, several HIV-1 vaccine trials have been performed all over the world. The first vaccine trial tested the recombinant envelope glycoprotein subunit (rgp160) in 72 adults. This vaccine showed induction of NAbs but not Fc-mediated Ab responses [66, 67]. The second HIV-1 trial (HiVAC-1e) used
recombinant vaccinia virus that expressed HIV-1 gp160, and its administration resulted in no induction of neutralizing Ab or Fc-mediated Ab responses, even though ADE was detected [68, 69]. Whether this lack of detectable Ab function was due to technical issues needs to be further assessed. Thereafter the following vaccine trials using envelop antigens succeeded in inducing both neutralizing and Fc-mediated Ab responses (Table 1). Of note, the CD4+ T cell-driven HIV immunogens used in the HVTN502 and HVTN503 vaccine trials did not contain envelop antigens, and led to an increased risk of infection [70–75]. FcR variants and their potential association with a decreased risk for infection were further investigated in three vaccine trials: Vax004, HVTN505 and RV144 (Fig. 1B). Although the Vax004 and HVTN505 vaccine strategies did not show efficacy, distinct FcγR polymorphisms have been associated with either an increased or decreased risk for HIV-1 acquisition (Table 1). For the RV144 vaccine trial conducted in Thailand, an association between the FCGR2C rs114940536, rs138747765, rs78603008 polymorphisms and a decreased risk for HIV-1 acquisition (Table 1). The RV144 vaccine trial conducted in Thailand, an association between the FCGR2C rs114940536, rs138747765, rs78603008 polymorphisms and a decreased risk for HIV acquisition was shown [51]. While focusing on fighting the HIV-1 pandemic in Africa, a similar strategy to that used in the RV144 trial was initiated in the South African area [76–79]. This trial, called HVTN702, did not reach the efficacy requirement of RV144 and was therefore stopped prematurely [80]. This failure could be explained by the fact that Black South Africans do not possess the FCGR2C haplotype that was associated with increased vaccine efficacy in the RV144 trial [63]. Collectively, the differences in FCGR2C polymorphisms in South Africa versus Thailand highlight the need for further mechanistic investigations to define the functional relevance of FcR polymorphisms in HIV-1 protection, especially in the context of vaccination. Interestingly, HVTN505 conducted in the USA showed different FcγR SNPs associated with a different hazard ratio of HIV-1 acquisition from that of RV144. In the HVTN505 trial, patients receiving the vaccine had significantly higher incidences of HIV acquisition than those receiving placebo among participants carrying the FCGR2C-TATA haplotype or the FCGR3B-AGA haplotype. Moreover, an FCGR2A SNP (rs2156088) and two FCGR2B SNPs (rs6666965 and rs666561) influenced the correlation of anti-gp140 antibody-dependent cellular phagocytosis with HIV risk [81]. Of note, the HVTN505 and RV144 trials differed in a number of points, i.e., canarypox prime/protein boost in a general low-risk Thai population in RV144 versus DNA prime/rAd5 boost in a high-risk U.S. population of men who have sex with men in HVTN505. These results indicate that the functional impact of a given FcγR polymorphism on the risk for HIV-1 acquisition is highly context specific, depending on the specific vaccine regimen but also on other factors, such as demographics, virus quasi-species, and genetic background [53, 81, 82].

**DISCUSSION OF FUTURE ASPECTS**

RV144 was the sole HIV-1 vaccine trial that showed a limited but statistically significant decreased infection risk [8, 10, 82]. As this protection was not associated with neutralization but with specific Ab types and Fc-mediated function, increased efforts were made to obtain a more in-depth characterization of the induced HIV-specific Ab response [10, 54, 82]. Indeed, in addition to HIV-specific Ab response and neutralizing activity, the specificity of the recognized epitope and Fc-mediated functions were investigated (Table 1). In addition, the FcR polymorphisms associated with infection outcome were explored [50–52, 54, 55, 81, 82]. However, taken individually, none of these factors could be associated with protection. For example, attempts to associate FcR genotypes with HIV outcome resulted in variable, sometime contradictory, results (Table 1). These results largely suggest that multiple Ab factors, including Ab class and subclass, structures, Fc domain interactions with Fc receptors, FcR locus copy number and FcR polymorphisms, may impact vaccine efficacy with synergistic or sometimes antagonistic effects [83]. Moreover, as Ab concentrations and FcR polymorphism frequencies vary according to ethnicities, analysis of correlates of infection risk need to take these additional parameters into consideration [63–65]. These results shed light on the complexity of the humoral response that may be correlated with a decreased risk of HIV-1 acquisition. Future vaccine strategies need to address humoral Ab induction as a whole, challenging the different characteristics of the Abs and FcRs required to obtain the most promising combination of humoral responses associated with protection.

**REFERENCES**

1. World Health Organization. Number of people (all ages) living with HIV—estimates by country. 2020. https://apps.who.int/gho/data/node.main.6207?lang=en.

2. Hemelaar J, Gouws E, Gysy PD, Osmanov S, WHO-UNAIDS Network for HIV Isolation and Characterisation. Global trends in molecular epidemiology of HIV-1 during 2000-2007. AIDS Lond Engl. 2011;25:679-89.

3. Lihana RW, Ssemwanga D, Abhimiku A, Ndemb N. Update on HIV-1 diversity in Africa: a decade in review. AIDS Rev. 2012;14:83–100.

4. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361:2209–20.

5. Bambouta A, Posada D, Clandall KA, Holmes EC. The causes and consequences of HIV evolution. Nat Rev Genet. 2004;5:52–61.

6. Gilbert PB, Mcgeague NW, Eiren G, Mullins C, Gulye-NDiaie A, Mboup S, et al. Comparison of HIV-1 and HIV-2 in infectivity from a prospective cohort study in Senegal. Stat Med. 2003;22:573–93.

7. Ng’mi T, Chasara C, Ndlovu ZM. Major scientific hurdles in HIV vaccine development: historical perspective and future directions. Front Immunol. 2020;11:2761.

8. Rerks-Ngarm S, Pitsuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361:2209–20.

9. Yates NL, Liao HK, Fong Y, deCamp A, Vandergrift NA, Williams WT, et al. Vaccine-induced Env V1-V2 IgG3 correlates with lower HIV-1 infection risk and declines soon after vaccination. Sci Transl Med. 2014;6:228ra39.

10. Fischner S, Dolutshali S, Jennewein MF, Rerks-Ngarm S, Pitsuttithum P, Nitayaphan S, et al. IgG3 correlates with IgG1 and IgG to recruit effector function in RV144 vaccinees. JCI Insight. 2020;5:e140925.

11. Tomasgard G, Ferrari G, Shen X, Alam SM, Liao HK, Pollara J, et al. Vaccine-induced plasma IgA specific for the C1 region of the HIV-1 envelope blocks binding and effector function of IgG. Proc Natl Acad Sci. 2013;110:9019–24.

12. Boesch AW, Brown EP, Ackerman ME. The role of Fc receptors in HIV prevention and therapy. Immunol Res. 2015;58:296–310.

13. Hessell AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, et al. Fc receptor but not complement binding is important in antibody protection against HIV. Nature. 2007;449:101–4.

14. Wines BD, Billings H, Mclean MR, Kent SJ, Hogarth PM. Antibody functional assays as measures of Fc receptor-mediated immunity to HIV-new technologies and their impact on the HIV vaccine field. Curr HIV Res. 2017;15:202–15.

15. Su B, Dispensieri S, Iannone V, Zhang T, Wu H, Carapito R, et al. Update on Fc-mediated antibody functions against HIV-1 beyond neutralization. Front Immunol. 2019;10:2966.

16. Mayr LM, Su B, Moog C. Non-neutralizing antibodies directed against HIV and their functions. Front Immunol. 2017;8:1590.

17. Bournaozi S, Wang TT, Ravetch JV. The role and function of Fc receptors on myeloid cells. Microbiol Spectr. 2016:4:4–6.

18. Vidarsson G, Dekkers G, Rispen T. IgG subclasses and allotopes: from structure to effector functions. Front Immunol. 2014;5:520.

19. Maddison SE, Stewart CC, Farshy CE, Reimer CB. The relationship of race, sex, and age to concentrations of serum immunoglobulins expressed in international units in healthy adults in the USA. Bull World Health Organ. 1975;52:179–85.

20. Yates NL, Lucas JT, Nolen TL, Vandergrift NA, Soderberg KA, Seaton KE, et al. Multiple HIV-1-specific IgG3 responses decline during acute HIV-1; implications for detection of incident HIV infection. AIDS. 2011;25:2089.

21. Moir S, Fauci AS. B-cell responses to HIV infection. Immunol Rev. 2017;275:33–48.

22. Alter G, Dowell KG, Brown EP, Suscovich TJ, Mikhailova A, Mahan AE, et al. High-resolution definition of humoral immune response correlates of effective immunity against HIV. Mol Syst Biol. 2018;14:e8788.

23. Hessell AJ, Haigwood NL. Neutralizing antibodies and control of HIV: moves and countermoves. Curr HIV/AIDS Rep. 2012;9:64–72.

24. Klasse PJ. Neutralization of virus infectivity by antibodies: old problems in new perspectives. Adv Biol. 2014;2014:e157895.
25. Saunders KO, Pegu A, Georgiev IS, Zeng M, Joyce MG, Yang ZY, et al. Sustained delivery of a broadly neutralizing antibody in nonhuman primate conveys long-term protection against Simian/human immunodeficiency virus infection. J Virol. 2015;89:5895–903.

26. Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol. 2010;17:1055–61.

27. Rusche JW, Lynn DL, Robert-Guroff M, Langlois AJ, Lyerly HK, Carson H, et al. Humoral immune response to the entire human immunodeficiency virus envelope glycoprotein made in insect cells. Proc Natl Acad Sci. 1987;84:6924–8.

28. Esparza J. A brief history of the global effort to develop a preventive HIV vaccine. Vaccine. 2013;31:3502–18.

29. Moore PL, Williamson C, Morris L. Virological features associated with the development of broadly neutralizing antibodies to HIV-1. Trends Microbiol. 2015;23:204–11.

30. Gray ES, Madiga MC, Hermans T, Moore PL, Wibmer CK, Tumbl NL, et al. Neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. J Virol. 2011;85:4828–40.

31. Reks-Ngarm S, Pitsutzthorn P, Esler JL, Nitisayaphan S, Kaezkwongwai J, Premshi N, et al. Randomized, double-blind evaluation of late boost strategies for HIV-infected vaccine recipients in the RV144 HIV vaccine efficacy trial. J Infect Dis. 2017;215:1255–63.

32. Richardson SL, Moore PL. Targeting Fc effector function in vaccine design. Expert Opin Ther Targets. 2021;25:467–77.

33. Dugas AT, Tonelli A, Berger CT, Ackerman ME, Sciaranghella G, Liu Q, et al. Decreased Fc receptor expression on innate immune cells is associated with impaired antibody-mediated cellular phagocytic activity in chronically HIV-1 infected individuals. Virology. 2011;415:160–7.

34. Holl V, Peressin M, Decoville T, Schmidt S, Zolla-Pazner S, Aubertin AM, et al. Nonneutralizing antibodies are able to inhibit human immunodeficiency virus type 1 replication in macrophages and immature dendritic cells. J Virol. 2006;80:1771–81.

35. Rossignol ED, Dugas AS, Compe H, Cotrell CA, Cops J, Lin S, et al. Mining HIV controllers for broad and functional antibodies to recognize and eliminate HIV-infected cells. Cell Rep. 2021;35:109167.

36. Lambotte O, Pollara J, Boufassa F, Moog C, Venet A, Haynes BF, et al. High prevalence of serum IgA HIV-1 antibody in South African persons infected with the human immunodeficiency virus type 1. J Acquir Immun Defic Syndr. 1992;5:325–32.

37. Chaisson RE, Fuchs E, Stanton DL, Quinn TC, Hendrickson C, Bartlett JG, et al. Racial heterogeneity of HIV antigenemia in people with HIV infection. AIDS Lond Engl. 1991;5:177–80.

38. Gallerano D, Ndlouv P, Makupe I, Focke-Tejkl M, Fauland K, Wollmann E, et al. Comparison of the specificity of IgG, IgG subclass, IgA and IgM reactivities in African and European HIV-infected individuals with an HIV-1 clade C proteome-based array. PLoS ONE. 2015;10:e0117204.

39. El-Madhus AS, Cox RJ, Haaimer LR. The effect of age and natural priming on the IgG and IgA subclass responses after parental influenza vaccination. J Infect Dis. 1999;180:1356–60.

40. Powers DC. Effect of age on serum immunoglobulin G subclass antibody responses to inactivated influenza virus vaccine. J Med Virol. 1994;43:57–61.

41. Londrinen R, Trennesson CT. Variability at the FCGR locus: characterization in Black South Africans and evidence for ethnic variation in and out of Africa. Genes Immun. 2016;17:93–104.

42. Nagelkerke SQ, Tacke CE, Breunis WB, Tanck MWT, Geissler J, Png E, et al. Extensive ethnic variation and linkage disequilibrium at the FCGR2/3 locus: different genetic behaviors in HIV-1 infected individuals. Virology. 2011;415:160–7.

43. Li SS, Gilbert PB, Tomaras GD, Kijak G, Ferrari G, Thomas R, et al. FCGR2C polymorphisms associated with HIV-1 vaccine protection in RV144 trial. J Clin Investig. 2014;124:3879–90.

44. Forthal DN, Gabriel EE, Wang A, Landucci G, Phan TB. Association of Fcy receptor IIIa genotype with the rate of HIV infection after gp120 vaccination. Blood. 2012;120:2836–42.

45. Lazzarone SR, Tiensmann CT. FcyR genetic variation and HIV-1 vaccine efficacy: context and considerations. Front Immunol. 2021;12:788203.

46. Neidich SD, Fong Y, Li SS, Geraghty DE, Williamson BD, Young WC, et al. Antibody Fc effector functions and IgG3 associate with decreased HIV-1 risk. J Clin Investig. 2019;129:4838–49.

47. Lamprey H, Bonney EY, Adu B, Kylc GB. Are Fc gamma receptor polymorphisms important in HIV-1 infection outcomes and latent reservoir size? Front Immunol. 2021;12:1336.

48. Shackelford PG, Granoff DM, Nahm MH, Scott MG, Suarez B, Pandey JP, et al. Relation of age, race, and allelotype to immunoglobulin subclass concentrations. Pediatr Res. 1985;19:9846–9.

49. McGowan JP, Shah SS, Small CB, Klein RS, Schnipper SM, Chang CJ, et al. Relationship of serum immunoglobulin and IgG subclass levels to race, ethnicity and behavioral characteristics in HIV infection. Med Sci Monit Int Med J Exp Clin Res. 2006;12:CR11–6.

50. Lucey DR, Hendrix CW, Andrzejewski C, Melcher GP, Butzin CA, Henry R, et al. Comparison of race by total serum IgG, IgA, and IgM with CD4+ T-cell counts in North American persons infected with the human immunodeficiency virus type 1. J Acquir Immun Defic Syndr. 1992;5:325–32.

51. Hosch FGS, Fuchs E, Stanton DL, Quinn TC, Hendrickson C, Bartlett JG, et al. Racial heterogeneity of HIV antigenemia in people with HIV infection. AIDS Lond Engl. 1991;5:177–80.

52. Niederer HA, Willcocks LC, Rayner TF, Yang W, Lau YL, Williams TN, et al. Copy number, linkage disequilibrium and disease association in the FCGR locus. Hum Mol Genet. 2010;19:3282–90.

53. Nashimoto G, Wright PF, Karzon DT. Antibody-dependent cell-mediated cytotoxicity against influenza virus-infected cells. J Infect Dis. 1983;148:785–94.

54. Bournazos S, Corti D, Virgin HW, Ravetch JV. Fc-optimized antibodies elicit CD8 T cell viral suppressive activity but not with B57 status in HIV-1 elite controllers. J Immunol. 2015;194:2748–53.

55. Lucey DR, Hendrix CW, Andrzejewski C, Melcher GP, Butzin CA, Henry R, et al. Comparison of the specificities of IgG, IgG subclass, IgA and IgM reactivities in African and European HIV-infected individuals with an HIV-1 clade C proteome-based array. PLoS ONE. 2015;10:e0117204.

56. El-Madhus AS, Cox RJ, Haaimer LR. The effect of age and natural priming on the IgG and IgA subclass responses after parental influenza vaccination. J Infect Dis. 1999;180:1356–60.

57. Powers DC. Effect of age on serum immunoglobulin G subclass antibody responses to inactivated influenza virus vaccine. J Med Virol. 1994;43:57–61.

58. Londarinos R, Trennesson CT. Variability at the FCGR locus: characterization in Black South Africans and evidence for ethnic variation in and out of Africa. Genes Immun. 2016;17:93–104.

59. Cooney EL, Collier AC, Greenberg PD, Coombs RW, Zarling J, Ardisi DE, et al. Safety and of immunological response to a recombinant vaccinia virus vaccine expressing HIV envelope glycoprotein. Lancet. 1991;337:567–72.

60. Montefiori DC, Graham BS, Kilks S, Wright PF, Serum antibodies to HIV-1 in recombinant vaccine virus recipients boosted with purified recombinant gp160. NIAID AIDS Vaccine Clinical Trials Network. J Clin Immunol. 1992;12:429–39.

61. Bushbinder SP, Mehrroda DV, Duerer A, Fitzgerald DW, Mogg R, Li D, et al. Fcγ effector function of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomized, placebo-controlled, test-of-concept trial. Lancet Infect Dis. 2008;8:372–80.

62. Duerer A, Huang Y, Bushbinder S, Coombs RW, Sanchez J, del Rio C, et al. Extended follow-up confirms early vaccine-enhanced risk of HIV acquisition and demonstrates waning efficacy over time among participants in a randomized trial of recombinant adenosine virus vaccine (Step Study). J Infect Dis. 2012;206:258–66.

63. Gray GE, Allen M, Moodie Z, Churchyard G, Bekker LG, Nchabeleng M, et al. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis. 2011;11:507–15.

64. Gray GE, Moodie Z, Methch B, Gilbert PB, Bekker LG, Churchyard G, et al. The phase 2b HVTN 503/Phambili study test-of-concept HIV vaccine study, investigating a recombinant adenovirus type 5 HIV gag/pol/nef vaccine in South Africa: unblinded, long-term follow-up. Lancet Infect Dis. 2014;14:388–96.
74. Li F, Finnefrock AC, Dubey SA, Korber BMT, Szinger J, Cole S, et al. Mapping HIV-1 vaccine-induced T-cell responses: bias towards less-conserved regions and potential impact on vaccine efficacy in the step study. PLoS ONE. 2011;6:e20479.

75. Janes H, Frahm N, DeCamp A, Rolland M, Gabriel E, Wolfson J, et al. MRKAd5 HIV-1 Gag/Pol/Env vaccine-induced T-cell responses inadequately predict distance of breakthrough HIV-1 sequences to the vaccine or viral load. PLoS ONE. 2012;7:e43396.

76. Bekker LG, Tatoud R, Dabis F, Feinberg M, Kaleebu P, Marovich M, et al. The complex challenges of HIV vaccine development require renewed and expanded global commitment. Lancet. 2020;395:384-8.

77. Pitisuttithum P, Gilbert PB, Carpp LN, Pyo CW, Janes H, Fong Y, et al. Fc gamma receptor polymorphisms modulated the vaccine effect on HIV-1 risk in the HVTN 505 HIV vaccine trial. J Virol. 2019;93:e02041–18.

78. Janssen Vaccines & Prevention BV. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2b Efficacy Study of a Heterologous Prime/Boost Vaccine Regimen of Ad26.Cold.SIV and Aluminum Phosphate-Adjuvanted Clade C GP140 in Preventing HIV-1 Infection in Adult Women in Sub-Saharan Africa. clinicaltrials.gov. 2021. https://clinicaltrials.gov/ct2/show/NCT0390629.

79. IAVI statement on results from Phase Ib immunobola HIV vaccine clinical trial. IAVI. https://www.iavi.org/news-resources/features/iaivi-statement-on-results-from-phase-ibb-immoboko-hiv-vaccine-clinical-trial.

80. Another HIV vaccine strategy fails in large-scale study. https://www.science.org/content/article/another-hiv-vaccine-strategy-fails-large-scale-study.

81. Li SS, Gilbert PB, Carpp LN, Pyo CW, Janes H, Fong Y, et al. Functional antibody response against V1V2 and V3 of HIV gp120 in the VAX003 and VAX004 vaccine trials. Sci Rep. 2018;8:542.

82. Kijak GH, Tovanabutra S, Rerks-Ngarm S, Nitayaphan S, Eamsila C, Kunasol P, et al. Molecular evolution of the HIV-1 epidemic between the time of RV144 immunogen selection to the execution of the vaccine efficacy trial. J Virol. 2013;87:7265–81.

83. Easterhoff D, Pollara J, Luo K, Tolbert WD, Young B, Mielke D, et al. Boosting with AIDSVAX B/E enhances Env constant region 1 and 2 antibody-dependent cellular cytotoxicity breadth and potency. J Virol. 2020;94:e02041–19.

84. Hammer SM, Sobieszczuk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, et al. Efficacy trial of a DNA/rAdS HIV-1 preventive vaccine. N Engl J Med. 2013;369:2083–92.

85. Fischinger S, Shin S, Boudreau CM, Ackerman M, Rekers-Ngarm S, Pitisuttithum P, et al. Protein-based, but not viral vector alone, HIV vaccine boosting drives an IgG1-biased functional humoral immune response. JCI insight. 2020;5:e135057.

86. Pitisuttithum P, Nitayaphan S, Charoenvit S, Kaewkungwal J, Dawson P, Dhitavat J, et al. Late boosting of the RV144 regimen with AIDSVAX B/E and ALVAC-HIV in HIV-uninfected Thai volunteers: a double-blind, randomised controlled trial. Lancet HIV. 2020;7:e238–48.

87. Shukla DK, Maunder RJ, Geertz A, Yum L, Kundu G, May K, et al. Monocyte-derived transcriptome signature indicates antibody-dependent cellular phagocytosis as a potential mechanism of vaccine-induced protection against HIV-1 eLife. 2021;10:e69577.

88. Gray GE, Huang Y, Grunenberg N, Laher F, Roux S, Anderssen-Nissen E, et al. Immune correlates of the Thai RV144 HIV vaccine regimen in South Africa. Sci Transl Med. 2019;11 eaaw1880.

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CM and LYL contributed to the writing. RC and BS corrected, amended and edited the paper. All authors provided feedback on the report.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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