Conserved HIV Epitopes for an Effective HIV Vaccine

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Abstract

Despite major advances in antiretroviral therapy against HIV-1, an effective HIV vaccine is urgently required to reduce the number of new cases of HIV infections in the world. Vaccines are the ultimate tool in the medical arsenal to control and prevent the spread of infectious diseases such as HIV/AIDS. Several failed phase-IIb to –III clinical vaccine trials against HIV-1 in the past generated a plethora of information that could be used for better designing of an effective HIV vaccine in the future. Most of the tested vaccine candidates produced strong humoral responses against the HIV proteins; however, failed to protect due to: 1) the low levels and the narrow breadth of the HIV-1 neutralizing antibodies and the HIV-specific antibody-dependent Fc-mediated effector activities, 2) the low levels and the poor quality of the anti-HIV T-cell responses, and 3) the excessive responses to immunodominant non-protective HIV epitopes, which in some cases blocked the protective immunity and/or enhanced HIV infection. The B-cell epitopes on HIV for producing broadly neutralizing antibodies (bNAbs) against HIV have been extensively characterized, and the next step is to develop bNAb epitope immunogen for HIV vaccine. The bNAb epitopes are often conformational epitopes and therefore more difficult to construct as vaccine immunogen and likely to include immunodominant non-protective HIV epitopes. In comparison, T-cell epitopes are short linear peptides which are easier to construct into vaccine immunogen free of immunodominant non-protective epitopes. However, its difficulty lies in identifying the T-cell epitopes conserved among HIV subtypes and induce long-lasting, potent polyfunctional T-cell and cytotoxic T lymphocyte (CTL) activities against HIV. In addition, these protective T-cell epitopes must be recognized by the HLA prevalent in the country(s) targeted for the vaccine trial. In conclusion, extending from the findings from previous vaccine trials, future vaccines should combine both T- and B-cell epitopes as vaccine immunogen to induce multitude of broad and potent immune effector activities required for sterilizing protection against global HIV subtypes.
Keywords
Vaccine epitopes; B-cell epitopes; T-cell epitopes; HIV vaccine

Introduction
In an USAID global survey, approximately two million new HIV-1 cases were reported in 2015 alone, despite the increased use of the antiretroviral therapies (ART) to control the global spread of the infection [1]. Daily administration of ART successfully lowered circulating HIV load to minimal to undetectable levels in HIV-positive (HIV+) individuals and prolonged their life to nearly normal lifespan [2]. In 2015, approximately 17 million of 37 million (46%) HIV+ individuals received ART, incurring tremendous toll on their country’s economy and on the global community [1,3]. To further minimize the global spread of the viral infection, ART must be provided to rest 54% of infected individuals including millions of HIV-negative high-risk groups as pre-exposure prophylaxis [3]. In 2016, UNAIDS and WHO projected approximately 33 million HIV+ individuals would be on ART by 2030, which would lead to a ten-fold decrease (<200,000 individuals) in newly infected individuals and a two-fold decrease (<400,000 individuals) in individuals succumbing to the HIV infection [1,3]. Although the rise in the drug resistance has so far been modest, there is a small portion of cases with high drug resistance in ART-naïve HIV+ individuals in certain countries; additionally, resistance also seen in individuals restarting the ART after treatment interruptions [3]. More importantly, the long-term use of the best drug combinations of ART is still unable to cure HIV infection [2]. The cost of treatment, potential drug resistance and inefficacy of the existing treatment underscore the urgent need to develop an effective prophylactic vaccine against HIV-1.

The current review will describe the findings important to the development of an effective HIV vaccine with emphasis on B-cell and T-cell vaccine epitopes through the coverage of the following topics: 1) Past and present understanding of HIV vaccination, 2) Conserved B-cell and T-cell epitopes on HIV, 3) B-cell epitopes generating broadly neutralizing antibodies (bNAbs), 4) Non–neutralizing antibodies (nAbs) during HIV vaccination and infection, 5) Conserved T-cell epitopes associated with anti-HIV activity(s), 6) Conserved T-cell epitopes associated with protective HLA allotypes prevalent in HIV endemic countries, 7) Antibodies and T-cell responses enhancing HIV infection, and 8) Conserved T-cell and B-cell epitopes with potent anti-HIV activity for HIV vaccine.

Past and present understanding of HIV vaccination
Vaccination changed the conventional disease management; an effective vaccine can reduce or even eradicate the infectious disease, which made vaccines as an essential tool against infectious agents. Several unsuccessful attempts made in the past in the development of such vaccines provided extensive information that can be used in the future for more effective vaccines against the virus. Here we reviewed several vaccination attempts and their cause of failures to protect against HIV-1. Since the initiation of the first phase-III clinical vaccine trial (VAX004) in 1998, three independent phase-III clinical vaccine trials ended with
marginal to no efficacy (Table 1) [4–6]. All of these trials tested HIV-1 vaccines containing viral envelope (Env) protein(s) [4,5] or its combination with viral Gag (matrix-p24-nucleoprotein) and protease (Pro) proteins [6]. The overarching goal of these trials was to induce HIV-1 neutralizing antibodies (NAbs) in the vaccinated subjects and to evaluate their efficacy [4–6]. Additionally, the last trial RV144 focused on inducing both humoral and cellular immunity against HIV-1, especially by generating broadly NAbs (bNAbs) using a prime-boost system with vectored gag-pro-env prime and boosting with Env proteins from two subtypes or clades [6]. Unfortunately, these trials were unsuccessful in inducing bNAbs against global HIV subtypes; however, the last trial conferred a modest prophylactic protection [4–6]. Nevertheless, these trials demonstrated the production of HIV-1 type (tier 1)-specific NAbs and substantial levels of Env-binding antibodies (Table 1).

The RV144 trial was minimally successful by conferring 31.2% protection in the combined low/medium/high-risk group but conferring only 3.7% protection in the high-risk group [6]. Since the type-specific NAbs did not correlate with the modest protection observed in the combined group, other immune correlates of protection were evaluated, such as non-neutralizing anti-HIV antibodies (nNAbs) and T-cell immunity [7]. Notably, the presence of Env-specific IgG nNAbs inversely correlated with HIV infection with a positive correlation with the protection [7–9]. However, Env-specific nNAbs with antibody-dependent cellular cytotoxicity (ADCC) activity and Env-specific CD4+ T cells directly correlated with the protection from active infection [7]. Conversely, Env-specific IgA antibodies positively correlated with HIV infection (i.e., inverse correlation with protection) [7]. A recent report showed IgA antibodies produced in RV144 trials inhibited the protective ADCC activity [10]. This observation raised concern since mucosal IgA immunity is considered more or equally important as IgG immunity against mucosal transmission of HIV infection, which is the major transmission route for HIV [11].

Prior to the completion of RV144 trial, two phase-IIb clinical vaccine trials (Step and Phambili trials) consisting of adenovirus type-5 (Ad5) vectored HIV gag/pol/nef vaccine were in progress and tested whether vaccines based solely on anti-HIV T-cell immunity could confer protection in vaccinated subjects (Table 1) [12–14]. Ad5-gag/pol/nef vaccination did not induce NAbs, bNAbs, or ADCC nNAbs to Env due to the absence of HIV env gene in the construct. Unfortunately, upon one-year evaluation, the vaccine group showed enhanced HIV infection compared to the placebo group in the Step trial, resulting in an abrupt termination of both Step and Phambili trials. Some reasons for the failure of the Step trial were attributed to: 1) the pre-existing anti-adenovirus antibodies in the enrolled subjects [12,15], 2) the induction of Ad5-specific CD4+ T cells with increased susceptibility to HIV and/or increased HIV trafficking to mucosal sites [12,15–18], 3) more uncircumcised subjects in the vaccinated group than in the placebo group [12,15], despite previous studies showed circumcision directly correlating with decreased HIV transmission [19,20], 4) the enhancement of HIV infection caused by the non-specific release of IFNγ [21], and 5) the poor induction of anti-HIV T-cell immunity [22,23]. In fact, the anti-HIV CD8+ T-cell responses were of low magnitude and narrow breadth, less polyfunctional, and targeted predominantly Pol and Nef proteins instead of Gag protein. CD8+ cytotoxic T lymphocyte (CTL) and other T-cell responses against HIV Gag are associated with control of HIV infection compared to the T cell responses directed against Pol [24–29]. Hence, insufficient
magnitude and quality of anti-HIV T-cell immunity were induced to counteract the HIV enhancing effects caused by adenovirus vector and experimental design of the Step trial that might have caused the failure of the trial. The initial nine-month results of the Phambili trial did not show any statistical change in the rate of infection; however, it was difficult to draw any conclusion due to early termination and low participation compared to the Step trial [13]. The findings from this trial indicated that neither pre-existing Ad5 titers nor circumcision status affected the vaccine efficacy, which was later confirmed in the median 42-months follow-up analysis [14]. Moreover, the follow-up analysis revealed more infection in the vaccine group than placebo group leading to the conclusion that vaccination significantly increased the risk of HIV infection.

Since none of the vaccines in the Phase-III vaccine trials induced potent bNAb, scientific efforts were subsequently focused on identifying the B-cell epitopes that induce potent bNAb against global HIV subtypes [30–32]. The findings from RV144 also sparked renewed interests in identifying B-cell epitopes on HIV Env that induced anti-HIV nNAb (e.g., ADCC Abs) as well as on identifying protective conserved HIV T-cell epitopes to be combined with protective B-cell epitopes as immunogens for an effective HIV vaccine [33–35]. The recent findings about bNAb as discussed below further support the need for combining B-cell epitopes for ADCC nNAb and bNAb with anti-HIV T-cell epitopes [22,34–36].

**Conserved B-cell and T-cell epitopes on HIV**

An epitope is defined as the site on a molecule or an antigen recognized by either an antibody or B-cell receptor (BCR), or by T-cell receptor (TCR) recognizing the antigenic peptide bound to the major histocompatibility complex (MHC) [37–39]. Hence, a B-cell epitope binds to the epitope-specific antibody as well as epitope-specific BCR on B cells. The binding of the antigenic epitope to the BCR(s) triggers the B-cell differentiation into epitope-specific antibody producing clonal B cells. A B-cell epitope can be either continuous (linear) or discontinuous (conformational) stretch of amino acids (aa) on the antigen [40]. Continuous or linear epitope consists of a consecutive aa sequence on the antigen. Whereas, a discontinuous or conformational epitope is formed with the help of more than one continuous aa series come in close vicinity due to protein folding and other proteinaceous and non-proteinaceous interactions. B-cell epitopes on HIV can also be found on lipid, glycan, and protein antigens or their combination (e.g., lipoprotein, glycoprotein) on HIV [30,31,34,41].

In recent studies, a majority of bNAb reacted to conformational epitopes than to linear epitopes (Table 2) [30,31,34,42] making it difficult to use them in vaccine development where isolated epitopes are used in vaccines. HIV epitopes for bNAb are described conserved because of their cross-reactivity due to broader affinity to multiple HIV subtypes [34,43]. However, not all bNAb contact site of the HIV epitopes are highly conserved in their aa sequence but can include highly variable segment(s), suggesting other than aa sequences controlling their binding. The binding of bNAb without a common aa sequence may be due to the common conformation of the epitopes despite variation in aa sequences or...
protein modifications (glycosylation, lipidation) that might be the cause of their binding that cannot be replicated in a vaccine with ease.

In comparison, T-cell epitopes are short linear peptides processed from a protein antigen, and presented on MHC molecules for their recognition by TCR on T cell to induce its effector function(s). The conserved T-cell epitopes on HIV are identical or similar (homologous) in aa sequences and are conserved among the HIV isolates from the same subtype (type-specific) or from multiple HIV subtypes [44–46], and those evolutionarily preserved are conserved among AIDS lentiviruses of humans, nonhuman primates (NHPs), and cats (HIV, SIV, FIV) [47,48]. Generally, those conserved among HIV/SIV/FIV are often conserved within and among HIV subtypes [47,48]. The evolutionarily conserved epitopes that maintained their existence among different hosts have lower likelihood to acquire mutation(s) compared to the non-conserved epitopes with variable aa sequences. It is generally perceived that the highly conserved epitopes are present on protein regions essential for viral survival, and any substantial mutation(s) would affect the fitness of the virus [49–51]. Immunization with conserved HIV T-cell epitopes can have diverse outcomes, ranging from infection-enhancing, neutral, beneficial, or protective effect. Therefore, careful selection of conserved T-cell epitopes that induce potent anti-HIV immunity is needed to develop a highly effective HIV vaccine against global HIV subtypes.

**B-cell epitopes generating broadly neutralizing antibodies (bNAb)**

The bNAb are those anti-HIV antibodies that potently neutralize a broad spectrum of heterologous HIV viruses including those among global HIV subtypes [34,43]. The existence of bNAb has been first detected in 20–50% HIV+ individuals with chronically infected for over 2–5 years [34,52,53]. According to the studies with bNAb isolated from infected subjects, bNAb target five epitopic regions of HIV Env [30,31,34] and these include (Table 2): 1) CD4-binding site (CD4bs), 2) V2 proteoglycan moiety on the trimer apex of surface Envs (SUs), 3) V3 proteoglycan moiety on the high mannose patch of SU, 4) membrane proximal external region (MPER) of Env transmembrane domain, and 5) gp120-gp41 interface with or without fusion protein. HIV antigenic epitope(s) that induce bNAb with above characteristics should be considered an ideal vaccine antigen(s) for prophylaxis. The gp120-gp41 interface epitopes are often transitional epitopes requiring initial contact to CD4 and/or CCR5 (co-receptor) molecules or requiring viral fusion process before they are sufficiently exposed to the bNAb [54]. Since the majority of the known human bNAb have been IgG isotypes (Table 2), such vaccine epitopes should at least induce IgG bNAb. The results from RV144 suggest that elevated levels of IgG1 and IgG3 subclasses correlated with vaccine protection, whereas high levels of IgA and IgG4 correlated with enhanced HIV viral titer [9,10,55]. As of to date, the HIV vaccine epitopes for bNAb have not been identified or developed [31,34,56,57]. Vaccines consisting of recombinant Env and trimeric Env proteins have not successfully induced bNAb [4,5,58,59]. However, information about the characteristics of the bNAb has been described as the first step towards developing their counterpart Env epitopic antigen or immunogen for vaccine [30,31,34].

The antigen binding site on an antibody that recognizes an antigenic epitope is called paratope of the antibody [37]. Antibodies stimulated by an antigen upon immunization or
infection possess different paratopes that bind to different epitopes on an antigen. The paratope of an antibody is found on complementarity determining regions 1, 2, and 3 (CDR1, CDR2, CDR3) of the antibody heavy and light chains. The characteristics of the bNAb paratopes derived from chronically HIV-infected subjects have recently been described [30,31,34,60]. The bNAbs with 50% breadth develop in 20–50% of chronically HIV-infected subjects [52]. The bNAb paratopes have unique characteristics [30,31,34,61,62] such as: 1) high levels of somatic hypermutations at the V(D)J antibody genes, 2) often possessing long heavy-chain CDR3 (HCDR3), 3) often showing polyreactivity and autoreactivity with self-protein, glycan, and lipid, and 4) taking years to develop the broad specificity of bNAb paratopes.

Although few occluded bNAb-inducing Env epitopes (e.g., CD4bs) may remain relatively constant in aa sequence, mutation(s) at other viral Env site (e.g., glycan insertion or deletion) of the viral escape variant(s) may expose the occluded bNAb epitopes [63,64]. For example, bNAbs developed to V2 proteoglycan moiety may lead to viral escape variant(s) with N167D which in turn exposes the occluded CD4bs resulting in the development of bNAbs to CD4bs. Such event can explain why a sizable number of chronically infected individuals possess multiple bNAbs with specificity to different targeted bNAb epitope region [64–67]. Another possibility is that the ancestral Env epitope of potential bNAb itself may need to undergo changes such as mutations with subtle conformational changes as part of viral escape from NAb or viral co-evolution [63,64,68]. The latter scenario of co-evolution of both virus and B cells takes many years to develop bNAbs. In either scenario, affinity maturation of the bNAb B-cell lineages in response to viral escape variants may induce multiple cycles of somatic hypermutation in the antibody genes [63,69,70].

Many bNAbs were determined to be polyreactive and autoreactive to self-antigen(s) [61]. These observations raised a concern that immunization with vaccine antigen(s) consisting of bNAb epitopes may induce autoreactive antibodies, which may cause autoimmune disease in the vaccinated hosts. However, initial passive transfer of autoreactive bNAbs in nonhuman primates (NHPs) was well tolerated, and no sign of autoimmune symptoms was observed in the passively immunized monkeys [71]. Furthermore, the difficulty in developing bNAbs in chronically infected individuals has been attributed to the development of tolerance to the bNAb epitopes that are recognized as self-epitopes by the host immune system [61]. This view is based on a well-established immunological concept that autoreactive B cells often undergo clonal deletion and/or anergy to prevent the production of autoreactive antibodies in a healthy individual [61,72]. Besides these undesirable features (i.e., autoimmune and tolerance) to overcome, high levels of somatic hypermutation of antibody genes are required to develop bNAbs with or without long HCDR3. Thus, these combinations of events needed for developing bNAbs raised a major concern on whether bNAbs can be developed by vaccination [33,73].

Non-neutralizing antibodies (nNAbs) during HIV vaccination and infection

Some nNAbs and many of the bNAbs have been reported to mediate ADCC and antibody-dependent cellular virus inhibition (ADCVI) of the infected cells [55,74–76]. Antibodies that mediate ADCC and/or ADCVI activity(s) use their Fab region to bind to the epitope on
gp120 or gp41 present on the surface of infected cells or on the virus attached to the infecting cell [55,74,76]. Meanwhile their Fc region binds to the Fc receptors (FcRs) on the effector cell which subsequently triggers cytotoxicity/cytolysis of the infected cells (ADCC) and/or non-cytotoxic antiviral activity(s) in the infected cell (ADCVI). The ADCC effector cells release cytolytic and cytotoxic molecules such as perforin and granzymes, respectively, whereas those with ADCVI activity produce chemokines (e.g., β chemokines) and/or cytokines that inhibit viral replication in the cell. The selective mutation(s) of the Fc region to remove FcR binding capability of the ADCC/ADCVI NAbs or ADCC/ADCVI nNAbs will result in the loss of ADCC and/or ADCVI activity(s). For example in an in vitro study, Fc mutated variants of wildtype (wt) ADCC-mediating bNAb (b12) retained potent viral neutralization activity similar to wt bNAb but lost ADCC activity [77]. However, a group of macaques passively immunized with wt bNAb b12 showed significant passive protection against SHIV challenge [78]. In comparison, the group passively immunized with Fc-mutant variant of wt b12 with diminished FcR binding potential had a significant loss in passive protection. The authors concluded that both bNAb activity and Fc-mediated activity(s) (ADCC, ADCVI) have synergist or additive effect on the protection against SHIV challenge.

NK cells, macrophages, dendritic cells, and neutrophils are the effector cells with FcRIIIa (CD16a) to mediate IgG-based ADCC activity [55,76]. ADCC antibodies target either linear or conformational epitopes on gp120 and gp41 [74]. In the RV144 trial, the nNAbs to the epitopes on V1V2 and C1 protein regions possessed ADCC activity which correlated with the modest protection observed in the vaccinated/protected subjects [7–9]. More specifically, the anti-V1V2 nNAbs with IgG3 subclass directly correlated with protection [8]. Although gp120 and gp41 are the predominant targets for ADCC antibodies [74], few studies have reported ADCC nNAbs to non-Env epitopes such as those on HIV Pol [79], Nef [80], and Vpu [81]. Nef [82–84] and part of Vpu [81,85] were reported to be present on the surface of HIV-infected cells, but such studies have not been reported for Pol [79]. Furthermore, serum from infected individuals showed a strong ADCC activity against a highly conserved, surface accessible linear Nef epitope (FLKEKGGLE) [80,84]. Overall, more studies will be needed to determine the importance of ADCC nNAbs to these HIV non-Env proteins.

Some nNAbs have been reported to enhance HIV infection by complement-mediated enhancement [86,87] or by FcR-mediated infection of dendritic cells and macrophages [33,88]. Whereas others may increase transcytosis of HIV-antibody IgG complex using FcR and DC-SIGN across the cell to present the HIV to the susceptible cells such as CD4+ T cells [89,90]. The binding of HIV-antibody complex to neonatal FcR (FcRn) on vaginal epithelial cells has been shown to enhance the transcytosis of HIV at low pH at the endosomal compartment [91], and these authors proposed that the FcRn detected in the genital tract may enhance the sexual transmission of HIV. In the RV144 trial, Env-specific blocking IgA nNAbs reduced the ADCC activity of the Env-specific IgG nNAbs by competing for the same epitope(s) [7,10]. Hence, an effective HIV vaccine should not induce HIV Env-specific blocking antibodies that will decrease the anti-HIV effects of ADCC and ADCVI antibodies or will decrease viral neutralization activity of the type-specific NAbs and bNAbs against HIV. The existence of enhancing and blocking Env-specific nNAbs suggests that a careful selection of protective B-cell epitopes on HIV Env may be needed for an effective HIV vaccine.

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Conserved T-cell epitopes associated with anti-HIV activity(s)

Conserved HIV T-cell epitopes for an effective HIV vaccine should induce broad (multiple subtype specificities) and potent (high magnitude) immunity against HIV. Conserved epitopes are often subdominant epitopes since excessive immunity against them or mutations will affect the fitness of the virus [92, 93]. In addition, the immune responses to the dominant non-protective epitopes could potentially mask the immune responses to the protective conserved epitopes in a vaccinated host. Therefore, a vaccine consisting of only protective conserved epitopes may be ideal for an effective prophylaxis. During early HIV infection, ART-naïve HIV+ subjects initially produced CD8+ T-cell responses to predominantly variable epitopes than to conserved epitopes [94]. Conserved epitopes were identified more predominately on Gag and Pol than on Env, Nef and accessory proteins [94–97]. Those HIV+ individuals who controlled HIV infection possessed CD8+ T-cell responses to conserved epitopes on Gag but not to those present on Pol [94]. Moreover, CD8+ T-cell responses to multiple conserved epitopes correlated with lower viral load set point. However, only a trend in lower viral load set point was observed in individuals possessing favorable HLA class-I alleles (e.g., HLA-B*27, HLA-B*57 [98]). Individuals who possess favorable HLA alleles are reported to undergo slow HIV/AIDS disease progression [98, 99].

The conserved T-cell epitopes must be able to induce potent CD8+ CTL [34, 35], polyfunctional CD8+ and CD4+ T-cell [100, 101], and possibly CD4+ CTL [102] activities against HIV. These anti-HIV T-cell activities are considered to be important for vaccine prophylaxis based on the findings from HIV+ long-term non-progressor (LTNP) and elite controllers [103, 104], RV144 trial [101], and NHP studies [105, 106]. Less than 1% of the HIV+ subjects are elite controllers who have <50 copies/mL of circulating HIV, normal CD4+ T-cell counts, and are clinically asymptomatic [107, 108]. Elite controllers maintain potent CD8+ CTL and polyfunctional T-cell responses against HIV [107, 109] but no bNAb and, if present, only a slight level of NAb which alone cannot explain the undetectable levels of circulating HIV [110]. Polyfunctional T-cell responses include the production of cytokines and chemokines that inhibit HIV infection [22, 111]. In particular, CD8+ CTLs in elite controllers produce higher levels of IL-2 and co-secretion of IL-2 and IFNγ but possess minimal breadth and level of IFNγ alone [22, 110]. LTNP also generate CD8+ CTLs [25] and non-lytic CD8+ T-cell antiviral factors (CAF) for the suppression of HIV replication [112].

In the modestly successful RV144 trial, the polyfunctional T-cell responses consisted of antigen-specific upregulation of IFNγ and IL-2 followed by TNF and IL-21 [101]. Some of these polyfunctional T cells also expressed CD107a, a marker for degranulation typically on CTLs. Furthermore, biological CTL analysis demonstrated the presence of anti-Env(V2) CD4+ CTLs. Notably, no CD8+ CTL activity was detected against HIV, whereas an earlier study using the same vaccine regimen showed CD8+ CTL activity against Env and Gag/Pol in 24% of the vaccines [113]. Recently, individuals with acute HIV infection were reported to have HIV-specific CD4+ CTLs with perforin/IFNγ or GrzA/IFNγ co-expression [102]. This study associates the early presence of CD4+ CTLs with slow disease progression.
A recent study demonstrated the importance of a vaccine capable of inducing CD8+ CTLs against a simian AIDS lentivirus, SIV. In this study, all macaques immunized with cytomegalovirus (CMV)-vectored SIV vaccine were positive for SIV infection shortly after the challenge with homologous SIV \[105,106\]. However, 50% of the vaccinated/infected macaques developed a transient infection which was completely cleared by CD8+ CTLs against SIV. This study demonstrates that at the early stage of infection, CD8+ CTLs can destroy and eliminate virus-infected cells. Moreover, this study establishes the importance of a vaccine inducing CD8+ CTLs for prophylaxis and immunotherapy.

**Conserved T-cell epitopes associated with protective HLA allotypes prevalent in HIV endemic countries**

The T-cell epitopes bound to HLA class I and II molecules are recognized by the TCRs on CD8+ and CD4+ T cells, respectively to exert their function(s). Certain HLA allotypes (i.e., proteins expressed by HLA allele) confer resistance to HIV infection, while certain others increase susceptibility to the HIV infection [114–117]. HIV-resistant and -susceptible alleles may differ according to the race of the subjects and the circulating HIV subtype(s) prevailing in the endemic country. Alleles of HLA-A and HLA-B have been further classified into supertypes based on the similarity in their structural motif and their pocket chemical specificity to the peptides [118]. HLA alleles of supertype A2 such as HLA-A2, HLA-A*0205, HLA-A*6802 are associated with resistance to HIV subtype B in Caucasians from Europe and North America [119] and to the HIV subtypes A, C, and D in African population from Kenya and Tanzania of Sub-Sahara Africa (Table 3) [114–116,120]. Conversely, HLA alleles of supertype B7 such HLA-B*3501, HLA-B*3502 and HLA-B*5303 are associated with increased susceptibility to subtype-B HIV in Europe and North America [119], whereas supertype B7 alleles such as HLA-B*0702 and HLA-B*4201 are associated with increased susceptibility to HIV subtypes A, C, and D circulating in Kenya [117]. These alleles are not the only ones associated with increased susceptibility in Sub-Sahara Africa. HLA-A*2301 (supertype A24) in Kenya [114,117] and HLA-C*0702 in Tanzania [116] are also associated with increased susceptibility to HIV transmission.

Additionally, certain HLA allotypes correlate with slow disease progression, while certain others correlate with a rapid progression of the disease as determined by virus load, CD4+ T-cell count, and/or disease status [98,99]. HLA alleles associated with slow disease progression in Europe, North America, and Sub-Sahara Africa are members of supertype A3 (HLA-A*74, HLA-A*7401), supertype B27 (HLA-B*14), and supertype B58 (HLA-B*57, HLA-B*5703) and few other alleles (HLA-B*8101, C*1203, C*18, C*1801) (Table 4) [116,117,121–127]. Interestingly, these alleles are not the same ones associated with resistance to HIV. Similar to HLA alleles associated with elevated susceptibility to HIV, alleles in HLA supertype B7 are found in individuals with rapid HIV-disease progression, but the specific alleles are not always the same between the HIV-susceptible and the rapid HIV progression groups. In fact, the HLA alleles related with rapid HIV progression commonly found in Europe, North America, and Sub-Sahara Africa are HLA-B*07, B*0702, B*3501, B*3502, B*3503, and B*5301 of HLA supertype B7, and HLA-B*08 and HLAB-0801 of HLA supertype B8 [122,128–130] (Table 4). HLA-B*8101 which belongs to

*J Clin Cell Immunol.* Author manuscript; available in PMC 2017 December 07.
supertype B7 presents an anomaly to the trend of unfavorable alleles belonging to HLA supertype B7. HLA-B*8101 is associated with resistance to HIV infection in African Americans of North America \cite{122} and Africans of Sub-Sahara Africa (South Africa, Botswana, Zimbabwe, Zambia) \cite{125,127}.

The HIV transmission studies evaluating resistant versus susceptible HLA alleles may help identify HIV epitopes and their corresponding immunity required for prophylaxis. In contrast, studies evaluating the control of the HIV infection in HIV+ subjects in terms of slow or rapid HIV progression may identify HIV epitope recognition and immunity more important for immunotherapy. In any event, the T-cell epitopes on HIV identified by these approaches should be tested for their ability to induce potent and broad anti-HIV T-cell activities.

Antibodies and T-cell responses enhancing HIV infection

Non-protective T-cell epitopes can induce either neutral or enhancing effect on HIV infection. For instance, stimulation of CD4+ T cells can cause enhancement of HIV infection \cite{131–133}. Autocrine and paracrine cytokine signaling, especially from TNF and IFN\(\gamma\) could increase in viral gene transcription simultaneously with the activation of CD4+ T-cells via NF-\(\kappa\)B pathway \cite{134–137}. Activated CD4+ T cells express high levels of HIV co-receptor CCR5 which in turn together with the primary receptor CD4 molecule will make the cell more susceptible to HIV infection \cite{137}. The stimulation of CD4+ regulatory T cells (Treg) can have opposing effects on HIV infection. Treg cells can suppress anti-HIV CD8+ CTL activity which in turn will increase HIV infection \cite{138}, whereas Treg cells can suppress the production of inflammatory cytokines such as TNF and IFN\(\gamma\) which could decrease HIV viral replication by decreasing CD4+ T-cell activation \cite{139,140}. In Step and Phambili trials, T cell-based (non-Env) vaccine caused enhancement of HIV infection (Tables 1 and 5) \cite{12–14,21}. Furthermore, vaccine-induced enhancement upon SIV challenge was observed in NHPs vaccinated with SIV Env protein \cite{141}. However, such enhancement was reported to be caused by CD4+ T-cell responses. In another animal AIDS model, FIV Env vaccination of cats enhanced challenge infection with FIV \cite{142,143}. In the RV144 trial, Env-specific IgA antibodies decreased the ADCC activity of Env-specific IgG \cite{5,8}. Therefore, an ideal vaccine should limit unwanted CD4+ T cell activation and non-specific cytokine production to minimize viral replication, whereas it should activate potent anti-HIV effector activities such those of anti-HIV CTL, anti-HIV polyfunctional T-cells, and bNAb/NAb/ADCC antibodies \cite{132}.

Conclusion

Conserved T-cell and B-cell epitopes with potent anti-HIV activity for HIV vaccine

As discussed above, significant progress has been made to identify the protective B-cell and T-cell epitopes for a highly effective HIV vaccine. Such HIV vaccine should consist predominantly of anti-HIV conserved T-cell epitopes (Table 5B) and selected B-cell epitopes that induce bNabs, NAbs, and ADCC/ADCVI antibodies (Table 5A) with exclusion of HIV-enhancing epitopes. To this end, studies are in progress using HIV mosaic vaccines consisting of anti-HIV conserved T-cell epitopes and epitope regions rather than whole HIV
proteins which may contain enhancing epitopes [45,46,144–147]. The development of conformational B-cell epitopes that induce bNAbs appears to be a major task since Env vaccine epitopes for bNAbs are still unavailable [31,34,56,57]. Concerted efforts have been made in developing Env trimers. However, current whole-Env trimer constructs still contain HIV-enhancing epitopes such as epitopes for blocking antibodies and T-cell epitopes that stimulate immunodominant responses without anti-HIV activity(s) while masking the subdominant protective responses. Consequently, if the trimer immunogen does not induce potent bNAbs as well as potent NAbs to multiple subtypes then HIV-enhancing epitopes and non-protective HIV immunodominant epitopes can counteract the potency of these antibodies, and the vaccine efficacy may not be detected such as those observed in VAX003 and VAX004 trials. Hence, the selection of minimally-constructed protective epitopes (without enhancing epitopes) is required.

Until minimally constructed, highly potent bNAb conformational epitopes become available, the use of bNAb linear epitopes (e.g., MPER) and most potent NAb linear epitopes from multiple subtypes (A,B,C) should be combined as mosaic vaccine and tested in SHIV/macaque model. Finally, besides bNAbs and type-specific NAbs, every effort should be made to include other conserved B-cell epitopes such as those that induce potent and broad ADCC/ADCVI antibodies as well as conserved T-cell epitopes that induce potent and broad anti-HIV polyfunctional T-cell responses and anti-HIV CD8+ and CD4+ CTLs. T cell-based conserved-mosaic vaccines were shown to enhance the breadth and potency of epitope recognition [147]. In another study, short conserved HIV epitopes devoid of immunodominant epitopes were shown to increase immunogenicity and to shift the immunodominance [148]. The RV144 trial is considered to be the first effort to combine B-cell and anti-HIV cellular immune effector activities (i.e., T cells and NK cells). More importantly, this trial is the only phase-III trial that demonstrated prophylactic efficacy although of modest level. In fact, the findings from this trial further support the contention that more anti-HIV immune effector activities are required to confer complete or sterilizing protection. In conclusion, an efficacious HIV vaccine may need to stimulate multitude of potent and broad immune effector activities against HIV in order to confer sterilizing protection against one of this century’s most challenging viral pathogen, HIV.

**Acknowledgments**

This work was supported by NIH R01-AI65276 (JKY), Miscellaneous Donors Fund (JKY), and Florida Department of Health, Biomedical Research Program (CQN, JKY).

**References**

1. UNAIDS. Global AIDS Update 2016. [http://www.who.int/hiv/pub/arv/global-AIDS-update-2016_en.pdf?ua=1](http://www.who.int/hiv/pub/arv/global-AIDS-update-2016_en.pdf?ua=1)
2. Siliciano JD, Siliciano RF. Recent developments in the effort to cure HIV infection: going beyond N = 1. J Clin Invest. 2016; 126:409–414. [PubMed: 26829622]
3. WHO. Progress Report 2016: Prevent HIV, test and treat all–WHO support for country impact. [http://www.who.int/hiv/pub/progressreports/2016-progress-report/en/](http://www.who.int/hiv/pub/progressreports/2016-progress-report/en/)
4. Pitisuttithum P, Gilbert P, Garwith M, Heyward W, Martin M, et al. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among
injection drug users in Bangkok, Thailand. J Infect Dis. 2006; 194:1661–1671. [PubMed: 17109337]
5. Flynn NM, Forthal DN, Harro CD, Judson FN, Mayer KH, et al. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis. 2005; 191:654–665. [PubMed: 15688278]
6. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009; 361:2209–2220. [PubMed: 19843557]
7. Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med. 2012; 366:1275–1286. [PubMed: 22475592]
8. Yates NL, Liao HX, Fong Y, deCamp A, Vandergrift NA, 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.
9. Gottardo R, Bailor RT, Korber BT, Gnanakaran S, Phillips J, et al. Plasma IgG to linear epitopes in the V2 and V3 regions of HIV-1 gp120 correlate with a reduced risk of infection in the RV144 vaccine efficacy trial. PLoS One. 2013; 8:e75665. [PubMed: 24086607]
10. Tomaras GD, Ferrari G, Shen X, Alam SM, Liao HX, 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 U S A. 2013; 110:9019–9024. [PubMed: 23661056]
11. Woof JM, Russell MW. Structure and function relationships in IgA. Mucosal Immunol. 2011; 4:590–597. [PubMed: 21937984]
12. Buchbinder SP, Mehrotra DV, Duerr A, FitzGerald DW, Mogg R, et al. Step Study Protocol Team. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet. 2008; 372:1881–1893. [PubMed: 19012954]
13. Gray GE, Allen M, Moodie Z, Churchyard G, Bekker LG, 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. 2011:507–515. [PubMed: 21570355]
14. Gray GE, Moodie Z, Metch B, Gilbert PB, Bekker LG, et al. Recombinant adenovirus type 5 HIV gag/pol/nef vaccine in South Africa: unblinded, long-term follow-up of the phase 2b HVTN 503/Phambili study. Lancet Infect Dis. 2014; 14:388–396. [PubMed: 24560541]
15. Koblin BA, Mayer KH, Noonan E, Wang CY, Marmor M, et al. Sexual risk behaviors, circumcision status, and preexisting immunity to adenovirus type 5 among men who have sex with men participating in a randomized HIV-1 vaccine efficacy trial: step study. J Acquir Immune Defic Syndr. 2012; 60:405–413. [PubMed: 22421748]
16. Chakupurakal G, Onion D, Cobbold M, Mautner V, Moss PA. Adenovirus vector-specific T cells demonstrate a unique memory phenotype with high proliferative potential and coexpression of CCR5 and integrin alpha4beta7. AIDS. 2010; 24:205–210. [PubMed: 19864932]
17. Masek-Hammerman K, Li H, Liu J, Abbink P, La Porte A, et al. Mucosal trafficking of vector-specific CD4+ T lymphocytes following vaccination of rhesus monkeys with adenovirus serotype 5. J Virol. 2010; 84:9810–9816. [PubMed: 20686023]
18. Benlahrech A, Harris J, Meiser A, Papagatsias T, Hornig J, et al. Adenovirus vector vaccination induces expansion of memory CD4 T cells with a mucosal homing phenotype that are readily susceptible to HIV-1. Proc Natl Acad Sci U S A. 2009; 106:19940–19945. [PubMed: 19918060]
19. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005; 2:e298. [PubMed: 16231970]
20. Bailey C, Moses S, Parker CB, Agot K, Maclean I, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. Lancet. 2007; 369:643–656. [PubMed: 17321310]
21. Huang Y, Duerr A, Frahm N, Zhang L, Moodie Z, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial reveals an association of nonspecific interferon-? secretion with increased
HIV-1 infection risk: a cohort-based modeling study. PLoS One. 2014; 9:e108631. [PubMed: 25369172]

Chanzu N, Ondondo B. Induction of potent and long-lived antibody and cellular immune responses in the genitofecal mucosa could be the critical determinant of HIV vaccine efficacy. Front Immunol. 2014; 5:202. [PubMed: 24847327]

McElrath MJ, De Rosa SC, Moodie Z, Dubey S, Kierstead L, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis. Lancet. 2008; 372:1894–1905. [PubMed: 19012957]

Ogg GS, Jin X, Bonhoeffer S, Dunbar PR, Nowak MA, et al. Quantitation of HIV-1-specific cytotoxic T lymphocytes and plasma load of viral RNA. Science. 1998; 279:2103–2106. [PubMed: 9516110]

Betts MR, Krowka JF, Kepler TB, Davidian M, Christopherson C, et al. Human immunodeficiency virus type 1-specific cytotoxic T lymphocyte activity is inversely correlated with HIV type 1 viral load in HIV type 1-infected long-term survivors. AIDS Res Hum Retroviruses. 1999; 15:1219–1228. [PubMed: 10480635]

Betts MR, Nason MC, West SM, De Rosa SC, Migueles SA, et al. HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. Blood. 2006; 107:4781–4789. [PubMed: 16467198]

Kiepiela P, Ngumbela K, Thobakgale C, Ramduth D, Honeyborne I, et al. CD8+ T-cell responses to different HIV proteins have discordant associations with viral load. Nat Med. 2007; 13:46–53. [PubMed: 17173051]

Mothe B, Llano A, Ibarrondo J, Zamarreno J, Schiaulini M, et al. CTL responses of high functional avidity and broad variant cross-reactivity are associated with HIV control. PLoS One. 2012; 7:e29717. [PubMed: 22238642]

Streeck H, Lu R, Beckwith N, Milazzo M, Liu M, et al. Emergence of individual HIV-specific CD8 T cell responses during primary HIV-1 infection can determine long-term disease outcome. J Virol. 2014; 88:12793–12801. [PubMed: 25165102]

Wu X, Kong XP. Antigenic landscape of the HIV-1 envelope and new immunological concepts defined by HIV-1 broadly neutralizing antibodies. Curr Opin Immunol. 2016; 42:56–64. [PubMed: 27289425]

McCoy LE, Burton DR. Identification and specificity of broadly neutralizing antibodies against HIV. Immunol Rev. 2017; 275:11–20. [PubMed: 28133814]

Pegu A, Hessell AJ, Mascola JR, Haigwood NL. Use of broadly neutralizing antibodies for HIV-1 prevention. Immunol Rev. 2017; 275:296–312. [PubMed: 28133803]

Su B, Moog C. Which Antibody Functions are Important for an HIV Vaccine? Front Immunol. 2014; 5:289. [PubMed: 24995008]

Korber B, Hraber P, Wagh K, Hahn BH. Polyvalent vaccine approaches to combat HIV-1 diversity. Immunol Rev. 2017; 275:230–244. [PubMed: 28133800]

Hanke T. Conserved immunogens in prime-boost strategies for the next-generation HIV-1 vaccines. Expert Opin Biol Ther. 2014; 14:601–616. [PubMed: 24490585]

Lewis GK, DeVico AL, Gallo RC. Antibody persistence and T-cell balance: two key factors confronting HIV vaccine development. Proc Natl Acad Sci U S A. 2014; 111:15614–15621. [PubMed: 25349379]

Sela-Culang I, Kunik V, Ofran Y. The structural basis of antibody-antigen recognition. Front Immunol. 2013; 4:302. [PubMed: 24115948]

Wang LD, Clark MR. B-cell antigen-receptor signalling in lymphocyte development. Immunology. 2003; 110:411–420. [PubMed: 14632637]

Dyson HJ, Wright PE. Antigenic peptides. FASEB J. 1995; 9:37–42. [PubMed: 7821757]

Nielsen M, Marcutilli P. Prediction of Antibody Epitopes. Methods Mol Biol. 2015; 1348:23–32. [PubMed: 26424260]

Cerutti N, Loredo-Varela JL, Caillat C, Weissenhorn W. Antigp41 membrane proximal external region antibodies and the art of using the membrane for neutralization. Curr Opin HIV AIDS. 2017; 12:250–256. [PubMed: 28422789]
42. Yoon H, Macke J, West AP Jr, Foley B, Bjorkman PJ, et al. CATNAP: a tool to compile, analyze and tally neutralizing antibody panels. Nucleic Acid Res. 2015; 43:W213–W219. [PubMed: 26044712]

43. Burton DR, Mascola JR. Antibody responses to envelope glycoproteins in HIV-1 infection. Nat Immunol. 2015; 16:571–576. [PubMed: 25988889]

44. Létourneau S, Im EJ, Mashishi T, Brereton C, Bridgeman A, et al. Design and pre-clinical evaluation of a universal HIV-1 vaccine. PLoS One. 2007; 2:e984. [PubMed: 17912361]

45. Ondondo B, Murakoshi H, Clutton G, Abdul-Jawad S, Wee EG, et al. Novel Conserved-region T-cell Mosaic Vaccine With High Global HIV-1 Coverage Is Recognized by Protective Responses in Untreated Infection. Mol Ther. 2016; 24:832–42. [PubMed: 26743582]

46. Fischer W, Perkins S, Theiler J, Bhattacharya T, Yusim K, et al. Polyvalent vaccines for optimal coverage of potential T-cell epitopes in global HIV-1 variants. Nat Med. 2007; 13:100–106. [PubMed: 17187074]

47. Sanou MP, Roff SR, Mennella A, Sleasman JW, Rathore MH, et al. Evolutionarily conserved epitopes on human immunodeficiency virus type 1 (HIV-1) and feline immunodeficiency virus reverse transcriptases detected by HIV-1-infected subjects. J Virol. 2013; 87:10004–10015. [PubMed: 23824804]

48. Roff SR, Sanou MP, Rathore MH, Levy JA, Yamamoto JK. Conserved epitopes on HIV-1, FIV and SIV p24 proteins are recognized by HIV-1 infected subjects. Hum Vaccin Immunother. 2015; 11:1540–1556. [PubMed: 25844718]

49. Ferguson AL, Mann JK, Omarjee S, Ndung'u T, Walker BD, et al. Translating HIV sequences into quantitative fitness landscapes predicts viral vulnerabilities for rational immunogen design. Immunity. 2013; 38:606–617. [PubMed: 23521886]

50. Leslie AJ, Pfafferott KJ, Chetty P, Draenert R, Addo MM, et al. HIV evolution: CTL escape mutation and reversion after transmission. Nat Med. 2004; 10:282–289. [PubMed: 14770175]

51. Borthwick N, Ahmed T, Ondondo B, Hayes P, Rose A, et al. Vaccine-elicited human T cells recognizing conserved protein regions inhibit HIV-1. Mol Ther. 2014; 22:464–475. [PubMed: 24166483]

52. Hraber P, Seaman MS, Bailer RT, Mascola JR, Montefiori DC, et al. Prevalence of broadly neutralizing antibody responses during chronic HIV-1 infection. AIDS. 2014; 28:163–169. [PubMed: 24361678]

53. Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, et al. The 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; 85:4828–4840. [PubMed: 21389135]

54. Gohain N, Tolbert WD, Orlandi C. Molecular basis for epitope recognition by non-neutralizing anti-gp41 antibody F240. Sci Rep. 2016; 6:36685. [PubMed: 27827447]

55. Boesch AW, Brown EP, Ackerman ME. The role of Fc receptors in HIV prevention and therapy. Immunol Rev. 2015; 268:296–310. [PubMed: 26497529]

56. Burton DR, Hangartner L, et al. Broadly Neutralizing Antibodies to HIV and Their Role in Vaccine Design. Annu Rev Immunol. 2016; 34:635–659. [PubMed: 27168247]

57. Haynes BF, Kelsoe G, Harrison SC, Kepler TB. B-cell-lineage immunogen design in vaccine development with HIV-1 as a case study. Nat Biotechnol. 2012; 30:423–433. [PubMed: 22565972]

58. Sundling C, O’Dell S, Douagi I, Forsell MN, Mörrn A, et al. Immunization with wild-type or CD4-binding-defective HIV-1 Env trimers reduces viremia equivalently following heterologous challenge with simian-human immunodeficiency virus. J Virol. 2010; 84:9086–9095. [PubMed: 20610729]

59. Sundling C, Forsell MN, O’Dell S, Feng Y, Chakrabarti B, et al. Soluble HIV-1 Env trimers in adjuvant elicit potent and diverse functional B cell responses in primates. J Exp Med. 2010; 207:2003–2017. [PubMed: 20679401]

60. Binley JM, Lybarger EA, Crooks ET, Seaman MS, Gray E, et al. Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically infected with human immunodeficiency virus type 1 subtypes B and C. J Virol. 2008; 82:11651–11668. [PubMed: 18815292]
61. Kelsoe G, Haynes BF. Host controls of HIV broadly neutralizing antibody development. Immunol Rev. 2017; 275:79–88. [PubMed: 28133807]

62. Wibmer CK, Moore PL, Morris L. HIV broadly neutralizing antibody targets. Curr Opin HIV AIDS. 2015; 10:135–143. [PubMed: 25760932]

63. Moore PL, Williamson C, Morris L. Virological features associated with the development of broadly neutralizing antibodies to HIV-1. Trends Microbiol. 2015; 23:204–211. [PubMed: 25572881]

64. Wibmer CK, Bhiman JN, Gray ES, Tumba N, Abdool Karim SS. Viral escape from HIV-1 neutralizing antibodies drives increased plasma neutralization breadth through sequential recognition of multiple epitopes and immunotypes. PLoS Pathog. 2013; 9:e1003738. [PubMed: 24204277]

65. Bonsignori M, Montefiori DC, Wu X, Chen X, Hwang KK, et al. Two distinct broadly neutralizing antibody specificities of different clonal lineages in a single HIV-1-infected donor: implications for vaccine design. J Virol. 2012; 86:4688–4692. [PubMed: 22301150]

66. Mikell I, Stamatakis L. Evolution of cross-neutralizing antibody specificities to the CD4-BS and the carbohydrate cloak of the HIV Env in an HIV-1-infected subject. PLoS One. 2012; 7:e49610. [PubMed: 23152926]

67. Klein F, Gaebler C, Mouquet H, Sather DN, Lehmann C, et al. Broad neutralization by a combination of antibodies recognizing the CD4 binding site and a new conformational epitope on the HIV-1 envelope protein. J Exp Med. 2012; 209:1469–1479. [PubMed: 22826297]

68. Gao F, Bonsignori M, Liao HX, Kumar A, Xia SM, et al. Cooperation of B cell lineages in induction of HIV-1-broadly neutralizing antibodies. Cell. 2014; 158:481–491. [PubMed: 25065977]

69. Scheid JF, Mouquet H, Ueberheide B, Diskin R, Klein F, et al. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. Science. 2011; 333:1633–163. [PubMed: 21764753]

70. Wu X, Zhou T, Zhu J, Zhang B, Georgiev I, et al. Focused evolution of HIV-1 neutralizing antibodies revealed by structures and deep sequencing. Science. 2011; 333:1593–1602. [PubMed: 21835983]

71. Hessell AJ, Rakasz EG, Tehrani DM, Huber M, Weisgrau KL, et al. Broadly neutralizing monoclonal antibodies 2F5 and 4E10 directed against the human immunodeficiency virus type 1 gp41 membrane-proximal external region protect against mucosal challenge by simian-human immunodeficiency virus SHIVBa-L. J Virol. 2010; 84:1302–1313. [PubMed: 19906907]

72. Forthal DN, Moog C. Fc receptor-mediated antiviral antibodies. Curr Opin HIV AIDS. 2009; 4:388–393. [PubMed: 20048702]

73. Moldt B, Schultz N, Dunlop DC, Alpert MD, Harvey JD, et al. A panel of IgG1 b12 variants with selectively diminished or enhanced affinity for Fc? receptors to define the role of effector functions in protection against HIV. J Virol. 2011; 85:10572–10581. [PubMed: 21849450]

74. Isitman G, Chung AW, Navis M, Kent SJ, Stratov I. Pol as a target for antibody dependent cellular cytotoxicity responses in HIV-1 infection. Virology. 2011; 412:110–116. [PubMed: 21269655]
80. Yamada T, Watanabe N, Nakamura T, Iwamoto A. Antibody-dependent cellular cytotoxicity via humoral immune epitope of Nef protein expressed on cell surface. J Immunol. 2004; 172:2401–2406. [PubMed: 14764710]

81. Wren LH, Chung AW, Isitman G, Kelleher AD, Parsons MS, et al. Specific antibody-dependent cellular cytotoxicity responses associated with slow progression of HIV infection. Immunology. 2013; 138:116–123. [PubMed: 23173935]

82. Fujii Y, Nishino Y, Nakaya T, Tokunaga K, Ikuta K. Expression of human immunodeficiency virus type 1 Nef antigen on the surface of acutely and persistently infected human T cells. Vaccine. 1993; 11:1240–1246. [PubMed: 8898107]

83. Fujii Y, Otake K, Fujita Y, Yamamoto N, Nagai Y, et al. Clustered localization of oligomeric Nef protein of human immunodeficiency virus type 1 on the cell surface. FEBS Lett. 1996; 395:257–261. [PubMed: 8893047]

84. Yamada T, Iwamoto A. Expression of a novel Nef epitope on the surface of HIV type 1-infected cells. AIDS Res Hum Retroviruses. 1999; 15:1001–1009. [PubMed: 10445812]

85. Kramski M, Stratov I, Kent SJ. The role of HIV-specific antibody-dependent cellular cytotoxicity in HIV prevention and the influence of the HIV-1 Vpu protein. AIDS. 2015; 29:137–144. [PubMed: 25396265]

86. Robinson WE Jr, Montefiori DC, Mitchell WM. A human immunodeficiency virus type 1 (HIV-1) infection-enhancing factor in seropositive sera. Biochem Biophys Res Commun. 1987; 149:693–699. [PubMed: 3426595]

87. Robinson WE Jr, Montefiori DC, Mitchell WM. Antibody-dependent enhancement of human immunodeficiency virus type 1 infection. Lancet. 1988; 1:790–794. [PubMed: 2895317]

88. Homsy J, Meyer M, Tateno M, Clarkson S, Levy JA. The Fc and not CD4 receptor mediates antibody enhancement of HIV infection in human cells. Science. 1989; 244:1357–1360. [PubMed: 2786647]

89. van Montfort T, Nabatov AA, Geijtenbeek TB, Pollakis G, Paxton WA. Efficient capture of antibody neutralized HIV-1 by cells expressing DC-SIGN and transfer to CD4+ T lymphocytes. J Immunol. 2007; 78:3177–3185.

90. Baan E, de Ronde A, Stax M, Sanders RW, Luchters S, et al. HIV-1 autologous antibody neutralization associates with mother to child transmission. PLoS One. 2013; 8:e69274. [PubMed: 23874931]

91. Gupta S, Gach JS, Becerra JC, Phan TB, Pudney J, et al. The Neonatal Fc receptor (FcRn) enhances human immunodeficiency virus type 1 (HIV-1) transcytosis across epithelial cells. PLoS Pathog. 2013; 9:e1003776. [PubMed: 24278022]

92. Borthwick N, Lin Z, Akahoshi T, Llano A, Silva-Arrieta S, et al. Novel, in-natural-infection subdominant HIV-1 CD8+ T-cell epitopes revealed in human recipients of conserved-region T-cell vaccines. PLoS One. 2017; 12:e0176418. [PubMed: 2848594]

93. Karlsson I, Klawerpris H, Jensen KJ, Stryhn A, Buus S, et al. Identification of conserved subdominant HIV Type 1 CD8(+) T Cell epitopes restricted within common HLA Supertypes for therapeutic HIV Type 1 vaccines. AIDS Res Hum Retroviruses. 2012; 28:1434–1443. [PubMed: 22747336]

94. Kunwar P, Hawkins N, Dinges WL, Liu Y, Gabriel EE, et al. Superior control of HIV-1 replication by CD8+ T cells targeting conserved epitopes: implications for HIV vaccine design. PLoS One. 2013; 8:e64405. [PubMed: 23741326]

95. Sáez-Cirió A, Sinet M, Shin SY, Urrutia A, Versmisse P, et al. Heterogeneity in HIV suppression by CD8 T cells from HIV controllers: association with Gag-specific CD8 T cell responses. J Immunol. 2009; 182:7828–7837. [PubMed: 19494307]

96. Edwards BH, Bansal A, Sabbaj S, Bakari J, Mulligan MJ, et al. Magnitude of functional CD8+ T-cell responses to the gag protein of human immunodeficiency virus type 1 correlates inversely with viral load in plasma. J Virol. 2002; 76:2298–2305. [PubMed: 11836408]

97. Klein MR, van Baalen CA, Holwerda AM, Kerkhof Garde SR, Bende RJ, et al. Kinetics of Gag-specific cytotoxic T lymphocyte responses during the clinical course of HIV-1 infection: a longitudinal analysis of rapid progressors and long-term asymptomatics. J Exp Med. 1995; 181:1365–1372. [PubMed: 7699324]
98. Goulder PJ, Walker BD. HIV and HLA class I: an evolving relationship. Immunity. 2012; 37:426–440. [PubMed: 22999948]

99. Stephens HA. Immunogenetic surveillance of HIV/AIDS. Infect Genet Evol. 2012; 12:1481–1491. [PubMed: 22575339]

100. Samri A, Bacchus-Souffan C, Hocqueloux L, Avetand-Fenoel V, Descours B, et al. Polyfunctional HIV-specific T cells in Post-Treatment Controllers. AIDS. 2016 Sep 24; 30(15): 2299–302. [PubMed: 27428742]

101. de Souza MS, Ratto-Kim S, Chuenarom W, Schuetz A, Avettand-Fenoel V, et al. The Thai phase III trial (RV144) vaccine regimen induces T cell responses that preferentially target epitopes within the V2 region of HIV-1 envelope. J Immunol. 2012; 188:5166–5176. [PubMed: 22529301]

102. Soghoian DZ, Jessen H, Flanders M, Sierradavidson K, Cutler S, et al. HIV-specific cytolytic CD4 T cell responses during acute HIV infection predict disease outcome. Sci Transl Med. 2012; 4:123ra25.

103. Zaunders J, van Bockel D. Innate and Adaptive Immunity in Long-Term Non-Progression in HIV Disease. Front Immunol. 2013; 4:95. [PubMed: 23630526]

104. Buckheit RW 3rd, Siliciano RF, Blankson JN. Primary CD8+ T cells from elite suppressors effectively eliminate non-productively HIV-1 infected resting and activated CD4+ T cells. Retrovirology. 2013; 10:68. [PubMed: 23816179]

105. Hansen SG, Piatak M Jr, Ventura AB, Hughes CM, Gilbride RM, et al. Immune clearance of highly pathogenic SIV infection. Nature. 2013; 502:100–104. [PubMed: 24025770]

106. Hansen SG, Sacha JB, Hughes CM, Ford JC, Burwitz BJ, et al. Cytomegalovirus vectors violate CD8+ T cell epitope recognition paradigms. Science. 2013; 340:1237874. [PubMed: 23704576]

107. O’Connell KA, Bailey JR, Blankson JN. Elucidating the elite: mechanisms of control in HIV-1 infection. Trends Pharmacol Sci. 2009; 30:631–637. [PubMed: 19837464]

108. Pereyra F, Palmer S, Miura T, Block BL, Wiegand A, et al. Persistent low-level viremia in HIV-1 elite controllers and relationship to immunologic parameters. J Infect Dis. 2009; 200:984–990. [PubMed: 19656066]

109. Owen RE, Heitman JW, Hirschkorn DF, Lanteri MC, Biswas HH, et al. HIV+ elite controllers have low HIV-specific T-cell activation yet maintain strong, polyfunctional T-cell responses. AIDS. 2010; 24:1095–1105. [PubMed: 20400885]

110. Pereyra F, Addo MM, Kaufmann DE, Liu Y, Miura T, et al. Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. J Infect Dis. 2008; 197:563–571. [PubMed: 18275276]

111. Makedonas G, Betts MR. Polyfunctional analysis of human T cell responses: importance in vaccine immunogenicity and natural infection. Springer Semin Immunopathol. 2006; 28:209–219. [PubMed: 16932955]

112. Barker E, Mackewicz CE, Reyes-Terán G, Sato A, Stranford SA, et al. Virological and immunological features of long-term human immunodeficiency virus-infected individuals who have remained asymptomatic compared with those who have progressed to acquired immunodeficiency syndrome. Blood. 1998; 92:3105–3114. [PubMed: 9787145]

113. Nitayaphan S, Pisitsittithum P, Karnasuta C, Eamsila C, de Souza M, et al. Safety and immunogenicity of an HIV subtype B and E prime-boost vaccine combination in HIV-negative Thai adults. J Infect Dis. 2004; 190:702–706. [PubMed: 15272397]

114. MacDonald KS, Fowke KR, Kimani J, Dunand VA, Nagelkerke NJ, et al. Influence of HLA supertypes on susceptibility and resistance to human immunodeficiency virus type 1 infection. J Infect Dis. 2000; 181:1581–1589. [PubMed: 10823757]

115. MacDonald KS, Embree JE, Nagelkerke NJ, Castillo J, Ramhadin S, et al. The HLA A2/6802 superotype is associated with reduced risk of perinatal human immunodeficiency virus type 1 transmission. J Infect Dis. 2001; 183:503–506. [PubMed: 11133384]

116. Koehler RN, Walsh AM, Saathoff E, Tovananbutra S, Arroyo MA, et al. Class I HLA-A*7401 is associated with protection from HIV-1 acquisition and disease progression in Mbeya, Tanzania. J Infect Dis. 2010; 202:1562–1566. [PubMed: 20923372]
117. Peterson TA, Kimani J, Wachihi C, Bielawny T, Mendoza L, et al. HLA class I associations with rates of HIV-1 seroconversion and disease progression in the Pumwani Sex Worker Cohort. Tissue Antigens. 2013; 81:93–107. [PubMed: 23330720]

118. Sidney J, Peters B, Frahm N, Brander C, Sette A. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008; 9:1. [PubMed: 18211710]

119. Liu C, Carrington M, Kaslow RA, Gao X, Rinaldo CR, et al. Association of polymorphisms in human leukocyte antigen class I and transporter associated with antigen processing genes with resistance to human immunodeficiency virus type 1 infection. J Infect Dis. 2003; 187:1404–1410. [PubMed: 12717621]

120. Farquhar C, Rowland-Jones S, Mbopi-Ngacha D, Redman M, Lohman B, et al. Human leukocyte antigen (HLA) B*18 and protection against mother-to-child HIV type 1 transmission. AIDS Res Hum Retroviruses. 2004; 20:692–697. [PubMed: 15307911]

121. Kaslow RA, Carrington M, Apple R, Park L, Muñoz A, et al. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. Nat Med. 1996; 2:405–411. [PubMed: 8597949]

122. Pereyra F, Jia X, McLaren PJ, Teleni A, et al. International HIV Controllers Study. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. Science. 2010; 330:1551–1557. [PubMed: 21051598]

123. Lazaryan A, Song W, Lobashevsky E, Tang J, Shrestha S, et al. HIV Epidemiology Research Study Group; Reaching for Excellence in Adolescent Care and Health Study Group. The influence of human leukocyte antigen class I alleles and their population frequencies on human immunodeficiency virus type 1 control among African Americans. Hum Immunol. 2011; 72:312–318. [PubMed: 21262311]

124. Tang J, Tang S, Lobashevsky E, Myracle AD, Fideli U. Favorable and unfavorable HLA class I alleles and haplotypes in Zambians predominantly infected with clade C human immunodeficiency virus type 1. J Virol. 2002; 76:8276–8284. [PubMed: 12134033]

125. Tang J, Malhotra R, Song W, Brill I, Hu L, et al. Human leukocyte antigens and HIV type 1 viral load in early and chronic infection: predominance of evolving relationships. PLoS One. 2010; 5:e9629. [PubMed: 20224785]

126. Leslie A, Matthews PC, Listgarten J, Carlson JM, Kadie C, et al. Additive contribution of HLA class I alleles in the immune control of HIV-1 infection. J Virol. 2010; 84:9879–9888. [PubMed: 20660184]

127. Carlson JM, Listgarten J, Pfeiffer N, Tan V, Kadie C, et al. Widespread impact of HLA restriction on immune control and escape pathways of HIV-1. J Virol. 2012; 86:5230–5243. [PubMed: 22379086]

128. Steel CM, Ludlam CA, Beatson D, Peutherer JF, Cuthbert RJ, et al. HLA haplotype A1 B8 DR3 as a risk factor for HIV-related disease. Lancet. 1988; 1:1185–1188. [PubMed: 2897006]

129. Gao X, Nelson GW, Karacki P, Martin MP, Phair J, et al. Effect of a single amino acid change in MHC class I molecules on the rate of progression to AIDS. N Engl J Med. 2001; 344:1668–1675. [PubMed: 11386265]

130. Baba M. Recent status of HIV-1 gene expression inhibitors. Antiviral Res. 2006; 71:301–306. [PubMed: 16488488]
136. Chan JK, Greene WC. Dynamic roles for NF-κB in HTLV-I and HIV-1 retroviral pathogenesis. Immunol Rev. 2012; 246:286–310. [PubMed: 22435562]

137. Ostrowski MA, Justement SJ, Catanzaro A, Hallahan CA, Ehler LA, et al. Expression of chemokine receptors CXCR4 and CCR5 in HIV-1-infected and uninfected individuals. J Immunol. 1998; 161:3195–3201. [PubMed: 9743388]

138. Kinter A, McNally J, Riggin L, Jackson R, Roby G, et al. Suppression of HIV-specific T cell activity by lymph node CD25+ regulatory T cells from HIV-infected individuals. Proc Natl Acad Sci U S A. 2007; 104:3390–3395. [PubMed: 17360656]

139. Ipp H, Zemlin A. The paradox of the immune response in HIV infection: when inflammation becomes harmful. Clin Chim Acta. 2013; 416:96–99. [PubMed: 23228847]

140. Roff SR, Noon-Song EN, Yamamoto JK. The Significance of Interferon-γ in HIV-1 Pathogenesis, Therapy, and Prophylaxis. Front Immunol. 2014; 4:498. [PubMed: 24454311]

141. Staprans SI, Barry AP, Silvestri G, Safrit JT, Kozyr N, et al. Enhanced SIV replication and accelerated progression to AIDS in macaques primed to mount a CD4 T cell response to the SIV envelope protein. Proc Natl Acad Sci U S A. 2004; 101:13026–13031. [PubMed: 15326293]

142. Siebelink KH, Tijhaar E, Huisman RC, Huisman W, de Ronde A, et al. Enhancement of feline immunodeficiency virus infection after immunization with envelope glycoprotein subunit vaccines. J Virol. 1995; 69:3704–3711. [PubMed: 7745719]

143. Richardson J, Moralllon A, Baud S, Cuisinier AM, Sonigo P, et al. Enhancement of feline immunodeficiency virus (FIV) infection after DNA vaccination with the FIV envelope. J Virol. 1997; 71:9640–9649. [PubMed: 9371628]

144. Kong WP, Wu L, Wallstrom TC, Fischer W, Yang ZY, et al. Expanded breadth of the T-cell response to mosaic human immunodeficiency virus type 1 envelope DNA vaccination. J Virol. 2009; 83:2201–2215. [PubMed: 19109395]

145. Barouch DH, O'Brien KL, Simmons NL, King SL, Abbnick P, et al. Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys. Nat Med. 2010; 16:319–323. [PubMed: 20173752]

146. Santra S, Liao HX, Zhang R, Muldoon M, Watson S, et al. Mosaic vaccines elicit CD8+ T lymphocyte responses that confer enhanced immune coverage of diverse HIV strains in monkeys. Nat Med. 2010; 16:324–328. [PubMed: 20173754]

147. Ondondo B, Murakoshi H, Clutton G, Abdul-Jawad S, Wee EG, et al. Novel Conserved-region T-cell Mosaic Vaccine With High Global HIV-1 Coverage Is Recognized by Protective Responses in Untreated Infection. Mol Ther. 2016; 24:832–842. [PubMed: 26743582]

148. Yang OO, Ali A, Kasahara N, Faure-Kumar E, Bae JY, et al. Short conserved sequences of HIV-1 are highly immunogenic and shift immunodominance. J Virol. 2015; 89:1195–1204. [PubMed: 25378501]

149. Montefiori DC, Karnasuta C, Huang Y, Ahmed H, Gilbert P, et al. Magnitude and breadth of the neutralizing antibody response in the RV144 and Vax003 HIV-1 vaccine efficacy trials. J Infect Dis. 2012; 206:431–441. [PubMed: 22634875]

150. Chung AW, Ghebremichael M, Robinson H, Brown E, Choi I, et al. Polyfunctional Fc-effector profiles mediated by IgG subclass selection distinguish RV144 and VAX003 vaccines. Sci Transl Med. 2014; 6:228ra38.

151. Gilbert PB, Peterson ML, Follmann D, Hudgens MG, Francis DP, et al. Correlation between immunologic responses to a recombinant glycoprotein 120 vaccine and incidence of HIV-1 infection in a phase 3 HIV-1 preventive vaccine trial. J Infect Dis. 2005; 191:666–677. [PubMed: 15688279]

152. Forthal DN, Gilbert PB, Landucci G, Fan T. Recombinant gp120 vaccine-induced antibodies inhibit clinical strains of HIV-1 in the presence of Fc receptor-bearing effector cells and correlate inversely with HIV infection rate. J Immunol. 2007; 178:6596–6603. [PubMed: 17475891]

153. Jones NG, DeCamp A, Gilbert P, Peterson ML, Gurwith M, et al. AIDSVac immunization induces HIV-specific CD8+ T-cell responses in high-risk, HIV-negative volunteers who subsequently acquire HIV infection. Vaccine. 2009; 27:1136–1140. [PubMed: 19071176]
154. von Bredow B, Arias JF, Heyer LN, Moldt B, Le K, et al. Comparison of Antibody-Dependent Cell-Mediated Cytotoxicity and Virus Neutralization by HIV-1 Env-Specific Monoclonal Antibodies. J Virol. 2016; 90:6127–6139. [PubMed: 27122574]

155. Ferrari G, Pollara J, Kozink D, Harms T, Drinker M, et al. An HIV-1 gp120 envelope human monoclonal antibody that recognizes a C1 conformational epitope mediates potent antibody-dependent cellular cytotoxicity (ADCC) activity and defines a common ADCC epitope in human HIV-1 serum. J Virol. 2011; 85:7029–7036. [PubMed: 21543485]

156. Mujib S, Liu J, Rahman AKMN, Schwartz JA, Bonner P, et al. Comprehensive cross-clade characterization of antibody-mediated recognition, complement-mediated lysis and cell-mediated cytotoxicity of HIV-1 envelope specific antibodies towards the eradication of the HIV-1 reservoir. J Virol. 2017 JVI.00634-17.

157. Pham TN, Lukhele S, Dallaire F, Perron G, Cohen ÉA. Enhancing Virion Tethering by BST2 Sensitizes Productively and Latently HIV-infected T cells to ADCC Mediated by Broadly Neutralizing Antibodies. Sci Rep. 2016; 6:37225. [PubMed: 27853288]

158. Moog C, Dereuddre-Bosquet N, Teillaud JL, Biedma ME, Holl V, et al. Protective effect of vaginal application of neutralizing and nonneutralizing inhibitory antibodies against vaginal SHIV challenge in macaques. Mucosal Immunol. 2014; 7:46–56. [PubMed: 23591718]

159. Hezareh M, Hessell AJ, Jensen RC, van de Winkel JG, Parren PW. Effector function activities of a panel of mutants of a broadly neutralizing antibody against human immunodeficiency virus type 1. J Virol. 2001; 75:12161–12168. [PubMed: 11711607]

160. Tudor D, Bomsel M. The broadly neutralizing HIV-1 IgG 2F5 elicits gp41-specific antibody-dependent cell cytotoxicity in a Fc?RI-dependent manner. AIDS. 2011; 25:751–759. [PubMed: 21330910]

161. Ding S, Tolbert WD, Prévost J, Pacheco B, Coutu M, et al. A Highly Conserved gp120 Inner Domain Residue Modulates Env Conformation and Trimer Stability. J Virol. 2016; 90:8395–8409. [PubMed: 27384653]

162. Taylor BS, Sobieszczyk ME, McCutchan FE, Hammer SM. The challenge of HIV-1 subtype diversity. N Engl J Med. 2008; 358:1590–1602. [PubMed: 18403767]

163. Lihana RW, Ssemwangwa D, Abimiku A, Ndembi N. Update on HIV-1 diversity in Africa: a decade in review. AIDS Rev. 2012; 14:83–100. [PubMed: 22627605]

164. Amornkul PN, Karita E, Kamali A, Rida WN, Sanders EJ, et al. Disease progression by infecting HIV-1 subtype in a seroconverter cohort in sub-Saharan Africa. AIDS. 2013; 27:2775–2786. [PubMed: 24113395]

165. Kageha S, Lihana RW, Okoth V, Mwau M, Okoth FA, et al. HIV type 1 subtype surveillance in central Kenya. AIDS Res Hum Retroviruses. 2012; 28:228–231. [PubMed: 21740274]

166. Arroyo MA, Hoelscher M, Sanders-Buell E, Herbinger KH, Samky E, et al. HIV type 1 subtypes among blood donors in the Mbeya region of southwest Tanzania. AIDS Res Hum Retroviruses. 2004; 20:895–901. [PubMed: 15320994]
Table 1

Selected prophylactic HIV vaccine trials with major contributions toward identifying vaccine epitopes and/or immunity.

| Vaccine Trial | Vaccine Immunogen | Efficacy [No. infected] | Vaccine-induced Immune Responses |
|---------------|-------------------|-------------------------|---------------------------------|
| **B-cell Based Vaccine** | | | |
| Phase-III VAX003 (Thailand) | AIDSVAX gp120 B/E Subtype-B MN & CRF01_AE | No efficacy [4] [83/1017 vaccine vs. 81/1013 placebo] | • Binding nNabs and tier-1 NAbs to gp120 (sporadic weak bNAb) [4,149]  
• IgG4 bias is associated with reduced Ab-mediated Fc-effector function [150] |
| Phase-III VAX004 (North America & Netherland) | AIDSVAX gp120 B/B Subtype-B MN & GNE8 | No efficacy [5] [241/3598 vaccine vs. 127/1805 placebo] | • Binding nNabs and NAbs to gp120 (no bNAb) [151]  
• ADCC Abs are associated with lower infection risk [152]  
• CD8+ T-cell proliferation significantly higher in HIV infected group than uninfected group [153] |
| **B-cell and T-cell Based Vaccine** | | | |
| Phase-III RV144 (Thailand) | Priming vaccine: ALVAC-gag-pro-env Subtype-B LAI gag & pro CRF01_AE gp120 Subtype-B LAI gp41* (*no ectodomain) Boosting vaccine: AIDSVAX gp120 B/E | Positive efficacy [6] All risk groups 31.2% [51/7960 vaccine vs. 74/7988 placebo] High risk group 3.7% [22/1896 vaccine vs. 23/1929 placebo] | • IgG to V1V2 has significant inverse correlation with infection [7]  
• Env-specific IgA Abs have significant direct correlation with infection [7]  
• ADCC and Env-specific CD4+ T cells correlate inversely with infection [7]  
• Tier-1 NAbs lower in peak tier than those in Vax003 and no bNabs [147]  
• IgG3 to V1V2 correlate with reduced infection risk [8]  
• IgG to V2 & V3 linear epitopes correlate with reduced infection risk [9]  
• IgA Abs to C1 block binding and ADCC effector function of IgG [10]  
• ADCV1-like activity correlate directly with IgG1 & IgG2 to gp120 [150]  
• Presence of Env V2-specific polyfunctional CD4+ T-cell responses of IFNγ and IL2 followed by TNFa and then IL21 [101]  
• Presence of Env V2-specific CD4+ CTLa [101]  
• No HIV-specific CD8+ T-cell (ICS) responses to Gag or Env [6]  

*J Clin Cell Immunol. Author manuscript; available in PMC 2017 December 07.*
| Vaccine Trial | Vaccine Immunogen | Efficacy [No. infected] | Vaccine-induced Immune Responses |
|---------------|-------------------|-------------------------|---------------------------------|
| Phase-IIb HVTN 502 or Step (North & South America, Caribbean, Australia) | Ad5-gag/pol/nef Subtype B | Negative efficacy [12] [Enhanced infection: 24/741 vaccine vs. 21/762 placebo] | • Nonspecific IFNγ secretion, but not HIV-specific IFNγ, is associated with increased HIV infection risk [21]  
• 43% vaccinees with HIV-specific CD8+ T-cell responses [23]  
• Low in breadth compared to SIV vaccine studies  
• Low in magnitude compared to LTNP with same assay  
• More HIV-specific IFNγ alone or IFNγ/TNFα than IL2  
• Small percentage of vaccinees express IL2  
• 41% vaccinees with HIV-specific CD4+ T-cell responses [23]  
• 31% vaccinees with HIV-specific CD4+ and CD8+ T-cell responses after all vaccinations [23]  
• Pre-existing anti-Ad5 Abs reduce HIV-specific productions of IFNγ, IL2, or both more profoundly in CD8+ T cells than in the CD4+ T cells [23] |
| Phase-IIb HVTN 503 or Phambili (South Africa, >98% Black population) | Ad5-gag/pol/nef Subtype B | Negative efficacy [14] [9 mos: 34/400 vaccine vs. 28/400 placebo [13]; enhanced in 42 mos: 63/400 vaccine vs. 37/400 placebo [14]] | • More vaccinees with IFNγ-secreting T-cell responses to Gag & Nef from subtype B than from subtype C with the exception of Pol [13]  
• Higher IFNγ titers to subtype-B Pol and Nef than to those of subtype C; similar IFNγ titers in response to subtype-B and -C Gags [13]  
• 53% vaccinees with IFNγ responses to all 3 subtype-B antigens but 15% vaccinees with responses to all 3 subtype-C antigens [13] |
## Table 2

B-cell epitope specificity of bNAbs.

| Env Target Specificity | bNAb ID | Discontinuous or Linear Epitope | Ab Isotype | ADCC Activity[a] | ADCC Reference[a] |
|------------------------|---------|---------------------------------|------------|------------------|-------------------|
| CD4bs                  | VRC01   | Discontinuous                   | IgG1       | ADCC             | [154, 155]        |
|                        | 3BNC117 | Discontinuous                   | IgG1κ      | ADCC             | [154, 156, 157]   |
|                        | CH103   | Discontinuous                   | IgG1       | na               | na                |
| b12                    | Discontinuous | IgG1       | ADCC             | [158, 159]        |
| V2 Proteoglycan        | PG9     | Discontinuous                   | IgG1       | ADCC             | [154, 156, 157]   |
|                        | CHO1    | Discontinuous                   | IgG1       | na               | na                |
|                        | PGT145  | Discontinuous                   | IgG        | ADCC             | [156]             |
|                        | VRC2609 | Discontinuous                   | IgG        | na               | na                |
| V3 Proteoglycan        | PGT121  | Discontinuous                   | IgG1       | ADCC             | [154, 156]        |
|                        | PGT128  | Discontinuous                   | IgG1       | na               | na                |
|                        | PGT135  | Discontinuous                   | IgG        | na               | na                |
| MPER                   | 10E8    | Linear                          | IgG3       | ADCC             | [154]             |
|                        | 4E10    | Linear                          | IgG3κ      | ADCC             | [156, 159]        |
|                        | 2F5     | Linear                          | IgG3       | ADCC             | [156, 159, 160]   |
| gp120-gp41             | PGT151  | Discontinuous                   | IgG        | Negative         | [161]             |
|                        | VRC34.01| Discontinuous                   | IgG        | na               | na                |
|                        | 35022   | Discontinuous                   | IgG        | ADCC             | [157]             |
|                        | 8ANC195 | Discontinuous                   | IgG        | Negative         | [161]             |

[a] Not available (na)
| HLA Class I | HLA Supertype<sup>a</sup> | HIV Subtype<sup>b</sup> | Cohort Size | Cohort & Study Description<sup>c</sup> | Reference  |
|-------------|------------------------|-----------------|-------------|-----------------------------------|-----------|
| Europe & North America: HIV-Resistant HLA | | | | |
| A*02/A*0205/A*6802 | A2 | B | 284 | Caucasian homosexual transmission | [119] |
| Sub-Sahara Africa: HIV-Resistant HLA | | | | |
| A*02/A*6802 | A2 | A,D,C | 433 | Kenya; M-C & perinatal transmission | [120] |
| | | A,D,C | 232 | Kenya; CSW heterosexual transmission | [114] |
| | | A,D,C | 171 | Kenya; M-C & perinatal transmission | [115] |
| A*0205 | A2 | A,C,D | 272 | Tanzania; seroconversion survey | [116] |
| Europe & North America: HIV-Susceptible HLA | | | | |
| B*3501/B*3502/B*3503 | B7 | B | 284 | Caucasian homosexual transmission | [119] |
| Sub-Sahara Africa: HIV-Susceptible HLA | | | | |
| A*2301 | A24 | A,D,C | 232 | Kenya; CSW heterosexual transmission | [114] |
| | | A,D,C | 338 | Kenya; CSW heterosexual transmission | [117] |
| B*0702 | B7 | A,D,C | 338 | Kenya; CSW heterosexual transmission | [117] |
| B*4201 | B7 | A,D,C | 338 | Kenya; CSW heterosexual transmission | [117] |
| C*0702 | C*07 | A,C,D | 272 | Tanzania; seroconversion survey | [116] |

<sup>a</sup>Two-digit resolution nomenclature for HLA-C.

<sup>b</sup>HIV-1 subtypes shown in order of prevalence and based on following references [162–166].

<sup>c</sup>Black populations from Sub-Sahara; mother-to-child (M-C) transmission; female commercial sex worker (CSW)
Table 4

HLA class-I alleles associated with HIV disease progression.

| HLA Class I | HLA Supertype$^{a}$ | HIV Subtype$^{b}$ | Cohort Size | Cohort Description | Reference |
|-------------|---------------------|-------------------|-------------|--------------------|----------|
| **Europe & North America: HLA for HIV Slow Progression** | | | | | |
| A*74/A*7401 | A3                  | B                 | 338         | African American   | [123]    |
| B*14        | B27                 | B                 | 2,945       | Caucasian & African American | [122] |
| B*57        | B58                 | B                 | 338         | African American   | [123]    |
| B           | 241                 | B                 | 2,945       | Caucasian, African American | [122] |
| B*5703      | B58                 | B                 | 3,622       | African American, Hispanic$^c$ | [122] |
| B*8101      | B7                  | B                 | 338         | African American   | [123]    |
| C*1203      | C*12                | B                 | 2,945       | Caucasian, African American | [122] |
| C*18/C*1801 | C*18                | B                 | 2,945       | African American, Hispanic$^c$ | [122] |
| B           | 338                 | B                 | 2,945       | African American, Hispanic$^c$ | [122] |

| Sub-Saharan Africa: HLA for HIV Slow Progression | | | | | |
| A*74/A*7401 | A3                  | C                 | 784         | Zambia            | [125]    |
|           | A,C,D               | B                 | 508         | Tanzania          | [116]    |
|           | A,D,C               | B                 | 663         | Kenya             | [117]    |
| B*14       | B27                 | A,D,C             | 663         | Kenya             | [117]    |
| B*57       | B58                 | A,D,C             | 259         | Zambia            | [124]    |
| B*5703     | B58                 | C                 | 1,211       | South Africa      | [126]    |
|           | C                    | B                 | 784         | Zambia            | [125]    |
|           | C                    | C                 | 2,126       | South Africa, Botswana, Zimbabwe | [127] |
|           | A,D,C               | B                 | 663         | Kenya             | [117]    |
|           | A,C,D               | A,C,D             | 329         | Tanzania (only females) | [116] |
| B*8101     | B7                  | C                 | 563         | Zambia            | [125]    |
| HLA Class I | HLA Supertype<sup>a</sup> | HIV Subtype<sup>b</sup> | Cohort Size | Cohort Description | Reference |
|------------|-----------------|-----------------|-------------|------------------|-----------|
| C          | C*1203          | C*12            | 2,126       | South Africa, Botswana, Zimbabwe | [127]     |
|            | C*18            | C*18            | 2,216       | South Africa, Botswana, Zimbabwe | [127]     |
|            | C*1801          | C*18            | 784         | Zambia            | [125]     |
|            |                  |                  | 329         | Tanzania (only females) | [116]     |
| Europe & North America: HLA for HIV Rapid Progression | | | | |
| B*07/B*0702 | B7              | B               | 2,945     | Caucasian<sup>d</sup> | [122]     |
| B*3501     | B7              | B               | 2,945     | Caucasian, African American | [122]     |
|            |                  | B               | 1,089     | Caucasian, African American, Hispanic | [130]     |
| B*3502/B*3503 | B7          | B               | 850       | Caucasian, African American | [129]     |
|            |                  | B               | 1,089     | Caucasian, African American | [130]     |
| B*5301     | B7              | B               | 850       | Caucasian, African American | [129]     |
|            |                  | B               | 2,945     | Caucasian | [122]     |
|            |                  | B               | 1,089     | Caucasian, African American, Hispanic | [130]     |
| B*08/B*0801 | B8              | B               | 32        | Caucasian | [128]     |
|            |                  | B               | 2,945     | Caucasian<sup>d</sup> | [122]     |
| Sub-Sahara Africa: HLA for HIV Rapid Progression | | | | |
| B*07/B*0702 | B7              | A,D,C           | 663       | Kenya            | [117]     |
| B*3501     | B7              | C               | 2,126     | South Africa, Botswana, Zimbabwe | [127]     |
| B*3502/B*3503 | B7          | A,D,C           | 663       | Kenya            | [117]     |
| B*5301     | B7              | A,D,C           | 663       | Kenya            | [117]     |
| B*08/B*0801 | B8              | C               | 2,126     | South Africa, Botswana, Zimbabwe | [127]     |

<sup>a</sup> Two-digit resolution nomenclature for HLA-C.

<sup>b</sup> HIV-1 subtypes shown in order of prevalence and based on following references [163–165].

<sup>c</sup> Not in Caucasian population.

<sup>d</sup> Not in African American population.
Table 5

Features of B- and T-cell epitopes for an efficacious HIV vaccine.

| **A. B-cell epitopes for prophylactic vaccine:** |
|-------------------------------------------------|
| - Generate potent bNAbs                         |
| - Generate bNAbs of known Env targets (e.g., linear epitope for 10E8) until more potent minimally constructed bNAb epitopes become available |
| - Generate potent type-specific NAbs to the subtype(s) prevalent in the country |
| - Generate broad and potent ADCC/ADCVI epitopes |
| - Must exclude HIV epitopes that induce neutralization-blocking Abs and HIV infection-enhancing Abs |

| **B. T-cell epitopes for prophylactic vaccine:** |
|-------------------------------------------------|
| - Should be highly conserved to prevent the development of escape mutants |
| - Generate broad and potent anti-HIV CD8+ CTLs secreting perforin and/or granzymes |
| - Generate broad and potent polyfunctional T-cell responses especially those that induce IL-2/proliferation and anti-HIV β-chemokines |
| - Possibly induce CD4+ CTLs without activation of HIV-susceptible CD4+ T cells |
| - Should recognize HLA allotypes prevalent in the countries |
| - Must exclude HIV-infection enhancing epitopes |