Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

A shot at AIDS

Wayne C Koff

In the almost 35 years since the discovery of HIV, there has been great progress in developing effective treatments. More recently, there have also been advances in developing novel prevention strategies. Yet a vaccine that could prevent HIV infection remains elusive. Most licensed vaccines provide protection by inducing antibodies. For HIV, vaccine-induced antibodies must be capable of protecting against the multiple variants of HIV in circulation around the globe, so-called broadly neutralizing antibodies. Recent progress in the identification and characterization of such antibodies, as well as advances in designing candidates that stimulate cellular immunity and results from recent clinical trials are fueling efforts to develop an HIV vaccine that could vanquish the virus once and for all.

Address
IAVI Chief Scientific Officer

Corresponding author: Koff, Wayne C (WKoff@iavi.org)

Current Opinion in Biotechnology 2016, **42**:147–151

This review comes from a themed issue on **Pharmaceutical biotechnology**

Edited by **Blaine Pfeifer** and **Yi Tang**

http://dx.doi.org/10.1016/j.copbio.2016.03.007

0958-1669/Published by Elsevier Ltd.

Nearly 35 years ago the first cases of a new retrovirus that would later become known as HIV were reported in the US. Ever since, scientists have worked on developing ways to treat those infected and prevent the virus from spreading.

In 1996, antiretroviral therapy was first shown to suppress HIV's feverish replication rate. A multi-drug approach now allows infected individuals to live relatively long and healthy lives.

In recent years, clinical trials have also borne out what researchers long suspected — effective HIV treatment is also prevention [1–4]. That is, the earlier infected persons are placed on therapy the less likely they are to transmit the virus to others. Initiating treatment as soon as possible also benefits the HIV-infected individual [5,6].

Clinical trials have shown that these same antiretrovirals are also highly effective at preventing infection when administered to healthy individuals at risk of contracting HIV [7,8,9]. Last year, the World Health Organization (WHO) recommended that this approach known as pre-exposure prophylaxis or PrEP, be offered to all individuals at risk of infection [6]. Adult male circumcision and educating at-risk individuals are also part of the panoply of HIV prevention strategies that have contributed to a declining rate of AIDS deaths and new infections over the past decade.

But even with these tremendous advances in treatment and prevention, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that 1.2 million people died of AIDS-related causes in 2014 and 2 million became newly infected with the virus [10]. Sub-Saharan Africa remains the epicenter of the epidemic — nearly one in every 20 adults there is infected with HIV, accounting for 71% of the world's HIV-infected people, according to the WHO.

One prevention strategy that remains elusive is an HIV vaccine, though it is not for lack of effort. Researchers have been stymied in their efforts to develop a vaccine by the virus's unprecedented level of genetic diversity, its ability to disseminate and establish persistent infection very quickly (including long-lived viral reservoirs that remain hidden from the immune system and are the greatest obstacle to curing HIV), its direct targeting of immune cells, and its ability to rapidly mutate to evade immune responses. There is not a single HIV-infected person who has cleared the virus on their own so there is no immunological roadmap for vaccine researchers to follow as there is with other viruses. Scientists are still figuring out how to elicit a durable protective immune response against HIV.

Yet a vaccine remains necessary to ending AIDS. Modeling studies indicate that even if current HIV treatment and prevention strategies in low and middle-income countries are scaled up substantially, a preventive vaccine is essential to ending AIDS [11]. Recent results and a flurry of discoveries related to broadly neutralizing antibodies (bNAbs) and cellular immunity are fueling progress toward developing a vaccine that could help vanquish this virus once and for all.

Progress in the clinic

Results from late-stage clinical trials of HIV vaccine candidates have largely been disappointing [12]. The only trial to demonstrate efficacy was the RV-144 trial, which showed a modest 31.2 percent efficacy of a combination of two vaccine candidates in Thailand [13,14].

Trial	Date	Vaccine	Sites	Primary Risk Groups	Outcome
VAX003	2003	gp120 protein	Thailand	Intravenous drug use	No efficacy
VAX004	2003	gp120 protein	US & Europe	MSM & high-risk women	No efficacy
STEP ---------- Phambili	2007	Ad5	South & North America + Australia ---------- South Africa	MSM & high-risk women ---------- Heterosexual men/women	Halted for futility; possible enhancement ---------- Terminated early
RV144	2009	ALVAC/gp120	Thailand	Community-based	31% efficacy
HVTN 505	2013	DNA/Ad5	United States	MSM & transgender women	No efficacy

A series of follow-up studies to elucidate the immune responses that may be responsible for the efficacy observed in RV-144 are ongoing and a new round of clinical trials testing a modified version of this prime-boost combination designed specifically for the clade of HIV circulating predominantly in South Africa are slated to begin later this year. These trials will also test modified immunization schedules and a different adjuvant in an effort to increase the level of protection observed in RV144 and extend its duration.

Antibody advances abound

Meanwhile, researchers pursuing vaccine candidates capable of inducing bNAbs against HIV are enjoying a renaissance spurred by multiple advances.

Neutralizing antibodies are considered to be the reason most licensed vaccines are effective [15], which is why HIV vaccine research set their sights on antibodies early on. But there are several impediments to eliciting such antibodies against HIV. The extraordinary genetic variability of HIV requires that a vaccine induce antibodies that can prevent infection from most or all circulating viral variants of HIV, so-called bNAbs. For decades, researchers had only identified a handful of such bNAbs, but in 2009 a consortium of research institutions reported the isolation of two bNAbs from an HIV-infected donor that was part of a large study known as Protocol G led by the International AIDS Vaccine Initiative (IAVI). These antibodies neutralized HIV 10–100 times more effectively than those previously identified and neutralized a broader swath of virus types [16]. Advances in B cell technologies, micro-neutralization assays, and access to large numbers of HIV-infected volunteers led to this discovery, which in turn set off a cascade of antibody discoveries. Now, hundreds of HIV-specific bNAbs have been identified [17].

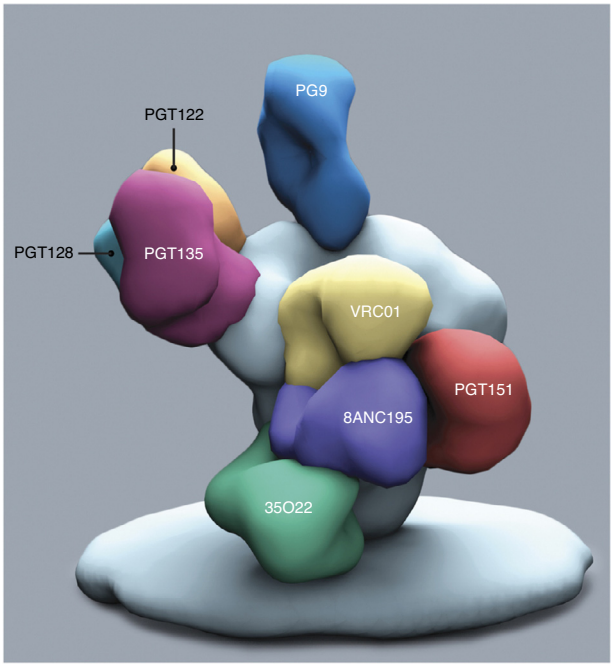
Despite the recent boon in antibody isolation, formation of the types of bNAbs a vaccine would ideally induce is still a rare occurrence — approximately 25 percent of HIV-infected individuals develop a bNAb response and only after two or more years of chronic infection [18]. The antibodies themselves are also unique; many have highly mutated variable regions, suggesting the B cells that gave rise to them underwent multiple rounds of somatic hypermutation in germinal centers in response to persistent exposure to HIV proteins that improved their affinity [19]. A vaccine must therefore be able to accomplish what occurs only rarely in natural infection and do so much more quickly. Scientists are using multiple approaches to accomplish this formidable task.

Some researchers are investigating whether administering a series of HIV envelope immunogens in a set sequence, starting with those that closely resemble the structure of transmitted founder viruses that establish infection, can spur the maturation of antibodies from their germline form to more highly mutated, broadly neutralizing versions [20]. This approach mimics the process that takes place naturally in a subset of chronically infected individuals and is now being tested in monkeys.

Another approach involves using structure-assisted vaccine design. Molecular characterization of the crop of recently isolated bNAbs indicates that there are a relatively small number of highly conserved sites on HIV's outer envelope protein that are targeted by many of the bNAbs [21] (Figure 1).

Scientists are now using these conserved viral epitopes in an effort to reverse engineer HIV vaccine immunogens. This strategy was recently validated for a vaccine candidate against pediatric respiratory syncytial virus (RSV). After identifying a site on the RSV envelope glycoprotein that was targeted by neutralizing antibodies prior to the virus' fusion with host cells, researchers stabilized the protein in this vulnerable conformation by introducing various mutations and then engineered a version of the target site that maintained the portion vulnerable to potent neutralizing antibodies. They then immunized mice and rhesus macaques with the engineered protein, which resulted in induction of high titers of RSV-specific

Figure 1



Broadly neutralizing Abs (antigen-binding (Fab) fragments) bound to the HIV-1 Env trimer. [38•]

neutralizing antibodies [22]. Similar results were also seen with computationally derived RSV proteins [23].

Researchers at The Scripps Research Institute in La Jolla, IAVI's Neutralizing Antibody Center, and the Ragon Institute have developed a computationally derived vaccine immunogen based on the CD4 binding site of HIV Envelope. This epitope is expressed on an engineered outer domain (eOD) of HIV gp120 that forms self-assembling 60-subunit nanoparticles. The CD4 binding site is critical for the virus' ability to attach to and infect CD4+ T cells, which are its main target. Several bNAbs targeting this site have been identified. The immunogen, known as eoD-GT8 60mer, can bind a presumed germline version of the CD4 binding site directed antibody known as VRC01. Immunization of transgenic mice with e0D-GT8 induces antibodies with characteristics similar to that of VRC01-like antibodies [24••]. These antibodies eventually accrue mutations that increase their binding activity to HIV Envelope by 1000-fold, suggesting this may be a reasonable first step in a sequential immunization strategy that could induce the type of broad neutralizing activity conferred by some CD4 binding site directed antibodies. It is likely that other immunogens in this sequential strategy would have to be more consistent with the native structure of the HIV Envelope trimer, which researchers now have a detailed structure of [25,26].

Taming the trimer

In 2013 researchers finally succeeded in engineering a stable HIV gp140 protein by introducing mutations into the notoriously unstable trimer that allowed it to take on a native-like conformation and revealed its structure using cryo-electron microscopy and X-ray crystallography [25,26]. This trimeric protein, known as BG505 SOSIP.664, was based on a clade A virus. Soon after, scientists also obtained a high-resolution structural model of the trimeric, pre-fusion form of HIV envelope [27]. Now, thanks to the trimerization method used to develop BG505 and others, dozens of stable, native-like HIV Envelope trimer structures have been identified from various clades, many of which are being studied as potential vaccine immunogens.

Initial immunogenicity data collected from studies of the BG505 SOSIP native-like trimer, as well as a clade B trimer known as B41 SOSIP.664, in rabbits and macaques indicate that these immunogens are capable of inducing broadly cross-reactive antibodies against viruses that are considered the easiest to neutralize, but did not elicit bNAbs against a wide variety of the harder to neutralize viruses that are more representative of those that are transmitted in natural HIV infection [28••], therefore suggesting these initial trimers are far from ideal vaccine immunogens. Although these trimeric immunogens only provide a modest improvement in immunogenicity over HIV Env monomers in pre-clinical studies, they do provide researchers with a starting point. Efforts are now focused on how to improve the breadth of neutralization for these immunogens. Some strategies include immunizing with a cocktail of different trimers from different clades or removing the non-neutralizing epitopes from the trimeric proteins that may be distracting the immune response.

While the hard work of designing and improving vaccine immunogens that are either computationally designed or more native-like is underway, researchers are also exploring other approaches to eliciting bNAbs that circumvent the complex role of the immune system in developing these proteins. One strategy is to use an adeno-associated virus (AAV) as a vector to deliver antibody genes to muscle cells where they could be taken up and expressed [29,30]. AAV vectors can also be used to express synthetic proteins that prevent the virus' entry into cells, a tactic that was shown to prevent SHIV infection in rhesus macaques [31••]. In another alternative strategy, referred to as passive administration, researchers try to determine whether directly injecting broadly neutralizing monoclonal antibodies is able to block HIV infection in humans.

Activating the other arm: cell mediated immunity

At the same time that antibody-based vaccine approaches are gaining momentum, scientists continue to investigate and exploit the role of cell-mediated immunity to HIV and its potential role in vaccination. Induction of CD4+ T

cells is a necessary component of the immune response, as they boost the potency and durability of bNAbs and also activate cytotoxic CD8+ T cells.

Immunogens aimed at inducing cellular immune responses must also contend with the overwhelming genetic diversity of HIV. To address this, scientists have developed so-called mosaic antigens that are computationally derived proteins consisting of genetic sequences that provide broad coverage across the HIV genome [32,33]. One such mosaic antigen delivered via an adenovirus serotype 26 (Ad26) vector is now in Phase I/IIa clinical testing in combination with either an additional Ad26 vectored candidate, a modified vaccinia Ankara (MVA) vectored candidate, or a gp140 protein boost [34]. There are also mosaic antigens that are focused solely on the conserved regions of the HIV proteome and these are now undergoing pre-clinical testing [35].

Additionally, scientists are studying cytomegalovirus (CMV) as a potential HIV vaccine vector that could evoke a unique subset of cellular immune responses against the virus. In monkey studies, immunization with CMV vectors expressing proteins from simian immunodeficiency virus (SIV) led to durable control of SIV infection and, most notably, the apparent clearance of pathogenic SIV infection in some of the vaccinated monkeys [36]. Effector memory T-cell responses appear to be correlated with this control/clearance, though the precise mechanism is still under investigation. Recent studies have suggested that CMV as a vector stimulates cell-mediated immune responses restricted by Major Histocompatibility Complex (MHC) class II as well as class I, and that Human Leukocyte Antigen (HLA)-E responses might also play a role in protection [37]. A modified prototype CMV vector is expected to advance into human studies this year.

Unlocking the secrets

There are without a doubt still several roadblocks to developing an HIV vaccine, however, recent discoveries are reinvigorating the quest. The next years will provide invaluable information as more HIV vaccine strategies are refined and evaluated in humans. This, together with advances in developing vaccines against other disease areas and improved technologies, will continue to shape our understanding of the human immune response to complex pathogens and hopefully remove some of the barriers to developing a vaccine that will help conclusively end AIDS.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH *et al.*: **Prevention of HIV-1 infection with early antiretroviral therapy**. *N Engl J Med* 2011, **365**:493-505 http://dx.doi.org/10.1056/NEJMoa1105243.

2. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, Tappero JW, Bukusi EA, Cohen CR, Katabira E *et al.*: **Antiretroviral prophylaxis for HIV prevention in heterosexual men and women**. *N Engl J Med* 2012, **367**:399-410 http://dx.doi.org/10.1056/NEJMoa1108524.

3. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, Henderson FL, Pathak SR, Soud FA, Chillag KL *et al.*: **Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana**. *N Engl J Med* 2012, **367**:423-434 http://dx.doi.org/10.1056/NEJMoa1110711.

4. Das M, Chu PL, Santos G-M, Scheer S, Vittingoff E, McFArland W, Colfax GN: **Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco**. *PLoS ONE* 2010, **5**:e11068 http://dx.doi.org/10.1371/journal.pone.0011068.

5. INSIGHT START Study Group: Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, Avihingsanon A, Cooper DA, Fätkenheuer G *et al.*: **Initiation of antiretroviral therapy in early asymptomatic HIV infection**. *N Engl J Med* 2015, **373**:795-807 http://dx.doi.org/10.1056/NEJMoa1506816.

6. World Health Organization: *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*. 2015:. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf [accessed 22.01.15].

7. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapía M, Guanira-Carranza JV, Ramirez-Cardich ME: **Preexposure chemoprophylaxis for HIV prevention in men who have sex with men**. *N Engl J Med* 2010, **363**:2587-2599 http://dx.doi.org/10.1056/NEJMoa1011205.

8. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, Henderson FL, Pathak SR, Soud FA, Chillag KL: **Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana**. *N Engl J Med* 2012, **367**:423-434 http://dx.doi.org/10.1056/NEJMoa1110711.

9. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, Chiamwongpaet S, Kitisin P, Natrujirote P, Kittimunkong S: **Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial**. *N Engl J Med* 2013, **381**:2083-2090 http://dx.doi.org/10.1016/S0140-6736(13)61127-7.

10. UNAIDS 2015: *AIDS by the Numbers*. 2015:. http://www.unaids.org/sites/default/files/media_asset/AIDS_by_the_numbers_2015_en.pdf [accessed 21.01.15].

11. Harmon TM, Fister KA, McGlynn MG, Stover J, Warren MJ, Teng Y, Naveke A: **Exploring the potential health impact and cost-effectiveness of AIDS vaccine within a comprehensive HIV/AIDS response in low- and middle-income countries**. *PLOS ONE* 2016 http://dx.doi.org/10.1371/journal.pone.0146387.

12. Sekaly R-P: **The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development?** *J Exp Med* 2008, **205**:7-12 http://dx.doi.org/10.1084/jem.20072681.

13. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, Premsri N, Namwat C, de Souza M: **Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand**. *N Engl J Med* 2009, **361**:2209-2220 http://dx.doi.org/10.1056/NEJMoa0908492.

14. Merlin L, Robb MD, Rerks-Ngarm S, Nitayaphan S, Pitisuttihum P, Kaewkungwal J, Kunasol P, Khamboonruang C, Thongcharoen P, Morgan P, Benenson M *et al.*: **Risk behaviour and time as covariates for efficacy of the HIV vaccine regimen ALVAC-HIV (vCP1521) and AIDSVAX B/E: a post-hoc analysis of the Thai phase 3 efficacy trial RV 144**. *Lancet* 2012, **12**:531-537 http://dx.doi.org/10.1016/S1473-3099(12)70088-9.

15. Plotkin SA: **Correlates of protection induced by vaccination**. *Clin Vacc Immunol* 2010, **17**:1055-1065 http://dx.doi.org/10.1128/CVI.00131-10.

16. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, Goss JL, Wrin T, Simek MD, Fling S, Mitcham JL *et al.*: **Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target**. *Science* 2009, **326**:585-589 http://dx.doi.org/10.1126/science.1178746.

17. Hessell AJ, Haigwood NL: **Animal models in HIV prevention and therapy**. *Curr Opin HIV/AIDS* 2015, **10**:170-176 http://dx.doi.org/10.1097/COH.0000000000000152.

18. Klein F, Mouquet H, Dosenovic P, Scheid JF, Scharf L, Nussenzweig MC: **Antibodies in HIV-1 vaccine development and therapy**. *Science* 2013, **341**:1199-1204 http://dx.doi.org/10.1126/science.1241144.

19. Mascola JR, Haynes BF: **HIV-1 neutralizing antibodies: understanding nature's pathways**. *Immunol Rev* 2013, **254**:225-244 http://dx.doi.org/10.1111/imr.12075.

20. Haynes BF, Kelsoe G, Harrison SC, Kepler TB: **B-cell-lineage immunogen design in vaccine development with HIV-1 as a case study**. *Nature Biotechnol* 2012, **30**:423-433 http://dx.doi.org/10.1038/nbt.2197.

21. Kwong PD *et al.*: **The changing face of HIV vaccine research**. *J Int AIDS Soc* 2012, **15**:17407 http://dx.doi.org/10.7448/IAS.15.2.17407.

22. McLellan JS, Chen M, Gordon Joyce M, Sastry M, Stewart-Jones GBE, Yang Yongping, Zhang Baoshan, Chen Lei, Srivatsan S, Zheng Anqi *et al.*: **Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus**. *Science* 2013, **342**:592-598 http://dx.doi.org/10.1126/science.1243283.

23. Correia BE, Bates JT, Loomis RJ, Baneyx G, Carrico C, Jardine JG, Rupert P, Correnti C, Kalyuzhniy O, Vittal V: **Proof of principle for epitope-focused vaccine design**. *Nature* 2014, **507**:201-206 http://dx.doi.org/10.1038/nature12966.

24. •• Jardine JG, Ota T, Sok D, Pauthner M, Kulp DW, Kalyuzhniy O, Skog PD, Thinnes TC, Bhullar D, Briney B *et al.*: **HIV-1 VACCINES. Priming a broadly neutralizing antibody response to HIV-1 using a germline-targeting immunogen**. *Science* 2015, **349**:156-161 http://dx.doi.org/10.1126/science.aac5894.
This study showed that mice immunized with an engineered HIV Env-based immunogen designed to bind to the presumed precursors of a class of HIV-specific broadly neutralizing antibodies can induce antibodies with characteristics similar to those broadly neutralizing antibodies.

25. Lyumkis D, Julien JP, de Val N, Cupo A, Potter CS, Klasse PJ, Burton DR, Sanders RW, Moore JP *et al.*: **Cryo-EM structure of a fully glycosylated soluble cleaved HIV-1 envelope trimer**. *Science* 2013, **342**:1484-1490 http://dx.doi.org/10.1126/science.1245627.

26. Julien JP, Cupo A, Sok D, Stanfield RL, Lyumkis D, Deller MC, Klasse PJ, Burton DR, Sanders RW, Moore JP<EL-AL>: **Crystal structure of a soluble cleaved HIV-1 envelope trimer**. *Science* 2013, **342**:1477-1483.

27. PanceraF M., Zhou T, Druz A, Georgiev IS, Soto C, Gorman J, Huang J, Acharya P, Chuang GY, Ofek G *et al.*: **Structure and immune recognition of trimeric pre-fusion HIV-1 Env**. *Nature* 2014, **514**:455-461 http://dx.doi.org/10.1038/nature13808.

28. •• Sanders RW, van Gils MJ, Derking R, Sok D, Ketas TJ, Burger JA, Ozorowski G, Cupo A, Simonich C, Goo L, Arendt H *et al.*: **HIV-1 VACCINES. HIV-1 neutralizing antibodies induced by native-like envelope trimers**. *Science* 2015 http://dx.doi.org/10.1126/science.aac4223.
This study showed that immunization with two trimeric HIV envelope proteins that assume a native-like conformation induced neutralizing antibody responses that were cross reactive against easier to neutralize tier-1 viruses and against autologous tier-2 viruses in rabbits, with similar but weaker responses seen in macaques.

29. Johnson PR, Schnepp BC, Zhang J, Connell MJ, Greene SM, Yuste E, Desrosiers RC, Clark KR: **Vector-mediated gene transfer engenders long-lived neutralizing activity and protection against SIV infection in monkeys**. *Nat Med* 2009, **8**:901-906 http://dx.doi.org/10.1038/nm.1967.

30. Balazs AB, Chen J, Hong CM, Rao DS, Yang L, Baltimore D: **Antibody-based protection against HIV infection by vectored immunoprophylaxis**. *Nature* 2012, **481**:81-84 http://dx.doi.org/10.1038/nature10660.

31. •• Gardner MR, Kattenhorn LM, Kondur HR, von Schaewen M, Dorfman T, Chiang JJ, Haworth KG, Decker JM, Alpert MD, Bailey CC *et al.*: **AAV-expressed eCD4-Ig provides durable protection from multiple SHIV challenges**. *Nature* 2015, **519**:87-91.
This study shows that an eCD4-Ig molecule binds conserved regions of HIV Env and that macaques vaccinated with an adeno-associated virus vector expressing rhesus eCD4-Ig were protected against subsequent challenge with a hybrid SIV/HIV.

32. Barouch DH, Stephenson KE, Borducchi EN, Smith K, Stanley K, McNally AG, Liu J, Abbink P, Maxfield LF, Seaman MS *et al.*: **Protective efficacy of a global HIV-1 mosaic vaccine against heterologous SHIV challenges in rhesus monkeys**. *Cell* 2013, **155**:531-539.

33. Barouch DH, O'Brien KL, Simmons NL, King SL, Abbink P, Maxfield LF, Sun Y-H, La Porte A, Riggs AM, Lynch DM *et al.*: **Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys**. *Nat Med* 2010, **16**:319-323 http://dx.doi.org/10.1038/nm.2089.

34. Barouch DH, Liu J, Li H, Maxfield LF, Abbink P, Lynch DM *et al.*: **Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys**. *Nature* 2012, **482**:89-93 http://dx.doi.org/10.1038/nature10766.

35. Ondondo B, Murakoshi H, Clutton G, Abdul-Jawad S, Wee EG, Gatanaga H, Oka S, McMichael AJ, Takiguchi M, Korber B: **Novel conserved-region T-cell mosaic vaccine with high global HIV-1 coverage is recognized by protective responses in untreated infection**. *Mol Ther* 2016 http://dx.doi.org/10.1038/mt.20163. [Epub ahead of print].

36. Hansen SG, Piatak M Jr, Ventura AB, Hughes CM, Gilbride RM, Ford JC, Oswald K, Shoemaker R, Li Y, Lewis MS: **Immune clearance of highly pathogenic SIV infection**. *Nature* 2013, **502**:100-104 http://dx.doi.org/10.1038/nature12519.

37. Hansen SG, Wu HL, Burwitz BJ, Hughes CM, Hammond KB, Ventura AB, Reed JS, Gilbride RM, Ainslie E, Morrow DW *et al.*: **Broadly targeted CD8+ T cell responses restricted by major histocompatibility complex E**. *Science* 2016 http://dx.doi.org/10.1126/science.aac9475.

38. • Burton DR, Mascola JR: **Antibody response to envelope glycoproteins in HIV-1 infection**. *Nat Immunol* 2015, **16**:571-576.
This paper summarized the recent advances in isolation of many HIV-specific broadly neutralizing antibodies and discusses how they are being used to guide HIV vaccine development.