Published in final edited form as:

Curr Opin HIV AIDS. 2010 September ; 5(5): 404–408. doi:10.1097/COH.0b013e32833d1fca.

Cofactors that may influence vaccine responses

Guy de Bruyn

Perinatal HIV Research Unit, University of the Witwatersrand

Abstract

Purpose of review—This review summarizes recent developments related to cofactors that may influence response to vaccination.

Recent findings—The unexpected increased HIV acquisition among vaccinees in the Step trial with prior exposure to Adenovirus type 5 (Ad5) led to several studies trying to understand whether an underlying biological risk factor may have been responsible for this observation. Demographic factors and genetic background of the human populations in HIV vaccine trials remain a source of potential variation in responses observed in vaccine trials, yet empirical data remains limited on the impact of those factors. Co-infections, particularly those that may modulate the immune response, are a further concern for HIV vaccine trialists, with recent data providing further insight into effects of coinfections on innate and adaptive immunity and vaccine responses.

Summary—Individuals and human populations display variation in response to vaccination. Key explanatory variables for this variation include host factors, such as host genetics, and environmental factors, such as prior exposure to the vaccine vector, coinfection with other pathogens, and demographic factors. This review will outline some of the recent developments investigating the role of various cofactors on vaccine responses, with a particular emphasis on studies of HIV vaccines.

Keywords

HIV; vaccine; demographic factors; coinfection

Introduction

Humans display variation in immune responses to vaccination with defined antigens at individual and population levels. Several human vaccines have well illustrated the variability in immune responses among human populations. The efficacy of Bacille Calmette Guérin (bCG), perhaps the world's most widely-used vaccine, varied significantly between studies, with a significant fraction of that variation being explained by geographic location (latitude) (1,2). Similarly, the immunogenicity of candidate cholera vaccines was >90% among North American and European adult volunteers (3), and protective efficacy in challenge studies was commensurately high (4). Yet in endemic areas, the CVD103-HgR vaccine yielded poor immunogenicity and poor levels of protective efficacy in field trials (5).

Defining the possible sources of such variation is useful for modifying therapy in relation to individual characteristics. Anticipating variation in response to vaccination is also relevant to the design of clinical trials to evaluate new vaccines. Trial eligibility criteria may be modified to address some of these cofactors. Vaccine formulation with adjuvants or incorporating a broader range of antigens in a novel vaccine may be other responses to deal with response

variation. Few of the many potential influences have been examined within the context of HIV vaccine clinical trials. Clinical trials of candidate HIV vaccines have thus generally addressed known cofactors in defining trial eligibility among low and high risk populations.

The review will not deal with vaccine regimen issues such as dose, vaccination schedule, or route of delivery, nor with the role of adjuvants—the latter is dealt with elsewhere in this issue—nor with prediction of adverse responses to vaccination. In this overview, I will focus on new developments in the understanding and role of some of these vaccine response cofactors (Table 1). In recent trials of candidate HIV vaccines, a key cofactor has been pre-existing immunity to the vaccine vector. This important topic is also dealt with in other contributions to this edition.

Pre-existing immunity to vaccine vectors

Reduction in vaccine effectiveness due to pre-existing immunity to vaccine vectors is a well-described limitation of the vector-based approach (6–9). This is the key rationale for development of alternative vectors to which human populations have limited prior exposure, as described elsewhere in this edition (10).

An unanticipated finding of the Step trial was the increased rate of HIV acquisition among vaccinees seropositive for adenovirus 5 (Ad5) compared to placebo recipients (11,12). While it remains unclear whether a biological explanation was responsible for this finding, the observation stimulated close examination of this question. Several hypotheses were advanced to explain the increased rate of HIV acquisition, as outlined elsewhere (13): i) the Ad5 vector boosted pre-existing vector-specific T-cell immunity, which resulted in increased numbers of activated target cells, and thereby an increased susceptibility to infection, given exposure; ii) prior Ad exposure to natural infection may have resulted in responses primarily directed to mucosal responses and boosting of these pre-existing responses by the vector may have resulted in greater concentration of activated T cells at mucosal surfaces; iii) vaccination may have resulted in generation of antibodies that may have enhanced HIV acquisition.

Subsequent analyses have cast doubts on the tenability of at the least the first of these proposed mechanisms. Hutnick and colleagues studied the Ad5-specific T cell responses following vaccination with an earlier prototype of the Step vaccine (14), and found that both Ad5 seronegative and seropositive individuals had detectable Ad5-specific CD4+ T cell responses, of similar magnitude. Moreover, the Ad5 neutralizing antibody titres did not correlate with Ad5-specific CD4+ T cell frequencies. Following vaccination, CD4+ T cell responses expanded in both baseline Ad5 seropositive and seronegative vaccinees. Ad5 NAb developed in all baseline Ad seronegative vaccinees by week 8 following first vaccination. There were no observed differences in magnitude of T cell responses between vaccinees and placebo recipients that may support vector-induced CD4 T cell expansion as the mechanism for the Step results.

Other investigators have reported that vector-antibody immune complexes may have led to effects on dendritic cells, such as promotion of DC maturation, and higher levels of HIV replication in cell cultures following Ad5-immune complex stimulation of dendritic cells (15). The true relevance of these experimental findings to the interpretation of the Step and Phambili results remain uncertain and await analysis of final follow-up of study volunteers.

Koup and colleagues reported that following administration of an Ad5 vector containing deletions in the adenovirus E1, E3, and E4 genes, no expansion of vector-specific CD4+ T cells was detectable (16). This would support continued examination of Ad-vectored vaccines, particularly among Ad-seronegative individuals, and possibly favour vaccines containing multiple gene deletions.

It also appears important to consider the role of non-human primate studies compared to human trials when considering the unanticipated nature of the Step result. Pre-clinical non-human primate or mouse studies of vector-based approaches may yield important data, yet cannot fully elucidate all of the relevant biology. For example, mice and non-human primates such as rhesus macaques are non-permissive for human adenovirus replication. Animal models have typically induced 'pre-existing immunity' by immunization with adenovirus vectors bearing alternative antigens(8,17). As these vectors are delivered by an alternative route to natural infection, and are delivered to a non-permissive host, this 'pre-existing immunity' is likely to be associated with differences in the type and quality of immune responses induced. This would, in turn, impact on the findings if animals receive a viral challenge. An examination of human antibody specificity elicited by natural infection or vaccination demonstrated that natural infection is associated with antibodies directed to the Ad5 fiber, whereas antibodies elicited by vaccination were mainly directed to non-fiber capsid proteins (18).

Demographic and Other Characteristics

Certain individual demographic characteristics are well known to be associated with vaccine immunogenicity or efficacy, such as age or gender(19–22). Analysis of HIV vaccine clinical trial data for such associations has been limited. In response to claims of efficacy in certain race/ethnicity groups in the first phase III trial of AIDSVAX B/B (23), data from NIH-funded trials of similar vaccine candidates was analysed to determine whether similar patterns of responses were noted among race/ethnicity subgroups (24). In this analysis, age was not an influential factor, when dividing participants into 18–35 and 36–59 year age strata. When examining responses to gp120 vaccines, sex did not influence geometric mean titres (GMT) of neutralizing antibody responses, while race/ethnicity did. Among those studies, African American participants had GMTs 2.6–4.7-fold higher than white participants. Trials of ALVAC vectors with gp120 or ALVAC alone did not demonstrate differences in neutralizing antibody responses by sex or race/ethnicity.

In other recent reports, age was a major modifying factor. Among 5 trials of quadrivalent human papillomavirus vaccine (HPV) given at 0,2, and 6 months to male and female participants between 9 and 23 years of age, titres of antibodies to each HPV type decreased with increasing age (25). The authors report that, after adjusting for age, no baseline characteristics consistently predicted antibody response titres to each of the four HPV types in multivariate analyses. For individual types, some characteristics were significant, including body mass index (BMI), race/ethnicity, and location. In addition, antibody titers were noted to be generally higher among male participants than female participants. No effect of smoking or contraceptive use was noted in these trials.

Genetic Factors

Multiple cellular mechanisms are required for the immune system to generate an immune response to vaccination. From cell entry and replication (in the case of vectored vaccines) to pathogen recognition to antigen uptake and processing to B and T cell function and so on, each is associated with polymorphic host genes(26). The heritability component of vaccine-induced immune responses also varies for different vaccines. Studies of monozygotic and dizygotic twins have been valuable in providing a quantitative estimate of the heritability contribution. Studies from the Gambia have illustrated that, among infants, antibody responses to HBV show heritability of 77%, oral polio vaccine 60%, tetanus toxoid 44%, diphtheria 49%, and *Haemophilus influenza* b 51% (27,28). Among adults and older children, hepatitis B and measles response have been best studied. It is estimated that for hepatitis B, heritability of the immune response is 61%, with approximately 40% being determined by HLA-encoded factors, and the majority by genes outside of the MHC complex (29).

Among the identified human genetic factors associated with HIV control, human leukocyte antigen (HLA) haplotype accounts for much of the explained human variation (30,31). As has been noted for other cofactors, few studies have as yet been reported that describe the role of either candidate genes or common genetic variation on vaccine responses to HIV vaccines. Prior work examining genetic factors predictive of responses to ALVAC demonstrated that individuals bearing HLA-B27 or HLA-B57 had a high response frequency than individuals without those alleles(32). These same alleles are associated with slower progression to AIDS among HIV-infected individuals. Further analyses from the Thai prime-boost and Step trial are eagerly awaited for what those studies can contribute to an understanding of this area.

Coexisting Conditions or Infections

Many viral, bacterial, and parasitic pathogens have effects on the human immune system that could affect responses to vaccination. Among viruses, HIV (33–35), HBV (36), CMV (37), and measles virus (38) are but a few that are known to impact immune responses. Thus, clinical trials of candidate HIV vaccines exclude participants with known HIV infection, chronic hepatitis, and acute medical illnesses.

Parasitic infections too have modulatory effects on the human immune system. These effects have been proposed as underlying the global patterns of allergic and autoimmune diseases. Experimental evidence also supports the ability of parasitic infestation to alter human immune responses to bystander antigens, such as in the setting of vaccination. These alterations are also manifest in clinical laboratory reference ranges for certain analytes, as recently shown in studies to define locally appropriate reference ranges for use in international clinical trials (39,40).

Helminths use several approaches to modulate the immune response (41). Broadly, helminth infections induce strong T helper 2 (Th2) responses. In addition, helminth infections induce regulatory T cells, anti-inflammatory cytokines, and other mechanisms. Specific helminth-derived products have been characterized as having immunomodulatory effects, including lysophosphatidylserine (42), phosphatidylserine (43), lacto-N-fucopentaose III (44), *Acanthocheilonema viteae* ES62 (45,46), *Schistosoma mansoni* dsRNA (47), cathepsin cysteine proteases (48), and others. These products may have effects that function via interactions with Toll-like receptors (TLR), including TLR-2, 3, or 4 in particular, or impact TLR signaling pathways. Certain immunomodulatory effects may also function via TLR-independent mechanisms.

Supportive data on the impact of parasitic co-infections from HIV vaccine clinical trials remain limited. A recent report demonstrated an impairment in vaccine-induced T cell responses by coexisting infection with *S. mansoni* in a mouse model (49). Treatment of the helminth infection with praziquantel prior to vaccination was associated with improved immune responses, compared to responses among persistently infected mice. A time-dependent improvement in responses was also apparent, with CD8 responses among mice immunized at four weeks following praziquantel treatment being inferior to naïve mice. Responses were essentially equivalent if the immunization series was initiated at eight weeks following treatment.

Studies addressing immunomodulatory effects to other antigens have raised other potentially important impacts of parasitic coinfections. A study among patients with symptomatic *Vibrio cholerae* infection in Bangladesh examined the impact of parasitic coinfection on development of immune responses to cholera infection(50). Symptomatic *V. cholerae* infection typically leads to development of protective immunity with both humoral and mucosal immune responses. Coinfection with helminths among cholera patients led to reduced mucosal immune responses to an immunodominant cholera antigen, Cholera toxin B (CTB).

Route of exposure

In both the Step and Phambili trials, the incidence of HIV varied considerably by route of exposure (11). The risk of HIV acquisition is known to vary according to gender (51), route of exposure (51), co-existence of genital tract infections (52–54), viral load in the source partner (55), male circumcision status (56), and possibly other factors (57,58). Immune protection against HIV may well require that candidate HIV vaccines be able to elicit immune responses at mucosal sites. To the extent that mucosal responses may be better elicited at some sites, differential efficacy according to varying routes of exposure may be observed. Similarly, even if immune responses are efficiently induced at all relevant route of exposure, differential efficiency of transmission via those routes may still yield differential vaccine efficacy. While these are still theoretical concerns for HIV vaccines, future trials will need to consider the potential for differential efficacy by route of exposure.

Conclusion

The range of cofactors that can influence human immune responses to vaccination is vast, and include both host and environmental factors. In the context of HIV vaccine development, few of these factors have been examined in any detail. Recent clinical trial results have highlighted the importance of gaining a better understanding of prior exposure to vaccine vectors. Future studies should also address the impact of socioeconomic factors, host genetics, and other environmental exposures on modifying vaccine responses.

Acknowledgments

GdB gratefully acknowledges support from the National Institutes of Health (U01AI069453).

Funding received: NIH

References

1. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *Jama* 1994 Mar 2;271(9):698–702. [PubMed: 8309034]
2. Wilson ME, Fineberg HV, Colditz GA. Geographic latitude and the efficacy of bacillus Calmette-Guerin vaccine. *Clin Infect Dis* 1995 Apr;20(4):982–91. [PubMed: 7795103]
3. Levine MM, Kaper JB, Herrington D, Ketley J, Losonsky G, Tacket CO, et al. Safety, immunogenicity, and efficacy of recombinant live oral cholera vaccines, CVD 103 and CVD 103-HgR. *Lancet* 1988 Aug 27;2(8609):467–70. [PubMed: 2900401]
4. Tacket CO, Cohen MB, Wasserman SS, Losonsky G, Livio S, Kotloff K, et al. Randomized, double-blind, placebo-controlled, multicentered trial of the efficacy of a single dose of live oral cholera vaccine CVD 103-HgR in preventing cholera following challenge with *Vibrio cholerae* O1 El tor inaba three months after vaccination. *Infection and immunity* 1999 Dec;67(12):6341–5. [PubMed: 10569747]
5. Richie EE, Punjabi NH, Sidharta YY, Peetosutan KK, Sukandar MM, Wasserman SS, et al. Efficacy trial of single-dose live oral cholera vaccine CVD 103-HgR in North Jakarta, Indonesia, a cholera-endemic area. *Vaccine* 2000 May 8;18(22):2399–410. [PubMed: 10738097]
6. Roberts DM, Nanda A, Havenga MJ, Abbink P, Lynch DM, Ewald BA, et al. Hexon-chimaeric adenovirus serotype 5 vectors circumvent pre-existing anti-vector immunity. *Nature* 2006 May 11;441(7090):239–43. [PubMed: 16625206]
7. Casimiro DR, Chen L, Fu TM, Evans RK, Caulfield MJ, Davies ME, et al. Comparative immunogenicity in rhesus monkeys of DNA plasmid, recombinant vaccinia virus, and replication-defective adenovirus vectors expressing a human immunodeficiency virus type 1 gag gene. *J Virol* 2003 Jun;77(11):6305–13. [PubMed: 12743287]

8. Fitzgerald JC, Gao GP, Reyes-Sandoval A, Pavlakis GN, Xiang ZQ, Wlazlo AP, et al. A simian replication-defective adenoviral recombinant vaccine to HIV-1 gag. *J Immunol* 2003 Feb 1;170(3):1416–22. [PubMed: 12538702]
9. Xiang ZQ, Yang Y, Wilson JM, Ertl HC. A replication-defective human adenovirus recombinant serves as a highly efficacious vaccine carrier. *Virology* 1996 May 1;219(1):220–7. [PubMed: 8623532]
10. Abbink P, Lemckert AA, Ewald BA, Lynch DM, Denholtz M, Smits S, et al. Comparative seroprevalence and immunogenicity of six rare serotype recombinant adenovirus vaccine vectors from subgroups B and D. *J Virol* 2007 May;81(9):4654–63. [PubMed: 17329340]
11. Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, Li D, et al. 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 Nov 29;372(9653):1881–93. [PubMed: 19012954]
12. McElrath MJ, De Rosa SC, Moodie Z, Dubey S, Kierstead L, Janes H, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis. *Lancet* 2008 Nov 29;372(9653):1894–905. [PubMed: 19012957]
13. Corey L, McElrath MJ, Kublin JG. Post-step modifications for research on HIV vaccines. *Aids* 2009 Jan 2;23(1):3–8. [PubMed: 19050380]
14. Hutnick NA, Carnathan DG, Dubey SA, Makedonas G, Cox KS, Kierstead L, et al. Baseline Ad5 serostatus does not predict Ad5 HIV vaccine-induced expansion of adenovirus-specific CD4+ T cells. *Nat Med* 2009 Aug;15(8):876–8. This study provides important insights into whether the biological mechanisms that were advanced in the aftermath of the STEP results could account for the observed increase in HIV acquisition attributed to pre-exposure to adenovirus. [PubMed: 19620962]
15. Perreau M, Pantaleo G, Kremer EJ. Activation of a dendritic cell-T cell axis by Ad5 immune complexes creates an improved environment for replication of HIV in T cells. *The Journal of experimental medicine* 2008 Nov 24;205(12):2717–25. [PubMed: 18981239]
16. Koup RA, Lamoereaux L, Zarkowsky D, Bailer RT, King CR, Gall JG, et al. Replication-defective adenovirus vectors with multiple deletions do not induce measurable vector-specific T cells in human trials. *J Virol* 2009 Jun;83(12):6318–22. [PubMed: 19339347]
17. McCoy K, Tatsis N, Koriath-Schmitz B, Lasaro MO, Hensley SE, Lin SW, et al. Effect of preexisting immunity to adenovirus human serotype 5 antigens on the immune responses of nonhuman primates to vaccine regimens based on human-or chimpanzee-derived adenovirus vectors. *J Virol* 2007 Jun; 81(12):6594–604. [PubMed: 17428852]
18. Cheng C, Gall JG, Nason M, King CR, Koup RA, Roederer M, et al. Differential specificity and immunogenicity of adenovirus type 5 neutralizing antibodies elicited by natural infection or immunization. *J Virol* 2010 Jan;84(1):630–8. This study illustrates the differential specificity of neutralizing antibody responses according to whether adenoviral exposure occurred via natural infection or vaccination. [PubMed: 19846512]
19. Targonski PV, Jacobson RM, Poland GA. Immunosenescence: role and measurement in influenza vaccine response among the elderly. *Vaccine* 2007 Apr 20;25(16):3066–9. [PubMed: 17275144]
20. Van Loveren H, Van Amsterdam JG, Vandebriel RJ, Kimman TG, Rumke HC, Steerenberg PS, et al. Vaccine-induced antibody responses as parameters of the influence of endogenous and environmental factors. *Environ Health Perspect* 2001 Aug;109(8):757–64. [PubMed: 11564609]
21. Cook IF. Sexual dimorphism of humoral immunity with human vaccines. *Vaccine* 2008 Jul 4;26(29–30):3551–5. [PubMed: 18524433]
22. Corey L, Langenberg AG, Ashley R, Sekulovich RE, Izu AE, Douglas JM Jr, et al. Recombinant glycoprotein vaccine for the prevention of genital HSV-2 infection: two randomized controlled trials. Chiron HSV Vaccine Study Group. *Jama* 1999 Jul 28;282(4):331–40. [PubMed: 10432030]
23. Mitka M. Critics bash HIV vaccine trial analysis. *Jama* 2003 Mar 26;289(12):1491. [PubMed: 12672747]
24. Montefiori DC, Metch B, McElrath MJ, Self S, Weinhold KJ, Corey L. Demographic factors that influence the neutralizing antibody response in recipients of recombinant HIV-1 gp120 vaccines. *J Infect Dis* 2004 Dec 1;190(11):1962–9. [PubMed: 15529261]

25. Giuliano AR, Lazcano-Ponce E, Villa L, Nolan T, Marchant C, Radley D, et al. Impact of baseline covariates on the immunogenicity of a quadrivalent (types 6, 11, 16, and 18) human papillomavirus virus-like-particle vaccine. *J Infect Dis* 2007 Oct 15;196(8):1153–62. [PubMed: 17955433]
26. Kimman TG, Vandebriel RJ, Hoebee B. Genetic variation in the response to vaccination. *Community Genet* 2007;10(4):201–17. [PubMed: 17895626]
27. Newport MJ, Goetghebuer T, Weiss HA, Whittle H, Siegrist CA, Marchant A. Genetic regulation of immune responses to vaccines in early life. *Genes and immunity* 2004 Mar;5(2):122–9. [PubMed: 14737096]
28. Lee YC, Newport MJ, Goetghebuer T, Siegrist CA, Weiss HA, Pollard AJ, et al. Influence of genetic and environmental factors on the immunogenicity of Hib vaccine in Gambian twins. *Vaccine* 2006 Jun 19;24(25):5335–40. [PubMed: 16701924]
29. Hohler T, Reuss E, Evers N, Dietrich E, Rittner C, Freitag CM, et al. Differential genetic determination of immune responsiveness to hepatitis B surface antigen and to hepatitis A virus: a vaccination study in twins. *Lancet* 2002 Sep 28;360(9338):991–5. [PubMed: 12383669]
30. Fellay J, Ge D, Shianna KV, Colombo S, Ledergerber B, Cirulli ET, et al. Common genetic variation and the control of HIV-1 in humans. *PLoS Genet* 2009 Dec;5(12):e1000791. [PubMed: 20041166]
31. Pelak K, Goldstein DB, Walley NM, Fellay J, Ge D, Shianna KV, et al. Host determinants of HIV-1 control in African Americans. *J Infect Dis* 2010 Apr 15;201(8):1141–9. [PubMed: 20205591]
32. Kaslow RA, Rivers C, Tang J, Bender TJ, Goepfert PA, El Habib R, et al. Polymorphisms in HLA class I genes associated with both favorable prognosis of human immunodeficiency virus (HIV) type 1 infection and positive cytotoxic T-lymphocyte responses to ALVAC-HIV recombinant canarypox vaccines. *J Virol* 2001 Sep;75(18):8681–9. [PubMed: 11507213]
33. Landrum ML, Hullsiek KH, Ganesan A, Weintrob AC, Crum-Cianflone NF, Barthel RV, et al. Hepatitis B vaccination and risk of hepatitis B infection in HIV-infected individuals. *Aids* 2010 Feb 20;24(4):545–55. [PubMed: 19487908]
34. Hung CC, Chang SY, Su CT, Chen YY, Chang SF, Yang CY, et al. A 5-year longitudinal follow-up study of serological responses to 23-valent pneumococcal polysaccharide vaccination among patients with HIV infection who received highly active antiretroviral therapy. *HIV Med* 2010 Jan;11(1):54–63. [PubMed: 19659943]
35. Veit O, Niedrig M, Chapuis-Taillard C, Cavassini M, Mossdorf E, Schmid P, et al. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. *Clin Infect Dis* 2009 Mar 1;48(5):659–66. [PubMed: 19191654]
36. Livingston BD, Alexander J, Crimi C, Oseroff C, Celis E, Daly K, et al. Altered helper T lymphocyte function associated with chronic hepatitis B virus infection and its role in response to therapeutic vaccination in humans. *J Immunol* 1999 Mar 1;162(5):3088–95. [PubMed: 10072562]
37. Roenhorst HW, Kallenberg CG, The TH. The cellular immune response to cell-associated and cell-free cytomegalovirus (CMV) antigens after primary CMV-infection in non-immunocompromised hosts: development and maintenance of CMV-latency and its influence on immunocompetence. *Clin Exp Immunol* 1988 Dec;74(3):326–32. [PubMed: 2853014]
38. Karp CL, Wysocka M, Wahl LM, Ahearn JM, Cuomo PJ, Sherry B, et al. Mechanism of suppression of cell-mediated immunity by measles virus. *Science* 1996 Jul 12;273(5272):228–31. [PubMed: 8662504]
39. Eller LA, Eller MA, Ouma B, Kataaha P, Kyabaggu D, Tumusiime R, et al. Reference intervals in healthy adult Ugandan blood donors and their impact on conducting international vaccine trials. *PLoS ONE* 2008;3(12):e3919. [PubMed: 19079547]
40. Kibaya RS, Bautista CT, Sawe FK, Shaffer DN, Saterren WB, Scott PT, et al. Reference ranges for the clinical laboratory derived from a rural population in Kericho, Kenya. *PLoS ONE* 2008;3(10):e3327. [PubMed: 18833329]
41. Harnett W, Harnett MM. Helminth-derived immunomodulators: can understanding the worm produce the pill? *Nature reviews* 2010 Apr;10(4):278–84.
42. van Riet E, Hartgers FC, Yazdanbakhsh M. Chronic helminth infections induce immunomodulation: consequences and mechanisms. *Immunobiology* 2007;212(6):475–90. [PubMed: 17544832]
43. van Riet E, Everts B, Retra K, Phylipsen M, van Hellemond JJ, Tielens AG, et al. Combined TLR2 and TLR4 ligation in the context of bacterial or helminth extracts in human monocyte derived

- dendritic cells: molecular correlates for Th1/Th2 polarization. *BMC Immunol* 2009;10:9. [PubMed: 19193240]
44. Harn DA, McDonald J, Atochina O, Da'dara AA. Modulation of host immune responses by helminth glycans. *Immunological reviews* 2009 Jul;230(1):247–57. [PubMed: 19594641]
 45. Goodridge HS, Marshall FA, Else KJ, Houston KM, Egan C, Al-Riyami L, et al. Immunomodulation via novel use of TLR4 by the filarial nematode phosphorylcholine-containing secreted product, ES-62. *J Immunol* 2005 Jan 1;174(1):284–93. [PubMed: 15611251]
 46. Melendez AJ, Harnett MM, Pushparaj PN, Wong WS, Tay HK, McSharry CP, et al. Inhibition of Fc epsilon RI-mediated mast cell responses by ES-62, a product of parasitic filarial nematodes. *Nat Med* 2007 Nov;13(11):1375–81. [PubMed: 17952092]
 47. Aksoy E, Zouain CS, Vanhoutte F, Fontaine J, Pavelka N, Thieblemont N, et al. Double-stranded RNAs from the helminth parasite *Schistosoma* activate TLR3 in dendritic cells. *J Biol Chem* 2005 Jan 7;280(1):277–83. [PubMed: 15519998]
 48. Donnelly S, O'Neill SM, Stack CM, Robinson MW, Turnbull L, Whitchurch C, et al. Helminth cysteine proteases inhibit TRIF-dependent activation of macrophages via degradation of TLR3. *J Biol Chem* 2010 Jan 29;285(5):3383–92. [PubMed: 19923225]
 49. Da'dara AA, Harn DA. Elimination of helminth infection restores HIV-1C vaccine-specific T cell responses independent of helminth-induced IL-10. *Vaccine* 2010 Feb 3;28(5):1310–7. [PubMed: 19941988]
 50. Harris JB, Podolsky MJ, Bhuiyan TR, Chowdhury F, Khan AI, Larocque RC, et al. Immunologic responses to *Vibrio cholerae* in patients co-infected with intestinal parasites in Bangladesh. *PLoS Negl Trop Dis* 2009;3(3):e403. [PubMed: 19333369]
 51. Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis* 2009 Feb;9(2):118–29. [PubMed: 19179227]
 52. Atashili J, Poole C, Ndumbe PM, Adimora AA, Smith JS. Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies. *Aids* 2008 Jul 31;22(12):1493–501. [PubMed: 18614873]
 53. Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS* 2006 Jan 2;20(1):73–83. [PubMed: 16327322]
 54. Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis. *Sexually transmitted diseases* 2008 Nov;35(11):946–59. [PubMed: 18685546]
 55. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *Aids* 2009 Jul 17;23(11):1397–404. [PubMed: 19381076]
 56. Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. *Cochrane Database Syst Rev* 2009;(2):CD003362. [PubMed: 19370585]
 57. Chen L, Jha P, Stirling B, Sgaier SK, Daid T, Kaul R, et al. Sexual risk factors for HIV infection in early and advanced HIV epidemics in sub-Saharan Africa: systematic overview of 68 epidemiological studies. *PLoS ONE* 2007;2(10):e1001. [PubMed: 17912340]
 58. Morrison CS, Richardson BA, Mmiro F, Chipato T, Celentano DD, Luoto J, et al. Hormonal contraception and the risk of HIV acquisition. *Aids* 2007 Jan 2;21(1):85–95. [PubMed: 17148972]

Table 1

Selected Factors that may influence responses to candidate HIV vaccines

Demographic and Patient Characteristics
Age
Gender
Race/ethnicity
Geographic location
Smoking
Body mass index
Nutritional status
Genetic Factors
HLA type
Other immune response genes
Comorbid diseases
Autoimmune conditions–SLE, RA, etc
HIV
Renal failure
Liver failure
Parasitic infections
Medications