**Appendix to “Ongoing Vaccine and Monoclonal Antibody HIV Prevention Efficacy Trials and Considerations for Sequel Efficacy Trial Designs” by Peter B. Gilbert**

*A. Brief summary of the HIV-1 prevention modalities that have shown partial efficacy in preventing HIV-1 acquisition in randomized, placebo-controlled phase 2b or phase 3 efficacy trials, or have been shown to be partially effective in observational studies:*

These interventions include male condoms (Weller and Davis 2002, Pinkerton and Abramson 1997), voluntary medical male circumcision (Siegfried et al. 2009, Wamai et al. 2011), and antiretroviral (ARV) drugs for both HIV-infected persons (e.g. treatment as prevention, TasP) (Cohen et al. 2016, Cohen et al. 2011) and HIV-uninfected persons (e.g. pre-exposure prophylaxis, PrEP) (Grant et al. 2010, Molina et al. 2015, Baeten et al. 2012, McCormack et al. 2016). Behavioral interventions such as individual-level risk reduction counseling have not demonstrated efficacy in randomized controlled trials in preventing sexual transmission of HIV [summarized in (Padian et al. 2010)], but have been shown efficacious in reducing incident sexually transmitted infections (Kamb et al. 1998) and in reducing self-reported high-risk behavior [e.g. (Johnson et al. 2008, Lyles et al. 2007)] and are thus also considered part of comprehensive HIV prevention strategies (Coates, Richter, and Caceres 2008). Together, these interventions comprise a broad spectrum of tools whose effectiveness has different degrees of dependence on human behavioral factors such as adherence and risk compensation [see (Padian et al. 2008) for further discussion of this point]. For instance, medical male circumcision is durably efficacious after a single invasive procedure, whereas daily pill-taking (e.g. oral PrEP) is non-invasive and requires daily or near-daily adherence (Donnell et al. 2014, Murnane et al. 2015). HIV prevention remains an area of intense research, and additional types of modalities have demonstrated partial efficacy in phase 3 trials but have not yet been licensed. Two such examples are a dapivirine-containing vaginal ring (Nel et al. 2016, Baeten et al. 2016) and coital dosing of topical PrEP that showed partial efficacy in one trial (Abdool Karim et al. 2010) but none in a follow-up trial (Delany-Moretlwe et al. 2018).

B. *Ongoing HVTN or HVTN/HPTN prevention efficacy trials of HIV-1 vaccine regimens or bnAb regimens (as of April, 2019) and elaborated details on vaccine and bnAb regimens being studied in current or planned clinical studies.*

Antibody-Mediated Prevention (AMP) trials (HVTN 704/HPTN 085 and HVTN 703/HPTN 081): Harmonized, phase 2b randomized, placebo-controlled monoclonal antibody prevention efficacy trials testing the concept that passive infusion of a monoclonal broadly neutralizing antibody (VRC01) can prevent HIV-1 infection over 80 weeks of follow-up post first infusion.

bnAb (monoclonal broadly neutralizing antibody): An antibody that neutralizes many different genetic variants of HIV-1.

Combination bnAb regimen: A pair or triple of individual bnAbs administered as a cocktail, or a single bispecific or trispecific molecule that was engineered to target two or three epitopes of HIV-1, respectively.

*Elaborated details on bnAb regimens under consideration for HIV-1 prevention efficacy trials.* Two close VRC01 variants are being tested in HVTN phase 1 trials − VRC01-LS and VRC07-523LS − which may have potency advantages compared to VRC01. VRC01-LS is a modified version of VRC01 that harbors two amino acid point mutations (M428L/N434S) shown to increase the antibody’s half-life by 4-fold compared to the parent VRC01 antibody and that retains the serum neutralization activity of the parent VRC01 antibody [as demonstrated in a phase 1 study conducted by the Vaccine Research Center (VRC) (Gaudinski et al. 2018)]. VRC07-523LS was derived from a separate clone from the same donor from whom VRC01 was isolated and is thus a close cousin of VRC01; it also harbors the same two point mutations conferring increased plasma half-life, has been found to be 5 to 8-fold more potent than VRC01, and to confer protection to NHPs at a lower plasma concentration than VRC01 and VRC01-LS (Rudicell et al. 2014).

HVTN 702: Phase 2b/3 randomized, placebo-controlled vaccine efficacy trial testing an ALVAC/gp120.CC.MF59 pox-protein HIV-1 vaccine regimen based on the RV144 vaccine regimen for prevention of HIV-1 infection over 2 years of follow-up post first vaccination.

The ALVAC/gp120.CC.MF59 vaccine regimen being tested in HVTN 702 combines a recombinant canarypox vector with HIV subtype C *env*, subtype B *gag*, and *pol* inserts (ALVAC-HIV [vCP2438]) with a recombinant MF59-adjuvanted bivalent HIV-1 subtype C Envelope (Env) glycoprotein (gp) 120 subunit.

HVTN 705/VAC89220HPX2008: Phase 2b randomized, placebo-controlled vaccine efficacy trial testing a bioinformatically-optimized mosaic Ad26.Mosaic.gp140.C.alum HIV-1 vaccine regimen for prevention of HIV-1 infection over 2 years of follow-up post first vaccination.

The Ad26.Mosaic.gp140.C.alum vaccine regimen being tested in HVTN 705 combines Ad26.Mos4.HIV with a recombinant alum‑adjuvanted subtype C gp140 subunit, where Ad26.Mos4.HIV is a tetravalent vaccine comprising four pre-mixed recombinant, replication-incompetent serotype 26 adenoviruses, in a 1:1:1:1 virus particle ratio, two encoding bioinformatically optimized Gag-Pol mosaic proteins and two encoding bioinformatically optimized Env mosaic proteins.

*Potential HIV-1 vaccine regimens for sequel efficacy trials.* Myriad types of candidate HIV-1 vaccines are being tested in the HVTN, defined by vector (e.g., DNA, poxvirus, vesicular stomatitis virus), recombinant Env protein (different strains of gp120 and gp140) or virus-like particle, core proteins such as conserved elements Gag, schedule, route, adjuvant, dose, and mRNA. Directly connected to the ALVAC/gp120.CC.MF59 regimen being tested in HVTN 702, the HVTN (with guidance from the P5) has been interrogating whether immunogenicity can be improved by swapping ALVAC or DNA; changing the gp120 insert-strains, dose, or adjuvant; or modifying the combinations, schedule, or order of vaccine product administration. Directly connected to the Ad26.Mosaic.gp140.C.alum regimen being tested in HVTN 705, the Janssen/HVTN partnership is testing refinements of this regimen, e.g., by making the gp140 boost bivalent by adding a bioinformatically optimized mosaic gp140 strain. The HVTN is also beginning phase 1 trials of novel candidate vaccines designed to make incremental progress toward vaccine regimens that elicit bnAbs, including lineage-based vaccine design that delivers immunogens sequentially to mimic development of bnAbs in natural infection, germline-targeting vaccine design with primes engineered to activate diverse precursors within a bnAb class and booster immunogens being successively more native-like, and immuno-focusing vaccine design that aims to focus responses to one or more particular epitopes (Havenar-Daughton et al. 2018). The research to develop vaccine regimens that elicit bnAbs is closely tied to the passive bnAb immunoprophylaxis research exemplified by AMP, as the AMP correlates of protection objective aims to estimate a bnAb potency threshold of high efficacy that sets a benchmark for the potency of response required by a bnAb vaccine, and the first bnAb phase 1 candidate vaccine trials that are now underway have as primary endpoints the activation of diverse bnAb precursors in the VRC01 class.

*Potential monoclonal bnAb regimens for sequel efficacy trials.* Given the discovery and development of many monoclonal antibodies that neutralize most strains of HIV-1 and that confer protection to NHPs in challenge studies, the HVTN and HPTN are testing several double and triple bnAb cocktail regimens, involving various combinations of bnAbs including VRC07-523LS, PGT121, and PDGM1400 (HVTN 130 / HPTN 089) (Moldt et al. 2012, Rudicell et al. 2014, Sok et al. 2014, Gautam et al. 2016); combinations with an LS-modified PGT121 are in ongoing development now, as well. The HVTN and HPTN also plan to test a Sanofi-Pasteur trispecific bnAb that combines different paratopes in a single molecule (HVTN 129/ HPTN 088). Trispecific broadly neutralizing HIV antibodies have been shown to completely protect rhesus macaques against a mucosal mixed SHIV challenge (Xu et al. 2017). If AMP shows evidence supporting serum neutralization titer as a correlate of protection, then the primary endpoint for ranking and down-selection of one or more bnAb regimens into a sequel efficacy trial could be based on a score that favors regimens with highest predicted serum neutralization titers against exposing viruses in the future efficacy trial. See Part C of the Appendix for one way to define this score.

C. *bnAb regimen score defined based on predicted serum neutralization titer to exposing HIV-1 viruses in a future planned prevention efficacy trial.*

One way to define such a score for an individual bnAb recipient would be the average across a set of potentially exposing viruses in the future efficacy trial of the area under the predicted bnAb regimen serum inhibitory-dilution 80% (ID80)-time curve over the future efficacy trial follow-up period. The details of defining such a score are beyond our scope; elements of such a score endpoint for a given bnAb regimen include: (1) Population pharmacokinetics modeling to estimate serum bnAb time-concentration curves for each bnAb regimen recipient in a phase 1 trial, for each individual bnAb in the regimen (Huang et al. 2017); (2) Measurements of neutralization sensitivity of Envelope pseudoviruses to clinical lots of each individual bnAb in the bnAb regimen (inhibitory concentration 80%, IC80), where the Envs are selected to represent potentially exposing viruses in the future efficacy trial [e.g., with IC80 data accessed at the Los Alamos National Laboratory “Compile, Analyze and Tally NAb Panels” (CATNAP) repository]; and (3) Prediction of serum ID80 for the bnAb regimen against each Env virus used in step (2), for each Phase 1 trial participant at each daily time point over a follow-up period. Step (3) would likely use a model for combination bnAb serum ID80 as a function of IC80 for each individual bnAb and the estimated concentrations of each bnAb at a given time point, for example based on an additivity assumption (Verrier et al. 2001, Kong et al. 2015) and/or the Bliss-Hill model detailed in (Wagh et al. 2016, Wagh et al. 2018). Such a formula is important for making efficient use of resources because a fully empirical analysis would need serum sampling and serum neutralization testing on a daily grid.

D. *Recommendations from the World Health Organization on the appropriateness of a placebo group in a vaccine or monoclonal antibody efficacy trial.*

We summarizerecommendations from the World Health Organization on the appropriate use of placebo in vaccine trials (Rid et al. 2014, World Health Organization 2013). These authors deem it unacceptable to use a placebo control when a highly efficacious and safe vaccine exists and is currently accessible in the public health system of the country in which the study is planned, as study participants would have unacceptably high risk of experiencing a delay in receiving benefit from the vaccine through the public health system. The Nuffield Council on Bioethics guidelines state that the use of a placebo control may be acceptable if participants are not deprived of a vaccine they would have otherwise received, but are provided with the standard of prevention/care that is the best available in the country’s public health system. The Council for International Organizations of Medical Sciences, the International Committee on Harmonization, and UNAIDS (Joint United Nations Programme on HIV/AIDS) guidelines state that researchers must take steps to minimize any risks associated with the use of controls. The protocol should explain clearly the scientific justification for using a placebo-controlled design, and specifically address all of the questions whether (1) the study questions (both efficacy and safety) cannot be answered with an active-controlled study design; (2) the risks of delaying an existing efficacious vaccine are adequately minimized or mitigated; (3) the use of a placebo control is justified by the potential public health value of the research; and (4) the research is responsive to local health needs.

Supplementary References

Abdool Karim, Q., S. S. Abdool Karim, J. A. Frohlich, A. C. Grobler, C. Baxter, L. E. Mansoor, A. B. Kharsany, S. Sibeko, K. P. Mlisana, Z. Omar, T. N. Gengiah, S. Maarschalk, N. Arulappan, M. Mlotshwa, L. Morris, D. Taylor, and Caprisa Trial Group. 2010. "Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women." *Science* 329 (5996):1168-74. doi: 10.1126/science.1193748.

Baeten, J. M., D. Donnell, P. Ndase, N. R. Mugo, J. D. Campbell, J. Wangisi, J. W. Tappero, E. A. Bukusi, C. R. Cohen, E. Katabira, A. Ronald, E. Tumwesigye, E. Were, K. H. Fife, J. Kiarie, C. Farquhar, G. John-Stewart, A. Kakia, J. Odoyo, A. Mucunguzi, E. Nakku-Joloba, R. Twesigye, K. Ngure, C. Apaka, H. Tamooh, F. Gabona, A. Mujugira, D. Panteleeff, K. K. Thomas, L. Kidoguchi, M. Krows, J. Revall, S. Morrison, H. Haugen, M. Emmanuel-Ogier, L. Ondrejcek, R. W. Coombs, L. Frenkel, C. Hendrix, N. N. Bumpus, D. Bangsberg, J. E. Haberer, W. S. Stevens, J. R. Lingappa, C. Celum, and E. P. Study Team Partners Pr. 2012. "Antiretroviral prophylaxis for HIV prevention in heterosexual men and women." *N Engl J Med* 367 (5):399-410. doi: 10.1056/NEJMoa1108524.

Baeten, J. M., T. Palanee-Phillips, E. R. Brown, K. Schwartz, L. E. Soto-Torres, V. Govender, N. M. Mgodi, F. Matovu Kiweewa, G. Nair, F. Mhlanga, S. Siva, L. G. Bekker, N. Jeenarain, Z. Gaffoor, F. Martinson, B. Makanani, A. Pather, L. Naidoo, M. Husnik, B. A. Richardson, U. M. Parikh, J. W. Mellors, M. A. Marzinke, C. W. Hendrix, A. van der Straten, G. Ramjee, Z. M. Chirenje, C. Nakabiito, T. E. Taha, J. Jones, A. Mayo, R. Scheckter, J. Berthiaume, E. Livant, C. Jacobson, P. Ndase, R. White, K. Patterson, D. Germuga, B. Galaska, K. Bunge, D. Singh, D. W. Szydlo, E. T. Montgomery, B. S. Mensch, K. Torjesen, C. I. Grossman, N. Chakhtoura, A. Nel, Z. Rosenberg, I. McGowan, S. Hillier, and Mtn-Aspire Study Team. 2016. "Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women." *N Engl J Med* 375 (22):2121-2132. doi: 10.1056/NEJMoa1506110.

Coates, T. J., L. Richter, and C. Caceres. 2008. "Behavioural strategies to reduce HIV transmission: how to make them work better." *Lancet* 372 (9639):669-84. doi: 10.1016/S0140-6736(08)60886-7.

Cohen, M. S., Y. Q. Chen, M. McCauley, T. Gamble, M. C. Hosseinipour, N. Kumarasamy, J. G. Hakim, J. Kumwenda, B. Grinsztejn, J. H. Pilotto, S. V. Godbole, S. Chariyalertsak, B. R. Santos, K. H. Mayer, I. F. Hoffman, S. H. Eshleman, E. Piwowar-Manning, L. Cottle, X. C. Zhang, J. Makhema, L. A. Mills, R. Panchia, S. Faesen, J. Eron, J. Gallant, D. Havlir, S. Swindells, V. Elharrar, D. Burns, T. E. Taha, K. Nielsen-Saines, D. D. Celentano, M. Essex, S. E. Hudelson, A. D. Redd, T. R. Fleming, and Hptn Study Team. 2016. "Antiretroviral Therapy for the Prevention of HIV-1 Transmission." *N Engl J Med* 375 (9):830-9. doi: 10.1056/NEJMoa1600693.

Cohen, M. S., Y. Q. Chen, M. McCauley, T. Gamble, M. C. Hosseinipour, N. Kumarasamy, J. G. Hakim, J. Kumwenda, B. Grinsztejn, J. H. Pilotto, S. V. Godbole, S. Mehendale, S. Chariyalertsak, B. R. Santos, K. H. Mayer, I. F. Hoffman, S. H. Eshleman, E. Piwowar-Manning, L. Wang, J. Makhema, L. A. Mills, G. de Bruyn, I. Sanne, J. Eron, J. Gallant, D. Havlir, S. Swindells, H. Ribaudo, V. Elharrar, D. Burns, T. E. Taha, K. Nielsen-Saines, D. Celentano, M. Essex, T. R. Fleming, and Hptn Study Team. 2011. "Prevention of HIV-1 infection with early antiretroviral therapy." *N Engl J Med* 365 (6):493-505. doi: 10.1056/NEJMoa1105243.

Delany-Moretlwe, S., C. Lombard, D. Baron, L. G. Bekker, B. Nkala, K. Ahmed, M. Sebe, W. Brumskine, M. Nchabeleng, T. Palanee-Philips, J. Ntshangase, S. Sibiya, E. Smith, R. Panchia, L. Myer, J. L. Schwartz, M. Marzinke, L. Morris, E. R. Brown, G. F. Doncel, G. Gray, and H. Rees. 2018. "Tenofovir 1% vaginal gel for prevention of HIV-1 infection in women in South Africa (FACTS-001): a phase 3, randomised, double-blind, placebo-controlled trial." *Lancet Infect Dis* 18 (11):1241-1250. doi: 10.1016/S1473-3099(18)30428-6.

Donnell, D., J. M. Baeten, N. N. Bumpus, J. Brantley, D. R. Bangsberg, J. E. Haberer, A. Mujugira, N. Mugo, P. Ndase, C. Hendrix, and C. Celum. 2014. "HIV protective efficacy and correlates of tenofovir blood concentrations in a clinical trial of PrEP for HIV prevention." *J Acquir Immune Defic Syndr* 66 (3):340-8. doi: 10.1097/QAI.0000000000000172.

Gaudinski, M. R., E. E. Coates, K. V. Houser, G. L. Chen, G. Yamshchikov, J. G. Saunders, L. A. Holman, I. Gordon, S. Plummer, C. S. Hendel, M. Conan-Cibotti, M. G. Lorenzo, S. Sitar, K. Carlton, C. Laurencot, R. T. Bailer, S. Narpala, A. B. McDermott, A. M. Namboodiri, J. P. Pandey, R. M. Schwartz, Z. Hu, R. A. Koup, E. Capparelli, B. S. Graham, J. R. Mascola, J. E. Ledgerwood, and V. R. C. Study Team. 2018. "Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: A Phase 1 open-label clinical trial in healthy adults." *PLoS Med* 15 (1):e1002493. doi: 10.1371/journal.pmed.1002493.

Gautam, R., Y. Nishimura, A. Pegu, M. C. Nason, F. Klein, A. Gazumyan, J. Golijanin, A. Buckler-White, R. Sadjadpour, K. Wang, Z. Mankoff, S. D. Schmidt, J. D. Lifson, J. R. Mascola, M. C. Nussenzweig, and M. A. Martin. 2016. "A single injection of anti-HIV-1 antibodies protects against repeated SHIV challenges." *Nature* 533 (7601):105-109. doi: 10.1038/nature17677.

Grant, R. M., J. R. Lama, P. L. Anderson, V. McMahan, A. Y. Liu, L. Vargas, P. Goicochea, M. Casapia, J. V. Guanira-Carranza, M. E. Ramirez-Cardich, O. Montoya-Herrera, T. Fernandez, V. G. Veloso, S. P. Buchbinder, S. Chariyalertsak, M. Schechter, L. G. Bekker, K. H. Mayer, E. G. Kallas, K. R. Amico, K. Mulligan, L. R. Bushman, R. J. Hance, C. Ganoza, P. Defechereux, B. Postle, F. Wang, J. J. McConnell, J. H. Zheng, J. Lee, J. F. Rooney, H. S. Jaffe, A. I. Martinez, D. N. Burns, D. V. Glidden, and Team iPrEx Study. 2010. "Preexposure chemoprophylaxis for HIV prevention in men who have sex with men." *N Engl J Med* 363 (27):2587-99. doi: 10.1056/NEJMoa1011205.

Havenar-Daughton, C., R. K. Abbott, W. R. Schief, and S. Crotty. 2018. "When designing vaccines, consider the starting material: the human B cell repertoire." *Curr Opin Immunol* 53:209-216. doi: 10.1016/j.coi.2018.08.002.

Huang, Y., L. Zhang, J. Ledgerwood, N. Grunenberg, R. Bailer, A. Isaacs, K. Seaton, K. H. Mayer, E. Capparelli, L. Corey, and P. B. Gilbert. 2017. "Population pharmacokinetics analysis of VRC01, an HIV-1 broadly neutralizing monoclonal antibody, in healthy adults." *MAbs* 9 (5):792-800. doi: 10.1080/19420862.2017.1311435.

Johnson, W. D., R. M. Diaz, W. D. Flanders, M. Goodman, A. N. Hill, D. Holtgrave, R. Malow, and W. M. McClellan. 2008. "Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men." *Cochrane Database Syst Rev* (3):CD001230. doi: 10.1002/14651858.CD001230.pub2.

Kamb, M. L., M. Fishbein, J. M. Douglas, Jr., F. Rhodes, J. Rogers, G. Bolan, J. Zenilman, T. Hoxworth, C. K. Malotte, M. Iatesta, C. Kent, A. Lentz, S. Graziano, R. H. Byers, and T. A. Peterman. 1998. "Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group." *JAMA* 280 (13):1161-7.

Kong, R., M. K. Louder, K. Wagh, R. T. Bailer, A. deCamp, K. Greene, H. Gao, J. D. Taft, A. Gazumyan, C. Liu, M. C. Nussenzweig, B. Korber, D. C. Montefiori, and J. R. Mascola. 2015. "Improving neutralization potency and breadth by combining broadly reactive HIV-1 antibodies targeting major neutralization epitopes." *J Virol* 89 (5):2659-71. doi: 10.1128/JVI.03136-14.

Lyles, C. M., L. S. Kay, N. Crepaz, J. H. Herbst, W. F. Passin, A. S. Kim, S. M. Rama, S. Thadiparthi, J. B. DeLuca, M. M. Mullins, and Hiv Aids Prevention Research Synthesis Team. 2007. "Best-evidence interventions: findings from a systematic review of HIV behavioral interventions for US populations at high risk, 2000-2004." *Am J Public Health* 97 (1):133-43. doi: 10.2105/AJPH.2005.076182.

McCormack, S., D. T. Dunn, M. Desai, D. I. Dolling, M. Gafos, R. Gilson, A. K. Sullivan, A. Clarke, I. Reeves, G. Schembri, N. Mackie, C. Bowman, C. J. Lacey, V. Apea, M. Brady, J. Fox, S. Taylor, S. Antonucci, S. H. Khoo, J. Rooney, A. Nardone, M. Fisher, A. McOwan, A. N. Phillips, A. M. Johnson, B. Gazzard, and O. N. Gill. 2016. "Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial." *Lancet* 387 (10013):53-60. doi: 10.1016/S0140-6736(15)00056-2.

Moldt, B., E. G. Rakasz, N. Schultz, P. Y. Chan-Hui, K. Swiderek, K. L. Weisgrau, S. M. Piaskowski, Z. Bergman, D. I. Watkins, P. Poignard, and D. R. Burton. 2012. "Highly potent HIV-specific antibody neutralization in vitro translates into effective protection against mucosal SHIV challenge in vivo." *Proc Natl Acad Sci U S A* 109 (46):18921-5. doi: 10.1073/pnas.1214785109.

Molina, J. M., C. Capitant, B. Spire, G. Pialoux, L. Cotte, I. Charreau, C. Tremblay, J. M. Le Gall, E. Cua, A. Pasquet, F. Raffi, C. Pintado, C. Chidiac, J. Chas, P. Charbonneau, C. Delaugerre, M. Suzan-Monti, B. Loze, J. Fonsart, G. Peytavin, A. Cheret, J. Timsit, G. Girard, N. Lorente, M. Preau, J. F. Rooney, M. A. Wainberg, D. Thompson, W. Rozenbaum, V. Dore, L. Marchand, M. C. Simon, N. Etien, J. P. Aboulker, L. Meyer, J. F. Delfraissy, and Anrs Ipergay Study Group. 2015. "On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection." *N Engl J Med* 373 (23):2237-46. doi: 10.1056/NEJMoa1506273.

Murnane, P. M., E. R. Brown, D. Donnell, R. Y. Coley, N. Mugo, A. Mujugira, C. Celum, J. M. Baeten, and E. P. Study Team Partners Pr. 2015. "Estimating efficacy in a randomized trial with product nonadherence: application of multiple methods to a trial of preexposure prophylaxis for HIV prevention." *Am J Epidemiol* 182 (10):848-56. doi: 10.1093/aje/kwv202.

Nel, A., N. van Niekerk, S. Kapiga, L. G. Bekker, C. Gama, K. Gill, A. Kamali, P. Kotze, C. Louw, Z. Mabude, N. Miti, S. Kusemererwa, H. Tempelman, H. Carstens, B. Devlin, M. Isaacs, M. Malherbe, W. Mans, J. Nuttall, M. Russell, S. Ntshele, M. Smit, L. Solai, P. Spence, J. Steytler, K. Windle, M. Borremans, S. Resseler, J. Van Roey, W. Parys, T. Vangeneugden, B. Van Baelen, Z. Rosenberg, and Team Ring Study. 2016. "Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women." *N Engl J Med* 375 (22):2133-2143. doi: 10.1056/NEJMoa1602046.

Padian, N. S., A. Buve, J. Balkus, D. Serwadda, and W. Cates, Jr. 2008. "Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward." *Lancet* 372 (9638):585-99. doi: 10.1016/S0140-6736(08)60885-5.

Padian, N. S., S. I. McCoy, J. E. Balkus, and J. N. Wasserheit. 2010. "Weighing the gold in the gold standard: challenges in HIV prevention research." *AIDS* 24 (5):621-35. doi: 10.1097/QAD.0b013e328337798a.

Pinkerton, S. D., and P. R. Abramson. 1997. "Effectiveness of condoms in preventing HIV transmission." *Soc Sci Med* 44 (9):1303-12.

Rid, A., A. Saxena, A. H. Baqui, A. Bhan, J. Bines, M. C. Bouesseau, A. Caplan, J. Colgrove, A. Dhai, R. Gomez-Diaz, S. K. Green, G. Kang, R. Lagos, P. Loh, A. J. London, K. Mulholland, P. Neels, P. Pitisuttithum, S. C. Sarr, M. Selgelid, M. Sheehan, and P. G. Smith. 2014. "Placebo use in vaccine trials: recommendations of a WHO expert panel." *Vaccine* 32 (37):4708-12. doi: 10.1016/j.vaccine.2014.04.022.

Rudicell, R. S., Y. D. Kwon, S. Y. Ko, A. Pegu, M. K. Louder, I. S. Georgiev, X. Wu, J. Zhu, J. C. Boyington, X. Chen, W. Shi, Z. Y. Yang, N. A. Doria-Rose, K. McKee, S. O'Dell, S. D. Schmidt, G. Y. Chuang, A. Druz, C. Soto, Y. Yang, B. Zhang, T. Zhou, J. P. Todd, K. E. Lloyd, J. Eudailey, K. E. Roberts, B. R. Donald, R. T. Bailer, J. Ledgerwood, Nisc Comparative Sequencing Program, J. C. Mullikin, L. Shapiro, R. A. Koup, B. S. Graham, M. C. Nason, M. Connors, B. F. Haynes, S. S. Rao, M. Roederer, P. D. Kwong, J. R. Mascola, and G. J. Nabel. 2014. "Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo." *J Virol* 88 (21):12669-82. doi: 10.1128/JVI.02213-14.

Siegfried, N., M. Muller, J. J. Deeks, and J. Volmink. 2009. "Male circumcision for prevention of heterosexual acquisition of HIV in men." *Cochrane Database Syst Rev* (2):CD003362. doi: 10.1002/14651858.CD003362.pub2.

Sok, D., M. J. van Gils, M. Pauthner, J. P. Julien, K. L. Saye-Francisco, J. Hsueh, B. Briney, J. H. Lee, K. M. Le, P. S. Lee, Y. Hua, M. S. Seaman, J. P. Moore, A. B. Ward, I. A. Wilson, R. W. Sanders, and D. R. Burton. 2014. "Recombinant HIV envelope trimer selects for quaternary-dependent antibodies targeting the trimer apex." *Proc Natl Acad Sci U S A* 111 (49):17624-9. doi: 10.1073/pnas.1415789111.

Verrier, F., A. Nadas, M. K. Gorny, and S. Zolla-Pazner. 2001. "Additive effects characterize the interaction of antibodies involved in neutralization of the primary dualtropic human immunodeficiency virus type 1 isolate 89.6." *J Virol* 75 (19):9177-86. doi: 10.1128/JVI.75.19.9177-9186.2001.

Wagh, K., T. Bhattacharya, C. Williamson, A. Robles, M. Bayne, J. Garrity, M. Rist, C. Rademeyer, H. Yoon, A. Lapedes, H. Gao, K. Greene, M. K. Louder, R. Kong, S. A. Karim, D. R. Burton, D. H. Barouch, M. C. Nussenzweig, J. R. Mascola, L. Morris, D. C. Montefiori, B. Korber, and M. S. Seaman. 2016. "Optimal Combinations of Broadly Neutralizing Antibodies for Prevention and Treatment of HIV-1 Clade C Infection." *PLoS Pathog* 12 (3):e1005520. doi: 10.1371/journal.ppat.1005520.

Wagh, K., M. S. Seaman, M. Zingg, T. Fitzsimons, D. H. Barouch, D. R. Burton, M. Connors, D. D. Ho, J. R. Mascola, M. C. Nussenzweig, J. Ravetch, R. Gautam, M. A. Martin, D. C. Montefiori, and B. Korber. 2018. "Potential of conventional & bispecific broadly neutralizing antibodies for prevention of HIV-1 subtype A, C & D infections." *PLoS Pathog* 14 (3):e1006860. doi: 10.1371/journal.ppat.1006860.

Wamai, R. G., B. J. Morris, S. A. Bailis, D. Sokal, J. D. Klausner, R. Appleton, N. Sewankambo, D. A. Cooper, J. Bongaarts, G. de Bruyn, A. D. Wodak, and J. Banerjee. 2011. "Male circumcision for HIV prevention: current evidence and implementation in sub-Saharan Africa." *J Int AIDS Soc* 14:49. doi: 10.1186/1758-2652-14-49.

Weller, S., and K. Davis. 2002. "Condom effectiveness in reducing heterosexual HIV transmission." *Cochrane Database Syst Rev* (1):CD003255. doi: 10.1002/14651858.CD003255.

World Health Organization. 2013. "Expert Consultation on the use of placebos in vaccine trials." accessed 15 July 2015. http://apps.who.int/iris/bitstream/10665/94056/1/9789241506250\_eng.pdf?ua=1.

Xu, L., A. Pegu, E. Rao, N. Doria-Rose, J. Beninga, K. McKee, D. M. Lord, R. R. Wei, G. Deng, M. Louder, S. D. Schmidt, Z. Mankoff, L. Wu, M. Asokan, C. Beil, C. Lange, W. D. Leuschner, J. Kruip, R. Sendak, Y. D. Kwon, T. Zhou, X. Chen, R. T. Bailer, K. Wang, M. Choe, L. J. Tartaglia, D. H. Barouch, S. O'Dell, J. P. Todd, D. R. Burton, M. Roederer, M. Connors, R. A. Koup, P. D. Kwong, Z. Y. Yang, J. R. Mascola, and G. J. Nabel. 2017. "Trispecific broadly neutralizing HIV antibodies mediate potent SHIV protection in macaques." *Science* 358 (6359):85-90. doi: 10.1126/science.aan8630.