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Could vaccination with AIDSVAX immunogens have resulted in antibody-dependent enhancement of HIV infection in human subjects?

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The immune-correlate analysis of the RV144 clinical trial revealed that human plasma IgA immune responses elicited by the RV144 vaccine correlated positively with a risk for HIV acquisition. This result once again emphasized that HIV vaccines can potentially have adverse effects leading to enhancement of infection. Here, we discuss previously reported evidence of antibody-dependent enhancement of HIV infection. We also describe how a structure-based epitope-specific sieve-analysis can be employed to mine the molecular mechanism underlying this phenomenon.

Keywords: antibody, antibody-dependent enhancement of infection, antibody epitopes, HIV vaccine, HIV vaccine clinical trials

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Introduction

Significant evidence suggests that the elicitation of a protective antibody (Ab) immune response by a vaccine could prevent acquisition of human immunodeficiency virus (HIV).[1,2] Indeed, the recent RV144 HIV vaccine clinical trial could be viewed as a proof-of-principle that a vaccine can prevent HIV infection in humans.[3] However, in addition to a protective effect, the RV144 vaccine appears to have elicited plasma immunoglobulin A (IgA) responses in vaccinated human subjects that correlated positively with an increased risk of infection.[4] Precisely understanding the mechanisms behind this potentially adverse immune response to RV144 vaccination may be extremely important to the design of a safe and effective anti-HIV vaccine.

A number of previous studies postulated that vaccination could potentially be not only ineffective, but actually harmful, by rendering vaccine recipients more susceptible to infection rather than protecting them. Such a phenomenon, called a vaccine-induced enhancement, is known for infections by various viral pathogens[5] including members of lentivirus family (e.g., feline immunodeficiency virus[6-8]). The first-ever clear evidence of vaccine-induced enhancement of HIV in clinical studies was also recently reported when an increased HIV acquisition risk was detected in selected subgroups of vaccinated subjects enrolled in the STEP study.[9,10]

Antibody-Dependent Enhancement of Viral Infection

Antibody-dependent enhancement (ADE) is the molecular mechanism of enhancement of viral infection which has been previously documented for various viral pathogens. The most studied example of ADE is dengue virus, where documented increases in pathogenicity in humans were associated with prior heterotypic Abs.[11,12] Additionally, ADE has also been reported for infection with Murray Valley encephalitis, respiratory syncytial, ebola, and measles.[13-16] Even though the first evidence of ADE in HIV was discovered *in vitro* in late 1980s,[17] the idea of ADE has been largely ignored by the HIV research community for many years until the recently completed immune-correlate analysis of RV144 clinical trial showed that the binding of non-neutralizing

plasma IgA Abs to *env* correlated directly with the rate of infection in vaccine recipients.[4] ADE, however, was likely not responsible for the infection enhancement observed in the STEP study mentioned in the Introduction section above as the STEP vaccine was not designed to elicit Abs.

ADE in HIV has historically been suspected to be associated with non-neutralizing functions of Abs: complement activation[18,19] and Fc receptor biding.[20] Such mechanisms increase local concentrations of fully functional virus in the proximity of target cell surface, substantially increasing the probability of binding and fusion of a virus to a target cell. Alternatively, both neutralizing and non-neutralizing anti-HIV Abs may also enhance the infection by inducing conformational changes and "locking" HIV's envelope gp41-gp120 spikes in conformations facilitating host receptor/co-receptor recognition by the virus.[21]

ADE of HIV Infection in Clinical Studies

Despite the fact that the ADE of HIV infection *in vitro* was discovered decades ago, no indication of ADE in clinical HIV trials had been observed until 2005, when statistical analysis of AIDSVAX clinical trials[22,23] revealed that VAX004 vaccinees with low rgp120 Ab responses had a rate of HIV infection higher than that of the 'placebo' cohort.[24] That observation was recently revived by the results of the RV144 immune-correlate analysis mentioned above.[23]

Enhancement of HIV Infection in AIDSVAX Vaccine Trials

Sieve-analysis is a powerful bioinformatics approach which allows mining and understanding immune responses elicited by vaccination.[25] Previously, we reported an epitope-specific sieve-analysis of the VAX003 and VAX004 clinical trials of AIDSVAX vaccine.[26] Specifically, we profiled the distributions of Ab-targeted epitopes of several anti-V3 neutralizing monoclonal Abs (mAbs) among the sequences of the breakthrough HIV viruses isolated from the volunteers infected during the AIDSVAX trials. We compared the epitope-specific infection counts between vaccinated and placebo cohorts statistically to see if any epitope-specific narrow protective immune responses could have been elicited by AIDSVAX vaccination. In this review, the same epitope distribution data is, however, used to test the reverse hypothesis: to see if a significant *increase* in the rates of epitope occurrence could be observed in vaccinees comparing to placebo recipients. In other words, we test the null hypothesis of no enhancement of the HIV infection in the 'vaccine' group by using the left-tailed Fisher Exact Test instead of the right-tailed test applied in our previous published analysis.

Reversed hypothesis testing reveals that the infection counts for the 3 epitopes, those targeted by mAbs 268-D, 447–52D, and 537–10D, are significantly ($p < 0.05$) higher in the 'vaccine' VAX004 cohort comparing to the 'placebo' VAX004 cohort (**Table 1**). Notably, 2 of the epitopes, the ones targeted by mAbs 268-D and 447–52D, are also statistically significant after Bonferroni correction for multiple hypothesis testing. None of the comparisons for the presence of other epitopes in breakthrough viruses result in detection of a statistically significant difference, including the comparison for the epitope targeted by the mAb 3791, which was not present in the AIDSVAX immunogens (internal negative control, as described by Shmelkov, et al[26]). These data suggest that the VAX004 vaccine resulted in the elicitation of Abs that increased the risk of infection of the vaccinees with viruses decorated with the epitopes targeted by mAbs 268-D, 447–52D, and 537–10D.

One could hypothesize that if the increase in epitope-specific infection counts in the 'vaccine' cohort of the VAX004 trial as compared to the 'placebo' truly occurred as a result of the AIDSVAX vaccination, there should be no such increase in counts for the same Ab-targeted epitopes in the STEP cell-mediated vaccine study. Therefore, the STEP study can serve as an external negative control. We performed the analyses described above on the breakthrough sequences from the STEP

Table 1. Mapping anti-V3 mAb epitopes in gp120 sequences of HIV breakthrough viruses infecting the AIDSVAX study population

AIDSVAX Trial ID:	VAX003				VAX004			
Viral sequence	**Placebo**	**Vaccine**	**Left-tailed p-value**	**Bonferroni correction**	**Placebo**	**Vaccine**	**Left-tailed p-value**	**Bonferroni correction**
2219 containing	23	12	0.9867	1.0000	85	156	0.5126	1.0000
2557 containing	21	13	0.9525	1.0000	75	153	0.1003	0.7021
268-D containing	1	2	0.4962	1.0000	33	105	0.0002	0.0014
3074 containing	84	82	0.6633	1.0000	103	181	0.8207	1.0000
3791 containing	9	9	0.5884	1.0000	1	1	0.8752	1.0000
447–52D containing	16	18	0.4126	1.0000	74	168	0.0024	0.0168
537–10D containing	9	12	0.3137	1.0000	64	142	0.0241	0.1687
Unknown sequence	6	8	n/a	n/a	8	24	n/a	n/a
Total infected	105	106	n/a	n/a	127	241	n/a	n/a

Note: Numbers in 'Placebo' and 'Vaccine' columns are the numbers of human subjects infected with viruses bearing specified Ab-targeted epitopes. 'Left-tailed p-value' columns show p-values computed with the left-tailed Fisher Exact test. Bonferroni correction bounds were computed using a factor of 7 for each of the 2 trials separately.

clinical trial[27] and, as expected, no significant difference in distribution of Ab-targeted epitopes was observed between 'vaccine' and 'placebo' cohorts (data not shown).

Elicitation of mAb 268-D By Vaccine Components May Enhance HIV Infection

The most obvious explanation of the statistically significant increase in infection counts for the epitopes targeted by mAbs 268-D, 447–52D, and 537–10D in the vaccinated VAX004 cohort is that elicitation of Abs with the same specificity as one or several of these mAbs by the AIDSVAX B/B immunogen resulted in ADE of HIV infection. Indeed, Kliks, et al. previously demonstrated that the outcome of HIV interaction with some mAbs depends on the sequence of the V3 loop of viral *env* and specifically, mAb 268-D can induce both neutralization as well as enhancement of infection by various HIV strains.[28] This study suggests that the highly significant ($p = 0.0002$) increase in infection rates of the epitope targeted by mAb 268-D (**Table 1**) seen in VAX004 trial may relate to activation of ADE mechanisms in trial subjects as a result of AIDSVAX B/B vaccination.

Conclusions

Statistically significant differences between the occurrences of overlapping epitopes targeted by mAbs 447–52D, 537–10D, and 268-D in VAX004 'placebo' and 'vaccine' cohorts could turn out to be an extremely important observation. The most obvious explanation of this difference is that a vaccine-induced enhancement (namely ADE) of infection has occurred as a result of AIDSVAX vaccination. A problem with this scenario is that in phase 1 and 2 of the AIDSVAX vaccine trials, there was no evidence of ADE.[29] On the other hand, there is experimental evidence that at least one of the 3 potentially enhancing in the VAX004 mAbs can induce ADE *in vitro*.[28]

It is important to note that the signature motifs of the epitopes targeted by mAbs 268-D (10-[R,K]xx[H,R]xxPxR-18), 447–52D (16-PxR-18), and 537–10D (9-Rxxxx[I,M]xPxR-18) have the same sequence pattern 16-PxR-18.[30,31] Therefore, a set of sequences bearing the motif 268-D as well as a set of sequences bearing the motif 537–10D are subsets of a bigger set of sequences with the 447–52D motif. That characteristic makes the results of the analysis for each of the 3 epitopes potentially interdependent. Therefore, it is likely that the true ADE effects induced by one of these mAbs (or even some other mAb with a similar epitope) could be responsible for the increase in numbers of breakthrough HIV sequences containing epitopes of the other mAbs.

Interestingly, the increase in epitope-specific infection rates only occurred in VAX004 trial vaccinees but not in VAX003 trial vaccinees. In addition to being a convincing internal control, this observation raises the possibility that the enhancement of HIV infection was only induced by the AIDSVAX B/B immunogen used in VAX004. Indeed, epitopes targeted by the mAbs 268-D, 447–52D, and 537–10D were present in both the GNE8 and the MN strains used for the VAX004 trial vaccine but none of them were present in the A244 strain used together with the MN strain for the VAX003 trial vaccine.[26] It is also possible that an increase could have also occurred in VAX003 vaccinees but was not detected by the statistical approach employed due to low infection rates with viruses bearing the 268-D-targeted epitope (primarily subtype B) in the VAX003 Thai population where subtype E is prevalent (only 3 subjects were infected with 268-D epitope-decorated viruses in VAX003 trial, see **Table 1**). Finally, it is important to remember that the study population in the VAX004 trial (men-who-have-sex-with-men and heterosexual transmission) was different from the population of the VAX003 trial (IVDU and heterosexual transmission).

Interestingly, following the completion of the AIDSVAX trials, Gilbert, et al.[24] reported that VAX004 vaccinees with low rgp120 Ab responses had a rate of HIV infection higher than that of the 'placebo' cohort while the vaccinees with medium responses had a rate of infection comparable to that of the 'placebo' cohort and the vaccinees with high responses had a rate of infection lower than that of the 'placebo' cohort.[24] In their paper Gilbert, et al. discussed the possibility of infection enhancement in VAX004 vaccinees with low Ab responses but rejected the idea due to the lack of evidence. However, our analyses of these data raise the question of a possible AIDSVAX vaccine-induced enhancement of HIV infection yet again.

Intricate mechanisms, many of which have been poorly studied, could form the basis of the vaccine-induced enhancement of HIV infection.[32] The detection of enhancement via the Ab-targeted epitopes, rather than any element of the Ab, revives the intriguing hypothesis that the observed enhancement is dependent on the tertiary structural presentation of epitopes on gp120[21] rather than on the Ab Fc region as has been most frequently studied previously for HIV.[33,34] The study by Kliks, et al.[28] suggests that there may be a very delicate balance between the induction of neutralization and enhancement of infection by the same Ab species. The analysis discussed in the current review and the constantly evolving state-of-the-art epitope-delineation informatics approaches[30,31,35-38] may be important for mining diverse HIV-host data, such as clinical trial data, and understanding the molecular basis underlying the effects of ADE. Further experimental assessment of the serum from patients infected during the AIDSVAX and RV144 trials may also reveal important insights into the possibility of antibody-dependent enhancement of HIV infection upon vaccination.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Stamatatos L, Morris L, Burton DR, Mascola JR. Neutralizing antibodies generated during natural HIV-1 infection: good news for an HIV-1 vaccine? Nat Med 2009; 15:866-70; PMID:19525964
2. Zolla-Pazner S. Identifying epitopes of HIV-1 that induce protective antibodies. Nat Rev Immunol 2004; 4:199-210; PMID:15039757; http://dx.doi.org/10.1038/nri1307
3. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, Premsri N, Namwat C, de Souza M, Adams E, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 2009; 361:2209-20; PMID:19843557; http://dx.doi.org/10.1056/NEJMoa0908492
4. Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, Alam SM, Evans DT, Montefiori DC, Karnasuta C, Sutthent R, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med 2012; 366:1275-86; PMID:22475592; http://dx.doi.org/10.1056/NEJMoa1113425
5. Huisman W, Martina BE, Rimmelzwaan GF, Gruters RA, Osterhaus AD. Vaccine-induced enhancement of viral infections. Vaccine 2009; 27:505-12; PMID:19022319; http://dx.doi.org/10.1016/j.vaccine.2008.10.087
6. Hosie MJ, Osborne R, Reid G, Neil JC, Jarrett O. Enhancement after feline immunodeficiency virus vaccination. Vet Immunol Immunopathol 1992; 35:191-7; PMID:1337397; http://dx.doi.org/10.1016/0165-2427(92)90131-9
7. Lombardi S, Garzelli C, Pistello M, Massi C, Matteucci D, Baldinotti F, Cammarota G, da Prato L, Bandecchi P, Tozzini F, et al. A neutralizing antibody-inducing peptide of the V3 domain of feline immunodeficiency virus envelope glycoprotein does not induce protective immunity. J Virol 1994; 68:8374-9; PMID:7966629
8. Siebelink KH, Tijhaar E, Huisman RC, Huisman W, de Ronde A, Darby IH, Francis MJ, Rimmelzwaan GF, Osterhaus AD. Enhancement of feline immunodeficiency virus infection after immunization with envelope glycoprotein subunit vaccines. J Virol 1995; 69:3704-11; PMID:7745719
9. Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, Li D, Gilbert PB, Lama JR, Marmor M, Del Rio C, 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; 372:1881-93; PMID:19012954; http://dx.doi.org/10.1016/S0140-6736(08)61591-3
10. Duerr A, Huang Y, Buchbinder S, Coombs RW, Sanchez J, del Rio C, Casapia M, Santiago S, Gilbert P, Corey L, et al. Extended follow-up confirms early vaccine-enhanced risk of HIV acquisition and demonstrates waning effect over time among participants in a randomized trial of recombinant adenovirus HIV vaccine (Step Study). J Infect Dis 2012; 206:258-66; PMID:22561365; http://dx.doi.org/10.1093/infdis/jis342
11. Dejnirattisai W, Jumnainsong A, Onsirisakul N, Fitton P, Vasanawathana S, Limpitikul W, Puttikhunt C, Edwards C, Duangchinda T, Supasa S, et al. Cross-reacting antibodies enhance dengue virus infection in humans. Science 2010; 328:745-8; PMID:20448183; http://dx.doi.org/10.1126/science.1185181
12. Kliks SC, Nisalak A, Brandt WE, Wahl L, Burke DS. Antibody-dependent enhancement of dengue virus growth in human monocytes as a risk factor for dengue hemorrhagic fever. Am J Trop Med Hyg 1989; 40:444-51; PMID:2712199
13. Iankov ID, Pandey M, Harvey M, Griesmann GE, Federspiel MJ, Russell SJ. Immunoglobulin g antibody-mediated enhancement of measles virus infection can bypass the protective antiviral immune response. J Virol 2006; 80:8530-40; PMID:16912303; http://dx.doi.org/10.1128/JVI.00593-06
14. Ponnuraj EM, Springer J, Hayward AR, Wilson H, Simoes EA. Antibody-dependent enhancement, a possible mechanism in augmented pulmonary disease of respiratory syncytial virus in the Bonnet monkey model. J Infect Dis 2003; 187:1257-63; PMID:12696005; http://dx.doi.org/10.1086/374604
15. Takada A, Feldmann H, Ksiazek TG, Kawaoka Y. Antibody-dependent enhancement of Ebola virus infection. J Virol 2003; 77:7539-44; PMID:12805454; http://dx.doi.org/10.1128/JVI.77.13.7539-7544.2003
16. Wallace MJ, Smith DW, Broom AK, Mackenzie JS, Hall RA, Shellam GR, McMinn PC. Antibody-dependent enhancement of Murray Valley encephalitis virus virulence in mice. J Gen Virol 2003; 84:1723-8; PMID:12810865; http://dx.doi.org/10.1099/vir.0.18980-0
17. Robinson WE, Jr., Montefiori DC, Mitchell WM. Antibody-dependent enhancement of human immunodeficiency virus type 1 infection. Lancet 1988; 1:790-4; PMID:2895317; http://dx.doi.org/10.1016/S0140-6736(88)91657-1
18. Robinson WE, Jr., Montefiori DC, Gillespie DH, Mitchell WM. Complement-mediated, antibody-dependent enhancement of HIV-1 infection in vitro is characterized by increased protein and RNA syntheses and infectious virus release. J Acquir Immune Defic Syndr 1989; 2:33-42; PMID:2465404
19. Willey S, Aasa-Chapman MM, O'Farrell S, Pellegrino P, Williams I, Weiss RA, Neil SJ. Extensive complement-dependent enhancement of HIV-1 by autologous non-neutralising antibodies at early stages of infection. Retrovirology 2011; 8:16; PMID:21401915; http://dx.doi.org/10.1186/1742-4690-8-16
20. 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; 244:1357-60; PMID:2786647; http://dx.doi.org/10.1126/science.2786647
21. Guillon C, Schutten M, Boers PH, Gruters RA, Osterhaus AD. Antibody-mediated enhancement of human immunodeficiency virus type 1 infectivity is determined by the structure of gp120 and depends on modulation of the gp120-CCR5 interaction. J Virol 2002; 76:2827-34; PMID:11861850; http://dx.doi.org/10.1128/JVI.76.6.2827-2834.2002
22. Pitisuttithum P, Gilbert P, Gurwith M, Heyward W, Martin M, van Griensven F, Hu D, Tappero JW, Choopanya K, 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; 194:1661-71; PMID:17109337; http://dx.doi.org/10.1086/508748
23. Flynn NM, Forthal DN, Harro CD, Judson FN, Mayer KH, Para MF. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis 2005; 191:654-65; PMID:15688278; http://dx.doi.org/10.1086/428404
24. Gilbert PB, Peterson ML, Follmann D, Hudgens MG, Francis DP, Gurwith M, Heyward WL, Jobes DV, Popovic V, Self SG, 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; 191:666-77; PMID:15688279; http://dx.doi.org/10.1086/428405
25. Edlefsen PT, Gilbert PB, Rolland M. Sieve analysis in HIV-1 vaccine efficacy trials. Curr Opin HIV AIDS 2013; 8:432-6; PMID:23719202; http://dx.doi.org/10.1097/COH.0b013e328362db2b
26. Shmelkov E, Nadas A, Swetnam J, Zolla-Pazner S, Cardozo T. Indirect detection of an epitope-specific response to HIV-1 gp120 immunization in human subjects. PLoS One 2011; 6:e27279; PMID:22076145; http://dx.doi.org/10.1371/journal.pone.0027279
27. Rolland M, Tovanabutra S, deCamp AC, Frahm N, Gilbert PB, Sanders-Buell E, Heath L, Magaret CA, Bose M, Bradfield A, et al. Genetic impact of vaccination on breakthrough HIV-1 sequences from the STEP trial. Nat Med 2011; 17:366-71; PMID:21358627; http://dx.doi.org/10.1038/nm.2316
28. Kliks SC, Shioda T, Haigwood NL, Levy JA. V3 variability can influence the ability of an antibody to neutralize or enhance infection by diverse strains of human immunodeficiency virus type 1. Proc Natl Acad Sci U S A 1993; 90:11518-22; PMID:7505441; http://dx.doi.org/10.1073/pnas.90.24.11518
29. Francis DP, Gregory T, McElrath MJ, Belshe RB, Gorse GJ, Migasena S, Kitayaporn D, Pitisuttitham P, Matthews T, Schwartz DH, et al. Advancing AIDSVAX to phase 3. Safety, immunogenicity, and plans for phase 3. AIDS Res Hum Retroviruses 1998; 14 Suppl 3:S325-31
30. Cardozo T, Swetnam J, Pinter A, Krachmarov C, Nadas A, Almond D, Zolla-Pazner S. Worldwide distribution of HIV type 1 epitopes recognized by human anti-V3 monoclonal antibodies. AIDS Res Hum Retroviruses 2009; 25:441-50; PMID:19320565; http://dx.doi.org/10.1089/aid.2008.0188
31. Swetnam J, Shmelkov E, Zolla-Pazner S, Cardozo T. Comparative Magnitude of Cross-Strain Conservation of HIV Variable Loop Neutralization Epitopes. PLoS One 2010; 5:e15994; PMID:21209919; http://dx.doi.org/10.1371/journal.pone.0015994
32. Fauci AS, Marovich MA, Dieffenbach CW, Hunter E, Buchbinder SP. Immunology. Immune activation with HIV vaccines. Science 2014; 344:49-51; PMID:24700849; http://dx.doi.org/10.1126/science.1250672
33. Gupta S, Gach JS, Becerra JC, Phan TB, Pudney J, Moldoveanu Z, Joseph SB, Landucci G, Supnet MJ, Ping LH, et al. The Neonatal Fc receptor (FcRn) enhances human immunodeficiency virus type 1 (HIV-1) transcytosis across epithelial cells. PLoS Pathogens 2013; 9:e1003776; PMID:24278022; http://dx.doi.org/10.1371/journal.ppat.1003776
34. Takeda A, Sweet RW, Ennis FA. Two receptors are required for antibody-dependent enhancement of human immunodeficiency virus type 1 infection: CD4 and Fc gamma R. J Virol 1990; 64:5605-10; PMID:1976824
35. Chuang GY, Acharya P, Schmidt SD, Yang Y, Louder MK, Zhou T, Kwon YD, Pancera M, Bailer RT, Doria-Rose NA, et al. Residue-level prediction of HIV-1 antibody epitopes based on neutralization of diverse viral strains. J Virol 2013; 87:10047-58; PMID:23843642; http://dx.doi.org/10.1128/JVI.00984-13
36. Ferguson AL, Falkowska E, Walker LM, Seaman MS, Burton DR, Chakraborty AK. Computational prediction of broadly neutralizing HIV-1 antibody epitopes from neutralization activity data. PLoS One 2013; 8:e80562; PMID:24312481; http://dx.doi.org/10.1371/journal.pone.0080562
37. Shmelkov E, Krachmarov C, Grigoryan AV, Pinter A, Statnikov A, Cardozo T. Computational prediction of neutralization epitopes targeted by human anti-V3 HIV monoclonal antibodies. PLoS One 2014; 9:e89987; PMID:24587168; http://dx.doi.org/10.1371/journal.pone.0089987
38. West AP, Jr., Scharf L, Horwitz J, Klein F, Nussenzweig MC, Bjorkman PJ. Computational analysis of anti-HIV-1 antibody neutralization panel data to identify potential functional epitope residues. Proc Natl Acad Sci U S A 2013; 110:10598-603; PMID:23754383; http://dx.doi.org/10.1073/pnas.1309215110