

# [Neutralization-enhancing rf antibodies for hiv vaccines](https://assignbuster.com/neutralization-enhancing-rf-antibodies-for-hiv-vaccines/)

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Efficient neutralization of HIV is a primary goal both for therapeutic and prophylactic HIV vaccines based on induction of neutralizing antibodies (NAbs) ( [1](#B1) , [2](#B2) ). Neutralization capacity of NAbs correlates with their affinity to HIV-1 gp120 envelope glycoprotein ( [3](#B3) ). In HIV-infected individuals, early IgM antibodies have low affinity for gp120 glycoprotein ( [3](#B3) ), which is slightly compensated by their pentameric structure and avidity to multivalent structures of the virus. Corresponding IgG1 antibodies ( [3](#B3) , [4](#B4) ), which appear later from IgM through the CSR and SHM processes ( [3](#B3) , [5](#B5) ), have high affinity and specificity to gp120, but low avidity due to monomeric structure of IgG. The question is how to induce HIV-specific NAbs with both high affinity and avidity to gp120?

Anti-HIV IgG antibodies 2F5 and 2G12, switched back to IgM isotype, showed increased avidity and neutralization efficacy ( [2](#B2) ). Dendritic antibody supramolecules (DAS) in one molecule combine high specificity of IgG with high avidity of IgM ( [6](#B6) ). It would be of interest to construct such a DAS with IgM as a core, carrying 10 anti-gp120 IgG monomers. Natural monomeric anti-gp120 IgG1 antibodies ( [3](#B3) , [4](#B4) ) not only have low avidity insufficient for effective neutralization of HIV but may also contribute to FcR-mediated infection enhancement ( [7](#B7) , [8](#B8) ). Does it mean that HIV may use high-affinity IgG antibodies for its own purposes? Fortunately, in nature there exist some helpful network-like regulatory mechanisms with a key role of RF antibodies ( [9](#B9) ).

Rheumatoid factor (RF) is an autoantibody which specifically binds Fc region of IgG ( [10](#B10) , [11](#B11) ). Apart from pathologic RF in rheumatoid arthritis ( [12](#B12) ), natural RF appears in many non-rheumatoid states ( [13](#B13) ). Possible beneficial physiological roles of RF include enhanced clearance of immune complexes (ICs) ( [14](#B14) ), amplification of IgG response to pathogens ( [15](#B15) ), and enhancement of virus neutralization ( [16](#B16) , [17](#B17) ). RF can be induced *in vivo* in a highly specific way either by secondary immunization with protein antigens or in response to immunization with the newly formed ICs ( [10](#B10) , [11](#B11) ). New antigenic determinants, which appear in the Fc region of IgG antibody upon antibody-antigen complex formation, may strengthen the specificity of RF ( [9](#B9) ).

The level of RF was significantly higher in some of HIV-infected individuals compared to control groups ( [18](#B18) – [22](#B22) ). RFs were mainly IgA, IgM immunoglobulins with specificity against anti-HIV IgG ( [20](#B20) ). RF-mediated enhancement of anti-HIV IgG neutralization activity was found in the sera from MCTD patients ( [17](#B17) ). Authors suggested that RF is promising for passive immunotherapy based on NAbs ( [17](#B17) ).

Can RF play a key role in specific enhancement of IgG-mediated neutralization of HIV *in vivo* ? Measurements of RF level both in long-term non-progressors ( [23](#B23) ) and dual-infected individuals ( [24](#B24) ) might give some clues. Repeated immunization of uninfected macaques with HIV-1 gp120 glycoprotein may allow researchers not only to track the kinetics of RF induction but also to elucidate whether neutralization-enhancing RF antibodies can protect macaques against subsequent challenge with SHIV. Repeated immunization of SHIV-infected macaques with HIV-1 gp120 glycoprotein might show whether neutralization-enhancing RF antibodies can prolong the asymptomatic period and delay the onset of AIDS.

The level of RF is not stable and has a tendency to decline during the acute phase of HIV infection ( [22](#B22) ). Prolonged repeated immunizations with gp120 (e. g., immunizations every 3 weeks; the actual time between immunizations will be adjusted according to measurements of RF level in patients) would be the solution to keep the level of neutralization-enhancing RF antibodies constantly high. Single-administration vaccine (SAV) technology, which is based on pulsatile release of gp120 from biodegradable polymeric microspheres, mimics repeated immunization scheme, and allows vaccination to be done in one shot ( [25](#B25) , [26](#B26) ).

Patient-specific therapeutic HIV vaccines ( [1](#B1) ) even in simplified version, using the only one gp120 variant formed after completion of HIV population homogenization process ( [27](#B27) ), can be performed via repeated immunizations from biodegradable polymeric microspheres under SAV ( [25](#B25) , [26](#B26) ) technology platform. Prophylactic HIV vaccines can be based on the variations of sequential scheme ( [28](#B28) ) for prolonged pulsatile release of gp120 glycoproteins from biodegradable polymeric microspheres in single-shot ( [25](#B25) , [26](#B26) ) way convenient for both patients and doctors.

Studies ( [15](#B15) , [17](#B17) ) have shown the high potential of neutralization-enhancing RF antibodies, but several principal questions arise:

(i) Can neutralization-enhancing RF antibodies (NeRFa) be induced after repeated immunization of humans with recombinant gp120 glycoprotein?

(ii) Will the power of gp120 immunogen design ( [29](#B29) – [31](#B31) ) combined with an optimal vaccination regimen help the induction of NeRFa?

(iii) Could NeRFa help to improve the efficacy of previous ( [32](#B32) ) and future HIV vaccines based on induction of NAbs?

(iv) Might induction of NeRFa be a future promising method not only against malaria as suggested in Ref. ( [33](#B33) ), but also against life-threatening viruses like Ebola ( [34](#B34) )?

Repeated immunization with gp120 glycoprotein might lead to prolonged induction of neutralization-enhancing RF antibodies with a potential to be explored for finding the ways to extend lives of HIV-infected individuals and to stop current HIV pandemic.

## Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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