Towards HIV-1 remission: potential roles for broadly neutralizing antibodies

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Current antiretroviral drug therapies do not cure HIV-1 because they do not eliminate a pool of long-lived cells harboring immunologically silent but replication-competent proviruses — termed the latent reservoir. Eliminating this reservoir and stimulating the immune response to control infection in the absence of therapy remain important but unsolved goals of HIV-1 cure research. Recently discovered broadly neutralizing antibodies (bNAbs) exhibit remarkable breadth and potency in their ability to neutralize HIV-1 in vitro, and recent studies have demonstrated new therapeutic applications for passively administered bNAbs in vivo. This Review discusses the roles bNAbs might play in HIV-1 treatment regimens, including prevention, therapy, and cure.

Introduction

Combination antiretroviral therapy (ART) suppresses viremia and extends the life span of infected individuals, but the daily burden of ART and its associated toxicities make an HIV cure highly desirable. Current therapies are not curative because they do not eliminate a pool of long-lived cells harboring immunologically silent but replication-competent proviruses — termed the latent reservoir. This reservoir is refractory to ART and, although not proven, is believed to be the source of viral rebound shortly after discontinuation of standard therapy (1). However, the precise anatomic location of this persistent reservoir remains unknown, and recent studies suggest that viral rebound following treatment interruption may arise from many cells at multiple sites (2). Completely eliminating this reservoir, referred to as sterilizing cure, or stimulating the immune response to control infection in the absence of therapy, referred to as functional cure, are the primary aims of cure research. However, both strategies present unresolved challenges, and the potential characteristics of a broadly applicable cure regimen remain unclear. While many approaches, ranging from gene therapy to immune modulation, are being investigated, this Review focuses on the roles that broadly neutralizing antibodies (bNAbs) might play in therapy and how these roles could extend to cure strategies.

In the decades after HIV-1 was discovered, the identification of anti–HIV-1 bNAbs with extensive breadth and potency was difficult; however, technological advances in antibody cloning from single B cells and microneutralization assays have led to the recent discovery of hundreds of naturally arising bNAbs, referred to as “next-generation” bNAbs (3–10). Some of these bNAbs exhibit remarkable breadth and potency in vitro, and many of these bNAbs can prevent infection in animal models when passively administered at low doses before challenge (11–14). Therefore, it is widely believed that a vaccine could elicit such antibodies would be protective against infection, and the development of such a vaccine remains an important goal. However, most next-generation bNAbs only arise after at least a year of active infection (15, 16), and many show a number of unusual features, such as high levels of somatic hypermutation, long heavy chain complementarity-determining region 3 regions, and restricted germline use. Together, these features suggest that it will be difficult if not impossible to elicit bNAbs against HIV-1 by standard vaccine approaches. The uncertainties associated with a vaccine have led us, and others, to explore the use of bNAbs in passive transfer experiments for HIV-1 prevention, therapy, and eradication.

bNAb passive immunotherapy

Next-generation bNAbs have rapidly progressed through preclinical and clinical studies, with therapeutic efficacy being demonstrated first in humanized mice (17, 18), then in nonhuman primates (NHPs) (19, 20), and finally in humans (21) — all in the span of three years (refs. 17, 19–21 and Table 1). Next-generation bNAb monotherapy (~20 mg/kg) produced transient drops in viral load of 0.23 to 1.5 log10 copies in humanized mice, with viral suppression in most cases (18). When ART was administered to humanized mice to suppress viral load before bNAb therapy, a single bNAb was able to maintain viral suppression in most cases (18).

In light of successful antibody therapy in humanized mice, bNAbs were tested in NHPs. Before these studies, NHPs were believed to pose a significantly tougher challenge to bNAb therapy relative to humanized mice, because infected NHPs contain orders...
of magnitude more infected cells and, consequently, increased viral diversity. However, two independent studies in NHPs chronically infected with an SIV/HIV chimeric virus, either SHIV SF162P3 or SHIV AD8, showed that viral escape to antibody therapy was less prevalent in NHPs than in mice (19, 20). A single bNAb, without ART, was sufficient to suppress viremia without escape in most cases, as long as bNAbs remained above 1 to 5 μg/ml. In contrast, earlier studies showed that first-generation anti–HIV-1 antibodies failed to alter the course of viremia in humanized mice (22) and humans (23, 24). The success of next-generation antibodies is likely due to their increased breadth and potency. The studies of next-generation bNAbs in animal models provided proof of principle for antibody therapy against HIV-1 and prompted a reexamination of antibody therapy in humans.

The first clinical trial of a next-generation bNAb tested the safety and efficacy of 3BNC117, a CD4-binding site-directed bNAb (5). Dose escalation showed that the antibody was well tolerated up to 30 mg/kg, the highest dose tested, and that the antibody had a mean half-life of 9.9 days in HIV-1-infected individuals and 17.5 days in uninfected individuals (21). A single infusion of 30 mg/kg reduced the viral load in viremic individuals by an average of 1.48 log10 copies/ml (range 0.8–2.5 log10), and viremia remained significantly reduced for 28 days. The results indicate that 3BNC117 can reduce viremia in humans, opening the door to further testing of next-generation bNAbs.

**Antibodies to host cell receptors**

An alternative to antibodies that directly bind HIV-1 involves antibodies that target the host cell receptors CD4 and CCR5, both of which are used for viral entry. The two main candidates in this class are ibalizumab (iMab), which binds domain 2 of human CD4 without blocking the portion of CD4 necessary for MHC class II binding, and PRO 140, which targets a conformational epitope comprising domain 2 and extracellular loop 2 of human CCR5. Both iMab and PRO 140 exhibit good breadth and potency in vitro (25, 26) and have therapeutic efficacy in vivo (27, 28). Although iMab binds a nonmutating target, resistance still emerges with the selection of HIV-1 mutants that gain viral entry in its presence (25, 29).

Unfortunately, iMab and PRO 140 have short half-lives in vivo (both measured at a mean of 3 to 4 days; refs. 30, 31) compared with other humanized mAbs, which have half-lives that are typically 2 to 3 weeks. The short half-lives of these antibodies are likely related to their targeting of host cell receptors, which create large antigenic sinks for the antibodies. Additionally, both iMab and PRO 140 have minimal Fc functionality by design. Both were originally derived from murine mAbs but are expressed with the human IgG4 constant region because of IgG4’s reduced ability to bind Fcγ receptors (FcγRs) and thus avoid IgG effector functions that would deplete human CD4+ or CCR5-expressing cells. In contrast, next-generation bNAbs are derived from human patients and are generally of the IgG1 subclass, giving them the potential to engage the immune system to amplify antiviral effects without cross-species modifications. In addition to the long half-life of bNAbs and their exceptional breadth and potency, their ability to directly bind virions as well as their potential for Fc-mediated effector functions distinguish them as important reagents for cure strategies.

**Antibody effects on virions**

In contrast to current drug therapies, bNAbs bind to virions directly (Figure 1). Chun and colleagues used magnetic protein A beads to isolate bNAb-bound virions produced by infected cells. They reported that the bNAbs PG9, PGT121, and PG16 increased the amount of viral RNA isolated 9.3- to 184-fold relative to nonspecific human IgG (32).
Direct binding to virions not only neutralizes the virus before entry but also raises the possibility of accelerating viral clearance from plasma. Indeed, the half-life of cell-free virus in the plasma, as measured by viral RNA, was 2.3-fold shorter in macaques that had circulating Env-binding antibodies compared with that in macaques measured rather than viral RNA, there were no infectious particles detected within 10 to 15 minutes of virus infusion in 4 of 5 macaques with Env-binding antibodies, suggesting that Env-binding antibodies neutralize virions in plasma even before they are cleared. It is possible that bNAbs, which are far more potent than the pooled IgG used in this study, could exhibit even greater effects on virions (Figure 1).

Overall, cell-free virus is cleared from plasma very rapidly, even in the absence of antibodies (33, 34), but bNAbs may be able to clear viruses in tissues as well. This could prove clinically important, given the high levels of viral spread within lymphoid tissue, which has high densities of target cells. Virions are likely to contact target cells rapidly in these tissues and gain cellular entry within an hour of initial contact (35).

**Fc-mediated effects of antibodies**

In addition to their ability to bind and neutralize pathogens directly, antibody molecules also engage potent immune effector mechanisms (Figure 1). Antibodies can bind complement to stimulate cell lysis by the classical pathway, they can engage Fc receptors (FcRs) on immune cells to clear infected cells by antibody-dependent cellular cytotoxicity (ADCC), and antibodies can form immune complexes that activate dendritic cells to enhance antigen presentation (36). Which, if any, of these immune effector mechanisms plays a significant role in passive immunotherapy against HIV-1 is not known. However, the potent effects of antibodies in therapy as well as the results of the RV144 vaccine trial have renewed interest in the role of ADCC in the context of HIV infection. The immune correlates analysis of the RV144 trial showed that nonneutralizing antibodies targeting the V2 loop protected against infection, suggesting that ADCC played a role in preventing viral acquisition (37). Subsequently, mAbs that mediated increased infected cell killing in vitro were isolated from RV144 vaccinees (38); however, the data supporting an antibody-mediated clearance effect on virus or cells in humans remain indirect.

To date, direct evidence for Fc-mediated effects in HIV infection comes entirely from animal models. To determine whether bNAbs are effective as postexposure prophylaxis, we infected humanized mice with HIV-1 YU2, and then initiated ART or combination bNAbs 96 hours after infection. While plasma viremia remained undetectable in both treatment groups during ART or bNAb therapy, a significantly higher proportion of ART-treated mice showed rebound plasma viremia compared with antibody-treated mice when therapy was discontinued. This suggests that, although ART was able to block viral replication, bNAbs may have reduced the pool of cells capable of producing viral rebound or maintained durable suppression because of their long half-life (39).

To determine whether Fc-mediated effects contributed to the antiviral function of bNAbs in humanized mice, we tested the same combination of bNAbs carrying point mutations in the Fc regions that abrogate binding to mouse and human FcRs and complement. While plasma viremia was suppressed comparably to WT bNAbs during Fc mutant bNAb therapy, viral rebound in mice receiving Fc mutant bNAbs occurred significantly earlier following the last bNAb injection (39). This result suggested that bNAbs lacking the ability to engage Fc receptor–expressing (FcR-expressing) cells were capable of blocking new infections, but Fc-mediated cell-clearing effects are required for the full potency of bNAbs.

Bournazos and colleagues extended these findings to preexposure prophylaxis in an immunocompetent mouse model for HIV entry. They found that bNAbs engineered to express the murine IgG2a Fc subclass, which preferentially binds murine activating FcRs (mFcγRI and mFcγRIII) relative to inhibitory FcRs, were
The finding that single bNAbs were able to suppress viremia without escape in macaques — a result rarely seen in immunocompromised mice — suggests differences between the two models or the different challenge viruses used. Klein and colleagues investigated significantly more effective at preventing viral entry than their IgG1 Fc subclass counterparts (40). This effect was abolished in FcγRα−/− mice. Similar findings were reported in macaques. In models using both single high-dose viral challenge and repeated low-dose viral challenges, prophylactic treatment with WT b12 antibody markedly reduced viral acquisition relative to a variant of b12 that could not bind FcRs (L234A/L235A) (12, 41).

These findings show that Fc-mediated effects are important for both preventing and clearing infection. However, these studies did not produce direct evidence that productively infected cells were cleared by bNAbs. Rather, indirect measurements, such as time to rebound or onset of peak viremia, were reported. If bNAbs directly clear infected cells, viral clearance should be accelerated relative to ART, since new rounds of replication are blocked and infected cells are also cleared. These kinetic measurements are difficult in humanized mice because of the small number of infected cells, but such measurements were attempted in two separate macaque studies. In one study, Barouch and colleagues reported that plasma viremia declined at an accelerated rate in PGT121-treated macaques (0.383 log/day) (19) compared with that in ART-treated macaques (0.229 log/day) (42) or ART-treated humans (0.264 log/day) (43). However, Shingai and colleagues reported that an infusion of a combination of 3BNC117 and 10-1074 led to a plasma viremia decline of 0.225 log/day (20). Thus, the data from macaque studies are inconclusive in terms of viral clearance rates.

Overall, the evidence suggests that eliminating Fc-mediated function impairs the protective antiviral activity of bNAbs, but it is unclear whether enhancing ADCC activity improves protective efficacy. A nonfucosylated variant of b12 that had enhanced viral inhibitory and killing abilities in vitro failed to improve protection efficacy in vivo relative to WT b12 (44). Thus, definitive evidence for ADCC remains elusive. The development of sensitive assays to detect infected cells is likely necessary to clarify the role of bNAbs in these processes. While ADCC could impact the speed with which viremia becomes undetectable in patients treated with passive bNAbs, ADCC by itself is not sufficient for achieving viral remission. Boosting the immune system’s ability to control HIV and interfering with the latent reservoir are also necessary to achieve cure.
whether part of the difference was attributable to the macaques’ intact humoral immune system. They showed that sera taken from SHIV<sub>Ad8</sub>-infected NHPs was more potent against viruses carrying signature escape mutations to bNAbs than the corresponding primary WT isolates (45), suggesting that endogenously produced antibodies could keep viruses harboring bNAb escape mutations in check. Going forward, the critical question is whether passively administered bNAbs are capable of preventing viral escape in the presence of endogenous IgG. It is especially important to determine whether infected individuals whose viremia has been suppressed for protracted periods with ART harbor HIV-specific antibodies capable of neutralizing viruses carrying bNAb escape mutations. The answer should be borne out by ongoing clinical trials in which there is an opportunity to investigate the synergy between bNAbs and endogenously produced antibodies.

In addition to synergizing with endogenous antibodies, passive mAbs may stimulate the immune system (Figure I). Antibody therapy in macaques was shown to decrease expression of the exhaustion marker programmed death-1 on CD4<sup>+</sup> and CD8<sup>+</sup> T cells and increase the ability of cytotoxic T lymphocytes (CTLs) to suppress viral replication ex vivo (19). Modest increases in neutralizing titers were seen in some macaques, suggesting that the passive mAbs may have stimulated endogenous B cell responses. Immune complexes of antibody-bound viral particles are highly effective at stimulating dendritic cell maturation and immune responses and may provide a mechanism to explain the increased neutralizing titers (36). Although additional studies are necessary to clarify the magnitude, generality, and underlying mechanisms of these effects, the potential to augment anti-HIV-1 immune responses suggests that passive bNAbs should be explored in functional cure strategies. However, the utility of bNAbs in sterilizing cure requires targeting of the latent reservoir, which likely requires interventions in addition to bNAbs.

### Targeting the latent reservoir

Currently available therapies do not clear the latent reservoir. Studies in macaques and humans treated with ART shortly after infection demonstrated that an ART-refractory reservoir capable of producing rebound viremia is established as early as 24 to 72 hours after exposure (42, 46–48). Furthermore, the size of the latent reservoir is stable over time, even with continued ART (49). Although the complete cellular composition of the clinically relevant reservoir remains a subject of debate, resting memory CD4<sup>+</sup> T cells are certainly an important component. An estimated 10<sup>4</sup>–10<sup>7</sup> latently infected resting memory CD4<sup>+</sup> T cells are found within an individual (50). The exact half-life of these cells is difficult to measure accurately or precisely because of the limitations in the assays available to measure the reservoir. As a result, the average half-life of latently infected cells has been reported to vary from 6 to 44 months (49, 51–54), with an even wider range reported for individual patients.

Irrespective of the reservoir’s precise half-life, latently infected cells remain in the infected host for prolonged periods of time, and the mechanisms by which they persist are unknown. Intensifying ART from the normal three-drug regimens to five-drug regimens fails to measurably reduce the size of the latent reservoir (55, 56). Thus, interventions beyond ART are necessary to clear the latent reservoir. The leading proposed strategy, termed “shock and kill,” uses either immunologic or pharmacologic interventions to administer a “shock” that activates HIV replication within latently infected cells in the presence of ART. The objective is to induce viral transcription and activate productive infection, with the idea that productively infected cells die by cytopathic effects or immunologic attack (Figure II). ART is continued during this process to prevent the spread of infection (57). This strategy was first tested clinically by administering IL-2 and/or IFN-γ with the hope of stimulating T cell activation and HIV-1 transcription (58–60). However, cytokine therapy was too toxic for systematic evaluation, and the data indicated little or no impact on the latent reservoir.

More recent efforts have focused on histone deacetylase inhibitors (HDACis), which stimulate HIV transcription from latently infected cells, without inducing global T cell activation and cytokine storm (61, 62). The HDACis vorinostat, panobinostat, and romidepsin were shown to stimulate HIV transcription in latently infected cells obtained from ART-suppressed patients in vivo (63–65), as measured by cell-associated unspliced Gag transcripts. However, clinical studies showed no effect on latent reservoirs, as measured by quantitative viral outgrowth assays or the time to rebound after analytic treatment interruption (65, 66).

Why there was little or no measurable effect on the reservoir after HDAC inhibition despite increased Gag transcription is not known. However, the levels of transcription were low and, perhaps, insufficient to induce cell death. Consistent with this idea, Shan and colleagues showed that cells treated with vorinostat failed to die at the normal rate, despite reactivating an HIV-1 indicator gene, suggesting that vorinostat-reactivated cells do not die by cytopathic effects alone (67). Additionally, vorinostat induces transcription in only a small subset of latent cells (68, 69), making it unlikely that the subsequent disappearance of reactivated cells from the reservoir could be measured accurately. In total, the available data highlight the need for advances in both the “shock” and “kill” arms of the approach.

#### bNAbs and “shock and kill”

The role of bNAbs in “shock and kill” is linked to their ability to neutralize virions released from reactivated latent cells, kill infected cells, and access immune-privileged anatomic sites. Chun and colleagues showed that bNAbs bind and neutralize virions released from ART-suppressed patients’ resting CD4<sup>+</sup> T cells that are stimulated with CD3/CD28 antibodies (32). Because most proviruses archived in the latent reservoir of ART-treated patients are resistant to autologous CTL responses (70) and HDACis such as romidepsin and panobinostat may impair the function of virus-specific CTLs (71), relying on an infected individual’s CD8<sup>+</sup> T cells to kill reactivated cells likely requires therapeutic vaccination. In contrast, passive immunotherapy may block viral spread and can be individually tailored based on the resistance and sensitivity profiles of inducible viruses from a patient’s latent reservoir.

In addition to neutralizing virions released from reactivated cells, bNAbs may be able to kill reactivated cells directly. To function as effective killing agents, bNAbs have to bind reactivated cells and recruit cytolytic innate immune cells. bNAbs have been shown to bind Env on the surface of the latency reporter cell lines ACH2 and J89 stimulated with panobinostat
and romidepsin (72), but to date, bNAbS have not been shown to bind reactivated primary CD4+ T cells. Nevertheless, it is likely that reactivated cells express Env in response to inducing agents because viral particles bud and are detectable in supernatant (73, 74). New pharmacologic agents that induce detectable plasma viremia in patients who were previously viremia suppressed on ART could enable bNAbS to find and kill reactivated cells. GS-9620, a TLR7 agonist, was reported to induce detectable plasma viremia in ART-suppressed macaques (75); romidepsin was reported to do the same in humans (76). Determining the proportion of latent cells that are reactivated is critical for predicting whether these candidate inducers are likely to significantly impact the reservoir in patients.

The theoretical contribution of bNAbS to HIV eradication efforts is based on the general mechanisms of antibody function. This idea has only been tested in vivo in humanized mice with a combination of three bNAbS (PG16, 10-1074, and 3BNC117) and three viral inducers ([I-BET151, vorinostat, and anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA4)]. In that experiment, the combination of inducers and bNAbS reduced the proportion of mice showing viral rebound when antibody levels decayed, whereas treatment with antibodies alone or antibodies plus a single inducer did not reduce the proportion of mice with rebound viremia (39). The results highlight the likely necessity of a combination of mechanistically independent inducers to achieve sufficient viral transcription and viral spike cell surface expression to allow antibodies to exert their effects (77). However, the induced combination and dosing schedule were not optimized in that study, and efforts to identify optimal combinations of inducers (78) as well as technologies to effectively administer them (79) will be paramount for maximizing the ability of bNAbS to kill latent cells. Additionally, limitations of the mouse model required that viral suppression before administration of inducers was limited to several weeks as opposed to months in human trials. Furthermore, the size of the reservoir in mice is much smaller than in humans, and the composition of the reservoir is likely to be different. Clinical trials testing inducer combinations with bNAbS are required to see how this approach translates to humans.

bNAbS and anatomical sanctuaries
In addition to direct binding to infected cells, the role of bNAbS in HIV cure is attributable to their widespread tissue penetration where sufficient concentrations of ART may be limiting. While the existence of anatomic sanctuaries in which drug levels do not reach high enough levels is debatable, some tissues clearly support higher levels of viral spread than others, such as gut-associated lymphoid tissue and lymph nodes (80–82). It is possible that direct cell-to-cell spread of HIV in these tissues is less sensitive to ART because of the high multiplicity of infection that occurs in these tissues (82). In contrast, antibodies are found in high concentrations in interstitial fluids, and some bNAbS can prevent cell-to-cell viral spread in vitro (83, 84).

Certain cellular subsets may preferentially shield infected cells from autologous immune responses but are likely to remain sensitive to bNAbS. Fukazawa and colleagues showed that typical progressor monkeys exhibit widespread SIV infection across many CD4+ T cell subtypes, whereas elite controller monkeys with potent antiviral CD8+ T cell responses harbor infection predominantly in CD4+ follicular helper T cells (Tfh) in B cell follicles (85). Depletion of CD8+ T cells in elite controller monkeys causes reversible redistribution of SIV into non-Tfh cells, suggesting that the Tfh cells within the follicles are protected from CD8+ T cell-mediated clearance. Unlike CD8+ T cells, antibodies are not anatomically restricted from B cell follicles, and direct testing of effects of bNAbS on infected Tfh cells should be investigated.

While passively infused antibodies have widespread tissue distribution (13), a potential caveat is that they have poor penetration into the brain. The brain penetration of anti–HIV-1 bNAbS has not been measured in humans, but other human IgG1 class antibodies have been reported to achieve 500 to 1,000 times lower concentrations in the cerebrospinal fluid relative to serum (86, 87). Although the role of viral replication and viral reservoirs in the central nervous system and other potential sanctuaries such as reproductive organs remains unclear, the effects of bNAbS in these tissues require further investigation.

bNAbS and prevention
In addition to playing a role in eradication, bNAbS offer promise as prophylaxis though passive immunization (Figure 2). The initial phase I clinical data showing that 3BNC117 is effective and safe in humans support testing of this approach (21). As a result of their potency, low concentrations of bNAbS are able to prevent mucosal transmission in high-dose challenge models in humanized mice and macaques (13, 14, 88). Probit analysis of a large cohort of macaques treated with several different antibodies indicated that the amount of antibody needed for 50% protection against intraocular infection in macaques corresponds to serum levels of 100 times the IC_{50} of the antibody, as determined by in vitro infection assay of TZM-bl cells (15). However, humans infected by mucosal routes are typically exposed to low doses of HIV-1, and existing data indicate that the protective bNAb level may be lower than that required for high-dose challenge (11).

Because bNAbS are naturally arising, fully human products, they can have long half-lives on the order of 2 to 3 weeks. Based on the serum antibody levels reached by passive infusions of 3BNC117 and VRC01 in humans as well as the 17.5 day half-life of 3BNC117 in uninfected individuals (21), it appears that a serum level of 100 times the IC_{50} is achievable for long periods of time with infrequent infusions, making a biannual passive antibody injection within the realm of possibility for protection (Figure 2). As an alternative to mAb infusions, adeno-associated viral vectors expressing bNAbS have also been shown to provide lasting protection against HIV infection (89, 90). Clinical trials testing these concepts are necessary to determine how often anti–HIV-1 bNAbS can be administered and interfere with protection.

Perspectives
Despite the rapid progress of HIV antibody therapy, many challenges remain for eradication. The greatest obstacle is likely the identification of agents that sufficiently reactivate latent cells. With regards to bNAbS, determining which effector cells mediate ADCC most effectively — and ensuring that these cells are optimally targeted — is critical to maximizing therapeutic effects. Additionally,
determining which subclasses of antibodies exert the strongest effects in certain tissues could inform antibody-engineering efforts.

Finally, many potential modifications can enhance the antiviral functions of antibodies in vivo, such as mutations that enhance half-life, FcR binding, and potency (40, 91–93). Bispecific antibodies that express two different Fab regions have shown increased potency in vitro (94, 95), and coupling antibodies to immunotoxins to enhance killing of infected cells is being explored in vivo (96). Both strategies remain active areas of investigation. Considering the disappointments from HIV vaccine and cure trials performed to date, we must move forward with guarded optimism and a focus on the basic science behind HIV antibody functions. Hopefully the lessons learned will not only improve HIV treatment, but also accelerate development of mAbs for other highly mutable pathogens.

Acknowledgments

We thank all members of the Nussenzweig laboratory for critical reading of the manuscript. This work was supported by NIH Medical Scientist Training Program grant T32GM07739 to the Weill Cornell/Rockefeller/Sloan-Kettering Tri-Institutional MD-PhD Program (to A. Halper-Stromberg), NIH F30 grant AI09830-02 (to A. Halper-Stromberg), NIH Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (AI100663-04 to M.C. Nussenzweig), and National Institute of Allergy and Infectious Diseases grant AI100148-03.

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