paid. In other words, Congress is always free to refuse to honor its debts — and it has refused to honor these particular debts.

The Republicans acknowledge that an existing, permanent appropriation known as the Judgment Fund normally allows the executive branch to settle lawsuits against the United States. By its terms, however, the Judgment Fund is available only when payment is "not otherwise provided for." Drawing support from a memo compiled by the Congressional Research Service, they believe that they "otherwise provided for" risk-corridor payments when they partially funded the program.

But in fact the Judgment Fund is not unavailable whenever Congress chooses to partially fund a program. It is unavailable only when Congress has designated an alternative source of funds to pay money judgments arising from a failure to fulfill the United States' financial obligations.[5] Because Congress has made no such designation here, the Judgment Fund appears to be available to settle the risk-corridor lawsuits.

Health insurers thus appear to have a strong claim to several billion dollars from U.S. coffers. Which is not to say that insurers are sure to be paid. Under the next president, for example, Congress could amend the Judgment Fund to prohibit payment. And lawyers continue to wrangle over the complexities of appropriations law, creating some uncertainty about the litigation.

Eventually, however, Uncle Sam may have no choice but to pay up. With that upshot in mind, the Obama administration's willingness to open settlement negotiations appears neither feckless nor unlawful. On the contrary, it is the responsible thing to do.

Disclosure forms provided by the author are available at NEJM.org.

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FOCUS ON RESEARCH

Broadly Neutralizing Antibodies for HIV-1 Prevention or Immunotherapy

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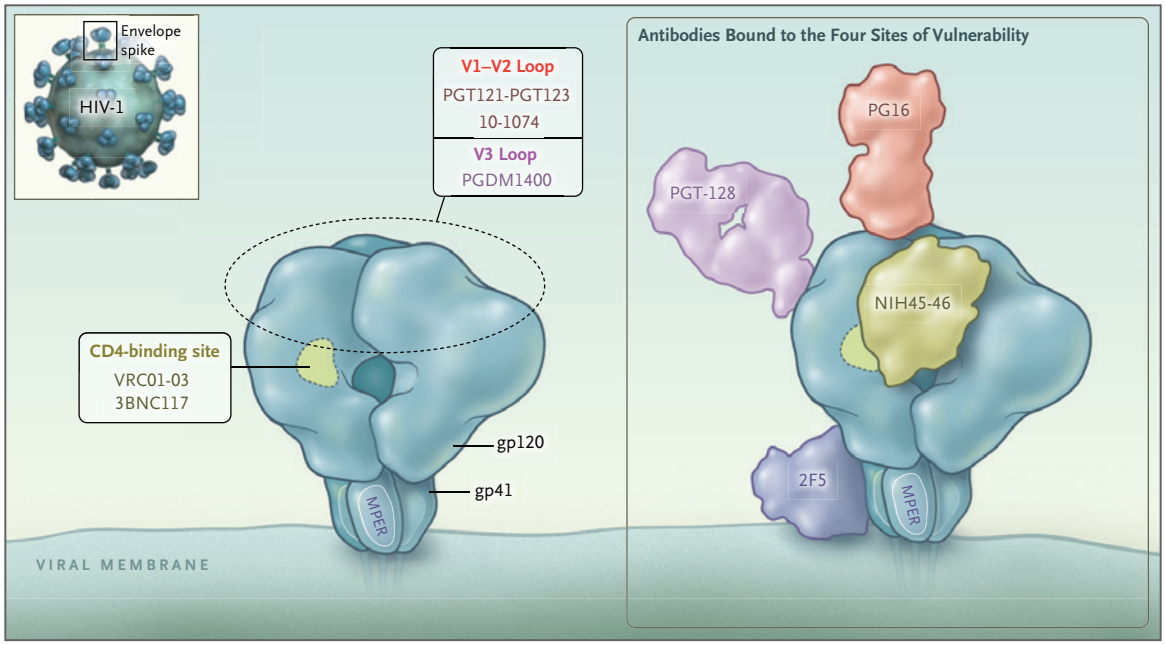
Despite tremendous efforts to prevent transmission of human immunodeficiency virus type 1 (HIV-1), new infections and AIDS-related deaths continue to be a global problem. Antiretroviral therapy (ART) can effectively suppress HIV-1 replication and limit disease progression. However, ART fails to eradicate the virus, and suppression requires lifelong therapy, which may have side effects and poses a risk of the development of resistance. New approaches to preventing and treating HIV-1 infection are therefore necessary to contain the epidemic and to bolster nascent efforts to find a cure.

A new generation of highly potent broadly neutralizing antibodies (bNAbs) may represent a promising approach to combating HIV-1 infection.[1] Although antibodies that neutralize HIV-1 were discovered shortly after the disease was first described, most HIV-1–infected people produce nonneutralizing antibodies or antibodies that neutralize only a limited number of different HIV-1 strains. However, high serum titers of HIV-1 neutralizing activity develop in a small fraction of infected persons. In contrast to the typical antibody response, bNAbs can take years to develop, and it has not yet proved possible to elicit them by standard immunization strategies.

Isolation of bNAbs from infected persons with high levels of HIV-1–neutralizing serum activity (so-called elite neutralizers) was not easily achieved until the advent of single-cell–based anti-HIV-1 antibody cloning techniques.[2] The anti–HIV-1 antibodies obtained



HIV-1 Spike Protein, Showing Sites Targeted by Broadly Neutralizing Monoclonal Antibodies.
The inset shows the virus with its surface spikes. The left panel shows target sites of monoclonal antibodies in clinical development. The right panel illustrates the binding of four different broadly neutralizing antibodies.

by this and subsequently developed related methods had a number of unusual characteristics that partially account for the difficulty of developing a vaccine that can elicit bNAbs. The most prominent of these features is a high level of somatic hypermutation, which is required to accommodate binding to the highly glycosylated viral envelope protein. Some of the new bNAbs can neutralize up to 90% of HIV-1 strains worldwide at low concentrations.[1] Moreover, bNAbs recognize many sites on the viral envelope spike (see diagram). Antibodies currently being tested or under development for clinical use target the CD4-binding site, a glycan patch surrounding the V3 loop, and the apex of the HIV-1 spike.[3] It thus seems possible that they could be used in combination to prevent or control HIV-1 infection. As with other drugs, the efficacy of any single anti-HIV-1 antibody in preclinical and clinical trials is related to the potency and breadth of its activity against different HIV-1 isolates. Like monotherapy with small-molecule antiretroviral (ARV) drugs, the administration of a single anti-idiotypic bNAb selects for resistant variants. As recently reported,[3] in work that Bar et al. have extended, bNAbs are being studied as a potential way to suppress viremia during analytical treatment interruption. The degree of efficacy in maintaining viral suppression in these and other studies was most likely related to the potency of the bNAbs.[4,5]

However, antibodies are currently expensive to produce and must be administered parenterally. In contrast, small-molecule ARV drugs can be synthesized at low cost, are administered orally, and are highly effective. So it is important to ask why we should bother investigating the use of antibodies for HIV-1 prevention or therapy.

Several unique features of antibodies make them interesting to explore as drugs for HIV-1 prevention and therapy. First, antibodies differ from small-molecule drugs in having naturally long half-lives of 2 to 3 weeks. It was this property that made it possible, before the advent of an active hepatitis vaccine, to administer pooled antihepatitis immunoglobulins as a passive vaccine to prevent infection in travelers for up to 3 months. The same is true for bNAbs and HIV-1 prevention. A single administration of anti-HIV-1 bNAbs can protect macaques for up to 23 sequential weekly challenges.[5] Moreover, the antibody half-life can be increased by a factor of 2 to 4 by point mutations in the constant (Fc) re-

gion of the molecule. For example, in clinical investigations, an anti–respiratory syncytial virus antibody that carries half-life extension mutations showed neutralizing activity for 240 days after administration in humans. When similar mutations were introduced into anti-HIV-1 bNAbs, they resulted in a prolonged half-life and extended the protective effects in macaques.[5]

The pharmacokinetic properties of anti-HIV1 bNAbs with half-life–extending mutations are currently being tested in humans. It is entirely possible that bNAbs could be used as passive vaccines administered subcutaneously on a quarterly or a biannual basis. In contrast, the best small-molecule drugs in late-stage clinical testing have to be administered intramuscularly every 2 months for prevention or therapy. More important, decaying levels of these long-acting drugs may allow selection of resistant viral strains, and persons in whom oral or injectable small-molecule drugs fail to prevent infection because of breakthrough resistant viruses will probably have no response to antiretroviral regimens containing the same drug classes. In contrast, infections with breakthrough antibody-resistant strains would be very likely to be sensitive to standard ARVs, since the targets of the bNAbs that are currently in clinical testing do not overlap with those of approved ARVs.

Another reason to explore bNAbs in the context of HIV-1 infection is their potential as immunotherapeutics. This idea is similar to the rationale for using antibodies in cancer immunotherapy: antibodies engage the host immune system to fight disease. They do so by binding the target cell, which is then flagged for killing and phagocytosis by host leukocytes. One of the results of this type of immune opsonization is enhanced target-cell clearance. A second effect is to activate dendritic cells by opsonized immune complexes, leading to enhanced antigen processing and presentation to T cells. Activated T cells can kill target cells directly or act as helper cells for antibody responses. In the context of cancer therapy, host immune responses can produce lasting remissions. In the HIV-1 context, they can control viral replication in the absence of drugs, as seen in some HIV-1–infected patients.

The potential contribution of immunotherapy in the context of HIV-1 infection may be particularly important when it comes to the possibility of HIV-1 eradication. In phase 1 clinical trials, bNAbs enhanced clearance of HIV-1, infected cells, or both and boosted host humoral immunity to HIV-1.

These antibody-mediated immune-enhancing effects might lead to better control of viral replication and reduce the size of the long-lived latent reservoir that persists despite suppressive ART. It is important to note, however, that the immune-engaging features of antibodies are mediated through binding of antibody to available antigen. Suppressive ART may therefore dampen these potential effects by a nearly complete shutdown of viral replication. It will therefore be important to further evaluate the effects of bNAbs in combination with strategies aimed at reactivating latent proviruses in the presence or absence of standard ART.

Although bNAbs have attractive properties, particularly for HIV-1 eradication strategies, as compared with standard ART, resistance does develop during antibody monotherapy. Moreover, preexisting resistance to individual bNAbs, as described in our work[3,4] and by Bar and colleagues, may also pose a challenge to their use, especially during chronic HIV-1 infection. We speculate that a combination of bNAbs, like combinations of small-molecule ARV drugs, can avert selection of escape variants. Ongoing studies aim to explore their use for HIV-1 prevention and immunotherapy in infected persons.

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