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# NOVEL PREVENTIVE AND THERAPEUTIC STRATEGIES AGAINST HIV INFECTION

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**Abstract** Since its first isolation in 1983, the human immunodeficiency virus (HIV) has infected over 77 million people and only one patient from whom the virus was completely removed from the body was documented. A recent second case was reported that remains to be confirmed. Antiretroviral therapy (ART) manages to control blood viral replication and, consequently, to restore –at least partially– the functions of the immune system with a notable reduction of the morbidity and mortality associated with HIV infection. However, given the difficulty in eliminating the virus from the body, treatment has to be given for life. This long-term exposure to antiretroviral drugs implies the risk of generating intolerance, toxic effects, gaps in adherence and selection of resistance mutations. Another limitation is the high cost of treating 37 million persons living with HIV, most of whom are living in resource-limited countries and relying on international aid initiatives. Having these challenges in mind, there is general agreement that new approaches for preventing and treating HIV infection are needed to control the epidemic, while efforts on vaccine development continue. In this regard, new generation broadly neutralising monoclonal antibodies (bnMAbs) against the HIV envelope protein can prevent virus acquisition, reduce viremia, enhance immunity, and induce the killing of infected cells in animal models of HIV infection. Most importantly, some clinical trials have shown that bnMAbs could effectively decrease viremia and delay viral rebound in people chronically infected with HIV.

**Key words**: HIV, antiretroviral therapy, neutralizing antibodies, HIV treatment and prophylaxis

**Resumen** ***Nuevas estrategias para el control y la prevención de la infección por HIV.*** Desde su primer aislamiento en 1983, el virus de la inmunodeficiencia humana (HIV) ha infectado a más de 77 millones de personas y solo se ha documentado un caso en el cual el virus fue removido completamente del organismo; aún resta confirmar un segundo caso informado recientemente. El tratamiento antirretroviral logra controlar la replicación viral en el plasma y en consecuencia recuperar (al menos parcialmente) la actividad del sistema inmune, con una notable reducción de la morbilidad y la mortalidad asociadas a la infección por HIV. Sin embargo, ante la dificultad para eliminar completamente el virus del organismo, es necesario continuar el tratamiento de por vida. Esto implica la exposición a largo plazo a drogas antirretrovirales con riesgo de generar intolerancia, efectos tóxicos, brechas en la adherencia y selección de mutantes resistentes. Otro aspecto a considerar es la carga económica que implica tratar a 37 millones de personas infectadas con HIV, la mayoría de ellas en países que solo pueden afrontar esos costos con ayuda internacional. Por ello, hasta tanto se disponga de una vacuna capaz de prevenir la infección de todas las formas circulantes del HIV, es necesario desarrollar nuevas herramientas terapéuticas capaces de complementar y potenciar los efectos del tratamiento antirretroviral. Diversos ensayos preclínicos sugieren que la administración pasiva de anticuerpos monoclonales dirigidos contra la glicoproteína de envoltura viral podría prevenir la infección, reducir la carga viral, estimular la respuesta inmune y favorecer la eliminación de células infectadas con HIV.

**Palabras clave**: virus de la inmunodeficiencia humana, HIV, tratamiento antirretroviral, anticuerpos neutralizantes, tratamiento y profilaxis de HIV

The human immunodeficiency virus (HIV) targets CD4+ T-cells impairing irreversibly the immune system. Acquired immunodeficiency syndrome (AIDS) refers to the final stage of HIV infection, which is characterized by a compromised immune state (CD4+ T-cells counts < 200/ml) and the eventual presence of multiple concurrent opportunistic infections.

In order to control the HIV epidemic it is necessary to strengthen prevention programs targeting populations at high risk of acquiring infections (i.e., men who has sex with men, transgender people and sex workers). The idea of combined prevention measures includes sex education, promoting safe sex practices including the use

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and distribution of condoms, circumcision, treatment of other sexually transmitted infections, and pre-exposure prophylaxis (PrEP). In countries where the number of intravenous drug users is high, opioid substitution therapies and safe injection sites should be provided in order to reduce HIV transmission.

Heath care providers should give advice regarding the benefits of early HIV testing, counselling and therapy initiation. It has been demonstrated that HIV-infected people under antiretroviral therapy (ART) who are virally suppressed (i.e. < 200 HIV copies per blood millilitre for < 6 months) do not transmit the virus sexually and can even prevent transmission through syringe sharing and from mother-to-child during pregnancy. This underlies the concept of "treatment as prevention" or "U = U" (undetectable = untransmissable). It should also be considered that social stigma and discrimination increase vulnerability and hinder prevention, treatment and care of people living with HIV or at risk of acquiring it.

## Antiretroviral drugs to control and prevent HIV

In the absence of an effective vaccine, ART constitutes the most effective preventive and therapeutic strategy against HIV. Antiretroviral drugs interact with various viral components, interfering with their biological cycle. With adequate adherence to treatment, these drugs suppress viral replication, reaching undetectable plasma viral load levels both in plasma and genital secretions. At an individual level, this translates into an immunological and clinical improvement, as well as a reduction in mortality due to secondary diseases, such as opportunistic infections and cancer[1]. Further, the viral load suppression eliminates the risk of horizontal and vertical transmission of HIV[2]. These principles constitute the fundamental basis of the strategy called "treatment as prevention". Therefore, we must emphasize the importance of initiating treatment immediately, once the patient is ready[3].

Thanks to the recent availability of a wide spectrum of drugs that achieve virological control, the objectives are currently focused on simplifying therapeutic regimens. To this end, the trend is towards regimens including only two drugs with long half-life that allow weekly, monthly, or even semi-annual dosing. Dual therapy protocols improved safety, tolerability, and treatment adherence with lower risk of default[4-7]. In addition, this strategy reduces treatment costs, both for people without prior treatment (naïve) and for those on a triple therapy regimen with undetectable viral load levels. Also for aging persons living with HIV, dual therapy presents an effective alternative to prevent the appearance of side effects associated with prolonged antiretroviral treatment. Although the preferred regimens are still the combination of three agents active against HIV, international and local guidelines list dual therapy as an alternative[8, 9].

Another obstacle to HIV treatment is the emergence of HIV resistance to antiretrovirals. New therapeutic approaches are needed for treating patients who no longer have effective drug combinations available. One is ibalizumab (TMB-355), a monoclonal antibody that acts on the CD4 receptor of helper T-lymphocytes[10], instead of directly on the virus (as explained in the following section). Recent studies have shown a reduction in the viral load of patients infected with multi-resistant HIV, stemming from the use of ibalizumab as part of ART. Another novel aspect of this drug is that it has been approved for injectable dosing every two weeks. In this way, long-acting antiretrovirals gain further relevance. The main drawback of this compound is its exorbitant cost.

The possibility of administering monthly or bimonthly treatment would be an option for people with adherence problems. Along this line of research, clinical studies are being carried out to allow approval of long-acting injectable drugs, both for treatment and use in pre-exposure prophylaxis (PrEP)[11, 12]. The ATLAS study (NCT02951052) has demonstrated non-inferiority of an injectable regimen of two prolonged-release drugs (cabotegravir and rilpivirine) every 4 weeks compared to maintenance of the current ART regimen. Along this same line, the FLAIR study (NCT03299049) uses the same drug regimen, but with 8-week intervals, this time in naïve patients following 24 weeks of oral induction. With a similar model, new studies are being developed (NCT02720094 and NCT03164564) directed at high risk populations, which incorporate this type of dosing as PrEP in order to optimize adherence.

The efficacy of PrEP using antiretroviral agents (tenofovir/ emtricitabine, taken orally) has been established in clinical trials involving transgender women, men who have sex with men, heterosexual populations, and intravenous drug users. These results have generated the formal recommendation of PrEP by multiple agencies and scientific entities[13]. It is important to emphasize that the strategy of selection of potential candidates for these studies must include people in whom HIV infection has been ruled out and who are at marked risk of acquiring it. With the success of PrEP closely related to medication adherence, health services providing PrEP must analyse each case punctually, in addition to providing access to HIV testing and other sexually transmitted infections, including hepatitis B, and prescribing the corresponding vaccines when appropriate. The global increase in ART coverage has reduced the number of AIDS-associated deaths, mostly due to the reduction in new infections. However, several obstacles must still be overcome.

## Neutralizing antibody therapy and prophylaxis

The rapid establishment of a latent reservoir in its provirus form, the high mutation and replication rate, and the direct impairment of key immune components are some features that allow HIV to effectively evade the immune response. However, most HIV+ patients develop a strong and specific immune response against HIV. Moreover, a small number of HIV+ patients (1%) develop neutralizing antibodies accounting for a remarkable neutralization breadth (able of neutralize > 80% circulating viral variants)[14]. During natural infection, HIV evades the neutralization pressure exerted by the patient´s broadly neutralizing antibodies; however, the passive administration of broadly neutralizing monoclonal antibodies (bnMAbs) can modulate HIV viremia. In the last decade, several technological advancements allowed the recovery of a large group of bnMAbs targeting different epitopes on HIV envelope protein (Env)[15]; the efficacy of some of these antibodies preventing and controlling HIV infection have already been tested in different preclinical and clinical settings.

### *Preclinical testing of bnMAbs in animal models of HIV infection*

To date, several studies showed that, when administered in advance of virus challenge, the passive infusion of bnMAbs was able to block HIV or SHIV (simian-human immunodeficiency virus) infection in mouse and macaque models of HIV infection, respectively[16]. These results indicate that a vaccine able to elicit a similar humoral immune response in humans would effectively prevent HIV infection.

Another series of studies showed that the passive administration of different combinations of bnMAbs to macaques chronically infected with SHIV was effective in suppressing viremia and avoiding the emergence of resistant viral variants[17]. Remarkably, if administered during the first 24 hs after infection the combination of bnMAbs interfered with the establishment of the viral reservoir and allowed a complete clearance of the virus[18].

Importantly, preclinical trials have shown that the effect of bnMAbs exceeds its ability to neutralize free viral particles; in addition, bnMAbs can induce the killing of HIV-infected cells through the engagement of Fc-receptor (Fc-R) present in NK and phagocytes[19, 20]. Moreover, bnMAbs can control excessive virus replication, induce the formation of immune complexes, and exert an strong selective pressure on Env; altogether these features can boost the immune response against HIV[21, 22].

Of note, since bnMAbs have a particular biodistribution, they could reach different body compartments where ART do not penetrate, as is the case of the germinal centres in the lymph nodes.

### *Long-lasting HIV suppression by combined immunotherapy*

To date, two bnMAbs directed to the CD4-binding site (VRC01 and 3BNC17) and one bnMAb targeting a glycan site present in the third hyper variable loop (V3) on Env have been separately used in a series of clinical trials. In general, monotherapy with these powerful bnMAbs was safe and showed a modest effect in reducing viremia and delaying viral rebound in HIV-chronically infected people who were not receiving ART and those who were under analytical treatment interruption (ATI), respectively[23-27]. Treatment effectiveness (i.e. viremia reduction and time to rebound) was associated with the neutralization sensitivity of the different viral variants present at the initiation of treatment. However, single bnMAb therapy did not maintain long-term HIV suppression and resistant viral variants arose. Since no single bnMAb is able to neutralize all circulating HIV variants with sufficient potency, it is necessary to combine at least two bnMAbs, targeting different Env sites in order to increase immunotherapy efficacy and avoid the emergence of resistance. In this regard, two recent studies have shown that combined immunotherapy with 3BNC117 and 10-1074 induced long-lasting viremia control in people chronically infected with HIV[28, 29].

### *Challenges associated with the use of bnMAbs in clinical settings*

Apart from the emergence and selection of resistant viral variants, several challenges associated with the use of bnMAbs must be considered, as is the case of the high cost of bnMAb production, the frequency and route of administration, and bnMAbs biodistribution in vivo. These limitations prompted the rational design of different bioengineered bnMAbs with greater neutralization breadth, higher potency, enhanced Fc-function and extended half-life. As an alternative to combined immunotherapy, multivalent bnMAbs (targeting several vulnerability sites on Env) have been developed. Xu and col. developed a tri-specific-bnMAb with the highest potency and neutralization breadth (> 99% of 208 tested viral variants) for a single molecule described to date[30]. Moreover, the addition of particular point-mutations into the Fc region of the VRC01-LS molecule can increase the antibody binding to the neonatal Fc-R, leading to extended in vivo half-life. Based on preliminary data, it has been estimated that the VRC01-LS version of VRC01 could maintain its therapeutic effect if administered subcutaneously twice a year[31]. Further modifications in the Fc region of bnMAbs can enhance the antibody effector function, and consequently, increase the clearance of HIV-infected cells induced by bnMAbs[32]. Such antibodies might account

for a stronger reduction of the viral reservoir, potentially allowing a functional cure of HIV infection. Although most of these novel modified-bnMAbs remain yet to be tested in clinical settings, there is general agreement in that these upgrades will allow to reduce the number of doses and dosages, and most importantly, the treatment cost.

*Prophylactic effect of bnMAbs*

Currently, two large scale phase 2b clinical trials –enrolling 4200 participants– have been initiated to test the efficacy of VRC01 in preventing HIV acquisition in high risk populations[33]. If effective, these studies will also define protective antibody titres and other correlates of protection, which in turn will help to evaluate future vaccine candidates. In addition, a series of studies are evaluating the safety and efficacy of VRC01 for the prevention of mother-to-child transmission of HIV.

## Therapeutic vaccines

Therapeutic HIV vaccines aim to improve the immune response of HIV-infected persons in order to modulate the clinical progression of the disease and avoid the evolution of AIDS. Additionally, treating people with these vaccines would ideally keep HIV at undetectable levels without the need for daily ART. In the previous sections we explained how long-acting ART and bnMAbs with increased half-lives could contribute to this strategy. Other approaches include vector-mediated gene transfer to secrete bnMAbs into circulation (vectored immunoprophylaxis or VIP), the *ex vivo* stimulation of T-cells, and the use of cytokines to re-direct and potentiate the immune response. Another strategy known as shock-and-kill consists of a two-step process where latency-reversing agents induce HIV transcriptional reactivation in latently infected cells, and then, reactivated cells can be efficiently eliminated by the immune system or anti-HIV drugs. By targeting the latent viral reservoir, this approach could potentially eliminate HIV from the body thus achieving the functional cure of HIV infection. Although there is currently a large number of therapeutic HIV vaccines under development and evaluation, none of them is approved for use in patients.

## Final considerations

The history of ART has shown unprecedented advances in the field of medicine. Only 6 years elapsed between the description of the first AIDS cases (1981) and the approval of the first drug with proven antiretroviral activity, zidovudine (1987); today we have 32. Current formulations allow prescribing combination therapy of 2 or 3 drugs with only 1 or 2 tablets, taken daily. The efficacy of current regimens, especially those based on integrase inhibitors, exceeds 90%, with excellent tolerance and easier adherence to treatment. Despite the lack of an effective vaccine, the global increase in ART coverage has reduced the numbers of AIDS-associated deaths and new infections.

While ART suppresses viral load effectively, HIV rebounds rapidly once treatment is interrupted, even after years of viral suppression. For this reason, the possibility of combining ART with other therapies directed against the viral reservoir has gained interest. About ten years ago, a case of HIV cure has been reported in a patient undergoing stem cell therapy (a second case with similar characteristics still needs to be confirmed)[34]. However, the complexity and risks associated with this kind of interventions prevent their generalization. On the other hand, bnMAbs could complement ART due to their ability to neutralize free viral particles, enhance the immune response and induce the destruction of HIV-infected cells. The first clinical trials with bnMAbs have demonstrated that combination immunotherapy can contain viral loads for prolonged periods without the emergence of resistance. The current challenge is to optimize all available resources to design better therapeutic and prophylactic regimens until an effective vaccine against all circulating HIV variants is developed.

The future of this epidemic depends on the political will of governments to meet the goals of UNAIDS, which means diagnosing 90% of people living with the virus, treating 90% of those diagnosed, and maintaining undetectable viral load in 90% of those treated. This strategy of “treatment as prevention”, associated with the expansion of PrEP, could allow to control the epidemic in little more than a decade. No infectious disease has been eradicated in the absence of an effective preventive vaccine and/or a cure strategy. On the way to both objectives, a comprehensive approach would combine the excellence of available antiretroviral drugs with strategies to enhance immune system activity (e.g., immunotherapy with bnMAbs or a therapeutic vaccine). If we apply such an approach in a social context free of stigma and discrimination, we can look to the future with cautious, but renewed, optimism.

**Conflict of interest:** None to declare

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