

NEW PARADIGMS IN HIV THERAPY: BOOSTING HIV IMMUNITY

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INTRODUCTION

We are now at a crossroads in HIV therapy. As a result of the development of anti-retroviral drugs that interfere with HIV replication, it is possible to suppress the virus to undetectable levels. However, it is clear that we have yet to cure this insidious infection, because as soon as the drugs are discontinued, the virus returns within 2-3 weeks. The antiviral drugs, all of which interfere with the function of key viral gene products, impair viral replication so well that the total body viral burden can be reduced to only 1 infected cell per million. As there are approximately 10^{12} total lymphocytes in the body, there remain about 1 million infected cells after the application of effective antiviral therapy. Therefore, these residual infected cells constitute the problem now confronting us. Almost all of the residual infection consists of cells that contain virus integrated into the cellular DNA. For the most part, these residual viral genes remain dormant and are not expressed. Consequently, these viral genes are resistant to the effects of the antiviral agents, which by definition can only inhibit viral particles that are in the process of trying to express themselves and to reproduce. Accordingly, it is necessary to continue to expose the cells to antiviral drugs, in that as soon as they are discontinued, viral gene expression and replication resumes.

Thus, what can be done about the residual infection that remains after effective antiviral therapy? The answer to this question resides in the immune system.

The Basics of the Immune System

Before the advent of the Acquired Immunodeficiency Syndrome (AIDS), the immune system was poorly understood and taken for granted by most people. However, discussions of the immune system and immunology became commonplace when AIDS highlighted the consequences of immune system failure, which resulted in life-threatening “opportunistic infections” by microbes that rarely infected and caused disease in normal individuals. A normal immune system is obligatory to keep potential environmental pathogenic microbes from gaining entrance and causing disease. The immune system has evolved under the selective pressure of the microbial world, which constantly attempts to gain entrance to the warmth and nutrients inside the body.

We have gained a reasonable understanding of how the system recognizes and responds to the invasion by foreign microbes only within the past 20-30 years.¹ Superficially, the system functions quite simply. If the microbe is capable of replicating *outside* of cells, the “humoral” immune response, mediated by antibody molecules, is of primary importance. These specialized molecules are capable of recognizing the foreignness of the surface of the microbes, and can attach to them very effectively. Subsequently, specialized cells called phagocytes (from the Greek, an “eating cell”), identify the antibody-microbe complexes, ingest and digest them, thereby clearing the microbes from the body.

By comparison, if the microbe can only live and replicate *inside* cells, as most viruses do, then they can evade the

antibodies, and cell-mediated immunity (CMI) comes into play. The cells involved in CMI consist of the T cells, but as well, phagocytes are also players, as are a distinct kind of lymphocyte called Natural Killer (NK) cells. Of these cells, the Cytolytic (killer) T Lymphocytes (CTL), which are identifiable because they express molecules termed CD8, are of prime importance because they are actually capable of recognizing, binding to, and killing virus-infected cells. When viruses infect cells and replicate inside of them, parts of the viral components find their way to the surface of the infected cells, where they can be detected by the CD8+ killer T cells. This mechanism becomes of extreme importance, because otherwise the virus could replicate unimpeded, hiding within the host cells.

Given that CMI deals with virus-infected cells by actually killing them, it follows that the number of killer T cells, and how well they can kill becomes important. In this regard, the killer T cells receive “help” from helper T cells, which are recognized by their expression of CD4 molecules on their surface. Helper T cells aid killer T cells by producing molecules termed cytokines or interleukins (meaning “between white cells”). These molecules are like hormones, which function to provide signals from one cell to another. The signals delivered tell the recipient cells to multiply, to function and to survive.

One of the most important cytokines for the CMI response is interleukin 2 (IL2). This cytokine was originally called T Cell Growth Factor (TCGF),² which in many respects is a more apt name, in that it tells one about the target cell and function of the molecule. IL2 functions

to promote the proliferation, function and survival of T cells that have recognized the presence of an invading microbe.³ Most (~ 80%) of the IL2 produced during an immune reaction is derived from CD4+ helper T cells. Therefore, whereas CD8+ killer T cells need and use IL2, only 20% of the IL2 produced is actually attributable to the killer cells themselves.

Other important cytokines produced during an immune reaction include interferons (IFN) and a family of molecules originally termed Tumor Necrosis Factors (TNF).¹ These cytokines can impair viral replication within infected cells by sending signals to their interiors via surface receptors. IFN signaling pathways are activated that interfere (hence the name) with the ability of the virus to reproduce itself. It is important to note that killer T cells are among the biggest producers of these antiviral cytokines. Moreover, it has recently become recognized that deficiencies of these cytokines or defects in their abilities to signal lead to selective defects in CMI, which result in opportunistic infections by microbes that cause intracellular infections, such as TB and viral infections.

In HIV Infection, the Immune Response is “Good”

Most infections are combated by a combination of “Natural” or innate host defenses, mediated by NK cells and phagocytic cells, followed by the mobilization of microbe-specific host defenses, mediated by T cells and B cells. Some of the earliest reports on the host reaction to infection by HIV revealed that after infection there was a period of rapid increase of the

concentration of the virus detectable in the blood. Actually, the doubling time of the virus was calculated to be only ~ 0.4 days (~ 10 hours).⁴ This rapid replication rate reflects the capacity of the viral genome to reproduce itself in a host that has yet to recognize the presence of the virus and to mobilize the T cell response. Accordingly, the virus concentration increases exponentially for ~ 2-3 weeks, eventually reaching a peak concentration between 1-100 million viral particles/mL of plasma.^{4,5} In this “primary” infection, the natural or innate system is the only host defense operative.

After an interval of 2-3 weeks of viral replication, impeded only by the innate host defenses, the T cell immune responses eventually become evident. The reason that the T cell immune responses do not mobilize more rapidly relates to the small numbers of T cells initially that are capable of recognizing HIV. Of the approximately 1 trillion lymphocytes (10^{12}), only about 1 million (10^6) are estimated to be HIV-specific cells (0.0001%). Thus, it takes days and weeks for the HIV-specific cells to multiply enough to become capable of matching the replicative capacity of the virus. In viral infections of experimental animals, where we have the ability to identify and quantify the virus-specific cells more readily, the rate of doubling of the killer T cells has been found to be ~ 6 hours, and within a week the virus-specific cells expand > 100,000-fold (> 10^5).⁶ If this same magnitude of response occurs in human HIV infection, one would expect the frequency of HIV-reactive killer T cells to increase from 0.0001% to 1.0% within one week. This would amount to an absolute increase from 1 million (10^6) HIV-reactive killer

T cells to 100 billion cells (10^{11}), a quite impressive mobilization of forces.

Once this host reaction occurs, and the killer T cells begin to kill HIV-infected cells, as well as impair viral replication by the production of antiviral cytokines, such as the IFNs and TNFs, the concentration of the virus in the blood begins to decline. The rate of decline has been measured and calculated to yield a half-time ($t_{1/2}$) of ~ 2 ½ days.⁴ Thus, within 10 days, the peak viral concentration can decrease as much as 90-95%. Subsequently, the HIV concentration in the blood reaches a stable “trough” level, which has been termed the “set point”, and which usually remains quite stable for months and even years. This set point generally ranges from 10,000-1 million (10^4 - 10^6) HIV particles/mL.

Coinciding with the decline in viremia there is a rapid increase in CD8+ killer T cells in the blood. The increase is generally at least a doubling or tripling of the CD8+ T cell concentration, from a normal of ~ 500 cells/ μ L (500,000 cells/mL) to ~ 1,000-1,500 cells/ μ L (1-1.5 million cells/mL). Although it has yet to be shown conclusively, HIV-specific cells account for most, if not all of the increase in the killer T cells. Thus, if the peak virus concentration is 1 million particles/mL, the circulating HIV-specific killer T cell concentration also becomes ~ 1 million cells/mL. Then, when the HIV concentration declines ~ 100-fold from the peak to the set point, the CD8+ T cell concentrations remain elevated, so that the ratio of killer T cells: virus becomes 100: 1. Presumably, this host killer T cell response then maintains the HIV concentration at a relatively low level for

a long time, thereby accounting for the chronic nature of the infection.

This interpretation of the importance of the CD8+ killer T cell response in primary infection by HIV has received very convincing support from experiments in monkeys infected with the Simian Immunodeficiency Virus (SIV).^{7,8} Monoclonal antibodies reactive with the CD8 molecules on killer T cells were used to deplete monkeys of detectable circulating CD8+ T cells before inoculation with SIV. When CD8+ T cells were completely depleted before inoculation of virus, the peak levels of viremia were similar to non-depleted animals, but the viral levels of the CD8-depleted animals failed to decline from the peak viremia. By comparison, the SIV concentration declined 10-1,000-fold from a peak of $\sim 10^8$ particles/mL in control, non-CD8-depleted animals.

Even more compelling evidence of the importance of CD8+ T cells in the control of viral replication are the results from experiments depleting CD8+ T cells of monkeys infected chronically.⁷ Transient depletion of CD8+ T cells resulted in a 100-1000-fold increase in plasma SIV concentration, which then returned to baseline when the circulating CD8+ concentration also returned to baseline. Accordingly, the CD8+ T cell recognition and response to both acute and chronic infection is one of the major determinants of the host control of this viral infection, as it is in all other viral infections.

In HIV infection the Immune Response is “Bad”

With ongoing replication of virus and an ongoing attempt on the part of CD8+ T cells to kill infected cells, a slowly progressive decline in CD4+ T cells ensues. Individuals infected in 1982-1983 were followed for 10 years before effective antiviral therapy was available, and the rate of decline of circulating CD4+ T cells was found to have a half time of ~ 7 years. Therefore, this disease is not a medical emergency. However, it seems obvious that the rate of immune-mediated destruction of virus-infected cells is slightly faster than the rate of production of new cells, so that with continuing viral replication, there is ongoing destruction of infected cells. In this respect, because the immune system cannot totally reduce the infected cells to zero, eventually the immune system destroys itself.

Ultimately the Immune Response is Inadequate

If the CMI response is so effective in controlling viral replication, it is not immediately apparent why it cannot totally eradicate all HIV particles, as it does in other viral infections, such as those caused by the herpes virus family? This fundamental question still remains unanswered, although we have made considerable progress in narrowing the possibilities to those hypotheses focused on the virus vs. the immune system.

HIV is one of the smallest known viruses, containing only 10 genes. By comparison, the largest viruses, e.g. the poxviruses and the herpes viruses contain > 200 genes. These large viruses have incorporated many cellular genes

that allow the viruses to evade the immune system. Although HIV has not appropriated host cellular genes, one of the ways that HIV evades the immune system is by becoming dormant, integrating into the cellular genome. As long as the latent integrated viral genes are not expressed, the immune system has no way of detecting the infected cells. Another advantage of being small is that it is much easier to reproduce. Thus, the rate of replication of HIV is much more rapid than other, larger viruses. Accordingly, HIV establishes a race between itself and the capacity of CD8+ T cells to kill infected cells. Therefore, HIV takes either one of two extremes, it either hides as a latent genome, or it replicates so rapidly that it outstrips the capacity of the immune response to contain it.

Another possibility that has received a lot of attention is that the virus may undergo random mutations that allow HIV to evade the capacity of the killer T cells to recognize it. This phenomenon has been termed “CTL escape”.⁹ Although theoretically possible, it is unlikely that this process occurs to the extent that the CD8+ T cell response becomes totally ineffectual. If so, then one would expect that the viral set point would be ~ 100-fold higher than that actually observed, and similar to the levels found at the peak during a primary infection (i.e. 10^6 - 10^8 viral particles/mL), or as in the monkeys depleted of CD8+ T cells. Other considerations also argue against such a possibility. For example, it is estimated that the ~ 10,000 nucleotide HIV genome may encode hundreds of peptide sequences that CD8+ T cells could recognize, so that random mutation of a few gene sequences would have little

effect on the capacity of the CMI system to control the virus, due to the tremendous diversity of the T cell immune response.

Failure of the Immune System

Detailed studies in experimental viral infections have shown that the quantity and quality of the CD8+ T cell response is crucial for a successful outcome. Accordingly, various aspects of the immune system can impact the ability of CD8+T cells to proliferate and to differentiate into fully functional cells capable of killing infected cells, and capable of producing antiviral cytokines and chemokines. For example if there is inadequate T cell “help” provided by CD4+ T cells, then the CD8+ T cell response is compromised.¹⁰ Noteworthy in this regard is inadequate production of IL2 during chronic HIV infection.¹¹ Without adequate IL2, even though CD8+ T cells are activated by antigen, there is an attenuated proliferative and differentiative response, which results in a persistent infection.

Other experiments have shown that persistent viral infection produces a state of unresponsiveness or “anergy” on the part of CD8+ T cells.¹² Thus, even though antigen-specific T cells can be detected, when activated by specific antigen, they are unable to proliferate or differentiate into killer cells or cytokine-producing cells. The mechanisms responsible for this anergic state are still obscure, but they may well involve inadequate cytokine production, either on the part of CD4+ helper T cells or CD8+ T cells themselves.

Other investigators have explored the molecules used by CD8+ T cells to kill

infected cells and found them to be deficient. Thus, the primary molecule involved in damaging target cell membranes, perforin, has been found to be under-expressed in CD8+ T cells from chronically infected individuals.¹³ Accordingly, although HIV-specific CD8+ T cells may be present, they may be unable to function optimally, thereby compromising the capacity of the immune system to combat and control virus-infected cells.

Summary

The CMI system, which is comprised of T cells, NK cells and phagocytes, is of paramount importance for combating viral infections. In particular, killer CD8+ T cells must be present in adequate numbers and be fully functional to clear virus-infected cells. After primary infection by HIV, CD8+ killer T cells rapidly increase in number and their capacity to produce anti-viral cytokines and to actually kill HIV-infected cells results in almost a 100-fold reduction of virus, with maintenance of this reduced level of virus for years. However, as good as the CMI system appears to be, it is still inadequate to totally eliminate all virus-infected cells. Consequently, there results a slow but inexorable decline in the immune system as it combats the ongoing replication of the virus, eliminating the HIV-infected CD4+ T cells. Evidence points to several characteristics of the virus itself that favor viral persistence, including a rapid replication rate and the ability to integrate into cellular DNA and remain latent. However, there also appears to be a failure on the part of the immune system, which is manifest by deficiencies in the capacity to proliferate, as well as in the both the

ability to kill infected cells and to produce antiviral cytokines.

The Hypothesis

Of the 4 aspects of HIV infection mentioned above, i.e. viral replication, viral integration, inadequate numbers of killer T cells, and inadequate production of cytolytic molecules and anti-viral cytokines, 3 of these parameters are amenable to therapeutic intervention. Antiviral drugs can impair viral replication, and it is established that these agents are effective therapies. However, they cannot cure the infection by themselves. At present, once the virus becomes integrated into the cellular genome there is no known way to extricate the residual latent integrated virus. However, immune-based therapies (IBT), which are designed to improve the *quantity and quality* of the immune system, especially the CD8+ T cells, promise to provide a synergistic therapeutic approach to HIV infection that may well afford the containment of latent integrated virus, so that the antiviral drugs are no longer necessary. Accordingly, the hypothesis to be tested is that ***“Immune-based therapies can prevent viral replication by augmenting the capacity of the immune system to kill infected cells and to produce antiviral cytokines”***.

The Diagnostic Treatment Interruption: A Clinical Trial Design to Test IBTs

The first obstacle to overcome in devising and testing IBTs is monitoring for their efficacy. The present *in vitro* immunological assays cannot yet yield results predictive of an antiviral response *in vivo*. Therefore, we have developed a

clinical trial design termed a “Diagnostic Treatment Interruption” (DTI).^{14,15} In this trial, IBTs are administered while antiviral drugs are administered to suppress viral replication maximally, so that the immune system is unperturbed by the virus. Detailed studies of experimental animals have shown that while viral replication persists, the immune system is “paralyzed”, and unable to recognize and respond to immunological stimuli.

After the immune system has been stimulated by the IBT, it is possible to test its capacity to control viral replication by temporarily interrupting the suppression of replication afforded by the antiviral agents. We have found that a 12-week DTI allows ample time to discern the viral dynamics. Thus, after the discontinuation of antivirals, a 2-3 week latent period occurs, when HIV in the blood remains undetectable. Subsequently, HIV increases rapidly for about 2-3 weeks, eventually reaching a peak concentration. Thereafter, the HIV level in the blood declines with a half-time of 2 ½ days, so that after an additional 10 days, the virus concentration decreases by ~ 90-95%, ultimately reaching a plateau or “set point”. Accordingly, by monitoring the level of HIV in the blood frequently, it is possible to accurately and rapidly determine the capacity of the immune system to react to HIV and to regulate the concentration of the virus in the blood.

This is of utmost importance for the monitoring of the efficacy of IBTs, in that in order to achieve approval of a new therapy by the Food and Drug Administration (FDA), the therapy must be demonstrated to either confer a

“clinical benefit” or it can improve a “surrogate” of the clinical benefit. A clinical benefit is defined in one of 3 traditional ways, including 1) the capacity to cure the disease or at least a fraction of those afflicted, 2) prolong the disease-free survival, or 3) improve the quality of life while the drug is administered. In HIV therapy, the FDA has accepted the plasma HIV concentration as a “surrogate” for a clinical response. The word surrogate is from the Latin and means a substitute. Therefore, *all* of the currently available antiviral drugs have been approved by their capacity to reduce the blood HIV concentration for a period of at least 6 months. It follows that if IBTs can reduce the plasma HIV concentration, demonstrable by the capacity to control the HIV level after a DTI, they should become approvable by the FDA.

Correlation of Immune Assays with the *in vivo* Antiviral Response

The hallmark of HIV infection is a reversal of the CD4/CD8 ratio. Thus, the CD4+ T cell concentration in the blood is normally ~ 1,000 cells/μL, while the CD8+ T cell concentration is normally ~ 500 cells/μL, which yields a 2:1 ratio. Upon infection with HIV, the CD4+ T cell concentration decreases, while the CD8+ T cell concentration increases. For example, should the CD4+ T cell concentration decline to 500 cells/μL, and the CD8+ T cell concentration increase to ~ 1,000 cells/μL, then the ratio obviously changes from 2:1 to 1:2.

Most attention early on in the HIV epidemic was focused on the decline in the CD4+ T cell concentration, while the increase in CD8+ T cells was ignored. However, the increase in CD8+ T cells

was eventually realized to correlate with the immune response to the infection, so that it was the first immunological correlate to be recognized. We have still not ascribed all of the increase in CD8+ T cells as due to an expansion of HIV-specific CD8+ T cells, but most evidence now points to such an interpretation.

Therefore, the task today is to determine whether the total number of HIV-specific CD8+ T cells that occurs as a consequence of HIV infection is predictive of the *quantity* of the immune response *in vivo*. In addition, it is necessary to test the function of the HIV-specific cells so that one can determine the *quality* of the CD8+ T cell immune response. Only then will it be possible to use immunological assays to determine whether there is an adequate immune responsiveness to the virus, and only then will it be possible to design studies to try to correlate the immune responsiveness to the viral and clinical outcome.

Fortunately, new assays have been devised that permit the identification of the number of HIV-specific CD4+ and CD8+ T cells. It is possible to activate T cells from blood samples with HIV peptides and then assay for the percent of reactive cells in the population using methods that detect the activated cells by identifying activation molecules on the cell surface or inside the cells.¹⁶ An idea of the functional capacity of the cells can be obtained by monitoring the capacity of the cells to produce cytokines, such as IL2, IFN- γ , or TNF- α . Thus, it remains to perform these assays in a prospective clinical trial, to correlate the results of the quantity and quality of T cells with the capacity to control virus.

Immune-Based Therapy: The 2-Signal Hypothesis

Given the premise that IBTs should add benefit to antiviral therapies because the immune system itself is antiviral, the immediate question becomes what would constitute reasonable therapy. The results from our DTI trial where we discontinued antivirals but continued IL2 therapy indicated that at least 2 signals will be necessary to maximally activate the HIV-specific T cell immune responses: 1) HIV antigens and 2) IL2. This conclusion is based on the observation that activation of T cell proliferation requires 1st recognition of HIV antigens, which function to activate the antigen-selected cells, followed by an adequate source of IL2 to provide the signal to the cells to begin to multiply.^{3,17}

Investigators have attempted to use “Structured Treatment Interruption” (STI) as a therapeutic manipulation to allow viral replication to resume, and thereby serve as a source of HIV antigens.¹⁸ However, this manipulation has not proved beneficial by itself. The STI approach has not led to discernable control of viral replication. In addition, these data provide the rationale for at least 2 signals to stimulate antiviral immunity. As well, based upon the observations that persistent viremia results in immunodeficiency, it appears best to perform the IBT while viral replication is maximally suppressed, so as to provide as normal an immune system as possible to react to the IBT.

Accordingly, the safest way to deliver HIV antigens is via an HIV vaccine, while IL2 could be administered safely as

a daily low dose to supplement any IL2 produced as a result of the immunization.

Therapeutic Immunization

Before effective antivirals had been developed Jonas Salk proposed to treat AIDS with an HIV vaccine. Of course, at the time this proposal seemed an oxymoron, in that with high levels of virus in the blood, there was already a large amount of viral antigens available to stimulate the immune system. It was perplexing how the inoculation of a much smaller amount of HIV antigens via a vaccine could add any benefit. However, with the advent of effective antiviral therapy, the use of therapeutic vaccines to deliver HIV antigens and activate HIV-specific T cell responses now becomes logical. Even so, there are many parameters that must be tested to identify the best vaccine. For example, the best vaccine vector, dose, route and frequency of administration, and the best vaccine adjuvants must be examined in a setting that can yield quantitative data rapidly.

The Use of Cytokines as Adjuvants to Boost Vaccine Responses

Within the vaccine scientific community it is well established that most vaccines need to be boosted using adjuvants. Adjuvants traditionally have been considered to be agents such as Complete Freund's Adjuvant, which is comprised of an emulsion of oil and a water-soluble mixture of vaccine combined with heat-killed tuberculosis organisms. Although it was not obvious as to how such agents worked to improve immune responses, it was clear that they could be very effective. Now,

more than ever, vaccine adjuvants are important, because the vaccine themselves have been attenuated so that they cannot replicate. Consequently, replication incompetent vaccines are very safe, but they may not be immunogenic.

Returning to the 2-signal hypothesis as to how the T cell immune response operates, it follows that the antigen in the vaccine could be boosted by combining it with cytokines, which actually mediate the immune response after antigen activation.¹⁹ Accordingly, we have developed IL2 as a TCGF to expand the antigen-activated T cells, so that greater numbers would be available.

To deliver cytokines such as IL2 as an adjuvant, it is 1st important to deliver it safely and tolerably. Accordingly, we have carefully performed dose finding phase I safety studies and found that IL2 can be administered daily as a subcutaneous injection at a dose of 1.2 mU/M² body surface area.²⁰ This dose is about 10-fold lower than the high dose prescribed by others as an intermittent injection given for 5 days every 8 weeks.²¹ This distinction is important because the higher dose is toxic. It leads to fatigue, high fever, chills, rigor, and ultimately hypotension, often requiring vasopressors and dose reduction. By comparison, a 10-fold lower dose can be given daily for months and even years without side these effects. Consequently, normal daily routines such as work, school etc. can proceed without interruption.

Accordingly, we have initiated a new IBT trial in New York City, which is designed to test whether an HIV vaccine and daily low dose IL2 therapy can

augment antiviral immune responses *in vivo* as determined by a DTI (for more information and a full description of the study, see www.hivhcvttrials.net). Volunteers are randomized to different IBT groups while they continue antivirals, and the efficacy of the IBT is tested by the level of viral control observed after a DTI. It is important to emphasize how important it is now for the entire community, patients and physicians alike, to support IBT trials. Only by determining the most effective IBTs, the best therapeutic vaccines and the best cytokines and other adjuvants will it be possible to develop the strategies that will allow the immune system to control HIV replication, so that antivirals will no longer be necessary. In addition, determination of the best therapeutic vaccines and cytokines should provide a rapid way to predict which of these approaches will be the most effective prophylactic vaccines and cytokines. Therefore, the HIV+ community in the 1st world can contribute to the HIV problem in the 3rd world, and hasten the development of an effective way to prevent the spread of this insidious disease worldwide.

Conclusions

The immune system recognizes and responds to infection by HIV, and is responsible for containing viral replication for extended intervals, usually several years. However, because the immune response cannot completely eliminate the virus, nor keep residual virus latent even after suppressive antiviral therapy, it is clear that new therapy capable of targeting the immune system, so-called immune-based therapy (IBT), will provide for a new treatment paradigm. The combination of

therapeutic HIV vaccines to stimulate HIV specific immunity, combined with cytokines used as immune adjuvants to augment the response, takes advantage of the tremendous amount of knowledge gained in the past 2 decades as to how the immune system operates. Therefore, these advances, combined with the “Diagnostic Treatment Interruption” clinical trial design, should allow for the rapid testing of the most promising IBTs. Furthermore, those vaccines and cytokines that are most efficacious as therapies for HIV+ individuals, promise to provide hope that they will also be efficacious as prophylactics to prevent HIV infection.

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