Will it be possible to live without antiretroviral therapy?

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Purpose of review: Some individuals are able to control HIV infection (either viral replication or chronic immune activation) in the absence of therapy. We will consider recent insights into the mechanisms underlying control in these patients and how this has already encouraged the search for therapeutic approaches to induce a similar HIV functional cure in other patients.

Recent findings: Spontaneous reduction of HIV viremia to undetectable levels as observed in a few HIV-infected patients is associated with an efficient HIV-specific CD8+ T cell response, the characteristics of which are now better understood. However, maintenance of such control may involve alternative mechanisms. In particular, the presence of a very small viral reservoir seems necessary, although not sufficient, to ensure HIV control in the long term. Approaches designed to limit the early establishment of these reservoirs, to eliminate infected cells, or to avoid replenishment of the reservoirs have led to HIV remission in the absence of therapy in a few cases. Alternatively, other rare patients seem to deal with HIV infection by controlling immune activation despite high levels of viremia like the natural African monkey hosts do with SIV. These observations suggest that regulation of immune activation should be considered as a serious complement to conventional therapies targeting the virus itself.

Summary: Better understanding of the mechanisms underlying control of HIV infection or disease in some patients has already led to successful approaches in certain individuals. However, much work is still needed to generalize these results to the global population of HIV-infected patients.

Key-words: control of viremia; HIV controller; HIV remission; functional cure; post-treatment control; control of activation; HIV pathogenesis; viremic non progressor; natural host

KEY POINTS

- The control of HIV replication in the absence of therapy in rare infected individuals (HIV controllers) has been associated with protective Class I HLA alleles and strong and efficient T cell responses.
- Many HIV controllers do not present such responses: other mechanisms, including intrinsic cell resistance to HIV infection and innate immune responses may contribute to restrain HIV replication.
- Protection from disease may be achieved also by controlling immune activation and its deleterious effects on the immune system, as shown in African monkeys naturally infected by SIV and in a few individuals who maintain normal levels of CD4+ T cells despite high viral loads.
- Therapeutic intervention (stem cell transplantation, prolonged treatment since acute infection) have allowed some patients to maintain control of viral replication and very low viral reservoirs after treatment interruption.
- Most post-treatment controllers do not present common characteristics with “natural” HIV controllers. Understanding the mechanisms of viral control in these individuals will help in designing new approaches to achieve a functional cure.

Introduction

The introduction of combined antiretroviral therapy (cART) has met with huge success in the fight against HIV/ AIDS. Daily therapy virtually stops viral replication and has transformed a deadly infection into something more like a chronic disease. Despite this achievement, cART seems to have reached its limits. Current antiretrovirals target different steps of the HIV replication cycle (entry, reverse transcription, integration, assembly), but they are not able to eliminate infected cells. In fact, following acute infection, HIV establishes viral reservoirs in long-lived cells which allow its persistence even after prolonged treatment [1]. As a consequence, viral replication readily restarts at pretreatment levels upon treatment interruption in most patients [2]. Although greatly extended by cART treatment, life expectancy does universally not reach that of healthy individuals [3]. This may be because of adverse effects of long-term therapy, the deleterious effect of persistent inflammation or lifestyle risk factors [4]. These issues, together with the difficulty of achieving and ensuring global life-long therapy, are stimulating the search for new possibilities that will allow HIV cure or at least long-term remission without therapy in HIV-infected patients. The unresolved question is: how might HIV-infected patients live without cART? The answer might be found in individuals who are already doing so.

HIV controllers: restraining the virus

The pathogenesis of HIV infection is determined by both host and viral factors. From the very beginning of the AIDS pandemic, it was observed that not all patients progress to disease at the same rate [5]. Some individuals known as HIV controllers (HIC) are able spontaneously to control replication of HIV, which is undetectable for long periods of time [6]. In recent years, numerous efforts have been made to establish cohorts of these rare patients in order to

understand the mechanisms underlying their extraordinary capacity to control viremia [7,8,9,10].

It is now well documented that many HIC carry fully competent pathogenic viruses [11] which suggests that viral control is mediated by active host mechanisms . The observation that some HLA alleles (HLA B57 and to a lesser extent B27) associated with lower viral loads were overrepresented in these individuals soon focused attention on adaptive cellular responses [12,13]. These initial observations have been confirmed in all cohorts of HIC described to date [7,9,10] and larger genome-wide studies have shown that the most solid polymorphisms associated with control of viral load are localized in the MHC region [14]. Interestingly, the same type of associations have been found in macaque models of SIV control developed in parallel to studies in human HIC [15].

"The" CD8+ T cell response

The role of an efficient CD8+ T cell response in the establishment of viral control in vivo has been recently argued for by an elegant study in a group of rhesus macaques bearing the Mamu B08 allele [16]. This MHC class I molecule has been associated with control of SIV replication in rhesus macaques and has been shown to bind similar peptides that HLA-B*27 [17,18]. Pre-vaccination of naive animals with three SIV epitopes known to be restricted by the B08 allele allowed all of them (but only one of the unvaccinated B08 matched controls) to control viremia after infection with a particular high dose of the pathogenic $SIVmac_{239}$. In addition, loss of viral control has been reported in different macaque models of SIV control upon in vivo depletion of CD8 T cells [15,19] and has been associated, both in macaques and humans, with the emergence of viruses carrying CTL escape mutations [20,21].

We and others have helped unveil the many facets of the particular CD8 T cell response that is found in many HIC. Despite their low level of viral replication, these HIC maintain a high frequency of HIV-specific CD8 T cells which are able to proliferate in response to antigen

stimulation, to produce multiple cytokines simultaneously, and to suppress HIV infection by eliminating infected CD4 T cells [22,23]. The latter has been associated with higher cytolytic content and rapid upregulation of perforin [22]. Although no particular differentiation phenotype has been associated so far with viral control in HIC, the levels of effector cells among HIC are higher than in patients with uncontrolled viremia [23,24]. Effector CD8+ T cells from controllers rapidly suppress HIV in co-cultures with HIV-infected CD4 T cells, and memory CD8+ T cells in controllers are also able to acquire such effector capacities after just a few days of culture [25]. This suggests that HIC are equipped with significant numbers of cells able to ensure the rapid elimination of reservoir cells after reactivation of latent proviruses [26]. The magnitude of the Gag-specific CD8 T cell response in HIC bearing the protective HLA B27 or B57 allele is inversely correlated with the frequency of long-lived central memory cells carrying HIV-DNA [27]. Interestingly, the presence of high frequencies of SIV-specific effector-memory T cells in rhesus macaques vaccinated with a CMV vector is associated with striking control of $SIVmac_{239}$ after infection [28].

It is still unknown whether cells from viremic individuals lack some or all the capacities found in HIC because of exhaustion due to continual exposure to high antigen levels. Attempts are being made to revert the status and function of cells from non-controllers by means of anti-exhaustion strategies, which seem to improve cellular functions and make them close to those in controllers [29]. But will close be close enough? It is possible that some of the characteristics of the CD8 T cell response in HIC are due to intrinsic cellular peculiarities of HIC. Most HLA B57 individuals are not able to control infection to the levels that HIC do. A recent report has compared HIC and viremic patients carrying the protective B2705 or B5701 allele and whose cells restrict the same immunodominant HIV epitopes. Interestingly, the TCR clonotypes selected after infection in controller patients were different from those found in viremic individuals and provided cells from the former with a greater capacity to suppress HIV infection, enhanced loading and delivery of perforin, and greater cross-reactivity to epitope

variants [30]. Along these lines, selection of high-avidity clonotypes has also been associated with efficient control of infection and linked to the capacity of cells from HIC to proliferate, produce cytokines, and efficiently suppress infection [31]. Many of these characteristics of CD8 T cells from controllers may also be related to the reported capacity of these individuals to decrease HCV viral loads [32] or even to clear this infection [33], for which HLA B57 has also been associated with better viral control [34].

It remains largely unknown what determines clonotype selection in HIC and in viremic patients. The myeloid dendritic cells in HIC have enhanced antigen-presenting properties compared with progressors and with healthy individuals [35]. In addition, HLA B57 molecules in HIC present peculiarities in the epitope-binding pockets [14] which may allow an optimal presentation of the HLA epitope complex to the CTL, and even flexibility to accommodate escaping variants which would facilitate the occurrence of multiple de novo responses in these individuals [36]. Further studies are needed to determine if these clonotypic differences also apply to HIC not bearing protective HLA alleles.

Helper and regulatory T cells: friends, foes, or a little bit of both?

As in the case of HIV-specific CD8+ T cells, many HIC maintain functional central memory HIV-specific CD4+ T cells able to proliferate and produce various cytokines, including IL-2, [37] in response to low doses of antigens thanks to the selection of high-avidity TCR [38]. Also, despite the low antigenemia and in contrast to long-term treated patients, HIC are characterized by the presence of significant frequencies of HIV-specific Th1 effector cells [39]. These cells may be critical to ensure the optimal priming and persistence of cytolytic CD8+ T cells by providing an ideal signaling and cytokine environment. Moreover, HIV-specific CD4+ T cells from HIC may

have some cytotoxic potential themselves [40,41] and their direct role in control of infection deserves further exploration. However, the continuous presence of a pool of HIV-specific CD4+ T cells that are readily activated in response to low levels of virus may by itself provide a mechanism of viral persistence, as these cells are perfect targets for viral replication. Higher levels of activated HIV-specific CD4+ T cells have been associated with higher levels of cell-associated viremia in HIC [42]. Thus, while a robust T helper response may be essential for maintaining efficient cellular immunity, it may also contribute to the low levels of viral replication that have been evidenced by ultrasensitive techniques in HIC [43]. This vicious circle implies that there may be a "small price" to pay for being a HIV controller.

It is undeniable that most HIC have higher levels of immune activation than healthy individuals, but lower than non-controllers [44]. Some immune activation may be important to ensure optimal antiviral activity of CD8+ T cells. However, chronic immune activation and low-level viremia are associated with a slow decay of CD4+ T cell numbers in HIC [9,44]. HIV controllers are also more at risk of developing premature atherosclerosis than healthy individuals [45,46] and some show signs of exhausted lymphopoiesis [47]. Regulatory T cells (Tregs) are important controllers of chronic immune inflammation, but the impact of Tregs in the pathogenesis of HIV infection is an open debate. While they could have a beneficial impact by controlling deleterious immune activation, they may also have harmful effects by facilitating viral replication by suppressing the activation and proliferation of effector lymphocytes [48]. Although the percentage of Tregs among CD4+ T cells appears to increase after HIV-1 infection, their absolute numbers decrease as a consequence of the depletion of the CD4+ T cell compartment. However, sorted Tregs from HIV-1-infected patients have been shown to preserve their suppressive capacities [49]. Although some studies suggest that HIC and healthy donors have similar levels of Tregs [49,50], several reports point to a decrease in the numbers of Tregs in HIC [51,52] and this diminution may affect in particular Tregs with an effector phenotype [52]. In addition, CD8 T cells targeting HIV epitopes restricted by "protective" HLA

alleles may have a superior capacity to evade suppression by Tregs [53]. Therefore, a blunted regulatory response in HIC may contribute to the persistence of an efficient T cell response, but allows a certain level of global immune activation [51]. These observations raise the question about treating HIC with anti-inflammatory therapies, and the effect that such treatment may have on their capacity to spontaneously control infection.

Control despite weak immune responses

As mentioned above we have profoundly improved our knowledge of the optimal cellular responses associated with efficient HIV control. However, a significant fraction of HIC do not possess this type of cellular response [7,37,54,55], and CD8 T cell responses in some HIC shrink during control of infection to extremely low levels (our own unpublished observations). Moreover, it is interesting to consider that HIC with the tightest control of infection over time, with undetectable viral loads even when employing ultrasensitive techniques of detection, and who keep stable CD4+ T cell numbers are, in general, characterized by weak immune activation and weak CD8+ T cell responses ([23] and unpublished). It is possible that the emergence of less fit viruses as a consequence of immune escape [56] may decrease viral replication and provoke the shrinking of CD8+ T cell responses. The HIV-specific CD8+ T cells in these individuals tend to have a memory phenotype [54] and may constitute a pool of highly efficient cells which may react in response to small virus bursts. It has recently been shown that CD8+ T cells from HIC with weak T cell responses acquire HIV-suppressive capacities upon in vitro expansion [57]. However, the same property has been shown for the CD8+ T cells of cART-treated individuals [26], and this does not preclude resumption of viral replication to pre-cART levels after treatment interruption in most subjects. Moreover, the quiescent nature of the cells from weak responders [54] suggests that these cells are not actively operating in maintaining control of infection in these individuals .

Although neutralizing antibodies are unlikely to play a major role in HIC [7,58], both the quality of non-neutralizing antibodies and the levels of FCγ receptors on the surface of cells from HIV controller point to a greater ADCC potential in controllers [58,59,60]. Such a mechanism may have a greater impact in HIC with weak CD8 T cell responses. Nevertheless, HIC with the best control of infection have extremely low antibody levels and weakly reactive/partial western blots have even been described for a few of them [55].

An extremely low viral reservoir, as found in most HIC [61,62], seems to be a major requisite in ensuring efficient control of viremia. Viral reservoirs are established very early during primary infection and it is therefore possible that components of the innate immune response help to limit their size in HIC. The concurrency of protective HLA B alleles with certain NK cell inhibitory receptors has been consistently associated with control of infection in immunogenetic epidemiological studies [63]. Although data about NK function in HIC remain scarce [64], a recent report has shown enhanced NK cell function after IFNα stimulation in HIC with weak HIV-specific CD8 T cell responses [65]. Plasmacytoid dendritic cells, another key component of the innate response, are not decreased in HIC and are able to produce high levels of IFNα and induce T cell apoptosis in response to HIV [66,67]. These cells are also able, to some extent, to suppress HIV replication when co-cultured with infected cells [67]. An intrinsic resistance of HIV controller cells to HIV infection might also limit the viral reservoir. Reduced HIV susceptibility has been reported for both unactivated and activated CD4 T cells and macrophages from HIC [62,68,69]. All these reports point to a pre-integration block in these cells, which would reduce the number of integrated proviruses in cells from HIC [61]. Along these lines, we documented a correlation between the in vitro susceptibility of HIV controller cells to HIV infection and the levels of HIV DNA carried by these cells in vivo [62].

Different mechanisms have been associated with cellular restriction, which might reflect the heterogeneity of HIV controller populations or the lability of the mechanism. This might explain why these observations have not been confirmed in another study [70].

Is it possible to induce an HIV controller-like status through therapeutic intervention?

Although HIC are an appealing example of what a functional HIV cure may represent, these individuals represent a small minority of HIV-infected individuals, and the phenomenon is strongly (although not absolutely) associated with a favorable MHC background. Timothy Brown is the first patient to have been declared cured of HIV infection [71]. He received, as a consequence of acute myeloid leukemia, double stem cell transplantation from a donor with a homozygous CCR5-Δ32 variant , which has been associated with HIV protection [72]. Over three years after the initial transplant and despite discontinuing antiretroviral therapy, no virus could be found in this patient [71]. Recent studies employing state-of-the-art ultrasensitive techniques have found some traces of virus (Yukl et al, International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies, Sitges, Spain 2012). It is still unclear whether these traces are due to background noise related to pushing these ultrasensitive techniques beyond their limit of detection, or if they are due to autologous sequences, which would imply that this patient has achieved an equally astonishing functional cure rather than a total cure. In any case, this case has served to boost global initiatives in the search for an HIV cure. Two additional patients, who were heterozygous for CCR5-Δ32, have achieved undetectable HIV levels following stem cell transplantation from CCR5 wild-type donors (Kuritzkes et al, AIDS 2012, Washington, USA). Although it is not yet known whether these patients will be able to keep controlling infection once they stop cART, they may provide important information about the precise mechanisms that have allowed Timothy Brown to

control infection. However, these approaches cannot be generalized to most HIV-infected patients.

A couple of astonishing experiments mentioned above have shown that some macaques are able of elite control of SIV infection when they are exposed to the virus after vaccination. Control of infection in already infected individuals might be harder to achieve through vaccination, as defects in immune function may be established early in infection. In contrast, although HIV replication readily resumes in most patients after treatment interruption, some patients are able to maintain off therapy control of infection, to HIV controller levels, for many years [73,74,75,76]. These post-treatment controllers (PTC) have usually been treated since primary infection and for many years before discontinuing cART. A few cases of control after interruption of a treatment initiated in the chronic phase of infection have also been described [77], but they seem much rarer. Treatment during primary infection has been shown to preserve immune responses from the deleterious effect of chronic immune activation [78,79,80], to limit viral diversity [81], and to have a higher impact in reducing the viral reservoir [82] than treatment in chronic infection. A low ratio between the time to treatment initiation and the length of the treatment, and weaker viral reservoirs at treatment interruption have been proposed to differentiate PTC from non-controllers [73,74]. Although a weak reservoir is not sufficient to ensure control of infection [83], it may be necessary. Post-treatment controllers have low viral reservoirs similar to those of HIC, with a small contribution of long-lived cells, and these even shrink off therapy in some individuals [76]. Interestingly, the incidence of control of viremia among patients following this therapeutic approach seems much higher than for spontaneous control in treatment-naive patients. The strong CD8 T cell responses observed in many HIC is not found in PTC, who also have very weak immune activation. The protective HLA alleles are not over-represented in PTC either

[76]. These patients therefore seem to have achieved control of infection thanks to early therapeutic intervention. Further studies will be necessary to understand the mechanisms underlying control of infection in PTC and to explain why they only operate in a minority of treated patients. Nevertheless, these results hold much promise in the search for a functional HIV cure and argue in favor of a generalized treatment in primary infection. Recent experiments in macaque models propose additional therapeutic intervention that may favor control of infection. Among them, injection of the pro-differentiation gold drug auranofin in cART-treated SIV-infected macaques induced the differentiation and apoptosis of long-lived memory cells, the diminution of the viral reservoir, and favored control of infection after cART interruption [84].

The coexistence of virus and host

Although it may take longer in some patients, uncontrolled viral replication generally results in progression to disease if not treated. A couple of studies have reported the existence of a handful of patients who are able to maintain stable CD4 T cell levels despite very high levels of viral replication [85,86]. These highly viremic non-progressors maintain weak immune activation and seem to ignore the virus much in the way that African non-human primates coexist with SIV infection [87]. A common transcriptomic profile has been described between these patients and SIV-infected sooty mangabeys [86], including the down-regulation of the IFNα response in chronic infection [88]. SIV infection of African non-human primates provokes immune activation as in the case of the pathogenic model of infection. However, unlike the latter, immune activation resolves a few weeks later despite continuously high levels of viremia. It is believed that this capacity to modulate immune activation is an adaptational ability that has allowed these animals to survive infection [87]. In HIV infection in humans, independently of the viral load or the CD4 T cell count, immune activation is a strong

predictive marker of pathogenesis, progression to disease, and deficient immune recovery in treated patients [89,90]. There is renewed interest in the development of therapies specifically targeting immune activation. In this sense, the use of the immunomodulatory drug hydroxychloroquine has yielded promising results by decreasing immune activation in cART-treated patients [91]. However, this drug had deleterious effects when given to cART-naive patients, by increasing viral loads and accelerating progression [92]. These contrasting results suggest that we need to improve our understanding of when and where modulation of immune activation will be beneficial.

Conclusions

The existence of rare HIV-infected individuals who are able to remain healthy in the absence of cART holds the promise that a functional HIV cure may be achievable. We are gaining knowledge of the mechanisms contributing to protection against disease in these individuals. This knowledge is already helping us to design new therapeutic approaches, which have yielded promising preliminary results. An HIV remission-like status has been documented in a few individuals after therapeutic intervention, although these interventions cannot be generalized to all infected patients or have shown only modest efficacy. Further efforts are needed to shed light on the successes and failures of these approaches and to develop new and more efficient ones that will allow an overall HIV cure.

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