Immune activation is a dominant factor in the pathogenesis of African AIDS

Zvi Bentwich, Alexander Kalinkovich and Ziva Weisman

The AIDS epidemic in Africa is very different from the epidemic in the West. As suggested here by Zvi Bentwich, Alexander Kalinkovich and Ziva Weisman, this appears to be primarily a consequence of the over-activation of the immune system in the African population, owing to the extremely high prevalence of infections, particularly helminthic, in Africa. Such activation shifts the cytokine balance towards a T helper 0/2 (Th0/2)-type response, which makes the host more susceptible to infection with human immunodeficiency virus (HIV) and less able to cope with it.

Several features of the AIDS epidemic in Africa mark it as a distinct entity from the disease that is present in North America and Europe: (1) it is primarily a heterosexually transmitted disease with a male-to-female ratio of 1:1, and lacks the known 'classical' risk groups of male homosexuals and intravenous (i.v.) drug users[1,2]; (2) it is probably transmitted more easily[2–4]; (3) the progression of infection and disease is faster – the time from infection to onset of clinical manifestations and overall survival may be shorter[5–7]; and (4) the clinical manifestations are different, particularly the main opportunistic infections and the main organ systems involved[6].

It is probably because of these features that the AIDS epidemic in Africa has reached such catastrophic dimensions, with a prevalence of human immunodeficiency virus (HIV) infection in the general population reaching 30% or more in several African countries and with mounting numbers of AIDS patients[1,8]. This pattern of epidemic is also fast emerging in other parts of the world, particularly in the developing countries of Southeast Asia (Thailand and India) and of South America and the Caribbean[8]. Common to all regions showing this pattern is the pivotal role of prostitutes, who constitute the major, initial 'reservoir' of the virus and the source of its further spread into the general population as a sexually transmitted disease (STD)[2,9]. Quite remarkably, this pattern of spread has not been observed in the West or in other developed countries such as Japan, Australia or New Zealand, where the prevalence of HIV infection among prostitutes has remained surprisingly low and is mostly associated with i.v. drug use[8].

Hypothesis

Our view is that profound changes in the host immune response may account for the dramatic differences in the behavior of the AIDS epidemic in Africa and in other developing countries. Such changes make the host more susceptible to HIV infection and less capable of controlling the infection once it is acquired. Infectious diseases, mostly helminth infections endemic in Africa and the developing countries, activate the immune system and alter its balance in such a way that makes the host more receptive to HIV and more vulnerable to its effects. This altered 'backgound' immune response must be taken into consideration when designing vaccines and devising new therapies for HIV in Africa and other developing countries.

Type and variety of infections

The average African host is exposed to a huge number of infectious diseases from early childhood onwards. These include various bacterial, viral and parasitic infections[10–14]. Noteworthy is the wide prevalence of helminth infections, malaria and tuberculosis in most parts of Africa: especially in sub-Saharan Africa, and in East and West Africa[10,11,13–17]. Also of central importance is the very high prevalence of STDs, particularly genital ulcer diseases (GUDs), which play an important role in facilitating the dissemination of HIV infection into the general population[2,9]. Although there are only a few controlled studies addressing this subject, there clearly appears to be a high rate of HIV transmission in Africa. Furthermore, recent studies on HIV transmission among army recruits in Thailand have shown a 50-fold higher rate of transmission when compared with rates of transmission observed in the West[18]; this could not be accounted for by STDs alone[18], indicating the involvement of other, as yet undefined, factors. It is very plausible that a similar situation also exists in Africa. Israel has received two waves of immigration from Ethiopia during recent years, and it has been possible to study this Ethiopian population shortly after their arrival in Israel. These studies have revealed a very high prevalence of most infections, helminth infections being almost universal[10].

Immune activation in Africans

With the high background of infections in Africa, it could be expected that increased signs of immune activation occur in the general African population. Although the number of studies addressing this question has been small, increased immune activation has been

Table 1. Immune activation in Africans

Parameter	HIV seronegative[a]	HIV seropositive
Blood levels		
IgG	↑[21,23]	↑[21,22]
IgM	N[14]	↑[22]
IgA	N[14]	↑[14]
IgE	↑[21,23]	↑[21]
Eosinophils	↑[21]	↑[21,23]
Neopterin	↑[13], N[24]	↑[13,24]
Placental isoferritin	↑[25]	↑[25]
IL-6	N[21]	↑[21]
TNF-α	↑[26], N[24]	↑[24]
Soluble TNF receptors	↑[21]	↑[21]
Levels in PBMC supernatants		
IL-2	↑[21]	N[21]
IL-4	↑[21]	↓[21]
IL-6	↓[21]	↓[21]
IL-10	↑[21]	N[21]
Soluble TNF receptors	↑[21]	↑[21]
Membrane expression		
$CD3^+HLA\text{-}DR^+$	↑[14]	↑[14]
IL-6 receptor	↓[21]	↓[21]
TNF receptors	↑[21]	↑[21]

Abbreviations: IL-6, interleukin 6; TNF-α, tumor necrosis factor α; PBMC, peripheral blood mononuclear cell.
[a]↑, ↓ and N indicate increased, decreased or normal range of levels when compared with healthy non-African individuals.

observed in members of the African population not infected by HIV. This had previously been suggested as a possible important cofactor in the pathogenesis of AIDS (Refs 14,19), especially after activated T cells were shown to be more susceptible to infection with HIV and to produce more virus than resting cells[20]. A summary of immune response parameters reported both in HIV-infected and uninfected Africans is presented in Table 1 (which also includes a summary of recent studies of the Ethiopian population in Israel[21,25]). Together, these data reveal that the immune system is highly activated in individuals who have not been infected with HIV. In addition to increased levels of serum immunoglobulins (particularly IgE) and eosinophilia, these individuals had increased serum levels of interleukin 6 (IL-6), placental isoferritin and soluble tumor necrosis factor (TNF) receptors. Furthermore, their peripheral blood mononuclear cells (PBMCs) were found to secrete significantly higher amounts of IL-2, IL-4, IL-10 and soluble TNF receptors, and lower amounts of IL-6, in comparison with healthy non-Ethiopian controls. It is of great interest to note that a recent study of HIV-seronegative, Thai, temporary laborers in Israel revealed similar signs of immune activaton[27].

Box 1. Observations indicating that immune dysregulation can facilitate infection by human immunodeficiency virus (HIV)

- Activated $CD4^+$ cells show upregulation of CD4 receptors and increased viral replication[36]
- HIV replicates preferentially in T helper 2 (Th2)- and Th0-type clones[37], which are probably more dominant in African hosts
- Helminth infections, after shifting the balance towards a Th2-type response, are accompanied by a decreased ability to mount a specific immune response against HIV components[38]
- Elevated interleukin 4 (IL-4) levels downregulate Th1 differentiation and function[39]
- Programmed cell death is markedly enhanced by reduction of Th1-type cytokines[40]
- Production of IL-12, an inducer of Th1 development, is markedly impaired in HIV carriers[41,42]

The Th1–Th2 response

Since its introduction, the concept of T helper 1 (Th1)- and Th2-type immune responses has come to play a central role in the field of immunity to infection[28,29]. In the murine models of leishmaniasis and leprosy, the protective role of the Th1 type of response and the deleterious effects of its counterpart, the Th2 type of response, have become classical examples of this powerful, yet probably simplistic, concept[28,29]. Another interesting, though polar, example of this concept is the ability of helminthic infections of rodents and humans to steer the immune response of the host in the direction of Th2, which appears to be more protective for the host in these infections, and to downregulate the Th1 type of response[30]. Furthermore, following such helminthic infection, the response to mycobacteria was found to be modulated from a Th1 to a Th2 type[31]. However, it is now clear that the Th1–Th2 division is more easily defined in murine inbred strains than in the natural human setting, and that the clear distinction between protection and enhancement of infection can vary between different experimental systems. In malaria for example, both types of immune response are present and both seem to confer protection[32]. In tuberculosis, it seems that Th1 is protective in mice infected with Bacillus Calmette–Guérin (BCG), but this is probably not the case in human mycobacterial infection[33].

Clerici and Shearer have presented several lines of evidence in support of the central role of Th1 and Th2 responses in the course of HIV infection and AIDS (Ref. 34). They have suggested that the Th1 type of response confers protection and is associated with better prognosis, whereas a switch from a Th1 to a Th2 response is associated with worse prognosis. The presence of a specific Th1 type of response in individuals who have been exposed to HIV and yet are not seropositive has also been described, suggesting the presence of HIV-specific protective immunity in these individuals. Using the same methodology, we have repeated these studies and have confirmed their results in our population of individuals who may have been exposed to HIV and yet are not seropositive[35]. These studies of Ethiopian immigrants have revealed, in most cases, that the immune system is highly active with many features of a Th2- and Th0-type response (Table 1). It

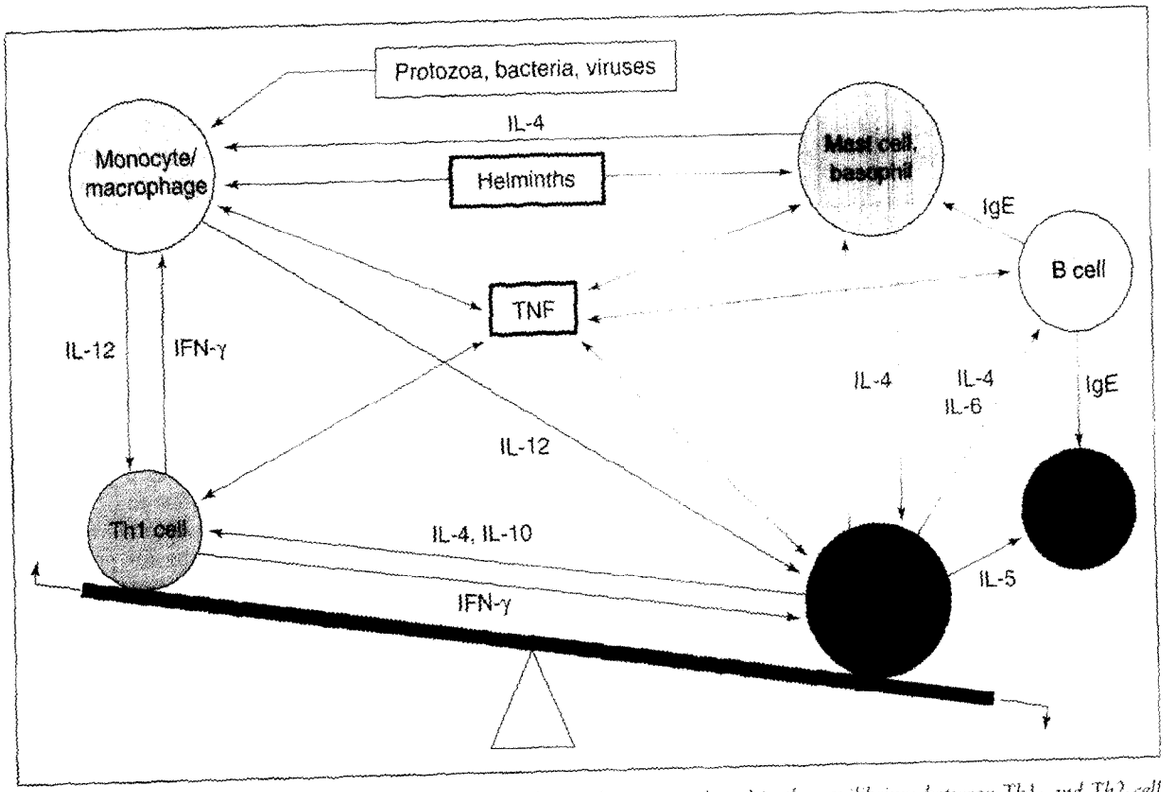

Fig. 1. *Helminthic and other infections tip the balance in the cytokine network and in the equilibrium between Th1- and Th2-cell populations. Positive and negative influences are indicated by blue and red arrows, respectively. Abbreviations: IFN-γ, interferon γ; IL-4, interleukin 4; Th1, T helper 1; TNF, tumor necrosis factor.*

is possible that such activation is commonly found in the majority of Africans living in Africa and precedes any exposure to HIV. We suggest that this kind of immune activation serves to facilitate HIV infection and also influences the course of the infection. These ideas are supported by several studies summarized in Box 1. However, it should be stated that the issue of the Th1-to-Th2 switch with progression of HIV infection is not yet resolved. Nevertheless, it is quite clear that a mixture of Th1 and Th2 clones can be derived from the peripheral blood of HIV-infected individuals[43,44] and, according to other investigators, the same clones are able to secrete Th1- and Th2-type cytokines (B. Autran *et al.*, unpublished).

Other types of immune activation

Is the immune activation observed in the Ethiopian immigrants and in Africans only a Th2 type of activation? The answer to this question is clearly negative. The only evidence for the presence of a 'pure' Th1 or Th2 response has been based on clonal proliferation of cells obtained from the peripheral blood of patients with atopy or immunity to BCG (Refs 45,46). More recently, a 'natural' clonal proliferation of Th2-type cells has been described in a patient with the hypereosinophilic syndrome[47]. However, in most situations, a mixture of responses exists, with shifts in either direction. The highly activated TNF system observed in the Ethiopians does not concur with the conventional definitions of the Th1–Th2 divisions. It is also known that TNF activation may have contradictory effects as far as HIV infection is concerned: it has activating effects on HIV replication through the NF-κB system and has been associated with rapid progression of the disease, probably also affecting other pathways of viral enhancement and decreased defense[48]. However, TNF is clearly associated with potentiation of antiviral effects through the enhancement of cytotoxicity, natural killer (NK)-cell activity and the interferon system[48]. Furthermore, the observed elevation in the level of IL-2 secretion from PBMCs does not fit easily with the accepted views on Th2 responses. However, it may accompany activation of cells less restricted in the determination of their Th profile.

The activation of the placental isoferritin system has not yet been categorized to one of the Th types. Isoferritin has a physiological immunosuppressive function, and it is consequently of great interest that increased levels of this molecule are also found during HIV infection and may be correlated with stages of the infection[49]. Activated $CD4^+$ T cells are its major source and, thus, the extremely high serum levels of placental isoferritin found in the HIV-seronegative Ethiopian population in Israel[25] indicate a high degree of $CD4^+$ T-cell activation, accompanied by a certain degree of immunosuppression[50].

Mechanisms of immune activation

A central question pertaining to the findings in African populations is: do certain infections have a specific or more general influence on immune activation? The immune response to the multitude of infections that are handled by the reticuloendothelial system, and other cellular components, is only vaguely

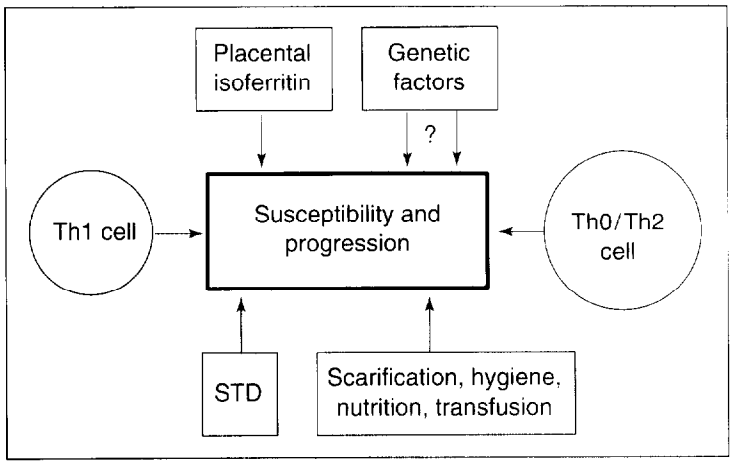

Fig. 2. *Factors determining increased susceptibility and progression of HIV infection in Africa. Protective and facilitating influences are indicated by blue and red arrows, respectively. Abbreviations: HIV, human immunodeficiency virus; Th1, T helper 1; STD, sexually transmitted disease.*

defined as far as its generation and its specific role in the context of T-cell activation. However, it is clear that there is a spectrum of cytokines that interact continuously and, thus, it is probably the net interaction of several cytokines that determines the final outcome. Yet one of the striking elements in the infectious load in Africa and other developing countries is the helminth infections, which are universal and are chronic lifetime infestations. Although our understanding of the mechanisms involved in the handling of such infections is limited, they are known to result in eosinophilia, high levels of IgE and mast cell activation, which is suggestive of an increase in the secretion of IL-4 and IL-5. This could then serve as a major element in shifting the balance towards the Th2-type pattern and in suppressing the Th1-type of response[28,30,51]. The activation of eosinophils may also result in upregulation of CD4 molecules on the cell surface, adding yet another facilitator for HIV enhancement[52]. Furthermore, recent studies have shown that helminth infections contribute to decreased immune responsiveness and to decreased specific immune responses to recall antigens, not just to HIV (Refs 31,38). On consideration of the other common infections in Africa, it is interesting to note that malaria has not been found to affect the course of AIDS, or to be influenced by HIV infection[53]. However, tuberculosis has been found to increase significantly with HIV infection, and to influence its course[16].

Balance of cytokine interaction

As outlined above, the orchestration of the immune network is dependent on a continuous balance among individual cytokines. This accounts for the sometimes polar outcomes of responses involving the same cellular components. We believe that this also holds true for the situation in Africa. There, a shift towards increased IL-4, IL-5 and IL-10 production is caused by helminth infections. Such interactions also lead to increased TNF levels, and probably to an extreme activation of the placental isoferritin system. Together, these factors create the receptive background for HIV infection that makes the African host so much more susceptible to the infection and its progression. The potential role of genetic components in this balance is unknown.

Conclusion

Figures 1 and 2 graphically summarize the model described above for the major interactions occurring between infections (particularly helminth infections) and the immune response of the host in Africa. In addition to the central role of STDs, important cofactors such as the cultural habit of scarification, as well as transfusion, hygiene and nutrition, may facilitate HIV transmission and infection. Immune activation is elicited through several positive and negative influences on the main cytokine systems that determine the response to HIV and the progress of its infection. The resulting type of immune activation may account for the African pattern of AIDS infection and progression, which threatens to be the dominant pattern of the epidemic in all developing countries. Unless a state of decreased activation is achieved, the African host will continue to be an easy and accessible prey for HIV. This background must be taken into consideration when planning for protective vaccines because, without decreasing the activation of the immune system, it is likely that no protection will be achieved.

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On the nomenclature for V-region serological markers

Alfred Nisonoff

A recent article in Immunology Today *raised significant questions concerning the appropriate use of the terms 'idiotype' and 'V-region isotype'. An alternative approach to the usage of these terms, which emphasizes their functional aspects, is presented here by Alfred Nisonoff.*

An article by Roy Jefferis, published in *Immunology Today*, questioned the validity of usage of the word 'idiotype' in specific instances in the literature[1]. One of the subjects he discussed was the appropriateness of referring to a serological marker designated CRI_A (CRI: cross-reactive idiotype) as an idiotype. This question has general relevance to the usage of the word and, since my laboratory has worked extensively with antibodies expressing CRI_A, this article was written to consider these arguments further. The term idiotype, originally introduced by Oudin and Michel[2], will be used to refer to the collection of idiotopes on an antibody molecule[3,4]; T-cell receptors will not be discussed.

CRI_A: requirements for expression

CRI_A is defined by polyclonal and monoclonal antibodies (mAbs), and is present on a substantial fraction (generally 20–70%) of the anti-*p*-azophenylarsonate (anti-Ars) antibodies that are induced in all adult strain A mice following inoculation with a conjugate