AIDS and Tuberculosis

A Deadly Liaison

Edited by
Stefan H. E. Kaufmann and Bruce D. Walker

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Contents

Preface

AIDS-TB: A Deadly Liaison

In ranking perfect storms, the intersection of the tuberculosis (TB) and acquired immunodeficiency syndrome (AIDS) pandemics is high on the list, and is occurring in places least equipped to deal with the broad health implications. Over the past two decades, the AIDS pandemic has exploded in Africa, increasing in some places from less than 1% of the population to well over 40% of certain age groups in certain regions of Southern Africa. The global burden of human immunodeficiency virus (HIV) infection is now over 33 million cases, most occurring in resource-scarce settings, and 25 million people have already died.

At the same time, and by no coincidence, the TB pandemic has also flourished. Currently, there are two billion people infected with the etiologic agent *Mycobacterium tuberculosis* (*Mtb*), and sadly the burden of the TB pandemic lies squarely in the same regions as the HIV pandemic. This is particularly obvious in Africa (Figure 1). At the center of this storm is KwaZulu Natal in South Africa, where up to 70% of persons with *Mtb* infection are dually infected with HIV, and 30% or more of persons who are HIV-infected have active TB. But other areas in Africa are similarly affected, and these two pandemics are finding each other on numerous other continents.

The reason for this deadly liaison between HIV and *Mtb* is rooted in the pathogenesis of these two infections. HIV infects cells of the immune system, gaining access to CD4 T lymphocytes and monocytes via coreceptors that bind the HIV envelope, namely the surface CD4 molecule and a chemokine coreceptor, usually CCR5. From the earliest stages of infection, there is a dramatic loss of CD4 T cells, particularly in the gut-associated lymphoid tissue, where the majority of these cells reside. This loss of the central orchestrator of effective immune responses leaves the body unable to successfully contain HIV, leading to persistent viremia and continued loss of CD4 T cells, and resulting in profound immune suppression in untreated persons.

This HIV-induced insult to the immune system could not be much worse for controlling *Mtb* infection, which depends on T-cell responses. *Mtb* has chosen macrophages as its preferred habitat. For many bacterial pathogens, macrophages

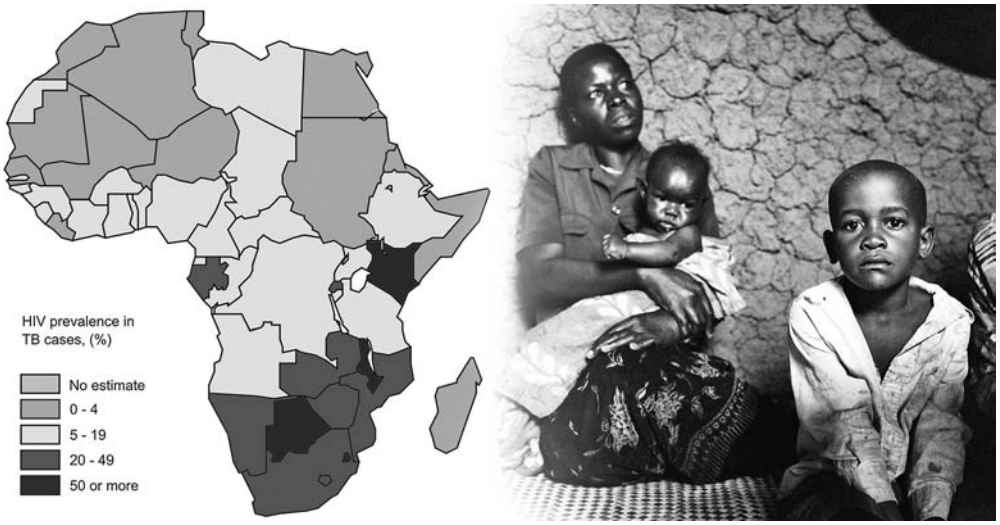

Figure 1 (left) Estimated HIV prevalence (as %) among new TB cases in Africa, 2006. Source: WHO Global tuberculosis control: surveillance, planning, financing (2008); (right) AIDS–TB patients in Uganda. Photograph courtesy of Keoki Flagg.

are a dead-end road and their engulfment results in bacterial death, at least after macrophage activation by CD4 T cells. Yet, *Mtb* has devised strategies to survive in these cells; this pathogen flourishes in resting macrophages and persists in fully activated ones. As long as CD4 T cells can fully activate macrophages, then *Mtb* persists, often without causing active disease. Once macrophage activation becomes impaired, *Mtb* multiplies and disease breaks out. This is exactly what happens in HIV–*Mtb* coinfection: impaired CD4 T cells fail to activate macrophages, which in turn fail to control *Mtb*. Although much remains to be learned, there is an expanding body of knowledge – much of it outlined in the following chapters – that indicate a particular defect in *Mtb*-specific immunity rendered by HIV, and similarly, immune dysregulation of HIV related to the pathogenesis of TB.

With the rapid expansion of these two pandemics, there is a critical need to better understand these interactions and to integrate research efforts, as the two pathogens are clearly impacting one another in ways that are yet to be fully defined. The reality is that the AIDS and TB research communities have been largely separate, similar to the treatment programs which, in most regions of the world, have yet to be effectively integrated despite overlapping infections and drug toxicities. The goal of this book is to bring together the key issues in both of these fields, as well as the key areas of overlap for which there are emerging data indicating how this deadly liaison plays out.

This book is intended to provide an overview of the key issues confronting these dual pandemics, bringing together state-of-the-art research in both fields in one volume. The book begins with an overview by Julg and Walker of the challenges in

developing an effective AIDS vaccine, together with a detailed assessment of the factors that have led to a lack of viable clinical candidate vaccines more than two decades after these efforts started.

Kaufman and Stenger then add to the initial immunologic theme, outlining the key elements in the immune response to TB, and the strategies being employed to develop an efficacious vaccination schedule. Their chapter also describes current achievements in biomarker characterization which will be instrumental for accelerating clinical trials.

Next, we move on to review the status of the one vaccine that is currently in use against TB, namely BCG, which has been administered to about four billion people worldwide since it was first introduced nearly a century ago. Hanekom and Hussey discuss the properties of this vaccine, which is poorly protective against the pulmonary form of TB in adults that accounts for most global transmissions, as well as the potential complications of this vaccine in HIV-infected infants and the need for new approaches in this age group.

The most dramatic change in the HIV pandemic in terms of health care has been the introduction of highly active antiretroviral therapy, which has now been administered to more than three million people worldwide. The huge arsenal of drugs available, as well as new approaches to treatment currently being pursued, are outlined in the next chapter by Gulick, who has been intimately involved in treating HIV infection since the beginning of the treatment era in the United States. Despite issues of access, cost, infrastructure and side effects, treatment has had a huge individual benefit, although there is little evidence that it has led to changes in the kinetics of the pandemic.

Böttger and Springer next discuss the treatment of TB, including the mechanisms of drug resistance and the genetics underlying this. This treatise takes a refreshingly new view on TB drug treatment and the susceptibility testing of *Mtb*, with its direct implications for appropriate therapy. Currently, TB is treated with three to four drugs over six to nine months, and poor compliance frequently leads to drug resistance. Because of lack of attention in the final quarter of the last century, new TB drugs have not been developed. Although we now envisage the entry of a number of promising drug candidates into the pipeline, it will still take several years before they become available for broad use. New regimens based on combinations of available drugs could bridge this gap.

One of the major global challenges related to the intersection of the AIDS and TB pandemics is the need to simultaneously treat both infections, which brings forth the major problem of HIV–*Mtb* drug interactions and overlapping toxicities. Oni, Pepper, and Wilkinson, who are leaders in the area of treatment of these two diseases in one patient, provide a detailed account of the issues related to attempts to contain both infections in the same individual.

As global treatment efforts related to HIV have expanded over the past few years, so too has the experience with clinical diagnosis and management of HIV disease. Dryden-Peterson, Sunpath and Gandhi, all of whom have experience in on-site treatment in resource-scarce settings, cover the clinical issues related to diagnosis and management of HIV. The issues around the diagnosis and treatment of HIV–

Mtb coinfection are covered in chapters by Neil Schluger and by Goldfeld and Corbett, who have considerable personal experience in these areas. Both chapters focus on the challenges of diagnosis, treatment and clinical care of AIDS-associated TB, and expand on effective ways of achieving early diagnosis at the community level as an urgently required step for effective control in resource-poor settings. By using appropriate therapy schemes that consider drug interactions, AIDS and TB in one patient are treatable, and TB even curable.

Emerging as one of the most threatening consequences of the deadly liaison between HIV and *Mtb* is the development of extensively drug-resistant (XDR) TB, which is covered in the chapter by Murray and Cohen. The chapter discusses the causal role of HIV in the development of multiresistant *Mtb* and the confounding effects of HIV coinfection on diagnosis and treatment. This is followed by the final chapter by Grobusch, Menezes and John, which deals with the effect of HIV-induced treatment leading to a robust adaptive immune response to HIV that can be so vigorous as to be lethal in some individuals, namely the immune reconstitution inflammatory syndrome (IRIS). Since IRIS is an undesired consequence of AIDS treatment in HIV–*Mtb* coinfected individuals with increasing occurrence, this chapter gains enormous importance, for both scientific and for societal reasons.

Together, we hope that these chapters provide an overview of not just the challenges being produced by the intersection of the TB and AIDS pandemics, but also the opportunities available to address critical research issues. These efforts will have a direct impact on future policies designed to contain these epidemics, and hopefully ultimately to end both of them. We thank the talented authors who have contributed to this volume, and hope that it serves to better integrate research in two fields that, through the intersection of pandemics, has forced our attention on them.

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Part One
Immunology and Vaccination Strategies for AIDS and TB

1
HIV Immunology and Prospects for Vaccines

Boris Julg and Bruce D. Walker

1.1
Introduction

As the HIV epidemic approaches its fourth decade, the world remains without a vaccine for a disease that has claimed more than 25 million lives, and currently infects over 33 million persons. The vast majority of these infections are in resource-scarce settings, and in most places the humanitarian crisis is enhanced because of overlap with the expanding global tuberculosis (TB) epidemic. The introduction of highly active antiretroviral therapy (HAART) in 1995–1996 resulted in a dramatic decrease in the mortality and morbidity of HIV infection in developed countries fortunate enough to have access to these life-extending medicines [1], and more recent expanded global access has resulted in more than three million persons receiving treatment in 2008. However, this still leaves an enormous gap in those who have advanced disease and are in desperate need of therapy, and in addition there are likely to be nearly 2.5 million new infections in 2009 (UNAIDS, http://www.unaids.org).

There is no doubt that the development of a safe and effective HIV-1 vaccine will be the best solution for the ultimate control of the worldwide AIDS pandemic [2], and this will likely also impact the TB epidemic. However, all attempts to achieve this have failed so far, reinforcing the fact that an AIDS vaccine is unlikely to be available in the near future [3]. As the TB and HIV epidemics intersect across the globe, the need for a vaccine to prevent the immunodeficiency induced by HIV that is accelerating expansion of the TB epidemic is even more acute [4]. In this chapter we will discuss the current challenges to the development of an effective AIDS vaccine, and address the progress made and persisting gaps in our quest for an effective method to prevent new infections.

1.2
Challenges for HIV Vaccine Design

The history of successful immunization dates back to the time of Jenner, whose success with a smallpox vaccine in 1796 was achieved with little understanding of the

actual mechanisms of protection that were being induced. By mimicking infection with smallpox by inducing a benign cowpox infection, Jenner laid the foundation for modern vaccinology. Most vaccines currently in use, if not all, do not actually prevent infection, but rather attenuate disease caused by the pathogen. In fact, most mimic something that happens naturally – namely that some fraction of people who become infected clear their infections [5].

The situation with HIV is quite different as HIV is an infection in which, to our knowledge, spontaneous clearance never occurs. The natural history of HIV infection is one of progressive viremia, in which the targets of the virus are cells of the immune system itself, particularly CD4+ T-lymphocytes. Following infection, there is a gradual decline in CD4+ cell number and an increase in viral load, typically resulting in AIDS within 8–10 years, which is defined by a CD4+ cell count of less than 200 or specific AIDS-defining illnesses. HIV is actually an infection of the immune system, with CD4+ T-lymphocytes being a key target of the virus, which enters these cells through its coreceptors CCR5 (or occasionally other chemokine coreceptors such as CXCR4) and CD4.

There are five main properties of HIV that render the development of an HIV vaccine an unprecedented challenge.

1. **Massive infection of immune cells:** HIV uses its envelope protein to gain access to cells bearing its coreceptors, CD4 and the chemokine receptor CCR5 or CXCR4. The major target of the infection are CD4+ T-cells, and because activated cells are preferentially infected by HIV, the infection preferentially appears to deplete HIV-specific CD4+ cells. The infection of CD4+ cells is massive at the acute stage of infection, when up to 60% of CD4+ T-cells in the gut-associated lymphoid tissue (GALT) are depleted [6].

2. **Integration into the host chromosome:** HIV is a retrovirus, and following viral entry the viral reverse transcriptase initiates the production of a double-stranded proviral DNA that can remain as free circular DNA and undergo processes of transcription and translation to make new virion particles. Alternatively, it can use the viral integrase protein to create a nick in the host chromosome, and integrate. Once integration occurs – which all indications suggest happens very early after acute infection [7] – the virus can remain in an immunologically latent state. This is possible because the lack of transcription and translation of viral proteins means that the normal immune mechanisms, which rely on the detection of foreign viral protein within cells to induce immune attack, do not occur.

3. **Viral diversity:** HIV is a retrovirus, and viral replication is dependent on an error-prone viral reverse transcriptase that has a poor proofreading function. As a result, with each replication cycle there is likely to be at least one nucleotide mis-incorporation. At least some of this diversity is driven by immune selection pressure, which has been shown to be progressively deleting some key epitopes of the virus at a population level [8]. Globally there are three main groups of HIV – M, N, and O – with group M (the largest) being further divided into nine distinct clades and additional circulating recombinant forms. Viruses within a clade may

differ by up to 20% in the highly variable Env protein, which is the target for neutralizing antibodies, and by up to 38% between clades. Even within a single individual HIV mutates such that individuals carry unique strains. Developing a vaccine to target all of these viruses simultaneously is an enormous task.

4. **Envelope glycosylation:** The HIV envelope is heavily glycosylated, and also very flexible, in that it allows for a high degree of random mutations to be stably incorporated. This combination of Env variability, together with heavy glycosylation that renders key epitopes poorly exposed to antibody-mediated immune attack, has been a major challenge for any vaccine to provide broad cross-neutralizing protective antibody responses (for a review, see Ref. [5]). Indeed, at the current time this is such a challenge that many in the field have focused not on a preventive HIV vaccine – which would require the induction of broadly cross-reactive neutralizing antibodies – but rather on a T-cell-based vaccine which would be intended to provide a durable reduction in viral load, and thereby retard disease progression and reduce the likelihood of transmission to others [9].

5. **Immune evasion:** The HIV accessory protein Nef interacts indirectly with the cytoplasmic tail of HLA A and B alleles, leading to endocytosis and a down-regulation of class I expression on infected cells [10]. This impairs the ability of cytotoxic T lymphocytes to recognize infected cells, and has been shown to have functional significance on the ability to contain HIV replication [11]. Neutralizing antibodies are unable to recognize the variants that arise *in vivo* [7, 12, 13], so that the humoral immune response is always playing "catch-up." In addition, mutations arising within targeted CD8+ T-cell epitopes also lead to either a loss of recognition by the T-cell receptor (TCR) of established responses, or to a loss of binding of the epitope to HLA class I, allowing immune escape.

1.3
What Immune Responses will be Required for an Effective AIDS Vaccine?

A fully preventive HIV vaccine would almost certainly require the induction of broadly cross-reactive and highly potent neutralizing antibodies, which would have to prevent the infection of cells and the establishment of latent infection. There is widespread agreement that this is not likely to occur, for the reasons outlined below. Indeed, most – if not all – vaccines currently in use do not achieve this level of protection. This reality has directed the field toward vaccine strategies that would prevent disease progression rather than prevent infection – which, at least in theory, would cause the epidemic to contract – if the viral load could be kept low enough to limit both disease progression and transmission.

The challenges to this direction for vaccine development are compounded by the fact that we still lack an understanding of the correlates of immune protection, despite an intricate understanding of the molecular biology of the virus (Figure 1.1). Despite marked differences in disease outcome following infection, we lack a fundamental understanding of the mechanisms that account for these differences.

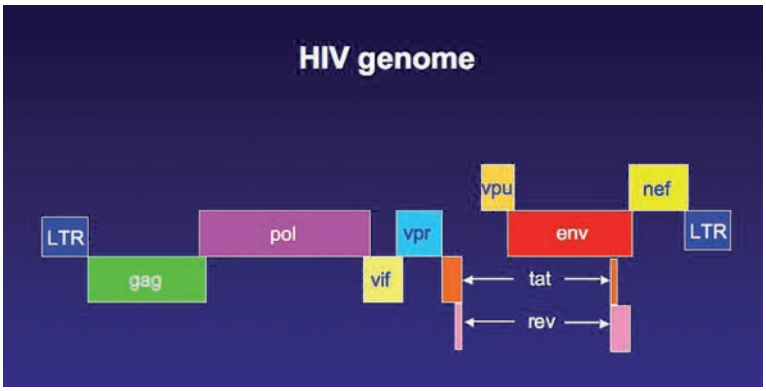

Figure 1.1 The HIV-1 genome. There are nine coding regions, in three different reading frames. *gag* is the main structural protein, *pol* encodes the replicative functions, and *env* encodes the heavily glycosylated outer envelope. The regulatory proteins include *vif*, *vpr*, *vpr*, *rev*, *tat*, and *nef*. LTR, long terminal repeat.

There is a growing body of data indicating that adaptive host immune responses play a role, but the key elements of protective immunity that would have to be induced by a vaccine are not known. What *is* known is that some persons are able to maintain successful control of HIV viremia for 30 years or more without therapy. This, in turn, provides some level of optimism that a vaccine might be able to result in a similar equilibrium with durable control of HIV, even if a totally preventive vaccine is not possible [14]. In contrast, others progress from acute infection to AIDS within six months [15]. Whilst the factors that account for these dramatic differences in outcome remain elusive, a growing body of data is beginning to shed light on the rational induction of specific arms of the immune response for HIV vaccine design (Figure 1.2).

1.3.1 Cytotoxic T Lymphocytes

Following acute HIV-1 infection, the resolution of acute-phase plasma viremia to a semi steady-state level, or set-point, coincides with the activation and expansion of HIV-1- specific cytotoxic T lymphocytes (CTL), suggesting that virus-specific CD8 + T-cells may be responsible for reducing the levels of virus at this stage of infection [16–18]. Direct evidence for the role of CD8 + T-cells in mediating the decline in viremia during acute HIV infection has come from studies of the simian immunodeficiency virus (SIV)-macaque model. Here, the administration of CD8-specific monoclonal antibodies s(MAbs) resulted in a transient depletion of CD8 + cells in both the peripheral blood and lymphoid tissues. When administered during primary chimeric simian/HIV infections, the CD8 MAb caused marked elevations of plasma and cell-associated virus levels in both the peripheral blood and lymphoid tissues, and led to a prolonged depletion of CD4 + cells. Eliminating CD8 + lymphocytes from monkeys during chronic SIV infection resulted in a rapid and marked increase in viremia that was again suppressed coincident with the reappearance of SIV-specific

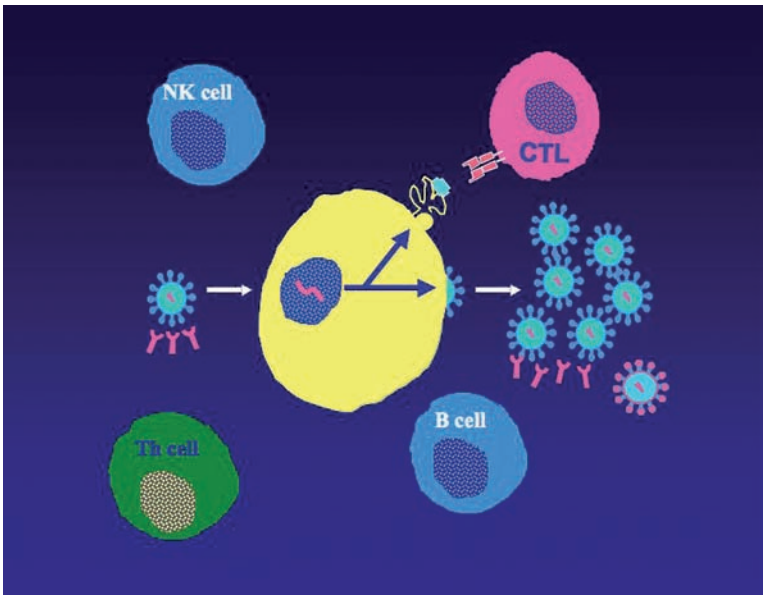

Figure 1.2 Immune responses to HIV. The B cells produce neutralizing antibodies, which are highly type-specific and poorly recognize diverse isolates, even those that arise within a single person due to reverse-transcriptase-induced errors in replication. The cytotoxic T cells (CTL) target virus-infected cells through recognition of viral proteins presented at the cell surface associated with HLA class I molecules, and deliver a lethal hit to the infected cell, ideally before progeny viruses are produced. Despite these responses, progression ensues in most persons. T helper (Th) cells, which express CD4 and CCR5, are the central orchestrator of effective cellular immunity, but are infected in large numbers in acute infection and never fully recover; they progressively decline over time until a CD4 count of 200 is reached, which defines AIDS. Natural killer (NK) cells target virus infected cells without requiring prior exposure; emerging data suggest that these may be important in HIV control.

CD8 + T-cells [19–21]. These results confirm the importance of cell-mediated immunity in controlling AIDS virus infection, and support the exploration of vaccination approaches for preventing infection that will elicit these immune responses.

An emerging body of data suggests that it is not just the magnitude but rather the specificity of the CTL response that may be critical for immune containment. Numerous population studies have determined that neither the total breadth nor the total magnitude of HIV-specific CD8 + T-cell responses correlate with the ability of an individual to control HIV-1 [22–24], which suggests that selected epitope-specific CD8 + T-cell responses play a relevant role. Large population studies conducted in South Africa have defined that a preferential targeting of Gag is associated with a lower viral load [25], while more recent data have indicated that the breath of the Gag-specific response is negatively correlated with the viral load in persons with chronic infection [26]. In contrast, broad Env-specific CD8 + T-cell responses are associated with a high viral load [26]. To some extent this may reflect differences in the quality of these responses, or in the relative efficacy of different responses to recognize and kill infected cells before progeny viruses are

produced [27]. The limited ability of these responses to provide durable containment may also be due to escape mutations emerging within targeted CD8+ T-cell epitopes, which arise during primary [28–31] and chronic [32, 33] HIV-1 and SIV infection, and demonstrates significant CD8+ T-cell pressure on these regions of the virus and impacts temporally on disease progression [33, 34]. In addition, functional impairment or exhaustion of these responses over time in the setting of chronic viral stimulation may play a role. The inhibitory receptor programmed death 1 (PD-1; also known as PDCD1), a negative regulator of activated T cells, is markedly upregulated on the surface of HIV-specific CD8+ T-cells, the expression correlating with impaired HIV-specific CD8+ T-cell function as well as with predictors of disease progression – positively with plasma viral load, and inversely with the CD4+ T-cell count [35]. In contrast, the inhibitory immunoregulatory receptor CTLA-4 is selectively upregulated in HIV-specific CD4+ T-cells, but not CD8+ T-cells, in all categories of HIV-infected subjects, except for a rare subset of individuals who are able to control viremia in the absence of antiretroviral therapy [36].

One of the strongest arguments in favor of a role for CTLs in the outcome of HIV infection is the association between certain HLA class I alleles and improved outcome [37]. Among these are the so-called protective alleles, the strongest of which include B*5701, B*5801, B51, and B*2705. These B alleles have in common that they are associated with strong immune responses to the Gag protein, and in some cases are associated with mutations that impair viral fitness [38]. Other HLA alleles, such as HLA B35, are associated with a worse outcome [39], although an understanding of the mechanism of this association remains obscure. One concern raised by these observations is that there may be genetic limitations to the efficacy of a particular vaccine candidate, in that it may be more immunogenic in certain HLA backgrounds, and may have limited immunogenicity in others. However, this concern remains unsubstantiated.

1.3.2 Neutralizing Antibodies

Following the identification of HIV as the causative agent of AIDS, it was predicted that a vaccine inducing neutralizing antibodies and thereby preventing infection would rapidly be available. Yet, a quarter of a century later an effective preventive HIV vaccine still eludes us. Neutralizing antibodies are induced by HIV, but fail to control viremia. Despite a pronounced antibody response to the viral envelope proteins, only a small fraction of these antibodies have neutralizing activity. This is partly due to the fact that the HIV-1 Env glycoprotein is a trimer on the virion surface with extensive N-linked glycosylation that effectively shields many conserved epitopes from antibody recognition [40]. Key conserved regions, such as the binding site of the chemokine coreceptor, are only formed after Env binds its cellular receptor CD4 and undergoes an extensive conformational change. The broadly reactive MAb b12 binds to the CD4-binding site, suggesting that this region of Env may represent a critical point of vulnerability that is potentially amenable to neutralization, although the CD4-binding site is recessed and only partially accessible to antibody binding. The membrane-