Title
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Permalink
https://escholarship.org/uc/item/3n83670z

Journal
European journal of immunology, 41(12)

ISSN
1521-4141

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Publication Date
2011-12-01

Peer reviewed
HIV/AIDS: 30 Years of progress and future challenges

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Acquired immune deficiency syndrome (AIDS) was first described 30 years ago in a report from the US Centers for Disease Control. Two years later the causative virus was identified and afterwards named the human immunodeficiency virus (HIV). This article reviews the progress made in the three decades since the recognition of AIDS and the discovery of HIV, with respect to the virus, the infected cell, and the host, as well as directions for future studies.

Key words: AIDS · HIV · Innate and adaptive immunity · Pathogenesis

Introduction

Acquired immune deficiency syndrome (AIDS) was first described 30 years ago in a report from the US Centers for Disease Control [1]. Two years later the causative virus was identified [2] and afterwards named the human immunodeficiency virus (HIV). HIV has spread throughout the world, killing half of the 60 million people infected thus far. Currently, there are about 2 million new HIV infections each year and an equal number of deaths due to AIDS [3]. This article reviews the progress made in the three decades since the recognition of AIDS and the discovery of HIV. Discussed are important findings with respect to the virus, the infected cell, and the host, as well as directions for future studies.

The virus

Prior to the discovery of HIV, the major proteins and replicative cycles of similar viruses had been described [4]. Therefore, many biologic features of HIV were readily demonstrated [5]. While lentiviruses were known to infect sheep, goats, cows, and horses, HIV was the first lentivirus found in primates. Like other retroviruses, the RNA genome of HIV is reverse transcribed into DNA that encodes the major genes gag, pol, and env. Distinguishing HIV from other types of retroviruses are its accessory genes (tat, rev, nef, vpr, vif, and vpu/vpx) that promote virus infectivity and modulate host cell functions.

Sequence diversity

HIV was discovered in 1983, as was a revolutionary molecular biology invention, the polymerase chain reaction (PCR). Restriction enzyme mapping (Fig. 1A) and later PCR-aided analyses of the HIV genome, revealed a variety of different subtypes (Fig. 1B) [5, 6]. The AIDS virus has now been classified into two major virus types: HIV-1 and HIV-2. Based on their genetic similarities, four major groups of HIV-1 (M, N, O, P) have been recognized [7]. Within group M, there are at least nine subtypes or clades that differ by about 15% in sequence [5]. Nearly 50% of all HIV infections belong to HIV-1 clade C. HIV-2 infection has a very low prevalence (<50 000 infections) with two dominant groups A and B and no clades. The sequence diversity of HIV-1 clades does not seem to substantially impact the disease course, except perhaps for a slower progression rate with subtype A [5, 8]. Proviral sequences obtained from 89 elite controllers (ECs) (see The Fortunate) revealed no striking differences from the viral sequences of progressors [9]. Furthermore, HIV has been transmitted from an AIDS patient to an individual who became an EC [10]. These and other findings indicate that host-specific factors are the major determinants of disease.

The most apparent trend in HIV diversity during the past decade is the increased proportion of circulating recombinant virus forms [7]. Recombinants can have different biologic and serologic properties but their basic modes of transmission are the same as other HIVs: intimate sexual activity, receipt of blood or blood products, mother to child transfer, and injection drug use [5]. Nonetheless, the extraordinary sequence diversity of prevalent HIVs presents a major challenge for host immune responses, treatment, and vaccine approaches.
The infected cell

CD4+ T cells first became evident as the primary targets of HIV with the reported severe decreases in the number of these cells in AIDS [11]. The identification of CD4 as the major virus receptor was very important, particularly as few virus receptors were known then [12]. Early studies revealed differences among HIV isolates to replicate in macrophages versus T-cell lines that correlated with their cytopathology (e.g. syncytium formation) [13, 14]. Generally, HIV isolates that grew in macrophages were nonsyncytium-inducing (NSI) and those in T-cell lines were syncytium-inducing (SI) viruses. This bimodal display of tropism was later explained when two viral co-receptors were identified. The first, CXCR4, is the chemokine SDF-1 receptor used for attachment by syncytium-inducing (X4) viruses. Subsequently, CCR5, a receptor for the β-chemokines (MIP-1α, MIP-1β, and RANTES) was found for nonsyncytium-inducing (R5) viruses [15]. Notably, some HIV isolates can utilize either co-receptor, thus identifying three main biologic phenotypes: R5, X4, and R5/X4 viruses. However, CD4 and CCR5/CXCR4 are not necessary for HIV infection of all the different cell types and tissues affected (Table 1).

To enable its replication, HIV must counter intracellular host factors that restrict virus production (Fig. 2) [16–18]. These defenses include APOBEC3G/F, TRIM5α, Lv2, tetherin, and most recently SAMHD1. Considerable attention has been given to APOBEC3G, a cytidine deaminase that introduces consequential mutations into the HIV genome, and can promote viral latency. HIV viral infectivity factor (Vif) counters this antiviral mechanism by targeting APOBEC3 proteins for ubiquitination and proteasomal degradation. TRIM5α, a cytoplasmic protein that binds to the virus capsid, prevents uncoating of the virus. Lv2 is a protein that similarly blocks HIV-2 replication at a post-entry step. Tetherin (CD317), a membrane protein that anchors mature virus particles to the cell, prevents HIV budding from the cell. Its effects can be countered by HIV Vpu [17]. SAMHD1 blocks proviral DNA synthesis during reverse transcription. HIV Vpx reduces cytosolic levels of this protein by targeting it for proteolytic degradation [18]. Importantly, the expression of some intrinsic resistance factors are increased by type I IFN [17, 19], thus linking them with innate immunity. Intracellular β defensins are other intrinsic proteins recently implicated in blocking HIV transcytosis through adult mucosae [20].

Autophagy, the major pathway for degrading long-lived proteins and recycling cytoplasmic nutrients, is another intracellular barrier to HIV replication. Although autophagy can...
infections likely result from exposure to HIV-infected cells [25]. Secretions, blood, and other bodily fluids can be infectious, many through sexual contact. Although cell-free HIV found in semen, vaginal secretions, blood, and other bodily fluids can be infectious, many infections likely result from exposure to HIV-infected cells [25].

The host

Most HIV-infected individuals have acquired the virus through sexual contact. Although cell-free HIV found in semen, vaginal secretions, blood, and other bodily fluids can be infectious, many infections likely result from exposure to HIV-infected cells [25].

Figure 2. Intrinsic factors influencing HIV infection. Intracellular intrinsic factors and their potential mechanisms for inhibiting HIV replication are illustrated. TRIM 5α binds to the viral capsid and prevents uncoating of the viral core. APOBEC 3G or F, cytidine deaminases, cause mutations in the HIV genome leading to virus inactivation. This effect can be countered by the viral protein, viral infectivity factor (Vif). Tetherin retains viral particles on the cell membrane preventing budding. Its effect is countered by the viral protein Vpu. MURR-1 has been reported to affect viral transcription. SAMHD1 blocks proviral DNA synthesis in DCs and macrophages and is countered by HIV Vpx. For details, see [5].

In most cases, the route of transmission, whether by sexual contact or injection drug use, does not seem to influence disease progression [5].

Acute HIV infection

Much insight has been gained into HIV pathogenesis from studies of primary HIV infection (Table 3) [26]. Initially, HIV appears to establish a localized infection via the vaginal or anal canals, with the transmitted/founder virus being highly homogeneous [27]. During the first weeks after HIV transmission, severe losses of CD4+ cells occur, particularly in the gastro-intestinal mucosal, as a ‘cytokine storm’ ensues and plasma viral loads reach very high levels (Table 3) [28, 29]. Following this acute infection period, virus levels decline to a ‘set point’ as host cellular immune responses become evident. The timely appearances of innate and then adaptive immune responses suggest that these host defenses determine the course of HIV infection (Fig. 3).

The fortunate

The first years of the epidemic offered no effective treatment for AIDS and the full HIV pathogenic capacity was manifested. In patients who died, HIV could be found in lymphatic, brain, bowel, lung, and kidney tissue [5]. Systemic infection helped explain the variety of diseases (e.g. opportunistic infections, cancers, neurologic disorders) associated with AIDS. However, a select group of HIV-infected people remained healthy beyond the typical asymptomatic period of 9 years [30]. These long-term survivors (LTSs), or long-term nonprogressors, exhibit low viral loads and slow CD4+ T-cell declines; they provide promising evidence of host anti-HIV immunity (Table 4). Recent focus has shifted to a subgroup of LTSs termed ‘elite controllers’ (ECs) who maintain virtually undetectable plasma viral loads for years, despite their infection with intact and fully pathogenic HIV [8, 31]. Other individuals of scientific interest are highly exposed seronegatives (HESNs) who remain uninfected despite multiple exposures to HIV [5, 32]. These optimistic outcomes with HIV have encouraged a focus on identifying the immunological features of protection from infection and disease (Table 4).

Table 2. Possible causes of HIV latency

<table>
<thead>
<tr>
<th>Mechanism</th>
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<tbody>
<tr>
<td>APOBEC3G expression</td>
</tr>
<tr>
<td>Site of virus integration</td>
</tr>
<tr>
<td>Methylation of viral DNA</td>
</tr>
<tr>
<td>Chromatin interaction with the HIV promoter</td>
</tr>
<tr>
<td>Lack of sufficient viral gene expression (e.g. Tat, Rev)</td>
</tr>
<tr>
<td>Histone suppression of gene expression (HDAC-1 activity)</td>
</tr>
<tr>
<td>Inhibition of virus expression by CAF</td>
</tr>
</tbody>
</table>

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The fortunate

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Table 3. Features of primary HIV-1 infection

Acute HIV infection (RNA⁺, Ab⁻)

Timing: 0–6 wk post infection

Clinical symptoms: May include fever, lymphadenopathy, skin rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leukopenia, thrombocytopenia, transaminase elevation

Virus levels: HIV RNA becomes detectable and later reaches maximal levels (>10⁵ copies/mL); HIV sequence diversity very limited

Host defenses: Intracellular resistance factors (APOBEC3, TRIM5α, tetherin); innate immune responses (CNAR/CAF, pDCs, NK cells, neutrophils)

Major events: Severe loss of GALT CD4⁺ cells; loss of GALT integrity; systemic spread of HIV

Post-acute early infection (RNA⁺, Ab increasing)

Timing: 6 wk to 6 months post infection

Clinical symptoms: Overlap with acute stage; generally asymptomatic

Virus levels: HIV plasma levels taper to a ‘set point’ that is usually about 1 log lower than the peak viral load reached during acute infection

Host defenses: Intracellular resistance factors and innate immune responses continue; adaptive immune responses (T and B cell) become detectable, increase in magnitude, and mature; immune activation levels increase

Major events: Virus evolution to escape from adaptive immune responses; antibody titers reach maximal levels

Immune activation

The direct infection of CD4⁺ cells does not appear to be the major mechanism for CD4⁺ cell loss or ensuing disease (Table 5). Instead, the extent to which the host immune system is activated during the infection is likely a major determinant of HIV pathogenesis (Table 6). As first suggested in studies by Giorgi et al. [33], chronic immune activation, evidenced by the elevated expression of HLA-DR and CD38 on CD8⁺ cells, can lead to telomere shortening, cellular anergy, and immunosenescence [34]. Notably, it promotes the apoptotic cell death of infected and uninfected CD4⁺ cells and contributes to the dysfunctions of various immune cells and tissues [5, 35]. A possible cause of the chronic immune activation is a compromise in the integrity of the intestinal mucosal barrier that permits bacteria and endotoxins, such as lipopolysaccharide (LPS), to enter the blood stream [28]. Associated with this effect is the loss of IL17-producing (Th17) CD4⁺ cells that recruit neutrophils to sites of active inflammation and help maintain the mucosal barrier [36]. Another potential cause of chronic immune activation is the production of IFN-α by innate immune responses to HIV-infected cells [37]. Supporting this role of immune activation are studies showing that persistently replicating SIV is nonpathogenic in its natural hosts (e.g. sooty mangabeyes) that do not develop chronic immune activation [38].

Regulatory T (Treg) cells

A subset of T cells, specifically Treg cells, may help slow HIV disease progression by controlling immune activation [39]. However, their suppression of beneficial antiviral activities of multiple immune cell types must be avoided [39, 40]. Treg cells having a CD4⁺CD25⁺Foxp3⁺ phenotype are the best described

![Figure 3. Innate immune responses to acute HIV infection.](image-url)
subsets (Table 7) \[39\], but CD8\(^+\) T\(_{reg}\) cells have also been reported \[41\]. Recent evidence suggests that ECs have HIV-specific CTLs that kill undesired T\(_{reg}\) cells \[42\]. Thus, a complex picture of the interplay between activated antiviral cells and multiple subsets of T\(_{reg}\) cells is unfolding.

The CD8\(^+\) cell noncytotoxic anti-HIV response

The first observation of host anti-HIV activity was made soon after HIV was identified \[43\]. CD8\(^+\) cells were found to suppress HIV replication without killing the infected cells. This finding uncovered a novel CD8\(^+\) cell noncytotoxic anti-HIV response (CNAR) that was distinct from the classic cytotoxic T-cell activity. CNAR is mediated by a soluble secreted component, the CD8\(^+\) cell noncytotoxic anti-HIV factor (CAF), that differs from other cytokines \[44\]. CNAR/CAF has been shown to block HIV transcription \[44\], perhaps by limiting the effect of the transcription elongation factor P-TEFb. Because CNAR appears during early primary infection and suppresses all HIV-1 and HIV-2 isolates via secretion of CAF, it has features of an innate immune response \[44, 45\]. Healthy asymptomatic individuals, particularly LTSs, exhibit increased frequencies of the CD8\(^+\) cells that mediate CNAR in comparison to those who progress to AIDS \[46, 47\]. Moreover, studies of SIV-infected rhesus monkeys depleted of CD8\(^+\) cells in vivo suggest that the virus level is maintained by a CD8\(^+\) cell noncytotoxic process \[48, 49\]. Also, CNAR appears to protect HESNs from infection via sexual contact \[50\] and children born to infected mothers \[51\].

Studies of CAF have uncovered a variety of other soluble factors that can inhibit HIV replication (Table 8). These include the β-chemokines that are the natural ligands for CCR5 and therefore compete with HIV (R5) for binding and entry into the cell \[52\]. Their recognition led to the identification of the most prominent protective factor against HIV infection: homozygosity for a CCR5 allele that encodes a truncated protein \[15\]. In turn, this knowledge of CD8\(^+\) cell anti-HIV factors led to the only known ‘cure’ for HIV (see Cure of HIV infection).

### Cytotoxic T-cell responses

Shortly after the discovery of CNAR, HIV-specific cytotoxic T lymphocyte (CTL) responses were reported \[53\]. Many studies have since focused on this adaptive anti-HIV immune response mediated by HLA class I-restricted CD8\(^+\) T cells. HIV-specific CD8\(^+\) CTL responses become detectable within weeks of infection and coincide with a decline in viral load, suggesting that they play a role in reducing virus levels \[54\]. The association between the CTL activity and control of HIV replication or disease progression is largely influenced by HLA class I determinants. Certain HLA class I single nucleotide polymorphisms (SNPs) and alleles (e.g. HLA-B27 and B57) are more frequently found in ECs \[55\] and are associated with the long-term control of HIV infection \[56\]. The HLA genotypes that are the most protective from disease progression seem to enable CTL to target immutable HIV epitopes \[57, 58\]. Furthermore, ECs appear to have increased functional avidities of Gag-specific and HLA-B-restricted CTL responses \[59\]. Importantly, HLA-associated effects can reflect CTL activity as well as other immune responses such as the killer Ig-like receptor (KIR)–HLA interactions involving NK cells \[60\] and CNAR \[44\].

A major limitation is that CTL responses appear to force the evolution of HIV toward variants that contain mutations in HLA.
class I epitopes that are poorly recognized by antigen-specific T cells [58]. These escape mutants can arise early in the course of infection [61] and their transmission allows HIV to adapt to HLA class I at the population level [62]. Consequently, some studies have not found a strong association of the CTL response with control of viral load [63]. Another finding is that HIV-specific CTLs are often functionally immature [64] or exhausted and are therefore unable to respond appropriately to their cognate antigens [65]. However, these cells may exhibit CNAR [47]. Observations of HIV-specific CTL responses in HIV-exposed uninfected individuals [66] have given some credulity to the concept of a vaccine that elicits protective CTL activity. Indeed, 25 years of research on the CTL response to HIV infection has provided much insight into adaptive immunity. Notably, the methods used can influence the interpretation of the antiviral effect [67]. The translation of this knowledge of CTLs into improved therapies and an effective vaccine for HIV infection remains a challenge.

**B cells and antibodies**

Although all HIV-infected individuals produce anti-HIV antibodies, the humoral response is protracted and, like the HIV-specific CTL response, leads to ‘escape’ mutants [68]. Moreover, HIV infection causes multiple defects in the B-cell compartment, including chronic B-cell activation and a progressive loss of memory B cells [69]. In fact, hypergammaglobulinemia was one of the first signs of HIV infection [5]. These defects could contribute to the very high risk of non-Hodgkin lymphoma in HIV-infected individuals [70]. Revitalizing this field are recent discoveries of broadly neutralizing antibodies (NAbs) [71] that may provide clues for vaccine development. Nevertheless, studies of ECs have failed to identify a direct relationship between elevated NAb levels and undetectable viral loads [72]; most HIV-infected individuals with sustained undetectable viral loads do not have appreciable levels of NAbs against HIV. This observation suggests that maintenance of NAbs requires virus expression.

However, ECs and other LTSs may benefit from antibody-dependent cellular cytotoxicity (ADCC) [73]. By this process, antiviral antibodies bind to infected cells that are killed by NK cells and neutrophils. A protective role of ADCC, but not NAbs, has been reported in macaques that were vaccinated for SIV [74]. Still, a recent study suggests that HIV can also escape from ADCC [75]. Importantly, early studies identified HIV-enhancing antibodies (EAbs) that would bind to the virus particle and facilitate infection of macrophages, T cells, and other Fc-expressing cells via the antibody Fc portion. HIV-enhancing antibodies can be found in patients advancing to AIDS [76].

**Innate immunity**

Increasing attention is being given to host innate immune responses (Fig. 3) that can react to molecular ‘patterns’ rather than specific peptide sequences and can exert a rapid anti-HIV activity without requiring an adaptive process [45]. In addition to CNAR, studies have identified the importance of the innate immune responses of DCs and NK cells in protecting against HIV infection and disease progression.

DCs are an essential component of both innate and adaptive immune activities [77]. In addition to their role as professional APCs, DCs produce cytokines that promote T- and B-cell functions. For example, the release of IL-15 by DCs enhances CD8⁺ T-cell responses, including CNAR activity [78]. Moreover, production of type 1 IFNs (e.g. IFN-α and IFN-β), particularly by plasmacytoid DCs (pDCs), can potently suppress HIV replication [45, 79]. However, defects in the DC compartment are known to limit the overall immune response to HIV. Moreover, the high

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**Table 6. Immune activation in HIV infection**

<table>
<thead>
<tr>
<th>Markers</th>
<th>Causes</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased HLA-DR and CD38 expression on T cells</td>
<td>Microbial translocation (GI tract)</td>
<td>Damage to LNs</td>
</tr>
<tr>
<td>Increased plasma LPS level</td>
<td>HIV replication</td>
<td>Increased T-cell turnover</td>
</tr>
<tr>
<td>Increased plasma soluble CD25 level</td>
<td>CMV and other coinfections</td>
<td>Endothelial cell thickening; cardiovascular disease</td>
</tr>
<tr>
<td>Increased plasma soluble β2-microglobulin and neopterin levels</td>
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<td></td>
</tr>
</tbody>
</table>

**Table 7. Characteristics of T<sub>reg</sub> cells**

<table>
<thead>
<tr>
<th>Subset</th>
<th>Phenotype</th>
<th>Suppressive mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produced in the thymus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural T&lt;sub&gt;reg&lt;/sub&gt; (nT&lt;sub&gt;reg&lt;/sub&gt;)</td>
<td>CD4&lt;sup&gt;+&lt;/sup&gt;CD25&lt;sup&gt;−&lt;/sup&gt;FoxP3&lt;sup&gt;+&lt;/sup&gt;CD152&lt;sup&gt;+&lt;/sup&gt;</td>
<td>TGF-β, cell contact</td>
</tr>
<tr>
<td></td>
<td>CD8&lt;sup&gt;−&lt;/sup&gt;CD25&lt;sup&gt;+&lt;/sup&gt;</td>
<td>TGF-β and CTLA4</td>
</tr>
<tr>
<td>Produced in the periphery</td>
<td>Induced T&lt;sub&gt;reg&lt;/sub&gt; (iT&lt;sub&gt;reg&lt;/sub&gt; -Th3)</td>
<td>CD4&lt;sup&gt;−&lt;/sup&gt;CD25&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Induced T&lt;sub&gt;reg&lt;/sub&gt; (iT&lt;sub&gt;reg&lt;/sub&gt; -Th1)</td>
<td>CD4&lt;sup&gt;−&lt;/sup&gt;CD25&lt;sup&gt;−&lt;/sup&gt;/ROG&lt;sup&gt;+&lt;/sup&gt;FoxP3&lt;sup&gt;−&lt;/sup&gt;CD152&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>T suppressor (Ts)</td>
<td>CD8&lt;sup&gt;−&lt;/sup&gt;CD28&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
production of IFN-γ can induce hyperimmune activation and apoptotic death of uninfected CD4+ cells [37].

Both pDC and myeloid DC (mDC) numbers are decreased in HIV infection concomitant with low CD4+ cell numbers and high viremia [80, 81]. In this regard, the extent of IFN release by pDCs after interaction with agonists for TLRs, particularly TLR9, is directly correlated with the blood CD4+ cell count. When pDCs are activated by high concentrations of HIV or the more clinically relevant HIV-infected cells there is also an up-regulation of CCR7, which directs the cells to lymphoid organs where they may have their most important role [82]. Myeloid DCs in HIV infection show reductions in APC function and cytokine production that inhibit their ability to elicit T-, B-, and NK-cell activity.

By directly destroying virus-infected cells and through cytokine production (e.g. IFN-γ, IL-12), NK cells can influence HIV infection and the pathogenic course [77]. The interaction of the KIRs on NK cells with HIV-infected cells can have activating and inhibitory effects on NK-cell functions [77]. As observed with adaptive T- and B-cell responses, recent evidence suggests that HIV can escape NK-cell activity by evolving away from recognition by activating KIRs [83].

### Immunogenetic factors

Some of the variations observed in the innate and adaptive immune responses to HIV infection can be associated with SNPs, deletions, and other differences in immune response genes [84]. Particular HLA genotypes (e.g. HLA-B57, B27, and B51) are repeatedly linked with long-term survival and slow HIV disease progression [56, 85]. These findings suggest that the recognition of some epitopes within the HIV proteome allows for improved control of virus replication. Nevertheless, these HLA genotypes can be found in progressors, reflecting the complexity of HIV pathogenesis (M. Carrington, personal communication). Further evidence of the protective effects of select HLA proteins is a recent genome-wide association study of nearly 1000 HIV controllers that identified more than 300 significant SNPs – all within the major histocompatibility complex (MHC) locus and primarily in the HLA-B region [55]. Of relevance is that HIV-specific HLA class I restricted CD8+ T cells can exhibit both CTL and CNAR activity [86]. Also, HLA-KIR interactions influence NK-cell responses to HIV [87]. Thus, the relative contribution of protective HLA associations to innate immune responses merits further attention (see Table 9). Associations of polymorphisms of TLR4, TLR9, IRF-3, TRIM5α, and ABOBEC3 genes with LTSs also underscore the importance of innate immunity and intrinsic resistance factors [88].

### Antiretroviral therapy

Certainly, the major HIV/AIDS achievement in the past 15 years has been the development of effective antiretroviral therapy (ART) [89]. Basic research and translational studies have enabled the discovery of drugs that target the viral enzymes (reverse transcriptase, integrase, and protease) and the cell binding steps necessary for HIV replication and entry. Nevertheless, side effects of life-long ART, including disorders of the heart, liver, pancreas, kidney, and bone marrow, along with the continued occurrence of drug-resistance viruses, emphasize the need for alternative treatment approaches. ART effectively reduces the transmission of HIV from mother-to-child and is now being evaluated for its prevention use in adults [89]. Recent results from a large randomized trial in HIV-serodiscordant couples showed that early treatment of the infected partner can greatly reduce virus transmission [90]. The application of ART as pre-exposure chemoprophylaxis (PrEP) for HIV+ persons at risk has been shown to be effective as well [91]. Still, meta-analyses of pre-exposure chemoprophylaxis studies have raised some concerns. Additional data are needed on durability of protection for uninfected partners, the potential for risk compensation, and the possible selection for drug-resistant viruses [92].

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**Table 8. Natural soluble factors having anti-HIV activity**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>Interferon-α, -β</td>
<td>TGF-β</td>
</tr>
<tr>
<td>Transforming growth factor-β (TGF-β)</td>
<td></td>
</tr>
<tr>
<td>Interleukin-8, 10, 16, 18, 27, 32</td>
<td></td>
</tr>
<tr>
<td>β chemokines: RANTES, MIP-1x, MIP-1β</td>
<td></td>
</tr>
<tr>
<td>Stromal cell-derived factor-1 (SDF-1)</td>
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<tr>
<td>Macrophage-derived chemokine (MDC)</td>
<td></td>
</tr>
<tr>
<td>Leukemia inhibitory factor (LIF)</td>
<td></td>
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<tr>
<td>Monocyte chemotactic protein-2 (MCP-2)</td>
<td></td>
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<tr>
<td>Lymphotactin</td>
<td></td>
</tr>
<tr>
<td>α-Defensins 1–3</td>
<td></td>
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<tr>
<td>β-Defensins</td>
<td></td>
</tr>
<tr>
<td>RNases</td>
<td></td>
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<tr>
<td>Secretory leukocyte protease inhibitor (SLPI)</td>
<td></td>
</tr>
<tr>
<td>α-1-Antitrypsin</td>
<td></td>
</tr>
<tr>
<td>Prothymosin-α</td>
<td></td>
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<td>Lysozymes</td>
<td></td>
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</table>

*See [5] for details.*

**Table 9. Important issues to be addressed in HIV/AIDS immunology**

<table>
<thead>
<tr>
<th>Mechanism(s) for the durable control of HIV replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism(s) of protection among HESNs</td>
</tr>
<tr>
<td>Mechanisms of viral latency; identity of other intrinsic cellular antiviral factors</td>
</tr>
<tr>
<td>The cause of immune activation in HIV infection</td>
</tr>
<tr>
<td>The role of Treg cells</td>
</tr>
<tr>
<td>Determinants of broadly NAbs</td>
</tr>
<tr>
<td>Role of select HLA alleles in determining HIV pathogenesis</td>
</tr>
<tr>
<td>Mechanisms of virus escape from innate and adaptive immune responses</td>
</tr>
<tr>
<td>Identity and full function of the CD8+ cell antiviral factor</td>
</tr>
<tr>
<td>Basis for the ‘functional cure’ of ‘the Berlin patient’</td>
</tr>
</tbody>
</table>

**HIGHLIGHTS**
Aging

As the median age of HIV-infected individuals is increasing in the ART era, particular attention should be given to the negative effects of HIV infection and its treatment on the incidence of cellular senescence, cardiovascular disease, cognitive decline, frailty, and other age-associated disorders [93]. The overall aging of the HIV-infected population is predicted to have a major effect in certain regions, where the fraction of HIV-infected individuals aged over 50 years may triple in the next 30 years [94].

Cure of HIV infection

The systemic eradication of HIV from its many reservoirs (Table 2) has been considered unattainable. However, recent reports on the HIV-infected ‘Berlin patient’ who received, for his leukemia, a heterologous BM stem cell transplant from a CCR5- donor have been encouraging. For over 5 years this patient has been free of any sign of HIV in lymphoid and mucosal tissues [95]. Considered a ‘functional cure’, researchers are examining approaches to mimic this promising result. One strategy is stem cell therapy, which uses autologous CD34+ cells or CD4+ cells engineered to lack CCR5 expression [96]. Alternatively, curing HIV without cell replacement approaches might be achieved with the eradication of HIV from latent reservoirs [97]. Therefore, another focus is the deacetylation of histones in the HIV promoter that allows virus production. Histone deacetylase (HDAC) inhibitors, such as valproic acid and trichostatin A, can enable the replication of latent virus that would then be targeted by concomitant ART and anti-HIV immune responses. Worrisome is evidence that histone deacetylase inhibitors may not be effective for use with primary T cells [98] and that antiviral immunity is reduced with ART [5].

Vaccine studies

The failure of the first vaccine efforts made apparent the difficulty in eliciting high-titer broadly NAbs upon vaccination with recombinant viral envelope antigens [99]. Subsequent vaccine efforts, promoting HIV-specific T-cell responses, have also been hampered by the inability to elicit broad T-cell diversity. Another shortcoming, as observed in the STEP trial, is that vaccines can inappropriately bias CTL responses toward less-conserved regions of the virus [100]. A recurrent theme among candidate vaccines is the ability to elicit HIV-specific antibodies or CTL responses and to demonstrate protection in animal studies while failing to prevent HIV-1 infection or to delay disease progression in human trials. Currently, the best results are from the Thai RV144 vaccine trial that showed a 31.2% efficacy in the modified intent-to-treat analysis, but had no effect on disease markers in vaccinees who subsequently became infected [101]. Additional approaches are needed for vaccine development in which the initial stages of HIV infection of the host should be considered (Fig. 3). Vaccines that elicit broadly NAbs, such as those recently characterized to be specific for the CD4 binding site of Env, could be effective [102]. Valuable insight could be gained by studies of the successful vaccines used to prevent retroviral infections in cats and horses [103, 104].

Conclusions and future challenges

The AIDS epidemic is one of the great tragedies of the 20th and 21st centuries. Upon reflection of the salient events in 30 years of HIV research, there are two very notable results. One is the associated advancement of human rights extended to not only gay men with AIDS and other historically marginalized groups, but to all individuals with health care needs. Second is the accelerated understanding of the human immune response to viral infection. This knowledge should enable us to prevent and control HIV infection and extend these observations to other infections, autoimmune diseases, and cancers. Three main goals remain: nontoxic immune therapy, a vaccine to prevent HIV transmission, and a cure for those infected. Among the topics in HIV/AIDS immunology that now need to be addressed (Table 9), priority should be given to studies of individuals who are highly resistant to HIV infection and to disease, with a main focus on innate immunity.

Acknowledgements: The research studies by the authors cited in this article were supported by grants from the National Institutes of Health (RO1 AI 056992), the California HIV/AIDS Research Program (ID09-SF-058), the Campbell Foundation, and the Peter and Shelagh Godsoe Foundation. The authors thank Kaylynn Peter for assistance with the manuscript and Drs. Cecilia Cheng-Meyer, Otto Yang, Paul Luciw, and Murray Gardner for their helpful comments.

Conflict of interest: The authors declare no financial or commercial conflict of interest.

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Received: 3/9/2011
Revised: 17/10/2011
Accepted: 21/10/2011