Bacterial sepsis is an important cause of morbidity and mortality in patients with HIV. HIV causes increased susceptibility to invasive infections and affects sepsis pathogenesis caused by pre-existing activation and exhaustion of the immune system. We review the effect of HIV on different components of immune responses implicated in bacterial sepsis, and possible mechanisms underlying the increased risk of invasive bacterial infections. We focus on pattern recognition receptors and innate cellular responses, cytokines, lymphocytes, coagulation, and the complement system. A combination of factors causes increased susceptibility to infection and can contribute to a disturbed immune response during a septic event in patients with HIV. HIV-induced perturbations of the immune system depend on stage of infection and are only in part restored by combination antiretroviral therapy. Immuno-modulatory treatments currently under development for sepsis might be particularly beneficial to patients with HIV co-infection because many pathogenic mechanisms in HIV and sepsis overlap.

Introduction
People infected with HIV are at increased risk of developing other infections. Reports from developed countries show that, with the introduction of combination antiretroviral therapy (cART), the incidence of opportunistic infections such as Pneumocystis jirovecii pneumonia has decreased substantially, and sepsis is now the principal cause of intensive care unit (ICU) admission and death in patients with HIV who are admitted to hospital.\(^1\) Worldwide, patients with HIV are at increased risk of developing bacterial bloodstream infections, particularly with non-typhoidal salmonella (NTS) and Streptococcus pneumoniae;\(^2,3\) even in those using effective cART.\(^4\) In developing regions with high admission and death in patients with HIV who are admitted to hospital.\(^1\) Worldwide, patients with HIV are at increased risk of developing bacterial bloodstream infections, particularly with non-typhoidal salmonella (NTS) and Streptococcus pneumoniae;\(^2,3\) even in those using effective cART.\(^4\) In developing regions with high

Overview
A sepsis event typically starts with a pathogen invading a normally sterile site. The first line of defence consists of epithelial cells of the skin, gut, and lungs. After breaching the epithelial barrier, pathogens are first detected by innate immune cells, including monocytes, macrophages, dendritic cells, and neutrophils.\(^5,6\) These cells express pattern recognition receptors (PRRs) on their surface and in the cytosol to enable recognition of conserved motifs expressed by pathogens.\(^2,6\) Four classes of PRRs have been identified: toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerisation domain leucine-rich-repeat containing receptors (NOD-LRRs), and retinoic acid-inducible gene I protein helicase receptors (RLRs).\(^7\) In the context of sepsis pathogenesis, TLRs have been studied the most extensively. They are expressed on the cell surface (TLRs 1, 2, 4, 5, and 6) to enable recognition of bacterial outer membrane components, and in intracellular compartments (TLRs 3, 7, 8, and 9) for detection of nucleic acids derived from intracellular pathogens, mainly viruses.\(^7\) For bacterial recognition, TLRs 2, 4, 5, and 9 are the most important. Additionally, TLR7 can sense bacterial RNA released within phagosomes,\(^7\) and TLR3 can function as an amplifier of host RNA-triggered inflammation during sepsis.\(^7\) Ligand recognition by TLRs triggers a signalling cascade, which results in the production of cytokines.\(^7\) Although essential for pathogen recognition and the innate immune response, uncontrolled stimulation causes excessive inflammation; hence TLR signalling is normally tightly regulated.

Innate immune cells have several specific functions in antibacterial immunity. Monocytes and macrophages have a crucial role in maintaining homeostasis by phagocytosis of apoptotic cells and microorganisms.\(^8\) As the main producers of proinflammatory cytokines, they are also thought to be key in sepsis pathogenesis.\(^6\) Dendritic cells are the main antigen-presenting cells; maturation is induced after ingestion of antigen, followed by migration to lymphoid tissue. Mature dendritic cells express co-stimulatory molecules on their surface, which synergise with antigen to activate T cells.\(^6\) Natural killer (NK) cells are implicated in
### Table 1: Burden of community-acquired bacterial bloodstream infections in patients with HIV in African countries where HIV is highly prevalent

<table>
<thead>
<tr>
<th>Study location and timeframe</th>
<th>Primary inclusion criteria</th>
<th>Patients infected with HIV (% of patients tested)</th>
<th>CA bacterial BSI in patients with HIV (%)</th>
<th>Main isolates in patients with HIV (%)</th>
<th>Mortality in patients with HIV with CA bacterial BSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Archbold, 1998&lt;sup&gt;8&lt;/sup&gt; Urban Tanzania, 1995</td>
<td>Febrile (≥38 °C) admission</td>
<td>282 (55%)</td>
<td>51 (18%)</td>
<td>NTS (45%), S pneumoniae (34%), Streptococcus pneumoniae (12%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Archbold, 2000&lt;sup&gt;9&lt;/sup&gt; Urban Malawi, 1997</td>
<td>Febrile (≥37.5 °C) admissions</td>
<td>173 (74%)</td>
<td>37 (21%)</td>
<td>S pneumoniae (57%), NTS (30%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Arthur, 2001&lt;sup&gt;10&lt;/sup&gt; Urban Kenya, 1988-97</td>
<td>Hospital admission</td>
<td>436 (32%)</td>
<td>87 (20%)</td>
<td>NTS (46%), S pneumoniae (33%), E coli (6%)</td>
<td>39%</td>
</tr>
<tr>
<td>Bell, 2001&lt;sup&gt;11&lt;/sup&gt; Urban Malawi, 1998</td>
<td>Febrile (≥37.5 °C) admissions</td>
<td>173 (73%)</td>
<td>36 (21%)</td>
<td>NTS (62%), E coli (7%), Salmonella Typhi (7%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Crump, 2001&lt;sup&gt;12&lt;/sup&gt; Rural Tanzania, 2007-08</td>
<td>Febrile (≥38 °C) admissions</td>
<td>161 (40%)</td>
<td>26 (16%)</td>
<td>S pneumoniae (54%), E coli (12%), NTS (8%), S Typh (8%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Grant, 1997&lt;sup&gt;13&lt;/sup&gt; Ivory coast, 1995</td>
<td>Admission to the infectious disease unit</td>
<td>198 (79%)</td>
<td>39 (20%)</td>
<td>NTS (59%), E coli (15%), S pneumoniae (10%)</td>
<td>46%</td>
</tr>
<tr>
<td>Mayanja, 2010&lt;sup&gt;14&lt;/sup&gt; Rural Uganda, 1996-2007</td>
<td>Fever (≥38 °C) with no detectable malaria parasites</td>
<td>488 (64%)</td>
<td>152 (31%)</td>
<td>S pneumoniae (43%), NTS (26%), E coli (6%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Merermo, 2012&lt;sup&gt;15&lt;/sup&gt; Urban Tanzania, 2011</td>
<td>Hospital admission with fever (≥37.5 °C)</td>
<td>156 (45%)</td>
<td>16 (10%)</td>
<td>NTS (75%)</td>
<td>35%</td>
</tr>
<tr>
<td>Ndagm, 2012&lt;sup&gt;16&lt;/sup&gt; Rural Tanzania, 2007</td>
<td>Fever and one severity criterion</td>
<td>69 (35%)</td>
<td>12 (17%)</td>
<td>NTS (25%), S pneumoniae (25%), Streptococcus pyogenes (17%)</td>
<td>25%</td>
</tr>
<tr>
<td>Pien, 2004&lt;sup&gt;17&lt;/sup&gt; Urban Malawi, 2000</td>
<td>Admissions with fever (≥37.4 °C) or history of fever in the past 4 days</td>
<td>291 (83%)</td>
<td>66 (23%)</td>
<td>NTS (67%), S pneumoniae (20%), E coli (6%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ssali, 1998&lt;sup&gt;18&lt;/sup&gt; Uganda, 1997</td>
<td>Admission with fever (≥38 °C)</td>
<td>222 (76%)</td>
<td>33 (15%)</td>
<td>Salmonella spp (29%), S pneumoniae (33%)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Data was derived from prospective observational studies, which were previously described by Huson and colleagues. CA=community acquired. BSI=bloodstream infection. NTS=non-typhoidal salmonella.

Likewise, natural killer T cells (NK T cells), a subset that shares cell-surface proteins with conventional T cells and NK cells, have been implicated in sepsis pathogenesis because of their strong proinflammatory cytokine release. Recruted neutrophils form an additional important first line of defence against invading pathogens. They kill microbes through phagocytosis, the release of lytic enzymes from their granules, the production of reactive oxygen intermediates, and the formation of neutrophil extracellular traps (NETs)—lattices of chromatin decorated with antimicrobial proteins with strong bactericidal capacity.

The innate immune system is thought to be mostly responsible for the excessive release of proinflammatory cytokines early in sepsis pathogenesis. The most extensively studied proinflammatory cytokines in sepsis are tumour necrosis factor α (TNFα) and interleukin 1β, both of which are capable of activating target cells and induce the production of more inflammatory mediators. Additionally, host cells release damage-associated molecular patterns (DAMPs) in response to pathogens or injury, which are recognised by PRRs, thereby enhancing immune activation. The most investigated DAMP is HMGB1, which signals via TLR2, TLR4, and TLR9 to induce cytokine release, activation of coagulation, and neutrophil recruitment. Proinflammatory cytokines and DAMPs seem to have a double role in sepsis pathogenesis; they are essential for an adequate innate defence during early stage infection, but also contribute to hyperinflammation during late phase uncontrolled infection. In patients with severe sepsis and in murine sepsis models, high concentrations of interleukins 1, 6, 8, and 17, CCL2, CSF3, and HMGB1 are associated with mortality.

HIV affects the first lines of defence in several ways. First, defects of epithelial barriers are common and have been particularly well described for the gut. In the gut, HIV causes barrier defects during acute infection, which are maintained during chronic infection, thereby enabling invasive infections by intestinal pathogens such as non-typhoidal salmonella. Furthermore, microbial products that translocate into the circulation fuel chronic immune activation and exhaustion.

### Toll-like receptors

HIV infection and AIDS are associated with increased TLR2, TLR3, TLR4, TLR7, and TLR9 expression on various cells, including T lymphocytes, monocytes, macrophages, and dendritic cells, although one study reported lower peripheral blood mononuclear cell (PBMC) RNA expression levels of TLR3, TLR4, and TLR9 in patients with chronic HIV unresponsive to cART. Reports on the functional effect of differential TLR expression are inconsistent. Ex-vivo studies with PBMCs from patients with HIV noted a correlation between increased expression of TLRs and increased TNFα production after stimulation with lipopolysaccharide, a...
TLR4 ligand. By contrast, alveolar macrophages from patients with HIV showed a classic activation phenotype with increased TLR4 expression, although binding, internalisation, and killing of opsonised S pneumoniae bacteria, which signal via TLR2, TLR4, and TLR9, were similar to HIV-negative controls. TLR3 and TLR7 are known to be key modulators in anti-HIV immunity, and HIV-induced changes in expression of these TLRs might have a role during antibacterial defence, but no studies have yet investigated this subject.

Most evidence suggests that upregulation of TLRs is responsible for cell activation in response to bacteria in patients with HIV, especially in those with advanced disease, although functional consequences differ according to cell type. Increased expression of TLRs on cytokine-producing cells might contribute to aberrant inflammation in the disturbed homeostasis in sepsis, although this possibility has not yet been addressed in in-vivo studies.

**Monocytes and macrophages**

The effect of HIV on monocytes and macrophages is mainly indirect because only a small percentage of these cells are infected with HIV. HIV-mediated defects in phagocytosis, cell signalling, and cytokine production have been described, although results vary between studies (appendix).

Ex-vivo studies using monocytes or monocyte-derived macrophages from patients with HIV, reported reduced phagocytosis of Escherichia coli and, in symptomatic patients with HIV, Staphylococcus aureus. By contrast, others observed normal phagocytic function of macrophages towards opsonised E.coli and S aureus in-vitro, and increased monocyte phagocytosis of these pathogens in cells harvested from patients with early HIV infection. In peripheral blood, both monocytes and macrophages appear to show an HIV-induced, primed, proinflammatory state, with increased cytokine release on stimulation with TLR ligands. A non-classic subset of monocytes with high expression of M-DC8, a subset that is also increased in inflamed tissue in chronic inflammatory diseases such as rheumatoid arthritis, was identified as the predominant cell type responsible for TNFα overproduction (table 2).

Several studies also examined the effect of HIV on the alveolar compartment. Although normal alveolar

### Table 2: Effect of HIV infection on the cytokine milieu by cell type

<table>
<thead>
<tr>
<th>Study condition*</th>
<th>HIV-induced changes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood</td>
<td>↑ Interleukin 6, interleukin 10, TNFα, interleukin 1α, interleukin 1β, interleukin 8, CCL2, interleukin 1R1, and interferon γ</td>
<td>Cytokine levels normalised after treatment with cART*</td>
</tr>
<tr>
<td></td>
<td>↓ interleukin 12, and CSF2</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood mononuclear cells</td>
<td>↑ TNFα</td>
<td>-</td>
</tr>
<tr>
<td>Ex-vivo and in-vitro stimulation</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>↑ Interleukin 6, interleukin 1β, TNFα</td>
<td>These cells were identified as the main cell type responsible for TNFα overproduction</td>
</tr>
<tr>
<td>Ex-vivo stimulation</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>M-DC8 monocytes</td>
<td>↑ TNFα</td>
<td>Increased levels of M-DC8 monocytes were recorded in viraemic patients with HIV, but not in virally suppressed patients on cART*</td>
</tr>
<tr>
<td>Ex-vivo stimulation</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Alveolar macrophages</td>
<td>↓ TNFα, interleukin 8, interleukin 12*</td>
<td>Reports conflict on this subject; other studies noted increased interleukin 8, 12 and 10 in alveolar macrophages of patients with HIV*</td>
</tr>
<tr>
<td>Ex-vivo stimulation</td>
<td>↓ interleukin 12, interferon γ, interferon γ, interferon α, interleukin 2, interleukin 6, and interleukin 10</td>
<td>Most reports describe decreased cytokine production after stimulation, but normal, or even increased cytokine responses to stimulation were also reported</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>↓ Interferon γ</td>
<td>The effect was observed in both cART-treated and untreated patients</td>
</tr>
<tr>
<td>In-vitro and ex-vivo stimulation</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Natural killer cells</td>
<td>↓ Interferon γ and interleukin 4</td>
<td>Stimulations were done with marine sponge-derived α-galactosylceramide (αGalCer) as a ligand, similar studies using bacterial ligands as a stimulus were not available</td>
</tr>
<tr>
<td>Ex-vivo stimulation</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Natural killer T cells</td>
<td>↑ Interleukin 10</td>
<td>Cytokine secretion was restored by cART*</td>
</tr>
<tr>
<td>Ex-vivo stimulation</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CD4 T cells</td>
<td>↑ Interleukin 10</td>
<td>Interleukin 10 production was increased in chronic progressors and recently infected individuals, but not in non-progressors with HIV*</td>
</tr>
<tr>
<td>In-vivo</td>
<td>↓ Interleukin 22, TNFα, and interferon γ*</td>
<td>Restoration of cytokine responses was seen after prolonged treatment with cART*</td>
</tr>
<tr>
<td>Gut mucosa Th17 cells</td>
<td>↑ Interleukin 10</td>
<td>-</td>
</tr>
<tr>
<td>Ex-vivo stimulation</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

cART=combination antiretroviral therapy. *All studies are in human beings or used human cells, or human cell lines; all stimulations were done with bacteria or bacterial products unless otherwise specified.
macrophage phagocytosis of *S pneumoniae* was previously reported, a study noted impaired phagocytosis in HIV-infected small alveolar macrophages, as well as impaired proteolysis of phagosomes in both infected and uninfected alveolar macrophages. Cytokine release, including that of interleukin 8, in response to *S pneumoniae*, and TNFα, in response to TLR2 and TLR4 ligands, was impaired in alveolar macrophages from patients with HIV (table 2). Considering the crucial role of TNFα in resisting experimental *S pneumoniae* infections in mice, and the established part in neutrophil recruitment to sites of infection by interleukin 8, a reduced cytokine response by alveolar macrophages might contribute to increased susceptibility to invasive pneumococcal disease in patients with HIV (figure 1). Another study noted increased production of both proinflammatory (interleukin 8 and 12) and anti-inflammatory (interleukin 10) cytokines by alveolar macrophages of asymptomatic patients with HIV after stimulation with *S aureus*. However, in patients with more advanced disease interleukin 12 release was reduced after stimulation, which was mediated by interleukin 10. Interleukin 12 is known to induce T-helper (Th) 1 development, which is essential for defence against intracellular pathogens, such as non-typhoidal salmonella, but also has a role in the immune response against *S pneumoniae*. Finally, alveolar macrophage apoptosis, a critical host cell response for control of infection, including pneumococcal pneumonia, might be impaired in patients with HIV.

Most evidence suggests impairment of phagocytosis by macrophages in individuals with HIV, which is accompanied by impaired proinflammatory cytokine release, especially in alveolar macrophages. These defects might contribute to increased susceptibility to bacterial infection and deregulated inflammation.

**Dendritic cells**

In patients with HIV, around 10–15% of dendritic cells are infected, but HIV also affects dendritic cell function in indirect ways (appendix). Patients with HIV have reduced peripheral blood dendritic cell numbers, which are inversely correlated to viral

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**Figure 1: Alterations in the host response of patient with HIV that might cause increased susceptibility to invasive infection with Streptococcus pneumoniae**

In the upper airways, impaired recruitment of macrophages due to CD4 T-cell depletion and low concentrations of interleukin 17 enable colonisation by *S pneumoniae* on the respiratory epithelium. In the lower airways, impaired antipneumococcal activity of IgA and IgG on the mucosal surface of the respiratory epithelium allows the attachment of *S pneumoniae* to the epithelial cells and migration of the pathogen across the epithelial barrier. Ineffective opsonisation also impairs phagocytosis by alveolar macrophages. Furthermore, alveolar macrophages from HIV-positive patients showed decreased TNFα production in response to TLR2 and TLR4 ligands, and concentrations of TNFα in bronchoalveolar lavage fluid are reduced in patients with HIV, thereby hindering an effective proinflammatory response. Alveolar macrophages from patients with HIV produce lower concentrations of interleukin 8 in response to *S pneumoniae*, resulting in less effective recruitment of neutrophils. Neutrophils of HIV patients are also less able to respond to chemotactic signals, such as interleukin 8, but also pneumolysin derived from the bacterium, further impairing a massive neutrophil influx. The combination of impairments in antipneumococcal defence enables the invasion of *S pneumoniae* into the bloodstream.

*TNFα=tumour necrosis factor α.*
load, and positively correlated with CD4 counts. Homing of dendritic cells in lymph nodes and increased apoptosis are possible explanations.

Reports on the effect of HIV on dendritic cell maturation are inconsistent. An atypical phenotype of immune activation without full maturation has been reported, as well as reduced capacity to mature in response to stimuli combined with interleukin 10 induction and immune suppression. By contrast, normal maturation in response to stimuli and HIV-induced maturation have also been described.

Stimulation-induced production of cytokines, including interleukin 12, interleukin 6, interferon γ, interferon α, interleukin 2, and interleukin 10, was impaired by HIV, as well as dendritic cell-mediated activation of T cells (table 2). Reduced interleukin 12 production was associated with impaired activation of NK cells in vitro. Some studies, however, reported normal or even increased cytokine responses of dendritic cells to stimuli.

The number of dendritic cells in peripheral blood is reduced in patients with HIV and, additionally, most studies report impaired dendritic cell function. HIV-induced tolerance to antigen and reduced maturation of dendritic cells might compromise immunity against various pathogens, rendering patients with HIV more susceptible to sepsis.

**NK cells and NK T cells**

Reduced NK cell numbers and function during HIV infection contribute to decreased resistance against HIV and other pathogens (appendix). Ex-vivo stimulation of NK cells from patients infected with HIV with *E coli* or *Salmonella typhimurium* showed that both untreated and treated patients had lower overall frequencies of responsive interferon-γ-producing NK cells (table 2). Although this study is the only one to specifically address antibacterial immune responses by NK cells from patients with HIV, many studies report on HIV-induced changes that prevent an effective anti-HIV NK cell response, which might also result in impaired antibacterial defence. First, correlating with viral load, HIV infection induces expansion of a CD56-negative NK cell subpopulation, which is unresponsive to stimulation and is thought to represent an exhausted state, with concomitant loss of responsive CD56-positive NK cell subsets due to increased apoptosis. CD56-negative NK cells are also defective in their interaction with dendritic cells, thereby contributing to the accumulation of immature dendritic cells. Second, HIV causes shedding of MHC class I chain-related molecules MICA and MICB from the surface of infected cells. By binding to the NK cell receptor NKG2D, soluble MICA and MICB provide a negative feedback signal, resulting in subsequent downregulation of NKG2D, thereby promoting the generation of anergic NK cells. Third, decreased production of chemokines impairs chemotactic signalling to other immune cells. NK cells from patients with HIV also showed increased expression of NK-cell inhibitory receptors that prevent lysis of target cells, but these effects were reversed in virally suppressed patients on cART. No studies on NK T-cell antibacterial defence in HIV-infected hosts were identified, but selective NK T-cell depletion might hinder the proinflammatory response to bacterial pathogens.

Various mechanisms contribute to expansion of an anergic NK cell population that is less capable of responding to pathogens in individuals with HIV. This expansion might impair direct NK-cell mediated defence against bacteria, and compromise crosstalk with other immune cells.

**Neutrophils**

In patients with HIV infection, neutrophils might not be able to function effectively because of several mechanisms (appendix). First, neutropenia is common in patients with HIV. Possible mechanisms include increased apoptosis due to the presence of auto-antibodies, activation in the absence of secondary infection, reduced production attributed to decreased levels of CSF3, and treatment-induced neutropenia.

Additionally, defects in neutrophil function have been described in patients with HIV, including reduced chemotaxis, impaired transepithelial migration (possibly explained by reduced expression of interleukin 8 receptors on neutrophils of these patients), and impaired phagocytosis. In one study phagocytosis of *S aureus* was only impaired when neutrophils were incubated with serum of patients with HIV, indicating reduced opsonisation with antibodies as the mechanism underlying defective phagocytosis. However, in other investigations decreased phagocytosis was observed after previous opsonisation in healthy serum, suggesting an antibody-independent mechanism. Although the aforementioned studies used neutrophils from patients with HIV with advanced disease, one study recorded an increased capacity for neutrophils to phagocytose *E coli* and *S aureus* from patients with early HIV infection. Superoxide production, a mechanism of microbial killing, was increased in unstimulated neutrophils from patients with HIV, but the response to pathogens, such as *E coli*, was reduced. Additionally, HIV causes impaired C5a (a complement constituent with proinflammatory properties) and interleukin-8-induced degranulation, which is associated with reduced expression of C5a and interleukin 8 receptors. Although HIV causes NET release from neutrophils, it can also counteract this response by inducing production of interleukin 10 by dendritic cells to inhibit NET formation. Hence, HIV-induced inhibition of NET formation in response to bacterial pathogens
could impair effective host defence. Finally, ex-vivo bacterial killing was reduced, especially in patients with advanced disease. However, one study reported normal killing of *S aureus* by neutrophils from patients with AIDS.

HIV-related defects in neutrophil numbers, chemotaxis, phagocytosis, superoxide production, cytokine release, bacterial killing, and NET formation have been described, suggesting that HIV renders the host more susceptible to bacterial infection, at least in part by impairing neutrophil-mediated host defence.

**Cytokines and DAMPs**

Abundant evidence suggests a change in cytokine profiles in patients with HIV, although very few studies have investigated this change in the context of sepsis (table 2). Two studies provided comparative data for inflammatory parameters in patients with sepsis admitted to the ICU with or without HIV co-infection. A wide range of cytokines were measured, but no significant differences were noted for most of them. In one study, high concentrations of interleukin 10 were reported in HIV-positive patients compared with HIV-negative patients, which was associated with increased mortality. However, the HIV-negative septic controls differed substantially in age and site of infection, which complicates interpretation of these results.

Studies using plasma from patients with HIV but without sepsis reported increased concentrations of several cytokines implicated in sepsis pathogenesis: interleukin 6, interleukin 10, TNFα, interleukin 1α, interleukin 1β, interleukin 8, CCL2, interleukin 1 receptor antagonist, and, in acute HIV infection, interferon γ. Concentrations of HMGB1 were also increased in patients with HIV. However, circulating concentrations of the proinflammatory cytokines interleukin 12, and CSF2, were decreased. Studies on the effect of cART noted normalisation of most cytokine perturbations.

Raised concentrations of circulating inflammatory markers might in fact be associated with the development of infection; a correlation was identified between raised concentrations of C-reactive protein in patients with HIV and an increased risk of bacterial pneumonia.

A possible explanation for raised cytokine concentrations is a primed state of immune cells in patients with HIV causing hyper-responsiveness to stimulation; for example, by microbial products translocated from the gut. Increased TNFα production in response to lipopolysaccharide was observed in PBMCs and monocytes isolated from patients with HIV. Decreased interleukin 12 concentrations might relate to the type of stimulus and stage of disease, with patients with AIDS showing the most profound deficiency.

There is abundant evidence for increased circulating concentrations of both proinflammatory and anti-inflammatory cytokines in patients with HIV, combined with ex-vivo evidence for a primed state of immune cells in response to stimulation, which could result in a more profound imbalance between these mediators during sepsis. However, the small number of studies available in patients with HIV and sepsis reported few differences in cytokine concentrations compared with HIV-negative patients with sepsis.

**Lymphocytes**

**Overview**

Antigen-presenting cells interact with lymphocytes to initiate the adaptive immune response. In response to the presentation of antigen, effector CD4 T cells secrete cytokines, such as interferon γ, to enhance phagocytic killing and interaction with B cells to initiate production of antibodies. B cells are the cornerstone of immunological memory, and represent the main defence mechanism against reinfection. B cells have also been shown to have an important role in the enhancement of innate immune responses during bacterial sepsis. Sepsis causes a substantial depletion of CD4, CD8, and B lymphocytes because of increased apoptosis, which is correlated with sepsis severity. Because T cells are important in coordinating innate immunity, increased apoptosis of T cells might hinder the proinflammatory response. Remaining lymphocytes also show significant reductions in cytokine release on stimulation.

**T lymphocytes**

During HIV infection, both T-cell numbers and function become compromised (appendix). CD4 T-cell depletion develops through various mechanisms, including direct virus-induced killing, induction of apoptosis, and an inability of the thymus to efficiently compensate for the lost T cells. In addition to depletion of CD4 T cells, HIV downregulates the CD4 receptor, which might reduce the immune functions of surviving cells. Of particular relevance in the context of sepsis, patients with HIV displayed increased apoptosis of CD3 T cells after in-vitro challenge with *S pneumoniae*. A particular subset of CD4 cells, Th17 cells, which predominate in the gastrointestinal tract and are important in antibacterial defence, are substantially depleted, and remaining Th17 cells have an enhanced interleukin 10:TNFα ratio, suggestive of an anti-inflammatory phenotype (table 2). Similarly, increased interleukin 10 production was identified in peripheral blood CD4 T cells. Mucosal-associated invariant T cells (MAIT cells), a subset of innate-like, tissue-infiltrating lymphocytes that produce interleukin 17, interleukin 22, interferon γ, and TNFα, were also shown to be severely depleted in blood of patients with HIV, and remaining cells showed an activated phenotype combined with functional exhaustion. Although numbers of MAIT cells in the...
The gut were relatively preserved in these studies,\(^{10,11}\) a third study reported MAIT cell depletion in the colon of patients with HIV.\(^{12}\) Since MAIT cells are known to be activated by a wide range of bacteria and fungi,\(^{13}\) their depletion might have an important role in increased susceptibility of patients with HIV to bacterial sepsis. Mucosal depletion of interleukin-17-producing cells, like TH17 cells and MAIT cells, might be related to increased risk of patients with HIV developing non-typhoidal salmonella bacteraemia, because interleukin 17 is known to have an important role in host defence against dissemination of enteric pathogens (figure 2).\(^{114}\) Additionally, interleukin-17-producing CD4 T cells were shown to be essential for recruitment of monocytes and macrophages to allow for effective pneumococcal clearance from the nasopharynx,\(^{115}\) suggesting that CD4 cell depletion has a role in the vulnerability of patients with HIV to the invasive pneumococcal infections (figure 1).

Although CD4 T-cell counts decrease, CD8 T-cell numbers expand during HIV infection.\(^{116}\) Nonetheless, both T-cell compartments display a phenotype of immune activation and exhaustion, as suggested by heightened expression of the activation markers HLA-DR and CD38, and of the inhibitory receptors PDCD1 and CTLA4 in untreated patients with HIV.\(^{117,118}\) Furthermore, the CD8 T-cell compartment has been shown to arrest at a late differentiated phenotype,\(^{119}\) and is unable to mount an effective cytolytic response.\(^{120,121}\)

Both reduction in CD4 T-cell numbers, and functional impairments of CD4 T cells and CD8 T cells might contribute to increased susceptibility of patients with HIV to develop invasive bacterial infections and sepsis. Most of these defects can be restored by cART,\(^{122}\) but impaired restoration of the CD4 T-cell proliferation response has been described in patients with HIV with lower nadir CD4 T-cell counts before therapy,\(^{123}\) thus providing one possible explanation for higher rates of bacteraemia in cART-treated patients compared with HIV-negative people.

**B-lymphocytes**

In patients with HIV, several defects in B-cell function have been detected, which could have a role in increased susceptibility to infections, especially in patients with non-typhoidal salmonella and *S pneumoniae* (appendix). Functional disturbances include hypergammaglobulinaemia, polyclonal activation and exhaustion, impaired class-switch recombination, dysfunctional interaction between T cells and B cells, blunted proliferation response to both T-cell-dependent and T-cell-independent antigens, poor immune responses against vaccination antigens, short duration of antibody response induced by pneumococcal vaccination, and increased apoptosis.\(^{125,126}\)

Additionally, patients with HIV show changes in the distribution of B-cell subsets. Resting memory B cells are severely depleted, whereas transitional B cells are expanded.\(^{127}\) An aberrant B-cell population, CD21\(^{+}\)CD27\(^{−}\) B cells, normally present in very low numbers in peripheral blood, was reported to rise in the blood of viraemic patients with HIV proportional to viral load,\(^{128}\) which showed features of immune activation and cellular exhaustion.\(^{129}\) Although changes in most B-cell subtypes are restored by cART, resting memory B cells usually remain depleted\(^ {26}\) because they can only be preserved when cART is started early in infection.\(^ {128}\) Additionally, IgG concentrations were shown to remain raised despite long-term CART in 45% of patients, indicating continuous B-cell activation.\(^ {130}\)

B-cell dysfunction probably has an important role in the increased risk of patients with HIV developing invasive infections with *S pneumoniae* (figure 1) and non-typhoidal salmonella (figure 2). Patients with HIV have reduced numbers of pneumococcal antigen-specific IgG antibody-secreting cells and lower concentrations of pneumococcal antibodies.\(^ {130,132}\) Additionally, IgA in the epithelial lining fluid of the lung showed impaired antipneumococcal activity.\(^ {135}\) Although some studies reported normal,\(^ {136}\) or even
increased risk of bleeding. Disseminated intravascular coagulation is triggered by a fulminant host response to infection, causing aberrant expression of tissue factor, impairment of physiological anticoagulant pathways due to endothelial dysfunction, and the suppression of fibrinolysis due to overproduction of SERPINE1 by endothelial cells.

Several abnormalities in the coagulation system and endothelial cell function of patients with HIV have been identified (figure 3). In general, HIV-induced alterations in haemostasis are remarkably similar to those described in sepsis. First, patients with HIV display a procoagulant state, as shown by their increased risk of thromboembolic events. Coagulation activation in these patients is further suggested by increased concentrations of D-dimer and fibrinogen, increased platelet activation, and increased expression of tissue factor on platelets and monocytes.

Anticoagulation is hindered by reduced concentrations of protein C, and protein S, and fibrinolysis might be impaired as a consequence of increased SERPINE concentrations in patients with HIV. Last, ample evidence shows endothelial activation and dysfunction in patients with HIV. Raised concentrations of VWF, soluble ICAM1, and soluble VCAM1 have been reported in several studies. Additionally, endothelial function, assessed by measuring flow-mediated dilation of the brachial artery, was impaired in patients with HIV.

Autopsy studies of patients with HIV, with or without AIDS-related complications, also reported endothelial injury. Finally, a study on angioenic factors in severe bacterial infection in Malawian children noted that HIV-positive cases had significantly higher concentrations of ANGPT2 compared with HIV-negative children with similar illness. High concentrations of ANGPT2, an angiogenic peptide that increases endothelial activation and vascular permeability, are associated with disseminated intravascular coagulation and mortality in sepsis. Studies on the effect of cART are inconsistent, with some recording complete normalisation and others reporting partial improvement, as well as studies describing a detrimental effect of cART, especially regimens containing protease inhibitors.

At present, no studies on the effect of HIV infection on the procoagulant response to sepsis exist. In view of the disturbed haemostatic balance in patients with HIV, with alterations that strongly resemble those detected in sepsis, it is conceivable that HIV causes an even greater disruption of procoagulant and anticoagulant mechanisms during sepsis.

The completemet system

The complement system is an important part of the first-line host defence against bacteria, by opsonisation, lysis of pathogens and infected cells, and production of chemoattractants. Clinical and experimental sepsis are...
associated with activation of the complement system, as shown by increased plasma concentrations of complement constituents C3a, C4a, and C5a. Although complement is essential in the host defence against bacteria, increased circulating C3a and C5a are likely to contribute to sepsis-induced tissue damage, multiorgan failure, and septic shock, because of their strong proinflammatory functions. C5a is important for the outcome of experimental sepsis, as reported by studies in which treatment with an anti-C5a antibody improved haemodynamic parameters, attenuated coagulopathy, and improved organ function.

Although the complement system is generally known for its activity against bacterial pathogens, many reports describe HIV-induced activation of the complement system through the classic pathway via interaction of gp41 with C1q, interaction of HIV with mannose-binding lectin, the triggering molecule of the lectin pathway, and activation of the alternative pathway through C3 binding of HIV-infected monocytes and lymphocytes. After seroconversion, HIV-specific antibodies further enhance complement activation via the classic pathway, and raised concentrations of circulating C5a have been recorded in patients with HIV. However, HIV can escape complement-induced lysis by acquiring regulators of complement activation, which allow the virus to use the complement system for transport to the lymphoid system and infection of susceptible cells.

Increased complement activation might contribute to the generalised immune activation observed in HIV and, hypothetically, have a detrimental role during sepsis pathogenesis by disturbing the balance between proinflammatory and anti-inflammatory mechanisms. However, at present, studies investigating the effect of HIV infection on complement activation in sepsis have not been reported.

**Future perspectives**

The present treatment of sepsis is based on antibiotics and supportive care. In past decades, many clinical trials have been done to investigate inhibition of the abundant inflammatory response generally held responsible for sepsis mortality. In more recent years, however, attention has shifted to findings that patients with sepsis invariably show evidence for immune suppression, which has been implicated as an important cause of secondary infections and late mortality. Preclinical studies have suggested that immune stimulatory therapy, which aims to overcome sepsis-induced immune suppression, could improve sepsis outcome. Interventions assessed in this context include immunomodulatory cytokines, such as interleukin 7, interleukin 15, and CSF2, as well as antibodies targeting co-inhibitory molecules, like PDCD1, CD274, and CTLA4 (table 3). Notably, similar strategies have been suggested to remedy increased complement activation in sepsis.

**Search strategy and selection criteria**

We searched PubMed using the following search string: “HIV” [MeSH Terms] or “acquired immunodeficiency syndrome” [MeSH Terms] and (“immunity” [MeSH Terms] or “monocytes” [MeSH Terms] or “macrophages” [MeSH Terms] or “dendritic cell” [MeSH Terms] or “neutrophils” [MeSH Terms] or “pattern recognition receptors” [MeSH Terms] or “lymphocytes” [MeSH Terms] or “cytokines” [MeSH Terms] or “complement system proteins” [MeSH Terms] or “blood coagulation” [MeSH Terms] or “disseminated intravascular coagulation” [MeSH Terms]) and (“bacteria” [MeSH Terms] or “sepsis” [MeSH Terms] or “bacteremia” [Mesh Terms]). We also combined the MeSH Terms for “salmonella” and “pneumoniae” with the MeSH Terms for “HIV” or “AIDS”. The search was limited to English-language articles published between Jan 1, 1990 and June 1, 2014. We reviewed relevant articles identified in this search, papers cited in these studies, and articles from the authors’ personal files.
HIV-induced immune suppression (table 3). Pro-inflammatory and procoagulant pathways targeted by novel sepsis therapies under clinical evaluation, such as anti-HMGB1 strategies and soluble thrombomodulin, could be of interest for patients with HIV and sepsis because HIV by itself already adversely affects these mechanisms. Many pathogenic mechanisms between sepsis and HIV overlap, so it is conceivable that patients with HIV presenting with sepsis form a group that will particularly benefit from new drugs targeting septic immunosuppression. In this light, the systematic exclusion of patients with HIV from sepsis trials might need to be reconsidered.

**Conclusion**

In the era of effective cART, bacterial sepsis has evolved as a major cause of mortality in patients with HIV. HIV infection affects many components of the immune response, which on the one hand renders the HIV-infected host more susceptible to invasive infection, and on the other hand might further exacerbate the deregulated host response to sepsis. Specific research on sepsis in patients with HIV is scarce and future studies are needed to gain more insight into the particularities of sepsis pathogenesis in these patients. Although cART greatly improves patients’ immune function, as shown by the strong reduction in opportunistic infections, patients continue to have an increased risk of developing invasive bacterial infection, suggesting the current and future relevance of this under-researched area.

**Declaration of interests**

We declare no competing interests.

**Contributors**

MAH conceived the idea, searched the scientific literature, interpreted the data, wrote the manuscript and created the figures. MPG and TvdP interpreted the data and wrote the manuscript.

**References**


Review


