Individuals with human immunodeficiency virus (HIV) infection have increased susceptibility to invasive disease caused by Salmonella enterica serovar Typhimurium. Studies from Africa have suggested that this susceptibility is related in part to the development of a high level of lipopolysaccharide (LPS)-specific IgG that is able to inhibit the killing of S. Typhimurium by bactericidal antibodies in healthy individuals. To explore this issue further, we examined the bactericidal activity against S. Typhimurium using serum and plasma samples from healthy controls and various clinical subgroups of HIV-infected adults in the United States. We found that the bactericidal activity in the samples from HIV-positive elite controllers was comparable to that from healthy individuals, whereas it was significantly reduced in HIV-positive viremic controllers and untreated chronic progressors. As demonstrated previously for healthy controls, the bactericidal activity of the plasma from the elite controllers was inhibited by preincubation with S. Typhimurium LPS, suggesting that it was mediated by anti-LPS antibodies. S. Typhimurium LPS-specific IgG was significantly reduced in all subgroups of HIV-infected individuals. Interestingly, and in contrast to the healthy controls, plasma from all HIV-positive subgroups inhibited in vitro killing of S. Typhimurium by plasma from a healthy individual. Our results, together with the findings from Africa, suggest that multiple mechanisms may be involved in the HIV-induced dysregulation of humoral immunity to S. Typhimurium.

Invasive disease caused by nontyphoidal Salmonella (NTS) strains, mainly Salmonella enterica serovar Typhimurium, has become a significant public health problem in sub-Saharan Africa (1, 2). Children <2 years of age constitute one population that is particularly susceptible to NTS sepsis, and a recent study from Malawi has helped to clarify the immunological basis of this susceptibility. This study showed in an in vitro assay that serum from most healthy adults and older children had antibodies that were able to kill S. Typhimurium, whereas most infants below the age of about 16 months lacked such bactericidal antibodies (3). These findings, which correlated inversely with the pattern of incidence of invasive salmonellosis (i.e., high in infants and low in older children and adults) suggested an important role for antibody-mediated protection in invasive NTS disease. The initial analysis indicated that the bactericidal antibodies present in healthy adults in Malawi were directed against Salmonella outer membrane proteins, but recent work from our laboratory, as well as that from other investigators, has focused on the O antigen of lipopolysaccharide (LPS) as the relevant antigenic target (4–8). Our experiments demonstrated that serum and plasma from the majority of healthy adults in the United States had bactericidal activity against S. Typhimurium and that this activity was mediated by antibodies to an epitope in the outer polysaccharide of LPS (5). We also found that the bactericidal activity was less robust in children <5 years of age, correlating with lower levels of S. Typhimurium LPS-specific IgM and IgG in this age group (5). In addition to young children, HIV-infected adults represent a second population that has a high risk of invasive NTS disease (9–12). The results from Malawi suggest that this susceptibility is at least partly related to an HIV-associated abnormality of the humoral response to S. Typhimurium. The abnormality manifests as high levels of anti-LPS IgG antibodies that are able to inhibit the killing of S. Typhimurium by bactericidal antibodies from healthy individuals (4). Interestingly, although these LPS-specific IgG antibodies inhibited bacterial kill-
nity to S. Typhimurium observed in HIV-infected adults in Africa applies to other populations or whether it is also seen in the clinical subgroups of infection that are associated with low viral loads. Clarifying these issues might provide insight into the immunological abnormalities induced by HIV infection, and it might also have implications for developing and applying strategies to prevent invasive NTs disease in vulnerable HIV-positive populations. Accordingly, we tested serum and plasma samples from HIV-infected individuals and HIV-negative healthy controls in the United States for the presence of bactericidal activity against S. Typhimurium. The HIV-infected group included elite controllers, viremic controllers, and untreated and treated chronic progressors. The results of our analysis confirm that HIV infection is associated with abnormalities of anti-Salmonella bactericidal activity and antibody responses. However, notable differences between our findings and those reported from Africa suggest that the mechanisms underlying the observed impaired bactericidal activity may vary depending on the geographic location and clinical characteristics of the HIV-infected population under consideration.

MATERIALS AND METHODS

Serum and plasma samples. Deidentified serum and plasma samples from healthy adults from the United States were collected during routine health maintenance visits to clinics in the United States at a parallel to provide reference hemolytic activity. The negative control consisted of 25 µl of gelatin-Veronal buffer instead of serum or plasma, while 25 µl of serum or plasma plus 75 µl of buffer was used as the blank. At the end of 30 min, the plate was centrifuged briefly and the absorbance at 540 nm (A540) of the supernatants used as a measure of the amount of hemoglobin released from the lysed erythrocytes. The hemolytic activity of the individual serum or plasma samples was calculated as a percentage of the activity of the reference sample as follows: (A540 of sample − A540 of negative control)/(A540 of reference − A540 of negative control) × 100.

Statistical analysis. The results from the groups of serum or plasma samples are displayed as scattergrams, with each symbol representing an individual sample and the error bars indicating the mean ± standard deviation (SD). The intergroup differences were analyzed by the Mann-Whitney U test using Prism version 6.0c (GraphPad Software, Inc., La Jolla, CA). A P value of <0.05 was considered to be significant.

RESULTS

Using an assay essentially identical to that described in previously published studies from Africa (3, 4) and our own work from the United States (5), we tested serum and plasma samples from groups of healthy HIV-negative adults and from HIV-infected adults for the presence of bactericidal activity against S. Typhimurium. As we reported earlier (5), all the healthy control samples significantly reduced the number of surviving bacteria by 1 to 2 logs relative to PBS over the course of 1 h (Fig. 1). In contrast, the samples from the HIV-infected individuals had various bactericidal activities that differed between the clinical subgroups (Fig. 1). The elite controllers had bactericidal activity that was comparable to that of the healthy individuals, whereas the viremic controllers and untreated chronic progressors had a significantly reduced ability to kill S. Typhimurium. Interestingly, antiretroviral treatment appeared to improve bactericidal activity to some extent, although the effect did not reach statistical significance (Fig. 1).

Earlier work has shown that serum bactericidal activity against S. Typhimurium is antibody mediated and complement dependent (3–5). The bactericidal activity of the samples from the elite controllers was also complement dependent, as indicated by its abrogation by heating to 56°C for 30 min (data not shown). Our experiments with serum and plasma from healthy individuals in the United States demonstrated that the antigenic target of the substrate. The intensity of color change was measured at 490 nm in a plate reader. In a subset of samples, the endpoint titers of LPS-specific IgG were determined by carrying out an enzyme-linked immunosorbent assay (ELISA) with serial 2-fold dilutions of the samples. The titer was defined as the reciprocal of the highest dilution that yielded an absorbance 3 times as high as the background (the background being the absorbance when the sample was replaced with PBS, with all other steps of the ELISA being the same). The total serum IgG was measured using an ELISA kit from eBioscience (San Diego, CA), according to their guidelines.

Hemolytic complement assay. As described in detail earlier, we estimated the hemolytic complement activity in our samples using a published microassay that has been shown to have good correlation with the traditional CH50 titration method (the CH50 measures the total hemolytic activity of a test sample and is the reciprocal of the dilution of serum complement needed to lyse 50% of a standardized suspension of sheep erythrocytes coated with antiserum to sheep erythrocytes) (3, 22). In brief, 25-µl aliquots of serum or plasma were incubated with 75 µl of antibody-coated sheep erythrocytes suspended at 5 × 10⁶ cells/ml in gelatin-Veronal buffer (Complement Technology, Inc., Tyler, TX) for 30 min at 37°C in a microtiter plate. Twenty-five microliters of human serum complement (Sigma-Aldrich, St. Louis, MO; derived from pooled normal human plasma, with a nominal activity of 41 CH50 units/ml) was assayed in parallel to provide reference hemolytic activity. The negative control consisted of 25 µl of gelatin-Veronal buffer instead of serum or plasma, while 25 µl of serum or plasma plus 75 µl of buffer was used as the blank. At the end of 30 min, the plate was centrifuged briefly and the absorbance at 540 nm (A540) of the supernatants used as a measure of the amount of hemoglobin released from the lysed erythrocytes. The hemolytic activity of the individual serum or plasma samples was calculated as a percentage of the activity of the reference sample as follows: (A540 of sample − A540 of negative control)/(A540 of reference − A540 of negative control) × 100.

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activity was LPS (5). To determine if the bactericidal activity detected in the samples from the elite controllers was also directed against LPS, we preincubated a subset of these samples with an excess of S. Typhimurium LPS before carrying out the bactericidal assay. As shown in Fig. 2, the LPS preincubation significantly inhibited bactericidal activity, suggesting that LPS was the target of the activity. Based on this finding, we sought to elucidate the mechanism responsible for the reduced bactericidal activity of the HIV-positive samples by examining their levels of S. Typhimurium LPS-specific antibodies. The samples from all subgroups of the HIV-infected individuals had LPS-specific IgG levels that were significantly lower than those in the healthy controls, as indicated by the relative absorbances detected using a standard ELISA (Fig. 3A). We also carried out endpoint titer measurements using a subset of the samples. The results demonstrated a pattern similar to that observed in the standard ELISA, i.e., the titers of LPS-specific IgG in all the HIV-positive subgroups were lower than those in the healthy controls, with the difference reaching statistical significance (P < 0.0001; **, P = 0.0008; ***, P = 0.025).

FIG 1 Bactericidal activity in serum and plasma samples from healthy and HIV-positive individuals. The bactericidal assays were carried out using PBS or samples from healthy or HIV-positive individuals. The numbers of bacteria surviving at the end of the 1-h incubation with the indicated samples are shown (mean ± SD). *, P < 0.0001; **, P = 0.0008; ***, P = 0.025.

FIG 2 Effect of LPS competition on bactericidal activity. The bactericidal assays were carried out with PBS or plasma samples from elite controllers with and without preincubation with 100 μg/ml of S. Typhimurium LPS. The numbers of bacteria surviving at the end of 1 h are shown (mean ± SD). *, P = 0.008.

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treated chronic progressor subgroups, have a significant impairment in plasma bactericidal activity against *S. Typhimurium* compared to healthy adults (Fig. 1). The mechanism of this impairment appears to involve a significant decrease in the circulating levels of IgG against *S. Typhimurium* LPS (Fig. 3), the antigen that we have shown is the target of this bactericidal activity in healthy individuals (5) and in elite controllers (Fig. 2). However, the decrease in LPS-specific IgG cannot be the only factor since, despite this abnormality, the elite controllers have bactericidal activity comparable to that of the healthy controls. A decrease in complement activity may be an additional factor contributing to reduced bactericidal activity: unlike elite controllers, viremic controllers were found to have significantly reduced hemolytic complement activity compared to that of healthy individuals, and the untreated chronic progressors displayed a similar trend (Fig. 4). In further support of this idea, antiretroviral treatment reversed the decline in complement activity in the chronic progressors (Fig. 4) and also improved their bactericidal activity to some extent (Fig. 1). Thus, our data suggest that it may be a combination of low levels of LPS-specific IgG and reduced complement activity that results in impaired bactericidal activity against *S. Typhimurium*. We cannot completely exclude the possibility that decreases in complement activity may be related to storage conditions. However, we think it is unlikely, since the samples from all the HIV-positive subgroups were stored and handled similarly. Interestingly, HIV infection has been associated with disease severity-dependent activation of the complement pathway (23, 24), providing a plausible explanation for the reduced complement activity in our plasma samples from the viremic controllers and untreated chronic progressors.

The presence of inhibitory activity that prevents the killing of *S. Typhimurium* by healthy plasma may be another factor contributing to impaired bactericidal activity in HIV infection (Fig. 5). Currently, we can only speculate on the nature of the inhibitory activity present in the samples from the HIV-positive individuals. In HIV-infected patients in Malawi, the inhibition of bactericidal activity...
activity was dependent on high levels of LPS-specific IgG (4). This mechanism is unlikely to apply to our population, since the LPS-specific IgG levels in the HIV-infected individuals were lower than those in the healthy controls (Fig. 3). It is possible that subtle differences in the epitope targeted by the anti-LPS IgG between healthy and HIV-positive individuals might lead to bacterial killing or the inhibition of bacterial killing, respectively. Such epitope-specific differences in the functional outcome of antibody binding, including complement activation, have been described in the case of antibodies directed against the capsule of Cryptococcus neoformans (25, 26). It is also possible that difference in the glycosylation of LPS-specific IgG between healthy and HIV-infected individuals affects complement activation. Glycosylation of the Fc region has been shown to contribute to the ability of some anti-Neisseria meningitidis IgG to block bactericidal activity (27), and IgG glycosylation is known to be influenced by HIV infection (28, 29). LPS-specific antibodies of isotypes other than IgM might also play a role in the inhibitory activity. For instance, it is possible that an HIV infection–associated increase in the relative level of LPS-specific IgA is a factor, since IgA does not activate complement and might block the binding of complement-fixing IgG or IgM. There are precedents for this type of IgA-mediated blocking of complement activation in meningococcal infection (30–33).

We found that LPS-specific IgM was increased in some of the HIV-positive subgroups in our study (data not shown), raising the possibility that high levels of such antibodies inhibit bacterial killing in a manner similar to the high levels of LPS-specific IgG in HIV-infected individuals in Malawi (4). All the potential mechanisms discussed above merit further investigation. Definitive proof of their involvement in HIV–associated inhibition of bactericidal activity will require a more focused investigation in which sufficient volumes of serum or plasma are collected to allow the use of depletion and purification strategies. Currently, the sample volumes available to us are not adequate for such studies, which, in any case, may be premature given that we do not yet have evidence that the inhibition is antibody mediated.

It is interesting that a decrease in S. Typhimurium LPS-specific IgG was observed in all the HIV–positive subgroups in our study. This abnormality might be related to HIV-induced impairments of CD4+ T-cell function, since T-cell help is required for switching from IgM to other isotypes. Thus, our findings suggest that CD4+ T lymphocytes from elite and viremic controllers might have functional deficiencies that impair their ability to provide help for B-cell isotype switching, even though their numbers were relatively normal in these subgroups (1,004 ± 395 cells per μL blood and 698 ± 117 cells per μL blood in the elite and viremic controllers, respectively).

Our results provide insights into the potential functional importance of bactericidal antibodies against S. Typhimurium. Although the clinical status of elite and viremic controllers may ultimately deteriorate (16), they are not known to be unusually susceptible to opportunistic infections during the period that they are able to suppress viral replication. That being the case, our observations that viremic controllers have decreased plasma bactericidal activity against S. Typhimurium (Fig. 1) and that the plasma of both elite and viremic controllers inhibits killing of S. Typhimurium by healthy plasma (Fig. 5) raise questions about the relevance of bactericidal antibodies in the protection against this pathogen. Long-term follow-up studies of HIV-positive controllers will be required to clarify this issue.

There are similarities and contrasts between our observations and those from Malawi (4). Both studies clearly demonstrate that HIV infection is associated with impaired bactericidal activity against S. Typhimurium. However, the mechanisms involved in the United States and Africa appear to be quite different. In contrast to our findings, HIV-infected adults in Malawi have high levels of S. Typhimurium LPS-specific IgG, which were shown to inhibit the bactericidal activity of serum from healthy individuals (4). The explanation for this striking difference in circulating LPS-specific IgG between HIV-infected individuals in the United States and Malawi is not clear. One possibility is that the high rates of gastrointestinal infection in Africa might chronically compromise the intestinal epithelial barrier, leading to increased LPS translocation and immune activation (34–37). Our results, together with those from Malawi, suggest that there are multiple ways in which anti-S. Typhimurium humoral immunity can be compromised by HIV infection. The exact mechanisms involved are likely to depend on the geographic and clinical context. Further clarification of these mechanisms will help shed light on how HIV infection impairs B- and T-cell responses and predisposes to invasive NTS disease.

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