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MAJOR ARTICLE

Anti-Human Immunodeficiency Virus Antibodies in the Cerebrospinal Fluid: Evidence of Early Treatment Impact on Central Nervous System Reservoir?

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Background. Despite effective antiretroviral therapy (ART), human immunodeficiency virus (HIV) likely persists in the central nervous system (CNS) in treated individuals. We examined anti-HIV antibodies in cerebrospinal fluid (CSF) and blood as markers of persistence.

Methods. Human immunodeficiency virus antibodies were measured in paired CSF and serum before and after long-term treatment of chronic (n = 10) and early infection (n = 12), along with untreated early infection (n = 10).

Results. Treatment of chronic infection resulted in small reductions of anti-HIV antibodies in CSF and serum despite >10 years of suppressive ART. In untreated early infection, anti-HIV antibodies emerged in blood by day 30, whereas CSF antibodies reached similar levels 2 weeks later. Compared with long-term treatment of chronic infection, early ART initiation reduced CSF antibodies by 43-fold ($P > .0001$) and blood antibodies by 7-fold ($P = .0003$). Two individuals receiving pre-exposure prophylaxis and then ART early after infection failed to develop antibodies in CSF or blood, whereas CSF antibodies were markedly reduced in the Berlin patient.

Conclusions. To the extent that differential CSF and blood antibodies indicate HIV persistence, these data suggest a relative delay in establishment of the CNS compared with the systemic HIV reservoir that provides an opportunity for early treatment to have a greater impact on the magnitude of long-term CNS infection.

Keywords. antibodies; anti-retroviral therapy; cerebrospinal fluid; central nervous system; early infection; HIV-1; persistence; serology.

Treatment with antiretroviral therapy (ART) is highly effective in suppressing human immunodeficiency virus (HIV) replication, not only systemically but in the central nervous system (CNS), resulting in HIV ribonucleic acid (RNA) levels in blood and cerebrospinal fluid (CSF) below clinical detection [1]. This suppression of HIV replication is associated with a marked reduction in mortality and morbidity, including those related to CNS injury [2]. However, ART fails to eliminate HIV, and when treatment is interrupted, active replication and viremia resume and are followed by a rise in CSF HIV RNA as well [3]. In addition, even well treated persons living with HIV frequently exhibit elevated levels of immune activation and inflammation systemically [4–7] and in the CNS [8]. Increasing evidence suggests that persistent HIV infection may contribute to immune activation [9] and consequently to a spectrum of "nonacquired immune deficiency syndrome" systemic morbidity and perhaps continued CNS injury detected in neuropsychological test impairment [10].

Most studies of the HIV reservoir have focused on cells of the lymphatic system, particularly memory T cells that maintain the principal systemic reservoir [11]. Various methods provide direct or partial measurements of the systemic lymphocyte reservoir. By contrast, the CNS reservoir is much more difficult to assess. The cells supporting this reservoir are less clear, with tissue myeloid cells being a major candidate, although astrocytes and CNS-resident memory $CD4^+$ T cells may be a source [12]. The deep and inaccessible location of these cells in the CNS presents a formidable technical obstacle to measurement, as well as for evaluating cure strategies [13].

Although it is well accepted that the quantity and avidity of antibodies produced against a foreign agent are antigen-dependent [14], very little is known about antibody dynamics in relation to the level of antigen produced during acute and chronic infection or after treatment. In primary HIV infection, anti-HIV antibodies first appear 3 weeks after detection of viremia and p24 antigen expression and continue to rise relatively linearly over the next year [15]. Detailed quantitative studies of serum anti-HIV antibody profiles against a panel of defined

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viral antigens using the luciferase immunoprecipitation systems technology have detected novel profiles in elite HIV controllers [16], HIV-treated patients [17], and HIV-infected subjects with multiple reservoir measurements [18]. Particularly encouraging was the finding that the Berlin patient, an HIV-infected subject who received a stem cell transplant resulting in a functional cure [19, 20], showed a serum antibody profile approaching the uninfected controls with low antibodies against HIV p24, integrase, and reverse transcriptase [17]. Studies with a detuned enzyme-linked immunosorbent assay demonstrated that HIV antibodies decreased in treated patients and correlated with a lower level of viral replication [21]. Despite direct evidence that anti-HIV antibodies are proportional to the dynamic level of HIV antigens, antibody profiles may reflect the relative level of continued antigen expression and present a broad, albeit imprecise, method for assessing the HIV reservoir and treatment outcomes [16–18]. Antibody measurements might also be useful for assessing the CNS reservoir, because CSF antibodies may be dissociated from those of blood and require persistent local antigenic stimulation for maintenance [22].

In this study, we hypothesized that CSF antibodies serve as a parallel index of active CNS infection during early and chronic infection and of persistent CNS infection during ART. More specifically, we hypothesized that the emergence of CNS antibodies during early infection would allow us to assess the rate the CNS reservoir is established and maintained, compared with the periphery.

METHODS

Study Design and Characteristics of the Participants

This retrospective study analyzed archived, cross-sectional, and longitudinal CSF and blood samples collected from participants enrolled in Institutional Review Board-approved protocols with informed consent at 3 clinical sites: University of Gothenburg, University of California San Francisco, and Yale University. As summarized in Table 1, 33 HIV-infected and 12 uninfected individuals were evaluated. The chronic group included 10 HIV-infected individuals studied before and after >10 years of suppressive ART. Although the precise timing of infection was uncertain, their low blood $CD4^+$ T-cell counts at baseline (median 157 per μL) and clinical information suggests that they had been infected for several years before ART initiation. Their median duration of treatment was 12.5 years, their plasma and CSF HIV RNA levels were 5.36 and 3.88 $\log_{10}$ copies/mL before treatment, and <1.69 $\log_{10}$ copies/mL in both fluids after treatment.

The early infection groups were diagnosed within 20–132 estimated days of exposure [23], and they have been included in studies characterizing primary HIV infection of the CNS [24, 25]. The treated subgroup initiated ART within 1–3 weeks of diagnosis, except for 2 who started ART later at 147 and 256 days after infection. Baseline blood $CD4^+$ T-cell counts were higher in the untreated group (604 cells/μL) compared with the treated group (480 cells/μL). Samples were analyzed before treatment and in several individuals at varying intervals after treatment. Of note, only CSF, but not serum, from several of the untreated early infected participants were tested.

In addition, 2 individuals were included who coincidentally initiated pre-exposure prophylaxis (PrEP) within an estimated 10 and 12 days after infection and subsequently transitioned to ART at 18 and 24 days postinfection, and we refer to them as hyperacute [26]. Cerebrospinal fluid and serum from the Berlin patient, sampled 4 years after stem cell transplant were analyzed to serve as a comparative benchmark for the effects of functional cure [17, 19, 20]. Cerebrospinal fluid and serum from 12 HIV uninfected volunteers served as controls.

Luciferase Immunoprecipitation Systems Human Immunodeficiency Virus Antibody Measurement

Luciferase immunoprecipitation systems use recombinant chimeric fusion proteins with luciferase producing light and specific antigens for quantitative detection of antibodies. In the current study, HIV antigens for p24, matrix, gp41, gp120, reverse transcriptase, integrase, and protease were used for antibody profiling [17, 18, 27]. Serum and CSF samples were stored frozen at −80°C until use. For antibody testing, 1 μL of serum and 10 μL of CSF were used, respectively, producing approximately the same dynamic range of antibody detection. All assays were performed with a master plate of serum and CSF samples, and data were presented as light units (LU) [17]. For analysis, the antibody values against the 7 antigens were combined and presented as total HIV antibody levels. Antibody levels against the individual HIV proteins are provided as Supplementary Information.

Virological and Other Clinical Methods

Plasma and CSF HIV-1 RNA levels were measured at the local site laboratories using Cobas TaqMan assay version 1 or 2 (Hoffman La-Roche, Basel, Switzerland) or Abbott RealTime HIV-1 assay (Abbott Laboratories, IL), with 20 and 40 copies/mL, respectively, as lower limits of quantification. Both plasma and CSF HIV levels were measured at the same time points assessed for antibodies. All participants with chronic and acute HIV infection treated with ART, for more than 40 days, showed CSF HIV viral loads <50. Local laboratories also generated the background data including CSF cell counts, differential, and albumin and blood $CD4^+$ T-cell counts and albumin [8]. As shown in Table 1, the CSF/blood albumin ratio in most of the HIV-infected subjects were normal, suggesting that there was no breakdown of the blood-brain barrier.

Data Analysis

Antibody levels in the chronic HIV infection group are reported as the geometric mean level (GML) and 95%

Table 1. Subject Characteristics (At First Visit)

Subject Groups	N	Site (SF/GOT) Ratio	Gender (M/F) Ratio	Age (Years)	Time Since Infection (Years)	CD4 (Cells/μL)	Plasma HIV RNA (Log_{10} Copies/mL)	CSF HIV RNA (Log_{10} Copies/mL)	CSF WBC (per μL)	CSF Neopterin (nMol/L)	CSF/Blood Albumin Ratio Mean (SD)	CSF NFL (Log_{10} ng/L)
				Mean (SD)					Median (IQR)			
Chronic infection	10	10:0	7:3	40.2 ± 8.3	?	137.6 ± 98.7	4.38 ± 0.49	3.55 ± 0.56	1.5 (2.8–11.3)	24.9 ± 10.5	6.1 ± 2.2	2.84 ± 0.29
Primary infection											4.8 ± 1.9	2.78 + 0.14
No treatment	12	8:3:1*	12:0	40.1 ± 10.0	0.09 ± 0.02	608.8 ± 152.0	4.17 ± 1.50	2.80 ± 1.17	3.5	10.2 ± 9.2	5.0 ± 2.0	2.74 ± 0.28
Treatment	8	2:6	7:1	48.3 ± 9.7	0.14 ± 0.10	807.8 ± 413.4	1.63 ± 0.22	1.66 ± 0.05	0	5.8 ± 1.9	5.8 ± 1.9	2.64 ± 0.20
Hyperacute	2	2:0	2:0	42.0 ± 17.0	0.20 ± 0.04	1059 ± 636.4	1.59 ± 0	1.59 ± 0	5.5 (0–12.5)	11.1 ±	4.6 ± 0.9	3.48 ± 0.54
Berlin	1	1:0	1:0	50	16.31	364	5.46 ± 0.44	4.91 ± 0.47	0	4.5	9.7	4.5
HIV negative	12	12:0	7:5	48.8 ± 19.6	NA	NA	NA	NA	0	NA	7.1 ± 4.0	2.56 ± 0.26

Abbreviations: CSF, cerebrospinal fluid; GOT, Gothenburg; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NFL, neurofilament light; RNA, ribonucleic acid; SD, standard deviation; SF, San Francisco; WBC, white blood cells.

*Yale.

confidence interval. Cutoff limits for determining positive antibodies in the HIV-infected samples were based on the mean plus 5 standard deviations of the serum and CSF values derived from the 12 uninfected controls. The Wilcoxon rank non-parametric test was used to study statistically significant antibody level changes in the paired samples. Additional analysis of antibodies against the 7 individual HIV proteins in the HIV participants are shown in the Supplementary Figures. A heatmap (Supplementary Figure 8) provides an overview of the serum and CSF antibody responses against the 7 different HIV antigens responses in the different groups and impact of treatment. The heatmap was generated essentially as previously described [28], in which a cutoff value (10 000 LU) based on receiver operator characteristic was used for data transformation.

RESULTS

Long-Term Treatment of Chronic Human Immunodeficiency Virus (HIV) Infection Participants Results in a Small Decrease in Serum and Cerebrospinal Fluid HIV Antibody Levels

Using a panel of 7 HIV antigens, serum antibody levels were determined in the uninfected HIV controls and chronic HIV-infected subjects before and after >10 years of ART. To generate an overview for each subject, the antibody levels against the 7 antigens were combined into the total HIV antibody levels. As shown in Figure 1A, the GML of HIV serum antibodies observed in the pre- and posttreatment samples were 10 810 000 LU and 5 736 000 LU, respectively, which were more than 250-fold higher than the uninfected controls (22 980 LU). Comparing the paired pre- and posttreatment serum sample from each subject revealed a significant decrease in antibody levels (Wilcoxon rank analysis; $P = .02$) with treatment (Figure 1A). Further analysis revealed that 6 of 10 subjects showed little or no change in overall antibody levels, whereas 4 subjects showed a pronounced 3- to 6-fold antibody decrease with treatment (Figure 1A). Consistent with these findings, there was a corresponding significant ($P < .03$ to $P < .001$) decline in the serum antibody responses against 6 of 7 HIV antigens, in which gp120 and integrase showed the greatest drop in serum antibody levels between pre- and posttreatment (Supplementary Figure 1). The 1 exception was serum antibodies to p24, which did not decrease significantly with treatment (Supplementary Figure 1). Overall, these results show that long-term ART in this group causes only a modest drop in serum HIV antibodies although with some variability amongst the individual subjects.

Cerebrospinal fluid humoral responses against the 7 HIV antigens were also measured at the same time points. The combined CSF antibody profile revealed that the GML in the pretreatment and posttreatment samples was 5 503 000 LU and 2 753 867 LU, respectively (Figure 1B). Although well above the uninfected volunteers (20 460 LU), these CSF HIV antibody levels from before and after ART showed a significant ($P = .01$) decrease. Except for the p24, all other CSF antibody levels against individual antigens were significantly lower ($P = .04$ to $.002$) after treatment (Figure 1B and Supplementary Figure 2). Comparison of the serum and CSF profiles for each HIV antigen showed that they tracked each other well; correlation coefficients for integrase, protease, p24, matrix, reverse transcriptase, gp120, and gp41 were 0.87, 0.84, 0.82, 0.69, 0.60, 0.58, and 0.43, respectively. These results highlight how anti-HIV antibodies levels between the systemic blood and CSF of chronic-infection subjects align closely and that long-term ART associates with a significant, although modest, decrease in anti-HIV antibody levels in both compartments.

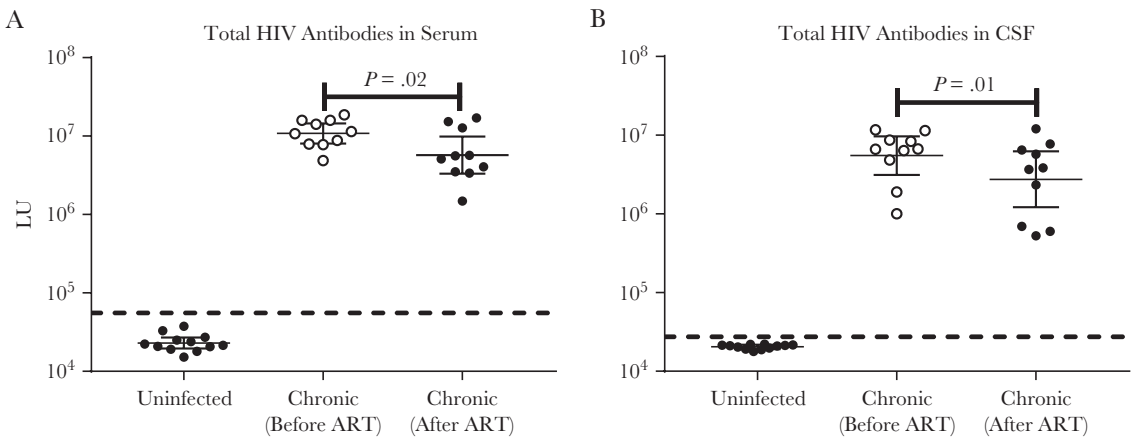

Figure 1. Serum and cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) antibody levels in patients with chronic HIV infection before and after long-term treatment. Antibody measurements were made in (A) serum and (B) CSF samples taken from before and after long-term treatment of subjects with chronic HIV infection and uninfected controls. The y axis reflects the antibody levels in light units determined by luciferase immunoprecipitation systems. The total HIV antibody levels were derived from the sum of antibody values against 7 antigens. The geometric mean antibody levels and 95% confidence interval are shown for each group. The geometric mean level in the chronic HIV-infected participants after treatment was further used as reference for Figure 2. The black dotted line is the cutoff value, based on the uninfected controls, for determining seropositivity of the combined antibody total for serum and CSF. Wilcoxon rank statistical analysis was used to statistically evaluate differences between the paired before and after treatment samples. Abbreviations: ART, antiretroviral therapy.

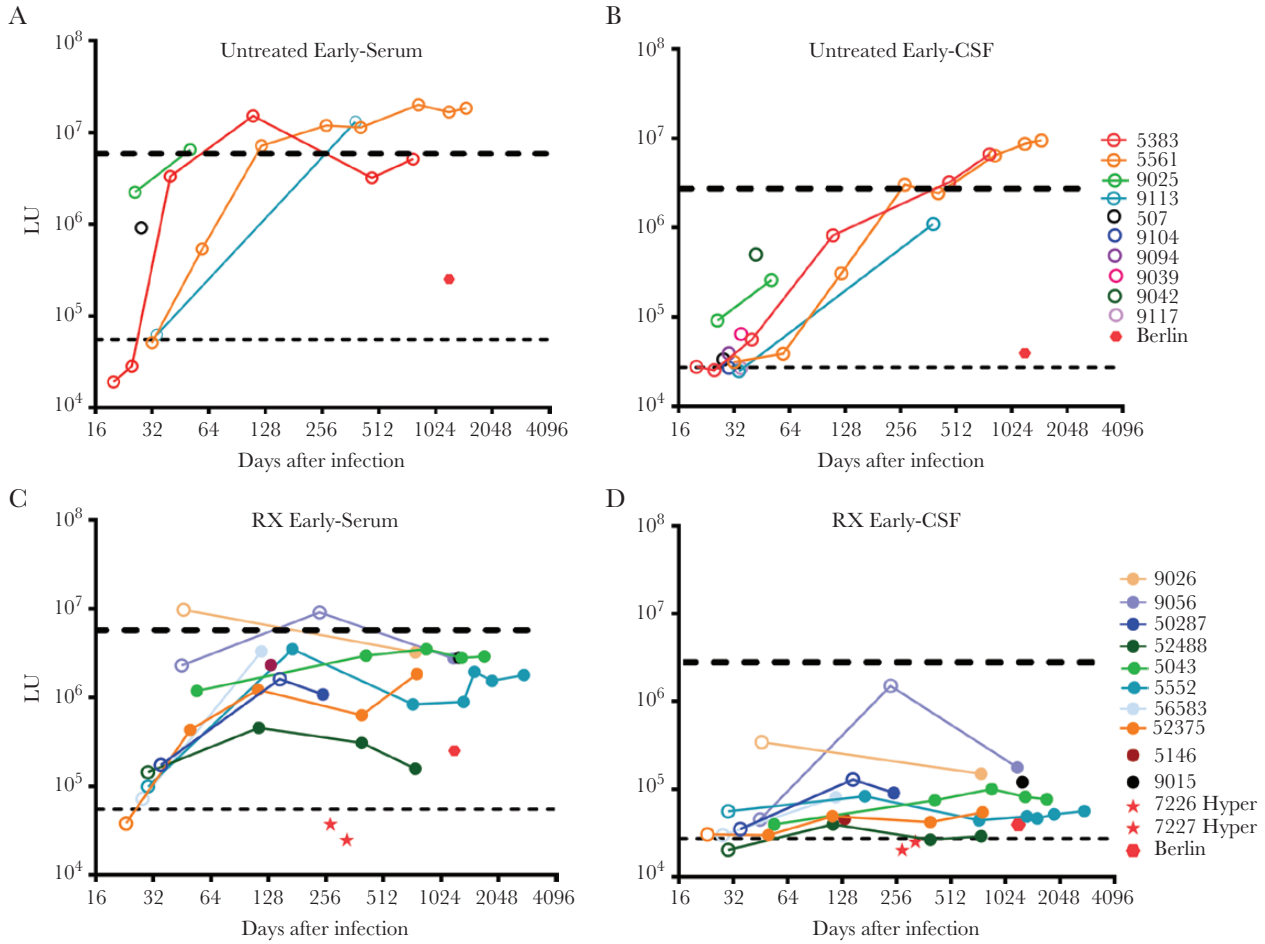

Figure 2. Serum and cerebrospinal fluid (CSF) antibody levels in untreated and treated early human immunodeficiency virus (HIV) infection. Untreated subjects with early HIV infection were evaluated for (A) serum and (B) CSF antibodies in paired cross-sectional and longitudinal samples. Similarly, treated subjects with early HIV infection were evaluated for (C) serum and (D) CSF antibodies in paired cross-sectional and longitudinal samples. Each colored dot reflects an individual subject. An open circle reflects the absence of antiretroviral therapy at that time point. The black dotted line is the cutoff value for determining seropositivity and is based on the uninfected controls of the combined antibody total for serum and CSF. As a reference, the blue dotted line represents the geometric mean antibody levels found in the corresponding serum and CSF of the treated chronically infected subjects. The serum and CSF antibody values for the Berlin patient (red solid dot) are also shown. Abbreviations: LU, light units.

Robust Increases in Serum and Cerebrospinal Fluid Human Immunodeficiency Virus (HIV) Antibody Levels Over Time in Untreated Early HIV Infection

To understand temporal changes in the HIV antibody profile during the first year of infection in the absence of treatment, longitudinal serum and CSF samples were examined from early HIV-infected individuals. Analysis of the first available serum samples from 26 to 46 days after infection revealed measurable HIV antibody responses (Figure 2A). Two participants (5383 and 5561) lacked detectable antibodies between days 20 to 32, but analysis at day 40 and beyond revealed high levels of HIV antibodies. Examination of additional longitudinal time points from participants of early, untreated HIV-infected subjects showed that the antibody levels then rose substantially during the next 300 days to levels of >1 000 000 LU, approximating the levels observed in the chronically infected subjects. Inspection of the humoral responses against the different HIV antigens revealed that the individual antibody levels increased similarly against the 7 HIV proteins (Supplementary Figure 3).

The corresponding CSF antibody profiles from the untreated early subjects also showed very low levels of CSF HIV antibodies at the earliest time, with all but 1 above the healthy control cutoff value (Figure 2B). However, CSF antibodies rose rapidly rose more than 100-fold between days 32 and 64 and continued to increase through 18 months, eventually attaining levels of >1 000 000 LU observed in the CSF of the chronically infected participants (Figure 2B). Neither in these individuals nor in the chronic group was there a correlation between the changes in HIV antibodies and the CSF-plasma albumin ratio, a marker of the blood-brain barrier disruption [29]. Compared with the serum profile, the CSF antibodies at the early time points were mainly directed against matrix, reverse transcriptase, gp41, and gp120 (Supplementary Figure 4). In general, the CSF antibodies

were lower than those of serum during the initial weeks of infection but rose over the next 6–18 months to levels equivalent to the chronic group.

Attenuated Antihuman Immunodeficiency Virus Antibodies in Serum and Cerebrospinal Fluid With Treated Early Infection

To understand the impact of ART administered early, longitudinal samples were examined from individuals who initiated treatment early between 10 and 256 days after initial HIV infection. As in the untreated individuals, these subjects showed initial low serum antibody levels at the earliest sample before 40 days. With treatment, the subsequent antibody trajectories appeared to be attenuated (Figure 2C), reaching levels well below the treated chronic infection and the untreated early infection groups, with some approaching serum antibody levels near those of the Berlin patient [17].

Direct comparison of serum antibody levels from the last time point available after at least 240 days of infection from the treated early were reduced 7-fold (P = .0003) compared with with the long-term treated chronic subjects, highlighting the impact of early treatment (Supplementary Figure 5). Further analysis revealed that the subject who started treatment before day 40 developed high levels of serum antibodies to p24, gp41, and gp120 but completely lacked antibodies to integrase and protease (Supplementary Figure 6). Finally, a substantial drop in antibodies was noted in 2 cases (ie, 50287 and 9056) who initiated ART later at 148 and 256 days after infection.

The blunting effect of early ART on antibody responses was even greater in CSF than serum (Figure 2D). Strikingly, the very low levels of HIV antibody levels noted at the earliest time points of 14–62 days remained stable during the ensuing period from 100 to 2000 days, clearly diverging from the increase seen in their untreated counterparts. The CSF values observed in these early-treated subjects were less than 10-fold higher than the cutoff derived from the uninfected subjects, close to or in the same range as those of the Berlin patient or nearing the uninfected controls (Figure 2D). In one individual (52488), the antibody levels reverted close to the seronegative cutoff value at 2.5 years after infection. Analysis of CSF antibody profile against the individual proteins revealed that most of the observed immunoreactivity was contributed by p24 antibodies (Supplementary Figures 7 and 8). The 2 hyperacute individuals who started PrEP very early after infection without seroconversion before treatment remained antibody-negative months later. (Figure 2C and D). Unlike the chronically infected group, comparison of the serum and CSF antibody levels in these treated individuals showed a marked discordance in values, suggesting that these 2 compartments did not equilibrate over time (Supplementary Figure 8). More importantly, the CSF antibodies from the last time point available after at least 240 days of infection from the early treated subjects showed a 43-fold lower level (P > .0001) compared with the long-term ART-treated chronic subjects, emphasizing the important impact of early treatment on the CNS response (Supplementary Figure 9). Compared with blood, these CSF results also support the relative independence and greater reduction of the CNS response to early treatment.

DISCUSSION

The impact of ART on serum and CSF HIV antibodies was investigated after initiation of treatment during chronic or early infection. A major finding was that early initiation of treatment after infection had a markedly greater impact in selectively sparing the CNS from acquiring HIV antibodies compared with the blood. To the extent that the serum and CSF HIV antibody levels reflect responses to continued expression of viral antigens, these results suggest that early treatment can abort or reduce the magnitude of the CNS HIV reservoir to a greater degree than its systemic counterpart.

Individuals with chronic HIV infection years after sustained treatment showed only modest, largely parallel decreases in HIV antibody levels. Although there was considerable heterogeneity among the chronically infected subjects, these findings are in general agreement with recent studies showing a similar decrease in serum antibodies with ART [21, 30]. More importantly, our study demonstrates that the serum and CSF antibodies seen in the long-term treated chronically infected subjects remain about the same as the untreated early infected subjects 1 year after infection. A likely explanation for limited antibody decay is the continued expression of HIV antigens within lymphoid tissue despite viral "suppression" in plasma [31], which is consistent with the frequency of low-level viremia detected by sensitive measures [32] and the capacity to detect persistent HIV outgrowth in suppressed patients [33]. We speculate that the large reservoir, established both systemically and in the CNS of subjects with chronic infection despite therapy, continues to produce HIV proteins, which in turn provides continued antigenic stimulation of the corresponding B cells.

Analysis of matching serum and CSF from longitudinal samples from untreated early infection revealed that HIV antibodies were first detectable in serum and then subsequently appeared in CSF. These results are in line with the known delay of detectable HIV RNA and cellular immune responses in the CSF compared with the systemic blood during early stage acute infection [34, 35]. In the untreated group, there was no enrichment in antibodies against the different HIV proteins in serum and CSF, in which the different antibodies generally tracked each other, including seropositive responses against integrase and protease. In the absence of treatment, these subjects at 1 year attained HIV antibodies in both blood and CSF comparable with the chronic HIV group.

In contrast, early ART dramatically blunted the CSF HIV antibody response. Early treated individuals exhibited very low antibodies over the extended period of observation. The 2

hyperacute individuals treated during very early infection at Fiebig stage 1, while antigen positive and antibody negative on days 10 and 12 after infection, remained seronegative when studied 10–11 months later. Those diagnosed in the days and early weeks later exhibited low antibodies at these time points. Early treatment attenuates further antibody increases in both fluids, but it is more strikingly in the CSF. This suggests that not only are the CSF antibodies slower to develop in the CNS, but that local antigen expression is also delayed, and that with early treatment the development and perhaps "maturation" of CNS infection and reservoir is likewise blunted. Hence, the attenuation of the CSF antibody response in early treatment may well be an indicator of the long-term impact of early treatment on the CNS reservoir.

The finding that the 2 treated hyperacute subjects never generated HIV antibodies in serum or CSF is also consistent with other studies showing that individuals who start therapy very early in acute infection have low or no HIV antibodies in serum and occasionally serorevert using standard antibody tests [36, 37]. However, as part of another study, these 2 hyperacute subjects underwent treatment interruption and experienced recurrence of plasma HIV viremia [26]. Although CSF was not collected to evaluate viral RNA in the CNS, this provides a cautionary note that the absence of HIV antibodies in the systemic reservoir for a prolonged period does not signify a cure.

The serum antibody findings appear consonant with observations comparing the impact of early versus delayed ART on HIV deoxyribonucleic acid (DNA) levels [38]. Antiretroviral therapy administration in early infection caused a larger decrease in cell-associated HIV-DNA than seen with treatment initiated during the chronic phase [39, 40]. The finding that early ART causes a modest reduction in serum HIV antibodies is consistent with these molecular findings. The blunted serum antibody profile observed in many of the treated early-infected subjects, stabilizing at intermediate values between chronic and uninfected participants, likely reflects their lower systemic reservoir. Antiretroviral therapy administered early may be more effective at blocking HIV replication in a limited pool of infected cells. This is reflected by the antibody profile of some early (<day 40) treated participants who showed low levels of serum antibodies to integrase and protease (Supplemental Figure 7) but modest antibodies to structural HIV proteins resembling the antibody profile in super-elite controllers [16]. The relative stable HIV antibody levels observed in the different ART-treated early patients depended on how soon after infection therapy was initiated and highlights the potential benefit of very early treatment.

CONCLUSIONS

Despite the small number of participants and retrospective nature of our study, the results have important implications for understanding and preventing CNS infection. First, the observation that high levels of HIV antibodies exist in the blood several weeks after initial infection, but are reduced in the CSF, supports the notion of independent HIV replication within the CNS that is delayed compared with systemic infection. The markedly lower HIV antibody levels in CSF compared with serum in the early treated subjects, even years later, points to the stability and durability of ART protection. These results also suggest that in these subjects, it is unlikely that there is systemic contamination of the CNS with serum antibodies. Although several other biomarkers are useful for studying HIV infection of the CNS [13], none appear to clearly suggest a relationship with the CNS reservoir as HIV antibodies. Additional studies of the analysis of CSF antibodies with detailed HIV reservoir measurements and long-term neurological morbidity assessment should further clarify their clinical importance.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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