

Intravenous Immunoglobulin (IVIG) Treatment for Modulation of Immune Activation in Human Immunodeficiency Virus Type 1 Infected Therapy-Naive Individuals

JOOST N. VERMEULEN,^{1,2} JAN M. PRINS,² EVELIEN BUNNIK,³ C. ERIK HACK,^{3,*}
SUZANNE JURRIAANS,⁴ FRANK MIEDEMA,^{3,5} JOEP M.A. LANGE,^{1,2}
and HANNEKE SCHUITEMAKER³

ABSTRACT

We evaluated the ability of intravenous immunoglobuline (IVIG) to diminish immune hyperactivation, which is considered a major cause of CD4⁺ T cell loss during chronic HIV-1 infection and whether this affected CD4⁺ T cell counts and plasma HIV-1 RNA (pVL). Therefore, we treated six chronically HIV-1-infected, antiretroviral-therapy-naive patients with IVIG (0.4 g/kg) at weeks 0 and 4, with a follow-up of 12 weeks after the second dosage during which pVL, T cell numbers, and T cell activation were measured. At baseline median CD4⁺ T cell counts were 300 (range 200–460) × 10⁶/liter and median pVL was 5.0 (range 3.2–5.2) log₁₀ copies/ml. IgG plasma levels peaked during the first days after administration. We observed a decrease in the percentage of activated (CD38⁺ HLA-DR⁺) CD4⁺ and CD8⁺ T cells [3.5% (range 1–7%) and 5% (1–10%), respectively (*p* = 0.027)], but no effect on the fraction of proliferating CD4⁺ or CD8⁺ T cells as measured by Ki67 expression. CD4⁺ T cell counts were significantly increased on day 4 (median +55 cells, range 0–150, *p* = 0.043). pVL was significantly increased on day 1 after IVIG infusion (median +0.13 log₁₀, range 0.01–0.55, *p* = 0.028). All these parameters returned to baseline levels within 1 week after infusion. In conclusion, administration of IVIG caused a temporary decrease in T cell activation and an increase in CD4⁺ T cell counts, despite an increase in pVL. Our results support the hypothesis that T cell activation, rather than direct HIV-1 infection, mediates the loss of CD4⁺ T cells and suggest that immunomodulating therapy in HIV-1 infection could indeed be effective.

THE OUTLOOK FOR HIV-1-INFECTED INDIVIDUALS has improved tremendously since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s.^{1–4} However, the use of HAART is limited by toxicity, high costs, the need for strict adherence to the medication, and the risk of development of viral resistance against the antiretroviral drugs. Therefore, the search for alternative treatment strategies is ongoing.

The hallmark of disease progression in chronic HIV-1 infection is the loss of CD4⁺ T cells. The percentage of circulating CD4⁺ T cells infected with HIV-1 is too low to explain this loss by direct cytopathic effects of HIV-1.^{5,6} The current hypothesis is that HIV-1 leads to massive depletion of CD4⁺ T cells in lymphoid tissue in the gastrointestinal tract, especially during the acute phase of the infection.⁷ During chronic infection continuous hyperactivation of the immune system leads to

¹IATEC, Amsterdam, the Netherlands.

²Center for Poverty-related Communicable diseases, Department of Internal Medicine, Center for Infection and Immunity Amsterdam, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

³Sanquin Research and Landsteiner Laboratory, Center for Infection and Immunity Amsterdam, University of Amsterdam, Amsterdam, the Netherlands.

⁴Department of Human Retrovirology, Academic Medical Center, Center for Infection and Immunity Amsterdam, University of Amsterdam, Amsterdam, the Netherlands.

⁵University Medical Center Utrecht, Utrecht, the Netherlands.

*Present address: Crucell Holland B.V., Leiden, the Netherlands.

enhanced T cell turnover and exhaustion of the naive T cell compartment.⁸ HIV-1 activates the immune system because of the high virion production and possibly by viral products.^{8,9} Activated and proliferating T cells in HIV-1-infected patients have a short half life and die after several rounds of division.^{10,11} The proportion of activated and proliferating cells is a strong predictor of disease progression.¹²

Suppression of viral replication by HAART prevents the loss of CD4⁺ T cells by preventing new infections of CD4⁺ T cells, but mainly by reducing the antigenic trigger that leads to immune activation. An alternative therapeutic option is to decrease the state of immune activation directly without suppressing viral replication itself. Several immunosuppressive agents have been used for this purpose, such as hydroxurea,¹³ thalidomide,¹⁴ and cyclosporine A,¹⁵ but are not attractive for various reasons.

Intravenous immunoglobulins (IVIG) are safely used for several autoimmune disorders characterized by a certain degree of immune activation.¹⁶ In a previous study¹⁷ IVIG treatment diminished the increased tumor necrosis factor (TNF)- α activity in HIV-1-infected patients, which was accompanied by a small increase in CD4⁺ T cell count. In the current proof-of-concept study we investigated whether IVIG treatment during chronic HIV-1 infection can mitigate the state of T cell activation and thus decrease the rate of CD4⁺ T cell turnover.

We included six antiretroviral therapy (ART)-naive adults (median age 39 years, range 31–65) with chronic HIV-1 infection [median CD4⁺ T cell count 300 (range 200–460) $\times 10^6$ /liter and median pVL (Versant HIV-1 RNA 3.0 assay) 5.0 (3.2–5.2) log₁₀ copies/ml] from our outpatient clinic at the Academical Medical Center in Amsterdam, the Netherlands in this open label, single center study. The primary objective was to evaluate the effect of IVIG on the state of chronic immune activation and the pVL in HIV-1-infected therapy-naive patients. Secondary objectives were to evaluate of the effect of IVIG on complement activation, cytokine production, and immunoglobulin levels.

The hospital Institutional Review Board approved the study and written informed consent was obtained from all participating patients before any study procedure was performed. Exclusion criteria were acute HIV-1 infection (defined as duration of infection <6 months), signs or history of AIDS-defining events, IgA deficiency, hypogammaglobulinemia, autoimmune disease, other infectious diseases besides HIV-1 infection, recent or current treatment with immunomodulating or anti-inflammatory medication, or a history of allergic reactions against human plasma or plasma products. Female patients were excluded if they were pregnant or lactating. Patients remained in follow-up until 12 weeks after the second dosage, with study visits at day 0, 1, and 4 and week 1, 2, 4, 6, 8, and 16.

Patients were treated with IVIG (Sanquin Plasma Products, Amsterdam, the Netherlands) at a dosage of 0.4 g/kg body weight, at week 0 and 4, which was well tolerated. Only one patient did not receive the second dosage of IVIG because of nonmedical personal reasons. Immunoglobulin G (IgG) levels [measured by nephelometry (Behring Nephelometer Analyzer, Marburg, Germany), according to standard procedures] showed a peak during the first days after the first dosage and approached baseline levels within 1 week (Fig. 1). After the second infusion at week 4 this peak was not observed, which might be due to less frequent sampling.

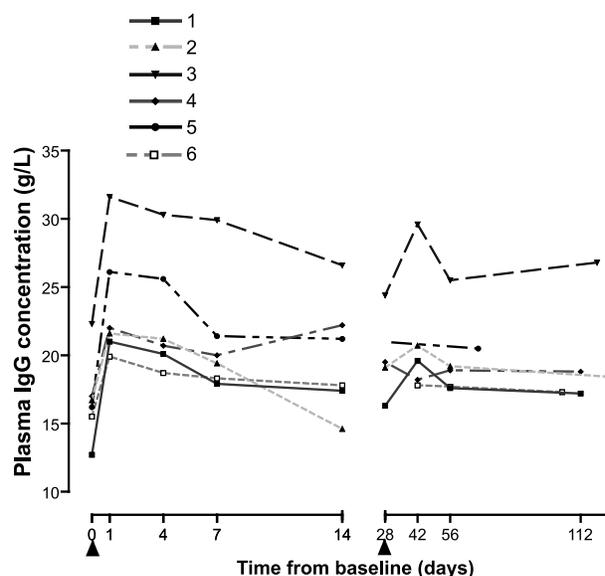


FIG. 1. Plasma IgG levels (g/liter) after administration of IVIG in six HIV-1-infected antiretroviral-naive patients. Arrows indicate the administration of IVIG on days 0 and day 28. Patient no. 5 did not receive the second dosage because of non-medical personal reasons.

We observed a decrease in flow cytometry analyses during the first 7 days after the first infusion. Compared to baseline levels, the median relative decreases of the proportion of activated lymphocytes in the CD4 and CD8 compartments in the first week were 3.5% (range 1–7%) and 5% (1–10%), respectively ($p = 0.027$ for both CD4 and CD8 compartment, Wilcoxon signed rank test, not corrected for multiple testing; Fig. 2). This decrease in activation state was not accompanied by a change in the fraction of proliferating CD4⁺ or CD8⁺ T cells measured by Ki67 expression *ex vivo*¹⁸ (Fig. 3). However, we did observe a slight increase in CD4⁺ (Fig. 4A), as well as in the CD8⁺ and total lymphocyte counts (data not shown). For the CD4 compartment, this increase was significant only on day 4 (median +55 cells compared to baseline, range 0–150, $p = 0.043$, Wilcoxon signed rank test, not corrected for multiple testing), and for the CD8⁺ compartment on day 1 and day 7 (+60 cells compared to baseline, range 2–72, $p = 0.027$; and +175 cells, range 70–1040, $p = 0.028$ respectively, Wilcoxon signed rank test, not corrected for multiple testing). We also observed a slight increase in pVL during the first days after IVIG infusion, which was statistically significant on day 1 only (median +0.13 log₁₀ compared to baseline, range 0.1–0.55, $p = 0.028$, Wilcoxon signed rank test, not corrected for multiple testing; Fig. 4B). None of these changes was statistically significant when repeated measurement techniques were applied.

All parameters returned to baseline levels within a week after the first IVIG infusion. After the second infusion these signs of immune activation and changes in CD4⁺ T cell counts or pVL were not documented, due to the lack of blood sampling during the first days after the second infusion. However, some patients showed some signs of increased CD4⁺ T cell counts and pVL and decreased activation markers at the time of first sampling, 2 weeks after the second infusion.

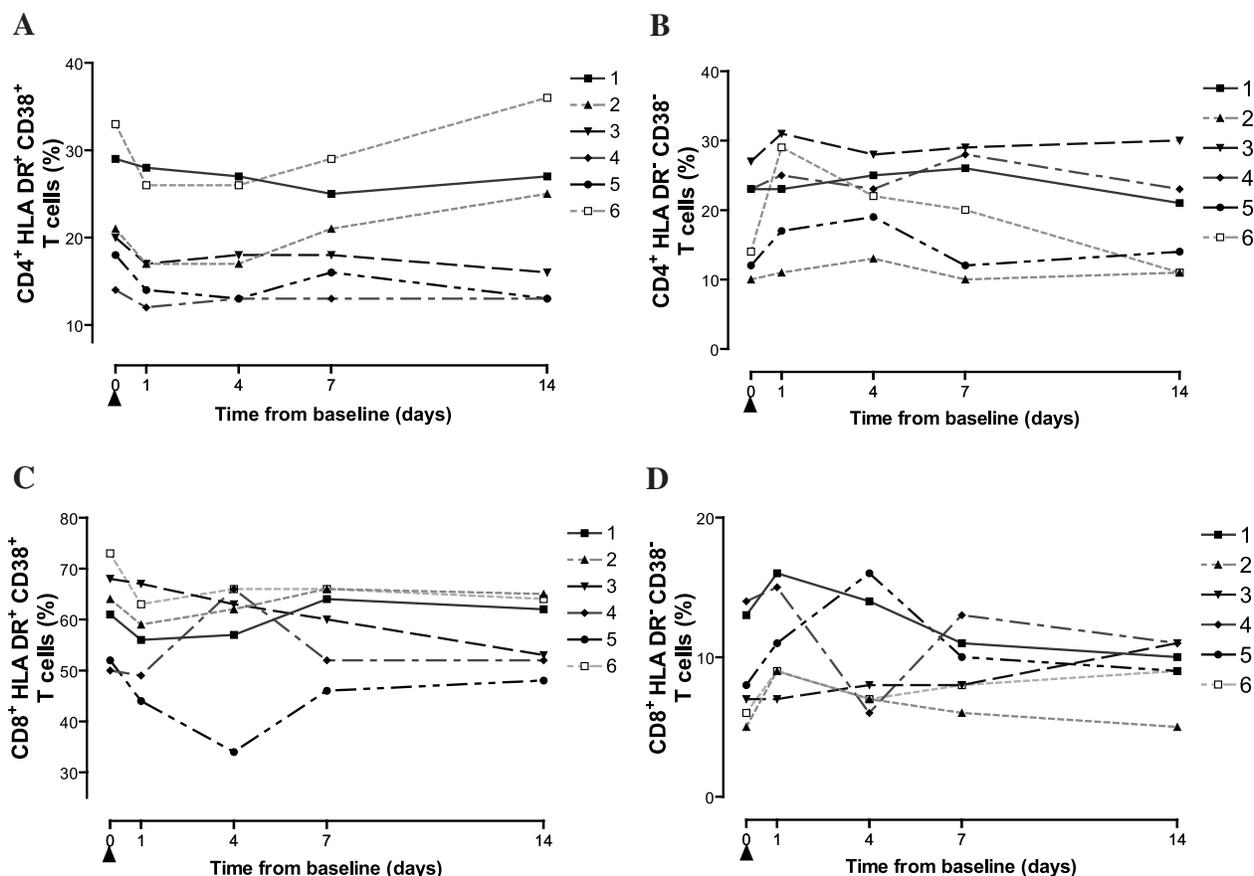


FIG. 2. Percentages of activated (CD38⁺ HLA DR⁺) peripheral blood CD4⁺ and CD8⁺ T cells (A and C, respectively) and nonactivated (CD38⁻ HLA DR⁻) CD4⁺ and CD8⁺ T cells (B and D) during the first 14 days after the first administration of IVIG (arrow) in six HIV-1-infected antiretroviral-naive patients.

There were no clear changes in the maturation stage of the CD4⁺ or CD8⁺ T cell subsets measured by additional flow cytometry [i.e., % naive (CD45RA⁺ CD27⁺), CD27⁺ memory (CD45RA⁻ CD27⁺), and CD27⁻ memory (CD45RA⁻ CD27⁻) subsets within the CD4⁺ and CD8⁺ T cells, and effector (CD45RA⁺ CD27⁻) subset within the CD8⁺ T cells;^{19,20} data not shown]. The proliferative capacity of lymphocytes upon stimulation with monoclonal antibodies against CD3 and CD28^{21,22} was unchanged (data not shown). In all patients, TNF- α , interleukin (IL)-6, and IL-8 (assay Sanquin, Amsterdam, the Netherlands), interferon- γ , and IL-10 levels (measured as described previously²³) in plasma were below the lower limit of quantification at almost all time points, including baseline. There was also no effect on the levels of the complement factors C3bc and C4bc, the acute phase protein CRP, or elastase (measured as described previously,²⁴⁻²⁷ data not shown).

In our study, treatment of therapy-naive HIV-infected individuals with IVIG resulted in a small, temporary decrease in T cell activation, as reflected by a reduction of CD38 and HLA DR expression on both CD4⁺ and CD8⁺ T lymphocytes. Although our data support the hypothesis that chronic immune activation, rather than direct HIV-1 infection, mediates the loss of CD4⁺ T cells in chronic HIV-1 infection, the limited number of patients and the lack of a control group do not allow rec-

ommendations on the use of IVIG as an immunomodulatory agent in inhibiting immune activation. The relatively small changes in T cell activation state, T cell numbers, and plasma HIV-1 RNA were not statistically significant after applying repeated measurements techniques or correction for multiple testing.

We and others have demonstrated that immune hyperactivation associated with HIV-1 infection drives accelerated T cell turnover, ultimately resulting in CD4⁺ T cell loss and disease progression.^{7,12,28} In agreement with this we observed that the decrease in immune activation was accompanied by a slight increase in CD4⁺ and CD8⁺ T cell numbers. However, we did not observe an increase in the percentage of Ki67⁺ cells, indicating that the reduction in T cell activation did not result in an increased CD4⁺ and CD8⁺ T cell production. The lack of increase in the proportion of proliferating cells suggests that the increase in CD4⁺ and CD8⁺ T cell numbers in peripheral blood most likely resulted from redistribution of lymphocytes from peripheral lymphoid tissues, lungs, or the gastrointestinal tract, similar to the redistribution of T cells seen after the start of HAART.²⁹ The redistribution of CD4⁺ T cells after initiation of HAART has been attributed to the decrease in pVL that is achieved by therapy. However, since in our present study no decrease in viral load was achieved, concomitant with the ab-

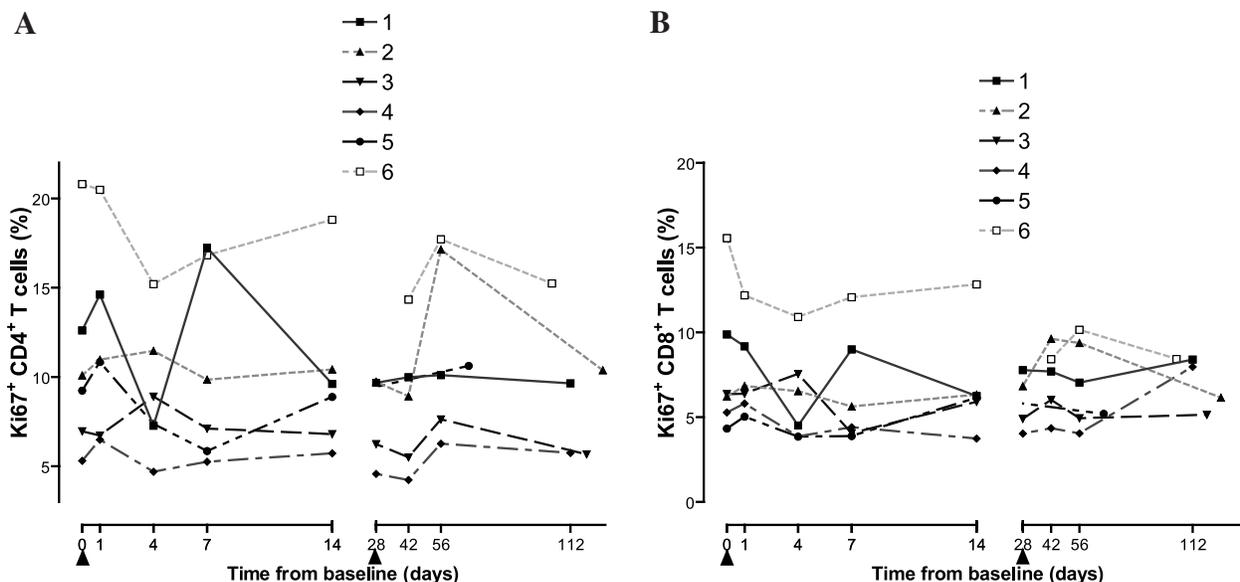


FIG. 3. Percentages of proliferating (Ki67⁺) peripheral blood CD4⁺ and CD8⁺ T cells (A and B, respectively) after administration of IVIG in six HIV-1-infected antiretroviral-naive patients. Arrows indicate the administration of IVIG on day 0 and day 28.

sence of a direct antiviral effect of the IVIG preparation on HIV replication *in vitro* (data not shown), the redistribution of CD4⁺ T cells observed here more likely is the result of a decrease in immune activation than the result of a decrease in pVL.

Since HIV-1 replicates more efficiently in activated CD4⁺ T cells, we expected that the decreased level of immune activation after IVIG administration would result in a lower pVL. Surprisingly, we observed an increase in pVL levels in all six patients during the first days after IVIG administration (Fig. 4B). This increase may have been missed in a previous trial with IVIG in HIV-1-infected patients⁷ because in that study pVL was measured only after 6 days. The increase in CD4⁺ T cells occurred a few days later than the increase in pVL (Fig. 4A), which makes it unlikely that the rise in pVL was due to an increase of potential target cells for HIV-1 replication. A more plausible explanation for the increase in pVL seems to be a temporarily diminished clearance of immune complexes containing HIV-1 virions due to occupation and saturation of Fcγ receptors by administered IgG.^{16,30} Furthermore, anti-idiotypic antibodies in IVIG may bind to anti-HIV antibodies, thereby inhibiting the opsonization of HIV and reducing the efficiency of clearance via Fcγ receptors.^{16,30} Finally, high levels of IgG in blood also saturate FcRn receptors, causing a faster clearance of all IgG, including endogenous anti-HIV-1 antibodies, and thus interfering with opsonization and efficient clearance of HIV-1 virions.³¹ The fact that the increase in pVL was only temporary can be explained by the rapid normalization of IgG concentrations. Alternatively or in addition, anti-idiotypic antibodies that were present in IVIG may have been absorbed by autologous anti-HIV antibodies within a few days after administration.

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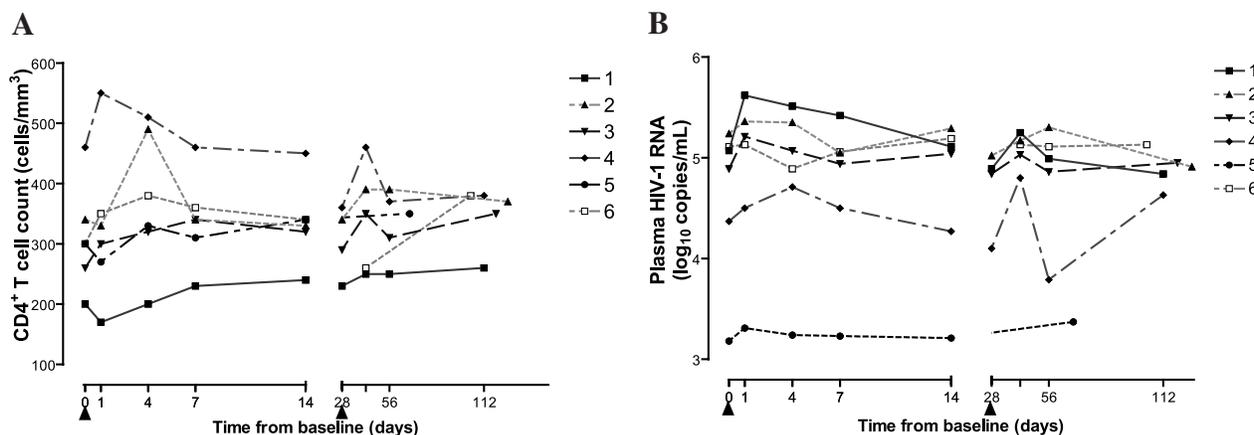


FIG. 4. Peripheral blood CD4⁺ T cell count (A) and plasma HIV-1 RNA (B) after administration of IVIG in six HIV-1-infected antiretroviral-naive patients. Arrows indicate the administration of IVIG on day 0 and day 28.

In a previous study with IVIG in HIV-1-infected patients¹⁷ the increase in CD4⁺ T cell count was more pronounced than what we observed here. In that study the increase in CD4⁺ T cell numbers correlated with a decrease in TNF- α activity. The effect on lymphocyte activation markers was not reported. We did not see any effect of IVIG treatment on TNF- α and other cytokine or complement levels, mainly because these parameters were all below the level of detection at almost all time points. Therefore, the greater increase in CD4⁺ T cell count after IVIG treatment reported previously¹⁷ could be explained by the lower baseline CD4⁺ T cell counts in that study, with a concomitant higher level of immune activation,³² thus allowing relatively more benefit of IVIG treatment.

In conclusion, we observed that IVIG treatment of HIV-1-infected individuals resulted in a temporary decrease in immune activation and a concomitant increase of T cell numbers, despite an increase in HIV-1 antigen exposure. Even though the effects we observed in this study were relatively small as compared to the effects of treatment with HAART and not statistically significant, our results do suggest that immunomodulating therapy in HIV-1 infection could contribute to a prolonged asymptomatic phase. Further studies with more convenient therapies should be performed to evaluate whether immunomodulating therapy can indeed be effective in reducing immune activation and CD4⁺ T cell decline, thus delaying clinical progression and the moment that ART needs to be initiated.

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Address reprint requests to:

Joost N. Vermeulen

IATEC

c/o Academic Medical Center of the

University of Amsterdam

Room T0-111

Meibergdreef 9

1105 AZ Amsterdam, the Netherlands

E-mail: j.n.vermeulen@amc.uva.nl

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