

RAPID COMMUNICATION

Passive Hyperimmune Plasma Therapy in the Treatment of Acquired Immunodeficiency Syndrome: Results of a 12-Month Multicenter Double-Blind Controlled Trial

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High-titer anti-human immunodeficiency virus (HIV) antibodies reduced circulating HIV viral burden and has shown promise in previous small uncontrolled studies, warranting a larger controlled study of passive hyperimmune therapy (PHT) in persons with acquired immunodeficiency syndrome (AIDS). The objective of this study was to determine the efficacy and safety of PHT in 220 AIDS subjects in a 12-month double-blind placebo-controlled dosing study. Subjects were randomized to receive monthly infusions of 500 mL of plasma (full dose), 250 mL of plasma diluted in 250 mL of 5% human serum albumin (half dose), or 500 mL of 5% human serum albumin (placebo). Positive treatment effects oc-

curred only in full-dose-treated subjects with baseline CD4 cell counts between 50 and 200 cells/mm³. Reduced mortality was observed, 1 death in 21 (full dose) versus 3 deaths in 21 (half dose) and 6 deaths in 30 (placebo) ($P = .065$). CD4 cells improved an average of 32.7 cells/mm³ over baseline (full dose) versus 0.9 cells/mm³ (half dose) and a loss of 3.5 cells/mm³ (placebo) ($P = .043$). No adverse effects or toxicity was noted in donors or recipients. Based on these findings, PHT appears to be a safe, promising therapy warranting further study.

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PASSIVE TRANSFER of Igs in the form of whole plasma or fractionated preparations has been used for both the prophylaxis and treatment of infections, complicating primary immunodeficiencies, as well as those secondary to transplantation, chronic leukemia, premature birth, and surgery.¹⁻⁵ Hyperimmune preparations directed against a single organism have been particularly useful in the treatment of cytomegalovirus, hepatitis B, tetanus, vaccinia, and herpes zoster.⁶⁻⁸

Observations by Karpas et al,⁹ that most individuals infected with human immunodeficiency virus (HIV) develop an early vigorous neutralizing antibody response prompted them to passively administer anti-HIV antibodies to symptomatic acquired immunodeficiency syndrome (AIDS) subjects with low antibody titers. In 1988 Karpas et al¹⁰ reported results of a preliminary uncontrolled trial in three AIDS-related complex (ARC) and seven AIDS subjects which demonstrated that HIV was neutralized and cleared after infusion.¹¹ A 22-month follow-up showed that monthly infusions maintained long-term neutralization of viremia, were safe, and appeared to improve laboratory and clinical parameters.¹² Jackson et al¹³ reported on six advanced AIDS subjects treated with high-antibody plasma. HIV antigen was cleared immediately after therapy and antibody titers lasted up to 11 weeks depending on the volume of plasma transfused. Subjects demonstrated fewer opportunistic infections, a transient increase in T lymphocytes, and improved Karnofsky functional scores. More recently Vittecoq et al,¹⁴ in a

controlled study of 18 symptomatic subjects, showed that hyperimmune HIV plasma infused over a 3-month period significantly reduced the number of opportunistic infections compared with HIV-negative plasma. p24 antigen became undetectable in the nine treated subjects compared with no effect in the nine control subjects.

Based on these preliminary studies we undertook a larger double-blind controlled dosing trial to more thoroughly investigate the safety and efficacy of passive hyperimmune therapy in symptomatic HIV disease. The trial was designed to establish treatment-response parameters and to determine the minimum effective dose.

MATERIALS AND METHODS

Study design. A total of 220 subjects with symptomatic HIV disease were randomized to one of three treatment groups: full dose or 500 mL of HIV hyperimmune plasma ($n = 68$); half dose or 250 mL of HIV hyperimmune plasma diluted in 250 mL of 5% human serum albumin ($n = 75$); and placebo consisting of 500 mL of 5% human serum albumin ($n = 77$). Subjects were not restricted by their baseline CD4 cell level. However, because of the widely observed differences in clinical outcomes between subjects with less than 50 CD4 cells/mm³ and 50 to 200 CD4 cells/mm³,^{15,16} a separate analysis for subjects in these two groups was planned. All subjects were required to be on maximum tolerated doses of AZT, ddI, ddC, or any combination thereof to provide a uniform background of antinucleoside drug therapy. All subjects were required to be receiving *Pneumocystis carinii* pneumonia (PCP) prophylaxis. The use of human subjects was in accordance with the ethical standards of the human subject protection committees of the six participating institutions.

Drug (either full or half dose) and placebo was administered monthly, double blind, intravenously through a 40- μ m microaggregate filter from a masked container. Full-dose subjects received an average of 611 U/kg/mo and half-dose subjects 320 U/kg/mo of p24 antibody (units = 1/titer). Subjects received comprehensive clinical and laboratory baseline evaluations before each monthly infusion. Serum for p24 antibody and antigen were frozen and batch-tested at 6-month intervals.

The following criteria were required to qualify as a donor: asymptomatic, a p24 antibody level $\geq 1:256$, p24 antigen-negative, RPR/FTA nonreactive, HTLV-1 nonreactive, HBsAg-negative, HCV-negative, ALT \leq twice the upper limit of normal (110), circulating immune complexes ≤ 40 mg/dL, CD4 cells/mm³ > 400 , isohemag-

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glutinin titer $\leq 1:180$, platelet count $75,000 \text{ mm}^3$ to $500,000 \text{ mm}^3$, total protein 6.0 to 10.0 g/dL , hemoglobin $\geq 12 \text{ g}$, hematocrit $\geq 35\%$; white blood cell (WBC) count $3,000$ to $12,000 \text{ mm}^3$, albumin 3.3 to 5.0 g/dL , gamma globulin 0.6 to 4.5 g/dL , abstinence from medications 12 hours before donation, no experimental AIDS drugs, no body piercing or tattoos within previous 12 months. Active donors received CBC, HCV, HBsAg, RPR, ALT, HTLV-1, p24 antibody, and antigen tested monthly; a lymphocyte subset panel was completed bimonthly; a physical exam was performed every 3 months; an SPEP and Chem 24 panel was completed every 4 months.

Study analysis. Primary endpoints used to evaluate efficacy were mortality, length of survival, number of opportunistic infections, and changes in CD4 cells/mm³ levels. Secondary endpoints included changes in p24 antibody, p24 antigen, serum β -2 microglobulin, and erythrocyte sedimentation rates. The comparison of mortality rates used the Armitage test for linear trend in proportions¹⁷ using an ordering of the dosing categories. Pairwise comparisons of mortality rates and other clinical features in full strength versus placebo were also measured using the standard χ^2 statistic. An intent-to-treat analysis as well as an analysis on those subjects who completed at least three infusions were performed to avoid short-term natural fluctuations in data. To combine laboratory results over the time points collected for each subject, the following statistic was calculated:

$$\frac{\sum_{i=1}^j (X_i - X_0)}{j}$$

where j = number of time points obtained for subjects; X_i = CD4, p24Ab, or p24Ag measurement at time i ($i = 1, \dots, 12$); and X_0 = baseline measurement for X .

Thus, the statistic represents the average monthly result adjusted for baseline. The average value was computed for each treatment group and the results compared using the Kruskal-Wallis test.¹⁸ Survival time data were analyzed by the method of Kaplan and Meier and compared between the treatment groups using Gehan's multigroup version of the generalized Wilcoxon test.¹⁹ Changes in laboratory data and assessment of comparability of the treatment groups were analyzed using the Kruskal-Wallis test. All P values reported were two-tailed, except where noted, with a 5% significance level used throughout. Analyses used BMDP solo (1991 version; Los Angeles, CA).

Hyperimmune plasma harvesting and processing. Asymptomatic HIV plasma donors were selected based on p24 antibody titers of at least 1:256 and CD4 cell counts of at least 400 mm^3 . Donors abstained from all medications either 12 hours before donation or for at least 5 half-lives of any drug and were not on any experimental AIDS treatment. They were required to be negative or nonreactive for RPR, anti-HTLV-I, HBsAg, anti-HCV, and p24 antigen and to have less than 40 mg/dL of circulating immune complexes. An average of 720 mL was collected per donation. Plasma was pooled from 20 to 70 different donors for any product lot to provide a heterogeneous variety of HIV-neutralizing antibodies. Neutralizing

Table 2. Baseline Values for Subjects With Baseline CD4 Cells 50 to 200 mm^3

Variable	Full	Half	Placebo	P*
CD4 cells/mm ³	111.9 \pm 47.6	103.6 \pm 38.1	106.6 \pm 48.9	.86
ESR mm/h	28.5 \pm 14.0	33.9 \pm 16.7	31.6 \pm 15.3	.53
p24 Ab†	330 \pm 705	265 \pm 629	192 \pm 378	.79
p24 Ag	222 \pm 257	201 \pm 364	184 \pm 272	.57
β 2MG	3.07 \pm 1.77	2.98 \pm 1.83	2.72 \pm 1.20	.89

* By Kruskal-Wallis test.

† Excluding 5 outliers of $>1:5,000$.

activity against HIV from final product lots was evaluated by two laboratories²⁰ and broad neutralization activity was observed over a variety of strains.

Two hundred seventy-five donors donated an average of 6.6 times. Twenty-seven percent of the screened individuals qualified on the basis of clinical and laboratory criteria. Active donors received CBC, anti-HCV, HBsAg, RPR, ALT, anti-HTLV-I, p24 antibody, and antigen testing monthly; a lymphocyte subset panel was completed bimonthly; a physical exam was performed every 3 months and an SPEP and Chem 24 panel was completed every 4 months. Donors were excluded if their CD4 cell count decreased to $<400 \text{ cells/mm}^3$ and/or their anti-p24 antibody titer dropped two or more tube dilutions from baseline.

Individual units of plasma were frozen and stored at -20°C or colder within 30 minutes of collection. The individual units of plasma were sterilized using β -propiolactone at a final concentration of 0.25% at a temperature between 20°C and 24°C . Sterilized plasma units were kept overnight for complete hydrolysis of β -propiolactone and then pooled, sterile filtered, and bottled in a pharmaceutical environment. β -Propiolactone has been shown to be highly effective in destroying viruses in human plasma and plasma products and leaves no residual.²¹⁻²⁴

RESULTS

Table 1 reviews the characteristics of all subjects at baseline, and shows no significant differences between the treatment groups. A similar analysis of the characteristics of subjects with CD4 cell levels between 50 and 200 mm^3 is given in Table 2 and shows that the full-strength, half-strength, and placebo groups are similar in their baseline characteristics.

Table 3 shows antinucleoside drug usage as measured by the total number of months of antinucleoside drug therapy as a fraction of study time in the three groups and reveals there to be no significant differences.

Positive clinical and laboratory effects were observed only in the subset of subjects with baseline CD4 cell counts of 50 to 200 mm^3 receiving full-strength drug. Of the 220 subjects enrolled, a total of 72 had baseline CD4 cell counts between 50 and 200 mm^3 (21, 21, and 30 for full, half, and placebo groups, respectively). Another 124 subjects had baseline CD4 counts below 50 mm^3 (40, 44, and 40 for full, half, and placebo groups, respectively). Another 24 subjects had baseline CD4 cell counts over 200 mm^3 and were too small a group to be statistically analyzed.

Fifty-seven deaths were recorded during the 12-month study period including the 30-day period after the subjects' last infusion as shown in Table 4. Two of these deaths (one

Table 1. Baseline Values for All Study Subjects

Variable	Full	Half	Placebo	Kruskal-Wallis (P value)
Karnofsky index	78.8 \pm 14.1	80.4 \pm 13.1	82.4 \pm 13.4	.23
β 2 MG $\mu\text{g/mL}$	3.46 \pm 1.68	3.37 \pm 1.65	2.93 \pm 1.15	.16
ESR mm/h	41.0 \pm 18.9	37.2 \pm 17.2	34.4 \pm 18.2	.09
CD4 cells/mm ³	67.9 \pm 81.1	76.9 \pm 92.7	76.2 \pm 84.9	.84
p24Ab* 1/titer	180 \pm 556	278 \pm 766	148 \pm 447	.61
p24Ag pg/mL	241 \pm 344	173 \pm 323	176 \pm 336	.11

*Excluding 6 outliers of $>1:5,000$ (1 in half dose; 5 in placebo).

Table 3. Antinucleoside Usage/Fraction of Study Time for All Subjects

CD4	Full	Half	Placebo	<i>P</i> (Kruskal-Wallis)
<50/mm ³	.70 ± .33	.64 ± .42	.68 ± .41	.88
50-200/mm ³	.82 ± .26	.87 ± .16	.87 ± .27	.68

full-dose subject and one placebo subject) were non-AIDS related.

In the subset of subjects with baseline CD4 counts of 50 to 200/mm³ the AIDS-related deaths in the three groups were 1/21, 3/21, and 6/30 for full, half, and placebo groups, respectively. These differences reached near statistical significance ($P = .065$) when testing for the natural ordering of dose categories by the Armitage test for trend in proportions (Table 5). In the subset of subjects with baseline CD4 cell counts less than 50/mm³ there was no evidence of survival benefit from full-dose hyperimmune therapy ($16 \nu 16 \nu 11$; $P = .82$). Kaplan-Meier plots of survival time for both subsets of subjects are shown in Figs 1 and 2 and show a favorable trend for full-dose drug in the 50 to 200 CD4 subset, but the number of events was too small to reach statistical significance.

The effects of treatment on CD4 cell counts are shown in Table 6. In the subset of subjects with baseline CD4 cell counts between 50 and 200/mm³, treatment with full-strength drug resulted in a statistically significant increased level of CD4 cells/mm³ ($P = .043$). Subjects with less than 50 CD4 cells/mm³ at baseline showed no significant increase in CD4 cells. In subjects with baseline CD4 counts between 100 and 200 cells/mm³ a greater improvement was observed ($P = .039$).

p24 antibody level increased in the full-dose and half-dose groups compared with placebo. This increase occurred regardless of the baseline CD4 sub-grouping (Table 7). Subjects in the full-dose group, with baseline CD4 cell counts between 50 and 200/mm³, experienced a concurrent, significant increase in CD4 cell counts. This did not occur in subjects with baseline CD4 counts less than 50/mm³.

p24 antigen decreased with full strength more than half strength or placebo in both subsets of subjects (Table 8). A correlation was suggested between an increase in p24 antibody dose and concurrent decrease in p24 antigen (using a cube root transformation $r = .15$, $P = .09$).

There were no significant differences, regardless of baseline CD4 level, between the treated and placebo groups when evaluating opportunistic infections, serum β -2 microglobulin, and erythrocyte sedimentation rate.

Analysis of toxicity. Toxicity was evaluated using clini-

Table 4. Deaths for All Subjects

	Full Dose	Half Dose	Placebo
AIDS-related	18	19	18
Non-AIDS-related	1	0	1
Alive	49	56	58
Total	68	75	77

Table 5. Deaths for Subjects With Baseline CD4 50 to 200/mm³

	Full	Half	Placebo
AIDS-related	1	3	6
Non-AIDS-related	0	0	0
Survivors	20	18	24
Total	21	21	30

$P = .065$ by dose-response trend analysis, test method: Armitage test. $P = .12$ by χ^2 comparing full with placebo.

cal criteria and comparing CBC, platelets, urinalysis, and Chem 24 data between treatment groups. There were no significant differences between the subjects in the treated groups and the placebo group. The most prevalent adverse reaction was a low-grade (<1°F) transient temperature elevation not requiring treatment. However, the morbidity rates for fever were not significantly different among the three treatment groups. There were no withdrawals because of toxicity or adverse reactions. No instances of viral transmission from the plasma were shown.

Two hundred seventy-five donors provided an average of 720 mL per donation and donated an average of 6.6 times each.

A safety analysis was performed to determine if a correlation existed between repeated donations and HIV disease progression as determined by lymphocyte subsets, p24 antibody levels, clinical history, and physical exams. For the 125 donors who had three or more CD4 evaluations: 7 (5.6%) had significantly increased CD4 counts, 6 (4.8%) showed significantly decreased CD4 values (but no value was <200), whereas 112 (89.6%) showed no significant change. No significant group effect based on number of donations was detected. Using a multivariate analysis and controlling for other factors, CD4 cell counts/mm³ slightly increased in repeat donors ($P = .04$).

Among donors with three or more p24 antibody evaluations, 10 donors (5.3%) showed a significant increase; 14 donors (7.4%) showed a significant decrease and 166 donors (87.3%) showed no significant change. No significant group effect was detected.

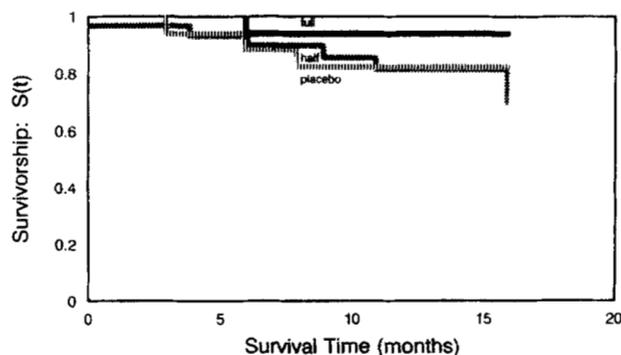


Fig 1. Kaplan-Meier plots showing survival time for AIDS patients receiving full-strength drug, half-strength drug, and placebo for subsets of patients with baseline CD4⁺ cells 50 to 200 cells/mm³.

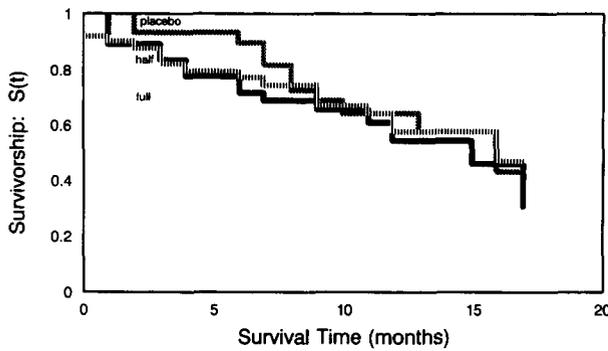


Fig 2. Kaplan-Meier plots showing survival time for AIDS patients receiving full-strength drug, half-strength drug, and placebo for subsets of patients with baseline CD4+ cells less than 50 cells/mm³.

DISCUSSION

Previous studies^{10,13,14} suggested a relationship between passively transferred high levels of neutralizing antibody, reduction in p24 antigen, increased CD4 cell count, and clinical well-being. This study sought to determine, under controlled conditions, not only whether passive hyperimmune therapy (PHT) benefitted AIDS patients, but also to establish disease-response parameters (ie, CD4 cell counts) and to establish an effective dose.

Normal fresh-frozen plasma (FFP) or it's equivalent intravenous Ig (IVIg) was considered as a placebo for our study but was rejected for the following reasons: (1) Studies by Jacobson et al²⁵ and Vittecoq et al¹⁴ have been conducted where HIV hyperimmune plasma was the experimental drug and FFP was the placebo. No improvement (clinical status or CD4 cells) was noted in the subjects receiving FFP. Both studies showed a positive response to the HIV hyperimmune plasma, with the Vittecoq study showing a statistically significant improvement in subjects receiving HIV hyperimmune plasma over normal FFP. (2) A number of clinical trials of IVIg therapy have been performed in HIV+ persons. Although beneficial with regard to bacterial infections in infants and children with AIDS, the results of studies in adults have been disappointing. Brunkhorst et al²⁶ studied 40 patients randomized to either IVIg or no IVIg therapy. The frequency and microbial spectrum of opportunistic infection, the most frequent cause of death, was not influenced in AIDS patients. There was also no affect on CD4+ lymphocyte counts. Schrappe-Bacher et al²⁷ studied 30 patients Walter-Reed categories 3-5, with patients randomized to either IVIg or placebo. They were unable to influence morbidity

Table 7. Changes in p24 Antibody Level Over Study Period

Treatment Group	Baseline CD4 50-200 Cells/mm ³ Mean ± SD	Baseline CD4 <50 Cells/mm ³ Mean ± SD
Full dose	330.8 ± 1,415.1 (n = 21)	4,713.2 ± 28,647.1 (n = 39)
Half dose	-103.4 ± 713.9 (n = 20)	2,907.7 ± 13,796.1 (n = 38)
Placebo	-102.0 ± 298.4 (n = 24)	-91.8 ± 332.3 (n = 34)
	P = .005	P = .001

or mortality with IVIg therapy. Again, no effect was seen on CD4 counts. Mofenson et al²⁸ treated children with IVIg every 4 weeks at a dose of 400 mg/kg and saw a reduction in the seriousness of proven bacterial infections, but there was no difference between IVIg and placebo when measuring opportunistic infections or CD4 cells counts. Mofenson et al concluded that there were no real effects that IVIg had on the progress of HIV disease in children. Therefore, we concluded from this group of studies that, given the end-points of our study, that no appreciable benefit has been observed using IVIg in adults and that this preparation was not necessary to use as a placebo. (3) Additionally, albumin as a control was chosen because of the nontoxic nature both in terms of lack of allergic reactions that can occur with some frequency with FFP or IVIg, and because of the theoretical safety of albumin with regard to the transmission of infectious diseases.

The results of our trial suggested benefit for the subset of patients with baseline CD4 levels between 50 and 200/mm³ who were treated with the higher dose of hyperimmune plasma. In this group of subjects a survival advantage is suggested by the data. Additionally, a significant increase in CD4 cells was also observed. Recipients receiving PHT showed an increase in p24 antibody and a reduction in p24 antigen. The dose of p24 antibody infused showed a positive correlation with a rise in CD4 cells/mm³ from baseline (P = .04). Additionally, the increase in CD4 cells from baseline correlated with improved survival time (P = .0005 by Cox proportional hazard regression) and survival (P = .0048 by linear logistic regression analysis).

The observation that subjects entering with CD4 cell counts between 100 and 200 cells/mm³ showed an even greater average increase in CD4 counts than subjects entering with 50 to 100 CD4 cell/mm³ may suggest that subjects with higher CD4 cell levels (ie, 200 to 400/mm³) would respond more favorably.

Recipients with baseline CD4 cell counts of less than 50 cells/mm³ were unable to increase or maintain CD4 cell levels despite the PHT-induced increases in the levels of circulating p24 antibody and decreases in p24 antigen com-

Table 6. Change in CD4 Cell Counts Over Study Period

Treatment Group	Baseline CD4 50-100 Cells/mm ³ Mean ± SD	Baseline CD4 100-200 Cells/mm ³ Mean ± SD	Baseline CD4 50-200 Cells/mm ³ Mean ± SD	Baseline CD4 <50 Cells/mm ³ Mean ± SD
Full dose	18.4 ± 27.0 (n = 11)	50.2 ± 69.9 (n = 9)	32.7 ± 52.0 (n = 20)	9.1 ± 17.2 (n = 37)
Half dose	-16.1 ± 38.0 (n = 11)	19.3 ± 61.8 (n = 11)	0.9 ± 54.4 (n = 21)	7.8 ± 12.8 (n = 38)
Placebo	8.0 ± 42.6 (n = 16)	-18.9 ± 55.4 (n = 12)	-3.5 ± 49.4 (n = 28)	9.3 ± 16.5 (n = 32)
	P = .054	P = .039	P = .043	P = .820

Table 8. Changes in p24 Antigen Level Over Study Period

Treatment Group	Baseline CD4 50-200 Cells/mm ³	Baseline CD4 <50 Cells/mm ³
	Mean ± SD	Mean ± SD
Full dose	-178.4 ± 240.6 (n = 21)	-223.5 ± 373.2 (n = 39)
Half dose	-80.1 ± 221.1 (n = 21)	-98.0 ± 253.0 (n = 38)
Placebo	-85.6 ± 151.1 (n = 28)	-102.4 ± 309.3 (n = 35)
	P = .320	P = .057

parable to that observed in subjects with 50 to 200 CD4 cell counts/mm³. These observations were consistent with the recently published report of Jacobson et al,²⁵ showing no benefit from passive immunotherapy with anti-HIV plasma in a controlled study of 63 patients with a mean baseline CD4 lymphocyte count of 39 cells/mm³. Furthermore, the study protocol called for infusion of only 250 mL of hyperimmune plasma per month, approximately the same as the half-strength dose in our study.

This study did not confirm the observations of Vittecoq of reduced opportunistic infections in subjects receiving PHT. This may have been caused by the selection of donors based on anti-HIV antibody titer and not for antibodies against the microorganisms responsible for opportunistic infections. In addition, the variability in the application of chemoprophylaxis among co-investigators for opportunistic infections may have precluded true randomization with regard to infection susceptibility. Although the incidence of infection was similar for all groups, more effective immune competence in the full-strength group may have provided a greater ability to resist and overcome infections resulting in reduced mortality.

Our study supports the hypothesis that monthly infusions of a sufficient quantity of anti-HIV antibodies provide adequate blood levels to greatly reduce or eliminate HIV from the circulation, allowing circulating CD4 cells to retain their ability for clonal expansion, thereby increasing CD4 cells and sustaining immune competence improving clinical outcome and survival.

The hyperimmune plasma infusions were well tolerated. There was no serious toxicity or a single withdrawal because of adverse reactions. With regard to donor safety, the study confirmed the observation of Karpas et al,¹⁰ Cummins et al,²⁹ and Vittecoq et al¹⁴ that repeated plasmapheresis neither adversely effects CD4 cell levels or p24 antibody in repeat donors followed over periods up to 1 year. It appears that plasma donations by healthy HIV-infected individuals with CD4 cell counts greater than 400 cells/mm³ is not only safe but may, based on our observation and those of Cummins et al, even be beneficial because most donors maintained or increased CD4 cell counts.

This 12-month double-blind controlled study suggests that PHT may be a promising nontoxic treatment for HIV disease. Further expanded trials of PHT in HIV-infected persons with CD4 cell counts between 50 and 400/mm³ are warranted.

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