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Passive immunotherapy in AIDS: A double-blind randomized study based on transfusions of plasma rich in anti-human immunodeficiency virus 1 antibodies vs. transfusions of seronegative plasma

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ABSTRACT **A randomized double-blind controlled trial was conducted to determine the efficacy of passive immunotherapy in the treatment of symptomatic human immunodeficiency virus (HIV) infection. This trial included 86 symptomatic patients randomized to receive plasma rich in anti-HIV-1 antibody or standard seronegative plasma. Each patient in both groups received a 300-ml infusion every 14 days over a 1-year period, and every 28 days thereafter, in addition to zidovudine and other conventional prophylactic treatments. Plasma donors were selected among symptomless seropositive individuals with a CD4 lymphocyte count ≥400 × 10^6 cells per liter, a negative p24 antigen assay, and a high concentration of anti-p24 antibody. The plasmas were heat-inactivated before infusion. During the study period (day 28–day 365) scheduled by the protocol, clinical benefit from passive immunotherapy was observed in delaying the appearance of the first AIDS-defining event ($P < 0.009$) and reducing the cumulative incidence of such events, which was estimated 3-fold higher in the control group compared to the treatment group. Seven deaths occurred in the treatment group vs. 11 in the control group ($P = 0.27$). A total of 47 patients died or exhibited new AIDS-defining events, 18 in the treatment group and 29 in the control group ($P = 0.009$). No clinical benefit was observed after the 1-year period with infusions performed every 4 weeks. These results indicate a favorable effect of passive immunotherapy on the evolution of advanced AIDS.**

Antiviral drugs active against human immunodeficiency virus (HIV) have demonstrated a limited benefit and may be responsible for important side effects and virus-induced resistance. The principle of passive immunotherapy (PI) in HIV infection, described by Karpas *et al.* (1), consists of infusions of inactivated plasma collected from symptomless HIV-infected individuals. Then, short and uncontrolled studies were based on monthly infusions of HIV-1-positive plasma and suggested a clinical benefit (2, 3). Our group underwent a randomized unblinded short-term trial based on serial infusions of 300 ml of HIV-positive plasma every 2 weeks in patients with AIDS, in comparison with HIV-negative plasma (4), leading to a presumption of short-term efficacy at an advanced stage of the disease. More recently, Jacobson *et al.* (5) identified a trend toward delayed occurrence of a new AIDS-defining event in HIV-positive-plasma-treated patients; in this latter study, a 250-ml infusion of HIV-positive plasma was given to the recipients every 4 weeks. We report the results of a prospective randomized double-blind trial in which symptomatic HIV-infected individuals were allocated to receive 300-ml infusions of HIV-positive plasma every 2 weeks for 1 year, with comparison to a control group receiving the same quantity of HIV-negative plasma with the same frequency.

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MATERIALS AND METHODS

Study Population. The eligibility criteria were as follows: symptomatic HIV infection (stage IV of the Center for Disease Control classification), >18 years old, CD4 lymphocyte count of $<200 \times 10^6$ cells per liter, the same antiretroviral treatment for the last 3 months, free of any evolutive opportunistic infection (OI), and a Karnofsky index of ≥60. Patients with pulmonary Kaposi sarcoma, cytomegalovirus (CMV) retinitis, disseminated infection due to *Mycobacterium avium* complex, or severe diarrhea were excluded. Written informed consent was obtained for all included patients. The trial was approved by the Necker Hospital Ethical Committee.

Study Design. This study was designed as a prospective, multicenter, randomized, double-blind, and controlled clinical trial. A total of 86 patients were recruited in 3 years. After their eligibility was confirmed, the patients were randomly assigned to the treatment groups, according to a blind randomization list. Recipients were infused every 2 weeks and clinically evaluated on the day of the infusion. The study was initially planned not to exceed 1 year. As the primary objective of the study was to determine the efficacy of PI in delaying disease progression among AIDS patients, the primary end point was the time to occurrence of a new AIDS-defining event within this period. This was restricted to the occurrence of an event not previously experienced by the patient. Another end point was the cumulative incidence of new AIDS-defining events within this period, as well as overall survival and disease-free interval (time to either new AIDS-defining event or death). AIDS-defining events were classified as AIDS-defining OI, neoplasms, and other diseases (HIV encephalopathy or HIV wasting syndrome) according to the Center for Disease Control criteria (6). An independent clinical-event committee including three specialists was constituted to validate eligibility for study entry, clinical events, and radiological parameters of all subjects enrolled and to carefully date all confirmed events according to the onset of symptoms. This latter committee was unaware of the randomization list and blindly checked the data. As secondary end points, we also studied and compared in randomized groups the number of days of hospitalization

Abbreviations: PI, passive immunotherapy; HIV, human immunodeficiency virus; CMV, cytomegalovirus; p24 Ag, p24 antigen; ICD, immune complex dissociation; OI, opportunistic infection.

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and the evolution of CD4 lymphocyte count, of p24 antigen (p24 Ag) concentration before and after immune complex dissociation (ICD), and of anti-p24 antibody concentration.

Given the expected immune response delay, the protocol scheduled that AIDS-defining events occurring within the first 28 days should not be analyzed to retain only the events that may be linked to the infusions of HIV-positive plasma. The main analysis was thus restricted to the 28–365 days after the first infusion. Another analysis was performed without such time restrictions.

Treatment Regimen. *Transfusion therapy.* HIV-positive plasma was collected from symptomless HIV-1-seropositive adults who agreed to give plasma every 28 days through plasmapheresis. Prior to each donation, each donor had to fulfill the following criteria: Center for Disease Control stage II/III, CD4 lymphocyte count of $\geq 400 \times 10^6$ cells per liter, nondetectable p24 Ag (ELISA; Abbott), serum concentration of p24 antibody determined by end-point dilution of ≥ 1000 (rDNA; Abbott), absence of hepatitis B surface antigen or presence of both anti-hepatitis B surface and core antibodies, absence of anti-hepatitis C virus antibody, absence of human T-lymphotropic virus antibody, and a serum transaminase level lower than the value excluding blood donations from transfusion use in French blood centers. Donors were suspended from donating their plasma if they did not fulfill all of these criteria. Donors were recruited with information given by physicians and through the participation of associations fighting AIDS; 600 ml of plasma was collected at each donation on a Haemonetics (Braintree, MA) separator. Before infusions to recipients, HIV-positive plasma and HIV-negative plasma were stored at −80°C in a site geographically distinct from that of the blood bank. Plasmas were never pooled. In the 5 h preceding infusion, plasma was heated at 56°C for 30 min to inactivate HIV and then centrifuged. Recipients received 300 ml of plasma infused in 30 min according to ABO blood group compatibility. Both types of heated plasma were contained in similarly labeled bags, so that it was impossible for physicians or recipients to identify the randomization group. Infusions in both groups were performed every 2 weeks for 1 year (i.e., 26 infusions). Periodicity of infusions could not be modified by the occurrence of AIDS-defining events. Due to the presumption of a rebound effect at the withdrawal of PI as observed (4), it was proposed to patients of both groups after the 26th infusion to pursue the trial, in a still blinded fashion. The accrual rate being slower than planned due to the difficulty of obtaining HIV-positive plasmas, an amendment to the protocol was brought concerning the schedule of infusions at the end of the first year. The rhythm of every 4 weeks was, therefore, adopted for the time following the study period of 1 year, with the approval of the Ethical Committee.

Other therapies. In both groups, a switch from zidovudine to dideoxyinosine could be performed at the physician's request according to consensual guidelines. Initial doses of zidovudine and dideoxyinosine were 750 mg/day and 400 mg/day, respectively. Prophylaxis against *Pneumocystis carinii* (aerosolized pentamidine or cotrimoxazole) was pursued or initiated at inclusion for patients of both groups.

Biological Parameters. CD4 lymphocyte count was determined at inclusion and every 3 months. Concentration of p24 Ag was quantified through commercial monoclonal immunoassay (Abbott) before and after the ICD procedure. Anti-p24 antibody concentration was determined by HIV p24 antibody (rDNA; Abbott). Concentrations of p24 Ag and of anti-p24 antibody were retrospectively determined at the end of the study on frozen samples (stored at −180°C). These samples were collected in patients of both groups at inclusion and then immediately before every other infusion during the study period. Serologies for the hepatitis B and C viruses were performed every month in recipients in both groups. CMV viremia was performed at inclusion and every 3 months.

Statistical Analysis. The study sample size (120 patients) was calculated to allow the detection of a 25% increase in 1-year rate of patients free of new AIDS-defining event among the treated patients, by assuming a 1-year rate of 25% in the control group, an α error of 0.05, and a β error of 0.20. During the study, all investigators were blinded to the randomization list. Interim analyses were performed by an independent monitoring board that met four times. At the last review, in July 1993, this board recommended that the study end, given the weak accrual rate and the results of the interim analysis. The statistician was blinded for the identity of assigned therapy until all analyses were computed and conclusions were drawn. The treatment groups were compared for clinical disease progression and survival according to the patient's original treatment assignment (intention-to-treat analysis). Time-censored criteria were estimated by the Kaplan–Meier method and compared with the log-rank test (7). A semiparametric Cox model was applied to estimate unadjusted and adjusted estimates of relative risks of disease progression and death. These adjustments controlled for imbalances of the groups in the following covariates at baseline: p24 Ag and anti-p24 antibody concentrations and CD4 lymphocyte count. The cumulative incidence of events was estimated in both randomized groups through the use of the Nelson–Aalen's estimator, based on a multivariate counting processes approach (8). Nonparametric testing was used to compare randomized groups. All tests of significance were two-tailed. The statistical analysis was performed at the reference date of July 21, 1993, the last update of data from the clinical files and their validation by the independent clinical-event committee.

RESULTS

Study Population. Between May 16, 1990 and April 28, 1993, 86 patients were enrolled in the study (namely, 46 in 1990, 15 in 1991, and 25 thereafter) and were randomized to receive either HIV-positive plasma ($n = 44$) or HIV-negative plasma ($n = 42$). Of the 86 patients, 4 (2 in each group) did not meet the entry criteria and were thus excluded by the independent clinical-event committee. The causes for exclusion were Center for Disease Control stage II, pulmonary Kaposi sarcoma, HIV encephalitis, and severe diarrhea at the time of randomization. Further results only deal with the 82 remaining patients. Table 1 gives the base-line characteristics of the 82 patients: there were no major differences between the two groups. Of the 82 patients, 37 (19 in the treatment group and 18 in the control group) had had from one to three AIDS-defining events before enrollment and 1 patient in the control group developed a new event (*Pneumocystis carinii* pneumonia) between randomization and treatment onset. The first event, which occurred on average 1 year before inclusion, was an OI in 18 (8 in the treatment group and 10 in the control group). The types of OI were similar in both groups. Twenty-one patients had disseminated cutaneous Kaposi sarcoma on study entry. All patients of both groups had anti-CMV antibodies. A positive CMV viremia was observed in 7 patients, 4 in the treatment group and 3 in the control group. The median length of follow-up from the time of randomization was 28 months (range, 3–38 months). The first plasma infusion was administered at day 15 of randomization on average (range, 1–88 days). Of the 82 studied patients, none was lost to follow-up. The median number of plasma infusions was 26 (range, 7–53). During the study period of 1 year, 1733 infusions were performed; after day 365, 373 infusions were performed. Furthermore, no antiretroviral therapy discontinuation was observed; a switch from zidovudine to dideoxyinosine was performed in 2 patients (1 patient in each group), in both cases at the 19th infusion.

Clinical Data over the Study Period (Day 28–Day 365, Infusions Every 2 Weeks). *Time of occurrence of a new*

Table 1. Demographic and baseline characteristics of the 82 HIV-infected patients included in the trial

Parameter	Control group (n = 40)	Treatment group (n = 42)	Total (n = 82)
Age, years	41 ± 10	39 ± 10	40 ± 10
Male, no.	36 (90%)	38 (90%)	74 (90%)
Homosexual or bisexual, no.	35	37	72
Other risk factors, no.	5	5	10
Before enrollment			
AIDS patients, no.	18 (45%)	19 (45%)	37 (45.1%)
First AIDS-defining event			
Kaposi sarcoma, no.	8 (20%)	11 (26%)	19 (23.2%)
OI, no.	10 (25%)	8 (19%)	18 (22%)
Days since first event	308 ± 416	371 ± 349	340 ± 379
No. patients with AIDS-defining events			
One event	14 (35%)	13 (31%)	27 (33%)
Two or more events	4 (10%)	6 (14%)	10 (12.2%)
At enrollment			
Patients receiving zidovudine, no.	37 (92.5%)	41 (97.6%)	78 (95.1%)
Patients receiving dideoxyinosin, no.	3 (7.5%)	1 (2.3%)	4 (4.8%)
Days since initiation of antiviral therapy	790 ± 402	653 ± 366	720 ± 388
Patients receiving pentamidine aerosolized, no.	38 (95%)	39 (92.8%)	77 (93.9%)
Patients receiving cotrimoxazole, no.	2 (5%)	3 (7.2%)	5 (6%)
Patients receiving pyrimethamine, no.	7 (16.6%)	6 (15%)	13 (15.8%)
Patients receiving disulone, no.	2 (5%)	0 (0%)	2 (2.4%)
At first infusion			
Days since enrollment			
Patients, no.	19 ± 20	12 ± 9	15 ± 16
CDC IVA	4 (10%)	7 (17%)	11 (13.4%)
CDC IVC2	17 (42.5%)	16 (38%)	33 (40.2%)
CDC IVD	5 (12.5%)	8 (19%)	13 (15.8%)
CDC IVC1	14 (35%)	11 (26%)	25 (30.5%)
Karnofsky index, %	91 ± 12	88 ± 14	89 ± 13
Body weight, kg	63 ± 8	65 ± 9	64 ± 8
CD4 lymphocyte count, no. × 10^{-6}/liter	46 ± 40	43 ± 36	44 ± 38
p24 Ag, pg/ml	36 ± 55 (n = 39)	29 ± 38 (n = 41)	32 ± 47
Patients with nondetectable p24 Ag, no.	14 (36%)	20 (50%)	34 (43%)
ICD-p24 Ag, pg/ml	62 ± 78 (n = 39)	54 ± 80 (n = 41)	58 ± 79
Patients with nondetectable ICD-p24 Ag, no.	10 (26%)	16 (39%)	26 (33%)
Anti-p24 antibody, end-point dilution	125 ± 430 (n = 39)	301 ± 821 (n = 41)	215 ± 662
Patients with nondetectable anti-p24 antibody, no.	14 (36%)	8 (20%)	22 (28%)

Data are mean ± SD.

AIDS-defining event. Forty-three patients (16 in the treatment group and 27 in the control group) developed at least one new event, OI, neoplasm, or other AIDS-defining diseases. Table 2 summarizes the types of first events (excluding death) experienced by patients in both groups. It appears that the development of toxoplasma encephalitis and CMV infection were the most common first events in both groups, whereas the reported frequency of toxoplasmosis was higher in the control group (25%) than in the treatment group (10%). The median time to the development of a new event after the first infusion was 230 days in the control group and was not reached at the 365th day in the treatment group (P = 0.009, log-rank test) (Fig. 1). The risk of developing a new event was estimated 2.2 times higher in the control group than in the treatment group (95% confidence interval, 1.2–4.2). After adjustments for differences between the treatment groups at baseline in p24 Ag concentration (before and after ICD) and for CD4 and CD8 lymphocyte counts, the relative risk of disease progression in the control group compared with the treatment group increased from 2.2 to 2.8 (95% confidence interval, 1.4–5; P = 0.002).

Cumulative incidence of new AIDS-defining events. Sixty-eight new events were diagnosed in 43 of the 82 patients, 18 events among 16 treated patients and 50 events among 27 control patients. The maximal number of new events per patient was 2 in the treatment group and 6 in the control group. Only 2 treated patients developed 2 or more events vs. 14 in the control group. Cumulative incidence of events was estimated in both groups, with a 2.9-fold increase of risk in the control group (95% confidence interval, 1.7–5.0) compared to the treatment group (Fig. 2).

Survival. Eighteen deaths occurred, 7 in the treatment group (including a suicide) and 11 in the control group (P = 0.27, log-rank test) (Fig. 3). An OI was the cause of death in 3 controls and in 2 treated patients. The risk of death was estimated 1.7 higher in the control group than in the treatment group (95% confidence interval, 0.7–4.4).

Disease-free interval. Forty-seven patients experienced a new event or death within the study period, 18 in the treatment group and 29 in the control group, with a median disease-free interval estimated at 230 days after first infusion in the latter group while not reached in the former (P = 0.009, log-rank test). Further examination of the data showed that 4 patients (2 in both groups) died before developing a new AIDS-defining condition, due to the recurrences of previous events (3 patients) or suicide (1 patient from the treatment group). In the treatment group, 14 patients were hospitalized 20 times for a total of 679 days; in the control group, 20 patients were hospitalized 34 times for a total of 1379 days.

Clinical Data over the Entire Follow-Up Period (Day 1–Day 365, Infusions Every 2 Weeks; After Day 365, Infusions Every 4 Weeks). *Time of occurrence of a new event.* At the reference date, 57 patients had developed a new AIDS-defining event after randomization, 28 patients in the control group and 29

Table 2. New AIDS-defining events observed in patients receiving HIV-positive plasma (treatment group) or HIV-negative plasma (control group)

	Within day 28–day 365			
	Control group (n = 40)	Treatment group (n = 42)	Before day 28 (n = 82)	After day 365 (n = 21)
New events, no.	20	11	4	6
OI, no.				
Pneumocystis pneumonia	0	0	0	1
Toxoplasma encephalitis	10	4	3	0
CMV infection	6	5	1	3
Esophageal candidiasis	1	0	0	2
Cryptosporidiosis	1	1	0	0
Mycobacterium avium	2	1	0	0
Neoplasms, no.	4	3	0	1
Kaposi sarcoma	4	2	0	1
Lymphoma	0	1	0	0
Other diseases, no.	3	2	0	3
Wasting syndrome	2	1	0	1
HIV encephalitis	1	1	0	2

in the treatment group (P = 0.49, log-rank test). Four patients in the treatment group vs. none in the control group developed an OI in the period from day 1 to day 28, consisting of toxoplasma encephalitis (n = 3, at day 11, day 16, and day 20) and one CMV infection (at day 13). Finally, after the first year of study, when 21 patients were still exposed (15 in the treatment group and 6 in the control group), 1 new patient in the control group vs. 9 patients in the treatment group developed a new event.

Cumulative incidence of new events. A total of 106 events was observed, 47 in the treatment group and 59 in the control group; the risk of an event was estimated 1.4-fold higher in the control group than in the treatment group (95% confidence interval, 0.96–2.07).

Survival. Of the 82 patients, 46 died after randomization, 21 in the treatment group (3 of 21 were suicides) and 25 in the control group (P = 0.25, log-rank test). The risk of death over the entire follow-up period was estimated 1.4 times higher in the control group (95% confidence interval, 0.8–2.5).

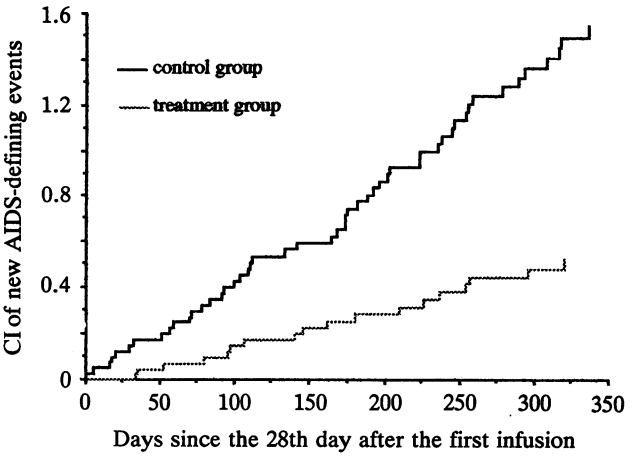

FIG. 2. Cumulative incidence (CI) of new AIDS-defining events (excluding recurrences of previous events) over the study period (days 28–365 after first infusion) in patients receiving HIV-positive plasma (treatment group) or HIV-negative plasma (control group).

Biological Data. In both groups, no significantly different decrease in CD4 lymphocyte counts from baseline was observed: 55% of the patients in the control group and 57% of those receiving PI had a decreased CD4 lymphocyte count $<10 \times 10^6$ cells per (P = 0.28, log-rank test). Among the patients having a baseline detectable p24 antigenemia, p24 Ag was found negative on at least two successive samples in all treated patients within a median time of 77 days after the first infusion vs. 6 of 25 controls in a median time not reached at 1091 days (P = 0.0001, log-rank test). Among the same patients, 13 of 25 treated patients had a negative p24 Ag after ICD with a median delay of 310 days after the first infusion vs. 5 of 29 controls with a median delay not reached at 1091 days (P = 0.0006, log-rank test). A difference of ICD-p24 Ag level was observed over time between both groups. The reappearance of a detectable p24 Ag was less frequent in the treatment group

	Number of exposed patients						
Group	D50	D100	D150	D200	D250	D300	D350
Control	35	29	25	23	15	10	7
Treatment	42	38	30	24	22	19	17

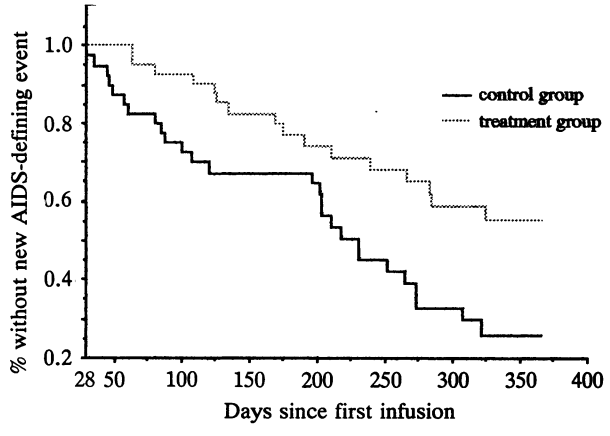

FIG. 1. Estimated time to occurrence of a new AIDS-defining event within the study period (days 28–365 after first infusion) in patients receiving HIV-positive plasma (treatment group) or HIV-negative plasma (control group). D, days since first infusion.

	Number of patients						
Group	D50	D100	D150	D200	D250	D300	D350
Control	40	40	36	33	30	26	23
Treatment	42	41	37	33	31	30	27

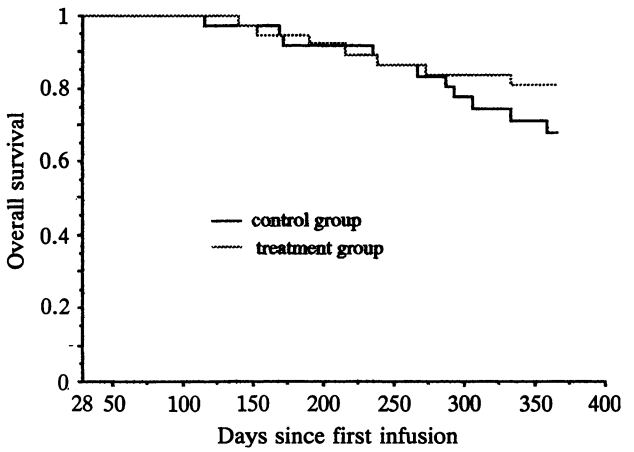

FIG. 3. Survival over the period from day 28 to day 365 after first infusion in patients receiving HIV-positive plasma (treatment group) or HIV-negative plasma (control group). D, days since first infusion.

(5 of 21) than in the control group (2 of 6). A reappearance of detectable ICD-p24 Ag was observed in 10 patients, all belonging to the treatment group. Among the 34 patients without baseline detectable p24 Ag, the appearance of p24 Ag was significantly less frequent and more delayed in treated patients (3 of 21) with a median delay of 861 days compared to a median delay of 567 days in control patients (5 of 13) ($P = 0.02$, log-rank test). Anti-p24 antibody, which was undetectable in 22 patients of the treatment group at study entry, became detectable or superior to the baseline value in all cases on the first sample collected after the first HIV-positive plasma infusion and remained detectable during the transfusional period. Over the study period, a positive CMV viremia was observed at least one time in 4 treated patients vs. 10 control patients.

Discontinuation and Safety of Treatment. No patient was withdrawn from the trial because of a side effect. Three control patients decided to cease the infusions before completion of the scheduled 26 infusions. Violation of the protocol occurred only once; a high concentration of anti-p24 antibody was retrospectively observed in a control patient having at inclusion an undetectable concentration; he received HIV-positive plasma in another country. The main causes of treatment discontinuations were progression of the disease (including death): 7 in the control group (3 within the first year and 4 after the first year) and 4 in the treatment group (all after the end of the study period) refused to pursue on a personal basis. The infusions were well-tolerated. The incidence of urticarial episodes was similar in both groups (14 in treatment group vs. 15 in control group over the study period). No seroconversion to hepatitis B and C viruses was observed.

Decision for the Patients of the Control Group. Due to the clinical benefit observed, all study participants receiving HIV-negative plasma were offered the opportunity to receive HIV-positive plasma, with the approval of the Ethical Committee.

DISCUSSION

The results obtained in this study show that plasma from symptomless HIV-infected individuals can slow down disease progression when passively administered to AIDS patients. These results confirm and extend preliminary open label pilot studies performed by our group (4) and others (2, 3). Indeed, within the first year of treatment, when administered every 2 weeks, PI was found to be efficacious in delaying disease progression. Moreover, PI provided a reduction in the cumulative incidence of AIDS-defining events, with a 2.9-fold estimated decrease of cumulative risk in the treatment group compared to the control group. This study was conceived to reach clinical end points in a double-blind fashion. Experience gained from our previous study (4) brought knowledge of two parameters important from an ethical view point: the problem involved in obtaining sufficient quantities of HIV-positive plasmas and the risk of a rebound effect at withdrawal, which led us to continue with the infusions after the end of the study period. The cumulative incidence of AIDS-defining events appears a pertinent end point to establish the benefit of treatment in HIV infection. We promoted as major end points the evolution of events rather than the survival, which is an end point difficult to reach.

The clinical benefit did not persist after the end of the study period. It cannot be determined at the present time whether this deterioration was due to the natural progression of the disease in patients at a very advanced stage of HIV infection. Alternatively, it might have been due to the reduction in the amount of infused plasma that occurred at the end of the study period. Accordingly, the less beneficial effects reported by Jacobson *et al.* (5) could be due to the smaller amounts of plasma (namely, 250 ml given once a month, while we gave 300 ml every 2 weeks). We did not observe the rebound phenomenon noticed during our previous trial, because the infusions of HIV-positive plasmas were pursued beyond the study period (although at a reduced rhythm). Finally, the small sample sizes after the 1-year study do not allow us to make conclusions.

PI appeared free of any side effect. There was no suggestion whatsoever of any clear case of disease acceleration, as could have been anticipated from *in vitro* data suggesting the enhancement of HIV infection by anti-HIV antibodies (9). Overcontamination of the recipients by HIV was prevented by heating the infused plasma; as reported (4), no plasma viremia was observed when inoculating phytohemagglutinin-stimulated peripheral blood mononuclear cells with heat-inactivated HIV-positive plasma and measuring both reverse transcriptase activity and p24 Ag in cell-free supernatants.

The mechanisms of the protective effect of PI remain unclear. One may assume that anti-HIV antibodies could constitute an important therapeutic factor. The mode of action of the infused antibodies more probably relates to the clearance of the neutralized extracellular virus; indeed, the level of ICD-p24 Ag assay in the treatment group compared to controls indicated that the complexing of p24 Ag with specific antibody was associated with a slower release of p24 Ag. One cannot exclude, however, that other known or unknown factors present in HIV-positive plasma did not intervene.

Our results suggest that PI is safe and offers a clinical benefit. However, if PI could take place in the therapeutic arsenal against AIDS, this approach is limited by the difficulty of obtaining large quantities of HIV-positive plasma, raising the question of the practical feasibility of long-term treatment of large numbers of patients. In our study, the HIV-positive plasma supply was made possible by the solidarity and the generosity of symptomless HIV-infected donors. Furthermore, obtaining HIV-positive plasma could have raised the problem of risking the depletion of protective anti-HIV antibodies in donors, but follow-up studies (10, 11) of HIV-infected donors indicate that plasma donations by healthy HIV-infected individuals do not affect the CD4 lymphocyte count or accelerate the disease progression. The results of this study could open additional paths toward HIV treatment since an *in vivo* benefit was demonstrated, even if *in vitro* mechanisms remain unclear.

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