

## THE IMPACT OF ANTIVIRAL THERAPY WITH ZIDOVUDINE: A RETROSPECTIVE STUDY ON HIV-POSITIVE HEMOPHILIACS IN ITALY

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### ABSTRACT

**Background.** The effects of zidovudine (ZDV) treatment on progression to AIDS are not completely clear. This study evaluated the effects of ZDV treatment on the progression to AIDS in HIV-positive hemophiliacs.

**Methods.** A retrospective study was carried out on HIV-infected hemophiliacs: it included 238 individuals, 119 each from the treated and the non-treated groups. For the group receiving ZDV, we included those for whom a CD4<sup>+</sup> count was available prior (median = 1 month) to beginning therapy. The cumulative incidence of developing AIDS was estimated by the Kaplan-Meier method. To identify factors independently associated with progression to AIDS, a Cox proportional hazards model was used.

**Results.** The cumulative incidence of developing AIDS at 8 years after HIV seroconversion was 10.4% [standard error (SE)=2.8%] for the treated group and 17.1% (SE=3.8%) for the non-treated group. The difference was statistically significant (p=0.01). By multivariate analysis, ZDV therapy and CD4<sup>+</sup> T-cell count >200/mm<sup>3</sup> were the parameters independently associated with a slower progression to AIDS.

**Conclusions.** Treatment with zidovudine seems to slow the progression to AIDS in HIV-positive hemophiliacs.

Key words: hemophiliacs, AIDS, anti-retroviral therapy

Anti-retroviral treatment with ZDV has been shown to reduce mortality among persons with AIDS and AIDS-related complex,<sup>1</sup> and to slow the progression to AIDS in individuals with asymptomatic HIV infection.<sup>2</sup> A randomized, double-blind clinical trial<sup>3</sup> demonstrated that in symptomatic HIV patients early treatment with ZDV delayed progression to AIDS, but it did not improve survival and was associated with more side effects. Furthermore, the Concorde study<sup>4</sup> did not find any significant benefit from the immediate use

of ZDV as compared with deferred therapy in asymptomatic HIV patients in terms of survival or disease progression to AIDS, irrespectively of the initial CD4<sup>+</sup> counts.

The most suitable time for beginning treatment with ZDV has still not been determined;<sup>5</sup> however, various authors have indicated a CD4<sup>+</sup> count less than 500/mm<sup>3</sup> as a starting point for treatment in pre-AIDS phases.<sup>2,6,7</sup> Moreover, prophylaxis against *Pneumocystis carinii* pneumonia has been recommended during pre-AIDS phases in individuals with CD4<sup>+</sup> <200/mm<sup>3</sup>.<sup>8</sup>

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Nonetheless, prolonged treatment with ZDV may result in 1) a reduction of clinical effects,<sup>9</sup> 2) the appearance of *in vitro* resistance,<sup>10</sup> and 3) therapeutic toxicity.<sup>11</sup>

The *Italian Group on Congenital Coagulopathies* (GICC) has been conducting a prospective cohort study on the natural history of HIV infection among hemophiliacs since 1988.<sup>12</sup> The present work is a retrospective, non randomized study aimed at evaluating the effects of ZDV on the progression to AIDS in HIV-positive hemophiliacs.

## Materials and Methods

### Study population

Individual data on persons affected by hemophilia in Italy are collected by the National Hemophilia Registry, which includes data from 1980 to the present.<sup>13</sup>

For the purposes of the present analysis we considered HIV-positive hemophiliacs divided into two groups: the first included persons treated with ZDV (ZDV group) before developing AIDS and for whom a CD4<sup>+</sup> count was available prior to treatment (but after 1987); the second group included those who did not undergo antiviral therapy (untreated group) and who had a CD4<sup>+</sup> count available after 1987 (but before developing AIDS). AIDS diagnosis was based on the Centers for Disease Control and Prevention (CDC) 1987 case definition.<sup>14</sup>

We paired individuals from the ZDV group with those from the untreated group according to CD4<sup>+</sup> T-cell count (three levels: <200/mm<sup>3</sup>, 201-400/mm<sup>3</sup>, >401/mm<sup>3</sup>) and duration of HIV infection. Duration of HIV infection was calculated from HIV seroconversion (estimated by the median under a Weibull distribution)<sup>12,15</sup> to the date in which the CD4<sup>+</sup> count was observed (the last CD4<sup>+</sup> count before treatment in the ZDV group and the last available CD4<sup>+</sup> count in the untreated group).

The average duration of infection was similar among the three groups established according to the levels of the CD4<sup>+</sup> count. However, these three groups were not homogeneous for clinical condition with respect to the decrease in CD4<sup>+</sup>

count over time. This decrease can be considered a proxy for the seriousness of the immunodeficiency, as was done in this study.

### Statistical analysis

We used the BMDP (1D, 2D, 7D, 4F, 1L and 2L applications) statistical package<sup>16</sup> on a SIEMENS 7-890 mainframe [Servizio Elaborazioni Dati, Istituto Superiore di Sanità]. The Kaplan-Meier survival analysis was used to estimate the cumulative incidence of AIDS for all persons included in the study, as well as for different subgroups in order to identify prognostic variables for faster progression. Statistical inferences were made using the generalized Wilcoxon statistics. Categorical data were analyzed by the chi-square and Fisher's exact probability tests.

In order to identify factors independently associated with progression to AIDS, a Cox proportional hazards model was used to generate point estimates and confidence intervals (CI) of relative hazard (RH). The fixed model included age at HIV seroconversion, type of hemophilia, CD4<sup>+</sup> levels and antiretroviral therapy: the stepwise procedure was performed using at each step a P-value of 0.15 as entry criterion and a P-value of 0.15 as removal criterion.

## Results

### Characteristics of the study population

As of December 31, 1993, 6003 cases were reported to the Registry, of whom 3661 (61.0%) were tested for HIV and 820 (22.4%) were found to be HIV positive. Of these, 272 were excluded because of 1) the presence of other risk factors for HIV/AIDS (n=15); 2) no information about treatment with antiviral drugs (n=133); 3) treatment with other antiviral drugs (n=19); 4) no available CD4<sup>+</sup> count before diagnosis of AIDS (n=105). Two hundred seventy-three hemophiliacs treated with ZDV and 275 not treated were considered eligible, but only 119 from each group were able to be paired and included in the study. Patients were randomly selected. Table 1 shows demographic and clinical characteristics of the two groups. At the time of the present analysis, 22

Table 1. Demographic and clinical characteristics of the hemophiliacs studied.

	ZDV group		Untreated group	
	N	(%)	N	(%)
<i>Type of hemophilia</i>				
Severe A	83	(69.8)	78	(65.5)
Severe B	18	(15.1)	24	(20.2)
Other	18	(15.1)	17	(14.3)
<i>Age at seroconversion*</i>				
≤12	28	(23.5)	32	(26.9)
13-34	72	(60.5)	72	(60.5)
>34	19	(16.0)	15	(12.6)
<i>PCP prophylaxis</i>				
	3	(2.5)	0	(0.0)
<i>HIV infection</i>				
Median length*	7.9 (SE=0.2)		8.0 (SE=0.2)	
Median CD4+#	281 (SE=12.7)		333 (SE=14.4)	

\*years; # (cells/mm<sup>3</sup>)

Table 2. Diseases that led to AIDS diagnosis.

	ZDV group		Untreated group		p
	N	(%)	N	(%)	
Pneumocystis carinii pneumonia	7	(31.8)	5	(19.3)	0.25
Esophageal candidiasis	2	(9.2)	2	(7.8)	0.62
Cytomegalovirus infection	1	(4.5)	1	(3.8)	0.71
Cytomegalovirus retinitis	0	(0.0)	1	(3.8)	0.54
Encephalopathy	1	(4.5)	1	(3.8)	0.62
Herpes simplex infection	5	(22.7)	3	(11.6)	0.26
Burkitt's lymphoma	1	(4.5)	0	(0.0)	0.45
Cerebral lymphoma	0	(0.0)	1	(3.8)	0.54
Tuberculosis	0	(0.0)	1	(3.8)	0.54
Multifocal leukoencephalopathy	0	(0.0)	1	(3.8)	0.54
Cerebral toxoplasmosis	2	(9.2)	1	(3.8)	0.43
Other bacterial infections	3	(13.6)	9	(34.7)	0.09
Total	22	(100.0)	26*	(100.0)	

\*for two cases this information was not available

(18.5%) hemophiliacs in the ZDV-group and 28 (23.5%) in the untreated group had developed AIDS, with no significant difference ( $p=0.63$ ). Table 2 shows that there were no statistically significant differences between the two

groups with respect to the type of AIDS indicative disease.

### Overall progression to AIDS

Table 3 present the data regarding the cumulative incidence (CI) of developing AIDS at 8 years from seroconversion for each group: the CI was 10.4% (SE=2.8%) for the ZDV group and 15.7% (SE=3.7%) for the untreated group, with a statistically significant difference between the two curves ( $p=0.01$ ) (Figure 1). This difference was still significant when adjusted for age at seroconversion ( $p=0.05$ ), CD4<sup>+</sup> count ( $p=0.05$ ) and type of hemophilia ( $p=0.002$ ). When the different strata were considered separately, treatment was more efficacious in slowing progression to AIDS among individuals > 34 years ( $p=0.01$ ), among hemophiliacs with a CD4<sup>+</sup> count < 200/mm<sup>3</sup> ( $p=0.02$ ; Figure 2) and among severe hemophilia A patients ( $p=0.003$ ).

No significant difference was found between two dosage regimens: ≤ 500 mg vs. >500 mg (10.3% SE=3.9% vs. 11.9% SE=4.7%;  $p=0.83$ ).

Table 3. Cumulative incidence of AIDS at 8 years from HIV seroconversion for prognostic factors in the ZDV group and the untreated group.

	ZDV group		Untreated group		p
	cumulative incidence (SE)		cumulative incidence (SE)		
Overall	10.4	(2.8%)	15.7	(3.7%)	0.01
<i>Age at seroconversion*</i>					
≤12	11.9	(6.4%)	17.5	(8.1%)	0.11
13-34	8.4	(3.2%)	14.6	(4.5%)	0.33
>34	20.6	(9.0%)	40.2	(16.0%)	0.01
<i>CD4<sup>+</sup> levels#</i>					
≤200	25.2	(7.6%)	37.8	(9.1%)	0.02
>200	4.9	(2.3%)	10.2	(3.6%)	0.46
<i>Type of hemophilia</i>					
Severe A	7.6	(2.9%)	18.9	(5.0%)	0.003
Severe B	15.5	(8.0%)	22.1	(8.7%)	0.18

\*years; # (cells/mm<sup>3</sup>)

@significance of difference between treated and untreated patients, adjusted for stratification variable (see text).

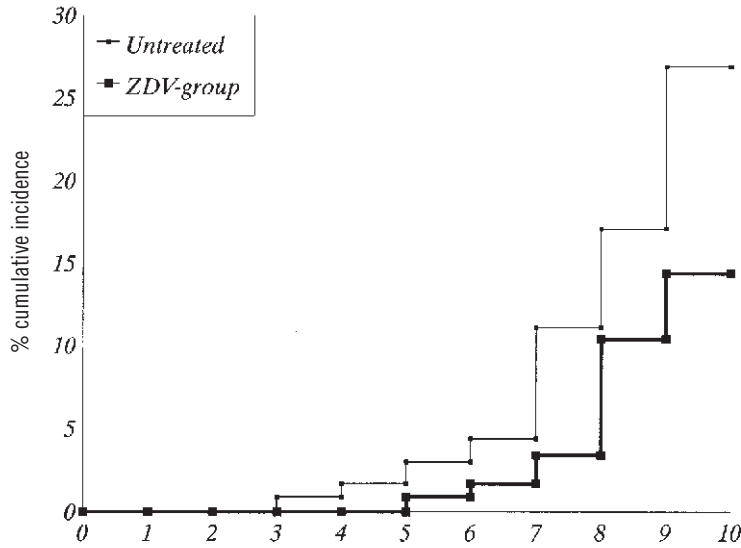


Figure 1. Cumulative incidence of developing AIDS in ZDV group and untreated group.

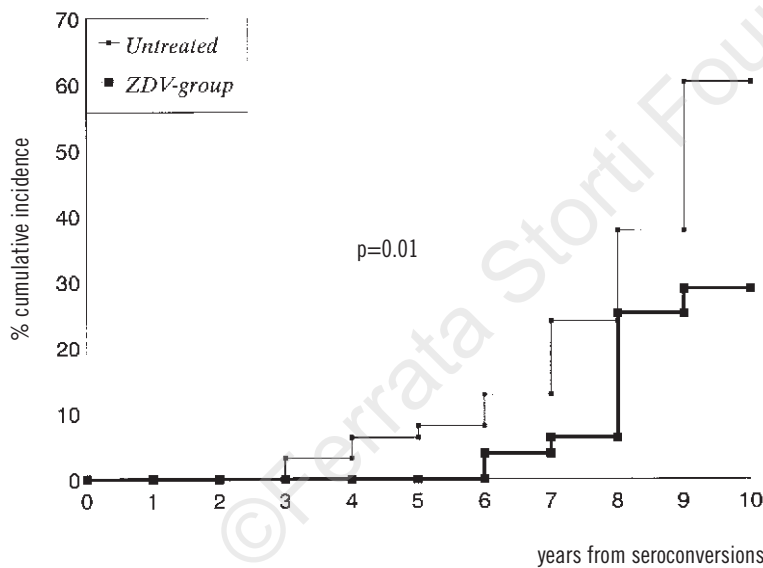


Figure 2. Cumulative incidence of developing AIDS in ZDV and untreated groups stratified by class of CD4+ (<200 cells/mm³).

**Multivariate analysis**

Multivariate analysis showed that two variables were independently associated with a slower progression to AIDS: therapy with ZDV (R.H.=0.38, 95% C.I.=0.20-0.71) and CD4+ count >200/mm<sup>3</sup> (R.H.=0.23, 95% C.I.=0.12-0.41) (Table 4).

**Discussion**

Overall, our results suggest that treatment with ZDV, when compared to no treatment, is

associated with a slower progression to AIDS. How concentrated is the population with respect to the pathogenesis of HIV.<sup>12</sup>

Multivariate analysis shows that ZDV seems to slow the progression to AIDS independently of the CD4+ level. Moreover, HIV-positive hemophiliacs with a CD4+ count > 200/mm<sup>3</sup> have a slower progression to AIDS than the other participants with a much more compromised immune system, and ZDV therapy further slows this progression, as shown by other studies.<sup>2,7,19</sup>

There was no association between the efficacy

Table 4. Relative hazard for different progression factors, Cox proportional hazards model for progression to AIDS.

	Relative hazard	95% CI
Age at seroconversion*		
≤34	1.00	
>34	1.02	0.99-1.04
Type of hemophilia		
Severe A	1.00	
Severe B	0.93	0.48-1.83
CD4 <sup>+</sup> levels#		
≤200	1.00	
>200	0.23	0.12-0.41
Therapy with ZDV		
Untreated	1.00	
Treated	0.38	0.20-0.71

\*years; #(cells/mm<sup>3</sup>)

of the therapy and the type of hemophilia. This phenomenon may be explained by the fact that fewer severe hemophiliac B patients (n=42) were enrolled than severe A hemophiliacs (n=161); nonetheless, among severe B hemophiliacs the rate of progression to AIDS for individuals treated with ZDV was markedly lower (15.2%) than for those not treated (22.1%).

This study seems to confirm that the efficacy of ZDV administered in small dosages (≤500 mg) is the same as that provided by large dosages (>500 mg), suggesting that ZDV should be used at lower dosages, which would perhaps result in reduced toxicity.<sup>2,20</sup>

Our data cannot be used to determine the most appropriate time for initiating treatment with ZDV. Other studies have stressed the importance of the degree of decrease in the CD4<sup>+</sup> count over time in relation to the risk of developing AIDS.<sup>21</sup> More specific studies should be conducted, comparing groups that are homogeneous for clinical severity of the disease,<sup>4,22</sup> that is, for the rate of decrease in CD4<sup>+</sup> count over time.

Possible biases in this study are represented by imperfect matching for clinical status and better overall medical care of treated patients. Besides, it should be mentioned that ZDV only became available in Italy in 1988. Consequently,

the number of studies and the length of observation periods are probably not sufficient for clearly establishing the effect of ZDV therapy in HIV-positive hemophiliacs in relation to different prognostic factors.

In conclusion, ZDV therapy seems to modify the natural history of HIV infection,<sup>23</sup> slowing the progression to AIDS in asymptomatic HIV-positive hemophiliacs. Next, a study will be carried out to evaluate the efficacy of ZDV on other end-points, such as survival, considering the population enrolled in this study.

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## Appendix

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*National Institute of Health, Rome:* D. Greco, NS, AG, RA, R. Bellocco, M. Palombi, L. Zanetti, (Laboratory of Epidemiology and Biostatistics, National AIDS Center); F. C., M. P. (Laboratory of Organ and System Pathophysiology).

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