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Original Article

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Survival of patients receiving zidovudine before or after AIDS diagnosis: results of a German multicenter study

German AIDS Study Group*,**

Summary. While efficacy of zidovudine (ZDV) in the acquired immunodeficiency syndrome (AIDS) is well established, the issue of survival after early ZDV treatment is still controversial. To assess survival benefits of ZDV treatment prior to AIDS, as compared to treatment after the onset of AIDS, we used an observational analysis of infected individuals infected with human immunodeficiency virus treated with ZDV and/or prophylaxis against *Pneumocystis carinii* pneumonia prior to or after AIDS in comparison to patients never treated with ZDV. Nine German AIDS treatment centers entered case reports dating from January 1988 to January 1992. A total of 1425 HIV-infected patients were included, mainly homo-/bisexuals: 1338 males and 87 females, with a mean age of 38.9 years. Of these, 262 had received ZDV prior to AIDS, 376 after AIDS, and 787 had never received ZDV. Survival from a first CD4 lymphocyte count below 0.200×10^9/l (or below 0.500×10^9/l) to death was assessed by means of Kaplan-Meier analysis. Survival did not differ significantly when the first CD4 count below 0.200×10^9/l was taken as baseline. The median survival of patients receiving ZDV prior to AIDS was 662 days as compared to 572 days in patients treated after AIDS. Patients with earlier therapy showed longer survival in a subset of patients who were observed from their first CD4 count below 0.500×10^9/l. Additional PcP prophylaxis significantly improved survival in all groups. We conclude that survival from the first CD4 count below 0.200×10^9/l to death does not differ in patients receiving ZDV prior to or after AIDS. Additional PcP prophylaxis improves survival in ZDV-treated patients and patients without ZDV.

Key words: HIV – AIDS – Zidovudine – Survival – *Pneumocystis carinii* pneumonia prophylaxis

The antiretroviral agent zidovudine (ZDV) has been shown to improve survival in individuals with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex [6, 15]. Moreover, the time of progression to AIDS is prolonged in patients receiving zidovudine in early-stage asymptomatic infection with human immunodeficiency virus [7]. ZDV- resistant strains of HIV have been identified mainly in patients treated for a period of at least 6 months [12] and the prevalence of strains showing resistance to ZDV seems to increase with duration of therapy [2]. The beneficial effect of ZDV on CD4 lymphocyte counts is known to occur in the first 3 months of therapy [3], and a return to baseline levels is commonly observed. These facts raise the question of how long HIV-infected individuals benefit from treatment with ZDV, especially if they start treatment during the asymptomatic stages of HIV infection. There are conflicting results concerning this question in the recent literature [5, 11]. Hamilton and colleagues [10] reported data from the Veterans Affairs Cooperative Study which revealed no significant prolongation of survival in a prospective trial of early treatment. Graham et al. [9] on the other hand, who analyzed data from the Multicenter AIDS Cohort Study in a retrospective observational analysis, supported the hypothesis that early treatment improves survival at up to 18 months observation period in addition to slowing the progression to AIDS [9]. Results of prospective clinical trials addressing the issue of survival after early ZDV, such as the Concorde trial

Abbreviations: AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus (type 1); MACS = Multicenter AIDS Cohort Study; PcP = pneumocystis carinii pneumonia; ZDV = zidovudine

*Participating centers (order according to number of patient's files in the study): Kamps B, Brodt HR: Zentrum der Inneren Medizin, Universität Frankfurt; Arastéh K, Heise W: II. Innere Abteilung, Auguste-Viktoria-Krankenhaus, Berlin; Sadri I, Goebel F-D: Medizinische Poliklinik, Universität München; Schedel I: Abteilung Immunologie, Medizinische Hochschule Hannover; Runge J, Schwander S: Bernhard Nocht Institut für Tropenmedizin, Hamburg; Jablonowski H, Szelenyi H: Medizinische Klinik und Poliklinik, Universität Düsseldorf; Emminger C, Loch O: IV. Medizinische Abteilung, Krankenhaus München-Schwabing; Schöfer H, Hochscheid I: Zentrum der Dermatologie, Universität Frankfurt; Baumgarten R: Krankenhaus Prenzlauer Berg, Berlin

**Manuscript preparation and corresponding address: J.R. Bogner

in Europe, and the continuation of the AIDS Clinical Trials Group protocols 016 and 019 [16] are not to be expected until 1993/1994. Therefore a retrospective observational analysis of survival seemed a reasonable tool to evaluate survival until further prospective observations are available.

We performed a multicenter observational analysis of survival in patients receiving ZDV either before or after AIDS diagnosis, taking into account the effects of prophylaxis for *Pneumocystis carinii* pneumonia (PCP) prophylaxis.

Patients and methods

Nine collaborating clinical centers in Germany performed a retrospective analysis of patients with HIV infection and AIDS. Files for each patient included sex, age, risk group, date of first CD4 count below 0.200×10^9/l, date of first CD4 count below 0.500×10^9/l, date of treatment initiation, date of AIDS diagnosis, AIDS defining condition, date of PcP and/or relapse of PcP, date of first PcP prophylaxis, date of death, and date of last visit.

The first complete year of approval of ZDV in Germany was 1988. Therefore all files with a date of a first AIDS defining condition before January 1988 were excluded from the analysis. Thus, comparison of treatment groups to historical patients without ZDV therapy and systematic errors in evaluation were ruled out. Of 3180 reported files, 1425 fulfilled this criterion and were included in a Kaplan-Meier survival analysis (January 1988 to January 1992). Only patients who developed AIDS at any time during the observation period were included for analysis ($< 0.200 \times 10^9$/l CD4 count to death). A CD4 count aobve 0.200×10^9/l was not necessary for inclusion (i.e., patients who first presented with a count below 0.200×10^9/l were also included for analysis). For 1010 patients absolute numbers of CD4 counts were also reported for the date of the first CD4 count below 0.200×10^9/l.

For another 345 patients a CD4 count was available dating form the first CD4 count below 0.500×10^9/l.

Only patients who had taken at least 50 g of ZDV were included in the treatment groups. This equaled a treatment period of 50–100 days depending on the daily dose, which tended to be higher in the early period after approval as compared to a standard dosage of 500 mg in 1990–1992. Assessment of treatment duration and reasons for interruption or cessation was not the objective of our study because an observational study additionally includes the practicability and feasability of therapy in a general clinical setting. PcP prophylaxis was given either as aerosolized pentamidine ($n = 559$, 93.5%), cotrimoxazole ($n = 2$, 0.3%), or fansidar ($n = 37$, 6.2%).

For analysis of survival on ZDV treatment patients were stratified into three groups: group 1, ZDV prior to AIDS; group 2, no ZDV; and group 3, ZDV after AIDS. For analysis of survival taking into account ZDV and PcP prophylaxis each group was dichotomized into patients receiving or not receiving PcP prophylaxis, as follows:

- Group 1a: ZDV prior to AIDS, no PcP prophylaxis
- Group 1b: ZDV prior to AIDS, PcP prophylaxis
- Group 2a: no ZDV, no PcP prophylaxis
- Group 2b: no ZDV, PcP prophylaxis
- Group 3a: ZDV after AIDS diagnosis, no PcP prophylaxis
- Group 3b: ZDV after AIDS diagnosis, PcP prophylaxis

For a total of 1425 patients sufficient data could be included in the analysis. There were 87 females and 1338 males. The mean age was 38.9 ± 9.6 years. There were 1123 (79%) homo/bisexual men and 157 (11%) intravenous drug users, 38 (3%) had received blood or blood products, 64 (4%) were heterosexuals, and for 43 (3%) the mode of infection with HIV remained unknown. The most frequent AIDS-defining diagnosis was PcP, occurring in 523 patients (37%), followed by Kaposi'sarcoma in 214 (15%) and esophageal candidiasis in 180 (13%). Patient groups 1 to 3 and subgroups a/b in our analysis did not differ significantly in sex, risk group distribution, age, or first AIDS-defining condition. Baseline characteristics of CD4 count, total leukocyte count and hemoglobin levels are shown in Table 1.

For survival analysis, actuarial survival probability curves were plotted according to the method of Kaplan and Meier, using the SPSS subroutine. Different survival curves and medians of survival were compared using the nonparametric generalized Lee-Desu test [13]. Analysis of baseline characteristics of different groups was performed by Student's t test and analysis of variance. Additionally, to determine the importance of different covariates a stepwise regression model was calculated.

All calculations were performed using the survival analysis routines of SPSS in the biometrics center of the German AIDS Study Group.

Results

Survival from first CD4 count below 0.200×10^9/l to Death

A total of 638 patients received ZDV while 787 had not received ZDV for various reasons. Information on the reason of ZDV nontreatment was not included in the report forms. In patients with known

Table 1. Baseline characteristics of treatment groups

	Group	PcP prophylaxis	*n*	CD4 cells ($\times 10^9$/l)	Leukocytes ($\times 10^9$/l)	Hemoglobin (g/l)
ZDV prior to AIDS	1		262	0.076±0.055*	4.10±1.77*,***	123±20**
	1a	No	105	0.070±0.059	3.80±1.85	118±24
	1b	Yes	157	0.079±0.053	4.38±1.67	128±15
No ZDV	2		787	0.060±0.054	5.19±2.99	119±19***
	2a	No	602	0.061±0.054	5.24±2.83	119±19
	2b	Yes	185	0.059±0.053	5.01±3.55	119±19
ZDV after AIDS	3		376	0.067±0.055	4.70±2.32	124±19
	3a	No	120	0.065±0.050	4.58±2.31	118±18
	3b	Yes	256	0.068±0.057	4.75±2.33	125±19

* $P<0.01$ versus group 2; ** $P<0.05$ versus group 2; *** $P<0.05$ versus group 3

reason the most frequent explanation was refusal because of possible adverse effects. However, baseline characteristics (Table 1) demonstrate that leukocyte counts were higher in patients without ZDV, and that anemia is an unlikely reason for nontreatment because patients in group 2 showed only slightly lower hemoglobin levels compared to treatment groups ($P < 0.05$). Kaplan-Meier survival curves are given in Fig. 1.

Median survival of patients in group 1 was 662 days compared to 273 days in group 2 ($P < 0.001$) and 572 days in group 3 ($P < 0.001$, versus group 2). Group 1 versus group 3 showed no significant difference. Baseline CD4 counts of groups 1 and 3 were not significantly different ($0.076 \times 10^9 \pm 0.055$ versus $0.067 \times 10^9 \pm 0.055$/l; NS) while groups 1 and 2 showed a mean difference of 0.016×10^9/l ($0.076 \times 10^9 \pm 0.055$/l versus $0.060 \times 10^9 \pm 0.054$/l; $P < 0.001$).

The median time from start of treatment with ZDV to AIDS was 301 days in group 1. The median time from AIDS diagnosis to initiation of ZDV treatment was 61 days in group 3. The average CD4 count at initiation of therapy was $0.130 \pm 0.106 \pm \times 10^9$/l in group 1 (known for $n = 151$) and $0.076 \pm 078 \times 10^9$/l in group 3 ($n = 271$).

Survival from first CD4 count below 0.500×10^9/l to death

For 349 patients the date and absolute count of a first CD4 value below 0.500×10^9/l were available. Nineteen of 80 patients who received early ZDV at

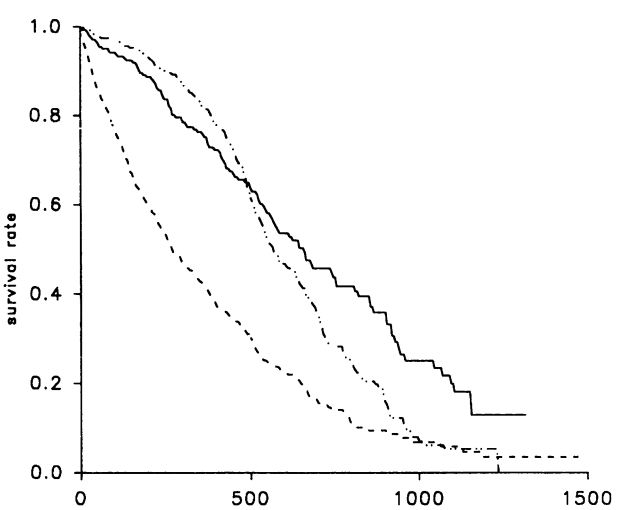

Fig. 1. Effect of ZDV on survival of patients with HIV infection in days from a first CD4 lymphocyte count below 0.200×10^9/l to death as estimated by Kaplan-Meier analysis. There is no significant difference between treatment groups 1 (early ZDV prior to AIDS diagnosis, –; $n = 262$, median 662 days) and 3 (ZDV after AIDS, – · · –; $n = 376$, median 572 days). Both groups show longer survival than patients never treated with ZDV (group 2, – – –; $n = 787$, median 273 days)

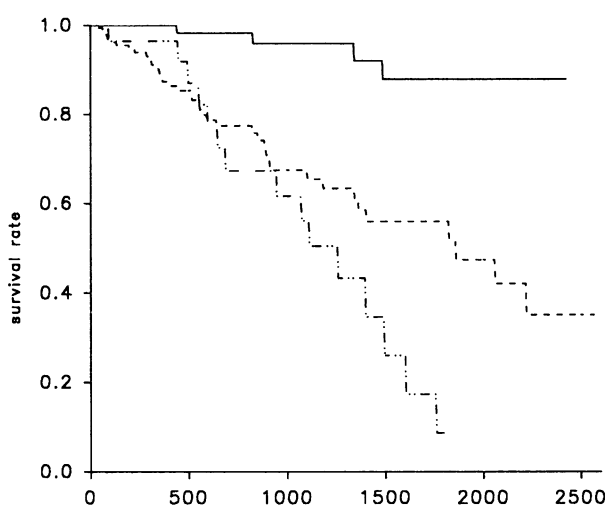

Fig. 2. Effect of ZDV on survival of a subset patients in days from a first CD4 lymphocyte count below 0.500×10^9/l to death as estimated by Kaplan-Meier analysis. Significant survival advantage for patients on early ZDV (prior to AIDS). – ZDV prior to AIDS ($n = 80$); – – –, no ZDV ($n = 241$); – · · –, ZDV after AIDS diagnosis ($n = 28$)

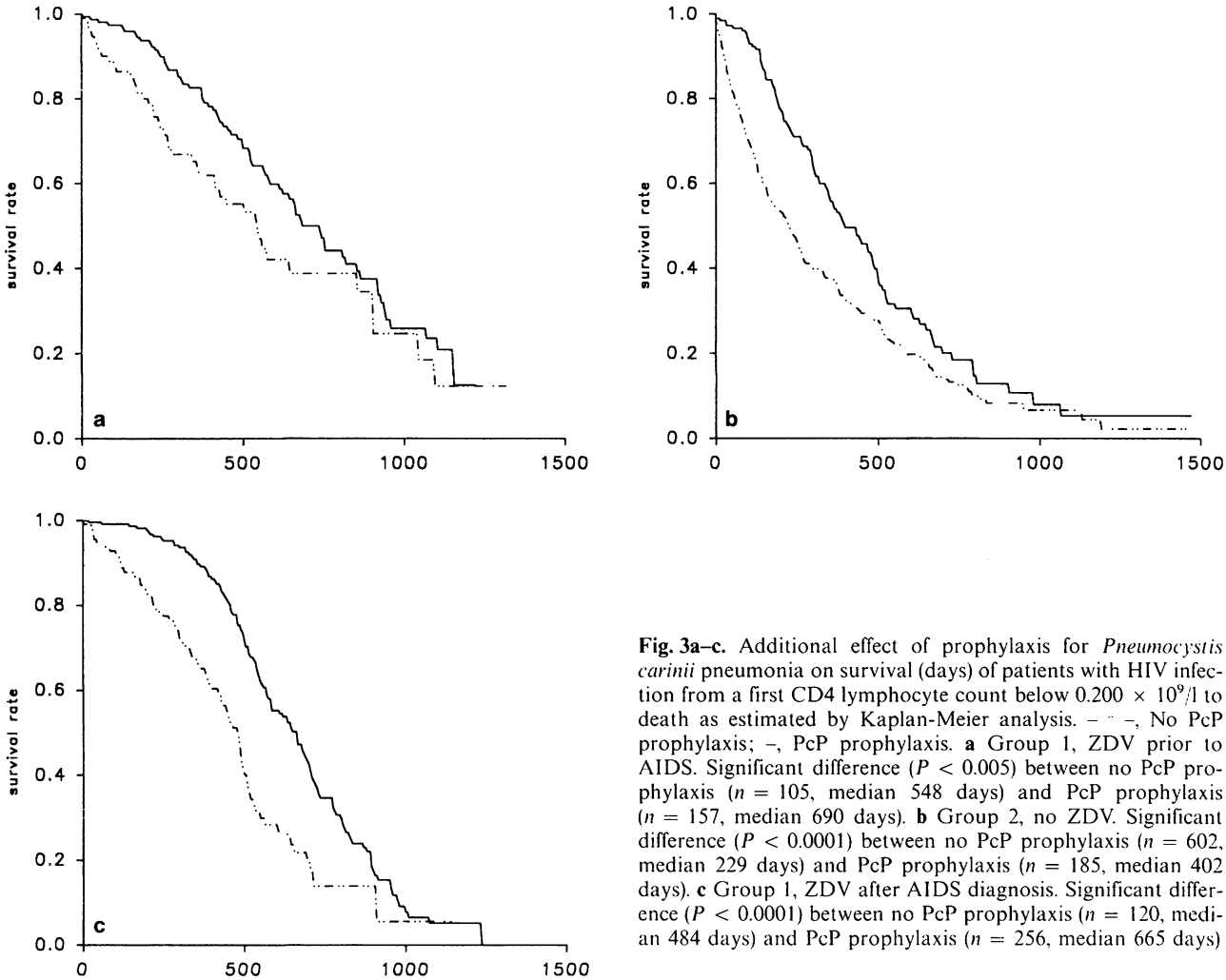

Fig. 3a–c. Additional effect of prophylaxis for *Pneumocystis carinii* pneumonia on survival (days) of patients with HIV infection from a first CD4 lymphocyte count below 0.200 × 10^9/l to death as estimated by Kaplan-Meier analysis. – ·· –, No PcP prophylaxis; –, PcP prophylaxis. **a** Group 1, ZDV prior to AIDS. Significant difference ($P < 0.005$) between no PcP prophylaxis ($n = 105$, median 548 days) and PcP prophylaxis ($n = 157$, median 690 days). **b** Group 2, no ZDV. Significant difference ($P < 0.0001$) between no PcP prophylaxis ($n = 602$, median 229 days) and PcP prophylaxis ($n = 185$, median 402 days). **c** Group 1, ZDV after AIDS diagnosis. Significant difference ($P < 0.0001$) between no PcP prophylaxis ($n = 120$, median 484 days) and PcP prophylaxis ($n = 256$, median 665 days)

a baseline CD4 count of 0.351 × 10^9 ± 0.082/l (mean CD4 count at ZDV start date 0.313 × 10^9 ± 0.125/l) eventually developed AIDS. Four patients in this group died during the observation period (Fig. 2). in contrast, 15 of 28 patients who were started on ZDV *after AIDS diagnosis* (mean CD4 count at start of observation period 0.321 × 10^9 ± 0.068/l; mean CD4 count at ZDV start date 0.239 × 10^9 ± 0.216/l; NS versus group 1) died during the observation period. Survival was significantly prolonged in group 1 versus groups 2 and 3 (Fig. 2).

Zidovudine treatment and combination with PcP prophylaxis

Of the 1425 patients 598 had received PcP prophylaxis and 827 had not. Median survival and Kaplan-Meier plots are given in Fig. 3. The baseline status of the six groups is reported in Table 1. Each group receiving PcP prophylaxis showed longer median survival compared to the corresponding group without prophylaxis. Patients receiving ZDV had an additional survival benefit from PCP prophylaxis (Fig. 3). The number of PcP episodes differed significantly in patients with (53 episodes of PcP) and without (355 episodes of PcP) prophylaxis ($P < 0.001$). This was also true when the three groups were analyzed separately: group 1a versus 1b, 32 versus 19 episodes ($P < 0.001$); group 2a versus 2b, 260 versus 16 episodes ($P < 0.001$); and group 3a versus group 3b, 63 versus 18 episodes ($P < 0.001$).

Stepwise regression was performed to determine the relative importance of different treatment parameters. ZDV therapy, PcP prophylaxis, age, and sex were introduced stepwise into the model. The most powerful predictor for survival was ZDV use, followed by PcP prophylaxis and age, while sex did not affect survival.

Discussion

To determine whether early treatment with ZDV, i.e., prior to the onset of AIDS, alters the natural history and survival of HIV-infected individuals we

performed an observational method using data from nine major AIDS clinics and hospitals in Germany. ZDV use was defined as treatment with at least 50 g, equaling a treatment period of 50–100 days. This definition was chosen for practical reasons and seems appropriate in an observational setting because assessment of treatment duration and reasons for interruption or cessation cannot be the objective of a study designed on an observational basis [8]. The practicability and feasability of therapy in a general clinical setting is already included in this type of analysis.

Unlike other reported studies, we determined survival from the time defined by CD4 count to death, instead of AIDS to death or treatment initiation to death. Thus we achieved comparability of different groups. In other recently published studies on the subject of survival prolongation by ZDV no statements on baseline comparability are included [4, 14]. Buira and colleagues [4] from the Barcelona area in Spain analyzed a cohort of 629 adult patients. They compared a group of patients treated with ZDV to another group of patients who refused treatment or were diagnosed before ZDV became available. They found age, risk group, and AIDS manifestation to be independent predictors of survival in addition to ZDV use. The CD4 lymphocyte counts as an important prognostic marker was not taken into account. Thus, the conclusion that patients treated with ZDV may benefit at least during 3 years may have been drawn from comparison of groups with different baseline CD4 status.

The effect of ZDV on survival of hemophiliacs was recently investigated by Ragni and colleagues [14]. In addition to a slowed progression to AIDS in ZDV-treated patients, they reported that patients treated with ZDV experienced improved survival after the onset of AIDS. Taken together, this means a survival advantage for patients treated with ZDV prior to AIDS. However, treatment groups were not stratified according to their CD4 counts at baseline, and, in addition to the effect of ZDV, survival was influenced by improvement of diagnostic and therapeutic management of opportunistic infections and by PcP prophylaxis because "historical" as well as "ZDV-era" patients were included in this analysis.

Data from the Multicenter AIDS Cohort Study (MACS) reported by Graham et al. [9] showed a delay of AIDS and an improved survival at 6, 12, and 18 months in the early treatment group; analysis at 24 months did not reveal improvement of survival in patients treated before the onset of AIDS. While the participants were evaluated at intervals of 6 months, in our study data were collected mostly at treatment centers where patients were seen continuously for routine follow-up and laboratory controls.

In a prospective trial of the Veterans Affairs Administration, Hamilton and coworkers [10] reported a delayed progression to AIDS but early ZDV – i.e., prior to AIDS – versus late ZDV did not result in a survival benefit. A high daily dosage of 1500 mg and the possible hematological adverse effects have been cited by discussants [9] as a possible reason for the missing survival advantage. Low dosage (500 mg/day) of ZDV became widely used in Germany in 1990, and a high percentage of patients in our study were presumably treated on low-dose ZDV. Nevertheless, a survival advantage was not detected in the early-treatment group when a first CD4 count below 0.200×10^9/l was taken as baseline. The high dose used in the Veterans Affairs Study may not have influenced survival in patients treated prior to AIDS. Possible reasons for the missing survival advantage in treatment prior to AIDS may be loss of efficacy after long-term treatment and limited duration of CD4 count improvement. However, in our study both groups (ZDV prior and ZDV after AIDS) were evaluated relatively late in the course of their disease. A baseline CD4 count above 0.200×10^9/l was not included in the analysis as it was not the aim of the study to follow patient's courses prior to that point. An underestimation of survival for patients who perhaps had remained below 0.200×10^9/l prior to inclusion is not to be expected because mean baseline counts were comparable. Thus, regarding the given baseline characteristics, a possible over- or underestimation of survival would apply to all groups. Other contributing factors such as a closer follow-up because of treatment may play a part but cannot be ruled out in an observational retrospective analysis. Even if a survival benefit was due to a more frequent examination, necessary because of treatment, the result would suggest an association with the compound used – a question which cannot be answered by placebo-controlled trials, and which favors observational methodology.

A group of patients was analysed for whom data regarding early therapy were available. In this subset of patients early treatment with ZDV prolonged survival from a first CD4 count below 0.500×10^9/l when therapy was implemented prior to AIDS diagnosis. However, the small number of patients who received ZDV after the onset of AIDS in this analysis may be a reason why no difference was found between ZDV and no ZDV after AIDS. One reason for a lack of efficacy in survival prolongation after long-term ZDV may be found in ZDV-resistant HIV strains. The clinical significance of ZDV-resistant strains in long-term therapy must still be evaluated, but this objective should be part

of a prospective trial. The Concorde trial and the continuation of the AIDS Clinical Trials Group 019 protocol will hopefully contribute data to the issues of survival prolongation and virus resistance.

Preliminary data from the Concorde trial [1] reporting that in asymptomatic patients the immediate use of ZDV shows no significant profit compared to a group with deferred treatment include only 103 patients with CD4 counts less than 0.200×10^9/l. In this subset of patients (as in the whole trial) there was no significant difference in the number of clinical events such as progression to AIDS or death [1]. This finding is in accordance with our results, despite a completely different methodology. In our study the inclusion criterion of first date with less than 0.200×10^9/l CD4 lymphocytes led to evaluation of the late courses of HIV infection. The time course from ZDV implementation to the baseline date of first CD4 count below 0.200×10^9/l was not included in our analysis. Our early treatment group was started on ZDV at a median of 301 days prior to the onset of AIDS. Early benefits of ZDV occurring in this interval therefore tend to be under- estimated.

As the independent effect of PcP prophylaxis in preventing PcP in patients receiving ZDV simultaneously contributes to changes of morbitity and survival, we assessed the additional effect of PcP prophylaxis. An important result of the MACS analysis showed that most of the treatment effect of combined ZDV therapy and PcP prophylaxis was attributable to ZDV and not to PcP prophylaxis [9]. Our survival analysis in groups receiving early ZDV, no ZDV, and late ZDV suggests that PcP prophylaxis is beneficial for survival in early ZDV treatment as well as late treatment.

Being well aware of the retrospective nature of our observational study and the limitations of a possible bias, we conclude from our data that the survival from a first CD4 count below 0.200×10^9/l to death is not different in patients receiving ZDV before or after development of AIDS. Both groups show better survival compared with patients without ZDV treatment. Additional PcP prophylaxis definitely improves survival in ZDV-treated patients and patients without ZDV. This is true in early ZDV treatment as well as in late treatment.

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Secretary of the GASG
Priv.-Doz. Dr. J.R. Bogner
Medizinische Poliklinik
Pettenkoferstrasse 8a
D-80336 München
Germany