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*Clinical Trial Report*

# The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS

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**To explore the respective roles of highly active antiretroviral therapy (HAART) and alpha-interferon in improving survival of patients with AIDS-related PML, we retrospectively analyzed all patients with AIDS and PML who were referred to Johns Hopkins University HIV Neurology Program from 1985 to 2000. For 97 evaluable patients, we compared survival of those who were on HAART (three or more antiretroviral drugs) to those who were not on HAART. The effect of alpha-interferon was also studied. Multivariate analysis showed no difference in survival among patients on none, one, or two forms of antiretrovirals; however, survival was significantly greater for those on HAART. Whereas alpha-interferon use was shown to be associated with longer survival ($P < 0.057$), this effect was not independent of the effects of HAART. HAART significantly increases survival for patients with PML and AIDS; however, alpha-interferon does not appear to provide additional benefit.** *Journal of NeuroVirology* (2001) **7,** 353–357.

**Keywords:** PML; highly active antiretroviral therapy; antiviral; survival; interferon-alpha; HIV

Progressive multifocal leukoencephalopathy is a demyelinating disease that has been estimated to affect 2.5–8% of AIDS patients (Albrecht *et al*, 1998; Berger and Major, 1999; Dworkin, 1999). It is caused by reactivation of a ubiquitous papova virus, JC virus, which 80–90% of the world's population is exposed to by early-adulthood. Reactivation of the JC virus causes destruction of oligodendrocytes, resulting in multifocal demyelination (Berger and Major, 1999). Until recently, survival of AIDS patients with PML was estimated to be about 3 to 6 months from the time of diagnosis. Treatment of PML has been disappointing given the limited therapeutic options. A randomized trial using Cytarabine (cytosine arabinoside) showed no benefit either for intravenous or intrathecal Cytarabine added to antiretroviral therapy (mostly dual- or mono-therapy) compared to antiretroviral therapy alone (Hall *et al*, 1998).

A previous nonrandomized study of alpha-interferon suggested improvement in survival and neurological deficits. This study, a retrospective chart review of 77 patients diagnosed with AIDS-associated PML at The Johns Hopkins Hospital between 1985 and July 1996, found alpha-interferon significantly increased survival by at least 150 days (Huang *et al*, 1998). Several recent retrospective studies and case reports have suggested that HAART treatment can improve the survival of groups of patients with PML (Elliot *et al*, 1997; Albrecht *et al*, 1998; Cinque and Casari, 1998; Miralles *et al*, 1998; Clifford *et al*, 1999; Dworkin *et al*, 1999; De Luca *et al*, 2000; Giudici *et al*, 2000). Because the prior alpha-interferon study looked at the pre-HAART era (Huang *et al*, 1998), we wanted to see if alpha-interferon provided additional survival benefit when added to a HAART regimen. This current study is the largest retrospective analysis examining the effect of HAART on survival and one of the few to compare HAART with additional treatments such as alpha-interferon.

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## Results

Based on the review of 3200 records from the longitudinal Johns Hopkins University HIV Neurology Program database, 144 patients (approximately 5%) were identified with either probable or definite PML. After careful medical record abstraction, 97 of these patients (67%) had sufficient medical information to verify the diagnosis and classify anti-HIV and anti-PML therapy. The study population was mostly male (94%) and predominantly non-white (52%). Diagnosis of PML was made by the following methods: clinical and radiological findings alone, 86 patients (65%); brain biopsy, 26 patients (20%); autopsy, 17 patients (13%); and CSF PCR positive for JC virus, 3 patients (2%). The risk factor break down of our cohort was: Homosexual 43%; Bisexual 2%; Heterosexual 2%; IV Drug Abuse 26%; Transfusion 2%; Unspecified 25%. There were 32 HAART users and 65 non-HAART users. Of the ninty seven patients with PML, 36 (37%) were treated with alpha-interferon, 9 (9%) were treated with cytosine arabinoside, and 2 (2%) were treated with topotecan. The Two groups were comparable in terms of demographics and immune status. HAART users tended to be older, with a median age of 42 [interquartile range, 25th and 75th percentile (IQR: 36, 51) compared to 39 (IQR: 36, 46)] and were somewhat more likely to be non-white (56% versus 49%) than non-HAART users. These differences were not significant. Both groups had similar levels of CD4+ T-cell counts (HAART users: median 45 cells/mm$^3$ (IQR: 19, 134) and non-HAART users: median 46 cells/mm$^3$ (IQR: 20, 90).

For the entire cohort, the mean survival postdiagnosis was 275 $\pm$ 45 days with a median survival of 118 days (IQR: 47,303). Patients on HAART had a median survival of 128 days (IQR: 31, 1094) and on non-HAART, 86 days (IQR: 47,268), whereas mean survival for patients on HAART was 235 days greater than the non-HAART users (440 $\pm$ 129 days versus 205 $\pm$ 32 days). Those patients taking alpha-IFN following diagnosis of PML survived approximately 6 weeks longer (median) than those not reporting use of alpha-IFN.

In a univariate analysis of patient characteristics, four factors were shown to be significantly associated with increased survival (Table 1). Those patients who reported the use of HAART had a significantly lower risk of death at any time than those not reporting the use of HAART (hazard ratio: 0.16, 95% confidence interval: 0.08, 0.32). Additionally, those patients reporting the use of the anti-PML medication alpha-IFN had a significantly lower risk of death at a given time that those not reporting use of this medication (hazard ratio: 0.24, 95% confidence interval: 0.12, 0.47). Additional univariate factors contributing to a decreased risk of death at any time point were the year of presentation of PML during or after 1996 and a CD4 cell count at PML diagnosis of $\geq$100 cells/mm$^3$. There was no significant association between sex, race, risk exposure, and postdiagnosis survival.

In a multivariate analysis, the influence of HAART use, CD4+ T-cell count greater than or equal to 100 cells/mm$^3$, and use of alpha-IFN on survival was assessed; each of these factors was significantly associated with decreased risk of death in the univariate analysis. Modeling postdiagnosis survival as a function of these covariates, it was found that HAART recipients had approximately 23% of the risk of death of those not reporting the use of HAART [hazard ratio: 0.23, 95% confidence interval (0.07, 0.76)] although the inferences on CD4+ T-cell count and use of alpha-IFN were similar to those from the univariate analysis, these results were not significant when adjusting for the influence of HAART use (Table 1).

Postdiagnosis survival is depicted using stratified curves of the survival function (Figure 1). In this representation, it can be seen that those patients

**Table 1** Analysis (univariate and multivariate) of factors influencing postdiagnostic survival of patients with PML

| *Univariate factors* | *Hazard ratio* | 95% *Confidence interval*[*] |
|---|---|---|
| HAART therapy ($\geq$3 agents) | 0.16 | (0.08, 0.32) |
| $\alpha$-IFN (reported use) | 0.24 | (0.12, 0.47) |
| Risk exposure (IV-D/transfusion) | 0.58 | (0.32, 1.07) |
| Year of presentation ($\geq$1996) | 0.24 | (0.10, 0.58) |
| CD4$^+$ cell count ($\geq$100 cells/mm$^3$) | 0.28 | (0.13, 0.60) |
| *Multivariate factors*[**] | *Hazard ratio* | 95% *Confidence interval*[*] |
| HAART therapy ($\geq$3 agents) | 0.23 | (0.07, 0.76) |
| CD4$^+$ cell count $\geq$100 cells/mm$^3$ | 0.48 | (0.22, 1.06) |
| $\alpha$-IFN | 0.19 | (0.31, 1.26) |

[*]A confidence interval is a measure of certainty with regards to the estimate of the hazard ratio. An interval that excludes 1.00 indicates a significant change in hazard ($p < 0.05$).
[**]There was no significant interaction between use of HAART and use of alpha-IFN in the multivariate analysis of postdiagnostic survival. The upper portion of the table displays the univariate hazard ratio and 95% confidence interval for each factor. The lower portion of the table displays the multivariate hazard ratios and 95% confidence interval for each of the three factors in the final model.

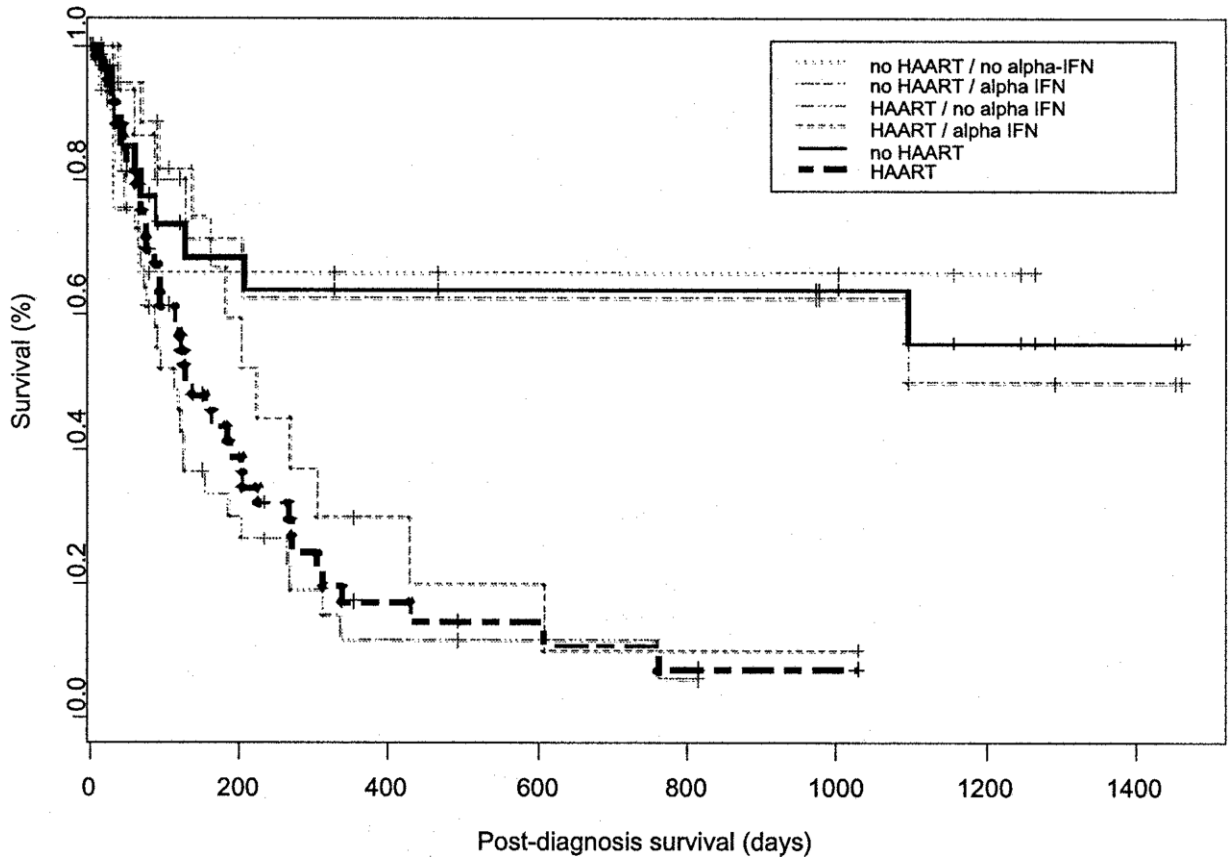


**Figure 1** Kaplan-Meier curves of postdiagnosis survival stratified by HAART use and then by use of alpha-IFN. The bold lines show survival curves for HAART users. The nonbold lines provide the additional stratification of each group by use of alpha-IFN. Data are "right censored," so that an individual contributes to follow-up time until last point of contact, at which point that patient is eliminated from the numerator and denominator. Each drop in the curve is a death. Multivariate analysis showed that there was a 23% decreased risk of death in HAART versus non-HAART users.

reporting the use of HAART survive approximately 8 months longer than those who do not use HAART. Additionally, it can be seen that there is a slight improvement in survival for those patients reporting the use of alpha-IFN between both HAART and non-HAART users, though this difference is not significant ($P = 0.41$) and multivariate analysis showed no additional benefit of alpha-interferon to patients also on HAART.

## Discussion

Our results confirm that HAART, independently of other variables, improves survival of patients with AIDS-associated PML. Patients with AIDS-associated PML who take HAART therapy ($\geq$3 antiretroviral agents) have a longer median survival than those not taking HAART therapy ($<$3 antiretroviral agents). This observation is consistent with other recently published reports with smaller numbers of patients (Albrecht *et al*, 1998; Miralles *et al*, 1998; Tassie *et al*, 1999; De Luca *et al*, 2000). This is the largest study to look at the effect of HAART on survival in PML (Albrecht *et al*, 1998; Cinque and Casari, 1998; Miralles *et al*, 1998; Clifford *et al*, 1999; De Luca *et al*, 2000; Giudici *et al*, 2000), and only one of these studies (Albrecht *et al*, 1998) also examined with multivariate analysis the effect of alpha-interferon.

Our median survival benefit of approximately 6 weeks for patients on HAART is smaller than that found in other smaller studies. A study by Clifford *et al* (1999; 25 patients) found median survival benefit of about 8 months, which was less than the $\geq$12.5 months and 16 months' median survival found by Albrecht *et al* (1999; 29 patients) and Miralles *et al* (2000; 25 patients), respectively. There are several possible reasons why our survival benefit is not as large as some other studies. In some other studies, HAART included a protease inhibitor, whereas in our study, any three antiretrovirals were considered as HAART. Many of our HAART patients may have been on a protease inhibitor as well, however, because for some of our patients only the amounts and not the type of antiretrovirals were specified, we did not subdivide the HAART group in this manner. It is possible

that our HAART users on a protease inhibitor would be in the highest quartile of survival. In our study, we also had several outliers, in particular several patients who died very shortly after starting HAART. It is possible that these patients had very high CSF JC viral loads and were not able to benefit from HAART (see next section). Furthermore, several of our HAART patients (approximately 10%) had very long survivals of greater than 1000 days. The discrepancy between our mean and median survival is likely due to such outliers at both ends of the survival spectrum.

In our prior study on alpha-interferon (Huang *et al*, 1998), we found significantly longer survival for those on alpha-interferon than those who were not treated with alpha-interferon (325 days versus 121–175 days). Importantly, however, in this current study, though univariate analysis did show some survival benefit of alpha-interferon, the multivariate analysis showed that for a group of patients on HAART, alpha-interferon does not appear to provide additional survival benefit. This is consistent with findings of Albrecht *et al* (1998), who found no added survival benefit from alpha-interferon in HAART (including a protease inhibitor) recipients. Our analysis suggests that for patients who respond to HAART, alpha-interferon does not improve survival. Given the cost and the need for subcutaneous administration, the use of alpha-interferon is probably not justified.

Notably, in our study (as in others), not all patients responded to HAART. This could reflect underlying HIV resistance to the regimen, or may reflect an intrinsically more aggressive PML course. Several authors have shown that patients who respond to HAART tend to have lower CSF JC viral loads at time of PML diagnosis, and that HAART had no clear survival benefit in PML patients with high CSF JC viral loads at PML diagnosis (De Luca *et al*, 2000; Giudici *et al*, 2000; Taoufik *et al*, 2000). De Luca *et al* (2000) also found that JC viral load in the CSF both before and after HAART therapy was predictive of survival. Additionally, they showed that clearance of JC viral DNA from the CSF was associated with a better neurologic outcome and longer survival. We were not able to ascertain HIV RNA-levels or CSF JC viral-levels for all of the patients in our database and thus did not include these factors in this study. It is possible that those who failed to respond to HAART in our study may have had higher CSF JC viral burdens, and these "nonresponders" might benefit from alpha-interferon or specific anti-JC viral treatments.

## Methods

The Johns Hopkins University HIV Neurology Program maintains a database of all HIV-1 seropositive patients seen for neurological consultation since 1985. A retrospective search of this database ($n = 3200$) was conducted to identify all patients who had been diagnosed with either possible or probable progressive multifocal leukoencephalopathy (PML) on the basis of clinical and radiological findings by one of two neurologists (JCM or WR). Each patient received a standard neurological assessment, most were followed longitudinally, and in addition, many patients had confirmation of PML diagnosis either by biopsy, detection of JC virus DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR), or subsequently autopsy. Having identified 144 patients with PML from the database, medical records were reviewed to determine method of PML diagnosis, specifics of anti-HIV and anti-PML therapy, date of diagnosis of PML, CD4+ T-cell count at diagnosis of PML, and post-PML survival for each patient in the study population. In 21 of the 144 patients, the diagnosis of PML could not be definitively verified either by biopsy, CSF JC virus PCR, or clinical and radiological criteria, and therefore these patients were excluded. An additional 16 patients were excluded due to uncertain antiretroviral regimens, and 10 more patients were excluded due to indeterminate postdiagnosis follow-up. Therefore, 97 patients diagnosed with PML were included in this study.

Antiretroviral regimens were classified as highly active antiretroviral therapy (HAART; at least three antiretroviral agents with no evidence of discontinuation) or, for those reporting a regimen of less than three antiretroviral agents, "non-HAART." Anti-PML medication was classified based on the reported use of alpha-interferon (alpha-IFN), Topotecan, or cytosine arabinoside (Cytarabine). Some of the patients on alpha-IFN were part of an earlier nonrandomized study and received 3 million units daily for a minimum of 3 weeks (Huang *et al*, 1999); others were treated on an open-label basis. Patients receiving Cytarabine had it administered either intrathecally or intravenously as part of a previously published clinical trial (Hall *et al*, 1998). Two patients received Topotecan, and are included in a companion paper. There were no time constraints on length of usage of either anti-HIV or anti-PML medication made in this study.

The primary endpoint for this analysis was death. Postdiagnostic survival was reported in days from initial diagnosis of PML until either death or last contact date through May 15, 2000. For those patients whose death status was unknown, an extension of Kaplan–Meier survival estimates was used to incorporate the date of last contact. This allows for the inclusion of right-censored data in the computation of nonparametric estimates of the survival distribution and to compute rank tests for association of the response variable with other variables of interest.

To assess the role that individual factors exert on postdiagnostic survival, univariate logistic regression methods were employed. Postdiagnostic survival was modeled as a function of each of the classification variables: year of presentation with PML, CD4+ T-cell count at diagnosis of PML ($\geq$100 cells/mm$^3$),

anti-HIV therapy classification (use of HAART), anti-PML therapy classification (use of alpha-IFN, topotecan, or Cytarabine), and HIV-risk exposure [intravenous drug user/blood transfusion (IV-D/transfusion)]. The results of the univariate analysis were used to model the influence of use of HAART on postdiagnostic survival adjusting for other significant predictors of survival in a multivariate setting. Using multivariate logistic regression methods, the relative hazard was estimated for use of HAART, CD4+ T-cell count at diagnosis of PML of greater than or equal to 100 cells/$mm^3$, and alpha-IFN treatment. Statistical inferences were tested using SAS software version 8.0 (SAS Institute, Cary NC).

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