

# Incidence and Outcome of Progressive Multifocal Leukoencephalopathy over 20 Years of the Swiss HIV Cohort Study

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**Background.** We investigated the incidence and outcome of progressive multifocal leukoencephalopathy (PML) in human immunodeficiency virus (HIV)-infected individuals before and after the introduction of combination antiretroviral therapy (cART) in 1996.

**Methods.** From 1988 through 2007, 226 cases of PML were reported to the Swiss HIV Cohort Study. By chart review, we confirmed 186 cases and recorded all-cause and PML-attributable mortality. For the survival analysis, 25 patients with postmortem diagnosis and 2 without CD4<sup>+</sup> T cell counts were excluded, leaving a total of 159 patients (89 before 1996 and 70 during 1996–2007).

**Results.** The incidence rate of PML decreased from 0.24 cases per 100 patient-years (PY; 95% confidence interval [CI], 0.20–0.29 cases per 100 PY) before 1996 to 0.06 cases per 100 PY (95% CI, 0.04–0.10 cases per 100 PY) from 1996 onward. Patients who received a diagnosis before 1996 had a higher frequency of prior acquired immunodeficiency syndrome-defining conditions ( $P = .007$ ) but similar CD4<sup>+</sup> T cell counts (60 vs. 71 cells/ $\mu$ L;  $P = .25$ ), compared with patients who received a diagnosis during 1996 or thereafter. The median time to PML-attributable death was 71 days (interquartile range, 44–140 days), compared with 90 days (interquartile range, 54–313 days) for all-cause mortality. The PML-attributable 1-year mortality rate decreased from 82.3 cases per 100 PY (95% CI, 58.8–115.1 cases per 100 PY) during the pre-cART era to 37.6 cases per 100 PY (95% CI, 23.4–60.5 cases per 100 PY) during the cART era. In multivariate models, cART was the only factor associated with lower PML-attributable mortality (hazard ratio, 0.18; 95% CI, 0.07–0.50;  $P < .001$ ), whereas all-cause mortality was associated with baseline CD4<sup>+</sup> T cell count (hazard ratio per increase of 100 cells/ $\mu$ L, 0.52; 95% CI, 0.32–0.85;  $P = .010$ ) and cART use (hazard ratio, 0.37; 95% CI, 0.19–0.75;  $P = .006$ ).

**Conclusions.** cART reduced the incidence and PML-attributable 1-year mortality, regardless of baseline CD4<sup>+</sup> T cell count, whereas overall mortality was dependant on cART use and baseline CD4<sup>+</sup> T cell count.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) that is caused by lytic replication of JC virus in the CNS [1–3]. PML is rare but frequently fatal as observed in the context of profound cellular immu-

nodeficiency. The underlying conditions are diverse and include hematological malignancy, chemotherapy, transplantation, lymphocyte depletion, and exposure to immunomodulatory antibodies that are administered for the treatment of autoimmune diseases [4–9]. However, PML has been most frequently diagnosed in the context of human immunodeficiency virus (HIV) infection and AIDS [10, 11]. The reported prevalence of PML among HIV-infected patients in the era before the

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introduction of combination antiretroviral therapy (cART) varied from 0.3% to 8%, with less than one-tenth surviving for >1 year [2, 10, 11]. Specific antiviral treatment targeting JC virus is lacking [12–16], and improvement of JC virus–specific immunity after suppression of HIV replication is the mainstay of therapy. Data from early after the introduction of cART described less dramatic improvements for PML than for other opportunistic diseases [17–19]. More recent studies report a patient survival rate of up to 63%, but persisting neurologic deficits occur in more than one-half of the survivors [13, 20–23]. Factors that appear to be associated with survival include PML as the primary manifestation of AIDS, high CD4<sup>+</sup> T cell count, low HIV RNA load, presence of JC virus–specific cytotoxic T lymphocytes, and low JC viral load in cerebral spinal fluid (CSF) at diagnosis [23–26].

However, most data were obtained from retrospective case series or were limited by small numbers and inconsistent case definitions. The Swiss HIV Cohort Study (SHCS) provides the unique opportunity to investigate PML from prospectively collected data from over the past 20 years. The aim of this study was to assess the incidence rate and risk factors for mortality among HIV-infected individuals with PML.

## PARTICIPANTS AND METHODS

**Study participants.** The SHCS is a prospective, clinic-based, observational study of HIV-infected adults that was initiated in 1988, with clinical and laboratory follow-up documented every 6 months. Enrollment is independent of disease stage and treatment [27]. The present study included all patients who had received a diagnosis of PML from 1988 through August 2007. The diagnosis of PML has been encoded in the SHCS database as either definitive (i.e., proven by histologic examination of a biopsy or postmortem tissue specimen) or presumptive (i.e., according to clinical, radiological, or laboratory evidence). For the purpose of this study, diagnoses of PML in the SHCS database were checked by individual chart review, and confirmed diagnoses were classified using the following previously established definitions [28]: (1) possible, by typical neuroradiologic and clinical findings; (2) laboratory confirmed, when JC virus DNA was detected in CSF; (3) definitive, when confirmed by histologic examination of a brain biopsy or autopsy specimen. Data related to HIV infection, including age, sex, transmission risk, prior AIDS-defining conditions, CD4<sup>+</sup> and CD8<sup>+</sup> T cell counts, HIV RNA load, treatment history, and cause of death (using the *International Statistical Classification of Diseases, 10th Revision* [29]) were obtained from the SHCS database. Additional data, such as clinical course, neuroradiological images, use of antiviral drugs, and supplementary laboratory values, were extracted from the chart review. After chart review, we excluded 10 patients who had received a diagnosis of another neurological disease and 30 additional pa-

tients who had received a diagnosis of presumed PML but lacked neuroradiological images; thus, data on 186 of 226 patients were used to estimate the annual PML prevalence. For the survival analysis, we excluded 25 additional patients for whom PML was only diagnosed postmortem and another 2 patients whose CD4<sup>+</sup> T cell counts at diagnosis were missing. PML-attributable mortality was defined as death due to neurological deterioration, including seizures and coma, that was directly associated with PML. All-cause mortality was defined as death due to any cause, including PML-attributable death. To investigate the effect of cART on the incidence and outcome of PML, 2 successive eras were defined according to the introduction of cART in Switzerland in 1996: the pre-cART era (1988–1995) and the cART era (1996–2007). cART was defined as at least 2 nucleoside reverse-transcriptase inhibitors plus either a protease inhibitor or a nonnucleoside reverse-transcriptase inhibitor. Monodrug and dual-drug ART were defined as 1 nucleoside reverse-transcriptase inhibitor or a combination of 2 nucleoside reverse-transcriptase inhibitors, respectively.

**Statistics.** Basic demographic characteristics, laboratory values, and use of ART were compared using the  $\chi^2$  test for categorical variables and the Mann-Whitney *U* test for continuous variables. Incidence rates of PML were calculated using the number of enrolled patients in the SHCS and the duration of follow-up according to the 2 defined periods of 1988–1995 and 1996–2007. Survival patterns were displayed using Kaplan-Meier plots of cumulative survival probabilities. Cox hazard proportional models were used to estimate the hazard ratios (HRs) of PML-attributable death during the first year after diagnosis of PML. All patients were censored at 1 year after diagnosis of PML if no death had occurred. Analyses were conducted using Stata software, version 9.2 (Stata), for Windows.

## RESULTS

**Patient characteristics.** From 1988 through August 2007, 186 patients received a diagnosis of PML in the SHCS. Figure 1 shows that the annual PML prevalence was highest during the pre-cART era (mean prevalence during 1993–1995, 0.9%). From 1996 onward, the annual mean prevalence decreased to 0.1%. For the survival analysis, we included 159 of 186 patients. Table 1 summarizes the demographic characteristics of the 159 patients. The median age was 37 years (interquartile range [IQR]: 33–42 years); 74.2% of the patients were male. Of the 159 analyzed patients, only 3 (1.9%) were of non-white ethnicity. Almost one-half of the patients had prior AIDS-defining conditions. It was not unexpected that *Candida* esophagitis and *Pneumocystis* pneumonia were the most frequently diagnosed diseases in patients with PML who had prior AIDS-defining disease. Only 5 patients had received a diagnosis of cytomegalovirus retinitis, and 6 had received a diagnosis of Kaposi

**Table 1. Characteristics of 159 human immunodeficiency virus (HIV)-infected individuals with progressive multifocal leukoencephalopathy (PML), according to the calendar period of PML diagnosis.**

Variable	Patients			P
	All (n = 159)	PML diagnosis before 1996 (n = 89)	PML diagnosis during 1996 or thereafter (n = 70)	
Age, median years (IQR)	37 (33–42)	35 (32–41)	39 (35–43)	<b>.002</b>
Male sex	118 (74.2)	65 (73.0)	53 (75.1)	.701
Transmission risk				
MSM	49 (30.8)	23 (25.8)	26 (37.1)	.414
Heterosexual contact	27 (17.0)	15 (16.9)	12 (17.1)	
IDU	79 (49.7)	49 (55.1)	30 (42.9)	
Other	4 (2.5)	2 (2.2)	2 (2.9)	
ART at time of PML diagnosis				
None	45 (28.3)	30 (33.7)	15 (21.4)	<b>&lt;.001</b>
Monodrug or dual-drug ART	65 (40.9)	59 (66.3)	6 (8.6)	
cART	49 (30.8)	0 (0)	49 (70.0)	
Prior AIDS-defining condition	76 (47.8)	51 (57.3)	25 (35.7)	<b>.007</b>
CD4 <sup>+</sup> T cell count, median cells/ $\mu$ L (IQR)	60 (23–140)	60 (20–140)	71 (31–132)	.250
CD8 <sup>+</sup> T cell count, median cells/ $\mu$ L (IQR)	488 (271–805)	480 (236–776)	514 (361–805)	.336
HIV RNA level, median log <sub>10</sub> copies/mL <sup>a</sup> (IQR)	4.9 (3.5–5.4)	4.9 (4.1–5.5)	4.9 (3.3–5.4)	.755

**NOTE.** Data are no. (%) of patients unless otherwise indicated. Boldface type indicates statistical significance. ART, antiretroviral therapy; cART, combination ART; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men.

<sup>a</sup> Data were available for 68 patients.

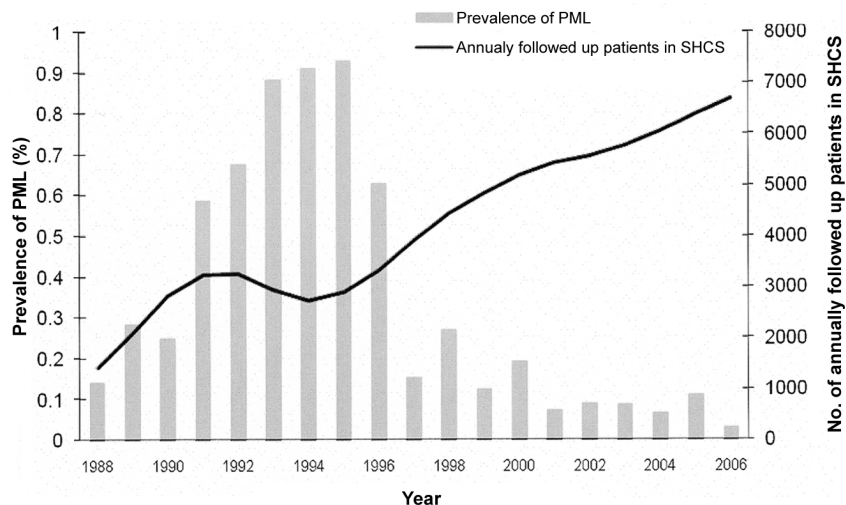
sarcoma, which could not be further analyzed. The median CD4<sup>+</sup> T cell count at PML diagnosis was 60 cells/ $\mu$ L (IQR, 23–140 cells/ $\mu$ L). Plasma HIV RNA levels were available for 68 patients; the median was 4.9 log<sub>10</sub> copies/mL (IQR, 3.5–5.4 log<sub>10</sub> copies/mL). Most patients (71.7%) were receiving ART when PML was diagnosed, but only 30.8% were receiving cART. Injection drug use was an HIV transmission risk factor for one-half of the patients, and one-third of the patients were men who have sex with men. PML was diagnosed on the basis of typical clinical and neuroradiological signs in 95 patients (60%), was laboratory confirmed in 38 patients (24%), and was definitive in 26 patients (16%). Magnetic resonance imaging was performed for 133 patients (84%). Polymerase chain reaction (PCR) of CSF specimens for JC virus DNA was performed for 81 patients (51%), and JC virus DNA was detectable in approximately one-half of these patients. The 25 patients with a postmortem diagnosis were similar with regard to baseline age, sex, transmission risk, and CD4<sup>+</sup> T cell count at baseline; however, these patients had more frequently received a diagnosis of another AIDS-defining condition before 1996 than from 1996 onward.

**Outcome of PML in Switzerland.** After diagnosis of PML, 25 (15.7%) patients started cART, 8 (5.0%) received zidovudine, and 2 (1.2%) received cytarabine. Overall, 97 patients died within 1 year after diagnosis; the median survival time was 90 days (IQR, 53–312 days), which corresponds to a 1-year mortality rate of 119.0 deaths per 100 person-years (PY; 95% CI,

98.1–144.4 deaths per 100 PY). Of those 97 patients, 51 died of PML, corresponding to a PML-attributable 1-year mortality rate of 58.9 deaths per 100 PY (95% CI, 44.8–77.6 deaths per 100 PY). The median time from diagnosis to PML-attributable death was 71 days (IQR, 44–140 days). Of 62 patients with PML who lived for >1 year after diagnosis, long-term follow-up data were available for 47. Of these 47 patients, 39 (83%) had persisting neurological deficits and only 8 (17%) showed clinical improvement.

**PML during the pre-cART and cART eras.** Of 159 patients with PML, 89 (56.0%) received a diagnosis during the period 1988–1995 and 70 (44.0%) received a diagnosis during the period 1996–2007. The incidence rate of PML decreased by 4-fold from 0.24 cases per 100 PY (95% CI, 0.20–0.29 cases per 100 PY) during the pre-cART era to 0.06 cases per 100 PY (95% CI, 0.04–0.10 cases per 100 PY) during the cART era. Sex, transmission risk, and importantly, CD4<sup>+</sup> T cell counts were similar in the 2 groups (table 1). Individuals in the pre-cART era had significantly more prior AIDS-defining conditions ( $P = .007$ ), were more likely to have been receiving monodrug or dual-drug ART ( $P < .001$ ), and more frequently received a diagnosis of possible PML ( $P = .002$ ), compared with patients in the cART era.

**Risk factors for PML-attributable mortality.** The PML-attributable 1-year mortality rate decreased by approximately one-half, from 82.3 deaths per 100 PY (95% CI, 58.8–115.1 deaths per 100 PY) during the pre-cART era to 37.6 deaths per



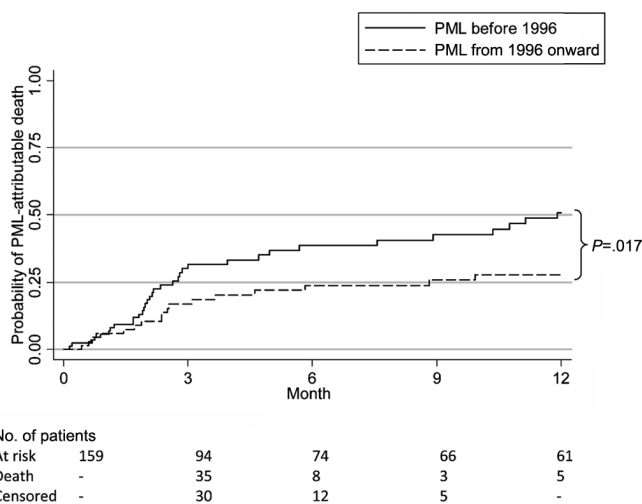
**Figure 1.** Prevalence of progressive multifocal leukoencephalopathy (PML) per year among the participants of the Swiss HIV Cohort Study (SHCS) who received annual follow-up.

100 PY (95% CI, 23.4–60.5 deaths per 100 PY) during the cART era. The Kaplan-Meier estimates were significantly different between both time periods (figure 2).

In the univariate analysis, patients treated with cART (HR, 0.20; 95% CI, 0.09–0.48;  $P < .001$ ) and those who received a diagnosis from 1996 onward (HR, 0.50; 95% CI, 0.28–0.90;  $P = .020$ ) had a lower risk of PML-attributable death within the first year after PML diagnosis (table 2), compared with patients who were not treated with cART and received a diagnosis before 1996. We did not observe any association between female sex and survival (HR, 1.51; 95% CI, 0.85–2.69;  $P = .159$ ) when all patients were included (table 2) or when

only injection drug users were considered (HR, 1.06; 95% CI, 0.50–2.27;  $P = .881$ ). In the multivariate analysis, after adjustment for age, CD4<sup>+</sup> T cell count, ART, and calendar period, treatment with cART at PML diagnosis was the only prognostic factor for survival (HR, 0.18; 95% CI, 0.07–0.50;  $P < .001$ ) (table 3). cART use also remained the only prognostic factor when HIV RNA load was included in a model (HR, 0.25; 95% CI, 0.08–0.79;  $P = .01$ ) with 68 patients whose HIV RNA load data were available. Kaplan-Meier estimates, stratified by treatment modality at PML diagnosis, are shown in figure 3.

**Risk factors for all-cause mortality.** In the univariate analysis, a CD4<sup>+</sup> T cell count  $>100$  cells/ $\mu$ L (HR, 0.66; 95% CI,



**Figure 2.** Kaplan-Meier estimates of survival after diagnosis of progressive multifocal leukoencephalopathy (PML), according to the calendar year of PML diagnosis.

**Table 2. Risk factors and univariate hazard ratios (HRs) of progressive multifocal leukoencephalopathy (PML)–attributable death among 159 human immunodeficiency virus (HIV)–infected individuals.**

Variable	HR (95% CI)	P
Age, per 10-year increase	1.19 (0.81–1.73)	.373
Female vs. male sex	1.51 (0.85–2.69)	.159
Transmission risk		
MSM	1 <sup>a</sup>	
Heterosexual contact	0.71 (0.29–1.72)	.442
IDU	1.12 (0.61–2.08)	.710
Prior AIDS-defining condition	1.37 (0.79–2.38)	.258
CD4 <sup>+</sup> T cell count, cells/ $\mu$ L		
<50	1 <sup>a</sup>	
50–100	1.27 (0.63–2.53)	.501
>100	0.75 (0.40–1.43)	.389
HIV RNA level, log <sub>10</sub> copies/mL <sup>b</sup>		
<4.0	1 <sup>a</sup>	
4.0–5.0	3.12 (0.61–16.1)	.173
>5.0	4.09 (0.88–19.0)	.072
ART at time of PML diagnosis		
None	1 <sup>a</sup>	
Mono or dual ART	0.68 (0.38–1.23)	.206
cART	0.20 (0.09–0.48)	<b>&lt;.001</b>
PML diagnosis during 1996 or thereafter	0.50 (0.28–0.90)	<b>.020</b>

**NOTE.** Boldface type indicates statistical significance. ART, antiretroviral therapy; cART, combination ART; IDU, injection drug use; MSM, men who have sex with men; 95% CI, 95% confidence interval.

<sup>a</sup> Reference category.

<sup>b</sup> Data were available for 68 patients.

0.45–0.98;  $P = .044$ ), use of cART (HR, 0.33; 95% CI, 0.19–0.58;  $P < .001$ ), and PML diagnosis from 1996 onward (HR, 0.51; 95% CI, 0.34–0.76;  $P = .01$ ) were associated with lower all-cause mortality. In the multivariate analysis, after adjustment for age, CD4<sup>+</sup> T cell count, ART, and calendar period, a CD4<sup>+</sup> T cell count >100 cells/ $\mu$ L (HR, 0.52; 95% CI, 0.32–0.85;  $P = .010$ ), and use of cART (HR, 0.37; 95% CI, 0.19–0.75;  $P = .006$ ) were associated with a higher survival rate (table 4).

## DISCUSSION

PML is a devastating disease that confronts patients and physicians with progressive disability and high mortality. Although the pathology and its viral etiology have been known for >40 years [30, 31], PML has been difficult to study, in part, because of the erratic manifestation in patients characterized by severe chronic conditions with profound cellular immunodeficiency. This hallmark has also been emphasized in the recent PML cases in patients with autoimmune diseases treated with new potent immunosuppressive therapies [4–9]. Even for patients with HIV infection or AIDS, in whom most cases occurred in the past, few studies enrolled >50 patients with consistently collected longitudinal data [13, 22, 23, 26].

Our comprehensive study of almost 200 PML cases diagnosed over 20 years of the SHCS enumerates the incidence rate of PML as 0.24% during the pre-cART era of HIV infection and AIDS. The introduction of cART in Switzerland in 1996 was associated with a 4-fold decrease in PML incidence to 0.06%. The decrease in PML incidence from 1996 onward supports the notion that preservation of overall immune functions by cART is a key factor protecting against the manifestation of PML. Indeed, we found that the median CD4<sup>+</sup> T cell counts were similarly low in both eras (60 cells/ $\mu$ L and 70 cells/ $\mu$ L during the pre-cART and cART eras, respectively) at the time of PML diagnosis. In addition to preventing decreases in CD4<sup>+</sup> T cell count, however, cART-mediated suppression of HIV replication may exert a direct beneficial effect in the CNS by interfering with HIV-tat mediated activation of JC virus replication [32, 33].

Our study also revealed that cART has significantly reduced the PML-attributable 1-year mortality rate from 82.3 deaths per 100 PY during the pre-cART era to 37.6 deaths per 100 PY during the cART era. This improvement of the 1-year survival rate in association with cART was independent of HIV RNA load and the total CD4<sup>+</sup> T cell count at diagnosis. However, a case-control study that compared HIV-infected patients with PML and HIV-infected control subjects matched by CD4<sup>+</sup> T cell count supports the view that the JC virus–specific T cell responses, not the overall CD4<sup>+</sup> T cell count, may be critical for PML survival [34]; JC virus–specific cytotoxic CD8<sup>+</sup> T cell responses seem to be the most critical [24]. Conversely, our study indicated that all-cause mortality among patients with PML was associated with a lower CD4<sup>+</sup> T cell count at baseline, which reflects the higher risk of opportunistic disease burden with increasing immunodeficiency. No corresponding data

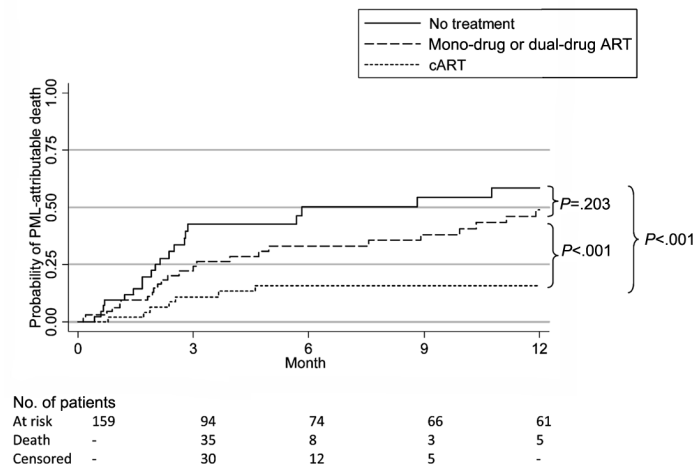
**Table 3. Risk factors and multivariate hazard ratios (HRs) of progressive multifocal leukoencephalopathy (PML)–attributable death among 159 human immunodeficiency virus–infected individuals.**

Variable	HR <sup>b</sup> (95% CI)	P
Age, per 10-year increase	1.36 (0.94–1.98)	.103
CD4 <sup>+</sup> T cell count, cells/ $\mu$ L		
<50	1 <sup>a</sup>	
50–100	1.08 (0.53–2.19)	.832
>100	0.69 (0.36–1.33)	.267
ART at time of PML diagnosis		
None	1 <sup>a</sup>	
Monodrug or dual-drug ART	0.70 (0.37–1.31)	.265
cART	0.18 (0.07–0.50)	<b>&lt;.001</b>
PML diagnosis during 1996 or thereafter	1.03 (0.49–2.17)	.941

**NOTE.** Boldface type indicates statistical significance. ART, antiretroviral therapy; cART, combination ART; 95% CI, 95% confidence interval.

<sup>a</sup> Reference category.

<sup>b</sup> Adjusted for all variables listed in the table.



**Figure 3.** Kaplan-Meier curve of progressive multifocal leukoencephalopathy (PML)-attributable death, according to antiretroviral treatment (ART) modality, among 159 patients who received a diagnosis of PML. cART, combination ART.

from other immunodeficient HIV-uninfected patients are available, but case series support the view that the prognosis of PML may be significantly worse in conditions that do not allow improvement of anti-JC virus immunity without adverse outcomes for the underlying condition (e.g., neoplasia, transplantation, or autoimmune disease) [6, 35, 36]. On the other hand, brisk recovery of immunity may cause immune reconstitution inflammatory syndrome (IRIS), a potentially fatal complication after initiation of cART [37–39]. The frequency of IRIS may be more pronounced among patients with low CD4<sup>+</sup> cell counts [38]. The rate of IRIS among patients with PML varied considerably between different studies and was as high as 23% [40]. In our study, only 4 patients (2.5%) with IRIS were reported in the SHCS, most likely because of underdiagnosis. Of interest, in a recent study, no difference in mortality among patients with PML with or without IRIS was observed [40].

PML is typically diagnosed on the basis of examination of focal neurological deficits in immunodeficient patients and represents a late complication of HIV infection or AIDS. Therefore, during the cART era, patients with PML must have either received a late diagnosis of HIV infection or must have had deferred treatment because of personal choice, drug intolerance, or comorbidities, including psychiatric disorders. In this context, it is interesting to note that there was a higher proportion of injection drug users among patients with PML in both eras, compared with the entire SHCS population. However, we cannot exclude that injection drug use might also represent a behavioral risk factor for JC virus transmission.

Limitations of our study are those inherent to observational cohort studies in which patients are not randomized. Therefore, diagnosis, examination, and interventions are dependent on the treating physician and are subject to selection bias. The gold

standard of PML diagnosis is histologic examination of a brain biopsy specimen, which is highly specific but also invasive and costly, and results may be false negative as a result of necrosis [41]. Detection of JC virus in CSF by PCR became available in the 1990s and is now widely accepted for laboratory-confirmed diagnosis [28]. In HIV-infected patients with typical radiological lesions, the specificity of JC virus PCR of CSF is >90%, but the sensitivity ranges from 70% to 90% [42, 43]. In the SHCS, JC virus DNA was not detectable in CSF specimens from two-thirds of patients who received a histological diagnosis. In addition, we cannot account for changes in these

**Table 4. Risk factors and multivariate hazard ratios (HRs) of all-cause mortality among 159 human immunodeficiency virus-infected individuals with progressive multifocal leukoencephalopathy (PML).**

Variable	HR <sup>b</sup> (95% CI)	P
Age, per 10-year increase	1.05 (0.80–1.39)	.716
CD4 <sup>+</sup> T cell count, cells/ $\mu$ L		
<25	1 <sup>a</sup>	
25–50	0.56 (0.29–1.07)	.100
50–100	0.73 (0.42–1.26)	.257
>100	0.52 (0.32–0.85)	<b>.010</b>
ART at time of PML diagnosis		
None	1 <sup>a</sup>	
Mono or dual ART	0.79 (0.49–1.27)	.328
cART	0.37 (0.19–0.75)	<b>.006</b>
PML diagnosis during 1996 or thereafter	0.87 (0.48–1.57)	.644

**NOTE.** Boldface type indicates statistical significance. ART, antiretroviral therapy; cART, combination ART; 95% CI, 95% confidence interval.

<sup>a</sup> Reference category.

<sup>b</sup> Adjusted for all variables listed in the table.

parameters, because the methodology of JC virus detection in CSF changed from nested PCR to a real-time format during the past 10 years. Therefore, neither the performance of the JC virus PCR test used at the SHCS centers nor the potential role of the test result as a marker for patient survival could be assessed. A recent study reported that the sensitivity of JC virus DNA detection decreased from 90% to ~60% during the cART era. Exposure to cART and a high CD4<sup>+</sup> T cell count were identified as predictors of diagnostic failure [44]. Therefore, PML diagnosis is frequently based on compatible clinical and radiological findings. Together, these emphasize the need for cautious interpretation of negative CSF findings in patients with otherwise typical PML.

To date, there are no successful antiviral therapies for PML that effectively suppress JC virus replication. In HIV-infected patients with PML, the additional use of cidofovir, a nucleotide analogue with in vitro activity against JC virus, has shown contradictory results in several studies [12–16]. A prospective nonrandomized analysis and a recent large multicenter cohort study report lack of additional efficacy with the addition of cidofovir to cART [13, 16]. In our population, cytarabine and cidofovir were rarely used, and the efficacy of these drugs could not be investigated.

In conclusion, the results of this study, covering 20 years of the SHCS database, demonstrate that the introduction of cART has led to a decrease in the incidence of PML among HIV-infected patients and has reduced PML-attributable 1-year mortality, regardless of baseline CD4<sup>+</sup> T cell count.

## MEMBERS OF THE SWISS HIV COHORT STUDY

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## References

1. Padgett BL, Walker DL, ZuRhein GM, Eckroade RJ, Dessel BH. Cultivation of papova-like virus from human brain with progressive multifocal leukoencephalopathy. *Lancet* **1971**; 1:1257–60.
2. Berger JR, Kaszovitz B, Post MJ, Dickinson G. Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection: a review of the literature with a report of sixteen cases. *Ann Intern Med* **1987**; 107:78–87.
3. Weber T, Major EO. Progressive multifocal leukoencephalopathy: molecular biology, pathogenesis and clinical impact. *Intervirology* **1997**; 40:98–111.
4. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* **2005**; 353:369–74.
5. Garcia-Suarez J, de Miguel D, Krsnik I, Banas H, Arribas I, Burgaleta C. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. *Am J Hematol* **2005**; 80:271–81.
6. Berger JR, Houff S. Progressive multifocal leukoencephalopathy: lessons from AIDS and natalizumab. *Neurol Res* **2006**; 28:299–305.
7. Castillo J, Winer E, Quesenberry P. Newer monoclonal antibodies for hematological malignancies. *Exp Hematol* **2008**; 36:755–68.
8. Yousry TA, Major EO, Ryschewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* **2006**; 354:924–33.
9. Yokoyama H, Watanabe T, Maruyama D, Kim SW, Kobayashi Y, Tobinai K. Progressive multifocal leukoencephalopathy in a patient with B-cell lymphoma during rituximab-containing chemotherapy: case report and review of the literature. *Int J Hematol* **2008**; 88:443–7.
10. Gillespie SM, Chang Y, Lemp G, et al. Progressive multifocal leukoencephalopathy in persons infected with human immunodeficiency virus, San Francisco, 1981–1989. *Ann Neurol* **1991**; 30:597–604.
11. Martinez AJ, Sell M, Mitrovics T, et al. The neuropathology and epidemiology of AIDS: a Berlin experience—a review of 200 cases. *Pathol Res Pract* **1995**; 191:427–43.
12. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. *N Engl J Med* **1998**; 338:1345–51.
13. De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. *AIDS* **2008**; 22:1759–67.
14. Wyen C, Hoffmann C, Schmeisser N, et al. Progressive multifocal leukoencephalopathy in patients on highly active antiretroviral therapy: survival and risk factors of death. *J Acquir Immune Defic Syndr* **2004**; 37:1263–8.
15. De Luca A, Giancola ML, Cingolani A, et al. Clinical and virological monitoring during treatment with intrathecal cytarabine in patients with AIDS-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis* **1999**; 28:624–8.
16. Marra CM, Rajcic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS* **2002**; 16:1791–7.
17. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA* **1999**; 282:2220–6.
18. Ammassari A, Cingolani A, Pezzotti P, et al. AIDS-related focal brain lesions in the era of highly active antiretroviral therapy. *Neurology* **2000**; 55:1194–200.
19. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS* **1999**; 13:1933–42.
20. Albrecht H, Hoffmann C, Degen O, et al. Highly active antiretroviral

- therapy significantly improves the prognosis of patients with HIV-associated progressive multifocal leukoencephalopathy. *AIDS* **1998**; *12*: 1149–54.
21. Clifford DB, Yiannoutsos C, Glicksman M, et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology* **1999**; *52*:623–5.
  22. Tassie JM, Gasnault J, Bentata M, et al. Survival improvement of AIDS-related progressive multifocal leukoencephalopathy in the era of protease inhibitors. Clinical Epidemiology Group. French Hospital Database on HIV. *AIDS* **1999**; *13*:1881–7.
  23. Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis* **2003**; *36*: 1047–52.
  24. Koralnik IJ, Du Pasquier RA, Kuroda MJ, et al. Association of prolonged survival in HLA-A2+ progressive multifocal leukoencephalopathy patients with a CTL response specific for a commonly recognized JC virus epitope. *J Immunol* **2002**; *168*:499–504.
  25. Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. *Ann Neurol* **1998**; *44*: 341–9.
  26. Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis* **2005**; *40*: 738–44.
  27. Ledergerber B, von Overbeck J, Egger M, Luthy R. The Swiss HIV Cohort Study: rationale, organization and selected baseline characteristics. *Soz Praventivmed* **1994**; *39*:387–94.
  28. Cinque P, Koralnik IJ, Clifford DB. The evolving face of human immunodeficiency virus-related progressive multifocal leukoencephalopathy: defining a consensus terminology. *J Neurovirol* **2003**; *9*(Suppl 1): 88–92.
  29. World Health Organization. International statistical classification of diseases, 10th revision. **2009**. Available at: <http://www.who.int/classifications/icd/en/>. Accessed 28 March 2009.
  30. Richardson EP Jr. Progressive multifocal leukoencephalopathy. *N Engl J Med* **1961**; *265*:815–23.
  31. Zurhein G, Chou SM. Particles resembling papova viruses in human cerebral demyelinating disease. *Science* **1965**; *148*:1477–9.
  32. Kaniowska D, Kaminski R, Amini S, et al. Cross-interaction between JC virus agnoprotein and human immunodeficiency virus type 1 (HIV-1) Tat modulates transcription of the HIV-1 long terminal repeat in glial cells. *J Virol* **2006**; *80*:9288–99.
  33. Mischitelli M, Fioriti D, Videtta M, et al. Investigation on the role of cell transcriptional factor Sp1 and HIV-1 TAT protein in PML onset or development. *J Cell Physiol* **2005**; *204*:913–8.
  34. Khanna N, Wolbers M, Mueller NJ, et al. JCV-specific immune responses in HIV-1 patients with progressive multifocal leukoencephalopathy. *J Virol* **2009** (Epub ahead of print).
  35. Kharfan-Dabaja MA, Ayala E, Greene J, Rojiani A, Murtagh FR, Anasetti C. Two cases of progressive multifocal leukoencephalopathy after allogeneic hematopoietic cell transplantation and a review of the literature. *Bone Marrow Transplant* **2007**; *39*:101–7.
  36. Pelosini M, Focosi D, Rita F, et al. Progressive multifocal leukoencephalopathy: report of three cases in HIV-negative hematological patients and review of literature. *Ann Hematol* **2008**; *87*:405–12.
  37. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis* **2002**; *35*:1250–7.
  38. Hirsch HH, Kaufmann G, Sendi P, Battegay M. Immune reconstitution in HIV-infected patients. *Clin Infect Dis* **2004**; *38*:1159–66.
  39. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology* **2009** (Epub ahead of print).
  40. Falco V, Olmo M, del Saz SV, et al. Influence of HAART on the clinical course of HIV-1-infected patients with progressive multifocal leukoencephalopathy: results of an observational multicenter study. *J Acquir Immune Defic Syndr* **2008**; *49*:26–31.
  41. Karahalios D, Breit R, Dal Canto MC, Levy RM. Progressive multifocal leukoencephalopathy in patients with HIV infection: lack of impact of early diagnosis by stereotactic brain biopsy. *J Acquir Immune Defic Syndr* **1992**; *5*:1030–8.
  42. Hirsch HH, Meylan PR, Zimmerli W, Iten A, Battegay M, Erb P. HIV-1-infected patients with focal neurologic signs: diagnostic role of PCR for *Toxoplasma gondii*, Epstein-Barr virus, and JC virus. *Clin Microbiol Infect* **1998**; *4*:577–84.
  43. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS* **1997**; *11*:1–17.
  44. Marzocchetti A, Di Giambenedetto S, Cingolani A, Ammassari A, Cauda R, De Luca A. Reduced rate of diagnostic positive detection of JC virus DNA in cerebrospinal fluid in cases of suspected progressive multifocal leukoencephalopathy in the era of potent antiretroviral therapy. *J Clin Microbiol* **2005**; *43*:4175–7.