

## Effect of Smoking on the Clinical Progression of HIV-1 Infection

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**Summary:** Cigarette smoking as a risk factor in progression of HIV-1 disease was investigated in the Multicenter AIDS Cohort Study of homosexual men. Longitudinal data for T-cell subsets, HIV-related clinical symptoms, smoking behavior, and AIDS medication use were collected semiannually from 2,499 HIV-1-seropositive men for up to 9 years. Survival methods, including Kaplan-Meier analysis and multivariate Cox regression models, were used to assess the effect of cigarette smoking on development of *Pneumocystis carinii* pneumonia (PCP), AIDS, death, and self-reported oral thrush. After adjustment for CD4<sup>+</sup> lymphocyte count and use of antiretroviral and anti-PCP medications, smoking was not significantly associated with progression to PCP, AIDS, or death in either the HIV-seroprevalent or-seroincident cohort members. Among men who had baseline CD4<sup>+</sup> cell counts >200/ $\mu$ l, smoking was associated with a 40% increase in the hazard of oral thrush ( $p \leq 0.01$ ). These data indicate that cigarette smoking does not have a major effect on the progression of HIV-1 infection to AIDS or death but may affect the incidence of oral thrush. **Key Words:** HIV-1 disease progression—Cigarette smoking—AIDS—Oral thrush.

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Cigarette smoking is well known as a risk-factor for cardiovascular disease, lung disease, and cancer, but whether cigarette smoking is a risk factor in HIV-1 disease progression is controversial. Effects of smoking on the immune system include short-term

effects on the functioning of various leukocyte subtypes (1-3) and increased numbers of circulating leukocytes (4) ("smokers' leukocytosis"), which appears to be primarily a nonspecific increase in all blood cell types (5). It is not clear, however, whether any of these effects would influence the progression of HIV disease.

In a cohort of 131 homosexual men studied prospectively, Burns et al. (6) found no difference between smokers and nonsmokers in the risk of developing AIDS or *Pneumocystis carinii* pneumonia (PCP) from an estimated seroconversion time. Nieman et al., on the other hand, reported in a case series of mostly homosexual or bisexual men that smokers progressed to AIDS and PCP more rapidly than nonsmokers (7). Craib et al. (8) found no relationship between smoking and AIDS rates during an 8-year follow-up of 391 homosexual men. In a

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surveillance study, Buskin et al. (9) reported an increased risk of PCP in heavy lifetime smokers compared with light smokers among 598 persons with HIV-1 infection.

Given these conflicting findings, we examined in detail cigarette smoking as a risk factor for HIV-1 disease progression among the 2,499 HIV-infected men in the Multicenter AIDS Cohort Study (MACS). We looked at reported smoking behavior over time and analyzed the relationship between smoking and a spectrum of HIV-1 clinical outcomes, including thrush, PCP, AIDS, and death.

## METHODS

### Study Population and Variables

A detailed description of the study design of the MACS has been published elsewhere (10). Briefly, 4,954 homosexual men without a prior diagnosis of AIDS have been monitored semiannually since mid-1984 in four U.S. cities. Enrollment was reopened from 1987 to 1991, and an additional 624, predominantly minority, participants were recruited. Seropositivity to HIV-1 was determined at each visit by enzyme-linked immunosorbent assay and confirmed by Western blot. The analysis presented here was based on the 2,499 participants who were either seropositive for HIV-1 at study entry ( $n = 2,132$ ) or seroconverted during follow-up and whose date of seroconversion was known to within  $\pm 5$  months ( $n = 367$ ). Follow-up through the first 9 1/2 years of the MACS has been described by Dudley et al. (11).

At each visit, blood samples were collected for hematologic studies, including determination of percent and number of T-lymphocyte subsets by flow cytometry (12,13). A questionnaire elicited information on a wide variety of behavioral practices, including smoking, in the 6 months prior to the visit. Also collected at each visit were self-reported occurrences of HIV-related symptoms, including oral thrush, and prophylactic use of medications against HIV (zidovudine, zalcitabine, or didanosine) or PCP (aerosolized pentamidine, dapsone, trimethoprim/sulfamethoxazole, or trimethoprim). The AIDS outcomes and mortality data were collected on an ongoing basis in the cohort and confirmed by medical records and death certificates. The present analysis includes data collected up to April 1, 1993.

### Statistical Analysis

Cigarette smoking was categorized according to the number of packs per day (ppd) consumed: 0, <1, 1-2, or  $\geq 2$  ppd, which corresponds to the questionnaire categories except that the <1/2 pack and 1/2 to 1 pack categories were combined because of the small number of participants who reported smoking <1/2 pack per day.

The longitudinal changes in smoking behavior of the cohort were summarized by comparing smoking level at baseline with average smoking over the study period. An average smoking score was calculated for all available visits after baseline (with the four smoking levels defined above numbered as 1-4). This average score was recoded into three categories as being less than, equal to, or greater than the reported smoking level at baseline.

The clinical endpoints considered for the analyses included PCP,

AIDS (1987 CDC definition) (14), death, and self-reported oral thrush. Survival analysis methods used included Kaplan-Meier curves with log-rank tests for significance and Cox multiple regression models. All Kaplan-Meier analyses were stratified by smoking level at baseline. To control for the possibility that the effect of smoking differed for different levels of immunosuppression, Kaplan-Meier analyses were further stratified by the baseline CD4<sup>+</sup> lymphocyte count (categorized as <200, 200-500, and >500 cells/ $\mu$ l). To adjust for several covariates simultaneously, Cox proportional hazard models were applied, which included smoking, CD4<sup>+</sup> lymphocyte count, and antiretroviral and anti-PCP therapy as time-dependent covariates.

The results we present here are based on the combined cohorts of seroconverters and seroprevalent men (a total of 2,420 men with complete data on covariates). The date of the baseline visit used as the time origin for this analysis was the first study visit for the seroprevalent men and the first HIV-positive visit for the seroconverters. By combining the cohorts (while adjusting for CD4<sup>+</sup> lymphocyte levels and HIV-related medications), we maximized the power to detect any effect of smoking on the health outcomes studied. For comparison, the seroconverter cohort was also analyzed separately. The final Cox models performed included (a) smoking as a time-dependent binary (yes/no) variable; (b) smoking as a time-dependent variable with four categories treated as a continuous variable, estimating the incremental risk per increase in smoking category; (c) smoking as a time-dependent cumulative score calculated by summing the smoking scores (levels 1-4 as defined above) up to a given visit and dividing by the total number of visits up to that point; and (d) models with baseline smoking only, as fixed covariates, defined as either a four-level variable or a binary (yes/no) variable. Results are presented for Model 1.

## RESULTS

### Smoking Behavior in the Cohort

Table 1 shows the baseline and longitudinal smoking behavior of the cohort. Of the 2,499 subjects, 973 men (38.9% of the cohort) were smokers at their baseline visit, that is, the first visit for prevalent seropositive men and the first seropositive visit for seroconverters. The vast majority of these men remained smokers during the follow-up period, although many reduced their smoking level at some point in the study (Table 1). Of the men who did not smoke at

TABLE 1. Baseline<sup>a</sup> and follow-up smoking behavior in HIV-seropositive MACS participants

Smoking at baseline (packs/day)	No. of patients (% of total)	Average smoking after baseline (% of group)		
		Decreased	Unchanged	Increased
0	1526 (61.1)	0	87.9	12.1
<1	344 (13.8)	45.1	26.0	28.9
1-2	446 (17.8)	54.8	28.9	16.3
$\geq 2$	183 (7.3)	67.7	32.3	0

MACS, Multicenter AIDS Cohort Study.

<sup>a</sup> Baseline = first seropositive visit.

their baseline visit, 88% remained nonsmokers during the follow-up period. Thus, smoking behavior was largely consistent during this study. Probably because of this, all the statistical analyses performed yielded essentially equivalent results whether they modelled smoking as a continuous or cumulative variable or simply stratified by smoking level at the baseline visit. Therefore, we present here the results of the model based on smoking as a time-dependent covariate.

Table 2 shows the raw data on progression of HIV infection to AIDS, death, PCP, and oral thrush from baseline as a function of baseline smoking behavior. The outcomes of AIDS, death, and PCP were quite similar for smokers and nonsmokers, but thrush was more frequent in smokers. In the following sections, these data are further analyzed to quantify the effect of smoking on these outcomes.

### Progression to AIDS and PCP

During the follow-up period, 1,110 men developed AIDS. Kaplan-Meier plots of AIDS-free survival time from baseline, stratified by smoking level at baseline, are presented in Fig. 1a. No dose of smoking (none, 0-1, 1-2, >2 ppd) was associated with accelerated progression to AIDS, and no significant difference in time to AIDS among the four smoking levels was observed (log-rank test  $p = 0.11$ ). This conclusion was not affected by stratification by baseline CD4 cell count ( $\leq 200$ , 201-500 cells,  $> 500$  cells/ $\mu$ l), which also showed no association between smoking and AIDS-free time or any trend toward increased progression with smoking (Fig. 1b-d; log-rank tests:  $p = 0.82$ , 0.36, and 0.12, respectively, for the three levels of CD4<sup>+</sup> lymphocytes). Similar trends were

observed when the seroconverters were analyzed separately from the seroprevalent men (data not shown).

Cox proportional hazards regression models for time to AIDS were fit to assess the effect of smoking on progression to AIDS controlling for other factors. After time-dependent adjustment for CD4<sup>+</sup> lymphocyte count and use of anti-AIDS medications, smoking was not significantly associated with the hazard of AIDS (relative hazard = 0.96,  $p = 0.7$  for smokers versus nonsmokers, with smoking analyzed as a time-dependent covariate).

Kaplan-Meier plots and Cox models of time from baseline to a first episode of PCP showed no association between smoking and progression to PCP. The log-rank statistic for the entire population was not significant ( $p = 0.12$ ), and the same was true when stratified by CD4<sup>+</sup> lymphocyte count at baseline. The relative hazard of PCP estimated from the Cox model, after time-dependent adjustment for CD4<sup>+</sup> lymphocyte count and anti-AIDS medication use, was 1.03 ( $p = 0.8$ ) for smokers versus nonsmokers (with smoking analyzed as a time-dependent covariate).

### Smoking and Survival

During the follow-up period (Table 2), 986 men died, the vast majority from AIDS-related causes. The Kaplan-Meier plots in Fig. 2 summarize time to death from baseline, stratified by smoking at baseline (Fig. 2a) or further stratified by baseline CD4<sup>+</sup> lymphocyte count (Fig. 2b-d). No significant difference was observed in survival times for the various smoking categories either overall (log rank  $p = 0.61$ ) or stratified by starting CD4<sup>+</sup> lymphocyte count ( $p = 0.59$ , 0.45, and 0.39 for  $\leq 200$ , 201-500, and  $> 500$

TABLE 2. Clinical outcomes by baseline smoking status among HIV-seropositive MACS participants over 9 years of follow-up

Smoking at baseline (packs/day)	n	AIDS n (%)	Death n (%)	PCP n (%)	Thrush n (%)
None	1,526	699 (45.8)	616 (40.4)	354 (23.2)	509 (33.3)
$\leq 1$	344	153 (44.5)	131 (38.1)	63 (18.3)	128 (37.2)
1-2	446	174 (39.0)	162 (36.3)	82 (18.4)	190 (42.6)
>2	183	84 (45.9)	77 (42.1)	39 (21.3)	79 (43.2)
Total	2,499	1,110 (44.4)	986 (39.5)	538 (21.5)	906 (36.2)
Total seroprevalent	2,132	1,016 (47.7)	908 (42.6)	488 (22.9)	811 (36.3)
Total seroconverter	367	94 (25.6)	78 (21.3)	50 (13.6)	95 (25.9)

MACS, Multicenter AIDS Cohort Study; PCP, *Pneumocystis carinii* pneumonia.

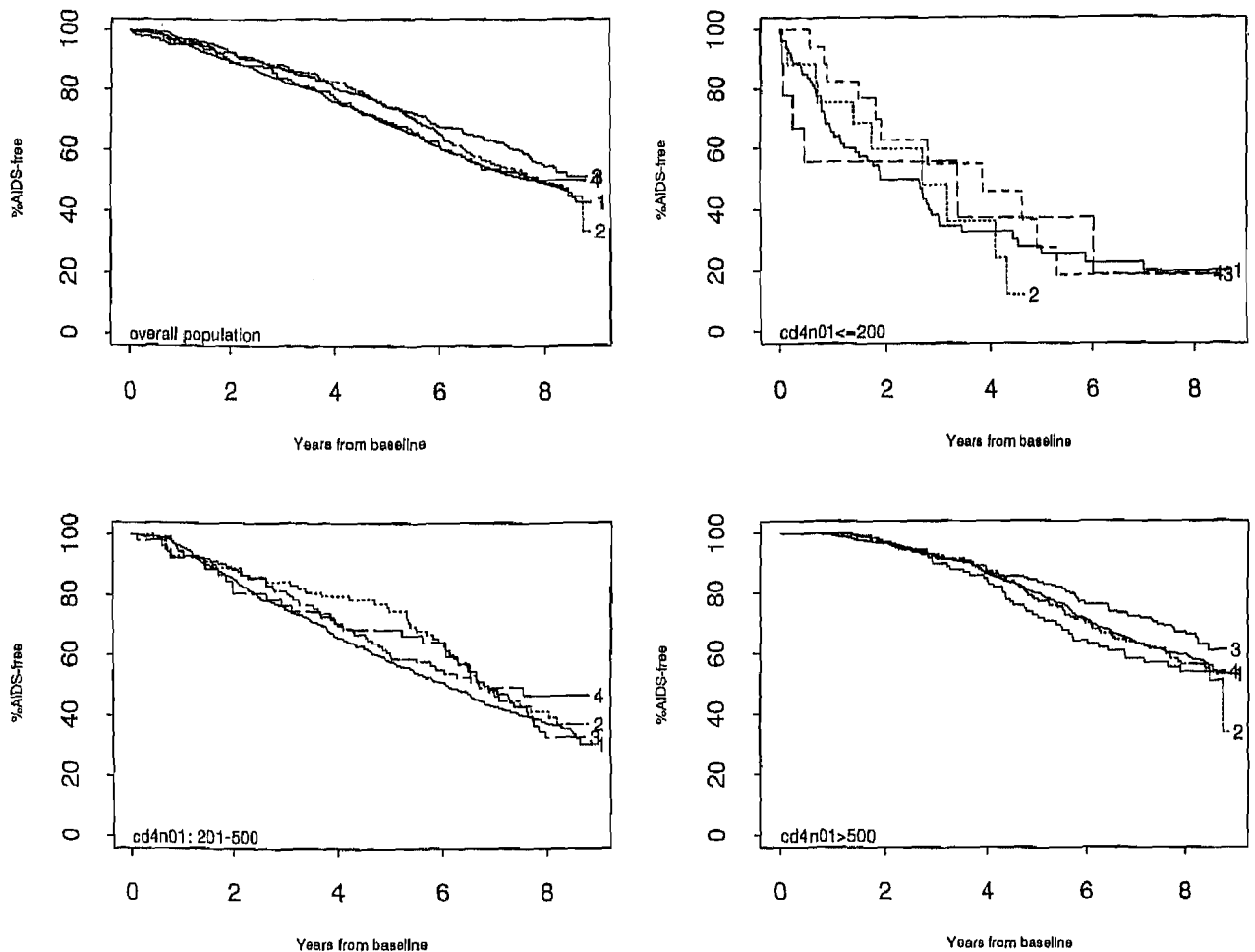


FIG. 1. Kaplan-Meier plots showing AIDS-free survival among HIV-seropositive Multicenter AIDS Cohort Study participants as a function of smoking level at the baseline visit. 1, no smoking; 2, <1 pack/day; 3, 1–2 packs/day; 4,  $\geq 2$  packs/day. The individual plots show the survival by baseline CD4<sup>+</sup> lymphocyte count: (a) top left, all HIV-seropositive participants; (b) top right, baseline CD4<sup>+</sup> lymphocyte count  $\leq 200/\mu\text{l}$ ; (c) bottom left, baseline CD4<sup>+</sup> lymphocyte count = 201–500/ $\mu\text{l}$ ; (d) bottom right, baseline CD4<sup>+</sup> lymphocyte count  $> 500/\mu\text{l}$ .

CD4<sup>+</sup> lymphocytes/ $\mu\text{l}$ , respectively). Smoking was not significantly associated with survival when included in Cox models similar to those used for time to AIDS. After adjustment for CD4<sup>+</sup> lymphocyte count and AIDS medications, the overall relative hazard of death for smokers versus nonsmokers was 1.03 ( $p = 0.7$ ). Thus, the results from analyses of smoking and death were virtually identical to those from smoking and development of AIDS.

#### Smoking and Thrush

In contrast to the above findings, smoking was significantly associated with time from baseline to self-reported thrush. Figure 3 presents the Kaplan-Meier plots of time to thrush overall (Fig. 3a) and stratified

by baseline CD4<sup>+</sup> lymphocyte number (Figs. 3b–d). Overall, nonsmokers had a lower risk for thrush (log rank  $p = 0.013$ ). Among the CD4<sup>+</sup> lymphocyte levels, smokers with  $\leq 200$  cells/ $\mu\text{l}$  showed no association between smoking and thrush ( $p = 0.54$ ), but smokers with CD4<sup>+</sup> lymphocyte counts between 201 and 500 or  $> 500$  cells/ $\mu\text{l}$  had a significantly higher risk of thrush than nonsmokers ( $p = 0.019$  and  $0.025$ , respectively). The higher risk of smokers was not related to the number of cigarettes smoked per day.

In Cox models including smoking, CD4<sup>+</sup> lymphocyte count, use of antiretroviral drugs, and PCP and AIDS prophylaxis as time-dependent covariates, smoking was associated with a 55% increase in risk of thrush ( $p = 0.0001$ ) for smokers versus nonsmokers. This result also held when smoking was included

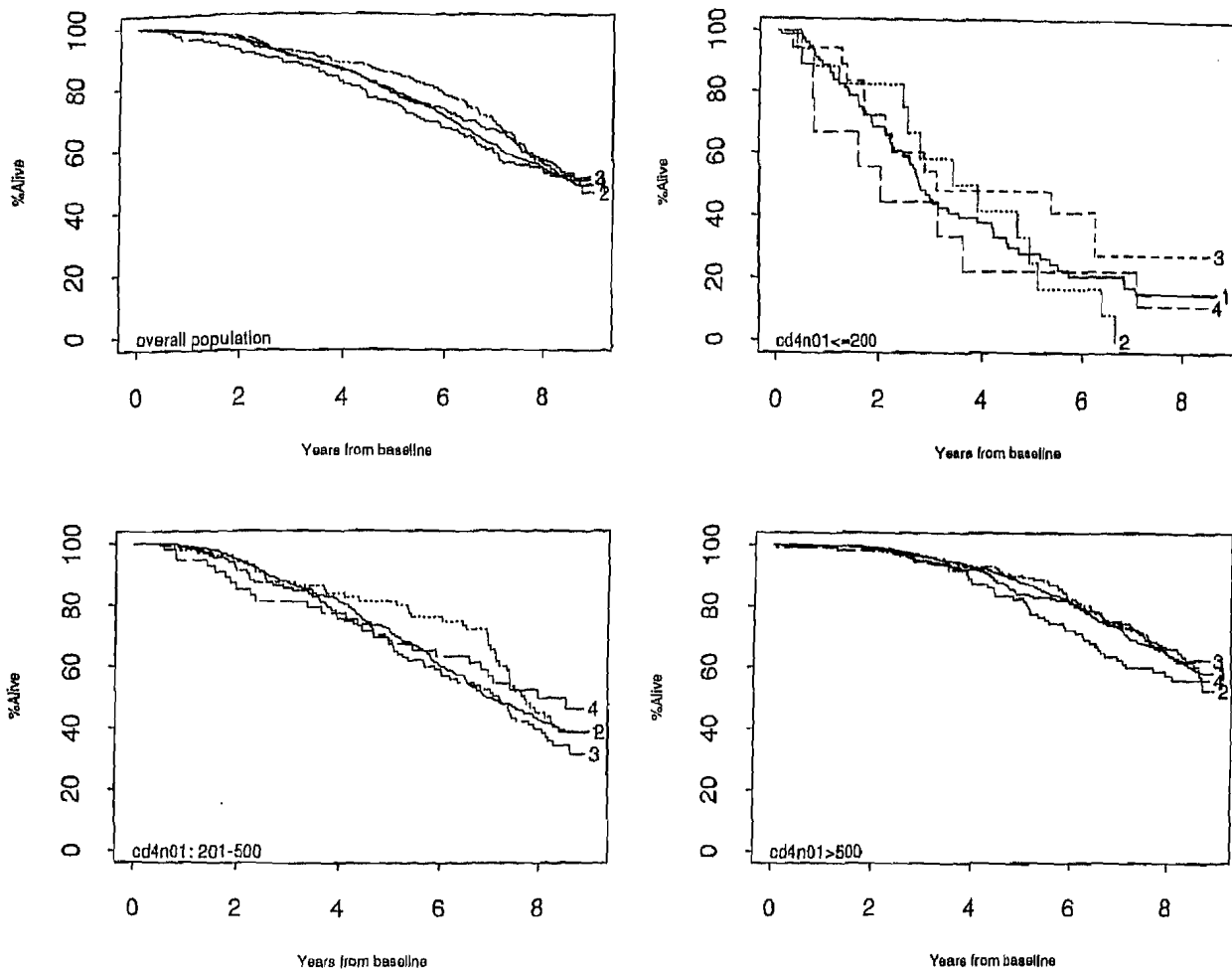


FIG. 2. Kaplan-Meier plots showing overall survival among HIV-seropositive Multicenter AIDS Cohort Study participants as a function of smoking level at the baseline visit. Symbols and plots are as described in the legend to Fig. 1.

as a four-level variable (as described above), with a relative hazard of 1.17 associated with each increase in smoking level. When the seroconverters were analyzed separately, they also showed a significant effect of smoking on thrush, with a relative hazard of 1.6 ( $p = 0.04$ ) for smokers compared with nonsmokers. None of the other outcomes showed a significant association with smoking.

Table 3 summarizes the results of Cox models fit separately for the three baseline CD4 strata and including smoking as a binary predictor. Smoking for the HIV+ cohort as a whole was significantly associated with about a 40% increase in hazard of thrush for those with baseline CD4  $>200$  cells/mm<sup>3</sup>. For all outcomes, similar results were obtained when cumulative cigarette consumption was used as the independent variable.

## DISCUSSION

This study demonstrates in a large cohort of homosexual men that smoking had no impact on the progression of HIV-1 infection to the endpoints of AIDS, PCP, or death. This finding was true regardless of the amount smoked or the baseline level of CD4<sup>+</sup> lymphocytes. The MACS cohort is by far the largest cohort of HIV-infected persons in which the effect of smoking has been investigated, and the present analysis was based on 9 years of follow-up. The MACS also has the advantage of frequent, quality controlled measurements of CD4<sup>+</sup> lymphocyte count (12,13) and excellent data on clinical follow-up and behavior. The data obtained and the inferences made in this study were the same whether the seroprevalent or seroconverted cohorts of the MACS were analyzed, the latter having well-defined times of seroconversion. For these rea-

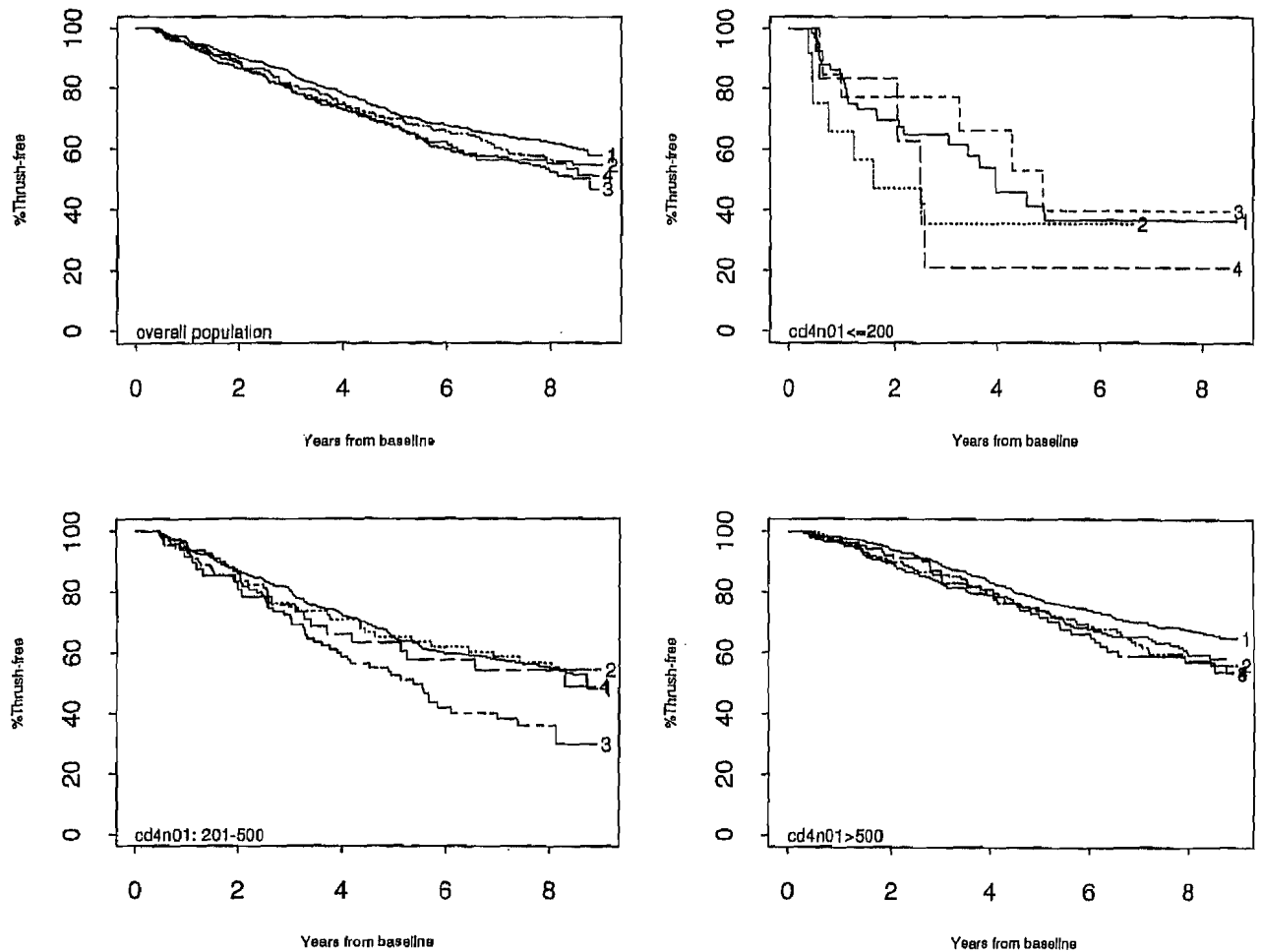


FIG. 3. Kaplan-Meier plots showing thrush-free survival among HIV-seropositive Multicenter AIDS Cohort Study participants as a function of smoking level at the baseline visit. Symbols and plots are as described in the legend to Fig. 1.

sons, our results provide very strong support for studies that have shown no effect of smoking on the rate of HIV-1 disease progression (6,8,15,16). Of course, the possibility remains that specific AIDS-related conditions not examined in the present study might be affected by smoking. Cigarette smoking was associated with a decreased incidence of Kaposi's sarcoma in the

MACS (17), and smoking of drugs, but not tobacco, has been associated with a higher incidence of bacterial pneumonia (18,19).

Previous studies have investigated the effect of smoking on HIV-1 disease progression, but the data have been conflicting and limited by many factors, including small sample size, lack of standardization for baseline CD4<sup>+</sup> count, retrospective data collection, short-term follow-up, and lack of data on HIV-related treatments, including zidovudine and PCP prophylaxis. In particular, the report of Nieman et al. who found more rapid disease progression in smokers (7), was subject to severe sample bias because it did not control for length of HIV infection and included only people who developed AIDS, as we have pointed out (20). In the present study, we included as time-dependent covariates CD4<sup>+</sup> lymphocyte counts and use of HIV-related therapy; so these factors were

TABLE 3. Adjusted effect of smoking at baseline on risk of thrush among HIV-seropositive MACS participants

Baseline CD4 <sup>+</sup> lymphocytes	OR	p Value
≤200	1.16	0.6
201-500	1.37	0.01
>500	1.43	0.0007

MACS, Multicenter AIDS Cohort Study; OR, odds ratio.  
<sup>a</sup> Effect of smoking is adjusted, in a time-dependent fashion, by CD4<sup>+</sup> lymphocyte strata and use of HIV-related therapy.

adjusted for in the analysis. Furthermore, the conclusions were confirmed in the cohort of seroconverters. Finally, the conclusions were not changed when amount of smoking was analyzed as a cumulative variable rather than as a cross-sectional variable (i.e., dosage at baseline). Thus, the present study addressed many of the limitations that were present in the earlier studies. The possibility that an important effect of smoking was negatively confounded by other drug use is remote, because the drugs commonly used in the MACS (i.e., alcohol, nitrites, cocaine, and psychoactive drugs) have been shown not to affect disease progression (21).

We previously showed that the "smoker's leukocytosis," i.e., the higher white blood count in smokers compared with nonsmokers, is attenuated beginning at HIV-1 seroconversion and disappears entirely by 3 years after seroconversion (5). This leukocytosis was for the most part nonspecific, affecting all types of leukocytes and all T-cell subsets approximately equally. Thus, smokers may have higher CD4<sup>+</sup> counts than nonsmokers for a few years after seroconversion but would be indistinguishable for most of the incubation period of AIDS, which exceeds 3 years in virtually all HIV-infected persons (22). Based on these data, we inferred that the CD4<sup>+</sup> lymphocyte count had the same prognostic value for the development of AIDS in smokers as in nonsmokers. The present study extends this finding by showing explicitly that smoking does not affect development of clinically defined AIDS.

The diagnosis of thrush on which the present analysis relied was based on self-report and thus could be subject to bias. Although clinical examination data to confirm the diagnoses are not available, this study has the support of previous smaller studies in which smoking has been associated with candidiasis in both HIV+ and HIV- men (16,23) and of the generally high reliability of self-reported data in the MACS (24). Smoking was also associated with increased periodontal disease which may, in turn, predispose to candidiasis, especially in HIV+ individuals (25). In the present study, oral thrush was clearly associated with immune suppression, similar to observations in immunosuppressed renal transplant recipients (26). Moreover, the lack of effect of smoking at lower CD4<sup>+</sup> levels (i.e., <200 cells/ $\mu$ l) suggests that at these levels immune suppression is the major factor predisposing to oral thrush. At higher CD4<sup>+</sup> lymphocyte counts, and thus presumably lower degrees of immune suppression, smoking could have local effects that favor development of thrush, such as irritation, immune suppression, or creation of favorable microenvironment for

candida species. Systemic immunomodulatory effects of smoking have been postulated to contribute to the higher rates of carcinoma of the cervix (27) and detection of HPV DNA and abnormal cytology in anal cells (28) seen in smokers, and smoking has also been associated with reduced numbers of Langerhans' cells and CD4<sup>+</sup> lymphocytes in the uterine cervix (29). Thus, it is possible that both local and systemic factors may predispose to oral candidiasis. Further study is needed to address these questions and to determine whether HIV-infected smokers who develop thrush are at increased risk for development of AIDS compared with nonsmokers with the same duration of HIV infection.

A comment is due on the use of smoking information in the present analysis and in similar studies. Clearly, smoking has both long-term and short-term effects on health. The information we collected included smoking level at baseline and at each semiannual visit, (i.e., describing behavior during the preceding 6 months). By including smoking as a time-dependent covariate in the analyses, we can explicitly capture the short-time association with health outcomes. Because smokers at baseline remained mostly smokers and nonsmokers remained mostly nonsmokers during the follow-up, however, the short-term association probably also reflects the long-term, cumulative effects of smoking. In addition, the decrease in smoking levels during follow-up, as shown in Table 1 (which may be partially explained by "regression to the mean"), tended to occur more frequently when individuals became sicker. This tendency would dilute the estimated effects of smoking on clinical outcomes and should be kept in mind. We have addressed this issue by applying models with either baseline or cumulative smoking levels in our analyses and have been seen that the results were consistent with what we have presented above. Thus, it is highly likely that the lack of association between smoking and AIDS outcomes in this study is not due to limitations in the information on life-time smoking.

Smoking cannot be recommended for anyone, HIV-infected or not. The available evidence, however, does not support an important negative (or positive) influence of smoking on progression of HIV infection.

#### **Multicenter AIDS Cohort Study (MACS) Participants**

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**Data Coordinating Center:** The Johns Hopkins University School of Hygiene and Public Health: Alvaro Muñoz, Principal Investigator; Cheryl Enger, Stephen Gange, Donald R. Hoover, Lisa P. Jacobson, Steven Piantadosi, Sol Su.

**NIH:** National Institute of Allergy and Infectious Diseases: Lewis Schrager, Project Officer; National Cancer Institute: Daniela Seminara.

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