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The Relationship of Preventable Opportunistic Infections, HIV-1 RNA, and CD4 Cell Counts to Chronic Mortality

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Background: Both HIV-1 RNA and absolute CD4 cell counts have been identified as important predictors of HIV-1 disease progression and mortality. The independent impact of opportunistic infections on the risk of chronic mortality, defined as death beyond 30 days of an opportunistic infection, has not been studied when controlling for HIV-1 RNA. Our objective was to determine the relationship between a history of any of five preventable opportunistic infections (*Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex, toxoplasmosis, cytomegalovirus, and candida esophagitis) and chronic mortality.

Methods: Using the Multicenter AIDS Cohort Study (MACS) public use data set of 2193 HIV-infected men in four U.S. cities, we employed a Cox regression model to estimate the impact of a history of preventable opportunistic infection on chronic mortality while controlling for maximum HIV-1 RNA, CD4 cell count, use of antiretroviral drugs, and age.

Findings: The chronic mortality rate among individuals with a history of preventable opportunistic infection was 66.7 per 100 person-years compared with 2.3 per 100 person-years for those without a history of preventable opportunistic infection (RR = 28.4, 95% CI: 24.7–32.8). In the adjusted analysis, the relative hazard of death for those with a history of preventable opportunistic infections was 7.0 (5.8–8.3), whereas antiretroviral therapy was associated with a decreased risk of death (0.37 [0.30–0.44]). We found no association between maximum HIV-1 RNA and chronic mortality. There was statistically significant effect modification between preventable opportunistic infections and CD4 cell count ($p < .0001$).

Interpretation: Preventable opportunistic infections cause not only short-term mortality in HIV-1 disease but appear to have a major impact on chronic mortality.

Key Words: HIV-1 mortality—Opportunistic infections—HIV-1 RNA—CD4 cell counts.

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Recent developments in the treatment of HIV-1 disease and the prevention of opportunistic infections have been dramatic (1–3). The use of combination antiretroviral agents to suppress HIV-1 RNA and regimens to treat and prevent opportunistic infections have improved survival in HIV-1–infected patients (3). Although these treatments have decreased the incidence of opportunistic infections, the burden of adhering to multiple and complicated treatment regimens has led many to question the importance of continuing opportunistic infection prophylaxis in the era of effective antiretrovirals (2,4–9). Several studies have shown that the risk of *Pneumocystis carinii* pneumonia (PCP) is very low in patients who have responded to highly active antiretroviral therapy (4–8), and a recent trial suggests that among individuals who respond to therapy, stopping *Mycobacterium avium* complex (MAC) prophylaxis after 12 months has no effect on the subsequent occurrence of MAC or bacterial pneumonia (9). The results of these studies have led to recommendations supporting the discontinuation of prophylaxis among patients with CD4 counts >200 cells/µL (2). These recommendations may not reflect the impact of previous opportunistic infections on both acute and chronic mortality, defined as death beyond 30 days of an opportunistic infection. Thus, understanding the relationship between a history of preventable opportunistic infection and chronic mortality is critical to developing guidelines for HIV-1 care and prioritizing among the many available therapies for HIV-1 disease (10,11).

The natural history of HIV infection has been well described (12–14), and there is general agreement that immune function and viral load as measured by absolute CD4 cell count and HIV-1 RNA level, respectively, are the most critical predictors of disease progression and mortality (15–17). However, few natural history studies have addressed the impact of a history of preventable opportunistic infection on chronic mortality independent of other markers of disease progression. Although previous reports have evaluated the relationship between preventable opportunistic infections and survival (17–23), only three studies have estimated the additional mortality risk associated with preventable opportunistic infections beyond the acute episode (21–23). Chaisson et al. (21) found an increased risk of death for individuals with a history of MAC, cytomegalovirus (CMV), toxoplasmosis, or PCP (relative hazards of 2.56, 1.63, 1.85, and 1.29, respectively) after controlling for CD4 cell count. Osmond et al. (22) found a median survival of 23 months for individuals diagnosed with PCP compared with a median survival of 30 months in matched controls without PCP. Unfortunately, these studies were not able to control for HIV-1 RNA, evaluated only one or two opportunistic infections, or had small sample sizes (24).

Our objective was to determine the relationship between a history of preventable opportunistic infection and chronic mortality, controlling for HIV-1 RNA, absolute CD4 cell counts, use of antiretroviral therapy, and age.

METHODS

We obtained the Multicenter AIDS Cohort Study (MACS) public use data set, which contains interview and medical record data from 1984 through 1994. Details of the MACS have been published elsewhere (12–16). Briefly, between March 1984 and April 1985, the MACS enrolled a total of 4954 homosexual men over 18 years of age at four sites in the United States. Our study sample consisted of the 2193 of these men who were HIV-1 infected but asymptomatic (Fig. 1). Median follow-up was 94 months (7.8 years).

For each individual in the study sample, CD4 cell counts were measured, clinical evaluations were conducted, and serum was obtained and saved at baseline and every 6 months thereafter (16). Missing CD4 cell counts were imputed from available CD4 cell counts using a ran-

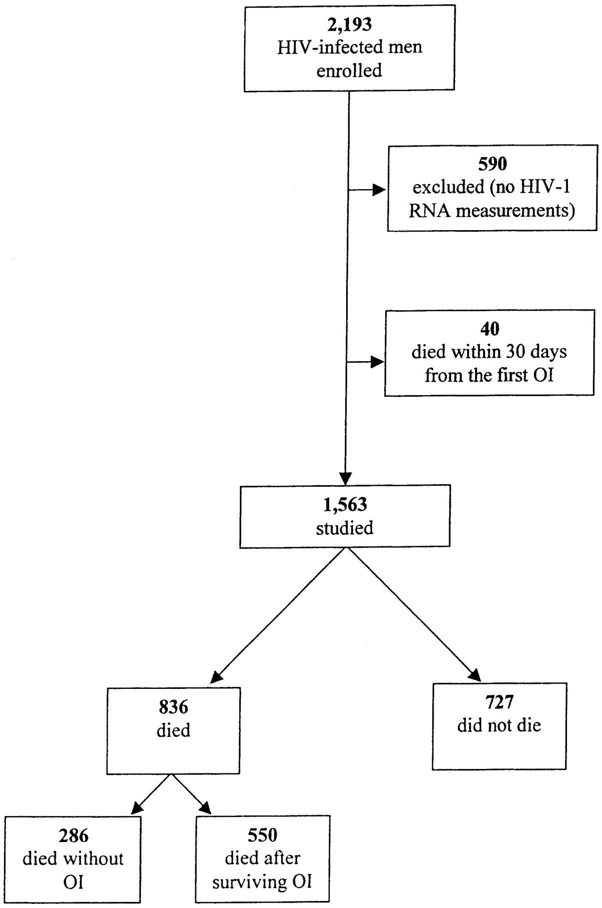

FIG. 1. Study profile of 2193 HIV-1–infected men from the Multicenter AIDS Cohort Study.

dom effects model (25,26). Measurement of HIV-1 RNA was conducted using a branched DNA assay (Chiron Corp., Emeryville, CA, U.S.A.) on available specimens (16). Subjects with no HIV-1 RNA measurements were excluded from the analysis, and if individuals had more than one HIV-1 RNA assessment ($n = 665$), we used their maximum HIV-1 RNA value. The median number of HIV-1 RNA assessments conducted in the MACS was 1.5, with 50% of the sample having an assessment 18 months after enrollment.

Since our objective was to evaluate the relationship between a history of preventable opportunistic infection and chronic mortality, we excluded individuals who died within 30 days of a preventable opportunistic infection ($n = 40$). Any death that occurred beyond the 30-day period was defined as a "chronic death." A preventable opportunistic infection was defined as the initial occurrence of any one of the following: PCP, MAC, toxoplasmosis, CMV, or candida esophagitis. Dates of diagnosis of opportunistic infections were obtained from medical chart review, and dates of death were obtained by matching name and date of birth with U.S. Vital Records as per the MACS protocol (15). All participants who had not been identified as deceased by September 30, 1994, were censored as of that date.

Incidence rates of preventable opportunistic infections were calculated using an incidence density analysis (27), and 95% CIs were calculated by the method of Rothman and Greenland (28). We used a proportional hazards model to develop estimates of the adjusted relative hazards and their corresponding 95% CIs (29) for the following variables: 1) any acute preventable opportunistic infection, 2) three HIV-1 RNA strata (≤30,000 copies/mL, 30,001–100,000 copies/mL, and >100,000 copies/mL), 3) three CD4 cell count strata as time-varying covariates (≤50 cells/μL, 51–200 cells/μL, and >200 cells/μL), 4) age (<33 years or ≥33 years), and 5) use of antiretroviral therapy (primarily zidovudine monotherapy).

To determine if CD4 cell count modifies the relationship between preventable opportunistic infections and chronic mortality, a second analysis compared the relative hazards for preventable opportunistic infection across CD4 cell count strata, adjusting for maximum HIV-1 RNA, antiretroviral therapy, and age. This model included the following strata: 1) a "true" referent category, which included individuals with no history of a preventable opportunistic infection and CD4 count >200 cells/μL; 2) no history of a preventable opportunistic infection and CD4 count between 51 and 200 cells/μL; 3) no history of a preventable opportunistic infection and CD4 count ≤50 cells/μL; 4) history of a preventable opportunistic infection and CD4 count >200 cells/μL; 5) history of a preventable opportunistic infection and CD4 count between 51 and 200 cells/μL; 6) history of a preventable opportunistic infection and CD4 count ≤50 cells/μL; 7) maximum HIV-1 RNA (≤30,000 copies/mL, 30,001–100,000 copies/mL, and >100,000 copies/mL); 8) any use of antiretrovirals (coded as a time-varying covariate); and 9) age at enrollment (median split at 33 years of age as per previous MACS analyses) (3,15,16,18). We conducted a test of homogeneity by comparing the relative hazards for chronic mortality for those with and without a history of preventable opportunistic infection across CD4 cell count strata (28).

To examine whether maximum HIV-1 RNA modifies the relationship between a history of preventable opportunistic infection and both CD4 cell count strata and chronic mortality, a third proportional hazards model was developed. This third model employed a series of indicator variables to compare the relative hazards for preventable opportunistic infection across categories of maximum HIV-1 RNA (≤30,000 copies/mL, 30,001–100,000 copies/mL, and >100,000 copies/mL) and across CD4 cell count strata, adjusted for antiretroviral therapy and age.

Finally, we evaluated whether having a history of preventable opportunistic infection has an effect on CD4 cell counts. We compared changes in CD4 cell count before and after a preventable opportunistic infection among individuals with a preventable opportunistic infection with changes in a random sample of individuals with CD4 counts <300 cells/μL and no preventable opportunistic infection. A Student *t* test was conducted to evaluate these differences.

RESULTS

Among the 2193 asymptomatic HIV-1–infected individuals enrolled in the MACS, 590 (26.9%) were excluded because they did not have an HIV-1 RNA measurement and an additional 40 (1.8%) were excluded because they died within 30 days of their first opportunistic infection (Fig. 1). Of the 1563 (71.2%) who remained eligible for the analysis, 836 (38.1%) died during the follow-up period, resulting in a chronic mortality rate of 6.42 per 100 person-years (95% CI: 6.0–6.8). Of the 836 deaths, 550 occurred in persons with a history of a preventable opportunistic infection (66.75 per 100 person-years) compared with 286 in patients with no prior preventable opportunistic infection (2.35 per 100 person-years), resulting in an RR of 28.43 (24.65–32.80) (Table 1).

In the initial unadjusted analysis, we found higher rates of chronic mortality among those with higher levels of HIV-1 RNA and lower CD4 cell counts. For example, for individuals with HIV-1 RNA >100,000 copies/mL, 30,001 to 100,000 copies/mL, and ≤30,000 copies/mL, the chronic mortality rates were 10.76, 6.99, and 3.05 per 100 person-years, respectively. Similarly, the chronic mortality rate among those individuals with CD4 counts ≤50 cells/μL, 29.97 per 100 person-years, was significantly higher than in patients with CD4 counts from 51 to 200 cells/μL or >200 cells/μL. Chronic mortality was higher among individuals over the age of 33 years as well as among individuals who received antiretroviral therapy, primarily zidovudine monotherapy, from 1987 through 1994.

We then used a Cox regression model to estimate the effect of a history of preventable opportunistic infection, maximum HIV-1 RNA, and current CD4 cell count on chronic mortality (Table 1). The relative hazard for chronic mortality among individuals with a history of preventable opportunistic infections was 6.97 (5.85–8.32) compared with all other individuals without a history of preventable opportunistic infection. The risk of chronic mortality was greatest among individuals with CD4 cell counts ≤50 cells/μL (relative hazard of 8.68) compared with those with CD4 counts >200 cells/μL. Older men had a higher risk of chronic mortality (relative hazard of 1.34), whereas use of antiretroviral therapy

TABLE 1. *Chronic HIV-1 mortality rates: crude and adjusted hazard rate ratios by history of a preventable opportunistic infection, HIV-1 RNA level, CD4 stratum, age, and antiretroviral therapy*

Risk factor	Deaths	Time to follow-up (years)	Rate per 100 person-years	Hazard rate ratio	
				Crude (95% CI[a])	Adjusted (95% CI[a])
Overall	836	13,106	6.42	—	—
Preventable opportunistic infection					
Yes	550	825	66.75	28.43 (24.65–32.80)	6.97 (5.85–8.32)
No	286	12,191	2.35	1.00	1.00
Maximum HIV-1 RNA level (copies/mL)					
>100,000	431	4007	10.76	3.53 (2.96–4.21)	1.18 (0.97–1.43)
30,001–100,000	231	3305	6.99	2.29 (1.88–2.79)	1.15 (0.93–1.41)
≤30,000	174	5704	3.05	1.00	1.00
CD4 stratum (cells/μL)					
>200	189	9898	1.91	1.00	1.00
51–200	234	1740	13.45	7.04 (5.81–8.53)	4.33 (3.34–5.61)
≤50	413	1378	29.97	15.69 (13.28–18.73)	8.68 (6.73–11.20)
Age at enrollment (years)					
≥33	454	6190	7.33	1.31 (1.14–1.50)	1.34 (1.17–1.53)
<33	382	6826	5.60	1.00	1.00
Antiretroviral therapy					
Yes	142	1917	7.41	1.18 (0.99–1.42)	0.37 (0.30–0.44)
No	694	11,099	6.25	1.00	1.00

[a] 95% CIs were calculated by the method of Rothman and Greenland (28).

was associated with a decreased hazard (relative hazard of 0.37). We found no association between maximum HIV-1 RNA and chronic mortality.

We found that a history of preventable opportunistic infection modified the relationship between CD4 cell count and chronic mortality, after adjusting for maximum HIV-1 RNA, age, and antiretroviral therapy (Table 2). Among individuals without a history of preventable opportunistic infection, there was an inverse relationship between the relative hazard and both chronic mortality and CD4 cell counts, with adjusted relative hazards of 6.6 in those with CD4 counts between 51 and 200 cells/μL and 18.1 in those with CD4 counts ≤50 cells/μL. Among those individuals with a history of preventable opportunistic infection and CD4 counts >200 cells/μL, the relative hazard for chronic mortality was 68.3 (46.0–101.4) compared with those without a history of preventable opportunistic infection and CD4 counts >200 cells/μL. This effect was of smaller magnitude among individuals with CD4 counts between 51 and 200 cells/μL (relative hazard of 46.9) and of greater magnitude in those with CD4 counts ≤50 cells/μL (relative hazard of 87.0). Similar to individuals without a history of preventable opportunistic infection, there was effect modification by CD4 cell count among those with a history of preventable opportunistic infection ($p < .0001$). As in the initial adjusted analysis, there was no association between maximum HIV-1 RNA and chronic mortality.

TABLE 2. *The effect of CD4 cell count on chronic HIV-1 mortality stratified according to history of preventable opportunistic infection*[a]

Risk factor	Hazard rate ratio (95% CI)
No preventable opportunistic infection history	
CD4 >200 cells/μL	1.0
CD4 51–200 cells/μL	6.6 (4.8–9.1)
CD4 ≤50 cells/μL	18.1 (13.4–24.5)[b]
Preventable opportunistic infection history	
CD4 >200 cells/μL	68.3 (46.0–101.4)
CD4 51–200 cells/μL	46.9 (33.4–65.9)
CD4 ≤50 cells/μL	87.0 (66.0–114.6)[b]
Maximum HIV-1 RNA level	
>100,000 copies/mL	1.0
30,001–100,000 copies/mL	1.1 (0.9–1.4)
≤30,000 copies/mL	1.1 (0.9–1.4)
Antiretroviral therapy	0.36 (0.3–0.4)
Age (≥33 years)	1.3 (1.2–1.5)

[a] Adjusted for maximum HIV-1 RNA level, age, and antiretroviral therapy.

[b] $p < .0001$ for the test of homogeneity of the effect of preventable opportunistic infection on chronic HIV-1 mortality across CD4 strata.

These data also suggest that CD4 cell count modifies the effect of a history of a preventable opportunistic infection on chronic mortality. This was most pronounced when comparing the effect (relative hazard of 68.3) on individuals with a history of preventable opportunistic infection and CD4 count >200 cells/μL with the effect on individuals in the referent category (no history of preventable opportunistic infection and CD4 count >200 cells/μL) (Fig. 2). The effect of having a history of preventable opportunistic infection in the CD4 stratum of 51 to 200 cells/μL (RR = 7.1) was estimated by dividing the relative hazard (46.9) for individuals with a history of

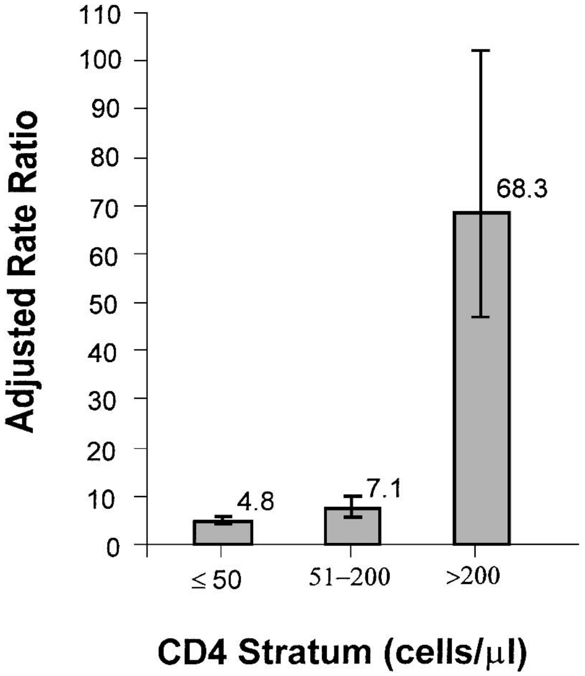

FIG. 2. Adjusted rate ratios of the association between a history of preventable opportunistic infections and chronic HIV-1 mortality stratified by CD4 stratum (Multicenter AIDS Cohort Study, 1985–1994).

preventable opportunistic infection and CD4 count between 51 and 200 cells/μL by the relative hazard (6.6) of individuals without a history of preventable opportunistic infection. Among individuals with CD4 cell counts ≤50 cells/μL, the effect of a history of preventable opportunistic infection was smaller (relative hazard of 4.8) but still measurable.

In the third analysis, we examined whether maximum HIV-1 RNA and a history of preventable opportunistic infection modifies the relationship between CD4 cell count and chronic mortality (Table 3). When we compared individuals without a history of preventable opportunistic infection, CD4 counts >200 cells/μL, and HIV-1 RNA ≤30,000 copies/mL with individuals with a history of a preventable opportunistic infection, we found the latter group substantially more likely to die (relative hazards ranging from 40.3–107.4) depending on HIV-1 RNA levels. Maximum HIV-1 RNA significantly increased the hazard of death among individuals without a history of preventable opportunistic infection and CD4 counts ≤50 cells/μL (relative hazards of 12.8, 22.8, and 26.8, respectively; $p < .0001$).

We performed a series of sensitivity analyses to examine the implications of both redefining acute mortality and excluding those individuals with missing CD4 cell counts from the analysis. When we expanded the definition of acute mortality to include all deaths within 90 days of a preventable opportunistic infection, the effect of a history of preventable opportunistic infection on chronic mortality decreased slightly (relative hazard of 6.3, 95% CI: 5.3–7.6). However, the relative hazards for chronic mortality from the proportional hazards models evaluating effect modification were virtually identical to those shown in Tables 2 and 3. When we excluded persons with missing CD4 cell counts from the analysis, the effect of a history of preventable opportunistic infection was slightly higher (relative hazard of 8.8, 95% CI: 6.9–11.3). However, the relative hazards from the models evaluating effect modification were substantially higher (and remained statistically significant) than those reported in Tables 2 and 3 (results not shown).

In our final analysis, we evaluated whether a history of preventable opportunistic infection changes CD4 cell counts. Over a 12-month interval, individuals with a history of preventable opportunistic infection experienced a mean CD4 count decrease of 110 cells/μL compared with 47 cells/μL in those who had no history of preventable opportunistic infection ($p < .0001$).

TABLE 3. *The effect of HIV-1 RNA on chronic HIV-1 mortality stratifed according to history of preventable opportunistic infection and CD4 cell count*[a]

	Hazard rate ratio by HIV-1 RNA level (copies/mL)			
CD4 stratum (cells/μL)	≤30,000	30,001–100,000	>100,000	*p* value[b]
No preventable opportunistic infection				
>200	1.0	1.8	0.7	0.02
51–200	7.0	9.4	7.4	0.55
≤50	12.8	22.8	26.8	0.01
Preventable opportunistic infection				
>200	101.7	76.1	67.4	0.51
51–200	74.5	40.3	51.1	0.14
≤50	103.7	104.6	107.4	0.96

[a] Adjusted for age and antiretroviral therapy.
[b] *p* value for the test of homogeneity across HIV-1 RNA level.

DISCUSSION

In addition to the well-documented acute mortality that occurs in the setting of an opportunistic infection, we found that a history of a preventable opportunistic infection serves as an independent risk factor for (and immune function effect modifier of) chronic mortality. Although the impact of opportunistic infections on chronic mortality has been previously reported (18–23), this is the first analysis that includes both CD4 cell counts and HIV-1 RNA level.

Kaplan et al. (24) have questioned whether the relationship between preventable opportunistic infections and chronic mortality is causal or whether these infections simply represent clinical markers for disease progression. Our results are consistent with a causal hypothesis. When we controlled for maximum HIV-1 RNA level and CD4 cell count, having a history of preventable opportunistic infection appeared to be an independent risk factor for chronic mortality. For example, in the crude analysis, having a history of preventable opportunistic infection was highly associated (RR = 28.43) with chronic mortality, as was CD4 count $\leq$50 cells/μL (relative hazard of 15.7). In the adjusted analysis (Table 1), individuals with a history of preventable opportunistic infection were seven times more likely to die of chronic HIV-1, which suggests that either CD4 cell counts, maximum HIV-1 RNA level, or both were confounders. After adjusting only for maximum HIV-1 RNA, the relative hazard of a history of preventable opportunistic infection on chronic mortality decreased somewhat, from 28.43 to 19.3 (results not shown). This is in contrast to the effect of adjusting only for CD4 cell count, in which the relative hazard was reduced substantially, from 28.43 to 7.04. Thus, we conclude that CD4 cell count is an independent risk factor for chronic mortality, since in the absence of a history of preventable opportunistic infection, the relative hazard of chronic mortality increased with lower CD4 cell counts. In addition, CD4 cell count serves as an effect modifier of the relationship between a history of opportunistic infection and chronic mortality.

The possibility that a history of preventable opportunistic infection is causally linked to chronic mortality is biologically plausible. In vitro, bacterial (30), mycobacterial (31), fungal (32), viral, and parasitic (33) organisms have facilitated HIV-1 replication, possibly by activating target CD4 cells and macrophages (34,35). Activated CD4 cells are more susceptible to HIV-1 infection (36–38), and once infected, they have decreased survival. In addition, case reports and case series suggest that HIV-1 RNA increases after an acute preventable opportunistic infection (39–42). Although this could be associated with relatively short-term outcomes, we observed an effect of preventable opportunistic infection over an extended period of time. One possibility is that a history of preventable opportunistic infection may increase the HIV-1 RNA "set point" to a higher level; this would account for a more rapid decline in immune function (24). When we attempted to test this hypothesis by comparing CD4 cell counts both before and after a preventable opportunistic infection, we found a significant decline in CD4 cell counts associated with the occurrence of a preventable opportunistic infection. Unfortunately, the time interval between the CD4 cell count assessments (mean of 12 months) may have been too long to identify an initial rapid increase in CD4 cell count prior to the observed decline.

Just as CD4 cell counts have been shown to serve as an independent risk factor for preventable opportunistic infections, HIV-1 RNA has also been shown to be an independent risk factor for both preventable opportunistic infections (4) and HIV disease progression (15,16). Thus, it is reasonable to suggest that once we controlled for HIV-1 RNA, the effect of a history of preventable opportunistic infection on chronic mortality would be greatly reduced. However, in the adjusted analysis, we observed virtually no effect of maximum HIV-1 RNA level as an independent risk factor for chronic mortality, a confounder, or an effect modifier of preventable opportunistic infection on chronic mortality.

These results are especially intriguing given that a prior published analysis using the same data reported a strong effect of HIV-1 RNA level on HIV-1–related mortality (15). There are three possible explanations for this apparent discrepancy. First, unlike other published studies, this analysis focuses on chronic mortality, which is a different outcome than in previous analyses (15,16). Second, HIV-1 RNA assessments were conducted on available stored specimens, and, on average, 2.3 assessments were conducted per individual. Thus, although we used maximum HIV-1 RNA values when available, the accuracy of the assessment was hindered by the sampling of available specimens. In addition, the lack of serial HIV-1 RNA assessments prohibited us from evaluating the hypothesis that the HIV-1 RNA set point is altered following a preventable opportunistic infection. In contrast, CD4 cell counts were usually obtained at each 6-month visit. It should not be surprising that CD4 cell counts used as a time-varying covariate could predict chronic mortality more accurately. This is because they were obtained both more frequently and in closer proximity to the clinical outcome than HIV-1 RNA assessments. Finally, in previous analysis of the MACS data set, only baseline CD4 cell counts were used.

Our results also showed that the use of antiretroviral monotherapy, primarily zidovudine, was associated with an increased risk of death (RR = 1.18); however, after adjustment, antiretroviral therapy was associated with a significantly reduced risk of chronic mortality (relative hazard of 0.36). This appears to be an example of "confounding by severity," which can occur in observational studies that attempt to assess the impact of new and effective therapies. Here, individuals in greatest need of an intervention, as measured by disease severity, receive therapy (43,44). This distorts the effect of therapy when one compares efficacy measures from clinical trials with "effectiveness" from observational data, usually showing the new intervention to have lower effectiveness. Our results suggest that using a history of preventable opportunistic infection, CD4 cell counts, and maximum HIV-1 RNA is a reasonable approach to control for confounding by severity (45,46).

This analysis has a number of limitations. First, we used a single maximum HIV-1 RNA measure in patients on no therapy or zidovudine monotherapy and made the assumption that it represented the viral load set point. Although additional data on HIV-1 RNA would be valuable in refining this analysis, it is unlikely the major results would change. Second, the MACS public use data set contains data from 1984 through 1994, and clinical care has changed dramatically since this period due to the use of combination antiretroviral therapy. However, analyzing data collected prior to the routine use of combination therapy allowed us to make causal inferences about the relationship between the history of preventable opportunistic infection, maximum HIV-1 RNA, CD4 cell count, and chronic mortality. Although it is true that the generalizability and relevance of these findings may be somewhat diminished in the era of antiretroviral therapy, 22% to 25% of all HIV patients in the United States still present for HIV care at the time of their first opportunistic infection (47). Thus, these data suggest there is even more value in identifying these patients and linking them to care before their first opportunistic infection. In addition, because the vast majority of the world's population does not currently have access to antiretroviral therapy, these data remain relevant. Finally, since the data set includes predominantly adult gay men, the results may not be representative of women or other adult HIV-1–infected populations.

The relationship between a history of preventable opportunistic infection and chronic mortality is complex, and our results support the idea that HIV-1 may cause mortality through a number of different pathways. As the clinical care for HIV continues to evolve in the setting of combination antiretroviral therapy and the role of prophylaxis against opportunistic infections is questioned, it is important to consider these multiple pathways when estimating the benefits of prophylaxis against opportunistic infections.

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