

# Application of Case–Crossover and Case–Time–Control Study Designs in Analyses of Time-varying Predictors of T-cell Homeostasis Failure

MICHAEL F. SCHNEIDER, MS, STEPHEN J. GANGE, PHD, JOSEPH B. MARGOLICK, MD, PHD, ROGER DETELS, MD, JOAN S. CHMIEL, PHD, CHARLES RINALDO, PHD, AND HAROUTUNE K. ARMENIAN, MD, DRPH

**PURPOSE:** To evaluate the association of sexual behavior and recreational drug exposures with T-cell homeostasis failure (TCHF), which corresponds to the onset of a rapid decline in an individual's T lymphocyte count, which occurs on average approximately 1.75 years prior to an initial diagnosis of acquired immunodeficiency syndrome (AIDS).

**METHODS:** A case–crossover design and a case–time–control design, both nested within the Multicenter AIDS Cohort Study of 4954 homosexual and bisexual men initiated in 1983.

**RESULTS:** In the case–crossover analysis, use of both recreational drugs and hashish were found to be protective against TCHF (odds ratios  $\leq 0.41$ ), based on comparisons with four earlier control periods. However, a significant decreasing trend in the prevalence of these exposures was observed over time, thus motivating the implementation of the case–time–control design. Using the latter approach, the associations of drug use (odds ratio = 0.53; 95% confidence interval (CI): 0.22, 1.28) and hashish use (odds ratio = 0.46; 95% CI: 0.20, 1.05) with TCHF were no longer statistically significant.

**CONCLUSIONS:** The difference in inferences between these approaches demonstrates the importance of evaluating temporal trends in exposures when using a case–crossover design.

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**KEY WORDS:** HIV/AIDS, Epidemiological Methods, Biological Markers, Crossover Studies.

## INTRODUCTION

Since the beginning of the human immunodeficiency virus (HIV) epidemic, there have been intense efforts to investigate factors that influence HIV disease progression,

From the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (M.F.S., S.J.G., H.K.A.); Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (J.B.M.); Department of Epidemiology, University of California Los Angeles School of Public Health, Los Angeles, CA (R.D.); Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL (J.S.C.); and Department of Infectious Diseases and Microbiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA (C.R.).

Address correspondence to: Michael F. Schneider, M.S., Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, 615 N. Wolfe Street, Room E7012, Baltimore, MD 21205. Tel.: (410) 955-4320; Fax: (410) 955-7587. E-mail: mschneid@jhsph.edu

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in particular those that affect the occurrence or timing of death and clinical manifestations of acquired immunodeficiency syndrome (AIDS) (1). Despite these efforts, relatively few epidemiological and behavioral factors have been associated with disease progression or intermediate events. Age at time of seroconversion is well established (2), while co-infection with hepatitis C virus or GB virus C, ethnicity, and sex are suggestive but less clear (3–7).

Compared with factors associated with the development of clinical disease, relatively little investigation has gone into identifying factors associated with intermediate events. The modeling of  $CD4^+$  lymphocyte counts may be an exception, where the approximate linear decline of this marker over time has facilitated the identification of predictors of fast or slow  $CD4^+$  declines over time. The paucity of studies using markers is partly due to the relatively recent understanding of intermediate pathogenesis (5, 8, 9) as well as the introduction of highly active antiretroviral therapy (HAART), which complicates evaluation of natural history and marker trends. An advantage of using intermediate biomarkers is that they may provide more insight than studies of clinical disease into mechanisms of pathogenesis and may eliminate some of the variability inherent in clinical outcomes (e.g., opportunistic infection prophylaxis) (10). However, substantial efforts including standardized, prospective follow-up, are required to obtain high-quality intermediate biomarker data.

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**Selected Abbreviations and Acronyms**

AIDS = acquired immunodeficiency syndrome  
CI = confidence interval  
HAART = highly active antiretroviral therapy  
HIV = human immunodeficiency virus  
IQR = interquartile range  
MACS = Multicenter AIDS Cohort Study  
STD = sexually transmitted disease  
TCHF = T-cell homeostasis failure

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Beginning in the mid 1990s, a series of studies identified the occurrence of a rapid decline in total T lymphocyte counts, closely corresponding to the sum of the CD4<sup>+</sup> and CD8<sup>+</sup> cell counts, prior to the onset of clinically defined AIDS (11-14). This rapid decline, the onset of which is termed T-cell homeostasis failure (TCHF) (11), begins at variable times after HIV infection but is more well-defined in relation to the onset of AIDS, beginning an average of 1.75 years before the initial diagnosis of AIDS. A variety of investigations have evaluated immunologic and virologic characteristics around TCHF, but no studies have investigated whether modifiable epidemiologic factors are also associated with TCHF (15, 16).

Therefore, the goal of the present study was to understand whether continued exposure to factors associated with the acquisition of HIV infection (e.g., sexual and drug use behaviors) might precipitate TCHF. To undertake this initiative, we identified the approximate time of TCHF on an individual level for participants in the Multicenter AIDS Cohort Study (MACS), and used two designs that facilitate the evaluation of time-varying behavioral factors: a case-crossover and a case-time-control design (17-22). In both of these designs, individuals were treated as their own controls and exposures near the time of TCHF were compared with previous time points when an individual was at risk for, but did not develop, TCHF.

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**MATERIALS AND METHODS****Study Population**

The MACS was initiated in 1983 to study the natural history of HIV-1 infection among homosexual and bisexual men in the United States. The study design has been previously described (23), and only aspects pertinent to this analysis are presented here. In 1984 and 1985, 4954 men were enrolled in Baltimore/Washington, Chicago, Los Angeles, and Pittsburgh. In 1987, recruitment was reopened and an additional 668 men were enrolled, most of whom were ethnic minorities. The institutional review board at each of the participating centers approved the MACS study protocols and informed consent was obtained from all participants.

At semiannual visits, study participants returned to the clinics to provide specimens for laboratory analyses, undergo

a physical examination and complete self-administered data forms as well as an interviewer-administered questionnaire. AIDS diagnoses were consistent with 1987 clinical criteria and confirmed by a physician's or hospital record (24). Analyses used data collected prior to 1995, before the widespread use of HAART.

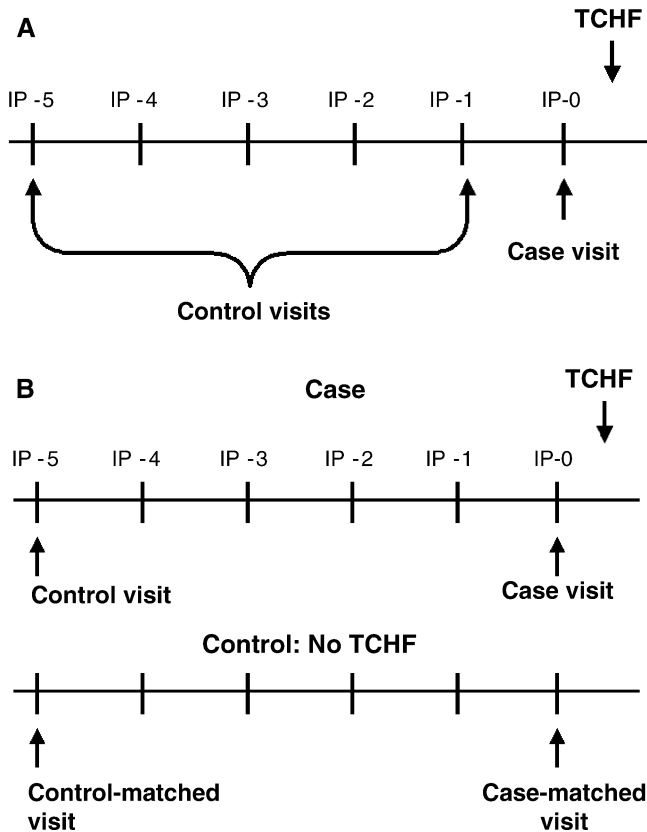
**Identification of T-cell Homeostasis Failure (TCHF)**

Segmented regression methods have previously been implemented to estimate the time point at which TCHF was most likely to have occurred for each individual (13). Briefly, for each participant, an eligible candidate inflection point was defined as the midpoint in time between any two semiannual study visits. For each individual, the eligible inflection point that provided the smallest residual variability between the data and the fitted regression line (i.e.,  $\min \sum \hat{\epsilon}_{ij}^2$ ) was chosen as the actual inflection point (i.e., the estimated time of TCHF).

**Case-Crossover Design and Analysis**

The case-crossover design is similar to a matched-pair case-control study and allows for estimation of time-varying exposures at time points when individuals were at risk for TCHF (control periods) as compared with exposures occurring immediately before the time point where TCHF was estimated to have occurred (case period) while controlling for within-person confounding. Figure 1a illustrates the case-crossover design. The case visit was defined as the study visit immediately prior to the estimated time of TCHF (IP - 0). We investigated a range of control visits up to approximately 2.5 years (five study visits) prior to the time of TCHF. There were approximately 6 months between each of the control visits.

The cases included in this analysis were a subset of the 706 MACS participants who developed AIDS as of October 1994 as described in detail elsewhere (13). Specifically, we restricted our analysis to data from 312 MACS participants who had a decline in CD3<sup>+</sup> T-cell counts of at least 10% per year after the estimated time of inflection, had more than 10 CD3<sup>+</sup> T-cell counts available (with at least six of the CD3<sup>+</sup> T-cell counts occurring prior to AIDS), and had at least 4.5 years of follow-up prior to TCHF. Restricting to individuals with AIDS and a decline in CD3<sup>+</sup> T-cells of at least 10% per year after the estimated time of inflection was done to ensure that the cases homogeneously demonstrated true inflection, different from the natural variability in CD3<sup>+</sup> T-cell count changes over time that has been reported previously (13). Limiting the analysis to those with more than 10 marker measurements and 4.5 years of follow-up before TCHF ensured an adequate amount of observation time while the men were at risk for TCHF. Among these 312



**FIGURE 1.** Illustration of (a) case-crossover study design and (b) case-time-control study design, Multicenter AIDS Cohort Study, 1984-1995. AIDS, acquired immunodeficiency syndrome; IP, inflection point; TCHF, T-cell homeostasis failure.

participants, 270 were HIV positive at study entry and 42 seroconverted after their initial baseline study visit.

Individual self-reported drug use and sexually transmitted disease (STD) exposures were investigated independently and also in aggregate measures. While data on these exposures were collected every 6 months, the duration of use was generally not known. Hence, exposures were categorized into dichotomous variables.

The Mantel-Haenszel odds ratio for matched-pairs was used as the measure of analysis (17). This odds ratio was calculated by taking the number of participants exposed in the case period and unexposed in the control period divided by the number of participants unexposed in the case period and exposed in the control period.

### Case-Time-Control Design and Analysis

The most critical assumption of the case-crossover analysis was that there were no overall temporal trends in exposure, since these trends would induce an artificial association between the exposure and the outcome of interest. To evaluate this assumption, we estimated the trends in pre-

valence of exposures over calendar time among the 312 participants included in the case-crossover analysis. Because of these trends, we conducted a second analysis using a case-time-control design.

We restricted the case-time-control analysis to the 278 MACS participants with exposure data at both the study visit immediately prior to the time of TCHF (case visit) and also at the study visit approximately 2.5 years before TCHF (control visit). Since the time of TCHF was estimated, we were reasonably certain that this control visit was indeed earlier than the time when TCHF occurred. Furthermore, we required the control visit to occur after the second follow-up study visit, thus ensuring the elimination of possible changes in exposure around the time of seroconversion for the early visits of the 238 seroprevalent participants. Among the 40 participants who seroconverted after study entry, the average time between seroconversion and the control visit was nearly 2.5 years.

The external controls used in this analysis consisted of 286 HIV-infected men who were AIDS-free and showed no evidence of TCHF as of October 1994. As described previously (13), those without a decline in CD3<sup>+</sup> cell counts of at least 10% per year after the estimated time of TCHF were classified as non-infectors. Unlike the cases, who had a well-defined time of TCHF, the controls had no specific time at which to anchor exposure assessment. We selected visits randomly among the controls using an incidence-density sampling mechanism, whereby the frequency distribution of visits matched the distribution of case visits among the cases. These case-matched visits defined an anchoring time point for the controls which we could use to evaluate exposures and compare relative to visits occurring approximately 2.5 years before the case-matched visits (we refer to these visits as control-matched visits since they match in frequency the control visits of those demonstrating TCHF). Figure 1b illustrates the case-time-control design.

Odds ratios were obtained for period and exposure effects by using a conditional logistic regression model with exposure and the interaction between exposure and group (case with TCHF or control without TCHF) included as independent variables and time period as the dependent variable (18). To use this conditional logistic regression model, we assumed the conditional independence of exposures within each participant (i.e., no carryover effect of exposure from control period to case period).

### RESULTS

Table 1 displays the characteristics of the 312 participants included in the case-crossover analysis. The median date of TCHF for these participants was October 1990 (interquartile range [IQR]: September 1989, March 1992) and the median time from TCHF to AIDS diagnosis was 1.2 years

**TABLE 1.** Characteristics of 312 cases at visit immediately preceding T-cell homeostasis failure, Multicenter AIDS Cohort Study, 1984-1995

Demographics	
% Caucasian (white Hispanic and non-Hispanic)	95.2
Age (years) median (interquartile range)	39.1 (35.0, 43.8)
Markers (median, interquartile range)	
CD4 <sup>+</sup> T-cell count (cells/ $\mu$ l)	291 (162, 468)
CD3 <sup>+</sup> T-cell count (cells/ $\mu$ l)	1530 (1103, 1922)
log <sub>10</sub> HIV RNA (copies/ml)	4.94 (4.51, 5.32)
Prevalence of exposures (% reporting)	
Use of any drug <sup>††</sup>	57.3
Use of hashish/marijuana	44.0
Use of poppers	29.6
Use of crack/cocaine	12.7
Any sexually transmitted disease <sup>‡</sup>	7.4
Gonorrhea	0.6
Syphilis	0.6
Warts	6.1
> 5 sexual partners	22.4
Any anal receptive intercourse	40.6

<sup>†</sup>Acquired immunodeficiency syndrome.

<sup>††</sup>Any report of hashish/marijuana, poppers, crack/cocaine.

<sup>‡</sup>Any report of gonorrhea, syphilis, or warts.

(IQR: 0.3, 1.9). This time was somewhat shorter than the previously reported median time between TCHF and AIDS of 1.75 years (13), reflecting the selection of a subset of individuals who demonstrated rapid post-TCHF decline. Indeed, the median post-inflection CD3<sup>+</sup> T-cell slope was -43.1% (IQR: -59.6, -29.9) per year compared with the median decline in CD3<sup>+</sup> T-cells of 32.0% per year following TCHF previously reported (13).

### Case-Crossover Analysis

Mantel-Haenszel odds ratios showing the association between exposures and TCHF over all control periods and the case period immediately prior to TCHF are shown in Table 2. Control periods up to approximately 2.5 years prior to TCHF (IP - 5) were included. Use of any drug and use of hashish were both statistically significant ( $p < 0.01$ ) in each of the four earliest control periods. The odds ratios associated with each of these four control periods relative to the case period immediately prior to TCHF were all less than one, indicating that having the exposure was protective against TCHF. The aggregate exposure "crack/cocaine" was also significantly associated with a lower odds of TCHF in the three earliest control periods ( $p < 0.01$  in the earliest control period and  $p < 0.05$  in the second and third earliest control periods). Cocaine use alone was significantly associated with a lower odds of TCHF in the earliest control period ( $p < 0.01$ ) and in the third control

period ( $p < 0.05$ ) but not in the two control periods closest to TCHF (data not shown). No significant differences were found in the odds of any self-reported STDs in any of the control periods compared with the case period immediately prior to TCHF, nor was having more than five sexual partners or anal receptive intercourse in the previous 6 months significantly associated with TCHF.

We next investigated whether the matched-pair odds ratios based solely on the cases might be a reflection of the natural decrease in recreational drug use over time, rather than a decreased risk for TCHF. Figure 2a shows the trends in drug use over time during the 10-year period from October 1984 through April 1995 for the 312 participants included in the case-crossover analysis. There were significant decreasing trends ( $p < 0.01$ ) in all recreational drug use exposures over time. Specifically, the prevalence of any drug use decreased from 87.9% between October 1984 and April 1985 to 48.2% between October 1994 and April 1995. In the same 10-year period, use of crack and cocaine decreased from 39.0% to 5.4%, use of hashish decreased from 77.0% to 41.1%, and use of poppers decreased from 70.2% to 16.1%. Similar trends in drug use exposures over the same time period can be seen in Fig. 2b among the 286 controls that will be included in the case-time-control analysis. These significant temporal trends in drug use exposures suggest that the case-crossover design did not properly account for the decreasing trends in recreational drug use over time.

### Case-Time-Control Analysis

The motivation for the case-time-control design is that it permits adjustment for trends in exposure over time. Figure 3 shows that our incidence-density sampling method achieved a distribution of case-matched anchoring visits for the 286 controls that was essentially identical to the cumulative distribution of visits immediately before TCHF among the 278 cases.

The results from the case-time-control design are shown in Table 3. Using a case period immediately prior to TCHF (columns headed IP - 0), the effect of temporal trends on each of the exposures was strong, reflected in odds ratios of significantly less than one for three out of the four exposures. Specifically, the odds ratios of 0.42, 0.56, and 0.42 for any drug use, popper use, and crack/cocaine use, respectively, indicate that the prevalence of these exposures significantly decreased over time between the control and the case period.

The odds ratios from the case-time-control analysis reveal that the decreasing trend in drug use over time accounts for most of the association found in the case-crossover analysis (which by definition only included the cases). The odds ratios for each of the drug use exposures in

**TABLE 2.** Case-Crossover analysis of exposures associated with T-cell homeostasis failure, Multicenter AIDS Cohort Study, 1984-1995

Exposure	Matched-pair odds ratios and 95% confidence intervals across varying control periods				
	IP <sup>††</sup> - 5	IP <sup>††</sup> - 4	IP <sup>††</sup> - 3	IP <sup>††</sup> - 2	IP <sup>††</sup> - 1
Recreational drug use					
Any drug use	0.22 0.12, 0.43	0.38 0.20, 0.72	0.35 0.19, 0.66	0.39 0.20, 0.79	0.83 0.46, 1.51
Hashish	0.28 0.15, 0.51	0.41 0.22, 0.77	0.38 0.21, 0.70	0.34 0.17, 0.68	0.74 0.37, 1.47
Poppers	0.34 0.20, 0.57	0.41 0.24, 0.71	0.55 0.33, 0.90	0.73 0.42, 1.27	0.77 0.43, 1.38
Crack/Cocaine	0.27 0.13, 0.57	0.43 0.20, 0.94	0.42 0.21, 0.86	0.47 0.21, 1.05	0.38 0.17, 0.86
STD <sup>‡</sup>					
Any STD	0.70 0.35, 1.39	0.47 0.21, 1.05	0.71 0.32, 1.61	1.14 0.56, 2.34	1.00 0.43, 2.31
Gonorrhea	0.50 0.09, 2.73	0.20 0.02, 1.71	2.00 0.18, 22.06	NA	NA
Syphilis	0.33 0.03, 3.20	1.00 0.14, 7.10	0.50 0.05, 5.51	2.00 0.18, 22.06	NA
Warts	0.75 0.35, 1.59	0.47 0.19, 1.14	0.67 0.27, 1.63	0.92 0.42, 2.02	0.83 0.36, 1.93
Sexual behavior					
> 5 sexual partners	0.66 0.38, 1.14	0.87 0.48, 1.58	0.86 0.47, 1.60	0.88 0.43, 1.79	0.53 0.24, 1.19
Anal receptive intercourse	0.40 0.08, 2.06	2.00 0.37, 10.92	0.83 0.25, 2.73	0.57 0.17, 1.95	0.80 0.21, 2.98

<sup>†</sup>Acquired immunodeficiency syndrome.

<sup>††</sup>IP: inflection point.

<sup>‡</sup>Sexually transmitted disease.

the case-time-control analysis in Table 3 are equal to the estimated odds ratio from the case-crossover analysis divided by the odds ratio measuring the temporal trend of each exposure. For example, the odds ratio 0.61 showing the effect of poppers on TCHF is equal to the odds ratio from the case-crossover analysis (0.34) divided by the odds ratio for temporal trends in use of poppers (0.56).

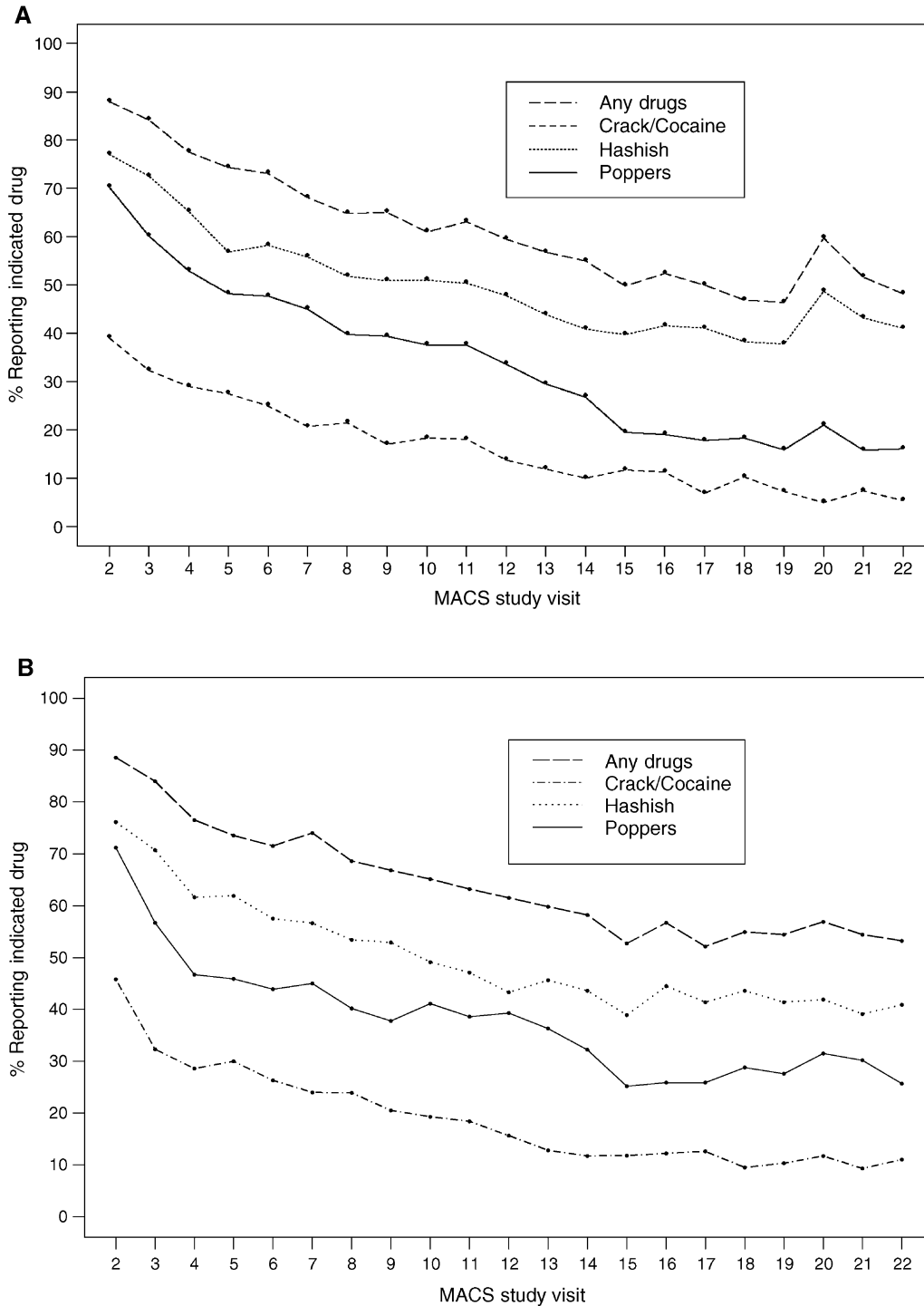
While the odds ratios relating the effect of the various exposures on TCHF often remained less than one, none of the recreational drug use exposures that were significant in the case-crossover analysis remained statistically significant in the case-time-control design after adjusting for the decrease in prevalence of exposure over time. For example, the effect of any drug use on TCHF, which had an odds ratio of 0.22 (95% confidence interval [CI]: 0.12, 0.43) in the case-crossover analysis, had a statistically insignificant odds ratio of 0.53 (95% CI: 0.22, 1.28) in the case-time-control analysis. In a similar manner, the main effects from each of the other three exposures on TCHF were attenuated compared with the results from the case-crossover analysis.

It was possible that a case period at approximately 3 months prior to TCHF might not accurately represent the true exposure before TCHF, since many of the changes in behavior and life style may have already occurred because of

deteriorating health associated with incipient TCHF. To test this hypothesis, we varied the case periods (Table 3), whereby we used data from either two study visits (IP - 2) or three study visits (IP - 3) prior to TCHF as the reference point to examine if this would change any of the above inferences. Results from using the two earlier case periods showed that the effect of each exposure on TCHF was of similar magnitude and statistical significance as when the case period was defined as the period immediately prior to TCHF.

## DISCUSSION

Our current analyses were conducted both to understand the time-varying exposures that may contribute to TCHF and to compare two different epidemiological methods of approaching this question. The case-crossover analysis, which included a subset of MACS study participants previously identified as having TCHF, indicated that recreational drug exposures approximately 2.5 years before TCHF were protective against TCHF. However, the case-time-control design, which adjusted for time trends in exposures by including individuals without TCHF, revealed that after adjusting for these trends, recreational drug exposures were not protective against TCHF. The comparison of these two

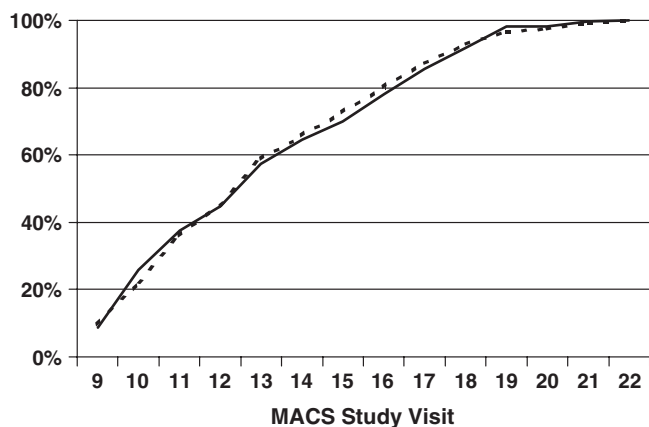


**FIGURE 2.** Prevalence of drug use over time from October 1984 through April 1995 among (a) 312 cases included in case–crossover analysis and (b) among 286 controls included in case–time–control analysis, Multicenter AIDS Cohort Study (MACS), 1984–1995. AIDS, acquired immunodeficiency syndrome.

methods shows the need to account for time trends in exposures when using a case–crossover design.

The results from the case–time–control analysis showed that while the odds ratios were non-significant after ad-

justing for time trends, they were often less than one, regardless of which of the three case periods chosen. These magnitudes must, however, be viewed with caution. First, while we used controls to estimate the trend in exposures



**FIGURE 3.** Cumulative distribution of case visits and case-matched visits for the case-time-control design. The dashed line describes the distribution of visits among cases; the solid line describes the distribution among the case-matched controls, Multicenter AIDS Cohort Study (MACS), 1984-1995. AIDS, acquired immunodeficiency syndrome.

over the course of disease progression, there may be residual exposure trends that are not accounted for in the analysis. Selecting case-matched and control-matched visits for the controls via an incidence-density sampling method decreases the likelihood that differences in exposures between cases and controls are due to time. The case-time-control design is best used when the exposure trends can be estimated with great precision, and the degree to which this method provides unbiased results is dependent upon how well these trends are estimated. Second, the standard errors of the estimates of the main effects of exposure on TCHF are important indicators of the small number of participants with discordant exposures at the two time periods. Previous studies have also shown that the standard error associated with the estimated odds ratio used in the case-time-control

design is larger than the standard errors from both traditional case-control studies and case-crossover studies (25). For example, a case-control analysis of the association of any drug use with TCHF using the case-matched visit for the controls produced an estimated  $\log_e$  (odds ratio) of  $-0.14$  with a standard error of  $0.17$ . This contrasts with the case-crossover estimated  $\log_e$  (odds ratio) of  $-1.49$  with standard error of  $0.33$  and the case-time-control design estimated  $\log_e$  (odds ratio) of  $-0.63$  with standard error of  $0.45$ . These results demonstrate that the refined case-time-control analyses may be overly conservative with respect to variance despite reductions in bias. Furthermore, we are unable to rule out the possibility of reverse-causation bias, whereby the subtle deterioration of health in the cases may reduce the urge to indulge in risky behaviors more than the changes in behavior in controls, thereby leading to a protective effect for TCHF. Despite these considerations, our results concur with other reports (9, 26), which have demonstrated a lack of association between modifiable risk factors and disease progression. To the extent that the epidemiologic factors analyzed in this study (sexual and drug use behaviors) are associated with increased risk for exposure to HIV, our results suggest that TCHF is likely not due to external factors.

Lastly, in our analyses, we selected controls so that their case-matched visits would be frequency-matched to the distribution of case visits among the cases. While risk-set sampling has been described for case-crossover studies (21), the selection of controls has not been discussed in the descriptions of the case-time-control design. Since the purpose of including the control group is to estimate the association of disease with exposure after adjustment for time trends in exposures, the selection of this group is of great importance. Figures 2a and 2b demonstrate that the time trends in exposure are not uniform. Furthermore,

**TABLE 3.** Results of case-time-control analysis using multiple case periods from the study visit immediately prior to TCHF (IP-0) through three study visits prior to TCHF (IP-3) and a control period approximately 2.5 years prior to TCHF, Multicenter AIDS<sup>†</sup> Cohort Study, 1984-1995

Exposure	Odds ratio and 95% confidence interval associated with time trends in indicated exposure at indicated case period			Odds ratio and 95% confidence interval of TCHF associated with indicated exposure at indicated case period		
	IP <sup>††</sup> - 0	IP <sup>††</sup> - 2	IP <sup>††</sup> - 3	IP <sup>††</sup> - 0	IP <sup>††</sup> - 2	IP <sup>††</sup> - 3
Any drugs	0.42 0.24, 0.76	0.58 0.31, 1.09	0.58 0.31, 1.09	0.53 0.22, 1.28	0.78 0.32, 1.92	0.73 0.28, 1.90
Hashish	0.60 0.35, 1.03	0.75 0.41, 1.38	0.42 0.22, 0.80	0.46 0.20, 1.05	0.77 0.32, 1.86	1.14 0.45, 2.94
Poppers	0.56 0.34, 0.91	0.63 0.38, 1.03	0.74 0.42, 1.32	0.61 0.30, 1.25	0.48 0.22, 1.07	0.63 0.27, 1.47
Crack/Cocaine	0.42 0.24, 0.76	0.63 0.36, 1.13	0.57 0.31, 1.03	0.65 0.25, 1.66	0.76 0.30, 1.90	0.71 0.26, 1.95

<sup>†</sup>Acquired immunodeficiency syndrome.  
<sup>††</sup>IP: inflection point.

estimates from this design are averaged effects over all controls, and the method is sensitive to the assumption of no confounding of this time trend (19). This suggests that the controls should be as similar to the cases as possible, both temporally as well as in other fixed characteristics. Frequency matching to case-visits, as used in this study, is one approach to ensure similar timing, but does not guarantee other factors will be similar. A possible solution to this problem is to further match the controls to cases. This type of matched case-time-control design would address some of the concerns regarding measured (but not unmeasured) confounders and deserves further study.

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