

Survivor Treatment Selection Bias in Observational Studies: Examples from the AIDS Literature

Marshall J. Glesby, MD, and Donald R. Hoover, PhD

Unlike patients in a randomized, clinical trial, patients in an observational study choose if and when to begin treatment. Patients who live longer have more opportunities to select treatment; those who die earlier may be untreated by default. These facts are the essence of an often overlooked bias, termed "survivor treatment selection bias," which can erroneously lead to the conclusion that an ineffective treatment prolongs survival. Unfortunately, misanalysis of survivor treatment selection bias has been prevalent in the recent literature on the acquired immunodeficiency syndrome. Approaches to mitigating this bias involve complex statistical models. At a minimum, initiation of therapy should be treated as a time-dependent covariate in a proportional hazards model. Investigators and readers should be on the alert for survivor treatment selection bias and should be cautious when interpreting the results of observational treatment studies.

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From Johns Hopkins University, Baltimore, Maryland. For current author addresses, see end of text.

Although the randomized, clinical trial is the gold standard for evaluating the effectiveness of treatment regimens for chronic diseases, observational treatment studies are useful and perhaps necessary. For many reasons, including ethical and economic considerations, clinical trials are not always feasible. For example, in diseases with a long natural history, such as human immunodeficiency virus (HIV) infection (1, 2), the long-term effectiveness of treatment is of obvious interest. However, a clinical trial will not provide data on long-term effectiveness if it is stopped early because one treatment shows greater short-term effectiveness in an interim analysis. Furthermore, the results of a prolonged clinical trial of one drug are difficult to interpret when new and potentially superior drugs become available to participants during the trial. Because of these difficulties, investigators have resorted to observational studies to evaluate therapies for chronic diseases. Although observational studies may complement clinical trials, they are prone to methodologic problems that create bias.

In treatment studies, bias results from any systematic error in design, conduct, or analysis that yields a mistaken estimate of treatment effect (3). Unlike clinical trials, in which patients are randomly assigned to treatment, observational studies allow patients and their physicians to select treatments. This can create an important bias; differences be-

tween patients who do and do not select a treatment exist and must be considered. For example, everything else being equal, sicker patients may elect to begin receiving treatment sooner than would patients who feel well (4).

Biases can also originate from the misanalysis of observational data rather than from the data themselves. One analytic bias has persistently appeared in many recently reported analyses of observational studies of therapy for HIV infection (5-19). Longer survival may increase a patient's chance to use treatment in an observational study. Patients who die sooner have less time to select treatment and thus, by default, are more likely to remain untreated. If this is not considered in the data analysis, the estimate of the treatment effect will be biased. This bias, which we have termed "survivor treatment selection bias," is the focus of our paper.

Survivor Treatment Selection Bias

Correlation of longer patient survival with use of the treatment in question is often interpreted as evidence that the treatment prolongs survival. However, even an ineffective treatment will correlate with longer survival in observational studies, because longer survival causes treatment use. That is, longer survival increases the likelihood of treatment selection because patients who live longer have more time and more opportunities to gain access to or decide to begin treatment. This survivor treatment selection bias, unless considered appropriately, can lead to the incorrect inference that an ineffective drug improves survival.

Consider the following extreme example of a hypothetical observational cohort of patients with the acquired immunodeficiency syndrome (AIDS), none of whom are using antiretroviral therapy at the start of the study. After 1 year of observation, a hypothetical new antiretroviral drug called placebovir becomes available; placebovir provides no survival benefit yet is widely believed to work. All patients who are alive at 1 year begin receiving treatment with placebovir, and all patients who have died by 1 year are untreated by default. If we compare survival in treated and untreated patients, the use of placebovir will obviously correlate strongly with longer survival: All of the patients surviving for more than

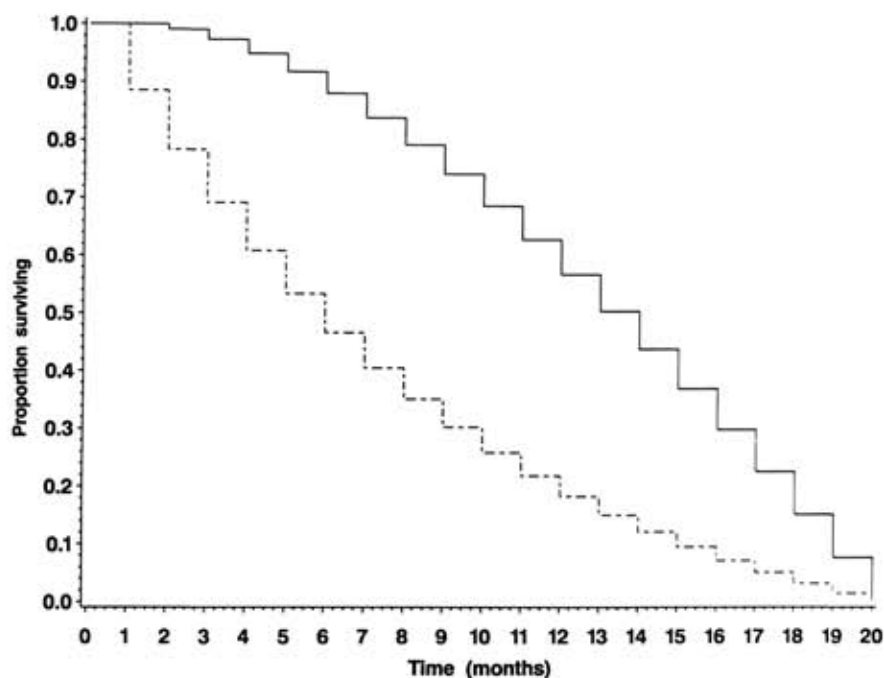


Figure 1. Hypothetical example of survivor treatment selection bias. Plots of expected Kaplan-Meier estimates of survival in a hypothetical observational cohort of 1000 patients with the acquired immunodeficiency syndrome who are untreated (dashed line) or treated (solid line) with a drug that has no effect on survival. Regardless of drug use, 50 patients die each month so that all have died by 20 months. Beginning after the first month of observation, 10% of patients who are alive and untreated at each successive monthly interval initiate therapy with the ineffective drug so that about 56% of patients will use the treatment before they die. Even though the treatment is ineffective, it erroneously appears to prolong survival because of survivor treatment selection bias: Living longer increases the chance to use the treatment.

1 year and none of the patients dying within 1 year use placebo. Attributing this improved survival of treated patients to placebo, however, is obviously erroneous and is an illustration of survivor treatment selection bias.

The next example more realistically simulates the survivor treatment selection bias that occurs in most observational studies. In a cohort study of 1000 patients with AIDS, a new treatment becomes available after the first month of observation. The treatment, placebo, again provides no survival benefit. Overall, 50 of the 1000 patients (5%) die each month regardless of placebo use, so that all patients are dead by 20 months of observation. Beginning after the first month, 10% of patients per month who are alive and not yet receiving treatment initiate treatment with placebo. Thus, at the end of the second month of observation, 100 patients will have died. The first 50 died during the first month and were untreated, and, of the subsequent 50 patients who died, 5 (10%) had begun treatment and 45 were untreated. As time passes, more patients who are still living will be using treatment because, as they survive longer, more of them gain access to the drug. Eventually 561 of the patients (56%) will use placebo. Of the 50 patients who died at 20 months, 43 used placebo.

A Kaplan-Meier analysis (20) of crude survival in those who did or did not gain access to treatment in this hypothetical example shows "greater" survival for the group that used placebo (Figure 1). The median survival is 13 months in the "treated" patients and 5.5 months in the "untreated" group.

With even a very few study participants (<100), the *P* values for differences in survival curves shown in Figure 1 are low ($P < 0.001$). Direct comparisons of these Kaplan-Meier survival rates makes an ineffective drug appear to improve survival, because of survivor treatment selection bias.

The problem of survivor treatment selection bias has been previously recognized in the medical and statistical literature. Similar length biases have been discussed in the context of disease screening (21) and analysis of prevalent cohorts (22). Several letters have been published in recent years commenting on the presence of this bias in observational studies of zidovudine use (23-27). Nonetheless, as shown by its continuing occurrence in recent publications, investigators and reviewers still do not recognize this problem (5, 7-10, 12, 13, 15-19) or do not address it thoroughly (6, 11, 14).

Several of these publications, which are biased toward overestimating treatment effects, are cited as showing the effectiveness of zidovudine for HIV infection. However, because clinical trials have proven the effectiveness (28, 29) (albeit time-limited [30, 31]) of zidovudine, one could argue that it may not be important if some biased analyses from observational studies have overestimated the treatment effect of zidovudine. Indeed, two studies (6, 11) that were perceived by critics to have been misanalyzed with respect to survivor treatment selection bias (23-26) were subsequently reanalyzed using methods that appropriately address this bias (32, 33). The investigators observed treatment ef-

fects of zidovudine that were similar to those from their original analyses.

We contend, however, that survivor treatment selection bias is more than an academic issue and can lead to erroneous conclusions. To support this contention, we describe two studies that we believe reached debatable conclusions because of biased analyses. We focus on these particular studies only to illustrate the potential for misleading conclusions when survivor treatment selection bias is not considered.

In the first study (10), the investigators compared survival after the onset of AIDS between male and female patients with AIDS whose cases were reported to a city public health department between 1981 and 1990. Using the Kaplan-Meier method, the investigators concluded that the median survival times of men and women who received antiretroviral therapy were similar, but that men who were untreated survived significantly longer than women who were untreated (median survival time, 14.6 months compared with 6.4 months). They postulated that factors such as less access to care, older age, competing health risks, and diagnosis later in the course of HIV infection might account for the decreased survival of untreated women relative to that of untreated men. We believe, however, that the survival difference could have been caused by a stronger effect of survivor treatment selection bias in women, given that zidovudine was not available in the initial years of the AIDS epidemic and that the epidemic affected women later than men in the United States. Of the many reasons why a given person with AIDS in this study might have died without having taken zidovudine, two important reasons are central to our argument: 1) The person may have died before 1987, the year in which zidovudine became available, or 2) the person may have received a diagnosis of AIDS after 1987 but may have died relatively soon thereafter, having had little opportunity to initiate zidovudine treatment. In this study, only 25% of the female patients with AIDS but almost 50% of the male patients with AIDS had received a diagnosis before 1987. Thus, many of the untreated women may have lacked treatment because they died relatively soon (after 1987), whereas more of the untreated men may have lived longer but remained untreated only because zidovudine was not yet on the market.

In the second study (19), the investigators analyzed data from a cohort of HIV-infected men and concluded that receiving both antiretroviral therapy and prophylaxis for *Pneumocystis carinii* pneumonia was significantly associated with longer survival time, but antiretroviral therapy alone was not. This finding is not consistent with those of other reports (34-36), and the data analysis was done so that

survivor treatment selection bias is a legitimate concern. Routine use of prophylaxis for *P. carinii* pneumonia began chronologically after antiretroviral therapy, and this prophylaxis is generally initiated at a later stage of HIV disease, often in patients who had previously started antiretroviral therapy (4). The survival benefit from antiretroviral therapy could be credited to prophylaxis for *P. carinii* pneumonia (through survivor treatment selection bias) if the patients who benefited most from the earlier initiation of antiretroviral therapy survived long enough to be able to use the prophylaxis later. Those who received little or no benefit from antiretroviral therapy would have died sooner and, by default, would never have used the prophylaxis.

Approaches to Mitigate Survivor Treatment Selection Bias

One approach with which to circumvent survivor treatment selection bias in the analysis of an observational treatment study is to classify patients as treated or untreated at the start of the study and then to ignore subsequent changes in treatment status, as in an intention-to-treat analysis of a clinical trial. For example, consider a cohort of 200 HIV-infected patients, 100 of whom are receiving zidovudine at the start of the study and 100 of whom are untreated. By the end of the first year of follow-up, 50 of the initially untreated patients have started receiving zidovudine therapy. In the data analysis, however, these 50 patients who switched from the untreated to the treated group are still counted as untreated; the fact that they survived long enough to begin therapy is therefore irrelevant. Although this type of analysis eliminates the problem of survivor treatment selection bias, it creates a conservatively biased estimate of treatment effect by not crediting any survival benefit to treatment in those patients who initiated treatment after the start of the study. Clearly, if substantial numbers of untreated patients switch to treatment and thereby benefit with respect to survival, this analytic approach will have limited power to detect a treatment benefit.

Other approaches with which to mitigate survivor treatment selection bias involve the use of multivariate regression techniques to adjust or control simultaneously for the effects of multiple factors on the outcome of interest. The analysis of treatment studies typically centers on the time to an event. For example, investigators might compare how rapidly groups of treated and untreated patients develop AIDS. To adjust for prognostic factors and the time at which treatment is initiated, investigators usually use a multivariate regression technique

known as the Cox proportional hazards model (37). Conceptually, the adjustment process in such a model allows the comparison of times to the event (in this case, onset of AIDS) between treated and untreated groups of patients after accounting for the effects of other measurable factors (covariates) that may differ in the two groups of patients. The end result is a relative risk (relative hazard) that compares the risk for the event between treated and untreated patients after adjusting for the covariates in the model. A relative risk of less than 1 is consistent with a beneficial effect of treatment. For example, a relative risk of 0.8 means that over a short time interval, the risk for the event in surviving treated patients is about 80% of the risk in similar, untreated patients.

In the proportional hazards model, survivor treatment selection bias can be eliminated by adjusting for the time at which treatment is initiated. The time of treatment initiation can be considered in proportional hazards analyses by using what is known as a time-dependent covariate (for examples, see references 34 and 38–40). A time-dependent covariate is a variable whose value in the model is allowed to change with the time component in the model. For example, in the computations made using time points before initiation of treatment for a given patient, the variable denoting treatment would be coded as “no,” and for those made using time points after initiation of treatment, the variable would be coded as “yes.” This enables the continual comparison of treated patients with untreated patients who survived to the same point in time. Treatment itself does not begin to get “credit” for the survival time of an individual participant until comparative evaluations are made at time points beyond the time of treatment initiation (because the covariate is coded as “no” until treatment initiation). To avoid any potential bias caused by sicker patients who discontinue treatment because of the severity of their illness, these models use an intention-to-continue-treating paradigm: Once treatment

is initiated, the patient is assumed to continue receiving treatment for the duration of follow-up.

Although the standard use of Kaplan–Meier product-limit estimation to generate survival curves does not deal with survivor treatment selection bias (Figure 1), a modification of the method can be used much as time-dependent covariates are used in a Cox proportional hazards model. Simultaneous use of left-truncation and right-censoring allows patients to switch from the untreated to the treated groups and incorporates the time of the switch into the survival estimates (41). The details of this approach are beyond the scope of this discussion; however, the reader should note that the authors must specifically state that they used left-truncation and right-censoring of individual persons who initiate therapy in order for the Kaplan–Meier estimates to be unbiased.

Unfortunately, although modeling treatment initiation as a time-dependent covariate as described above eliminates survivor treatment selection bias, it can simultaneously lead to a different bias in the opposite direction because sicker patients may be more likely to initiate treatment at any given time. This latter bias is conservative in that it reduces the likelihood of detecting a treatment effect. For example, consider two HIV-infected patients in a cohort study that begins in 1990 (Figure 2). Patient A initially has a CD4 cell count of 600 cells/mm³, and patient B initially has a CD4 cell count of 100 cells/mm³; the lower count indicates more advanced HIV disease. Because of his lower CD4 count, patient B selects treatment with zidovudine and (despite the benefits of treatment) develops AIDS 1 year later. Meanwhile, because of his higher CD4 count, patient A chooses to remain untreated and remains free of AIDS until the end of the 5-year study. The bias created by this scenario has the potential to make treatment look ineffective, if not harmful, because patients with a poorer prognosis are selecting the treatment and thus the treatment is associated with progression to AIDS in an analysis adjusted for selection time.

An approach to mitigating the bias caused by sicker patients initiating treatment is to adjust the model for measures of baseline health status. In an HIV treatment study, adjusting for baseline CD4 cell count in a multivariate regression model, such as the Cox proportional hazards model, seems to be one solution. Such adjustment would essentially stratify patients according to baseline CD4 counts and make survival comparisons within the same strata. For instance, in the previous example, survival among patients with baseline CD4 counts of 100 cells/mm³ would be compared with each other after treatment use is considered as a time-dependent covariate. Comparisons would be made simul-

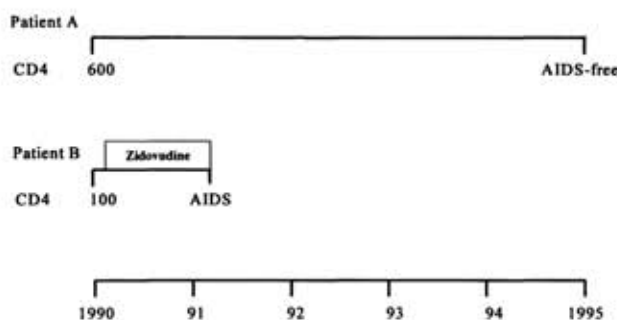


Figure 2. Hypothetical example showing that sicker patients are more likely to initiate treatment. AIDS = acquired immunodeficiency syndrome.

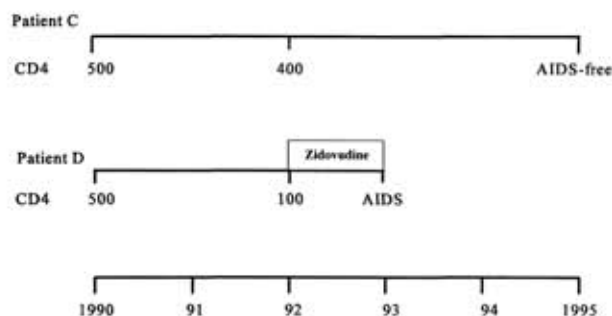


Figure 3. Hypothetical example showing the inadequacy of statistical adjustment for markers of patient health status that are measured only at baseline. AIDS = acquired immunodeficiency syndrome.

taneously among patients with baseline CD4 counts of 600 cells/mm³, and an overall stratified-adjusted treatment effect (relative hazard) would be reported from the model.

Although adjusting for baseline CD4 counts is an improvement, it may still be inadequate because the health status of patients changes over time; patients starting at the same level of health may diverge during the follow-up period of the study. For example, consider two patients, patients C and D, in a cohort study of HIV infection. At the beginning of the study, both patients have CD4 cell counts of 500 cells/mm³ (Figure 3).

After 2 years of follow-up, the CD4 count of patient C declines to 400 cells/mm³, and he remains both untreated and free of AIDS. Over the same period, the CD4 count of patient D declines to 100 cells/mm³, and, because of declining health, patient D opts for treatment yet still develops AIDS (which is diagnosed on the basis of an opportunistic infection rather than by the revised criterion for AIDS, a CD4 count < 200 cells/mm³ [42]). Adjusting for baseline CD4 cell count in this scenario would directly compare the healthier patient C (who remained untreated) and the sicker patient D (who opted for treatment) within the same health status stratum because the two patients had identical CD4 counts at study entry. This type of analysis would not consider that patient D had become sicker after study entry but before starting treatment and that it was his decline in CD4 count during the study, and not the subsequent treatment he received, that was related to his more rapid development of AIDS.

Assuming that serial measures of the surrogate marker of health status (such as CD4 count) are available, then another solution is to use these data for time-dependent adjustment purposes; the health status "stratum" for a given patient is continuously adjusted as his or her CD4 count changes. This is routinely done in Cox proportional hazards models using time-dependent covariates. Two problems are inherent in this form of adjustment. First, available surrogate markers are likely to be incomplete mark-

ers for true health status (43, 44), and time-dependent adjustment for an incomplete marker will incompletely adjust for health status. For example, after 2 years of observation in a cohort study, patients E and F both have CD4 cell counts of 200 cells/mm³ (Figure 4). Patient E, however, has daily fevers and thrush; patient F is asymptomatic. Patient E is likely to develop AIDS sooner than patient F (45) and also will probably decide to initiate zidovudine treatment earlier because of his symptoms (4). Adjusting for CD4 count as a time-dependent covariate will not completely adjust for the differing health status of these patients, and the bias created because the sicker patient selects treatment will remain. Incorporating additional time-dependent covariates related to health status (hemoglobin concentration and presence of symptoms, for example) into the model may alleviate this problem by better identifying the true health status strata for patients.

A second problem with serial, time-dependent adjustment procedures for health status manifests itself when health status or a marker for health status is influenced by the treatment being studied. Adjusting for any measure of health status that is in the causal pathway between treatment and outcome will statistically eliminate the beneficial effect of the treatment. For example, if an antiretroviral drug used for HIV infection exerts its beneficial delay in the onset of AIDS entirely by increasing CD4 cell count, then adjusting for CD4 cell count will eliminate the treatment effect. For example, consider patients G and H who in 1990 start with identical CD4 cell counts of 200 cells/mm³ and equivalent health status (Figure 5). A third patient, patient I, starts with a CD4 count of 350 cells/mm³. Patient G decides to use zidovudine, which increases his CD4 count to 300 cells/mm³ 1 year later and delays the onset of AIDS so that he develops AIDS at the same time as untreated patient I (whose CD4 count decreases to 300 cells/mm³ 1 year later) but later than patient H, who also remains untreated (and

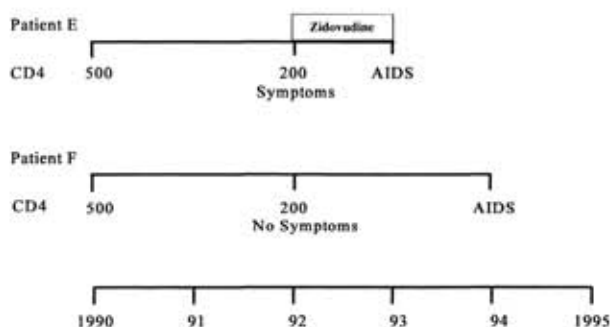


Figure 4. Hypothetical example showing that statistical adjustment for a sequentially measured (time-dependent) marker of health status may incompletely adjust for true health status. AIDS = acquired immunodeficiency syndrome.

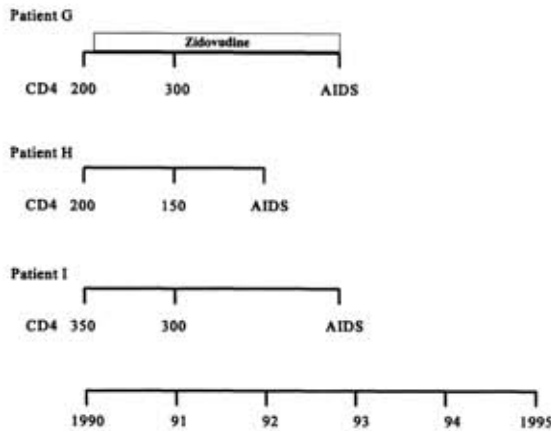


Figure 5. Hypothetical example showing that statistical adjustment for a marker of health status that is influenced by the treatment may eliminate the treatment effect. AIDS = acquired immunodeficiency syndrome.

has a further decline in CD4 count). If the entire effect of treatment in delaying the onset of AIDS is mediated through the increase in CD4 count, then adjusting for patient G's increased CD4 count in time-dependent models will in effect consider patient G to have the same health status as untreated patient I. This analysis does not allow the treatment to be credited with the improved health status of patient G relative to that of patient H and will consequently negate any beneficial effect of treatment.

Taken together, the two previous problems with time-dependent adjustment for measures of health status form a paradox: If a marker of health status is incomplete, then adjusting for it will lead to incomplete adjustment for health status. Yet, if the marker is perfect, then adjusting for it can eliminate the treatment effect whose measurement is the purpose of the study. Statistical approaches to circumvent this paradox are needed. Robins and colleagues (36, 46) have recognized this problem and have created methods known as G-estimation to resolve all of the biases previously described. Briefly, G-estimation uses currently available statistical models (such as proportional hazards) within a framework that adjusts for the measures of patient health status and measures the effect of treatment on survival while simultaneously accounting for treatment effects that are mediated through improving the measures of patient health status.

Conclusions

Survivor treatment selection bias is an important potential limitation of the analysis of observational treatment studies. Investigators must mitigate this bias to avoid reporting erroneous results. At a minimum, investigators should model treatment initia-

tion as a time-dependent covariate in regression models; studies that do not do this should not be published. Readers should use healthy skepticism even when reading studies that use time-dependent covariates, because simple adjustments still may not avoid significant biases. More complicated adjustments are challenging even to statistically sophisticated investigators and may still be biased. Investigators should recognize survivor treatment selection bias and the need for appropriate analytic methods and statistical and epidemiologic support to analyze observational data. Readers and reviewers should exercise particular caution when interpreting the results of observational treatment studies.

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Requests for Reprints: Donald R. Hoover, PhD, Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health, 624 North Broadway, Room 784, Baltimore, MD 21205.

Current Author Addresses: Dr. Glesby: Division of Infectious Diseases, The Johns Hopkins University School of Medicine, Ross Research Building, Room 1159, 720 Rutland Avenue, Baltimore, MD 21205.

Dr. Hoover: Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health, 624 North Broadway, Room 784, Baltimore, MD 21205.

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