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Journal
AIDS Research and Human Retroviruses, 28(12)

ISSN
0889-2229

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Publication Date
2012-12-01

DOI
10.1089/aid.2011.0188

Peer reviewed

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 28, Number 12, 2012

DOI: 10.1089/aid.2011.0188

The Impact of Impaired Kidney Function and HIV Infection on the Risk of Anemia

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Abstract

Chronic kidney disease and HIV infection both independently increase the risk of anemia. It is not known if individuals with both HIV infection and kidney dysfunction are at greater than expected risk of anemia resulting from the combined effect of these factors. Men from the Multicenter AIDS Cohort Study with AIDS-free time after 1996 were included in the analysis if they had an initial hemoglobin value greater than 13 g/dl and available serum creatinine measurements for the estimation of glomerular filtration rate. Hemoglobin data were fit parametrically using a linear mixed effects model and effects of medication use on hemoglobin levels were removed using censoring methods. The effect of both HIV infection and glomerular filtration rate less than 60 ml/min/1.73 m^2 on the mean hemoglobin value was assessed. The risk of having anemia (hemoglobin level falling below 13 g/dl) was estimated. There were 862 HIV-infected and 1,214 HIV-uninfected men who contributed to the analysis. Hemoglobin values across all 17,341 person-visits, adjusting for age, were generally lower in HIV-infected AIDS-free men with impaired kidney function by −0.22 g/dl (95% CI: −0.42, −0.03) compared to men with either HIV infection or impaired kidney function, but not both. HIV-infected AIDS-free men with impaired kidney function have a higher risk of anemia by 1.2% compared to HIV-uninfected men with normal kidney function. Comorbid conditions and medication use did not explain this increase in risk. HIV infection and impaired kidney function have a combined impact on lowering hemoglobin levels, resulting in a higher risk of anemia.

Introduction

Anemia is a common sequela of human immunodeficiency virus (HIV) infection and is considered to be a marker of disease progression.[1] Many studies have found HIV-associated anemia to be a predictor of increased mortality[2–5] and it shares many pathogenic aspects with anemia of chronic disease.[6] Chronic immune activation, a feature of HIV infection and other chronic conditions, can induce changes in iron homeostasis, affect erythropoietin (Epo) production, and decrease the lifespan of erythrocytes, all of which contribute to declining hemoglobin levels. HIV can further diminish erythropoiesis via direct effects on the bone marrow.

As in HIV, anemia occurs commonly in the context of chronic kidney disease (CKD), the result of decreased Epo production accompanying renal insufficiency. The prevalence of anemia increases significantly with progressive CKD.[7] Among persons with CKD, anemia has been associated with severe outcomes including an increased risk of poor cognitive function, poor quality of life, cardiovascular disease, and mortality.[8] Factors that impact kidney function can thus increase the risk of anemia. In the context of HIV, both coinfections such as hepatitis C and antiretroviral therapy (ART) can contribute to a loss of kidney function. Hepatitis C infection appears to hasten kidney disease progression in HIV-infected women with existing kidney dysfunction,[9] while ART use can result in kidney damage through nephrotoxicity[10–12] or metabolic abnormalities.[13,14]

HIV-associated kidney dysfunction may result in a more substantial reduction of hemoglobin levels as a result of the

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many potential insults to the kidney as well as the heightened inflammatory milieu. An increased risk of anemia could potentially contribute to the higher risk of CKD-related mortality noted among HIV-infected individuals.[15,16] In this report we examined the impact of CKD and HIV infection on hemoglobin levels in the ART era, controlling for other established causes of low hemoglobin in HIV-infected individuals. Using a sample of HIV-infected and HIV-uninfected men with normal hemoglobin (>13 g/dl), we assessed the risk of hemoglobin decline and anemia in those with impaired kidney function compared to men with normal kidney function.

Materials and Methods

Study sample and variable assessment

The Multicenter AIDS Cohort Study (MACS) is an ongoing multicenter prospective observational study of HIV-infected and HIV-uninfected men who are at risk for infection, which was established by the National Institutes of Health in 1984.[17] Four clinical sites contributed data from semiannual visits to the MACS: Baltimore MD, Chicago IL, Los Angeles CA, and Pittsburgh PA. $CD4^+$ cell count/μl (CD4) was measured with CD4-specific monoclonal antibodies using two-color flow cytometry.[18] Serum creatinine was measured locally at each site primarily using the modified Jaffe method.[19] Hemoglobin concentrations were measured using standard techniques. C-reactive protein (CRP) was measured annually in a subsample of MACS participants by means of a highly sensitive nephelometric assay. Informed consent has been obtained from each participant and each local institutional review board has approved the study.

Study definitions and design

The analysis was restricted to men contributing data after January 1, 1996 during the effective therapy era. We further limited the analysis to men with two consecutive hemoglobin measurements greater than 13 gm/dl at study entry (normal hemoglobin levels) to avoid prevalence bias and temporal ambiguities in the relationship between HIV infection and low hemoglobin levels. For men who were HIV infected, only AIDS-free time contributed to the analysis to exclude hemoglobin effects resulting from the occurrence of opportunistic infections and their treatment. The end of the analysis period was March 31, 2009.

Glomerular filtration rate (eGFR) was estimated at each 6-month visit using a serum creatinine-based estimating equation, the CKD-EPI equation.[20] To assess the effect of impaired kidney function on hemoglobin levels, eGFR was dichotomized using a threshold of 60 ml/min/1.73 m^2 following the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for defining moderate to severe CKD.[21]

Statistical analysis

Hemoglobin data were fit parametrically to a linear mixed model using a normal distribution with a random intercept to account for individual variability in mean hemoglobin level. Both the mean (μ) and the variance (σ; variability of the hemoglobin distribution) across subjects were allowed to vary as a function of HIV serostatus and impaired kidney function (eGFR <60 ml/min/1.73 m^2), which were dichotomous predictors. In this way we evaluated the degree to which HIV infection and an eGFR <60 ml/min/1.73 m^2 were associated with the average hemoglobin level and the risk of falling below 13 g/dl (World Health Organization definition of anemia[22]) in multivariate models controlling for age and black race. An interaction term between HIV serostatus and GFR <60 ml/min/1.73 m^2 was used to assess whether the effect of impaired kidney function on hemoglobin differed by HIV status. The impact of diabetes mellitus was assessed as a dichotomous indicator. The contribution of immunological status as assessed by CD4 and plasma HIV RNA levels (viral load, VL) was also examined among the HIV-infected men. In regression models, CD4 was treated as continuous with a spline term at 500 cells/μl. VL was $\log_{10}$-transformed. All predictor values were updated over time.

Individuals receiving treatments that impact hemoglobin levels [zidovudine (AZT) and/or recombinant Epo] were included in the models using censoring methods to account for the unknown untreated hemoglobin level. For example, men receiving recombinant Epo were included using only the information that their untreated hemoglobin values would be less than the (treated) observed value. Men receiving AZT were included using only the information that their untreated hemoglobin value would be greater than the (treated) observed value. In this way we could estimate the effect of HIV and eGFR on hemoglobin without the biasing influence of treatment or the selection issues and precision loss of removing treated individuals from the analysis. Separate analyses were done excluding visits at which participants were not receiving ART and excluding visits at which participants were receiving tenofovir in order to evaluate the impact on inferences of these therapies and their potentially nephrotoxic effects.

Though this analysis included only AIDS-free time, eliminating much of the occurrence of opportunistic infections, we evaluated associations between systemic inflammation and declining hemoglobin levels by including CRP serum level in multivariate analyses. Multiple imputation was used to complete missing data. Missing CRP and HIV RNA values were imputed five times based on the distribution of covariates (CRP, HIV RNA , $CD4^+$, age, eGFR, HIV serostatus, and black race) using a Markov chain Monte Carlo (MCMC) method[23] and assuming multivariate normality. The continuous CRP data were categorized to $\leq$1.2 mg/liter, >1.2 mg/liter to $\leq$2.3 mg/liter, and greater than 2.3 mg/liter. The categorization groups were chosen based on previous work in the MACS.[24] The five complete data sets were each analyzed and estimates combined to yield average effect estimates and standard errors incorporating the imputation variability [25].

Results

There were 2076 men with serum creatinine and an initial hemoglobin level greater than 13 g/dl after December 31, 1995 who contributed to the analysis. Of these men, 862 were HIV-infected or seroconverted during follow-up and contributed AIDS-free time. The baseline characteristics of the cohort (stratified by HIV and kidney function status) are shown in Table 1. HIV-uninfected men had a higher median age and were more likely to have an eGFR less than 60 ml/min/1.73 m^2. Median CRP levels were significantly higher among HIV-infected men. The distribution of hemoglobin values by

Table 1. Baseline Characteristics of HIV-Infected and -Uninfected Men (Overall and Stratified by Kidney Function) from the MACS with Hemoglobin ≥13 g/dl in the First Two Visits

	Baseline characteristics (participants with hemoglobin ≥13 g/dl in the first two visits)					
	HIV-negative			*HIV-positive*		
	Overall (N=1248)	*eGFR<60 (N=43)*	*eGFR≥60 (N=1205)*	*Overall (N=828)*	*eGFR<60 (N=15)*	*eGFR≥60 (N=813)*
Age, years	49 (41–55)[a]	60 (55–65)	48 (41–55)	44 (38–50)[a]	48 (40–52)	44 (38–49)
Race, *N* (%)						
White	945 (76)[b]	36 (84)	909 (75)	529 (64)[b]	10 (67)	519 (64)
Black	242 (19)	6 (14)	236 (20)	218 (26)	5 (33)	213 (26)
Other	61 (5)	1 (2)	60 (5)	81 (10)	0 (0)	81 (10)
CRP, mg/liter	0.90 (0.4–2.2)[a]	1.1 (0.4–1.8)	0.9 (0.4–2.2)	1.3 (0.6–3.4)[a]	1.6 (1.0–1.8)	1.3 (0.6–3.4)
$CD4^+$, cells/μl	NA	NA	NA	506 (348–681)	490 (339–655)	506 (348–686)
HIV RNA, copies/ml	NA	NA	NA	194 (<50–14,180)	52 (<50–22,681)	201 (<50–14,100)
On ART, *N* (%)	NA	NA	NA	443 (54)	11 (79)	432 (54)

[a] $p<0.05$ by Wilcoxon rank sum test comparing HIV^+ to HIV^-.
[b] $p<0.05$ by Chi-square test comparing HIV^+ to HIV^-.
Median (interquartile range) unless otherwise specified; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ART, effective combination antiretroviral therapy.

HIV status and kidney function status across all 17,341 person-visits is shown in Fig. 1, illustrating the association of kidney dysfunction with the risk of anemia (as defined by a hemoglobin falling below 13 g/dl).

When hemoglobin was modeled, black race had the largest effect, resulting in an estimated 0.71 g/dl lower average hemoglobin (Table 2). Impaired kidney function was nonsignificantly associated with a lower mean hemoglobin level among HIV-uninfected men. The combined effect of impaired kidney function and HIV infection was statistically significant and was associated with an average hemoglobin level 0.22 g/dl (95% CI: −0.42, −0.03) lower compared to HIV-uninfected men with good kidney function, an effect similar in magnitude to that of 10 years of additional age. HIV infection alone (without the presence of kidney function impairment) was associated with higher average hemoglobin levels by an estimated 0.17 g/dl (95% CI: 0.09, 0.25). Results were similar when restricted to participant-visits with no tenofovir use ($N=1357$ tenofovir visits) or participant-visits on ART ($N=2234$). Adding diabetes mellitus to the model did not change estimates and diabetes was not a significant predictor of hemoglobin levels in this population. The frequency of use of medications that cause anemia was also explored. Interferon-alpha and ganciclovir use were reported in only four person visits.

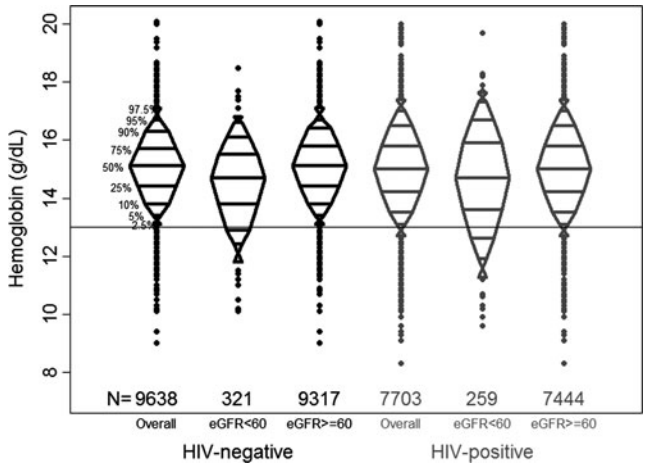

FIG. 1. The unadjusted distribution of hemoglobin levels stratified by HIV serostatus and kidney function [estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2 versus eGFR <60 ml/min/1.73 m^2]. The line at 13 g/dl represents the World Health Organization threshold defining anemia and the *N*s are the number of person-visits contributing to the distribution.

From the analysis we estimated that the joint risk factor of HIV infection and kidney dysfunction was associated with average hemoglobin and an increased percentage of men falling to lower hemoglobin values. To illustrate the magnitude of the impact, we examined the. percentage of men at risk of falling below 13 g/dl. Though each factor individually was not associated with a decline in mean hemoglobin level, both factors were associated with an increased risk of anemia. This scaling effect on the hemoglobin distributions (i.e., increased variability of the hemoglobin distribution) of HIV serostatus and kidney function can be seen in Fig. 2A, which depicts the full distribution of hemoglobin values in the four strata. Figure 2B highlights the increasing percentage of men with anemia as the risk factors of HIV infection and kidney function impairment accumulate. Among HIV-uninfected men with normal kidney function, the percent with hemoglobin levels below 13 g/dl is near 0%; among HIV-infected men with normal kidney function the percent is 0.08%; among HIV-uninfected men with impaired kidney function the percent was greater at 0.21%; and among HIV-infected men with impaired kidney function the percent was greatest at 1.21%.

The association of inflammation with hemoglobin levels was assessed by including CRP level in the model. CRP data were available for only 37% of the person-visits evaluated ($N=6334$ person-visits). We found that even the highest level of CRP was not associated with a significant change in

Table 2. Parameter Estimates from the Linear Mixed Effects Model

Parameter	*Estimate (95% CI)*	p
Effects on the mean (μ)		
Intercept[a]	15.27 (15.22, 15.33)	< 0.001
HIV^+	0.17 (0.09, 0.25)	< 0.001
eGFR < 60	−0.06 (−0.17, 0.05)	0.276
HIV^+*eGFR < 60	−0.22 (−0.42, −0.03)	0.020
Age (per 10 years)	−0.24 (−0.28, −0.21)	< 0.001
Black race	−0.71 (−0.81, −0.61)	< 0.001
Effects on the variability (σ)		
$\sigma_{Intercept}$[a]	0.59 (0.58, 0.60)	< 0.001
σ_{eGFR}	0.19 (0.13, 0.24)	< 0.001
σ_{HIV}	0.18 (0.17, 0.20)	< 0.001

[a]Hemoglobin (g/dl) level and standard deviation for an HIV^- man with eGFR ≥ 60 and mean age (49 years).

Effects on the mean and on the variance of the hemoglobin distribution were estimated for the factors of HIV serostatus and kidney function adjusting for age.

$N = 2076$ for multivariate analysis with 17,341 observations; eGFR, estimated glomerular filtration rate; HIV^+*eGFR < 60, the interaction between the effects of eGFR < 60 and HIV positivity.

Table 3. Parameter Estimates from the Linear Mixed Effects Model Limited to the Person-Visits from HIV-Infected Men

Parameter	*Estimate (95% CI)*	p
Effects on the mean (μ)		
Intercept[a]	15.64 (15.53, 15.76)	< 0.001
eGFR < 60	−0.29 (−0.47, −0.12)	< 0.001
CD4 T cell count (per 100 cells/μl)		
CD4 < 500	0.15 (0.11, 0.18)	< 0.001
CD4 ≥ 500	0.04 (0.02, 0.06)	< 0.001
$\log_{10}$(viral load)	−0.05 (−0.07, −0.03)	< 0.001
1.2 < CRP ≤ 2.3	−0.03 (−0.10, 0.05)	0.536
CRP > 2.3	−0.01 (−0.07, 0.05)	0.746
Age (per 10 years)	−0.37 (−0.43, 0.30)	< 0.001
Black race	−0.70 (−0.88, −0.53)	< 0.001
Effects on the variability (σ)		
$\sigma_{Intercept}$[a]	0.75 (0.74, 0.77)	< 0.001
σ_{eGFR}	0.32 (0.21, 0.43)	< 0.001

[a]Hemoglobin (g/dl) level and standard deviation for an HIV^- man with eGFR ≥ 60, mean age (49 years), and a $CD4^+$ cell count of 500 cells/μl with undetectable viral load.

Changes in the mean and the variance of the hemoglobin distribution associated with kidney function were estimated along with the effects on the mean associated with various immunological and inflammatory markers (adjusted for age).

$N = 862$ for multivariate analysis with 7703 observations; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.

hemoglobin level in the overall analysis. In a model restricted to HIV-infected men, controlling for the effects of CD4, VL, age, and impaired renal function, high CRP levels were not associated with average hemoglobin levels as seen in Table 3. However, CD4 was associated with hemoglobin levels such that for each 100 cell decline in CD4, there was an estimated reduction of 0.15 g/dl in average hemoglobin among HIV-infected men with CD4 counts less than 500 cells. Changes in CD4 above 500 had little impact (Table 3). VL was associated with decreases in average hemoglobin levels of 0.05 g/dl for every 10-fold increase in VL.

Discussion

Anemia is a strong predictor of mortality among persons with either CKD or HIV infection[2–5,8] and the results of this study suggest that HIV infection and impaired kidney function interact to exacerbate hemoglobin decline, even among persons receiving effective HIV treatment. The increased risk of anemia was not explained by opportunistic infections or wasting in this AIDS-free sample and was not the result of comorbidities such as diabetes or treatment for conditions such as hepatitis C. The additional decrease in hemoglobin among HIV-infected men with impaired kidney function when compared to HIV-uninfected men with normal kidney function was small but suggests a higher risk of anemia-associated morbidity and mortality. HIV-infected men with impaired kidney function had a risk of falling below 13 g/dl that was 5 to 15 times greater than that of men with either risk factor alone. While 13 g/dl represents a conservative threshold for defining anemia, it serves to illustrate the impact of the estimated joint effect of HIV infection and impaired kidney function. The use of a threshold more representative of severe anemia (e.g., 8 g/dl) would yield a similar ranking of risk among the groups but would be outside the range of observed

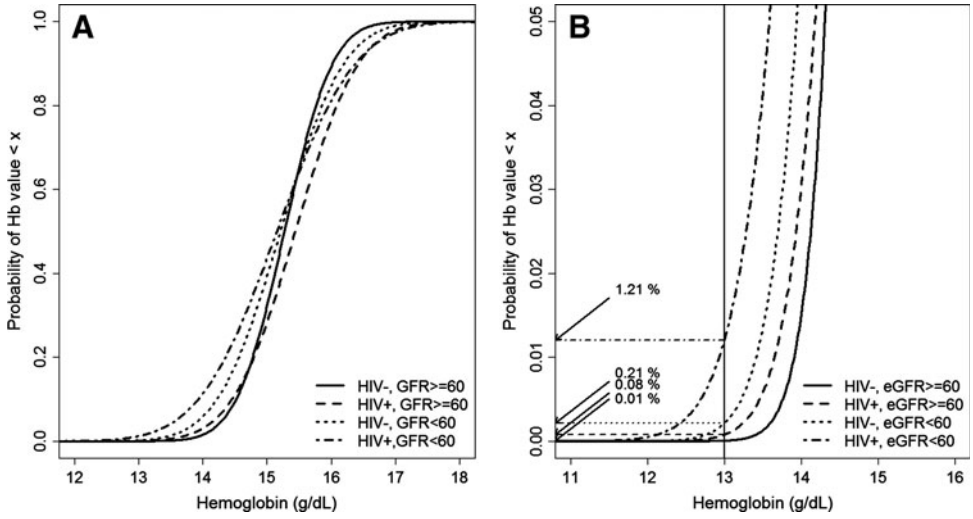

FIG. 2. The cumulative distribution functions (CDF) from the age-adjusted analysis representing the probability of having a hemoglobin level less than the specified value on the *X*-axis. **(A)** The left panel depicts the full CDF for the four strata of HIV serostatus and kidney function. **(B)** The right panel highlights the lower tail of the CDF and the proportion estimated to fall below 13 g/dl from each of the four strata of HIV serostatus and kidney function.

hemoglobin values in this cohort. Regardless of the threshold defining anemia, given the increasing prevalence of CKD,[26] any increased risk could result in a substantial number of additional cases of anemia among HIV-infected individuals.

While it is unclear whether the observed joint effect of HIV infection and impaired kidney function results from treatment or disease, subanalyses excluding visits at which participants were receiving tenofovir, and eliminating visits at which ART was not being received, did not suggest a negative impact of ART use on hemoglobin levels. On the contrary, eliminating visits at which ART was not being received raised the estimated average hemoglobin of HIV-infected men, suggesting that effective therapy is associated with increases, or at least maintenance of, serum hemoglobin levels, as has been previously reported,[27] likely through better HIV suppression. The higher noted average hemoglobin level in the HIV-infected men compared to the HIV-uninfected men presents a surprising result, but one that likely speaks to the effectiveness of therapy in conjunction with regular health care. The HIV-infected men on combination ART therapy with suppressed viral loads and free from AIDS may represent a population receiving more effective healthcare compared to their HIV-uninfected counterparts. Thus, without additional comorbidities such as CKD, HIV infection controlled through effective therapy represents no meaningful risk for anemia.

While we did find that markers of HIV disease severity, even in the absence of AIDS, were associated with a lower hemoglobin level, there was no evidence for an association between systemic inflammation (as assessed using CRP) and reductions in hemoglobin levels. Elevation of CRP, which is thought to be a marker of HIV disease progression,[24] has been associated with decreased hemoglobin levels in HIV-uninfected individuals with CKD.[28,29] The lack of such a finding in this sample of HIV-infected and HIV-uninfected men may be the result of the removal of AIDS time, when the occurrence of opportunistic infections might suppress red blood cell production as a result of a higher inflammatory state. From the participant-visits with CRP information, higher levels of plasma CRP were observed in the HIV-infected men and in men with eGFR $<60\,\mathrm{ml/min/1.73\,m^2}$, supporting a link between inflammation and HIV and CKD.

A limitation of the present study was the inability to examine the impact of more severe kidney function impairment. The threshold of $60\,\mathrm{ml/min/1.73\,m^2}$ is above the level of kidney function at which we would expect to see impairment in Epo production and consequent CKD-associated anemia. It is telling, however, that a joint effect of HIV and kidney function impairment persists even at moderate levels of CKD. Given an HIV-infected population with more severe CKD and the well-known impact of severe disease on hemoglobin levels, it would be informative to assess whether the magnitude of the joint effect on the mean hemoglobin level would increase.

In conclusion, our results suggest that HIV infection and impaired kidney function act synergistically to increase the risk for the development of anemia. HIV-infected persons, therefore, represent a population that could benefit from screening for CKD.

Acknowledgments

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) with centers located at The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland (principal investigator, Joseph Margolick, M.D., Ph.D.), Howard Brown Health Center and Northwestern University Medical School, Chicago, Illinois (principal investigator, John Phair, M.D.), University of California–Los Angeles (principal investigator, Roger Detels, M.D.), University of Pittsburgh, Pittsburg, Pennsylvania (principal investigator, Charles Rinaldo, Ph.D.), and the Data Coordinating Center, The Johns Hopkins University Bloomberg School of Public Health (principal investigator, Lisa Jacobson, Sc.D.).

This work is supported by grants UO1-AI-35042, 5-M01-RR-00052 (GCRC), UO1-AI-35043, UO1-AI-37984, UO1-AI-35039, UO1-AI-35040, UO1-AI- 37613, UO1-AI-35041, M01 RR00425, and 1K23DK081317 from the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland.

Author Disclosure Statement

No competing financial interests exist.

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