

# Impact of HIV Infection and HAART on Serum Lipids in Men

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**B**EFORE THE AVAILABILITY OF highly active antiretroviral therapy (HAART), studies in persons infected with human immunodeficiency virus (HIV) type 1 demonstrated lipid abnormalities. Men with HIV infection were reported to have hypocholesterolemia with and without hypertriglyceridemia.<sup>1-4</sup> An association between plasma triglyceride levels and circulating interferon  $\alpha$  levels has been observed in persons with AIDS; however, the mechanism for hypocholesterolemia in HIV and other infections is not known.<sup>1,2</sup> A pattern of hyperlipidemia (ie, elevated levels of total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], and triglycerides, and a reduced level of high-density lipoprotein cholesterol [HDL-C]) has been observed in patients treated with protease inhibitors (PIs).<sup>5-13</sup>

Several other metabolic abnormalities have been observed in HAART recipients (eg, morphological changes characterized by peripheral fat wasting and central fat accumulation, as well as insulin resistance).<sup>5</sup> Anecdotal reports of premature atherosclerosis in HAART recipients and the observed atherogenic plasma lipid profiles have

**Context** Alterations in serum lipid values have been widely reported among persons infected with human immunodeficiency virus (HIV) type 1 treated with highly active antiretroviral therapy (HAART), but no data have yet been reported on changes from preseroconversion lipid values.

**Objective** To describe changes in serum cholesterol levels associated with HIV infection and antiretroviral medication exposure, and 1-time assessment of triglyceride levels post-HAART initiation.

**Design, Setting, and Participants** The Multicenter AIDS Cohort Study, a prospective study in which homosexual and bisexual men were enrolled and from which 50 of 517 HIV seroconverters were drawn for the analysis herein, who later initiated HAART, involving measurements of stored serum samples obtained between 1984 and 2002.

**Main Outcome Measures** Changes in levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) at 6 time points during an average of 12 years; 1-time assessment of triglyceride levels from the third post-HAART clinic visit.

**Results** Among the 50 men, notable declines in mean serum TC ( $-30$  mg/dL [ $-0.78$  mmol/L]), HDL-C ( $-12$  mg/dL [ $-0.31$  mmol/L]), and LDL-C values ( $-22$  mg/dL [ $-0.57$  mmol/L]) were observed after HIV infection. Following HAART initiation, there were large increases in mean TC and LDL-C values ( $50$  and  $21$  mg/dL [ $1.30$  and  $0.54$  mmol/L], respectively); however, the mean changes from the preseroconversion values were  $20$  mg/dL ( $0.52$  mmol/L) (95% confidence interval [CI],  $-1$  to  $41$ ) and  $-1$  mg/dL ( $-0.03$  mmol/L) (95% CI,  $-25$  to  $22$ ), respectively. Mean HDL-C remained below baseline levels throughout follow-up. The median value (interquartile range) of triglycerides was  $225$  mg/dL ( $2.54$  mmol/L) ( $147$ - $331$  mg/dL).

**Conclusions** Before treatment, HIV infection results in substantial decreases in serum TC, HDL-C, and LDL-C levels. Subsequent HAART initiation is associated with increases in TC and LDL-C but little change in HDL-C. Increases in TC and LDL-C observed after about 3 years of HAART possibly represent a return to preinfection serum lipid levels after accounting for expected age-related changes.

JAMA. 2003;289:2978-2982

www.jama.com

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**Financial Disclosures:** Dr Riddler received research grants from Abbott Laboratories, Dupont Pharmaceuticals, Hoffman-La Roche, Trimeris, and VaxGen; honoraria from Bristol-Myers Squibb, GlaxoSmithKline, Merck, and Roche Pharmaceuticals; and salary support from NIH grants U01 AI 35041, P01 AI 43664, U01 AI 46383, and DE 15166. Dr Cole received NIH salary funding and provided biostatistical consulting for the Jaeb center for health research. Dr Chmiel received NIH grant U01-AI-35039 and has a family

member who is employed at Abbott Laboratories who owns stock in and has stock options with Abbott. Dr Dobs' employer (Johns Hopkins University) received NIH grant funding. Dr Palella received research grants or funding for investigator-initiated research from Agouron, honoraria for lectures, lecture sponsorship, or honoraria for continuing medical education programs from Agouron-Pfizer, Bristol-Myers Squibb, GlaxoSmithKline, Merck, and Roche. Dr Visscher was an investigator for the Natural History of AIDS study at University of California, Los Angeles, funded by National Institute of Allergy and Infectious Diseases.

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generated concern about the long-term health impact of HAART<sup>14</sup>; however, cohort studies evaluating the association of HAART with cardiovascular events have been inconclusive. One study of HIV-infected patients found no increase in the rate of cardiovascular events during more than 8 years of observation.<sup>15</sup> Conversely, a recent study indicated that myocardial infarction incidence was increased with longer HAART duration.<sup>16</sup> Drugs within each class of antiretroviral agents may have different effects on lipid values (eg, results of a recent trial demonstrated higher levels of fasting triglycerides, TC, and LDL-C in patients receiving stavudine vs tenofovir.<sup>17</sup> Longer follow-up and detailed analyses of regimens are needed to further clarify these issues. In the meantime, treatment of lipid abnormalities using the National Cholesterol Education Program (NCEP) guidelines has been suggested and reported in 1 cohort, in which many patients required drug therapy for control of lipid abnormalities.<sup>18</sup>

## METHODS

### Sample

The Multicenter AIDS Cohort Study (MACS) is an ongoing multicenter (Pittsburgh, Pa; Baltimore, Md; Chicago, Ill; and Los Angeles, Calif) prospective cohort study, which began enrollment of 5622 homosexual and bisexual men in 1984 who are followed up during a 6-month visit schedule. Each visit includes an interview (including questions about antiretroviral drugs used), physical examination, and collection of biological specimens. Institutional review boards at each site approved study protocols and forms, and each participant provided written informed consent.

For this analysis, 50 from a total of 517 HIV seroconverters were identified who had stored serum samples available from each of the following time points: preseroconversion (sample from the last seronegative visit) between 1984 and 1995 (median, January 1988), after seroconversion but before HAART initiation (pre-HAART, sample from the

last visit before HAART initiation) between 1990 and 1997 (median, April 1996), and at 2 time points after HAART initiation between 1997 and 1999. Because the current MACS protocol includes serum collection for real-time lipid determination, we included a third and fourth post-HAART measurement between 2000 and 2002.

### Measurements

Repository serum samples were collected without regard to fasting status and were tested (Heinz Nutrition Laboratory, University of Pittsburgh, Pittsburgh, Pa) for only those parameters largely unaffected by recent dietary intake (ie, TC, HDL-C, and LDL-C). Total cholesterol level was assessed by using the enzymatic method of Allain et al<sup>19</sup> (coefficient of variation = 1.3%). The HDL-C level was assessed after selective precipitation by heparin/manganese chloride and removal by centrifugation of very low-density lipoprotein and LDL-C (coefficient of variation = 2.1%).<sup>20</sup> The LDL-C level was measured directly via automated spectrophotometric assay (LDL Direct Liquid Select, Equal Diagnostics, Exton, Pa [coefficient of variation = 2%]).<sup>21</sup> Triglyceride measurements and data on fasting status and self-reported adherence were available for participants at the third and fourth post-HAART visits. The CD4 cell counts were determined by flow cytometry per National Institute of Allergy and Infectious Diseases laboratory protocols.<sup>22</sup>

The definition of HAART for analyses herein was guided by published guidelines<sup>23</sup> and defined as 2 or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least 1 PI or 1 nonnucleoside reverse transcriptase inhibitor (NNRTI); 1 NRTI in combination with at least 1 PI and at least 1 NNRTI; a regimen containing ritonavir and saquinavir in combination with 1 NRTI and no NNRTIs; or an abacavir-containing regimen of 3 or more NRTIs in the absence of both PIs and NNRTIs. Combinations of zidovudine and stavudine with either a PI or a NNRTI were not considered HAART. Adherence to

therapy was assessed by response to interviewer query of "On average, how often did you take medication as prescribed?" recorded in categories of 100%, 95% to 99%, 75% to 94%, or less than 75%, and presented herein as 95% or more. Evaluation of fasting status involved reporting of time of last food or drink consumed before the clinic visit. Fasting was defined as abstinence for 8 hours or more.

### Statistical Analysis

Linear regression models with robust variance estimates to account for dependent observations were used to estimate mean changes and 95% confidence intervals (CIs) in serum lipids from preseroconversion, as well as from pre-HAART, adjusting for age, body mass index (calculated as weight in kilograms divided by the square of height in meters), and CD4 cell count at the visit coinciding with the measurement. Missing CD4 cell counts and body mass index were carried forward from the most recent prior recorded value. For changes in proportions, logistic regression models with robust variance estimates to account for dependent observations were used to calculate robust *P* values and 95% CIs. Fifty men with a mean baseline cholesterol value of 200 mg/dL (5.2 mmol/L) and a SD of differences of 50 mg/dL (1.3 mmol/L) provide 79% power to detect a change of 20 mg/dL (0.52 mmol/L) in TC, by using a *t* test with a 2-sided  $\alpha$  of .05. Subsequent lipid measurements for 5 men who reported use of lipid-lowering medications during follow-up were excluded from analysis. Analyses were conducted by using SAS version 8 (SAS Institute, Cary, NC) for all available cases.

## RESULTS

At the preseroconversion visit, mean (SD) age was 35 years (8), mean body mass index was 24 (3), and 88% were white (TABLE 1). At the preseroconversion visit, mean (SD) values of TC (203 mg/dL [48], 5.26 mmol/L [1.24]), HDL-C (52 mg/dL [14], 1.35 mmol/L [0.36]), and LDL-C (121 mg/dL [37], 3.13 mmol/L [0.96]) were similar to mean values of 202, 46,

and 131 mg/dL (5.23, 1.19, 3.39 mmol/L), respectively, in men aged 20 years or older in the Third National Health and Nutrition Examination Survey (NHANES III).<sup>24,25</sup>

The mean (SD) CD4 cell count before HAART initiation for the 50 men was 307/ $\mu$ L (226). Before initiating HAART, 5 men (10%) were therapy-naive, 8 (16%) received monotherapy, and 37 (74%) received combination antiretroviral therapy. All but 2 men initiated HAART with a PI-containing regimen. Forty-six of the 50 men (92%) received regimens containing NRTIs

and PIs and 2 men received regimens that included NRTIs, NNRTIs, and PIs. Of the 48 men receiving PI-containing regimens, 39 (81%) had regimens with a single PI (indinavir [n=23], saquinavir [n=9], nelfinavir [n=3], ritonavir [n=4]), 6 had 2 PIs, and 3 had 3 PIs. For the NRTI components of the HAART regimens, 1 man had 1 NRTI (lamivudine), 38 had 2 NRTIs (25 received zidovudine and lamivudine, 8 received stavudine and lamivudine, 3 received stavudine and didanosine, 1 received zidovudine and stavudine, and 1 received didanosine and lamivudine),

7 had 3 NRTIs (4 received zidovudine, stavudine, and lamivudine; 2 received stavudine, didanosine, and lamivudine; and 1 received zidovudine, zalcitabine, and lamivudine), and 4 had 4 NRTIs (all 4 received zidovudine, stavudine, zalcitabine, and lamivudine). Although only 7 (16%) of 44 men were receiving the same antiretroviral drugs at the third post-HAART visit as were in their initial regimen, 35 (80%) of 44 had regimens representing the same drug classes (ie, PI, NNRTI, and NRTI). Overall ritonavir use was proportionally similar at the third post-HAART visit (about an equal number of men started and stopped it) to initial use; 10 men had ritonavir in the initial regimen and 9 of those contributing data at the third post-HAART visit were receiving it at that time. An increase in stavudine use occurred between the 2 time points (18 initially and 26 at third post-HAART visit).

Notable declines were observed in levels of TC (-30 mg/dL [-0.78 mmol/L]), HDL-C (-12 mg/dL [-0.31 mmol/L]), and LDL-C (-22 mg/dL [-0.57 mmol/L]) between preseroconversion and pre-HAART measurements (TABLE 2). There was an increase in mean body mass index between the preseroconversion and pre-HAART measurements (0.96; 95% CI, 0.51-1.42). Mean increases in TC and LDL-C levels from pre-HAART to third post-HAART measurements were 50 and 21 mg/dL (1.30 and 0.54 mmol/L), respectively. However, the changes from preseroconversion levels were 20 mg/dL

**Table 1.** Characteristics of 50 Men Before Seroconversion and of Remaining MACS Seroconverters at a Similar Time\*

Characteristic	Mean (SD)	
	Study Seroconverters (n = 50)	MACS Seroconverters (n = 467)†
Age, y	35 (8)	34 (8)
Race, No. (%)		
White	44 (88)	394 (84)
African American	2 (4)	43 (9)
Hispanic or other	4 (8)	30 (7)
Current smoker, No. (%)‡	11 (22)	197 (44)
BMI‡	24 (3)	24 (3)
CD4 cell count/ $\mu$ L‡	1066 (390)	978 (413)
Cholesterol, mg/dL		
Total	203 (48)	NA
High-density lipoprotein‡	52 (14)	NA
Low-density lipoprotein	121 (37)	NA

Abbreviations: BMI, body mass index calculated as weight in kilograms divided by the square of height in meters; MACS, Multicenter AIDS Cohort Study; NA, not available.

SI conversion factors: To convert high-density lipoprotein, low-density lipoprotein, and total cholesterol to mmol/L, multiply by 0.0259.

\*Data from last seronegative MACS visit.

†The MACS seroconverters minus the 50 seroconverters in the current study.

‡Three study seroconverters were missing BMI and CD4 cell count; 1, high-density lipoprotein cholesterol. Eighteen MACS seroconverters were missing smoking status; 47, BMI; and 43, CD4 cell count.

**Table 2.** Mean Change in Blood Lipids for 50 Seroconverters Initiating HAART\*

Lipid Measurements, mg/dL‡	Preseroconversion (n = 50)	Mean Change From Preseroconversion Values (95% Confidence Interval)†				
		Last Visit Before HAART (n = 50)	First Visit After HAART (n = 49)	Second Visit After HAART (n = 49)	Third Visit After HAART (n = 43)	Fourth Visit After HAART (n = 38)
Total cholesterol	201 (179 to 222)	-30 (-52 to -9)	4 (-17 to 25)	9 (-16 to 34)	20 (-1 to 41)	18 (-7 to 42)
HDL-C	51 (46 to 57)	-12 (-19 to -6)	-11 (-16 to -6)	-11 (-16 to -6)	-9 (-16 to -2)	-10 (-16 to -3)
LDL-C	122 (102 to 143)	-22 (-45 to 1)	-6 (-29 to 17)	-1 (-24 to 22)	-1 (-25 to 22)	5 (-20 to 30)

Abbreviations: HAART, highly active antiretroviral therapy; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol to mmol/L, multiply by 0.0259.

\*Linear regression with robust variance estimates, adjusted for age (1% missing), body mass index (12% missing), and CD4 cell count (2% missing). The preseroconversion values differ slightly from those given in Table 1 because of adjustment for age, body mass index, and CD4 cell count.

†Mean (SD) time between preseroconversion and seroconversion was 0.7 years (0.3); between preseroconversion and pre-HAART values, 7.8 years (2.6); between pre-HAART and first post-HAART values, 1.3 year (1); between first and second, second and third, and third and fourth post-HAART values, 0.5 (0.1), 2.1 (0.5), and 0.6 (0.3) years, respectively.

‡Follow-up for 5 men was censored due to use of lipid-lowering medications (1 prior to first visit and 4 prior to fourth visit after HAART); an additional 6 and 7 men were missing data for the third and fourth visit after HAART, respectively.

(0.52 mmol/L) (robust 95% CI, -1 to 41) for TC and -1 mg/dL (-0.03 mmol/L) (robust 95% CI, -25 to 22) for LDL-C. In contrast, the HDL-C level, which decreased by a mean of 12 mg/dL (0.31 mmol/L) (robust 95% CI, -19 to -6) between seroconversion and HAART initiation, did not appear to be affected by HAART and remained lower than the baseline mean throughout the study period. Because 4 men initiated lipid-lowering agents between the third and fourth post-HAART visit (for a fifth patient, before the first post-HAART visit), the third post-HAART visit was used for comparisons; however, the mean changes in TC, HDL-C, and LDL-C levels were similar for the third and fourth post-HAART visits. TABLE 3 gives the number and percentage of participants with abnormal lipid measurements at each time point by using NCEP cut points.<sup>26</sup> The pattern of changes in the proportion of men with abnormal values for TC, LDL-C, and HDL-C were consistent with results based on continuous measures.

Serum lipid changes for the 39 non-smokers were similar to those for the overall group (S.A.R., unpublished data, February 2003). The mean baseline TC value for the subgroup of 10 men having ritonavir as part of HAART was 177 mg/dL (4.58 mmol/L) and decreased by

only 3 mg/dL (0.08 mmol/L) at the pre-HAART visit. At the third post-HAART visit, the mean TC value increased by 60 mg/dL (1.55 mmol/L) (robust 95% CI, 25-96) and the mean LDL-C increased by 21 mg/dL (0.54 mmol/L) (robust 95% CI, -21 to 64). The small number of ritonavir recipients precludes our ability to establish differences between their values and those of the other patients. At the third post-HAART visit, 93% reported regimen adherence ( $\geq 95\%$  of prescribed doses taken) and 71% were fasting at the time of blood draw ( $\geq 8$  hours). At the third post-HAART visit, the median value (interquartile range) of triglycerides was 225 mg/dL (2.54 mmol/L) (147-331 mg/dL); this is higher than the 118 mg/dL (1.33 mmol/L) (83-173 mg/dL) for adult men observed in NHANES III.<sup>26</sup>

### COMMENT

In these 50 seroconverters, the mean TC level about 3 years after HAART initiation increased by about 20 mg/dL (0.52 mmol/L) compared with preseroconversion levels, measured 12 years (SD, 3) previously. Based on NHANES,<sup>24</sup> we would expect serum TC levels to increase about 15 mg/dL (0.39 mmol/L) for men aged 35 years; thus, our observed 20 mg/dL (0.52 mmol/L) increase is con-

sistent with expected change associated with aging. The mean LDL-C value for men in this study was essentially unchanged after HAART therapy compared with preseroconversion values, although we would expect about a 9 mg/dL (0.23 mmol/L) age-related increase in LDL-C level based on NHANES. Our data are consistent with prior reports of a minimal effect of HAART on HDL-C levels,<sup>7,11,13</sup> although one would expect a 1 mg/dL (0.03 mmol/L) decrease per decade among uninfected men aged 20 to 49 years.<sup>24</sup>

No prior study has reported changes in serum cholesterol values from preseroconversion values, but several prospective studies have compared TC levels before and after HAART initiation. In these studies, increases in mean TC levels of 28 to 39 mg/dL (0.73 to 1.01 mmol/L) and LDL-C of 10 to 29 mg/dL (0.26 to 0.75 mmol/L) were observed after 3 to 22 months of PI therapy.<sup>7,11,13</sup> These results are similar to our findings regarding changes following HAART initiation. However, comparison of pre- and post-HAART values alone is insufficient to fully interpret such changes since TC and LDL-C levels tend to decrease substantially early after HIV infection.<sup>4</sup> We compared preseroconversion and post-HAART initiation values and thus provide evi-

**Table 3.** Study Seroconverter Lipid Values Compared With NCEP Cut Points\*

Lipid Measurements, mg/dL†	No. of Participants (%)					
	Preseroconversion (n = 50)	Last Visit Before HAART (n = 50)	First Visit After HAART (n = 49)	Second Visit After HAART (n = 49)	Third Visit After HAART (n = 43)	Fourth Visit After HAART (n = 38)
Total cholesterol						
<200	23 (46)	42 (84)	24 (49)	23 (47)	17 (40)	13 (34)
200-239	17 (34)	6 (12)	12 (24)	15 (31)	13 (31)	15 (39)
$\geq 240$	10 (20)	2 (4)	13 (27)	11 (22)	12 (29)	10 (26)
HDL-C						
<40	8 (16)	34 (68)	27 (55)	30 (61)	19 (44)	19 (50)
$\geq 40$	41 (84)	16 (32)	22 (45)	19 (39)	24 (56)	19 (50)
LDL-C						
<130	34 (68)	43 (86)	32 (65)	31 (63)	25 (59)	20 (52)
130-159	7 (14)	6 (12)	12 (24)	11 (22)	9 (21)	13 (34)
$\geq 160$	9 (18)	1 (2)	5 (10)	7 (14)	8 (19)	5 (13)

Abbreviations: HAART, highly active antiretroviral therapy; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program.

SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol to mmol/L, multiply by 0.0259.

\*Data from NCEP.<sup>26</sup> The NCEP cut points are intended for use with fasting blood samples; the samples used in these analyses were collected without regard to fasting status.

†Follow-up for 5 men was censored due to use of lipid-lowering medications (1 prior to first visit and 4 prior to fourth visit after HAART); an additional 6 and 7 men were missing data for the third and fourth visit after HAART, respectively.

dence suggesting that a significant portion of the observed increase in TC and LDL-C levels may represent a return to preseroconversion levels. A competing explanation is that the results may have been affected by the timing of these analyses and future follow-up may yield further increases in serum cholesterol levels, attributed to a longer duration of HAART.

The size of the current study allows only moderately precise estimates of changes in these important lipid values. Changes in regimens were not assessed in detail, and adherence was estimated via self-report. This study is limited in that samples were collected without regard to fasting status; thus, changes in levels of triglycerides, insulin, and glucose were not quantified. In this study, serum triglyceride levels after about 3 years of HAART were higher than would be expected based on NHANES data. The impact of HAART on triglyceride levels, especially with

regimens containing ritonavir, needs further study. Likewise, data from women and minorities would be useful to determine the generalizability of these findings and to assess possible differences in populations at higher baseline risk of cardiovascular disease. Factors such as insulin resistance, fat redistribution, and smoking and diet may act synergistically with modest alterations in serum lipids and result in increased cardiovascular risk in HAART-treated persons. These issues require further study; at the current time, standard guidelines for the treatment of hyperlipidemia should be followed.<sup>26</sup> In the meantime, this study demonstrates the vital importance of comparing post-HAART lipid levels to preseroconversion levels whenever possible.

**Author Contributions:** *Study concept and design:* Riddler, Smit, Cole, Chmiel, Dobs, Kingsley. *Acquisition of data:* Riddler, Chmiel, Visscher, Evans, Kingsley.

*Analysis and interpretation of data:* Riddler, Smit, Cole, Li, Chmiel, Palella, Visscher, Evans, Kingsley. *Drafting of the manuscript:* Riddler, Smit, Cole, Chmiel, Evans, Kingsley.

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*Statistical expertise:* Cole, Li, Chmiel.

*Obtained funding:* Chmiel, Kingsley.

*Administrative, technical, or material support:* Evans, Kingsley.

*Study supervision:* Riddler, Cole, Kingsley.

**Funding/Support:** This work was supported by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute: U01-AI-35042, 5-M01-RR-00052 (GCRC), U01-AI-35043, U01-AI-37984, U01-AI-35039, U01-AI-35040, U01-AI-37613, U01-AI-35041.

**Previous Presentation:** Presented in part as a poster at the 10th Conference on Retroviruses and Opportunistic Infections, February 13, 2003, Boston, Mass.

**Additional Information:** Information regarding MACS can be found on the MACS Web site located at <http://www.statepi.jhsph.edu/mac/mac.html>.

**Acknowledgment:** We thank the participants and the clinical staff members at each of the MACS sites for their support. The MACS centers (principal investigators) are: The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Md (Joseph B. Margolick, MD, PhD, Alvaro Muñoz, PhD); Howard Brown Health Center and Northwestern University Medical School, Chicago, Ill (John P. Phair, MD); University of California, Los Angeles (Roger Detels, MD, MS, Beth Jamieson, PhD); and University of Pittsburgh, Pittsburgh, Pa (Charles Rinaldo, PhD).

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