Older Age and the Response to and Tolerability of Antiretroviral Therapy

Michael J. Silverberg, PhD, MPH; Wendy Leyden, MPH; Michael A. Horberg, MD; Gerald N. DeLorenze, PhD; Daniel Klein, MD; Charles P. Quesenberry, Jr, PhD

Background: The unique health needs of a growing older adult population infected with human immunodeficiency virus (HIV) require study, especially in terms of the response to and tolerability of highly active antiretroviral therapy (HAART).

Methods: Changes in HIV clinical markers after HAART initiation were compared among 2259 patients aged 18 to 39 years (reference group), 1834 patients aged 40 to 49 years, and 997 patients 50 years or older enrolled in an integrated health care system.

Results: Patients 50 years or older were more likely to achieve HIV RNA levels of less than 500 copies/mL within 1 year of HAART initiation (hazard ratio [HR], 1.15; \( P = .009 \)), but adjustment for adherence attenuated this finding (HR, 1.03; \( P = .59 \)). Subsequent HIV RNA level rebound (to \( \geq 1000 \) copies/mL) was less likely among patients aged 40 to 49 years (HR, 0.81; \( P = .01 \)), which persisted after adjustment for adherence (HR, 0.79; \( P = .004 \)). In year 1 of HAART, younger patients had larger CD4 T-cell count increases (131.8, 121.3, and 111.8 CD4 T cells/µL per year among patients aged 18-39, 40-49, and \( \geq 50 \) years, respectively; \( P = .046 \)). In years 2 through 6, older patients had larger CD4 T-cell count increases (4.5, 11.6, and 9.7 CD4 T cells/µL per year among patients aged 18-39, 40-49, and \( \geq 50 \) years, respectively; \( P = .04 \)). After adjustment for adherence, age differences in CD4 T-cell count changes remained in year 1 (\( P = .02 \)) but not in years 2 through 6 (\( P = .08 \)). Other factors, including comorbidities, had no effect on study results. Metabolic (glucose and lipids), hematologic (absolute neutrophils and hemoglobin), and renal (creatinine) abnormalities were more likely among older patients.

Conclusion: Despite a higher risk of adverse events, patients 50 years or older sustained high therapy adherence to maintain improved virological outcomes and to compensate for their early blunted CD4 T-cell count response compared with younger patients.

Arch Intern Med. 2007;167:684-691

HIGHLY ACTIVE ANTIRETROViral therapy (HAART) has transformed human immunodeficiency virus (HIV) infection into a chronic condition. The Centers for Disease Control and Prevention estimate that the number of AIDS cases among patients 50 years or older quintupled between 1990 and 2000.\(^1\) However, the extent to which age affects the response to HAART is unclear. Older patients reportedly have improved adherence to HIV medications,\(^2,3,24\) which is expected to result in improved outcomes. But, a higher prevalence of comorbidities\(^4\) and the natural decline in immune function with age\(^6\) could blunt the HAART response among older patients. The toxic effects of medication may also vary by age, further complicating HIV disease management in older adults, but this has received little attention in the literature.

Before the introduction of HAART, older age predicted faster progression to clinical AIDS and death.\(^7,13\) Studies on this topic in the HAART era are inconsistent. Some suggest that age is no longer a predictor of AIDS or death,\(^16\) while others\(^3,13,15,17,18\) demonstrate a continuing association of age with some poorer outcomes. Research that has focused on the effect of aging on HIV RNA levels and CD4 T-cell count responses have had varied results as well, ranging from worse outcomes\(^18,23\) to no effect\(^3,13,15,19,24,27\) to better outcomes\(^14,18,28,30\) among older patients.

To address these conflicting results from smaller studies, we evaluated changes in laboratory markers after HAART initiation among more than 5000 Kaiser Permanente Northern California (KPNC) health plan members. Our large and representative population of insured patients with HIV infection allows for a better estimation of age effects in the modern...
We performed a retrospective observational cohort study within KPNC, a large integrated health care system providing comprehensive medical services to more than 3 million members. The study population included patients with HIV infection who were 18 years or older at HAART initiation with at least 6 months’ prior membership. HAART was defined as a regimen containing 3 antiretroviral agents or more and was adapted from US Department of Health and Human Services guidelines. The follow-up period was between 1995 and 2004.

DATA COLLECTION

The KPNC HIV registry includes all known patients with HIV infection among members, with validation through manual medical record review. A total of 17 630 patients with HIV infection to date are included in the registry, 10 226 of whom were followed up after 1995. The HIV registry includes data on sex, birth date, race/ethnicity, HIV risk factors, dates of known HIV infection, and AIDS diagnoses.

We obtained antiretroviral agent prescription data from KPNC pharmacy databases. Approximately 97% of members fill their prescriptions at KPNC pharmacies, including patients whose prescriptions are obtained through the Ryan White AIDS Drug Assistance Program. Kaiser Permanente Northern California does not differentiate medical care based on Ryan White AIDS Drug Assistance Program coverage status. We obtained data regarding CD4 T-cell counts, HIV RNA levels, and other laboratory measurements from KPNC laboratory databases. Comorbidity diagnoses and health plan membership dates were obtained from KPNC clinical and administrative databases. We ascertained vital status from several sources, including hospitalizations, death certificates, and Social Security Administration data sets. The KPNC internal review board approved this study and provided a waiver of informed consent.

KEY OUTCOMES, PREDICTORS, AND COVARIATES

Virological outcomes of interest were (1) attainment of HIV RNA levels of less than 500 copies/mL within the first year after HAART initiation and (2) HIV RNA level rebound (to ≥1000 copies/mL) within 2 years after initially achieving less than 500 copies/mL. We also examined changes in CD4 T-cell counts up to 6 years after HAART initiation. We determined the incidence of laboratory abnormalities in year 1 of HAART for alkaline phosphatase, total bilirubin, creatinine, hemoglobin, alanine aminotransferase or aspartate aminotransferase, cholesterol (ie, total cholesterol or low-density lipoprotein cholesterol), and glucose levels and for neutrophil and platelet counts among patients with normal or mildly abnormal values at HAART initiation. Abnormal cutoffs for each were defined as at least grade 2 (ie, moderate, severe, or life threatening) according to Division of AIDS severity grading of adult adverse events. Finally, we determined rates of death and AIDS-defining illnesses by age. Patients were followed up until they achieved the outcomes of interest or the earliest among the following: death, disenrollment from KPNC, or December 2004 (the end of the follow-up period).

RESULTS

The analysis included 5090 patients with HIV and known dates of HAART initiation, among whom 2259, 1834, and 997 were 18 to 39, 40 to 49, and 50 years or older, respectively. Patients were followed up for a median 3.8 years after HAART initiation, with a shorter duration of follow-up for the youngest group (Table 1). Although most patients (61,4%) were active KPNC members at the end of the follow-up period, there were more losses because of death and fewer losses because of disenrollment from KPNC among the older age groups. Overall, patients had a median of 3.7 CD4 T-cell count tests and a median of 3.6 HIV RNA level tests per year. We found several differences in patient characteristics by age. Notably, patients 50 years or older had higher modified...
Table 2 gives the hazard ratios (HRs) for the association between age and achievement of HIV RNA levels of less than 500 copies/mL. Without adjustment for other factors (model 1), patients 50 years or older had a 15% increased probability of achieving HIV RNA levels of less than 500 copies/mL (HR, 1.15; \( P = .009 \)) compared with patients aged 18 to 39 years. However, adjustment for adherence in model 2 eliminated this effect (HR, 1.03; \( P = .59 \)). Other factors did not affect the HRs for age when evaluated separately (data only shown for the modified Charlson comorbidity index score in model 3). However, adjustment for all potential predictors in model 4 also diminished the association of age. Table 2 also gives the HRs for the association between age and HIV RNA level rebound to at least 1000 copies/mL. The older age groups were less likely to rebound compared with those aged 18 to 39 years, reaching statistical sig-
agents, initial CD4 T-cell count, hepatitis C virus coinfection, years of known HIV infection, and Ryan White AIDS Drug Assistance Program coverage.

years (4.5 CD4 T cells/µL per year) (Table 5). Age differences persisted after adjustment for other factors. By year 3, older patients had CD4 T-cell counts (131.8 CD4 T cells/µL per year) compared with those aged 40 to 49 years and those 50 years or older relative to those aged 18 to 39 years (data not shown). No statistically significant differences in CD4 T-cell counts by age were observed at year 6.

Changes in CD4 T-cell counts after HAART initiation are summarized in Table 3. In year 1, younger patients had faster increases in CD4 T-cell counts (131.8 CD4 T cells/µL per year) compared with those aged 40 to 49 years (121.3 CD4 T cells/µL per year) and those 50 years or older (111.8 CD4 T cells/µL per year) (P = .046). Age differences persisted after adjustment for adherence, modified Charlson comorbidity index score, and other potential predictors. We observed slower increases in CD4 T-cell counts in years 2 through 6 for all age groups, but we observed faster increases in CD4 T-cell counts for those 50 years or older (9.7 CD4 T cells/µL per year) and those aged 40 to 49 years (11.6 CD4 T cells/µL per year) compared with those aged 18 to 39 years (4.5 CD4 T cells/µL per year) (P = .04). Adjustment for adherence resulted in nonsignificant differences by age in CD4 T-cell count changes between 2 and 6 years after HAART initiation (P = .08). Separate adjustment for other factors did not diminish the age association with immunological changes in years 2 through 6 (data only shown for the modified Charlson comorbidity index score in model 3), but the fully adjusted model also eliminated the age effect (P = .45).

### IMMUNOLOGICAL MARKERS

The Figure shows the mean CD4 T-cell counts over time. The mean CD4 T-cell counts were similar at HAART initiation (year 0). At year 1, the mean CD4 T-cell counts were highest among the youngest subjects and were unaffected by adjustment for other factors. By year 3, older patients had CD4 T-cell counts similar to those among younger patients in the unadjusted model (P = .07), but adjustment for adherence in model 2 resulted in the persistence at 3 years of higher CD4 T-cell counts among younger patients (P = .01). The HIV RNA level before HAART initiation was the only other factor examined that resulted in statistically significant differences by age at 3 years (data not shown). No statistically significant differences in CD4 T-cell counts by age were observed at year 6.

### LABORATORY ABNORMALITIES

Certain abnormalities were more frequent among the older age groups, including higher creatinine, cholesterol, and glucose levels and lower hemoglobin levels and absolute neutrophil counts (Table 4). Higher risks for abnormal creatinine and hemoglobin levels were only observed in patients 50 years or older. However, higher risks for abnormal absolute neutrophil counts were observed in equal magnitudes for those aged 40 to 49 years and those 50 years or older. We found a dose-response relationship by age for abnormal cholesterol and glucose levels. For abnormal cholesterol levels, the odds ratios were 1.31 (95% confidence interval [CI] 0.84-2.06) for those aged 40 to 49 years and 1.66 (95% CI, 1.02-2.70) for those 50 years or older relative to those aged 18 to 39 years (P = .04 for linear trend across age categories). For glucose levels, the odds ratios were 1.92 (95% CI, 1.17-3.15) for those aged 40 to 49 years and 2.85 (95% CI, 1.71-4.75) for those 50 years or older relative to those aged 18 to 39 years (P < .001 for linear trend across age categories).

### CLINICAL OUTCOMES

Death and AIDS rates were similar for those aged 18 to 39 and 40 to 49 years; therefore, they were combined for comparison of the clinical outcomes. Overall, there were 424 and 177 deaths among those younger than 50 years and those 50 years or older, respectively, corresponding to rates of 28.8 and 47.4, respectively, per 1000 person-years (P < .001). We noted 419 and 136 hospitalizations for AIDS-defining illnesses among those younger than 50 years and those 50 years or older, respectively, corresponding to rates of 28.5 and 36.4, respectively, per 1000 person-years (data not shown). No statistically significant differences by age were observed at years 3, 5, and 6 (P = .97). Separate adjustment for other factors did not diminish the age association with clinical outcomes in years 3 through 6 (data not shown for the fully adjusted model 4).
The most common diagnosis overall was *Pneumocystis carinii* pneumonia (8.4 and 7.5 per 1000 person-years among those <50 years and ≥50 years, respectively; \( P = .05 \)). The following AIDS diagnoses had higher rates per 1000 person-years among those 50 years or older vs those younger than 50 years: candidiasis (5.9 vs 2.3), AIDS dementia (3.9 vs 1.6), and wasting syndrome (7.2 vs 2.3) (\( P \leq .001 \) for all). No statistically significant differences by age were found for other diagnoses.

**COMMENT**

Our study demonstrates modest differences in the response to HAART by age. Older patients had better virological responses to HAART compared with younger patients and, despite blunted initial immunological responses, had similar CD4 T-cell counts by 3 years. Higher HAART adherence was the key factor for older patients, who must overcome potential obstacles to a robust response, including an increased risk of adverse events, a higher comorbidity burden, and possible age-related immune senescence.

Research from previously published studies fails to present a consistent association between age and CD4 T-cell count and HIV RNA level responses to HAART. This may be due in part to small sample sizes or to lack of multivariate adjustment for key factors. Few studies have included more than 100 patients 50 years or older; few studies have adjusted for adherence or for comorbidities. Several features of the present study overcome these limitations. First, to our knowledge, this is the largest cohort study to date of HAART initiators 50 years or older that examines changes in laboratory markers and is among few studies to evaluate the association of age with adverse events. Second, our comprehensive patient data, including clinical, pharmaceutical, and laboratory variables, allows for a more complete analysis of potential confounders of the effect of age on response to HAART. Third, our demographically diverse cohort lends generalizability to most insured patients initiating HAART. Fourth, because study partici-
pants had similar insurance coverage, we reduced the possibility of confounding owing to different access to care by age.

We determined that patients 50 years or older have better short-term virological responses to HAART. This was explained entirely by better therapy adherence. However, there was an inconsistent effect of age on subsequent HIV RNA level rebound, and adjustment for adherence had no effect. The diminished association of age may be due to the selection of more adherent patients for the HIV RNA level rebound analysis, because those included were required to have an initial HIV RNA level of less than 500 copies/mL. In fact, the mean adherence levels in the year following the first HIV RNA level of less

### Table 3. Immunological Response After HAART Initiation by Age Group*

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Model 1 Age Only</th>
<th>Model 2 Age Adjusted for Adherence</th>
<th>Model 3 Age Adjusted for Modified Charlson Comorbidity Index Score†</th>
<th>Model 4 Age Adjusted for All Potential Predictors‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD4 T-Cell Count Increases per Microliter per Year 1 After HAART Initiation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>50</td>
<td>111.8</td>
<td>114.2</td>
<td>111.7</td>
<td>113.3</td>
</tr>
<tr>
<td>40-49</td>
<td>121.3</td>
<td>124.0</td>
<td>121.3</td>
<td>127.5</td>
</tr>
<tr>
<td>18-39</td>
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<tr>
<td><em>P</em> value for age effect</td>
<td>.046</td>
<td>.02</td>
<td>.04</td>
<td>.01</td>
</tr>
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CD4 T-Cell Count Increases per Microliter per Year 2 Through 6 After HAART Initiation

<table>
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### Table 4. Incidence of Laboratory Measurement Abnormalities After HAART Initiation by Age Group

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<th>Laboratory Measurement</th>
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<td>Alkaline phosphatase level</td>
<td>≥350 U/L</td>
<td>560 (5.9)</td>
<td>481 (5.4)</td>
<td>0.45 (0.16-1.27)</td>
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<tr>
<td>Bilirubin level</td>
<td>≥2.0 mg/dL</td>
<td>497 (13.1)</td>
<td>389 (15.2)</td>
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<tr>
<td>Creatinine level</td>
<td>≥1.8 mg/dL for men and ≥1.65 mg/dL for women</td>
<td>1265 (3.2)</td>
<td>1021 (5.8)</td>
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<td>Hemoglobin level</td>
<td>≥8.4 g/dL</td>
<td>1871 (6.9)</td>
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<td>Absolute neutrophil count</td>
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<td>Platelet count</td>
<td>&lt;100 ×10^9/µL</td>
<td>1802 (4.9)</td>
<td>1443 (5.1)</td>
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<td>Total cholesterol and LDL cholesterol levels</td>
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<td>Glucose level</td>
<td>≥161 mg/dL (random), ≥126 mg/dL (fasting), and ≥54 mg/dL (low)</td>
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**Abbreviation:** HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.

*Data are obtained from linear regression models that accounted for repeated measures (generalized estimating equations).

†Adjusted for age, sex, adherence, calendar year, comorbidities, race/ethnicity, HIV risk factors, prior AIDS diagnosis, HAART regimen class, prior antiretroviral agents, initial HIV RNA level, hepatitis C virus coinfection, years of known HIV infection, and Ryan White AIDS Drug Assistance Program coverage.

‡Excludes HIV infection and AIDS diagnosis.

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**Abbreviations:** CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; OR, odds ratio.

SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.1; creatinine to micromoles per liter, multiply by 88.4; cholesterol to millimoles per liter, multiply by 0.0259; and glucose to millimoles per liter, multiply by 0.0555.

*Abnormal cutoffs were defined as at least grade 2 abnormalities based on a table from the Division of AIDS, National Institute of Allergy and Infectious Diseases.32

†Obtained from multivariate logistic regression models adjusting for age, sex, adherence, calendar year, comorbidities, race/ethnicity, HIV risk factors, prior AIDS diagnosis, HAART regimen class, prior mild abnormality, prior antiretroviral agents, initial CD4 T-cell count, hepatitis C virus coinfection, years of known HIV infection, and Ryan White AIDS Drug Assistance Program coverage. The reference group is patients aged 18 to 39 years.
than 500 copies/mL were high and did not vary by age group (18-39 years [92%], 40-49 years [91%], and ≥50 years [94%]; P = .16). Some prior studies2,15,19,24,26 demonstrated no differences in virological response to HAART by age, while other studies3,14,18,28-30 demonstrate better outcomes among older patients. Two large studies by Lampe et al29 (n = 3825) and Paredes et al10 (n = 1469) indicate a reduced risk of virological failure with older age, but they did not adjust for adherence or comorbidities. Prior studies24,25,28 that considered differences in adherence or comorbidities had small sample sizes.

We found that patients 50 years or older had a blunted immune recovery in the first year after HAART initiation, which may be due to immune senescence because no other factors examined explained this finding. Subsequent recovery of immune function is faster among older patients, so that by 3 years there were no age differences in the mean CD4 T-cell counts. Our data support the concept that improved therapy adherence with greater HIV RNA control allows older patients to overcome the slower immune recovery expected with advancing age.

Prior studies looking at the effect of age on immune response to HAART have shown mixed results. Some studies18-23 demonstrate a blunted immune recovery among older patients, while other studies3,14,24-27 demonstrate no differences in CD4 T-cell count change by age, and a study28 among women indicated a greater immunological response with older age. A larger study was performed by Grabar et al18 (n = 3015) and is the only study to date (to our knowledge) to allow for nonlinear changes in CD4 T-cell counts within age groups. They reported faster increases in CD4 T-cell counts among younger patients following HAART initiation for all intervals. Few studies investigating age and CD4 T-cell count response have adjusted for adherence and comorbidities; 2 such studies by Tumbarello et al24,27 found no age differences in CD4 T-cell count responses before or after adjustment for these factors, but these studies were limited by small sample sizes.

Our analyses demonstrated a clear relationship between older age and high creatinine, cholesterol, and glucose levels and low hemoglobin levels and absolute neutrophil counts in our study population. A prior study2 reported an overall increase in adverse event rates with older age, while some studies15,19,26 showed no overall age differences. Few other investigators have reported age differences in individual laboratory abnormalities. Although not the primary focus of the study, Fellay et al38 indicated that older age was associated with a high prevalence of hyperlipidemia and hyperglycemia among 1160 patients enrolled in the Swiss HIV Cohort Study. Tumbarello et al24 reported a high prevalence of hyperglycemia (10% vs 2%) and low hemoglobin levels (10% vs 2%) among patients 50 years or older vs patients aged 20 to 35 years. Elevations in bilirubin levels were not associated with older age in other investigations.30

There are limitations to our study. First, differential losses to follow-up by age may have introduced bias. However, for most analyses, the follow-up period was limited to the first few years after HAART initiation before most losses to follow-up occurred. Also, the potential bias is likely conservative because older patients who disenrolled or died had lower recent HIV RNA levels and higher recent CD4 T-cell counts compared with younger patients who disenrolled or died (data not shown). Therefore, improved early virological outcomes and faster increases in CD4 T-cell counts in years 2 through 6 for older patients were not likely caused by differential losses of sicker older patients. Second, therapy adherence was based on prescription refill records and not actual pills consumed. Equating prescriptions filled with pills consumed may have led to a slight overestimate of adherence rates in our sample because it is conceivable that patients did not take medications once filled. However, the misclassification is probably small and is not likely to differ by age. Third, we evaluated adverse events only within 1 year of HAART initiation. Although we identified several adverse events associated with older age, a longer follow-up period might identify additional risks to older patients treated with HAART. Fourth, although internally valid, the results might not be generalizable to patients with HIV infection who do not have health insurance coverage.

In conclusion, we demonstrated a significant association between advancing age and an early blunted CD4 T-cell count response, with improvement by 3 years after HAART initiation. Improved adherence to HAART among older adults with HIV infection is associated with improved early virological response to HAART and probably accounts for later improved CD4 T-cell count responses. Therefore, the added importance of high adherence in older patients with regard to HAART response, coupled with a high first-year incidence of metabolic, hematologic, and renal abnormalities, indicates that close monitoring and potential treatment modifications may be needed in patients 50 years or older. Further research is needed to understand differences in clinical outcomes by age in light of our results indicating increased rates of death and certain AIDS-defining illnesses among older patients.

Accepted for Publication: December 15, 2006.
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Author Contributions: Dr Silverberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis for this study. Study concept and design: Silverberg, Leyden, Horberg, Klein, and Quesenberry. Acquisition of data: Silverberg, Leyden, and Quesenberry. Analysis and interpretation of data: Silverberg, Leyden, Horberg, DeLorenze, Klein, and Quesenberry. Drafting of the manuscript: Silverberg. Critical revision of the manuscript for important intellectual content: Silverberg, Leyden, Horberg, DeLorenze, Klein, and Quesenberry. Statistical analysis: Silverberg, Leyden, and Quesenberry. Obtained funding: Silverberg, Klein, Horberg, and Quesenberry. Administrative, technical, and material support: Silverberg, Leyden, and Horberg. Study supervision: Silverberg.

Financial Disclosure: None reported.
Funding/Support: This study was supported by grant 115-9716 from KPNC Community Benefit (Dr Silverberg).
Role of the Sponsor: The sponsor had no role in any of the following: (1) the design or conduct of the study; (2) the collection, management, analysis, or interpretation of the data; and (3) the preparation, review, or approval of the manuscript.

Previous Presentation: This study was presented as 2 posters at the 16th International AIDS Conference; August 15 and 16, 2006; Toronto, Ontario.

Acknowledgment: We thank Leo Hurley, MPH, for assistance with data analysis and for helpful discussions during preparation of the manuscript.

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