Social/Behavioral
1. Core aims

The goal of the WIHS IV Social and Behavioral Science Core (SBSC) is to promote and support the social, psychological, and behavioral aspects of new and ongoing research within WIHS. Our aims are to:

Aim 1. Conduct research on social, psychological, and behavioral factors associated with HIV-related morbidity, mortality, and quality of life, including sexual risk behavior, medication adherence, mental health, substance abuse, and the interrelationships between these factors.

Aim 2. Engage in interdisciplinary collaborations that serve to integrate social and behavioral science perspectives and methods into WIHS projects by providing ongoing input into study design, implementation, and analysis.

2. Progress report

During WIHS IV, SBSC collaborators have engaged in a number of activities to address key aims and have contributed to emerging collaborations and areas of investigation. Investigators participate in regularly scheduled and ad hoc conference calls and meetings focused on concept sheet development, project execution, analysis, and manuscript preparation. These activities have been important for advancing core WIHS science areas and for serving as a catalyst for new and emerging inquiries that integrate social and behavioral science theory and methods with multidisciplinary research questions of translational significance.

2.a. Progress related to aim 1

WIHS investigators continue to describe important factors related to the use of combination antiretroviral therapy (cART) and to adherence to therapy. Two WIHS papers described factors associated with non use of cART among eligible women in WIHS (Lillie-Blanton, Stone et al., 2010; Snow Jones, Lillie-Blanton, et al., 2010). Key factors associated with non use in these analyses included being African American, being uninsured or privately insured, recent exposure to interpersonal violence, and alcohol use. For women on antiretroviral therapy, lower adherence has been shown to be associated, across multiple WIHS analyses, with greater childcare burden (Merenstein, Schneider, et al., 2008), with an increase or decrease in fat in the chest, abdomen, or upper back (Plankey, Bacchetti, et al., 2009), and has been shown to increase with receipt of drug abuse treatment (Kapadia, Vlahov, et al., 2008). In addition, investigators have explored both the impact of mental health and substance use variables on HIV outcomes and HIV associated non-AIDS comorbidities, and how these factors influence the quality of life of women with HIV. One set of analyses showed that women using crack-cocaine had more rapid disease progression as measured by viral load, CD4, development of new AIDS-defining illnesses, and AIDS-related mortality, regardless of whether they adhered to HAART regimens and engaged in problem drinking and use of other drugs (Cook, Burke-Miller, et al., 2008). Other analyses have focused on trends in hazardous alcohol consumption and marijuana use over time among women with HIV infection and their impact on HIV-related outcomes (Cook, Zhu, et al., 2009; Cook, Zhu et al., 2012, D’Souza, Matson et al., 2012). A study of the prevalence of depressive symptoms and menopausal stage found that for HIV-infected and HIV-uninfected women, the odds of elevated depressive symptoms were significantly higher during early perimenopause, and that more severe depressive symptoms were associated with nonadherence to HAART, underscoring the need to screen and treat depression in HIV-infected women who have experienced a change in the regularity of their menstrual cycles (Maki, Rubin et al., 2012).

Recently, investigators have begun examining issues associated with smoking in the WIHS, reporting lower smoking cessation among those with a history of illicit drug use, but no differences as a function of HIV status (Goldberg, Weber, et al., 2010). Over the past several years, WIHS investigators have continued to describe factors related to the sexual behavior and sexual health of women with HIV infection. Some of these analyses focus on sexual decision making and risk, including an analysis describing trends over time in HIV seroconcordance in sexual partnerships, which showed a greater odds of seroconcordance among women.
with HIV infection (versus women without infection), and a higher likelihood of unprotected sex among partners of unknown or discordant serostatus (Liu, Hu, et al., 2011). Sexual health and behavior has begun to be explored in older women with HIV, as well. An analysis on condom use reported no significant shifts in unprotected sex between women who were pre and post menopausal (Massad, Evans, et al., 2008), although menopause was associated with greater reports of sexual problems in HIV-infected women (Wilson, Girardin, et al., 2010). In addition to adding to the knowledge base as it relates to mental health, substance use, cART adoption and adherence, and sexual risk behavior, WIHS investigators have also looked at other issues that may impact the quality of life of women with HIV, including sleep difficulties, experience of pain, pregnancy and parenthood, and use of complementary and alternative treatments. For instance, in an investigation of symptoms of insomnia in WIHS, there were no significant differences observed between HIV-infected and uninfected women (Jean-Louis, Weber, et al., 2011). In terms of pain perceptions, an analysis of women with HIV in the cohort revealed frequent and severe reports of pain, which were higher among women with a history of substance use, and with lower CD4 count and higher levels of depression (Richardson, Heikes, et al., 2009). Analyses have also focused on the use of complementary and alternative (CAM) treatment use (Merenstein, Hu et al., 2010; Liu, Yang et al., 2009; Merenstein, Yang, et al., 2008). These papers demonstrate that CAM users are less likely to use illicit drugs, are likely to initiate cART earlier than non-CAM users, and that those who use CAM and disclose use to their providers report higher adherence to HIV therapy than do those who do not disclose use. Finally, a recently published paper on depression and pregnancy found that the likelihood of elevated perinatal depressive symptoms did not differ by HIV serostatus, and that significant predictors of symptoms included preconception depression and use of mental health services (Rubin, Cook et al., 2011).

2.b. Progress related to aim 2

The SBSC core has been actively engaged in collaborations with other workgroups and cores throughout WIHS IV. This includes consultation and contributions to key measures of mental health and functioning relevant to the neurocognitive aims, development of measures specific to HPV screening and treatment knowledge, attitudes, and behavior, and collaboration with the hepatitis workgroup on measures of problem alcohol use. Collaborations with HPV investigators have resulted in a number of publications in the last several years, which focus on describing knowledge and attitudes related to cervical cancer prevention and treatment, and which describe how these cognitive factors relate to health behaviors such as compliance with colposcopy referrals (Massad, Weber 2012; Massad, Evans, Weber et al., 2010; Massad, Evans, Wilson et al., 2010) and which describe the contribution of health related behaviors, including smoking and sexual behavior, to oral HPV prevalence (Beachler, Weber, et al., 2012). Additional work by the HPV and SBSC workgroups did not find an association between stress and depression on cervical squamous lesions among WIHS participants (Massad, Agniel, et al., 2011). In addition to these collaborations, the SBSC has also worked with investigators on cardiovascular and metabolic aims. An analysis of chronic depressive symptoms and CVD risk documented a relationship between these variables, but did not find that HIV infection impacted the relationship between these variables over time (Schwartz, Lazar, et al., 2011). Interdisciplinary work involving SBSC members and WIHS geneticists has shown that a C17T polymorphism in the mu opiate receptor is associated with quantitative measures of drug use in African American women (Crystal, Hamon, Randesi et al., 2012).

3. Ongoing work

SBSC investigators are currently engaged in data collection, analysis, and writing related to more than forty approved concept sheets, which will expand the scope and impact of previous WIHS work in important ways. The investigators have developed a group of research projects that focus more specifically on the social determinants of HIV health and quality of life, including food insecurity, geographic risk for disease progression, co-occurring HIV and mental illness/substance use disorders and treatment, and racial/ethnic and sex discrimination. Investigators are also exploring more fully the factors that account for engagement in care in regard to retention in care and co-morbidity and adherence. We are also completing a number of analyses exploring the interrelationships between interpersonal violence, substance use, and mental health issues and their impact on HIV outcomes. Our new WIHS sites bring with them several nationally known HIV behavioral scientists, and together we have begun to develop a significant and cutting edge set of aims to be pursued in the coming years.
Appendix

List of WIHS-IV affiliated grant proposals linked to SBSC aims

Principal Investigator: Calabrese, Sarah
Grant number: 5F31MH085584
Years: 2010-2011
Funding institute: NIMH
Title: Cultural scripts influencing HIV prevention among African American

Principal Investigator: Cocohoba, Jennifer M.
Grant number: 1K23MH087218
Years: 2010-2013
Funding institute: NIMH
Title: Beyond pill-counting: Effect of pharmacist counseling on antiretroviral adherence

Principal Investigator: Cook, Judith
Grant number: 1R01MH089830
Years: 2010-2015
Funding institute: NIMH
Title: Prevalence of DSM-IV disorders in an multi-center HIV+ women's cohort

Principal Investigator: Mawhinney-Delson, Samantha
Grant number: 1R01DA030495
Years: 2011-2013
Funding institute: NIDA
Title: Sex, drugs and consequences of dropout on HIV outcomes in WIHS, MACS, and AIEDRP

Principal Investigator: Taylor, Tonya
Grant number: K01MH095670
Years: 2011-2015
Funding institute: NIMH
Title: Prevention needs of older women with HIV

Principal Investigator: Teplin, Linda
Grant number: 5R01DA028763
Years: 2011-2016
Funding institute: NIDA/NIAAA
Title: Drug Abuse, incarceration, & health disparities in HIV/AIDS: A longitudinal study

Principal Investigator: Weiser, Sheri
Grant number: 1R01MH095683
Years: 2012-2016
Funding institute: NIMH
Title: Pathways from Insecurity to Health and Treatment Outcomes in women with HIV
List of publications based on SBSC collaborations during WIHS IV

2012


2011


2010


2009


2008


Crack Cocaine, Disease Progression, and Mortality in a Multi-Center Cohort of HIV-1 Positive Women

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Abstract

Background—Longitudinal associations between patterns of crack cocaine use and progression of human immunodeficiency virus (HIV-1) disease are poorly understood, especially among women. This paper explores relationships between crack use and HIV-1 disease outcomes in a multi-center cohort of infected women.
**Methods**—Subjects were 1686 HIV-seropositive women enrolled at six U.S. research centers in the Women’s Interagency HIV Study. Approximately 80% were nonwhite and 29% used crack during the study period. Cox survival and random regression analysis examined bi-annual observations made April 1996 through September 2004. Outcome measures included: death due to AIDS-related causes; CD4 cell count; HIV-1 RNA level; and newly acquired AIDS-defining illnesses.

**Results**—Persistent crack users were over three times as likely as nonusers to die from AIDS-related causes, controlling for use of highly active antiretroviral viral therapies self-reported at >=95% adherence, problem drinking, age, race, income, education, illness duration, study site, and baseline virologic and immunological indicators. Persistent crack users and intermittent users in active phases showed greater CD4 cell loss and higher HIV-1 RNA levels controlling for the same covariates. Persistent and intermittent crack users were more likely than nonusers to develop new AIDS-defining illnesses controlling for identical confounds. These results persisted when controlling for heroin use, tobacco smoking, depressive symptoms, Hepatitis C virus co-infection, and intravenous drug use.

**Conclusions**—Use of crack cocaine independently predicts AIDS-related mortality, immunologic and virologic markers of HIV-1 disease progression, and development of AIDS-defining illnesses among women.

Recent research suggests that cocaine may directly affect the pathobiology of HIV by causing immune alterations in different lymphocytes such as helper T cells (CD4), suppressor/cytotoxic T cells (CD8), and natural killer (NK) cells. Studies show that cocaine interferes with the body’s ability to defend against infection by inhibiting the effector functions of neutrophils and macrophages, and by suppressing cytokine production, decreasing operation of important immune responses. Cocaine also enhances the replication of HIV in vitro. Cells from chronic cocaine users more readily support HIV replication and development of AIDS-defining opportunistic infections than cells from nonusers, suggesting a direct role for cocaine in the acquisition and progression of AIDS. Recently, cocaine has been shown to cause membrane permeability facilitating endothelial transmigration of infected dendritic cells across the blood brain barrier to the central nervous system. There is also evidence of cocaine-mediated alteration of immune responses and host resistance due to disturbances in the balance of Th1 pro-inflammatory versus Th2 anti-inflammatory cytokines and lipid bioeffectors.

Epidemiologic research confirms that crack users are at high risk for HIV infection and progression. In a prospective study of HIV-seropositive drug users, crack use was significantly associated with progression to AIDS. A study of HIV-positive current and former drug users found that active cocaine use was the strongest predictor of failure to maintain viral suppression; 13% of active users maintained suppression vs. 46% of non-users. In a prospective cohort study, compared with nonusers and former users, active cocaine and heroin users experienced smaller median reductions in HIV-1 RNA and smaller median increases in CD4 from baseline, controlling for antiretroviral exposure, adherence, and socio-demographic factors. Compared to nonusers, the risk of AIDS-related opportunistic conditions was greater for persistent users and intermittent users during periods of active use, with no difference during periods of abstinence.

Mixed results characterize studies of drug users in exclusively female U.S. cohorts. In a multi-center cohort of HIV-positive women, injection drug use was not associated with progression to AIDS. Another large multi-site cohort study found that hard drug use (i.e., cocaine, heroin, methadone, or injecting drugs) was significantly associated with AIDS-defining illnesses, but not with change in CD4, HIV-RNA, or mortality. In a third multi-site cohort of HIV+ women, non-injection drug use was associated with time to AIDS-defining event but not with AIDS-related mortality.
While suggestive, these studies and others focusing on injection drug use do not uniformly demonstrate a link between illicit drug use and HIV-1 disease progression. Possible reasons include: diverse definitions of illness progression; failure to differentiate between active and nonactive users; and lack of distinction between mortality due to AIDS versus non-AIDS causes. Other reasons include lack of controls for highly active antiretroviral therapy (HAART) use and adherence, and inadequate follow-up periods. We addressed all of these issues by examining patterns of crack use and their association with four distinct measures of HIV/AIDS disease progression in a multi-center cohort over an eight-and-one-half-year period during the HAART era.

**METHODS**

**Study Population**

The Women’s Interagency HIV Study (WIHS) is a prospective cohort study of HIV disease progression among 2058 HIV-positive women at six consortium centers: Brooklyn, NY; the Bronx, NY; Chicago, IL; Los Angeles, CA; San Francisco/Bay Area, CA; and Washington, DC. Our analysis includes biannual observations from 4/1/96 (commercial availability of protease inhibitors) through 9/30/04.

We analyzed data from cohort members completing two or more study visits (not necessarily consecutive). All women provided institutional review board-approved written informed consent for research participation and use of their medical records. Analyses were adjusted for covariates identified in prior research as being associated with illicit drug use, HIV disease progression, and mortality both in the WIHS cohort and other cohorts. These included age, race/ethnicity, education, income, baseline HIV-1 RNA and CD4, year of HIV+ diagnosis, and study site. We also controlled for problem drinking because of research reviewed by Cabral showing that cocaine in combination with alcohol places individuals at increased risk of infection with a number of pathogens, due to additive or synergistic effects resulting in impaired immune function.

**Measurements**

The first marker of disease progression was time-varying CD4 T lymphocyte levels of less than 200 cells/mm$^3$. The second was time-varying HIV-1 RNA greater than 100,000 copies/ml. Lymphocyte subsets were determined using flow cytometry at laboratories participating in the AIDS Clinical Trials quality assurance program. Plasma HIV-RNA levels were measured using a nucleic acid sequence-based amplification technique (Organon Teknika, Durham, USA). Third, newly acquired AIDS-defining illnesses were identified through medical record review using a case file abstraction protocol for participants’ primary and specialty care records described elsewhere, along with respondent self-report. Conditions were defined according to the Centers for Disease Control and Prevention AIDS definition excluding the criterion of low CD4 cell count. Cause of death was obtained from death certificates and the National Death Index, local death registries, hospital records, physician reports, and information from friends/relatives. Deaths were classified as AIDS-related if the cause was an AIDS-defining illness, or if the stated cause was organ failure or nonspecific infection and the CD4 cell count was below 200 cells/mm$^3$ using procedures described elsewhere.

At each study visit, women reported how often they took their regimens as prescribed during the past 6 months. Responses were classified as taking all drugs as prescribed $\geq 95\%$ of the time vs. $< 95\%$. This cutoff was based on past adherence research showing that HIV-1 RNA loads of $\leq 400$ copies/ml occurred $80\%$ of the time in patients with antiretroviral adherence of $\geq 95\%$. The construct validity of this measure is supported by WIHS research finding statistically significant relationships between adherence self-reports and subsequent virologic...
and immunologic parameters. For analysis, women were classified at each study visit as reporting HAART with $\geq 95\%$ adherence versus all others (i.e., non-adherent HAART use, other antiretroviral therapy use, and no therapy use).

Biannually, respondents reported the occurrence and frequency of alcohol and crack use in the past six months. Using National Institute on Alcohol Abuse and Alcoholism guidelines for women, at-risk drinking was defined as 8 or more drinks per week, and binge drinking as 4 or more drinks per day. Occurrence of either in the past six months was classified as problem drinking.

Following Lucas, four patterns of use were constructed and a value was assigned to the women’s reports for each visit, separately for crack and for alcohol use: 1) intermittent use with current abstinence (crack use or problem drinking reported previously with abstinence reported at the current visit), and 2) intermittent but currently active use (use reported at current visit but not all previous ones), 3) persistent use (use reported at every visit), and 4) nonuse (no reports of crack or problem drinking).

### Statistical Analysis

Time to AIDS-related death and time to AIDS-defining illness were each examined using Kaplan–Meier survival analysis to test for differences in survival and hazard function according to patterns of crack use. Data from women with non-AIDS-related mortality were retained in the analysis until the date of death, when they were right-censored. Women lost to follow-up were censored at their last interview date. We used the Cox proportional hazards model to examine whether different patterns of crack use were associated with mortality and with AIDS-defining illnesses controlling for illness duration, baseline immunologic and virologic factors, use of HAART at greater than or equal to 95\% adherence, socio-demographic characteristics, and study site. We used random effects logistic regression analysis (MIXOR) to examine the effects of different crack use patterns on CD4 cell count and HIV-1 RNA level controlling for the same covariates. Random effects analysis modeled intrasubject associations as a Gaussian process representing an individual’s propensity to develop an outcome indicating virologic, immunologic or clinical disease progression. Two random effects, for intercept and slope, fit the data better than one random effect.

### RESULTS

Data from 1686 women were analyzed: 1203 (71.4\%) were categorized as nonusers, 429 (25.4\%) as intermittent users, and 54 (3.2\%) as persistent users of crack. Their characteristics are presented in Table 1.

There were 419 deaths during the follow-up period: 197 (47.0\%) were AIDS-related, 138 (33.0\%) were non-AIDS related, and 84 (20.0\%) were indeterminate. Time to death was assessed with a Kaplan-Meier function (Figure 1). The estimated survival rates at 8.2 years (3000 days) were 89\% for nonusers, 90\% for intermittent users, and 65\% for persistent users (log-rank test $= 6.6, p < .05$). In a Cox proportional hazards model (Table 2) adjusting for age, race, income, education, problem drinking, adherent HAART use, CD4 count $< 200$ cells/mm$^3$ at baseline, HIV-1 RNA level $> 100,000$ copies/ml at baseline, illness duration, and study site, compared with that for nonusers, the risk of AIDS-related death was significantly higher for persistent users (hazard ratio $= 3.61, p < .001$), but not for intermittent users.

Of the total group of 1686 women, 543 (32.2\%) were found to have a newly-acquired AIDS-defining illness during the follow-up period. Significantly higher proportions of intermittent users (42.0\%, n=180) and persistent users (38.9\%, n=21) reported a new illness during this time period than did nonusers (28.4\%, n=342) (chi square $= 27.6, p < .001$). The most frequently
reported AIDS-defining illnesses were bacterial pneumonia (n=98, 18% of all cases), pneumocystis carinii pneumonia (n=52, 10%), herpes simplex virus-non-pulmonary (n=49, 9%), esophageal candidiasis (n=48, 9%), cryptosporidiasis (n=30, 6%), dementia/encephalopathy (n=27, 5%), wasting syndrome (n=27, 5%), and tuberculosis (n=20, 4%). Among these, persistent and/or intermittent users were significantly more likely than nonusers to report bacterial pneumonia (chi square=18.8, p<.001), tuberculosis (chi square=16.6, p<.01), and esophageal candidiasis (chi square=6.4, p<.05). Time to new AIDS-defining illness was assessed in the three groups with a Kaplan-Meier function (Figure 2). The average days to illness or censoring was 2592 days for nonusers, 2305 days for intermittent users, and 2211 days for persistent users (log-rank test=27.5, p<.001). In a Cox proportional hazards model (Table 2) the risk of AIDS-defining illness was significantly higher for intermittent crack users (hazard ratio=1.57, p<.001) and consistent users (hazard ratio=1.65, p<.05) than for nonusers, adjusting for all covariates.

Figures 3 and 4 present the unadjusted proportions over time by pattern of crack cocaine use of women with CD4 count<200 cells/mm$^3$, and HIV-1 RNA>100,000 copies/ml. Throughout most of the study period, those reporting persistent crack use had higher viral load concentrations and poorer immune function, while those reporting no use had the lowest HIV-1 RNA levels and best immune health, with intermittent crack users falling in between.

Table 3 presents the results of a time-varying random regression analysis of the effects of persistent and intermittent crack cocaine use on CD4 < 200 and HIV-1 RNA > 100,000. Across both models, persistent crack use, intermittent-active, and intermittent-abstinent crack use were significantly associated with HIV disease progression, controlling for adherent HAART use, problem drinking, women’s socio-demographic characteristics, study site, illness duration, baseline viral load (in the CD4 model), and baseline CD4 (in the viral load model). Persistent problem drinking was positively associated with disease progression defined by high viral load but not low CD4. In both models, adherent HAART use was protective against disease progression.

We tested five additional covariates that could account for the relationship between crack use and disease progression, with the same models used in the Cox proportional hazards and random regression analyses. Results (not shown) remained highly similar controlling, separately, for heroin use, intravenous drug use, tobacco smoking, Hepatitis C virus co-infection, and depressive symptoms (using the Center for Epidemiologic Studies-Depression Scale clinical cutoff of 16).$^{26}$ The only exceptions were for intermittent-abstinent crack use, which became non-significant in the viral load models when controlling for smoking and for depression.

Finally, to explore the impact of crack use on immune reconstitution, we conducted a supplementary analysis of associations between patterns of use (nonuse, inactive use, and active use) and immunologic response. Following Lucas and colleagues,$^9$ for all women remaining in the cohort at the end of the study period (n=1,053), we defined change in HIV-1 RNA ($\log_{10}$ copies/ml) as the difference between the most recent viral load and peak HIV-1 RNA level, and change in CD4 as the difference between the most recent and nadir CD4 lymphocyte counts. We found that the median reduction in HIV-1 RNA level was highest in nonusers, at $1.7 \log_{10}$ copies/ml, compared to $1.4 \log_{10}$ copies/ml in inactive crack users and $1.0 \log_{10}$ copies/ml in active users ($F=4.94$, df=2/1035, p<.01). The median CD4 increase was highest in nonusers, at 161 cells/mm$^3$, compared with 123 cells/mm$^3$ in inactive users, and 100 cells/mm$^3$ in active users ($F=6.99$, df=2/1035, p<.01). In multivariate linear regression models (not shown), active and inactive crack use remained significant after adjustment for race/ethnicity, use of HAART, HAART adherence 95% of time, prior HAART exposure, nadir CD4 count, and peak HIV-1 RNA level. Here, compared with nonusers, active and inactive crack
DISCUSSION

Ours is the first study to show that use of crack cocaine in a large, national cohort of HIV-positive women is longitudinally associated with subsequent deterioration in immune status, failure of virologic suppression, development of AIDS-defining conditions, and mortality due to AIDS-related causes, even among those who reported adhering to HAART regimens 95% of the time or more. Likely confounds such as heroin use, intravenous drug use, tobacco smoking, Hepatitis C virus co-infection, and depression do not appear to account for these significant associations, nor do socio-demographic factors, illness duration, or baseline immunologic or virologic indicators. Unlike prior research on a predominantly male sample, we did not consistently find that progression was less likely during periods of abstinence among women crack users, providing support for the notion that effects of cocaine on the immune system may vary by gender, as others have suggested.

Even in the face of this evidence, our analysis does not conclusively demonstrate that crack use causes AIDS-related morbidity and mortality. We have not ruled out other processes that could account for these associations, such as greater sexual risk taking, poorer diet and nutrition, substandard living conditions, and other unknown confounds.

Our findings suggest that a multi-pronged research agenda is needed to understand the effects of crack cocaine on HIV disease progression. In vivo studies can illuminate the specific role of the drug in HIV pathogenesis. In vitro research, such as the human lymphocyte/SCID (huPBL/SCID) mouse model, can shed light on how cocaine upregulates HIV and also acts as a co-factor in HIV pathogenesis. In vitro studies of peripheral blood samples from crack users can examine alterations in T cell and dendritic cell subsets, immune function, cytokine and chemokine expression, indicating predisposition to HIV infection. Studies of alveolar macrophages from the lungs of chronic crack users can help to understand impaired cytokine production and how intrapulmonary accumulation of contaminants may promote chronic lung diseases. However, neither in vivo nor in vitro research can control for the complex interactions that occur in human beings with repeated exposure to crack over time, necessitating rigorous, large-scale epidemiologic studies of morbidity and mortality among HIV+ and at-risk users, and potential differences associated with frequency, quantity, and mode of administration.

While prior research highlights difficulties crack users confront in using the medical care system, this was not true in our cohort. At their last interview, 100% of participants reported seeing a health care provider in the past 6 months: 93% said they saw the same health care provider consistently, including 94% of persistent crack users. Related to this are the findings of a recent study of HIV-positive African Americans in which women crack users reported more positive relationships with their physicians than did male crack users. Use of HAART in the WIHS cohort is significantly related to higher satisfaction with both medical care and with health care providers. This is a foundation on which to build care delivery models that are effective in engaging and retaining women crack users. One recommendation is that women using crack receive sustained follow-up with periodic reevaluations of therapy regimens to promote greater use of and adherence to HAART. Another suggestion is co-location of rapid HIV testing, risk reduction counseling, HIV therapies, psychiatric and substance abuse treatment, and other services to promote successful engagement and seamless access to multiple interventions. Finally, the importance of cultural competence is paramount,
calling for diversity in clinical staff, attention to patient-provider communication, and
sensitivity to the multiple vulnerabilities faced by these women.32-33

One caveat to our findings is the non-representativeness of our longitudinal cohort, limiting
the generalizability of our results. Another study limitation is use of self-report rather than
urine or toxicology screening to measure crack cocaine exposure. The same is true for self-
reported measures of alcohol use, HAART use, and adherence, which may be subject to
distortion due to recall errors or positive response bias. Study intervals were lengthy, number
of time-points varied by participant, and respondents entered the study at different stages of
illness. The use of death certificates and other administrative records to establish AIDS-related
deaths, and reliance on case record review to identify AIDS-defining illnesses also introduced
measurement error into our dependent variables. Finally, without direct measures of
pathobiology, the effect of crack on disease progression can only be assessed using proxy
variables.

The challenges involved in treating crack addiction are well documented, and include high
rates of treatment drop-outs, treatment repeaters, and relapse.34 This suggests the need for
models that acknowledge crack users’ diverse levels of readiness for change and recognize that
work can be done, even with women who are not yet ready to alter their behavior or are just
beginning to consider doing so. Helping individuals move from pre-contemplation to readiness
for change requires approaches that are assertive and “strengths-based,”35 building on low-
income, minority women’s intrinsic resources such as resilience and street smarts.27,35
Finally, culturally competent care is needed to promote the trust necessary for personal risk
taking that accompanies willingness to change through addiction treatment and commitment
to antiretroviral regimens.33,36

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in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation,
review, or approval of the manuscript. Judith A. Cook 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. There are no conflicts of interest for
any of the paper’s coauthors. J.A. Cook originated the study, supervised the data analyses and interpretation, and led
the writing, J.K. Burke-Miller and D.D. Grey conducted and interpreted the data analyses. All of the authors helped
to conceptualize ideas, interpreted findings, and reviewed drafts of the article.

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Figure 1.
Survival by patterns of crack use in a cohort of HIV-1 infected women. Compared with nonusers (dashed line), and intermittent users (dotted line), days to death for persistent crack users (solid line) was significantly shorter and survival rates significantly lower (p<.05).
Figure 2.
Time to newly acquired AIDS-defining illness by patterns of crack use in a cohort of HIV-1 infected women. Compared with nonusers (dashed line), days to illness for intermittent users (dotted line) and persistent crack users (solid line) were significantly shorter and hazard rates significantly higher (p<.001).
Figure 3.
Unadjusted proportions of women with CD4 lymphocyte count < 200 copies/mm³ over 18 semi-annual study visits. Nonusers (dashed line) had generally lower proportions, while persistent users (solid line) typically had the highest proportions, with intermittent users (dotted line) falling in between.
Figure 4.
Unadjusted proportions of women with HIV-1 RNA viral load >100,000 copies over 18 semi-annual study visits. Nonusers (dashed line) had consistently lower proportions, while persistent users (solid line) generally had the highest proportions, with intermittent users (dotted line) falling in between.
Table 1
Characteristics of 1686 HIV+ women in a multi-site cohort according to longitudinal patterns of crack use, 1996-2004

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonusers n = 1,203</th>
<th>Intermittent users n = 429</th>
<th>Persistent users n = 54</th>
<th>Chi Square/ANOVA Significance</th>
<th>Linear Trend Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>600 (50%)</td>
<td>305 (71%)</td>
<td>36 (67%)</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Hispanic/Latina</td>
<td>331 (28%)</td>
<td>60 (14%)</td>
<td>12 (22%)</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Caucasian/other</td>
<td>272 (23%)</td>
<td>64 (15%)</td>
<td>6 (11%)</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Less than high school education at baseline</td>
<td>414 (34%)</td>
<td>179 (42%)</td>
<td>33 (61%)</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Baseline income &lt;= $12,000/year</td>
<td>651 (55%)</td>
<td>334 (78%)</td>
<td>46 (85%)</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Age in years at baseline</td>
<td>36.5 (8.3)</td>
<td>37.4 (6.6)</td>
<td>38.0 (7.9)</td>
<td>n.s.</td>
<td>--</td>
</tr>
<tr>
<td>Baseline CD4 count (cells/mm$^3$)</td>
<td>364 (264)</td>
<td>433 (305)</td>
<td>257 (194)</td>
<td>***</td>
<td>--</td>
</tr>
<tr>
<td>Baseline CD4&lt;200 cells/mm$^3$</td>
<td>338 (29%)</td>
<td>91 (22%)</td>
<td>20 (40%)</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Baseline CD4 Percentiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25$^{th}$</td>
<td>175</td>
<td>227</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50$^{th}$</td>
<td>328</td>
<td>374</td>
<td>274</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75$^{th}$</td>
<td>508</td>
<td>564</td>
<td>366</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HIV-1 RNA level (copies/ml)</td>
<td>89424 (344409)</td>
<td>54815 (157806)</td>
<td>205160 (373550)</td>
<td>**</td>
<td>--</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA&gt;100,000 (copies/ml)</td>
<td>164 (15%)</td>
<td>52 (13%)</td>
<td>18 (37%)</td>
<td>***</td>
<td>ns</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA Percentiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25$^{th}$</td>
<td>4,000</td>
<td>4,000</td>
<td>4,250</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>50$^{th}$</td>
<td>8,100</td>
<td>8,950</td>
<td>38,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75$^{th}$</td>
<td>53,250</td>
<td>44,000</td>
<td>265,000</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Baseline log$_{10}$HIV-1 RNA</td>
<td>4.05 (0.93)</td>
<td>4.01 (.990)</td>
<td>4.53 (1.04)</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Baseline log$_{10}$HIV-1 RNA Percentiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25$^{th}$</td>
<td>3.60</td>
<td>3.60</td>
<td>3.63</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>50$^{th}$</td>
<td>3.91</td>
<td>3.95</td>
<td>4.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75$^{th}$</td>
<td>4.73</td>
<td>4.64</td>
<td>5.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of HIV+ diagnosis</td>
<td>1991 (2.5)</td>
<td>1991 (2.8)</td>
<td>1991 (2.5)</td>
<td>ns</td>
<td>***</td>
</tr>
<tr>
<td>Ever reported HAART</td>
<td>903 (75%)</td>
<td>307 (72%)</td>
<td>17 (32%)</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>HAART adherence &gt;=95% at all reports</td>
<td>346 (29%)</td>
<td>69 (16%)</td>
<td>4 (7%)</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonusers n = 1,203</th>
<th>Intermittent users n = 429</th>
<th>Persistent users n = 54</th>
<th>Chi Square/ANOVA Significance</th>
<th>Linear Trend Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline problem alcohol use&lt;sup&gt;3&lt;/sup&gt;</td>
<td>123 (10%)</td>
<td>114 (27%)</td>
<td>17 (32%)</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Number study visits completed</td>
<td>12 (6)</td>
<td>13 (5)</td>
<td>6 (6)</td>
<td>***</td>
<td>--</td>
</tr>
<tr>
<td>Date of first study visit (mo/year)</td>
<td>8/96</td>
<td>9/96</td>
<td>9/96</td>
<td>***</td>
<td>--</td>
</tr>
<tr>
<td>Follow-up time, (months)</td>
<td>86 (20)</td>
<td>85 (18)</td>
<td>66 (33)</td>
<td>***</td>
<td>--</td>
</tr>
<tr>
<td>Deceased during study (all cause mortality)</td>
<td>278 (23%)</td>
<td>104 (24%)</td>
<td>37 (68%)</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

<sup>1</sup>Values are expressed as frequency (%) for discrete variables and as mean (standard deviation) for continuous variables.

<sup>2</sup>For discrete variables, significance refers to chi-square and linear by linear associations, for continuous variables, to analysis of variance.

<sup>3</sup>Problem alcohol use is defined as >7 drinks/week and/or >=4 drinks per day.

Table 2
Cox proportional hazards models of effects of patterns of crack use on AIDS-related mortality and AIDS-defining illnesses, N=1686: Models control for study site.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dependent variable: AIDS-related mortality (200/1686 = 11.9%) Hazard Ratio</th>
<th>Dependent variable: Newly acquired AIDS-defining illness† (543/1686 = 32.2%) Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crack Use</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Intermittent</td>
<td>0.93</td>
<td>1.57***</td>
</tr>
<tr>
<td>Persistent</td>
<td>3.61***</td>
<td>1.65*</td>
</tr>
<tr>
<td>Problem Drinking²</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Intermittent</td>
<td>0.54**</td>
<td>1.05</td>
</tr>
<tr>
<td>Persistent</td>
<td>0.38</td>
<td>0.69</td>
</tr>
<tr>
<td>HAART &amp; &gt;=95% adherent</td>
<td>0.52***</td>
<td>1.13</td>
</tr>
<tr>
<td>CD4 lymphocyte count &lt;200 cells/mm³ at baseline</td>
<td>5.70***</td>
<td>1.05</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;100,000 copies/ml at baseline</td>
<td>2.46***</td>
<td>0.94</td>
</tr>
<tr>
<td>Year of HIV+ diagnosis</td>
<td>0.99</td>
<td>1.05**</td>
</tr>
<tr>
<td>African American</td>
<td>1.44</td>
<td>0.90</td>
</tr>
<tr>
<td>Latina</td>
<td>1.16</td>
<td>1.01</td>
</tr>
<tr>
<td>Low income (&lt;$12K/yr)</td>
<td>1.27</td>
<td>1.06</td>
</tr>
<tr>
<td>Less than high school education</td>
<td>1.16</td>
<td>1.10</td>
</tr>
<tr>
<td>Age (10 year increments)</td>
<td>1.04</td>
<td>1.01</td>
</tr>
</tbody>
</table>

* p<.05,
** p<.01,
*** p<.001

† Defined in accordance with the Centers for Disease Control and Prevention 1993 clinical surveillance conditions, excluding the criterion of low CD4 cell count (CDC, 1993).

² Problem drinking defined as = >7 drinks per week and/or binge drinking >=4 drinks per day.

Table 3
Random regression analysis of effects of time-varying patterns of crack use on markers of HIV disease progression, N=1686: Models control for study site.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dependent Variable: Time Varying CD4&lt;200 cells/mm$^3$ Estimate$^d$</th>
<th>Dependent Variable: Time Varying HIV-1 RNA &gt; 100,000 copies/ml Estimate$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.87</td>
<td>-1.00</td>
</tr>
<tr>
<td>Time (study visit number)</td>
<td>0.05***</td>
<td>0.03***</td>
</tr>
<tr>
<td>Crack use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crack use intermittent – abstinent</td>
<td>0.67***</td>
<td>0.45**</td>
</tr>
<tr>
<td>Crack use intermittent – active</td>
<td>0.98***</td>
<td>0.38***</td>
</tr>
<tr>
<td>Crack use - persistent</td>
<td>0.82**</td>
<td>2.24***</td>
</tr>
<tr>
<td>Problem drinking$^2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem drinking intermittent - abstinent</td>
<td>-0.18</td>
<td>-0.22</td>
</tr>
<tr>
<td>Problem drinking intermittent – active</td>
<td>0.08</td>
<td>-0.01</td>
</tr>
<tr>
<td>Problem drinking – persistent</td>
<td>-1.08</td>
<td>1.91*</td>
</tr>
<tr>
<td>CD4 lymphocyte count &lt;200 cells/mm$^3$ at baseline</td>
<td>--</td>
<td>2.21***</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;100,000 copies/ml at baseline</td>
<td>2.60***</td>
<td>--</td>
</tr>
<tr>
<td>Year of HIV+ diagnosis</td>
<td>-0.09***</td>
<td>-0.04</td>
</tr>
<tr>
<td>HAART &gt;=95% adherence</td>
<td>-1.10***</td>
<td>-2.13***</td>
</tr>
<tr>
<td>Caucasian</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>African American</td>
<td>0.24</td>
<td>0.16</td>
</tr>
<tr>
<td>Latina</td>
<td>0.69***</td>
<td>-0.16</td>
</tr>
<tr>
<td>Low income (&lt;$12K/yr)</td>
<td>0.20**</td>
<td>0.26**</td>
</tr>
<tr>
<td>Less than high school education</td>
<td>-0.10</td>
<td>0.22</td>
</tr>
<tr>
<td>Age (10 year increments)</td>
<td>0.42***</td>
<td>-0.05</td>
</tr>
</tbody>
</table>

* p<.05,
** p<.01,
*** p<.001

$^d$ Effect shown as unstandardized parameter estimate where negative sign indicates that outcome was less likely and positive sign indicates that outcome was more likely.

$^2$ Problem drinking defined as $\geq 7$ drinks per week and/or binge drinking $\geq 4$ drinks per day.
Association Between Living With Children and Adherence to Highly Active Antiretroviral Therapy in the Women's Interagency HIV Study
Daniel J. Merenstein, Michael F. Schneider, Christopher Cox, Rebecca Schwartz, Kathleen Weber, Esther Robison, Monica Gandhi, Jean Richardson and Michael W. Plankey

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http://pediatrics.aappublications.org/content/121/4/e787.full.html
Association Between Living With Children and Adherence to Highly Active Antiretroviral Therapy in the Women’s Interagency HIV Study

Daniel J. Merenstein, MDa, Michael F. Schneider, MSb, Christopher Cox, PhDc, Rebecca Schwartz, PhDc, Kathleen Weber, BSNd, Esther Robison, PhDe, Monica Gandhi, MDF, MPHg, Jean Richardson, DrPHg, Michael W. Plankey, PhDh

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The authors have indicated they have no financial relationships relevant to this article to disclose.

What’s Known on This Subject
Motherhood potentially places additional stresses on HIV-infected women, because mothers with HIV have been shown to have higher levels of depression, poorer family cohesion, less ability to perform daily functions, and more reliance on their children to perform daily responsibilities.

What This Study Adds
Women living with ≥2 children had a trend toward lower rates of adherence than women living without children. Furthermore, we found a consistently decreasing odds of >95% adherence to highly active antiretroviral therapy as the number of children in the household increased.

ABSTRACT

OBJECTIVE. The purpose of this work was to evaluate whether living with children adversely affects adherence to highly active antiretroviral therapy in HIV-infected women.

PARTICIPANTS AND METHODS. We conducted a prospective cohort study between October 1998 and September 2005. The study outcome was ≥95% adherence to highly active antiretroviral therapy evaluated at 5832 semiannual visits among 1366 HIV-infected women in the Women’s Interagency HIV Study. The primary exposure defined at the visit immediately before outcome ascertainment was the number of children ≤18 years of age reported living in the household.

RESULTS. The percentage of women who reported ≥2 children in the household who also reported ≥95% adherence ranged from 68% to 75% compared with adherence when either 1 child or no children were reported. Each additional child reported living in the household was associated with a 6% decrease in the odds of ≥95% adherence.

CONCLUSION. The impact of living with a child on the ability to take medications by HIV-infected women has not been examined thoroughly. Our data suggest that adherence to highly active antiretroviral therapy is inversely associated with the number of children living in the household.

HIGHLY ACTIVE ANTIRETROVIRAL therapy (HAART) has dramatically reduced both the morbidity and mortality among HIV-infected individuals.1–4 The evolution of HIV treatment in the developed world has dictated a shift from acute care, in which physicians and patients are most concerned with preventing death or opportunistic infections, to care for a chronic disease with novel considerations.5–7

Optimal adherence to HAART is often difficult to achieve because of factors such as lack of social support, complexity of treatment regimens, and adverse drug effects.8–14 Previous studies have also found that no illicit drug use, being white, higher education levels, presence of heath insurance, and having a regular primary care provider all positively influence adherence to HAART.15–17 Unlike other chronic diseases in which lower adherence rates allow for continued efficacy, greater compliance to HAART is necessary in HIV-infected individuals, because an increased risk of virologic failure has been directly linked to adherence levels <95%.10,18,19

In contrast to many other chronic conditions, HIV affects a younger patient population, and the majority of incident cases in the United States are in black women.20–23 Therefore, HIV-infected individuals may have an additional stress in simultaneously caring for children that would not be relevant to older persons living with other chronic diseases. Motherhood potentially places additional stresses on HIV-infected women, because mothers with HIV have been shown to have higher levels of depression, poorer family cohesion, less ability to perform daily

PEDIATRICS Volume 121, Number 4, April 2008
functions, and more reliance on their children to perform daily responsibilities. Lack of social support in mothers has been associated with nondisclosure of their HIV status, whereas higher levels of stress have been associated with nonadherence. The specifics of the relationship among HIV infection, adherence, and the stress involved in caring for children, however, need to be further elucidated. Using data from the Women’s Interagency HIV Study (WIHS), we examined whether HIV-infected women who reported living with children ≤18 years of age were less likely to adhere to their HAART regimens, and whether adherence to HAART was associated with the number of children living in the household.

METHODS

The WIHS is a multicenter prospective cohort study established in 1994 to investigate the progression of HIV in women with and at risk for HIV. A total of 3766 women (2791 HIV-infected and 975 HIV-uninfected) were enrolled either in 1994–1995 (n = 2623) or 2001–2002 (n = 1143) from 6 US locations: New York (Bronx and Brooklyn sites), Chicago, San Francisco, Los Angeles, and Washington, DC. Every 6 months, participants undergo a comprehensive physical examination, provide biological specimens for CD4 cell count and HIV RNA determination, and complete an interviewer-administered questionnaire, which collects data on demographic information, disease characteristics, and specific antiretroviral therapy (ART) use. An institutional review board at each site approves study protocols and consent forms, and each study participant provides written informed consent at each visit.

Assessment of ARV Use

At each semiannual visit, participants are shown photograph medication cards and are asked the names of specific ARV medications used since their previous visit. The WIHS uses a standard definition of HAART, adapted from the Department of Health and Human Services/Kaiser Panel guidelines. Specifically, HAART is defined as any combination of: (1) ≥2 nucleoside reverse transcriptase inhibitors (NRTIs) with ≥1 protease inhibitor (PI) or ≥1 nonnucleoside reverse transcriptase inhibitor (NNRTI) (except for combinations of zidovudine and stavudine with either a PI or NNRTI); (2) 1 NRTI with ≥1 PI and ≥1 NNRTI; (3) a regimen containing ritonavir and saquinavir in combination with 1 NRTI and no NNRTIs; and (4) an abacavir-containing or tenofovir-containing regimen of ≥3 NRTIs in the absence of both PIs and NNRTIs (except for the 3-NRTI regimens consisting of abacavir, tenofovir, and lamivudine or tenofovir, didanosine, and lamivudine). All of the non-HAART combination therapy regimens are classified as combination therapy; use of a single NRTI, PI, or NNRTI is classified as monotherapy.

Outcome Variable

Beginning in October 1998, participants were asked at each visit to indicate how often they had taken their ARV medications as prescribed in the previous 6 months. Participants categorized their level of adherence into 1 of 5 categories: 100% of the time, 95% to 99% of the time, 75% to 94% of the time, <75% of the time, or have not taken any of prescribed medications. For our analyses, participants were categorized dichotomously by whether they reported taking antiretroviral medications as prescribed ≥95% of the time. Only visits at which participants reported using a HAART regimen at some point since their last visit were included in our analyses; all of the visits at which only no therapy, monotherapy, or non-HAART combination therapy were reported since their last visit were excluded.

Primary Exposure

At each odd-numbered visit, participants were queried on the number of individuals with whom they currently lived and whether they were ≤18 years of age. Because of the wording of this study question, we could not ascertain whether the individuals ≤18 years of age who were reported to live in the household were necessarily the children of the study participant. Data on the number of children ≤18 years of age that the study participant reported at a given odd-numbered semiannual visit were concatenated with adherence data from the even-numbered semiannual visit immediately after the odd-numbered visit to preserve temporality of exposure and outcome. At the 16th semiannual WIHS visit, which occurred between April 2002 and September 2002, data on the number of children ≤18 years of age were collected as part of the interview instrument because of new WIHS recruitment. Data on the number of children at visit 16 were, therefore, paired with adherence data from visit 17. For analyses, the number of children living in the household was categorized at each visit into 1 of 5 groups: 0 (referent), 1, 2, 3, and ≥4 unless otherwise noted.

Statistical Analyses

The unit of analysis was a visit with adherence levels defined at the current visit and the exposure defined at the preceding visit. The odds of ≥95% adherence were compared between different exposure groups over time using logistic regression models with generalized estimating equations to account for the statistical dependence incurred by repeated measures of adherence on the same individual. For each participant who contributed data to analyses, a continuous time-varying covariate corresponding to the time (in years) after the first visit contributed to analysis was included in all of the univariate regression analyses except in the univariate analysis with age (in which age was treated as a time-varying covariate and date of first visit with adherence data were included as a fixed covariate). All of the adjusted regression models used to assess the relationship between the number of children and adherence to HAART were adjusted for study site; race (black, Hispanic, white, and other); cohort status (1994–1995 or 2001–2002 enrollment); education (at least high school graduate or less than high school graduate); time-up-
dated values of age (per 10 years); income (less than $6000, $6001 to $12,000, $12,001 to $18,000, $18,001 to $30,000, or $>30,000); marijuana/hash use; cocaine, crack-cocaine, or heroin use (all self-report since last visit); depression (Center for Epidemiologic Studies Depression Scale [CESD] ≥16 or CESD <16); quality of life score (per 10 points); health insurance status (presence or absence); and CD4 cell count (per 100 cells). In adjusted analyses, the date of the first semiannual visit with adherence data was also included as a fixed covariate for each individual.

RESULTS

Of the 2791 WIHS participants who were HIV infected at baseline, 2197 (79%) had a visit between October 1998 and September 2005. Of these 2197 women, 1764 (80%) reported HAART use for ≥1 visit between October 1998 and September 2005. Of these 1764 women, 1602 (91%) had a second visit wherein HAART use was reported. These 1602 women reported HAART at a total of 12,334 visits (median number of HAART visits: 7; interquartile range: 5–11). A total of 177 (11%) of the 1602 WIHS participants who were HIV infected at WIHS enrollment and reported using HAART for ≥2 study visits between October 1998 and September 2005 and had nonmissing adherence data also reported being pregnant concurrent with ≥1 visit in which HAART was reported and were excluded from all of the analyses. All of the longitudinal data for these 177 women were excluded, because adherence levels have been shown to vary greatly during pregnancy and immediately postpartum.33–36 Of the remaining 1425 women, 15 (1%) were excluded because they did not have data available to define the primary exposure of interest at any visit during follow-up. Of the remaining 1410 women, an additional 44 (3%) were excluded because the exposure of interest was not defined at the visit immediately before the visit with adherence data, resulting in a final study population of 1366 women. The 1366 women contributed a total of 5832 on-HAART study visits with both outcome and primary exposure data available. Although the 236 WIHS participants who initiated HAART but were not included in analysis (1366 from 1602 above) were younger, had higher CD4 cell counts, and were less likely to have AIDS at enrollment, they were similar to the 1366 women included with respect to race or ethnicity, level of education attained, income level, health insurance status, drug use, depression, and HIV RNA levels.

Characteristics of Study Population

Table 1 provides descriptive statistics at the first semiannual visit with adherence data for the study population of 1366 HIV-infected participants. The median age was 40 years, and the majority of women were racial and ethnic minorities, with 53% self-identifying as black and 29% self-identifying as Hispanic. Although only 16% reported a family income greater than $30,000 per year, 92% of participants reported having health insurance.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (quartile 1, quartile 3), y</td>
<td>40.0 (34.8, 45.4)</td>
</tr>
<tr>
<td>Cohort, n (%)</td>
<td></td>
</tr>
<tr>
<td>1994–1995</td>
<td>979 (72)</td>
</tr>
<tr>
<td>2001–2002</td>
<td>387 (28)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>718 (53)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>400 (29)</td>
</tr>
<tr>
<td>White</td>
<td>207 (15)</td>
</tr>
<tr>
<td>Othera</td>
<td>41 (3)</td>
</tr>
<tr>
<td>Completed high school, n (%)b</td>
<td></td>
</tr>
<tr>
<td>At or less than $6000</td>
<td>575 (43)</td>
</tr>
<tr>
<td>$6001 to $12,000</td>
<td></td>
</tr>
<tr>
<td>$12,001 to $18,000</td>
<td>206 (15)</td>
</tr>
<tr>
<td>$18,001 to $30,000</td>
<td>207 (15)</td>
</tr>
<tr>
<td>More than $30,000</td>
<td>216 (16)</td>
</tr>
<tr>
<td>Have health insurance, n (%)</td>
<td>1255 (92)</td>
</tr>
<tr>
<td>Used marijuana/hash, n (%)</td>
<td>225 (16)</td>
</tr>
<tr>
<td>Use cocaine, crack-cocaine, or heroin, n (%)</td>
<td>120 (9)</td>
</tr>
<tr>
<td>CESD ≥16, n (%)b</td>
<td>575 (43)</td>
</tr>
<tr>
<td>Quality of life score, median (quartile 1, quartile 3)b</td>
<td>68.0 (52.5, 82.7)</td>
</tr>
<tr>
<td>Have AIDS, n (%)</td>
<td>539 (39)</td>
</tr>
<tr>
<td>CD4 cell count, median (quartile 1, quartile 3), cells per mm3b</td>
<td>380 (235, 568)</td>
</tr>
<tr>
<td>log10 (HIV RNA), median (quartile 1, quartile 3), copies per mLb</td>
<td>2.20 (1.90, 3.71)</td>
</tr>
</tbody>
</table>

If data for a particular variable were missing at the first semiannual visit with adherence data, we used the data, if available at the semiannual visit immediately before this visit.

a Other category includes Asian/Pacific Islander, Native American/Alaskan, and other.

b Education was missing for 2 women; income level was missing for 3 women; CESD was missing for 20 women; quality of life score was missing for 18 women; CD4 cell count was missing for 6 women; and log10 (HIV RNA) was missing for 6 women.

Thirty-nine percent had ≥1 clinical AIDS diagnosis; the median CD4 cell count was 380 cells per mm3, and the median log10 (HIV RNA) was 2.20 copies per mL.

Adherence Levels and Presence of Children

At least 95% adherence to HAART was reported at 76% (n = 4430) of all 5832 of the visits. Fifty percent (n = 684) of the 1366 women in the study reported ≥95% adherence at all of the visits at which they reported HAART. Sixty-six percent (n = 897) of the 1366 women reported having ≥1 child ≤18 years of age living in the household at least once during follow-up; 65% (n = 583) of these 897 women reported having children living in the household at all of the visits.

To describe the cross-sectional relationship at each visit between the number of children ≤18 years of age reported living in the household and adherence, we calculated the percentage of women with ≥95% adherence to HAART stratified by whether ≥2 children, 1 child, or no children were reported (Fig 1). Across all of the follow-up visits, the percentage of women who had reported ≥2 children in the household, who also reported ≥95% adherence, was 72% on average (range: 68%–75%) compared with adherence reported among women who reported either 1 child (average: 76%; range: 71%–82%) or no children (average: 78%; range: 75%–80%). Women who reported ≥2 children had
lower adherence levels across almost all of the follow-up visits.

Univariate and Multivariate Longitudinal Analyses

To further examine the relationship between the number of children ≤18 years of age living in the household and adherence levels, we conducted univariate and multivariate logistic regression analyses. Because we anticipated an inverse relationship between adherence and the number of children, we treated the number of children as a continuous measure in the primary regression analyses. To limit the influence of a small number of visits wherein a relatively large number of children were reported, we categorized the number of children as 0 (referent), 1, 2, 3, and ≥4. Each additional child was associated with a 9% decrease in the odds of ≥95% adherence (odds ratio [OR]: 0.91; 95% confidence interval [CI]: 0.85–0.96) in an unadjusted analysis and a 6% decrease in the odds of ≥95% adherence (OR: 0.94; 95% CI: 0.88–1.00) in an adjusted analysis that included study site; age; cohort status; race; education; income; marijuana or hash use; cocaine, crack-cocaine, or heroin use; depression; quality of life score; health insurance status; and CD4 cell count (all variables defined as indicated in the “Statistical Analyses”). A similar result was obtained when ≥4 children were not combined into 1 group; however, this was not significant (adjusted OR: 0.95; 95% CI: 0.89–1.01). The ORs for the effect of each category of number of children (with report of no children as the reference group) are reported in Table 2, demonstrating a downward trend in adherence in both the unadjusted and adjusted analyses. Although none of the categories was significantly different from the reference group in the adjusted analysis, the overall trend reached borderline statistical significance in the primary analysis (OR: 0.94; P = .055).

Consistent with previous research, our results demonstrated that white women had an odds of self-reporting of ≥95% adherence levels that were 69% higher than black women. In addition, each 10-year increment in age was associated with a 40% increase in the odds of achieving ≥95% adherence. Any report of marijuana use or use of crack, cocaine, or heroin since the previous visit was associated with 26% and 44% lower odds of ≥95% HAART adherence, respectively. In addition, we ran a secondary analysis adjusting for whether the women saw a primary care physician, and the results presented in Table 2 were unchanged (data not shown).

DISCUSSION

The importance of family-centered care on children’s health has long been recognized. However, the role that the burden of child care plays in the health of parents or caregivers has not been as readily explored. We believe that this relationship is important and that health outcomes can be better predicted by examining the effects of children (and the responsibilities that come with their care) on parental health.

We evaluated whether the number of children ≤18 years of age living in the home was associated with adherence to HAART by using longitudinal data collected from the WIHS from October 1998 through September 2005. During follow-up, women living with ≥2 children had a trend toward lower rates of adherence than women living without children. Furthermore, in both univariate and multivariate analyses, we found a consistently decreasing odds of >95% adherence to HAART as the number of children in the household increased. The odds of ≥95% HAART adherence associated with no illicit drug use, white race, and older age in the WIHS were similar to those found by other investigators.

It will be particularly important for health care providers to discuss with HIV-infected mothers or caregiv-
ers, particularly mothers who have additional stressors such as living in poverty, how child care responsibilities may influence adherence. It may be necessary to establish support systems to alleviate the stress of child care responsibilities among these women based on the trends observed in this analysis.

Our analysis only examined basic stressors that the presence of a child in the household may present. Although the results of the multivariate analyses did not quite reach conventional statistical significance, the CIs and the direction of our estimates suggest association per our a priori hypothesis. Because HIV-infected women are surviving with more productive and active lives and are able to give birth to healthy children, future research needs to delve further into the relationship between child care responsibilities and adherence to medication.

### TABLE 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. Person-Visits</th>
<th>No. (%) With ≥95% Adherence</th>
<th>Unadjusted ORa</th>
<th>95% CI</th>
<th>Adjusted ORb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children ≤18 years of age reported living in the household</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2817</td>
<td>2193 (78)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>1</td>
<td>1402</td>
<td>1073 (77)</td>
<td>0.90</td>
<td>0.76–1.08</td>
<td>0.89</td>
<td>0.73–1.07</td>
</tr>
<tr>
<td>2</td>
<td>934</td>
<td>685 (73)</td>
<td>0.78</td>
<td>0.63–0.95</td>
<td>0.85</td>
<td>0.68–1.06</td>
</tr>
<tr>
<td>3</td>
<td>402</td>
<td>284 (71)</td>
<td>0.76</td>
<td>0.56–1.02</td>
<td>0.84</td>
<td>0.62–1.12</td>
</tr>
<tr>
<td>≥4</td>
<td>277</td>
<td>195 (70)</td>
<td>0.70</td>
<td>0.51–0.96</td>
<td>0.77</td>
<td>0.56–1.08</td>
</tr>
<tr>
<td>Study site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1188</td>
<td>995 (84)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>1093</td>
<td>753 (69)</td>
<td>0.43</td>
<td>0.33–0.58</td>
<td>0.39</td>
<td>0.29–0.53</td>
</tr>
<tr>
<td>3</td>
<td>770</td>
<td>555 (72)</td>
<td>0.49</td>
<td>0.36–0.67</td>
<td>0.47</td>
<td>0.34–0.64</td>
</tr>
<tr>
<td>4</td>
<td>1190</td>
<td>975 (82)</td>
<td>0.87</td>
<td>0.65–1.18</td>
<td>0.75</td>
<td>0.55–1.02</td>
</tr>
<tr>
<td>5</td>
<td>714</td>
<td>515 (72)</td>
<td>0.53</td>
<td>0.38–0.74</td>
<td>0.50</td>
<td>0.35–0.72</td>
</tr>
<tr>
<td>6</td>
<td>877</td>
<td>637 (73)</td>
<td>0.51</td>
<td>0.38–0.70</td>
<td>0.51</td>
<td>0.37–0.70</td>
</tr>
<tr>
<td>Age per 10 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5832</td>
<td></td>
<td>1.22</td>
<td>1.09–1.37</td>
<td>1.40</td>
<td>1.23–1.60</td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994–1995</td>
<td>4607</td>
<td>3488 (76)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>2001–2002</td>
<td>1225</td>
<td>942 (77)</td>
<td>1.12</td>
<td>0.91–1.39</td>
<td>1.63</td>
<td>1.18–2.25</td>
</tr>
<tr>
<td>Race or ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3000</td>
<td>2164 (72)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1669</td>
<td>1311 (79)</td>
<td>1.40</td>
<td>1.15–1.71</td>
<td>1.20</td>
<td>0.96–1.51</td>
</tr>
<tr>
<td>White</td>
<td>994</td>
<td>816 (82)</td>
<td>1.77</td>
<td>1.35–2.33</td>
<td>1.69</td>
<td>1.27–2.24</td>
</tr>
<tr>
<td>Other</td>
<td>169</td>
<td>139 (82)</td>
<td>1.78</td>
<td>0.97–3.26</td>
<td>1.60</td>
<td>0.86–2.99</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not completed high school</td>
<td>2043</td>
<td>1542 (75)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>Completed high school</td>
<td>3787</td>
<td>2887 (76)</td>
<td>1.04</td>
<td>0.87–1.25</td>
<td>1.00</td>
<td>0.83–1.22</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At or less than $60000</td>
<td>873</td>
<td>646 (74)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>$6001 to $12 000</td>
<td>2073</td>
<td>1558 (75)</td>
<td>1.00</td>
<td>0.84–1.20</td>
<td>0.99</td>
<td>0.81–1.20</td>
</tr>
<tr>
<td>$12 001 to $18 000</td>
<td>884</td>
<td>675 (76)</td>
<td>1.05</td>
<td>0.85–1.30</td>
<td>1.07</td>
<td>0.84–1.35</td>
</tr>
<tr>
<td>$18 001 to $30 000</td>
<td>933</td>
<td>695 (74)</td>
<td>1.02</td>
<td>0.82–1.27</td>
<td>0.98</td>
<td>0.77–1.24</td>
</tr>
<tr>
<td>More than $30 000</td>
<td>1046</td>
<td>839 (80)</td>
<td>1.29</td>
<td>1.00–1.65</td>
<td>1.14</td>
<td>0.86–1.50</td>
</tr>
<tr>
<td>Marijuana or hash use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported using</td>
<td>878</td>
<td>608 (69)</td>
<td>0.72</td>
<td>0.59–0.87</td>
<td>0.74</td>
<td>0.60–0.91</td>
</tr>
<tr>
<td>No report of using</td>
<td>4932</td>
<td>3805 (69)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>Crack, cocaine, or heroin use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported using</td>
<td>467</td>
<td>281 (60)</td>
<td>0.55</td>
<td>0.44–0.69</td>
<td>0.56</td>
<td>0.44–0.73</td>
</tr>
<tr>
<td>No report of using</td>
<td>5341</td>
<td>4131 (77)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CESD ≥16</td>
<td>2311</td>
<td>1671 (72)</td>
<td>0.79</td>
<td>0.68–0.90</td>
<td>0.97</td>
<td>0.82–1.15</td>
</tr>
<tr>
<td>CESD &lt;16</td>
<td>3342</td>
<td>2631 (79)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>Quality of life score per 10 points</td>
<td>5621</td>
<td>NA</td>
<td>1.09</td>
<td>1.06–1.13</td>
<td>1.09</td>
<td>1.05–1.14</td>
</tr>
<tr>
<td>Health insurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>360</td>
<td>281 (78)</td>
<td>1.00</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>Yes</td>
<td>5464</td>
<td>4142 (76)</td>
<td>0.84</td>
<td>0.64–1.12</td>
<td>0.75</td>
<td>0.55–1.01</td>
</tr>
<tr>
<td>CD4 cell count per 100 cells</td>
<td>5662</td>
<td>NA</td>
<td>1.07</td>
<td>1.03–1.10</td>
<td>1.06</td>
<td>1.02–1.09</td>
</tr>
</tbody>
</table>

All of the characteristics were evaluated as time varying except for study site, cohort, race, and education. NA indicates not applicable.

a All of the unadjusted models included a variable representing the time (in years) after the first visit with adherence data. In the unadjusted model with age, we included the date of the first visit with adherence data centered at 2001.0 in the model instead of elapsed time since first visit with adherence.

b A total of 1320 WIHS participants (of 1366 in study population) contributed 5386 visits with complete data and were included in adjusted analysis; 446 person-visits with missing data for ≥1 variable were not included. The date of the first visit with adherence data (centered at 2001.0) was included in adjusted analysis.
We postulate that there is a threshold of stress related to the number of children in the home, age of the child, health of the child, and other familial stressors among women with HIV that, when achieved, may diminish adherence to HAART. This information is important for health care providers, because they can work with treatment teams to erect safety net interventions to improve adherence. Future research should examine the role of social supports around HAART adherence in the context of child caregiving.

Our study has several important limitations. There is no single interview question in the WIHS that confirms that any children ≤18 years of age who the participant reports living in the household actually belong to the participant. It is likely that some of these children were not the participants’ biological children, but we assumed that the HIV-infected woman in the household was at least partially responsible for caring for the children. In addition, WIHS primarily collects data on the women themselves, and information about the children they report living with them is limited. Thus, data on the age and health status of the children or whether the participants have disclosed their HIV status to the children living in the household are not available. This is potentially important information, because mothers have been reported to approach their HIV status differently according to the age of their children.26 Also, because adherence was self-reported, there is a possibility of misclassification whereby HIV-infected participants, regardless of whether they report children living in the household, tend to overreport adherence rates. There is no reason to believe, however, that the rate of misclas-

sification would be any higher among women without children than among women with children (ie, differential misclassification), and any nondifferential misclassification would bias our estimates of association toward the null.38 In addition, previous WIHS research has shown self-reported adherence to be consistent with objective measures, such as CD4 count, HIV viral load, and self-report of physical functioning.17 Finally, although our results are consistent with previous adherence research, it is possible that the differences that we observed are because of other unmeasured confounders.

We believe that the number of children living in the household influences adherence to HAART among HIV-infected women. We acknowledge that further exploration of the familial relationship, the age and health status of the children, and HIV-related outcomes are necessary, because the relationship between HIV treatment and maternal health are likely to be tightly linked. To improve adherence in HIV-infected mothers, these relationships will need continued elucidation, and appropriate interventions will need to be investigated.

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Association Between Living With Children and Adherence to Highly Active Antiretroviral Therapy in the Women's Interagency HIV Study

Daniel J. Merenstein, Michael F. Schneider, Christopher Cox, Rebecca Schwartz, Kathleen Weber, Esther Robison, Monica Gandhi, Jean Richardson and Michael W. Plankey

*Pediatrics* 2008;121:e787

DOI: 10.1542/peds.2007-1586

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