ADHERENCE TO ANTIVIRAL DRUG REGIMENS IN HIV-INFECTED ADOLESCENT PATIENTS ENGAGED IN CARE IN A COMPREHENSIVE ADOLESCENT AND YOUNG ADULT CLINIC

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Inconsistent use of antiviral medications for the treatment of HIV may lead to the emergence of resistant strains in HIV-infected adults. Patterns of adherence with these drug regimens in adolescents remains unknown. Identifying nonadherence in HIV-infected patients to antiviral regimens and developing corrective measures could improve patient outcomes. This study was undertaken to understand adherence in HIV-infected youths engaged in care and to reduce patterns of nonadherence. A retrospective analysis of 25 charts (78%) of HIV-infected youths (n = 32, age 13 to 21 years) were consecutively reviewed from January 1993 to May 1998. Charts were reviewed for documentation of factors previously documented to be associated with adherence: housing stability, social support, prior sexually transmitted diseases (STDs) and/or pregnancy, HIV exposure category, number of clinic visits, number of pills per day, number of medications per day, knowledge of medication schedule, age, gender, race/ethnicity, health status as revealed by CD4 count and viral load, and recorded patterns of adherence to medications and clinic appointments. Thirteen of the 18 (72%) patients who were receiving antiretroviral medication were nonadherent. Sixty-seven percent of the females and 80% of the males reported missing doses. Housing instability ($p = 0.031$) and/or length of treatment with antiviral medications (months of treatment) ($p = 0.043$) were significantly correlated with nonadherence. The stability of the adolescents' living situations was the most significant correlate of medication adherence for this population of HIV-infected youth. (J Natl Med Assoc. 2000;92: 55–61.)

Key words: adolescents ◆ HIV ◆ adherence ◆ antiviral medications

HIV seroprevalence studies both nationally and internationally reveal that adolescents, particularly

females, are now being infected at increasingly higher rates, and in some regions at rates higher than adults.[1] As we fathom the fact that more youths are identified to be infected with HIV, new treatments to combat this epidemic are continuously developed. The new combination triple antiviral therapies have provided extraordinary changes in the treatment and survival of individuals with HIV. These combination therapies have resulted in drops in hospitalization days by 35%, new AIDS cases by 35%, and deaths by 46%.[2] However, studies designed to measure noncompliance or nonadherence with drug therapy, including with antiviral drug regimens, have documented rates from 13% to

93% (average rate, 40%).[3-5] Of note is that nonadherence to these antiviral regimens may foster the emergence of drug-resistant strains of this virus, thus aggravating treatment for adolescents living with HIV/AIDS.

The emergence of drug-resistant strains of HIV is a public health issue. As HIV-infected individuals engage in unprotected sex, such strains are potentially introduced into the community, making treatment difficult. Thus, monitoring adherence to these complicated antiviral regimens is a major component of providing comprehensive health to HIV-infected youths. We undertook this study to more accurately understand adherence in HIV-infected youths engaged in care, and to reduce patterns of nonadherence.

METHODS

A retrospective review was conducted of the medical records of all HIV-infected adolescent and young adult patients engaged in care in a hospital-based adolescent and young adult clinic from January 1993 to May 1998. This clinic registers about 2500 patient encounters per year of patients 13 to 21 years old seeking comprehensive health care. This cohort of HIV-infected clients engaged in care ($n = 32$) are adolescents and young adults between the ages of 13 and 21 years who attend a general adolescent and young clinic. This comprehensive care clinic offers medical and mental health services to all youths in our catchman area—the County of Cook, Illinois. Another 60 HIV-infected patients 21 to 24 years old are engaged in care by adult medicine providers within specifically identified HIV clinics for adult clients.

The clinic is located within Cook County Hospital, a public hospital documenting over 54,000 patient encounters in youths 13 to 24 years old through its inpatient, emergency room, and outpatient clinics. Cook County Hospital is an inner city public hospital, providing the majority of care to indigent patients who are primarily African American and Latino.

Criteria for adherence with "treatment" from data chart extraction include:

- *Medication nonadherence*—A patient was considered nonadherent or a "nonadherer" if the clinician noted on one visit that the patient missed one or more weeks of medication (including missing all medications, or taking medications every other day, i.e., not

consistent with the prescribed medication schedule) or if the clinician documented that the patient missed the prescribed medication schedule on two or more visits. Exclusion criteria for this category were patients who were reported to have missed one dose or just one day of medication[5] and any patient declining to take antiviral drug regimens. Subjects were thus assessed as "Adherers," "Nonadherers," or "Nonmedicated" based on this definition.

- *Appointment nonadherence*—A patient was considered nonadherent if the clinician documented missed appointments on more than one visit. Exclusion criteria for this category were patients who only missed one scheduled visit.

- *Independent variables*—Factors thought to impact adherence with "treatment" were also noted. These include housing stability, social support, prior sexually transmitted diseases (STDs) and/or pregnancy, HIV exposure category, number of clinic visits, number of pills per day, number of medications per day, knowledge of medication schedule, age, gender, and race/ethnicity. A patient was considered as having an unstable housing environment if the clinician noted that the patient had multiple residences over the period of treatment, had a history of being "kicked-out" of their home, or had lived at any time during treatment in a shelter.

Charts were also screened for CD4 count and viral load.

Examination of the relationship of the adherence variable and other categorical variables were conducted using chi square tests. Examinations of the univariate relationships of adherence and variables that were on at least an ordinal scale of measurement were conducted using the Kruskal Wallis and Wilcoxon tests for nonparametric comparisons to detect differences between adherers, nonadherers, and the non-medicated. The Kruskal-Wallis test is the nonparametric analog of one-way analysis of variance and detects differences in distribution location. The Wilcoxon test is the special case of the Kruskal-Wallis test applied to two groups.

RESULTS
Demographics and Clinical Data

Twenty-five charts (78%) of HIV-infected youths were consecutively reviewed from a total of 32 youths 13–21 years old who were engaged in care in our adolescent comprehensive health care clinic.

Table 1. Demographic and Clinical Data on Samples of HIV-Infected Adolescents at Enrollment into Treatment

Variable	No.	Frequency	%
Demographic data			
Gender	25		
Male		15	60
Female		10	40
Age (years)	25		
16–17		5	20
18–19		14	56
20–22		6	24
Race/Ethnicity	25		
African American		20	80
Latino		5	20
Exposure category	25		
MSM		12	48
Heterosexual (female)		10	40
Heterosexual (male)		1	4
Hemophilia		2	8
Housing stability	22		
Stable		12	55
Unstable		10	45
Clinical data			
Prior pregnancies/STDs	25		
None		6	24
One		7	28
Multiple		12	48
Medication adherence	23		
Adherers		5	22
Nonadherers		13	56
Nonmedicated		5	22
Medical appointment adherence	22		
Adherers		9	41
Nonadherers		13	59
Viral load	16		
Lower limits		2	13
<10,000		9	56
>10,000		5	31
CD4 count	22		
<50		1	4
51–200		3	14
200–500		9	41
>500		9	41

Patients were mostly male ($n = 15$; 60%) and were comprised of African Americans ($n = 20$; 80%) and Latinos ($n = 5$; 20%). The mean age at enrollment was 18 years (range 16 to 22) with 76% of patients being 19 years old and younger at the time they were engaged in care (Table 1).

The primary exposure category for HIV infection in males was MSM (male sex with male) ($n = 12$;

80%). Females reported heterosexual intercourse as their only exposure category ($n = 10$; 100%). Two males were hemophiliacs and one other male reported heterosexual intercourse as his only exposure category. On the initial clinic visit, 71% of youths in this sample had CD4 counts less than 500, and 31% of the sample had viral loads that were greater than 10,000 ($n = 5$) (see Table 1).

Prior STDs and/or pregnancies were also noted. Only 25% ($n = 6$) reported having no STDs and no prior pregnancy. Ninety-one percent and 51% of our females and males, respectively, reported a history of a prior STD. Forty-five percent of our females reported having been pregnant. Seventy-five percent of the females and 66% of males did not live with their parents; in fact, 50% of the females and 33% of males reported living on their own.

Adherence Data

Twenty-three of 25 patients were assessed as "Adherers," "Nonadherers," or "Nonmedicated" according to the criteria listed above. Two patients were excluded from this analysis because they had only one clinic visit documented—their initial visit. Thirteen of the 18 (72%) patients who were receiving antiretroviral medication were nonadherent (Table 1). Sixty-seven percent of the females and 80% of the males reported missing doses.

Housing instability ($p = 0.031$) and/or length of treatment with antiviral medications (months of treatment) ($p = 0.043$) were significantly correlated with nonadherence. No significant difference was observed between adherers, nonadherers, and nonmedicated patients for age of enrollment, prior STDs or pregnancy, or adherence with appointments (Tables 2 and 3).

A four-point health status change (1 = worsened viral load or CD4 count; 2 = no change in viral load or CD4 count; 3 = improved viral load or CD4 count; 4 = improved viral load and CD4 count) was assessed for each subject. No significant correlation was observed between adherers, nonadherers, and those not medicated and their health status (see Table 2).

DISCUSSION

"Noncompliance" or "nonadherence," which has been designated by the National Council on Patient Information and Education as "America's other drug problem,"[5] can jeopardize the outcome of

Table 2. Means and Standard Deviations of Study Variables for All Subjects by Adherence Group

Variable	No.	Adherers (N = 5) Mean ± SD	Non-Adherers (N = 13) Mean ± SD	Non-Medicated (N = 5) Mean ± SD
Age at enrollment	23	19.0 ± 1.4	18.8 ± 1.8	18.8 ± 1.4
Prior STDs/Pregnancy	23	2.3 ± .81	2.4 ± .89	2.4 ± .77
Housing instability	21	1.4 ± .51	1.0 ± 0*	1.6 ± .51*
Months of treatment	23	15.3 ± 14.5	9.0 ± 9.0*	22.1 ± 15.2*
Hx of keeping appts.	22	1.4 ± .52	1.5 ± .60	1.4 ± .52
Viral load				
First visit	14	27.3K ± 57.3K	55.9K ± 106.1K	19.4K ± 23.3K
Last visit	13	19.6K ± 59.9K	499 ± 0	25.3K ± 68.0K
Change	10	−12.2K ± 22.2K	−3.5K ± 4.9K	−16.1K ± 26.0K
CD-4 value				
First visit	20	414.4 ± 231.0	380.3 ± 145.8	327.7 ± 188.6
Last visit	20	398.7 ± 225.8	402.0 ± 205.0	297.9 ± 159.8
Change	19	−20.6 ± 134.2	21.8 ± 88.3	−39.5 ± 165.8
Health status change	15	2.6 ± .74	3.0 ± 0	2.4 ± .84

* $p < 0.05$.

Table 3. Kruskall-Wallis Test for Differences in Mean Ranks Among Adherers and Nonadherers (df = 1)

Variable	χ^2	Prob < χ^2
Age at enrollment	0.000	1.000
Prior STDs/pregnancies	0.012	0.913
Housing instability	4.667	0.031*
Months of treatment	4.100	0.043*
History of keeping appointments	0.262	0.609
Viral load-first visit	0.263	0.608
Viral load-last visit	3.061	0.080
Viral load-change	0.022	0.883
CD4 value-first visit	0.235	0.628
CD4 value-last visit	0.235	0.628
CD4 value-change	0.517	0.472
Health status change	1.880	0.170

* $p < 0.05$.

treatment and is one of the most important problems facing patients and health care professionals. Nonadherence to treatment regimens can contribute to the burden of morbidity and mortality, and to the overall cost of health care in this country. Only about 50% of the 1.6 million prescriptions written in the United States annually are taken properly, leading to $22 to $37 billion in excess health care costs.[6] The concept that inconsistent use of antiviral medications for the treatment of HIV may lead to the emergence of resistance strains, has highlighted the importance of adherence in clinical practice and in medical research.[7,8] Therefore, identifying nonadherence in HIV-infected patients on antiviral regimens and developing corrective measures could provide extraordinary savings for the health care system and improve patient outcomes.

Identified variables hypothesized to predict adherence in adults include: past behaviors or habits, health perceptions, individual characteristics, social circumstances, the practitioner-patient relationship, health knowledge, economic hardships, and clinical depression.[6,9] Varying degrees of nonadherence to prescribed regimens have been documented in the pediatric literature, with rates varying from 7% to 89% for short-term medication regimens and 11% to 83% for long-term ones.[10,11]

For HIV-infected adolescents, understanding issues of adherence to treatment regimens is less understood and becoming more important as increasing number of adolescents are identified as HIV infected. The literature addressing adolescents' compliance with medical regimens has focused on female compliance with contraception[12-14] and on compliance with medications for oncologic conditions and infectious diseases.[15,16] These studies also note that nonadherence in adolescents to medications ranged from 40% to 52%, and that for adolescents, understanding the relationship be-

tween social, developmental, and behavioral variables is key to understanding issues of adherence to treatment regimens. In several studies, teens were assessed as being less compliant with medical regimens than younger children.[16-19]

This study focused on identified HIV-infected youths and their adherence patterns to antiviral medications. Critical to adherence in this study of teens was housing instability for any period of time during medical treatment. Housing instability correlated with poor adherence with medications ($p <$ 0.03). Thus stable housing is pivotal in helping HIV-infected youths initiate and maintain difficult antiviral treatment regimens.

The experience of individuals providing care to HIV-infected youths in shelters is that HIV treatment is the least critical issue affecting them. Not until daily living requirements are met, especially housing and food, can youths and providers begin to address readiness for medical management of HIV disease (personal communication: Carl Siciliano, Program Director, HIV/AIDS Homeless Youth Housing Project, Center for Children and Families, Safespace, New York City. January 13, 1999). Youths with special situations like homelessness or those marginally housed have unstable lives, and need help with rudimentary daily living skills, such as earning a living, planning and eating nutritious meals, finding a regular place to sleep and live, and caring for themselves, and sometimes their children. Essentially, initiating and adhering to antiviral drug regimens is low on the priority list for youths infected with HIV. In addition, our findings reveal that it does not take the extreme condition of "living on the street" or "homelessness" to negatively affect adherence. The much more common condition of youths who are experiencing unstable living situations but who are never labeled as being homeless, are also demonstrating difficulties in maintaining adherence to their treatment regimens.

Nonadherence to antiviral medications did correlate with length of treatment ($p <$ 0.05). The longer the adolescent was documented to be on a prescribed antiviral medication, the greater the chance that there would be skipped or missing doses. This finding suggests that adherence is time-sensitive and could be enhanced with an enhanced clinical treatment structure or skills training in behavior maintenance techniques. Intensive education, frequent clinic visits, and/or frequent medical case management could lessen nonadherence of

antiviral medications as adolescent patients are treated chronically for this infection. Other variables had no significant correlation with adherence to medications.

A trend of lower viral loads were detected in patients found to be adherent to prescribed medications; however, no significant relationship was established between adherence and biologic markers. In large part, this was due to the fact that most of the patients taking antivirals demonstrated overall lower viral loads and increased CD4 counts regardless of their ability to maintain strict adherence. In general, CD4 counts were not as good an indicator of health status as were viral loads for this group of patients.

Other risk factors such as prior STDs and/or a prior pregnancy, health status change, and adherence with appointments did not influence medication adherence. The fact that adherence to medical appointments did not correlate with adherence to medications cautions us against overgeneralizing what should be considered "adherence" for adolescent patients. Whereas the profile of the nonadherent adult may include a lack of adherence to both appointments and medication regimes, this is not the profile for the nonadherent adolescent. For this adolescent population, more adolescents missed their appointments than missed their medications.

In addition, demographic variables like ethnicity/race, age of enrollment, or gender did not influence medication adherence. This is consistent with one study of a cohort of 1372 HIV-positive patients, which found no relation between disease progression and sex, race, injection drug user, income, level of education. or insurance status and concluded that differences found in other studies may reflect differences in the use of medical facilities.[3] This speaks highly of the need to provide developmentally appropriate and culturally sensitive care to HIV-infected youth, as well as for medical facilities to provide care to HIV-infected youths that is sensitive to how and under what conditions youths access and use medical services.

The limitations of this study are the small sample size and the reliance on archival medical chart data. The limited sample size makes generalizability difficult to other populations of youth. Our present clinic population of HIV-infected youth, represents approximately 8% of the estimated 963 HIV-infected adolescent population aged 13 to 24 years estimated by the Department of Public Health. This

small sample of identified infected youths reflects the difficulty in case finding experienced by most adolescent medicine centers across the country. Recent blinded HIV serosurveys indicate a range of estimates from 0.1% to 21% depending on the city and the behavioral risks of the subpopulation of adolescents studied.[20-24] Such studies indicate that HIV infection in teens in the United States over the next decade will continue to rise.[25] Sample size combined with missing data also affected what factors could be usefully analyzed.

This study's reliance on archival medical chart data resulted in our inability to systematically address factors that are known to influence adherence. Many of the variables of interest to this study, such as certain characteristics of the treatment regimen and the patient's social support, were not systematically recorded on the patient charts, resulting in a high amount of missing data. Other variables of interest, such as the patient-provider relationship and the patient's psychological functioning and stress, were not accessible with this method. A prospective multicentered study that would provide a larger, pooled sample of HIV-infected youths for systematic monitoring should be undertaken to understand and address adherence issues in this population.

In summary, HIV-infected adolescents demonstrate similar rates of nonadherence to treatment regiments as in HIV-infected adults. As with their adult counterparts, most of the HIV-infected youths taking antivirals demonstrated an overall decrease in their viral loads and an increase in their CD4 counts regardless of their ability to maintain strict adherence. Although many variables may impact adherence to antiviral medication regimens, in this population, the stability of the adolescents' living situations was the most significant correlate of medication adherence. In addition, the longer the adolescent is taking antiviral drug regimens, the greater the opportunity for skipping or missing doses.

ACKNOWLEDGMENTS

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