THE ADOLESCENT MEDICINE HIV/AIDS RESEARCH NETWORK

The REACH (Reaching for Excellence in Adolescent Care and Health) Project: Study Design, Methods, and Population Profile

CRAIG M. WILSON, M.D., JOLENE HOUSER, M.P.H., CYNTHIA PARTLOW, M.Ed., BRET J. RUDY, M.D., DONNA C. FUTTERMAN, M.D., LAWRENCE B. FRIEDMAN, M.D., AND THE ADOLESCENT MEDICINE HIV/AIDS RESEARCH NETWORK

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The REACH Project (Reaching for Excellence in Adolescent Care and Health) was designed as an observational study with the ultimate goal of achieving a better understanding of HIV disease progression and co-morbidity in adolescents and thus improving health care management. A standardized base protocol was developed through the collaborative efforts of the Basic Science and Clinical Science Groups of Adolescent Medicine HIV/AIDS Research Network. With little to no information available on the manifestations or progression of HIV disease in adolescents, the scope of the research objectives of REACH was focused on biomedical outcomes. However, extensive behavioral and psychosocial data were collected to provide necessary context to the biomedical data and to inform future primary, secondary or tertiary prevention interventions. The REACH Project targeted the following objectives:

1. To examine the pathogenesis of HIV infection and its spectrum of disease in adolescents (aged 12 to 18 years at study entry) and to compare them to those described in adults and children.
2. To examine the effect of HIV infection on normal physiologic growth and development in HIV infected adolescents, and in turn, to examine the effect of pubertal maturation on HIV progression.
3. To examine the morbidity associated with co-infections with sexually transmitted infections (STI) that commonly occur in adolescents and to compare these morbidities between HIV infected and HIV uninfected adolescents, with particular attention to the role of cervical maturation as a risk for STI acquisition in female subjects.
4. To examine potential immunologic markers in peripheral blood for disease progression specific to adolescents infected with HIV.
5. To examine the association between cytokine expression in endocervical secretions, STI acqui-

From the Departments of Pediatrics and Medicine, University of Alabama at Birmingham, Birmingham, Alabama (C.M.W., C.P.); Westat, Inc., Rockville, Maryland (J.H.); The Craig-Dalsimer Division of Adolescent Medicine, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania (B.J.R.); the Department of Pediatrics, Children's Hospital at Montefiore, Albert Einstein College of Medicine, New York, New York (D.C.F.); and the Department of Pediatrics, University of Miami School of Medicine, Miami, Florida (L.B.F.).

Address correspondence to: Craig M. Wilson, M.D., University of Alabama at Birmingham, Geographic Medicine BBRB 206F, 1530 3rd Ave South, Birmingham, AL 35294-2170. E-mail: cwilson@uab.edu.

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sition, and HIV disease progression in adolescent females.
6. To examine the association between mental health and behavioral patterns and disease progression in adolescents infected with HIV.

Given the nature of the REACH study and the targeted population there were a number of key issues that need to be addressed and subsequently monitored including subject safety, study integrity, confidentiality, permission and consent. These issues have been discussed extensively in other publications of the REACH project [1,2]. The study protocol was reviewed and approved by Institutional Review Boards (IRBs) at all participating institutions and youth provided informed consent or parental permission as required. Youth received IRB-approved levels of compensation for study visits at the majority of REACH sites. This article will provide an overview of the data collection methods and procedures and their frequency. A demographic and risk profile of the HIV infected and HIV uninfected cohorts within REACH at their baseline study visit, as well as a few unique observations within these groups will also be presented.

Cohort Identification, Enrollment, and Retention

The study design for the REACH project called for recruitment of both HIV infected youth and high-risk HIV uninfected youth between the ages of 12 through 18 years. Youth were to be enrolled at comprehensive, adolescent-specific medical care centers to manage any of the co-morbidities, biomedical complications or psychosocial issues that would be uncovered through the study. HIV infected youth were to have been those infected through risk behaviors, i.e., sexual activity or intravenous drug usage. Evidence of HIV infection through vertical transmission, contaminated blood products, or early childhood sexual abuse was an exclusion criterion. The HIV uninfected cohort was selected for a similar risk-behavior profile and subjects were to have no underlying chronic illnesses. Initially, all HIV infected youth who met the criteria were enrolled at a 2:1 ratio to the HIV uninfected youth and were matched as well as possible by age, gender, race, and ethnicity as well as clinical site or region as appropriate. The REACH study opened for enrollment in March of 1996 and continued enrollment through November 30, 1999 at which time 496 adolescents had been recruited (325 HIV infected and 171 HIV uninfected). The final cohort was 38% larger than originally anticipated. The study remained open for data and sample collection through November 30, 2000. Enrollment was closely monitored by the Data and Operations Center (DOC) and restrictions were applied at various time points to maximize recruitment efforts particularly of younger HIV infected youth. When it became evident that the HIV infected male cohort was nearly exclusively homosexual in sexual orientation, attempts were made to match the HIV uninfected male cohort on this profile. To maximize data collection in the last year of the study, enrollment was opened to any youth that met the criteria for the study.

Rates of subject accrual varied by clinical site and access to adolescent populations and testing programs. Older HIV uninfected youth were difficult to engage and retain in the protocol and it was this group, particularly the females, who had the lower retention rates. HIV infected youth demonstrated annual retention rates of 95%; HIV uninfected male and female annual retention rates were 89% and 88%, respectively. Ongoing analyses on study subjects' reasons for recruitment and retention in this protocol will potentially inform future studies of adolescents.

Study Measures and Data Collection

The REACH base protocol required extensive data collection to meet the primary study objectives. Five methods of data collection were used to accomplish these objectives: direct face-to-face interview, Audio Computer-Assisted Self-Administered Interview (ACASI), medical record abstraction, and physical and laboratory examinations. Both HIV infected and HIV uninfected subjects were seen every 3 months for data collection although the extent and depth of visits varied to minimize subject burden. All five forms of data collection were used at every visit for HIV infected subjects and at baseline, 6-month, and annual visits for HIV uninfected subjects. Only medical record abstraction and laboratory assessments were completed at 3 and 9 month visits for HIV uninfected subjects. An overview of each data collection method and their respective quality assurance will be discussed here and serve as a base Methods section for the other REACH articles in this publication.

Direct face-to-face interviews were administered at clinical visits by study coordinators. The content areas of this interview for HIV infected subjects are

Table 1. Measures Obtained Through HIV Infected Subject Interview

Interview
Demographic history
Baseline and annually
Ethnicity
Education
Living situation
Income
Health history
Baseline and every 3 months
Antiretroviral and contraceptive drug adherence
Health care utilization
Menstruation and contraception
Prior and interval pregnancy histories
Psychiatric treatment
Suicidal ideation and risk
Alcohol or drug treatment
Targeted review of systems
Interval sexually transmitted disease history
Audio Computer-Assisted Self-Administered Interview (ACASI)
Baseline and every 3 months
Social support (selected items from Arizona Social Support Inventory Scale-ASSIS) [3]
Depression (Center for Epidemiologic Studies-Depression/CES-D) [4]
Health-related anxiety
Health-related quality of life (from RAND Health Survey) [5]
Baseline and every 6 months
Life change events (adapted from Newcomb et al.) [6]
Coping (adapted by Murphy and Rotheram from Namir) [7]
Anxiety (subscales from Reynolds and Richmond's Manifest Anxiety Scale-RCMAS) [8]
Sexual and drug-related behaviors
HIV status disclosure
Tobacco use history

listed in Table 1 [3–8]. Study coordinators were most typically research nurses who were initially centrally trained on both interviewing techniques and the intent of the questions. Most items had specific "question by question" (Q × Q) narratives to facilitate accurate and reliable data collection. These Q × Qs were refined periodically as experience grew. Prescribed antiretroviral therapy (ART) adherence was assessed by self-report at each visit for the HIV infected subjects. Questions in the last 2 years of the study also assessed reasons for nonadherence to ART regimens. Direct questioning for depression and suicidal ideation was conducted so that interventions could be implemented if deemed necessary.

Ongoing medical chart abstraction was used to ascertain health service utilization, medications, and targeted incident medical conditions. The study was specifically interested in the occurrence of STI, Centers for Disease Control and Prevention (CDC) AIDS-defining conditions and Category B symptomatic conditions. Specific diagnostic criteria for each of these conditions were developed to enhance specificity and were coded as *definitive*, *presumptive*, *clinical*, or *insufficiently documented*. Source documentation for all AIDS-defining conditions was reviewed on routine semiannual site monitoring visits.

The ACASI was used to obtain sensitive information while providing complete confidentiality, promoting validity, engaging youth, and obviating effects of illiteracy through a talking computer and highlighted mouse-driven responses. The ACASI was specifically designed for the project and previewed by the Network's youth Community Advisory Board (CAB). The CAB was comprised of one youth from each of the AMHARN sites who was in the age range of study subjects. A timeline was used with the ACASI to assist the adolescents and orient them to the timeframe for certain scales. A procedure such as this has been recommended to improve recall of behavior [9], and has been used in numerous HIV and sexual behavior research studies. The ACASI content for HIV infected subjects is listed in Table 1. When a computerized interview session was completed by a subject, data were encrypted automatically, transferred to the data center, and were inaccessible at the clinical sites. Aside from the validated behaviorally related assessment scales, the two main areas of data collection in the ACASI were focused on drug taking and sexual activity risk behaviors. The sexual activity risk behaviors of interest included number and gender of partners, sexual activity practices including oral, anal, and vaginal sex, frequency of sexual practices over 3 month intervals, and use of protection during sexual activities. Questions relating to risk behaviors of the 3 most recent partners were also asked. Cross-validation of some of the ACASI sexual activity questions was done with questions asked in the face-to-face interview. Although these questions were not asked in an identical format, there was general agreement in the responses with only occasional discrepancies identified. Validation of the subject's self-report of illicit drug taking in the ACASI was done using urine drug screening results. For marijuana usage where the frequency was high enough for accurate comparison, there was reasonable correlation although the ACASI was shown to be more sensitive as a single screening tool [9].

Targeted, rather than full, physical examinations were required by the study protocol (Table 2), although the study did collect diagnostic information indicated by history or current symptoms and un-

covered by ancillary clinical examinations. Centralized training for the oral, skin, and gynecologic examinations and for sample collection was directed by experienced clinical collaborators. In addition, videotapes were made of the oral and gynecologic examinations and the gynecologic sample collection procedures; these tapes were reviewed annually by study personnel at the clinical sites. Centralized training for assessment of body composition using skin-fold measurements was provided initially by experienced personnel, and the assessment procedures were reviewed at the clinical sites as needed during site monitoring visits. Training for intradermal skin testing for response to specific antigens was also initially provided centrally and videotapes on tuberculin testing from the CDC were made available at each site for routine review of this procedure.

Content and periodicity of laboratory assessments are listed in Table 2. Tests performed at the local clinical sites were done in Clinical Laboratory Improvement Amendment (CLIA) certified laboratories. Immunophenotyping was done in laboratories certified through the flow cytometry quality control program sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). The frequency of laboratory testing done as part of the REACH protocol was consistent with the Public Health Service (PHS) guidelines for management of HIV infected adolescents and adults. More detailed description of other laboratory testing methods for specific tests is provided in other REACH publications: quantitative plasma HIV-1 RNA viral load testing [11], HPV testing [12], specific STI testing [12,13], cervical and anal cytology screening [12], quantitation of cervical ectopy [14], an expanded immunophenotyping panel of peripheral blood lymphocytes [15–17], measurement of specific cytokines in peripheral blood [18], urinary drug screening [9], and endocervical sample cytokine and immunoglobulin quantitation [19].

Quality Assurance

Provisions for quality assurance were built into the REACH protocol at multiple levels, including those mentioned above. All study coordinators and clinicians were initially trained centrally for protocol procedures; sample collection and processing; gynecologic, genitourinary, oral, and skin examinations; skin-fold measurements; and administration and completion of the Data Collection Forms (DCFs). Reviews of these procedures were provided in sessions at semiannual network meetings and with the mandated periodic review of training videotapes as described above. Requirements for source documentation were established and random partial review of source documents and DCFs at the clinical sites was completed on semiannual site monitoring visits. Standardized guidelines for training of replacement personnel were established and training was monitored and supplemented centrally as needed. Performance at the clinical sites was monitored through specified quality control measures at semiannual site monitoring visits. Quality assurance procedures used in all of the centralized laboratories were reviewed and monitored periodically. Data entry procedures were established at each of the centralized laboratories to ensure accurate data transmission.

DCFs were submitted to a central data repository for data entry and screened for inconsistencies. Appropriate data entry quality assurance procedures were established depending on the type of data being submitted. Where appropriate, range checks and quality assurance cross checks were established and sites were queried on variant values. Reiterative data cleaning was an ongoing process as the database was established. Patterned semiannual data lockdowns were done to establish interim datasets to allow for interim data analyses on consistent databases.

Selected Baseline Characteristics of the Cohorts Within REACH

All analyses in this issue of the Journal used the dataset that was established in September 1999. Enrollment in REACH remained open until December 1999, and thus the final REACH cohort was minimally different than that reported here. As of September 1999, there were 242 HIV infected females, 83 HIV infected males, 131 HIV uninfected females, and 40 HIV uninfected males who had completed a baseline visit. Selected baseline demographic and risk behavior characteristics of the cohorts are shown in Tables 3 and 4. Selected baseline clinical assessments of the HIV infected cohorts are given in Table 5. Highlights of these selected characteristics are described below.

HIV Infected Female Cohort

Seventy-six percent of the HIV infected female cohort of the REACH study was black non-Hispanic and 14%, Hispanic, consistent with the recent demographic trends in the United States HIV-1 epidemic

Table 2. Measures in the Physical and Laboratory Examinations for HIV Infected Subjects

Physical examination
Baseline and every 3 months
Height and weight
Tanner staging of sexual maturity
Skin-fold thickness
Biceps, triceps, subscapular and suprailiac regions
Mid-arm circumference
In-depth skin and oral examination

Baseline and every 6 months
Gynecologic and urogenital examination
Annual evaluation
All subjects have tuberculin testing
Delayed-type hypersensitivity (candida, mumps and tetanus) assessment for HIV+ subjects

Laboratory examination
Immunologic (peripheral blood cells)
Baseline and every 3 months
Total B cell
Activated B cell
Total T cell
Helper $CD4^+$ T cell
Suppressor/Cytotoxic $CD8^+$ T cell
Natural killer cell

Baseline and every 6 months
Activated T cell (IL-2 receptor)
Activated Cytotoxic cell
Naive $CD4^+$ and $CD8^+$ T cell
Memory $CD4^+$ and $CD8^+$ T cell
Activated monocyte
Natural killer cell function assay
Cytokine analysis (Th1 and Th2 cytokine protein and m-RNA)

Immunologic (endocervical secretion)
Baseline and every 6 months
Cytokines (IL-2, IL-10, IFN-gamma, ILN-12)
Immune globulins (IgG, IgA)
Virologic
Baseline and every 3 months
Quantitative plasma HIV-1 RNA
Sexually-Transmitted Infections

Baseline and annually
Syphilis screening (RPR or VDRL)
CMV, HBV, HCV, and HSV screening

Baseline and every 6 months
Gonococcal and chlamydial infections by LCR*
Trichomonal cultures
Wet prep for Trichomonas and vaginosis
KOH for candidal screening
HPV by PCR of cervical-vaginal lavage and anal samples*
Bacterial vaginosis by vaginal smear gram stain and clinical criteria [10]
Cervical-vaginal lavage (for measurement of HIV-1 quantitative viral load in selected samples)
Cervicography (Cervigram® National Testing Laboratories, Fenton, MO) pictorial technology and computerized mapping of cervical ectopy
Cervical and anal cytologies*

Continued

Table 2. Continued

Hormonal
Females: Baseline and every 6 months
LH/FSH, testosterone, free testosterone, testosterone binding protein, androstenedione, DHEAS, estrogen
Males: Baseline and every 6 months
testosterone, free testosterone, testosterone binding protein, androstenedione, DHEAS
Other
Baseline and every 3 months
Urinary drug screens

* Gynecologic testing every 6 months; anal testing annually for males and females.

CMV = Cytomegalovirus; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HPV = human papillomavirus; HSV = Herpesvirus; KOH = potassium hydroxide; LCR = ligase chain reaction; PCR = polymerase chain reaction; RPR = rapid plasma reagin; VDRL = venereal disease research laboratory.

in adolescents [20,21] (Table 3). Sixty-four percent had their health care supported through public health funding and 26% had no health insurance at study entry. Twenty-nine percent of the group had dropped out of school and 71% were living at home. Twenty-seven percent reported being homeless at some point and 24% had been in a detention facility for greater than two nights. Thirty-eight percent had living children and 10% were pregnant at the baseline visit. The majority (81%) of this female cohort had known their HIV status for 2 years or less (data not shown).

Risk-taking behaviors were common among the HIV infected females as is shown in Table 4. Although the number of reported lifetime sex partners was high, the majority of subjects reported either none or a single partner in the 3 months before the baseline visit. Sixty-three percent reported condom use at their last sexual encounter; 50% of those having sex in the last 3 months reported consistent condom use (data not shown). Marijuana (52%) and alcohol (44%) use were commonly reported, however use of other illicit drugs was not. Regular urine drug screening results were consistent with these self-report data [9]. Twenty-five percent reported daily cigarette smoking whereas 67% reported not smoking over the past 3 months. These behaviors and associated outcomes are analyzed further in other studies in this issue [22–25].

Assessments of HIV-1 disease status among the female cohort are presented in Table 5. The plasma HIV-1 RNA quantitative viral load and $CD4^+$ T cell data presented are for all subjects regardless of treatment status. The distribution of these values was similar for those subjects on ART at the baseline visit

Table 3. Selected Demographic Data of HIV Infected and HIV Uninfected Cohorts of REACH

	HIV+ Female Cohort N = 242		HIV− Female Cohort N = 131		HIV+ Male Cohort N = 83		HIV− Male Cohort N = 40	
Variables	*n*	(%)*	*n*	(%)*	*n*	(%)*	*n*	(%)*
Age at Entry (years)								
≤16	78	32	59	45	17	20	15	37
16	164	68	72	55	66	80	25	63
Race/Ethnicity								
Black non-Hispanic	183	76	83	65	49	60	22	55
Hispanic	33	14	27	21	25	30	12	30
White non-Hispanic	10	4	8	6	2	2	4	10
Other non-Hispanic	15	6	10	8	6	7	2	5
Missing	1		3		1			
Health care coverage								
No health insurance	63	26	42	32	21	25	11	27
Public health funding	155	64	61	47	48	58	19	48
Other/private insurance	16	7	19	15	12	15	8	20
Do not know	8	3	8	6	2	2	2	5
Missing			1					
High school dropout								
Yes	71	29	21	16	26	31	4	10
No	170	71	107	84	57	69	36	90
Living with parent(s)								
Yes	173	71	112	85	59	71	29	73
No	69	29	19	15	24	29	11	27
Ever homeless								
Yes	65	27	30	23	22	27	12	30
No	176	73	98	77	61	73	28	70
Missing			3					
Ever in detention								
Yes	58	24	13	10	22	27	7	17
No	184	76	115	90	61	73	33	83
Missing			3					
Have living children								
Yes	93	38	39	30	10	12	2	5
No	149	62	89	70	72	88	36	95
Missing			3		1		2	
Currently Pregnant	25	10	3	2				

* Missing values are excluded in the calculation of percentages

when compared to those on no ART (data not shown). Overall this cohort at baseline was early in their HIV-1 disease course as can be seen by the $CD4^+$ T cell distributions in Table 5. Of the 39 subjects (16%) who met the CDC criteria for an AIDS defining condition before the baseline visit, 34 exclusively met the $CD4^+$ T cell criteria. The definitively-established AIDS conditions identified in the 5 other subjects included 3 with protracted *Herpes simplex* infections, one with nontuberculous mycobacteriosis, and one with both pulmonary pneumocystosis and extrapulmonary cryptococcosis. Thirty-six percent of the HIV infected females were ART-naive at the baseline visit and, similar to the baseline data shown in Table 5, approximately half of the cohort was prescribed ART at some point during the study. This reflects the challenges of adherence to complex ART regimens found in this group [26]. One characteristic of the female HIV infected cohort that is being further explored is the distribution of the viral load values because greater than 70% have been below 10,000 copies per mL. This distribution was similar for those subjects on ART compared to those on no ART, 78% vs. 69%.

HIV Uninfected Female Cohort

Sixty-five percent of the HIV uninfected female cohort of the REACH study was black non-Hispanic and 21%, Hispanic. Forty-seven percent had their health care supported through public assistance and 32% had no health insurance. Sixteen percent had

Table 4. Risk Behavior Data of HIV Infected and HIV Uninfected Cohorts of REACH

Variables	HIV+ Females N = 242		HIV− Females N = 131		HIV+ Males N = 83		HIV− Males N = 40	
	n	(%)*	*n*	(%)*	*n*	(%)*	*n*	(%)*
No. different sex partners (lifetime)								
0–7	132	57	91	73	24	32	17	47
≥8	98	43	33	27	52	68	19	53
Missing	12		7		7		4	
No. different sex partners (past 3 months)								
0	77	33	34	27	20	26	11	31
1	92	40	58	47	21	28	16	44
2–4	53	23	27	22	23	30	8	22
≥5	8	4	5	4	12	16	1	3
Missing	12		7		7		4	
Condom use at last sexual encounter								
Yes	139	63	58	48	55	76	20	56
No	82	37	64	52	17	24	16	44
Missing	21		9		11		4	
Cigarette smoking past 3 months								
Daily	58	25	24	19	31	39	13	36
Weekly/Infrequently	20	9	19	15	15	19	2	6
None	157	67	82	66	34	42	21	58
Missing	7		6		3		4	
Drinking alcohol past 3 months								
Yes	121	52	72	58	50	63	18	50
No	113	48	53	42	30	37	18	50
Missing	8		6		3		4	
Marijuana use past 3 months								
Yes	101	44	46	38	37	50	19	53
No	131	56	76	62	37	50	17	47
Missing	10		9		9		4	
Hard drug use past 3 months**								
Yes	13	6	6	5	13	17	3	8
No	222	94	119	95	64	83	33	92
Missing	7		6		6		4	

* Missing values are excluded in the calculation of percentages.

** Hard drug use includes smoking marijuana or crack cocaine, snorting cocaine, injecting cocaine, heroin, or speedball, or using crystal methamphetamines, other amphetamines, or hallucinogenic drugs.

dropped out of school and 85% were living at home. Twenty-three percent reported being homeless at some point and 10% had been in a detention facility at least once for greater than two nights. Thirty percent had living children and 2% were pregnant at the baseline visit. Demographically this cohort was similar to the HIV infected females although slightly younger in age.

Risk-taking behaviors were also common in the HIV uninfected female cohort (Table 4). Twenty-seven percent reported eight or greater lifetime sex partners, although 27% reported none and 47% reported one partner in the last 3 months. Only 48% reported condom use at their last sexual encounter and only 23% of those having sex in the last 3 months reported consistent condom use (data not shown). In the 3 months before the baseline visit, 58% reported alcohol use, 38% reported marijuana use and 5% reported other illicit drug use. Nineteen percent reported daily cigarette use whereas 66% reported not smoking over the past 3 months. Thus the risk behavior profile of this cohort was similar to the HIV infected female cohort by most assessments.

HIV Infected Male Cohort

Sixty percent of the HIV infected male cohort of the REACH study was black non-Hispanic and 30%, Hispanic (Table 3). Fifty-eight percent had their health care supported through public health funding and 25% had no health insurance at study entry. Thirty-one percent of the group had dropped out of school and 71% were living at home. Twenty-seven percent reported having been homeless before the baseline visit and the same number reported being in a detention facility for greater than two nights. Of the

Table 5. HIV-1 Disease Data of REACH HIV-1 Infected Cohorts

Variables	Female HIV infected N = 242		Male HIV infected N = 83	
	n	(%)*	*n*	(%)*
HIV-1 RNA viral load (Copies/ml)				
Below detection	62	26	11	13
400 to <10,000	116	48	34	42
10,000–50,000	42	17	18	22
>50,000	22	9	19	23
Not yet evaluated	0		1	
$CD4^+$ T cell counts (cells/mm^3)				
0–199	17	7	10	12
200–500	99	42	45	54
>500	122	51	28	34
Missing	4		0	
History of AIDS at entry				
Yes	39	16	15	18
$CD4^+$ T cell only	34	14	12	14
Other Conditions	5	2	3	4
No	203	84	68	82
Antiretroviral Therapy (ART) at entry				
No ART	134	55	49	59
Monotherapy	19	8	4	5
>1 ART excluding PI	53	22	13	16
>1 ART including PI	36	15	17	20

* Missing values are excluded in the calculation of percentages.
PI = protease inhibitor.

63 subjects responding to the question, 90% had known their HIV status for less than 2 years, 58% for less than 1 year.

Fifty percent of the HIV infected males self-identified as homosexual and 22% self-identified as bisexual. Sixty-eight percent of this cohort reported greater than 8 lifetime sex partners and 46% reported two or more partners in the last 3 months (Table 4). Seventy-two percent reported having had anal receptive sex and a similar number reported anal insertive sex (data not shown). Seventy-six percent reported condom use at their last sexual encounter. Alcohol (63%) and marijuana (50%) use in the past 3 months were commonly reported and the illicit drug usage (17%) was higher than that reported in the female cohort. Thirty-nine percent reported daily cigarette smoking whereas 42% denied smoking cigarettes in the past 3 months.

Measures of HIV-1 disease status are presented in Table 5. The quantitative plasma HIV-1 RNA viral load and $CD4^+$ T cell counts are presented for this cohort as a whole regardless of treatment status. Forty-five percent of the HIV infected males had viral loads greater than 10,000 per ml at the baseline visit and 12% had $CD4^+$ T cell counts below 200 per mm^3. Fifteen (18%) of the male cohort met the CDC criteria for an AIDS defining condition before the baseline visit; twelve of these were by $CD4^+$ T cell criteria exclusively. The 3 subjects who had other definitively established AIDS conditions had the following diagnoses: one with extrapulmonary cryptococcosis, one with recurrent bacterial pneumonia, and one with both pulmonary pneumocystosis and esophageal candidiasis. Forty-eight percent of the HIV infected males were ART-naive at the baseline visit and 59% were on no ART at the time of the visit. Similar to the female cohort, approximately half of the HIV infected males were prescribed any ART at any particular REACH clinical visit.

HIV Uninfected Male Cohort

Fifty-five percent of the HIV uninfected male cohort of the REACH study was black non-Hispanic and 30%, Hispanic (Table 3). Forty-eight percent had their health care supported through public health funding and 27% had no health insurance. Ten percent of the group had dropped out of school and 73% were living at home. Thirty percent reported having been homeless before the baseline visit and 17% reported being in a detention facility at least once for greater than two nights.

Thirty-nine percent of the HIV uninfected males self-identified as homosexual, 8% self-identified as

Table 6. Data of Subjects Experiencing HIV-1 Related Deaths in the REACH Cohort

Gender	Age at Death (yr)	Time From HIV Diagnosis (mo)	Last $CD4^+$ T cell count (cells/mm^3)	Last HIV-1 RNA Viral Load (Copies/mL)	Clinical Diagnoses at Time of Death
Female	16	19	9	3,700,000	HIV-related renal failure with hypertension; cardiomyopathy
Female	16	9	1,197	<80	Severe lactic acidosis; probable complication of ART
Female	18	23	130	460,000	HIV-related renal failure; PCP
Female	19	47	479	<80	Pancreatitis and severe acidosis; probable complication of ART
Female	19	39	17	220	Disseminated aspergillosis; CNS leiomyoma
Female	20	35	80	4,300,000	HIV-related renal failure
Female	20	60	8	25,000,000	Chronic candidiasis and HSV; cardiorespiratory failure at home
Male	20	29	13	420,000	Idiopathic thrombocytopenia with intracranial hemorrhage; disseminated aspergillosis; HIV-related nephropathy

ART = antiretroviral treatment; PCP = *Pneumocystis carinii* pneumonia; CNS = central nervous system, HSV = herpesvirus.

bisexual, and 51% self-identified as heterosexual (data not shown). Fifty-three percent of this cohort reported 8 or greater lifetime sex partners and 25% reported two or more partners in the last 3 months (Table 4). Fifty percent reported having had anal receptive sex and 21% reported anal insertive sex (data not shown). Fifty-six percent reported condom use at their last sexual encounter. Alcohol (50%) and marijuana (53%) use in the past 3 months were commonly reported and 8% reported illicit drug usage in the past 3 months. Thirty-six percent reported daily cigarette smoking whereas 58% denied smoking cigarettes in the past 3 months. The sexual orientation profiles and thus sexual risk behaviors of this HIV uninfected male cohort differ from the HIV infected cohort slightly.

Other Observations of the REACH Cohorts

Seroconversions

Four of the HIV uninfected youth enrolled in the REACH protocol seroconverted during the study period. All 4 of these youth were male and self-identified as homosexual. There were a total of 25 HIV uninfected males enrolled in REACH who self-identified as homosexual or bisexual. We used data through September 2000 to obtain an estimate of the total time of observation of this homosexual/bisexual cohort (51.7 person-years). Thus the seroconversion rate in this group of high risk homosexual/bisexual youth was 7.7 per 100 person-years or nearly 8% risk of seroconversion per year. This rate of seroconversion occurred in spite of a standardized modular prevention plan that was part of the REACH protocol. There were no seroconversions among the HIV uninfected females (total observation time of 288.9 person-years).

Deaths

There were 8 deaths among the HIV infected youth enrolled in REACH, 1 male and 7 females. Six of these deaths were owing to complications related to HIV disease and two were complications of antiretroviral therapy. Causes of death, age at death, length of time knowing HIV status, and last recorded $CD4^+$ T cell count and HIV-1 plasma RNA levels for each of these subjects are given in Table 6. Four of the 6 subjects who died had renal failure that was believed to be HIV-related. Two subjects expired with severe lactic acidosis, most likely associated with ART. Neither of these two subjects was pregnant at the time of their death and both were on therapy for less than 1 year. One subject was prescribed lamuvidine (3TC), zidovudine (ZDV), and stavudine (D4T) and the other subject was prescribed didanosine (ddI), stavudine (D4T), and efaviranz.

Using data through September 2000, the total observation time of the 90 HIV infected male subjects was 203.3 person-years (mean follow-up time of 2.26 years). The observed death rate for the HIV infected males was thus .49 per 100 person-years. The total observation time of the 262 HIV infected female subjects was 634.4 years (mean follow-up time of 2.42 years). The observed death rate for the HIV infected females was thus 1.1 per 100 person-years.

Evidence for Acquisition of HIV-1 Virus With Resistance Mutations

Genotyping of the reverse transcriptase (RT) and protease (PR) genes of HIV-1 in plasma samples from ART-naive HIV infected subjects was completed looking for evidence of transmission of resistant HIV-1 virus to these subjects [27]. Four of the 92 examined samples (4.3%) had resistance mutations

in the RT gene including one with multiple mutations. Fifty-six of 82 (68%) samples examined had resistance mutations in the PR gene although all of these were considered secondary compensatory mutations and not associated with a resistant phenotype on their own. This analysis was performed on samples collected between March 1996 and October 1998. This finding would not support the need for routine ART resistance testing before initiating ART in adolescents in general. However, the emergence of resistant mutations in the general community is a dynamic situation as ART becomes more widely used and will need reassessment in the future.

Summary

The HIV infected cohorts in REACH as described here are believed to be sociodemographically representative of the HIV epidemic in adolescents in the United States, i.e., predominantly female and predominantly minority with sexual risk behaviors as the main mode of acquisition, heterosexual for females and homosexual or bisexual for males. As such, the biomedical, psychosocial and behavioral assessments completed within the REACH project are directly informative for future interventional studies. Given the reported risk profile of slightly older HIV infected youth who report intravenous drug using (IDU) risk behaviors (12% and 14% for females and males respectively) [21] there may be groups of older IDU youth who are not accessible to traditional comprehensive medical services and thus underrepresented in this study. However, the sociodemographic and sexual risk behavior profile represented in REACH is believed to be indicative of the most rapidly expanding subgroup in the domestic HIV epidemic [21]. The similarity of risk profiles for HIV infected and HIV uninfected groups in this study reinforces the relatively hidden nature of the HIV epidemic among youth as well as emphasizing the need for implementing more routine testing. The risk behavioral histories of both groups described here demonstrate the need for continuing both research and development of primary prevention strategies particularly those incorporating skill-building efforts directed at preadolescent and adolescent aged youth. The continuing risk behaviors among the HIV infected cohort [22] described here similarly demonstrate the need for theory-based development of secondary prevention programs for HIV positive youth.

The seroconversion rate in the homosexual/bisexual male cohort reported here is alarmingly high, reflecting trends reported by the CDC [28] and reinforcing the critical need for prevention and outreach programs directed at youth with this risk profile. The numbers of HIV infected females being identified and brought into care, although low compared to the estimated numbers of HIV infected females in the United States, similarly reinforce the need for multifaceted, consistent prevention messages and outreach programs directed at preadolescent and early adolescent groups.

These data and the number of youth who died of HIV during this study clearly indicate that HIV disease can be rapidly devastating in the adolescent population. The overall distribution of $CD4^+$ T cell numbers in this cohort suggests that HIV infected adolescents are generally early in their disease but nonetheless are progressing. Ongoing longitudinal analyses should elucidate markers or measures which may help identify which adolescents may benefit most from or need earlier interventions. It is clear more resources and efforts to help HIV infected youth adhere to maximally beneficial complex treatment and management regimens will be required. Ongoing analyses within REACH should inform the design of those interventions and underscore the need. The two deaths within this cohort that were associated with severe lactic acidosis and most likely owing to antiretroviral medications appear high for the number of subjects prescribed and adherent to antiretroviral therapy over the time of this study and requires further monitoring.

The excellent retention rates of these generally disenfranchised youth in this multi-year, complex, and demanding study reflect on the efforts of the well-staffed, organized, and dedicated research teams at the participating institutions. We gratefully recognize the contributions of all REACH personnel, and the study coordinators in particular, as well as the invaluable contributions of those youth who participated in this study.

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