

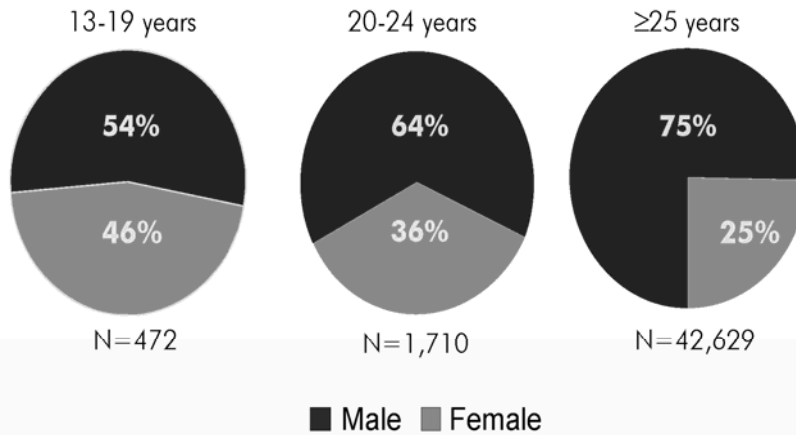
HIV and Family Planning: Breaking Down the Division

Bret J. Rudy, M.D.
Associate Professor of Pediatrics
The Children's Hospital of Philadelphia
The University of Pennsylvania School of Medicine

Goals and Objectives:

- To review epidemiologic trends in adolescents and young adults
- To review clinical and psychosocial data collected through two NIH-sponsored research networks
- To discuss the unique issues facing young women with HIV
- To review issues related to HIV counseling and testing

Proportion of AIDS Cases among Adults and Adolescents, by Sex and Age Group, Reported in 2003—United States



Note. Data based on person's age at diagnosis.



AIDS Cases among Male Adolescents and Young Adults by Transmission Category, Cumulative through 2003—United States

Transmission category	13-19 years		20-24 years	
	N	%	N	%
Male-to-male sexual contact	1,354	43	14,959	65
Injection drug use (IDU)	278	9	3,023	13
Male-to-male sexual contact and IDU	180	6	2,439	11
Hemophilia	773	25	701	3
Heterosexual contact	253	8	1,721	7
Transfusion recipient	111	3	133	<1
Other/not identified*	187	6	103	<1
Total	3,136	100	23,079	100



Note. Data adjusted for reporting delays and estimated proportional redistribution of cases in persons initially reported without an identified risk factor.

* Includes blood transfusion, perinatal, and risk factor not reported or not identified.



AIDS Cases among Female Adolescents and Young Adults, by Transmission Category Cumulative through 2003—United States

Transmission Category	13-19 years		20-24 years	
	N	%	N	%
Injection drug use	422	18	2,732	28
Heterosexual contact	1,576	66	6,904	70
Other/not Identified*	381	16	260	2
Total	2,379	100	9,896	100

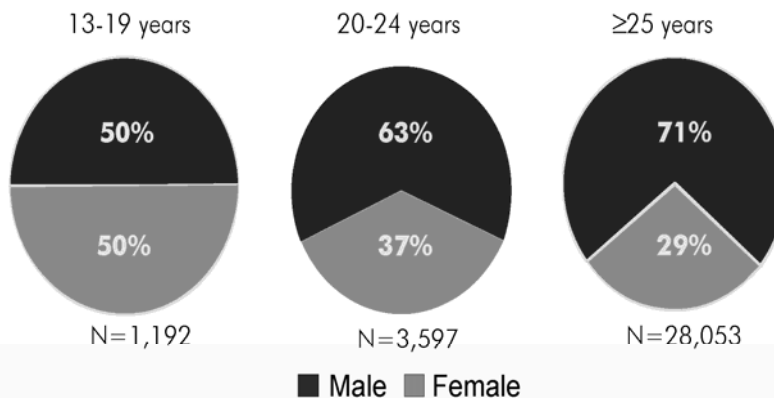


Note. Data adjusted for reporting delays and estimated proportional redistribution of cases in persons initially reported without an identified risk factor.

* Includes blood transfusion, perinatal, and risk factor not reported or not identified.



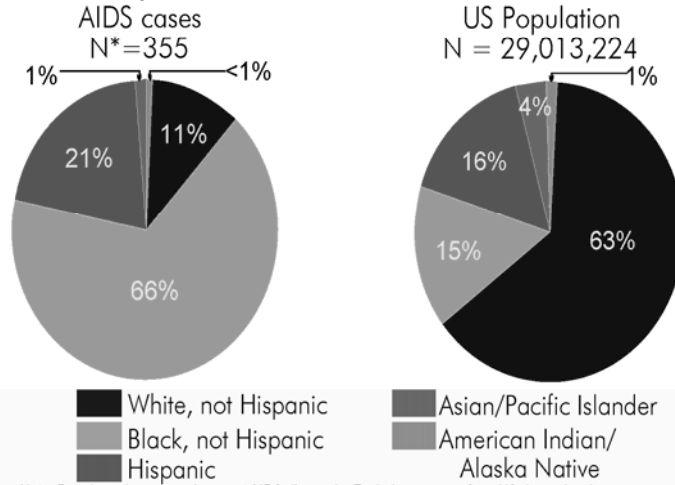
Proportion of Cases of HIV Infection (not AIDS) among Adults and Adolescents, by Sex and Age Group Reported in 2003—41 Areas



Note. Data from 41 areas with confidential name-based HIV infection reporting as of December 2003. Data based on person's age at diagnosis.



Proportion of AIDS Cases and Population among Adolescents 13 to 19 Years of Age, by Race/Ethnicity Reported in 2003—50 States and D.C.



Note. Data based on person's age at AIDS diagnosis. Excludes persons from US dependencies, possessions, and associated nations.
* Includes 1 person of unknown race or multiple races.



AMHARN Network

Adolescent Medicine HIV/AIDS Research Network

REACH Project

Reaching for Excellence in Adolescent Care and Health

Basic Science Group

Virologist

Immunologist

Mucosal Immunologist

STD/Adolescent
Medicine

Behavioral Psychologist

Epidemiologist

Clinical Science Group

15 Clinical Sites

13 Cities

Adolescent Trials Network

- Multicenter research network funded by the National Institutes of Health
- 15 clinical site
- Leadership Groups
 - Therapeutics Leadership Group
 - Behavioral Leadership Group
 - Community Prevention Leadership Group

ATN Mission:

- To conduct research, both independently and in collaboration with other research networks, on promising behavioral, microbicial, prophylactic, therapeutic, and vaccine modalities in HIV-infected and at-risk adolescents, ages 12 through 24 years

Demographics and Behavioral Data

REACH Project
Adolescent Trials Network

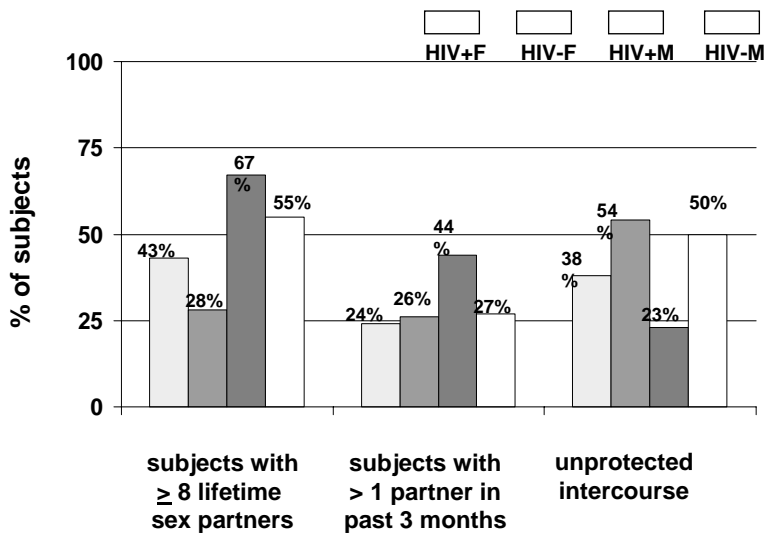
SEXUAL PREFERENCE (from ICI)

	N =	Homosexual	Heterosexual	Bisexual
HIV+ F	196		92%	8%
HIV- F	101		93%	7%
HIV+ M	64	41%	17%	42%
HIV- M	35	26%	54%	20%

DISCLOSURE OF HIV STATUS

	Female	Male
Disclosed to:		
Mother	81%	70%
Father	47%	33%
Others disclosed to:		
0	19%	23%
1-5	46%	45%
>5	32%	39%

SEXUAL RISK BEHAVIORS



Adolescent Trials Network (ATN)

ACASI Survey HIV - Positive Youth

**Funded by:
NICHD, NIMH, NIDA, NIAAA**

Sample Size

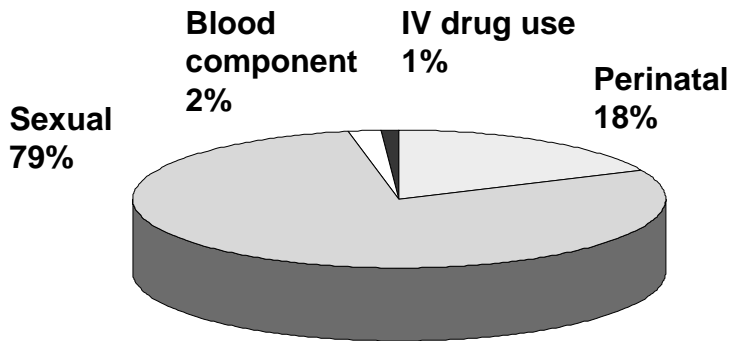
• *Target Sample Size* is 1125



• *To Date:*

- 508 HIV-Positive ACASI
- 460 Medical Chart Abstractions

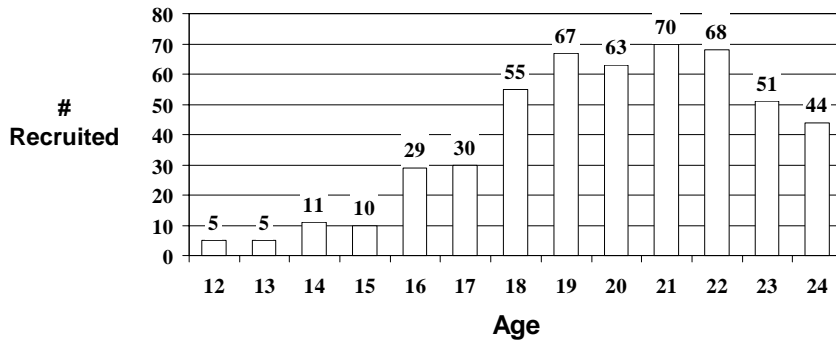
Most Likely Mode of Transmission



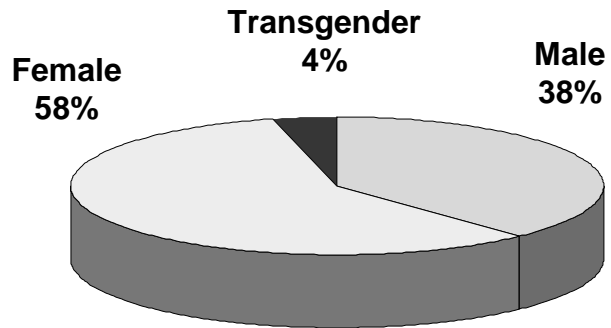
AGE

Male Age: M = 20.05, SD = 2.61

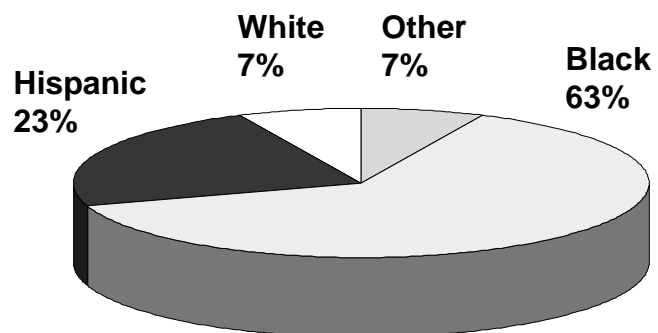
Female Age: M = 19.83, SD = 2.79



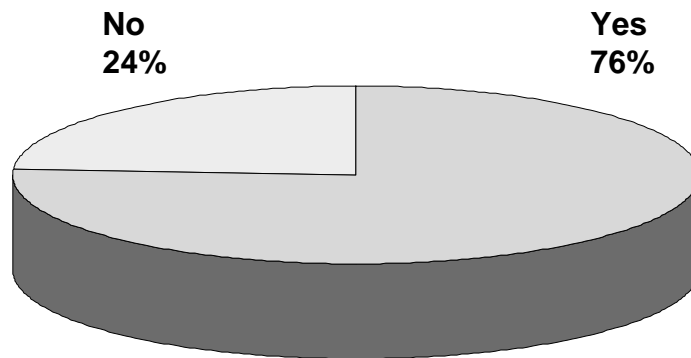
Gender



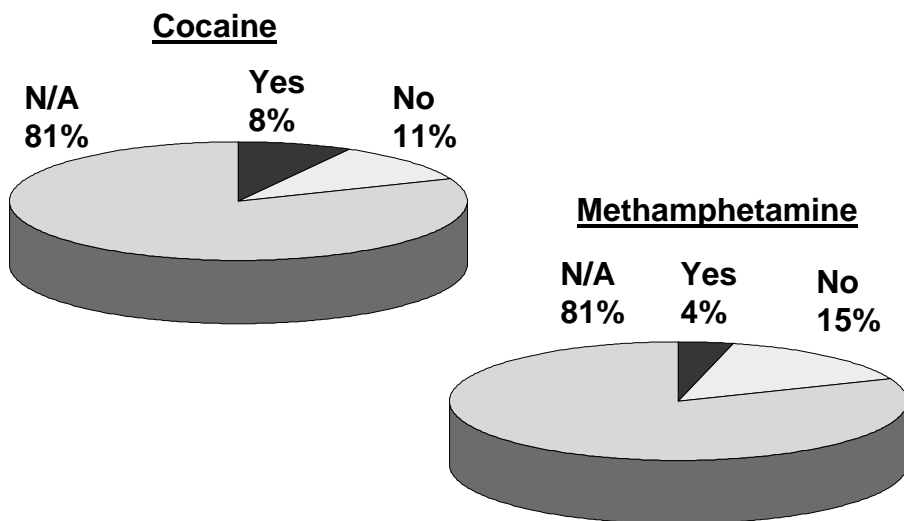
Race/Ethnicity



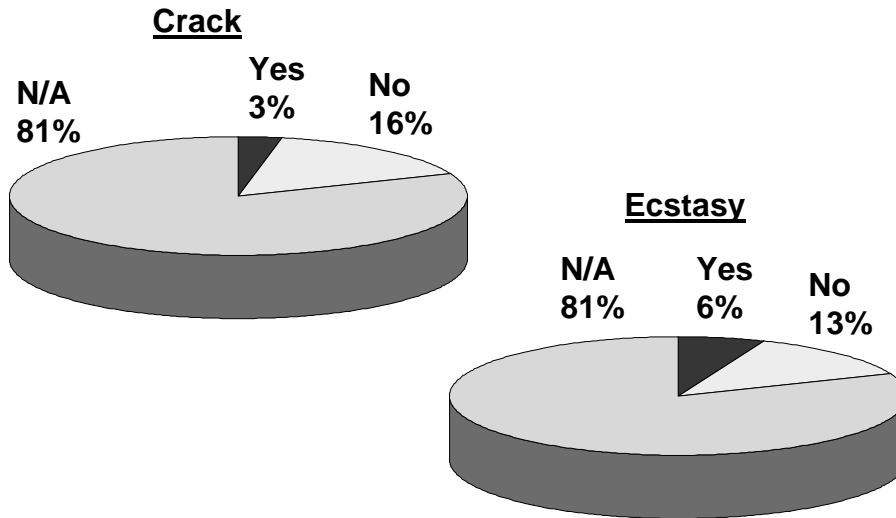
MSM (n = 209)



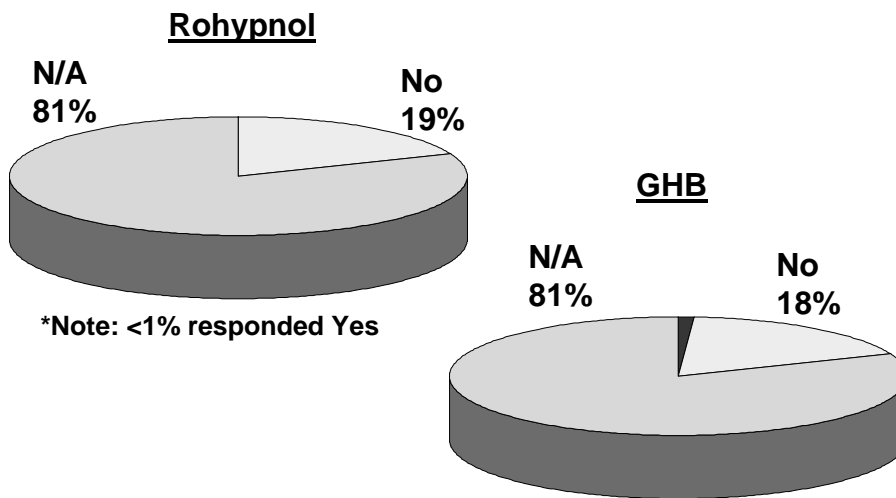
Substance Use, Past 90 Days



Substance Use, Past 90 Days (cont.)



Substance Use, Past 90 Days (cont.)

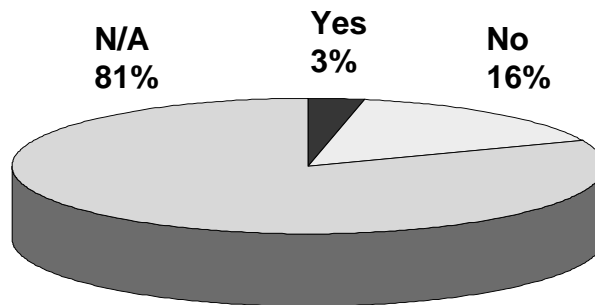


Substance Use, Past 90 Days (cont.)

Hallucinogens



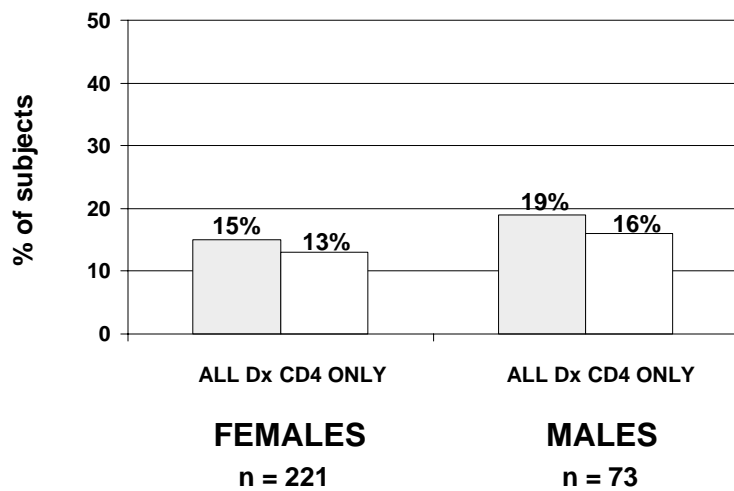
Ever Injected Drugs



Clinical and Research Data

REACH

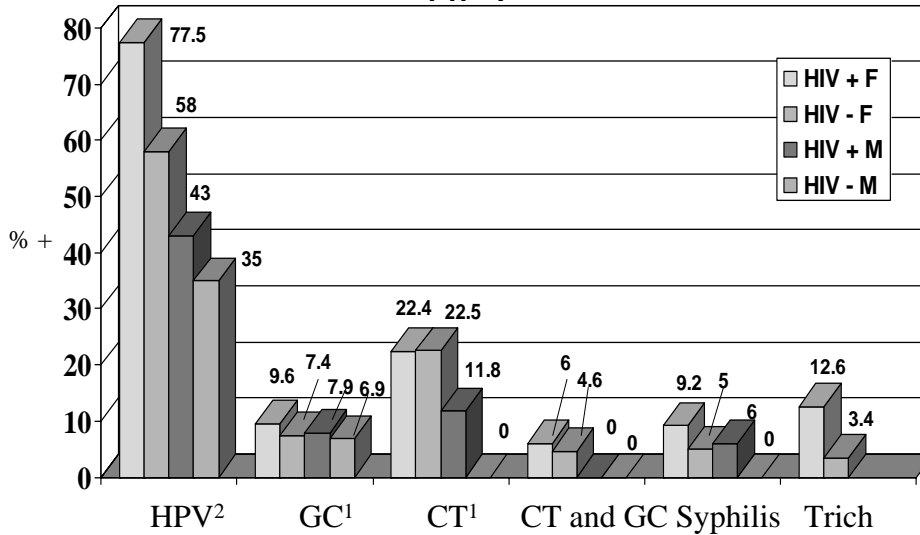
AIDS Dx AT ENTRY



VIRAL LOAD DISTRIBUTION IN REACH COHORT

<u>Viral Load</u>	<u>Male</u>	<u>Female</u>
Below Detection (BD)	12 (13.5%)	67 (26.3%)
BD – 10K	35 (39.3%)	122 (47.8%)
10K – 50K	21 (23.6%)	41 (16.1%)
➤50K	21 (23.6%)	25 (9.8%)
	89	255

PREVALENCE OF CT, GC, TV, SYPHILIS AND HPV



¹ includes urine, anus and cervix (females)

² cervical rates for females, anal rates for males

HBV, HCV AND CMV

	MALES		FEMALES	
	HIV + <u>N = 59</u>	HIV - <u>N = 30</u>	HIV + <u>N = 195</u>	HIV - <u>N = 83</u>
HB_cAb¹	(14) 28 %	0 %*	(34) 22.0 %	(7) 12.5 %
HB_sAg²⁺	(5) 36 %	0	(5) 15.0 %	0
HCV	(1) 1.7 %	0	(3) 1.5 %	(2) 2.4 %
CMV	(47) 80 %	(15) 50 %*	(153) 78.5 %	(51) 61.4 %

¹ excludes those vaccinated (20 males and 70 females)

² includes only those HB_cAb +

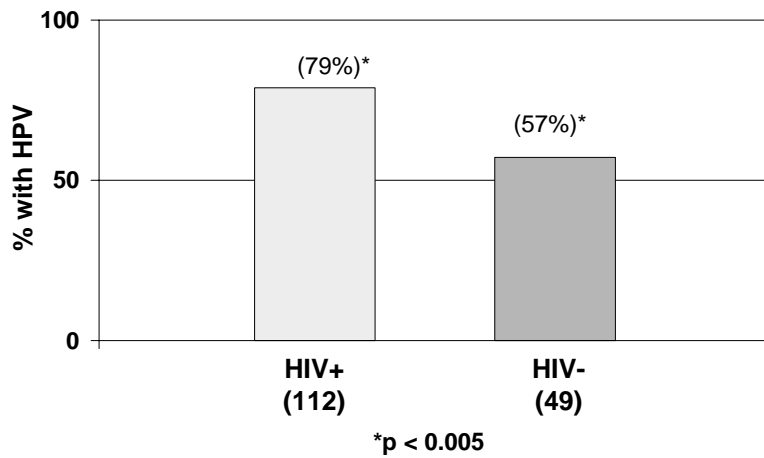
* p < 0.01

RISKS FOR HBV AND CMV (MULTIVARIATE MODELS)

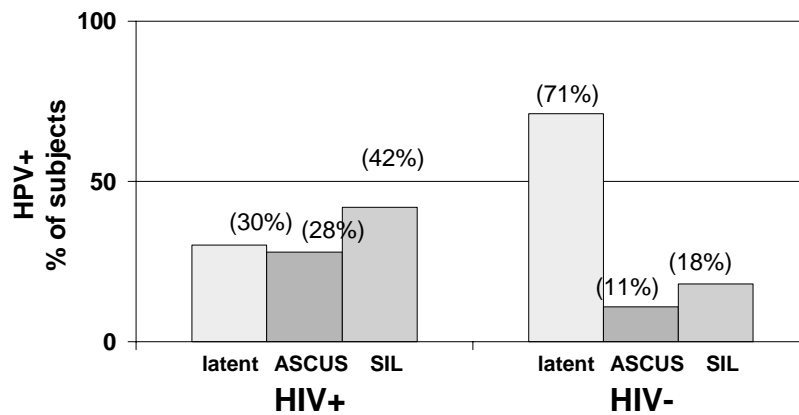
	MALES	FEMALES
	<u>O.R. [95 % C.I.]</u>	<u>O.R. [95 % C.I.]</u>
HBV		
> 10 lifetime partners	--	2.4 [1.2 - 5.1]
Age < 13 yr at 1st intercourse (anal or vaginal)	5.4 [1.1 - 26.9] ¹	--
CMV		
Homosexual/bisexual preference	5.32 [1.2 - 9.5]	--
HIV status	3.1 [1.1 - 8.8]	2.4 [1.3 - 4.3]

¹ HBV model for males included HIV+ only; no HIV uninfected males were HBV+

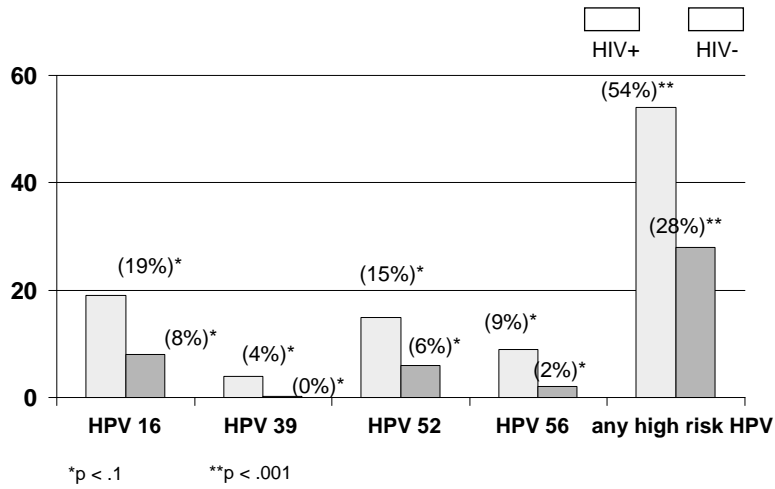
ASSOCIATION BETWEEN HPV AND HIV STATUS



PERCENT OF WOMEN WITH HPV WHO HAD A LATENT INFECTION BY HIV STATUS

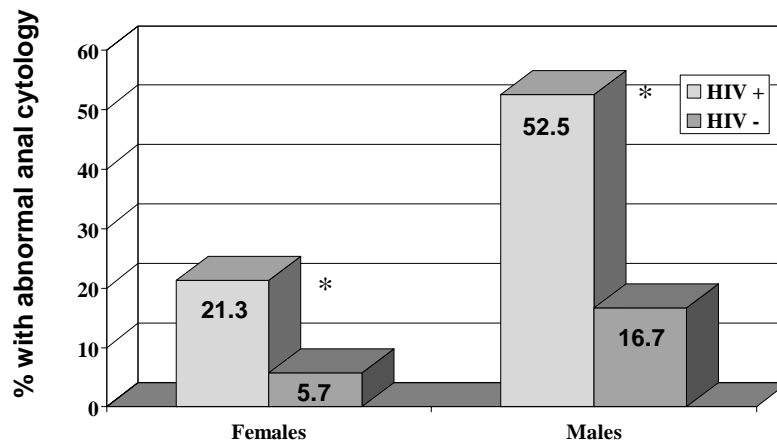


DISTRIBUTION OF HPV TYPES BY HIV STATUS (PREVALENCE IN WHOLE POPULATION)



No differences were found for LR, 18, 31, 45, 51, 58, untypeable

ABNORMAL ANAL CYTOLOGY



* p < 0.01

**RESULTS OF MULTIVARIATE ANALYSIS
OF RISK FACTORS FOR ANAL SIL IN
FEMALES**

Risk Factor	Odds Ratio (95% CI)	p-value
Anal HPV	47.4 (10.2 - 220.9)	0.0001
Ever smoked >100 cigs	3.8 (1.3 - 11.5)	0.0177

HIV Counseling and Testing

Providers are one of the keys

The HIV Epidemic in Adolescents

- 1 in 4 new infections occur in adolescents
- an estimated 110,000 to 220,000 youths are living with HIV
- only 19,904 youth have been reported in states with HIV reporting
- thus, only 16% of youth living with HIV may be aware of their status

– Arch Ped Adol Med 2000;154

Assessing Risk:

- Study done with adolescents early in the HIV epidemic revealed that risk factor assessment would only identify 38% of those at risk (D'Angelo, et al. Pediatrics 1991;88:982-986)
- Study done in young pregnant woman in Atlanta revealed that 59% were unaware of their risk for HIV infection (Lindsay, et al. Am J Obstet Gynecol 1992;167(4):1096-1099)

Unsafe Sexual Behavior and the Characteristics of Sexual Partners in HIV-Infected and Uninfected Adolescent Females

- Data from 153 HIV-infected and 90 HIV-uninfected females from REACH
- Baseline data

Sturdevant et al. J of Adol Health 2001;29s:64-71

Data:

- Current partners were 4-6 years older on average
- HIV-infected adolescents were older
- HIV-infected adolescents had more lifetime partners (12 vs 8)
- HIV-infected adolescents initiated vaginal sex earlier (14 vs 13 years of age)
- Perceived partner to be HIV-infected
- Had less unprotected sex

Data, con't:

- Length of relationship was associated with more unprotected sex in both groups
- Mean partner age was greater for HIV-infected than uninfected females (6.07 vs. 4.73 years)
- Less disclosure also associated with less protection

What puts some young women at more risk?

- Common risk factors
 - Number of partners
 - Age at sexarche
 - Risk of partner
- But are there others?
 - The older age of the partners may reflect young women who are more vulnerable to men at greater risk

Who to test:

- All women who are sexually active
- All women who report sexual abuse, even those with early childhood abuse
- All women who present with an STI
- All pregnant women
- All women who require emergency contraception
- All women who request a pregnancy test

Clinical Care of the HIV-infected adolescent

Clinical Care

- Women are under represented in most HIV clinical trials
- Current PHS guidelines do not suggest any gender differences in prescribing ART
- Issues specific to women include medication side effects, interactions with hormonal contraception, HIV viral load and CD4+ T cell differences between men and women

HIV Viral Load

- Some studies suggest women have lower VL than men while others do not
- Recent review of 13 studies, both cross-sectional and longitudinal:
 - 7/9 cross-sectional studies demonstrated that women had 0.13-0.35 log₁₀ (2 fold) lower levels than men
 - 4 longitudinal studies demonstrated that women had 0.33-0.78 log₁₀ lower levels than men adjusting for time since seroconversion
 - Age, race, mode of transmission, and ART did not affect the outcome
 - Gandhi G, et al. Clin Infect Dis 2002;35:313-22

CD4 + T Cells

- Data from REACH in uninfected adolescents:
 - Females had higher total CD4+ T cells
 - Regression coefficient 0.0734, $p=0.0004$
 - Rudy et al. CDLI September, 2002
- HIV infected women have higher CD4 + T cells than men
 - Approximately 100 cells/mm³

However.....

- Disease progression to AIDS or death is no different in women than men
- Differences in HIV viral load and CD4+ T cells decrease over time and are equal by about 5 years
- Adverse events to ART higher in women:
 - Rash and hepatotoxicity to NVP greater in women when CD4+ T cells > 250 cells/mm³
 - Increased central adiposity in women on HAART

Indications for Antiretroviral Therapy

- All patients with AIDS-defining illness or severe symptoms of HIV infection regardless of CD4+ T cell count
- Asymptomatic with CD4 + T cell count below 200 cells/mm³
- Asymptomatic with CD4 + T cells between 200 and 350 cells/mm³
- Asymptomatic HIV with CD4 + T cells >350 cells/mm³ but HIV RNA >100,000 copies/ml, some would treat

Preferred Initial Treatment Regimens

- General approach: at least three drugs from two classes of medications
- Preferred regimens:
 - Efavirenz plus (lamivudine or emtricitabine) or (zidovudine or tenofovir)
 - Lopinivir/ritonavir plus (lamivudine or emtricitabine) plus zidovudine

When to start therapy in the real world

- Consider the risks and benefits of therapy
- Consider patient's interest in ART
- Consider all of the barriers to adhering to ART
- Consider trends in both CD4 + T lymphocyte counts and plasma RNA levels
- Consider other concomitant medical conditions which could be impacted by therapy
 - Take home message: decisions about therapy is patient-based and should be individualized for each patient

Drug Resistance:

- In a recent ATN study of 55 subjects recently infected with HIV
 - 10/55 (18%) had major mutations
 - 8 (15%) had NNRTI mutations
 - 2 (4%) had NRTI mutations
 - 2 (4%) had PI mutations
- Genotypic drug resistance testing should be considered for all newly identified adolescents prior to initiating ART
 - Viani et al. CROI 2006, abstract #21



Immune Reconstitution and Predictors of Virologic Failure in Adolescents on HAART: Week 60 Results from the PACTG 381 Cohort

Bret J. Rudy, Jane C. Lindsey, Patricia M. Flynn, Ronald J. Bosch, Craig M. Wilson, Michael D. Hughes, Steven D. Douglas and the PACTG 381 Study Team

Methods:

- Observational cohort study
- Population: 120 behaviorally-infected adolescents, 11-22 years of age
- HAART: minimum of two NRTI's plus either a PI or Efavirenz
- Adherence measured by self report
 - “Perfect adherence” defined as no missed doses in previous three days
- Present data: complete to week 60

Methods:

- Short-term virologic success:
 - Plasma RNA OD <0.2 (400 copies/ml) on standard Roche Amplicor at weeks 12 and 16 OR
 - A 1- \log_{10} decline in plasma RNA by week 12 followed by a confirmed VL below 400 copies/ml before week 24
- Week 60 virologic success:
 - Short term virologic success
 - No confirmed plasma RNA >400 copies before week 60

Results:

- 120 subjects enrolled and started HAART
- Median age=19 years
- 111 antiretroviral naïve/9 with ART exposure
 - ZDV monotherapy
 - ZDV + NVP or 3TC for one week or less during pregnancy
- Median CD4+ T cells at entry= 400 cells/mm³
- Median HIV RNA=36,000 copies/ml
- Most common treatment regimens:
 - ZDV/3TC/NFV (n=44)
 - ZDV/3TC/EFV (n=57)

Results:

- 120 subjects enrolled
 - 111 naïve to ART
 - 69/120 (58%) subjects classified as short-term virologic successes
 - 55/69 (80%) classified as virologic successes to week 60
 - However, at three years, only 29 (24%) were on HAART and suppressed
 - Adherence was a major predictor of viral suppression

ATN 023B: Typology of Adherence in Adolescents- Phase II

ATN Network Meeting

October 27, 2005

Bret J. Rudy
Jonathon Ellen

STUDY OBJECTIVES

- ▶ To determine the prevalence of the specific barriers to adherence as classified by the Participant Assessment Tool
- ▶ To determine the most common clusters of specific barriers
- ▶ To develop and determine the validity of the cognitive-behavioral barriers schema

STUDY DESIGN

- ▶ Cross-sectional survey study
- ▶ Sample size
 - 600 to 1200 subjects at ATN sites (40 to 80 at each)
 - 100 to 400 at selected non-ATN sites (at least 25 at each)
 - For sites with access to patients infected perinatally and non-perinatally, approximately equal numbers should be enrolled in the two transmission categories

	Mental Health and/or Substance Abuse	Cognitive-Behavioral				Structural Barriers
		High OE ¹ High SE ²	High OE Low SE	Low OE High SE	Low OE Low SE	
Prescribed HAART but never started because subject refused (1)						
Started HAART but subject has now stopped(2)						
Prescribed HAART but currently taking less than HAART(3)						
Started HAART but currently not adherent(4)						
Started HAART and is currently adherent(5)						

Preliminary Results

- Total 764 subjects
 - 522 adherent (68.3%); 242 not adherent (31.7%)
- Mode of transmission
 - **Perinatal:** 48%
 - **Other:** 52%
 - Sexual partner: 35%
 - Uncertain: 8%
 - Contaminated Blood: 5%
 - Sexual abuse: 3%
 - Other: <1%

Adherence Group by Mode of Transmission

Table 1: ATN 023b, mode of transmission by adherence, $\chi^2(4)$ p-value < 0.0001

Mode	Adherence category				
	1	2	3	4	5
Not perinatal	9%	21%	1%	6%	63%
Perinatal	1%	9%	8%	8%	74%

- Adherence better in the perinatal than those infected through other means
- Only group 4 were comparable

Preliminary Results- OE/SE

- Reliability greater for self efficacy than outcome expectancy
 - Cronbach alpha values:
 - SE: 0.89
 - OE: 0.57
- Greater variability reported for SE than OE
 - Mean SE 75.8 ± 24
 - Mean OE 28.3 ± 4.7
- No distinct cutoffs were found for OE and SE

	OE quartile			
	1	2	3	4
SE quartile				
4	15, 17, 88%	30, 34, 88%	52, 54, 96%	83, 88, 94%
3	15, 26, 58%	43, 53, 81%	47, 59, 80%	60, 73, 82%
2	24, 40, 60%	31, 51, 61%	36, 54, 67%	22, 31, 71%
1	14, 71, 20%	22, 57, 39%	19, 38, 50%	9, 18, 50%

Preliminary Results

- Structural Barriers:
 - Place to sleep
 - Insurance
 - Transportation to pick up medicines
 - Transportation to clinic
 - Getting medication prescriptions filled
 - Job or School
 - Family or children

Preliminary Results

- Percentages of subjects without reported structural barriers:
 - No barrier sited by 43.2% of non-adherent subjects
 - No barrier sited by 66.2% of adherent subjects

Table 3: Proportion of subjects citing each barrier

Barrier	1	2	3	4	5	6	7
% citing	6.7%	12.2%	7.7%	13.7%	11.7%	11.4%	10.5%

- The most common structural barrier was “problem with transportation”

Table 4: Proportion citing 0 barriers, 1 barrier, ..., 7 barriers								
# barriers	0	1	2	3	4	5	6	7
% citing	58.9	22.6	10.1	4.8	2.0	1.0	0.3	0.3

- 18.5% reported more than one barrier

Table 5: Barriers cited by adherent and non-adherent subjects								
Barrier	none	1	2	3	4	5	6	7
adherent	225	28	43	28	56	48	44	42
Not-adherent	160	23	50	31	49	41	43	48

- Reported barriers were more common in non-adherent than adherent subjects
- Individual barriers did not differ between the two groups

Preliminary Results

- Subjects who reported low SE were more likely to report barriers related to problems with job/school or family/children than those with high SE
- No pattern of structural barriers was seen between adherent vs. non-adherent subjects

Contraception choices in HIV-infected adolescents

Belzer et al. JAH 2001;29s:93-100

- REACH evaluated contraceptive choices in HIV-infected and at-risk youth
- Of 261 females, 91 reported abstinence
- Of those sexually active
 - 51% of HIV+ and 50% of HIV- chose male condoms
 - 21% of HIV+ and 15% of HIV- chose DMPA alone

Contraceptive choices, con't

- 4% of HIV+ and 12% of HIV- chose OCP alone
- 4% of HIV+ and 9% of HIV- chose nothing
 - In multivariate analysis: HIV infected subjects and non-Hispanic AA were more likely to report reliable birth control methods

Interactions of ART and contraceptives

- Ethinyl oestradiol and progestogens are substrates of the cytochrome p450 CYP 3A4 system
- Many ART's induce this system
 - Ritonavir, nelfinavir, lopinavir/ritonavir, nevirapine, efavirenz
- Barrier methods should be added, increases in ethinyl oestradiol dosage to 50 µg/day should be considered, and progesterone only pills discouraged

Addressing HIV Infection in Family Planning:

- First, educate young women as to their risk
 - Risk may really reside with the partner and NOT the young woman
- Second, provide age-appropriate HIV counseling and testing
 - New strategies to streamline process is reasonable
- Third, be certain you know resources in your community for youth who test positive
 - HIV counseling and testing in areas where prevalence is below 1% is cost effective as long as the person is engaged in care!

Current Research Initiatives

- Therapeutics
 - Initiation of ART
 - Reducing ART exposure
 - Immune Modulation
 - Co-morbidities
- Behavioral
 - Community-based prevention research
 - Adherence

Therapeutics

- PACTG 1034: A Comparative Trial of Protease-Containing and Protease-Sparing HAART Regimens in HIV
- ATN 015: Short Cycle Therapy in Adolescents with Established Viral Suppression: Virologic and Immunologic Comparison to Adolescents on Non-interrupted Therapy
- PACTG 1040: Simplification to Abacavir-based Triple Nucleoside ART Following Induction with PI-based ART Regimens in HIV-infected adolescents (on hold)

Therapeutics

- ATN 021: Prevalence of Morphologic and Metabolic Abnormalities in HIV-infected and Uninfected Young Women
- ATN 022: A Novel Method to Determine HIV Incidence Among Youth

Therapeutics

- ATN 024: A Randomized, Open Label Trial of Three Hepatitis B Vaccination Schemas in HIV-positive Youth
- ATN 025: Hepatitis B Vaccination in Youth at Risk for Hepatitis and HIV Infection
- ATN 026: Evaluation of HIV-1 Specific CD8+ T-Cell Responses and Escape Mutations as Explanations for Observed Differences in Disease Progression Conferred by HLA Class 1 Alleles

Behavioral

- ATN 016a/b: Connect to Protect (C2P): Partnerships for Youth Prevention Interventions- Phase I and Phase II
- ATN 023 a/b: Typology of Adherence in Adolescents

Prevention

- Connect to Protect
 - Prevention research needs to be based within the community and successes must be sustainable within the community
 - Prevention will work best with community support and community ownership

Connect to Protect

- Community-based research initiative headed by the ATN units in all cities
- Step 1: Identify the hotspots in the community
- Step 2: Identify key community partners through a series of presentations and interviews
- Step 3: Establish with the community the specific target population
- Step 4: Take interventions known to work and implement these with community partners in new populations or in new settings that are consistent with the epidemic in that area.

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