

Experience with Research Involving HIV-Infected Adolescents



Lawrence B. Friedman, MD
Director, Division of Adolescent Medicine
XIV Seminario Integral del SIDA; Cali, Colombia

Research concerning HIV that involves teenagers-

- a) Requires informed consent.
- b) Utilizes special strategies to encourage enrollment and adherence
- c) with study protocols.
- d) Can be exciting and gratifying.
- e) Can be frustrating and tiring.
- f) All of the above.
- g) I do not know, I'm coming to learn.

Objectives

- Discuss the Division of Adolescent Medicine's experience with research involving youth at University of Miami
- Become familiar with selected research projects inclusive of HIV-infected adolescents and young adults

Participation by Youth in Research

- Same “informed consent” procedures as adults
- Requires parental or guardian consent, or court order as needed, plus own assent
- Waiver may be granted for some
- Regulation is different than for health care

Participation by Youth in Research (cont.)

- Retention challenges (burden of study's procedures, time of participation, type of intervention, etc.)
- Use of incentives or payments
- Flexibility of procedures “within reason”
- Sense of altruism

Possible Youth Concerns of Research Participation

- Time and commitment necessary
- Discomfort from medical procedures
- Side effects (real or anticipated)
- Feeling of being an experiment
- Fear of disclosure of diagnosis
- Reminder of HIV-positive status

Advantages of Participation

- Perception of receiving latest interventions
- A chance to be part of the solution
- Free lab work and some trial medicines
- Personalized, friendly, confidential care
- Partnership with primary care provider

Why HIV Clinical Trials?

- Is the investigational treatment safe?
- Do treatments work the same in women? In men? In children?
- What about side effects?



University of Miami

Division of Adolescent Medicine

- **Multi-disciplinary service** (MDs, ARNPs, SWs, health educators, youth outreach workers, etc.)
- **Clinical programs for adolescent health care** (primary care, gynecology, chronic diseases, school-based, diabetes, etc.)
- **Educational activities** for medical students, residents, community agencies and youth, middle and high school students and teachers, juvenile justice participants and personnel, etc.
- **Funded research efforts** (NIH, CDC, HRSA, SAMHSA, Florida DOH, Miami-Dade County, private foundations)
- **Advocacy** (Children's Trust, Board of Medicine, community)
- **Projects** in HIV testing and care, STD screening and treatment, mental health stressors, firearm injury reduction/violence prevention, sexual education of chronically ill youth, substance use prevention for Hispanics, school-based clinic education, community initiatives

University of Miami

Division of Adolescent Medicine

HIV Services

- **Special Adolescent Clinic (SAC)** for HIV-infected youth and young adults since 1990 as a **Ryan White Title IV-Miami Family Care Program** component (Division of Immunology and Infectious Diseases)
- Founding member of NIH's **Adolescent Medicine HIV/AIDS Research Network** for *REACH Study*, 1994-2001 (HD32858)
- Subsequent continual participation in NIH's **Adolescent Trials Network for HIV/AIDS Interventions (ATN)**, 2001-06 and 2006-11 (HD40494), including *Connect to Protect (C2P) Project*
- Collaboration on NIH's **Pediatric AIDS Clinical Trials Group (PACTG)** and **IMPAACT** (Division of Immunology and Infectious Diseases) studies since 1999
- **Adolescent Counseling and Testing Service (ACTS)** for HIV and STD testing (FL Department of Health) since 1997
- Component of **FL/Caribbean AETC** since 2001

NIH's Adolescent Medicine HIV/AIDS Research Network *Reaching for Excellence in Adolescent Care and Health* (REACH) Study – HD32858, 1994-2001

- Supported by NICHD, with supplemental funding from NIDA, NIMH, and NIAAA
- Observational study of 13-18 y/o's with acquired HIV infection after age of 9
- Quarterly visits, including high-risk HIV-negative control group of similar ages and genders
- Extensive interview, confidential ACASI survey, comprehensive PE (including pelvic), and extensive laboratory evaluation
- Miami site had highest enrollment (67) and greatest retention (91%) over four years of protocol!

REACH SITES



REACH STUDY

1994-2001

Observe/describe/explore:

- HIV pathogenesis and spectrum of disease in youth
- Effects of HIV on growth and development, and vice versa
- Morbidity of co-infections with STDs
- Effects of mental health and behavioral patterns on disease progression
- Immunologic markers for potential differences in adolescents

REACH Study

Selected Results

- ***Journal of Adolescent Health 2001;29S:1-129*** (special supplemental volume devoted entirely to project)
- Preliminary, introductory, and final results published continually since 1998
- Normal T-cell subset values established for teenagers
- No differences in G&D between HIV + and - subjects
- Reasons cited by youth for retention in research protocol were: care received and close connection to clinic felt by subject; perceived new and best quality of treatment at clinic; altruistic feelings of “doing good”; incentives and stipends rated only sixth.
- *Project ACCESS* started

Gettin' busy?

PUT IT ON BEFORE YOU - GET IT ON !

To buy the **Gettin' Busy ? CD**
log on to www.gettinbusymiami.com or call (305) 218 - 3950



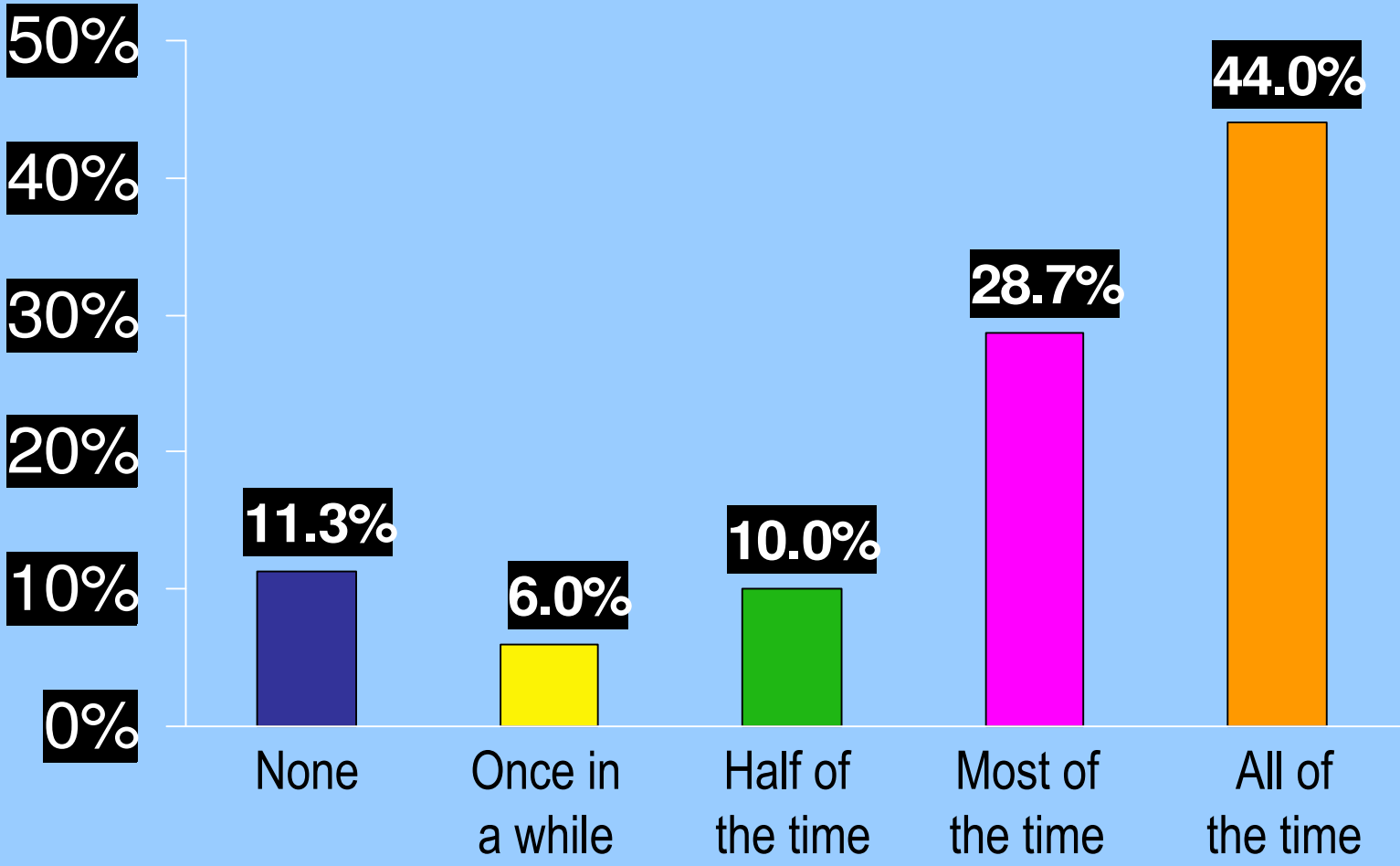
IF YOU'RE 13 TO 24 GET TESTED

CALL **1-877 HIV-TEEN** 448-8336

email: www.gettinbusymiami.com

Frequency of Taking Medication

REACH Study



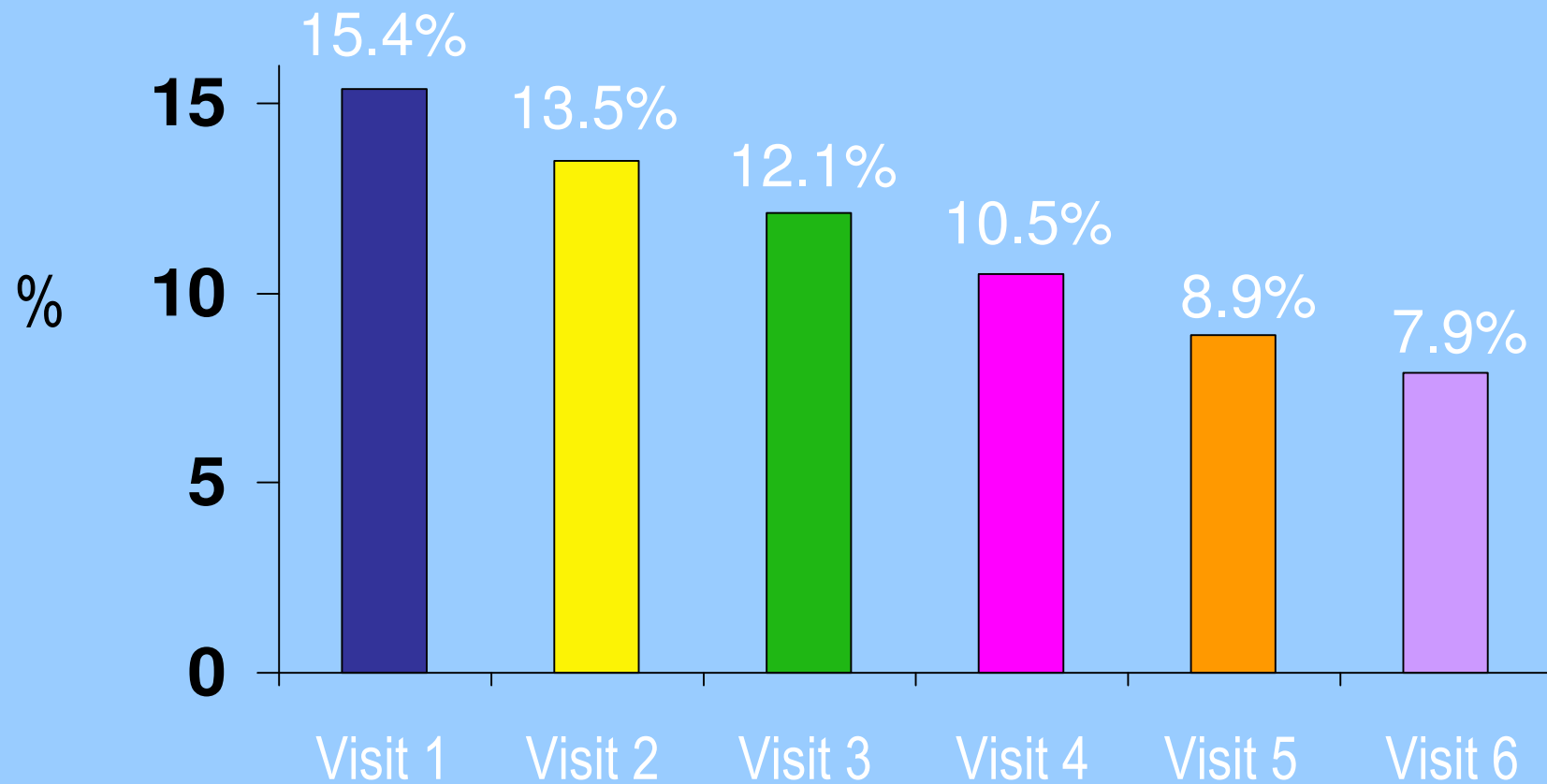
Logistic Regression: Adherence Rating

Ordinal logistic regression for adherence

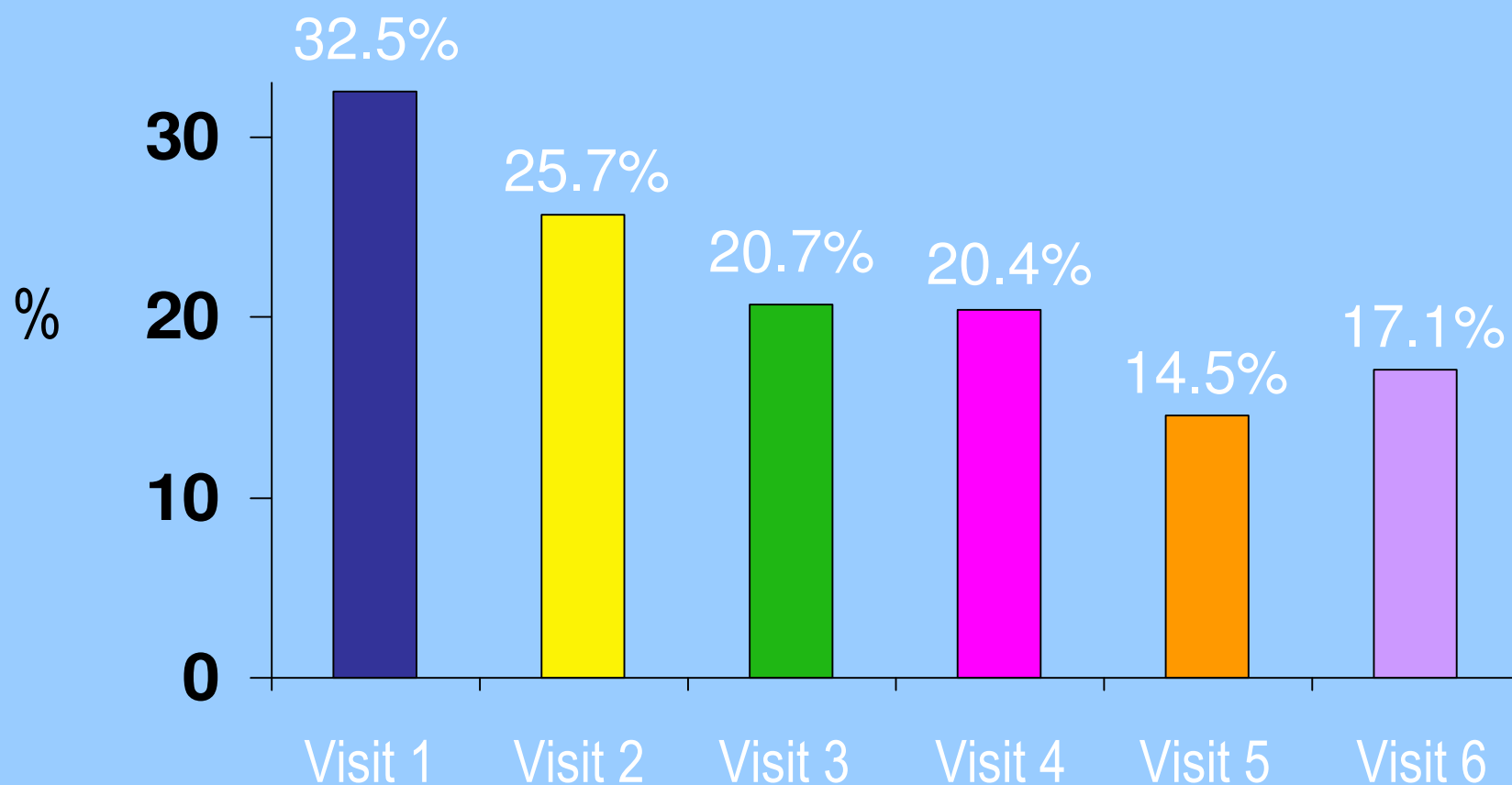
- **Higher level of depression significantly associated with lower reported adherence**

(OR = .210, $p = .0006$)

% Engaging in Frequent Alcohol Use Across Visits (*REACH* Study)



% Engaging in Frequent Marijuana Use Across Visits (*REACH* Study)



Differences between HIV-positive and HIV-negative subjects

- **Significant reductions in total CD4 cell counts were noted in both HIV-positive females and males**
- **Reductions in total CD4 cell counts were a result of both reduced memory and naïve CD4 cells**

Differences, cont'd:

- **Total CD8 cells were increased in HIV-positive males and females compared to uninfected subjects**
- **Increase noted in both memory and naïve CD8 cells (although the percentage of naïve CD8 cells actually decreased)**
- **Significant increase in cytotoxic T-lymphocytes in HIV-positive males and females compared to uninfected subjects**

Conclusions, cont'd:

- Reductions in both naïve and memory CD4 cells are similar to those found in other HIV infected populations
- The increase noted in naïve CD8 cells is a novel finding in this cohort
- The mean total CD4+ cells for females ($0.542 + 0.253 \times 10^9$) and males ($0.432 + 0.211 \times 10^9$) suggested that this population was relatively early in infection

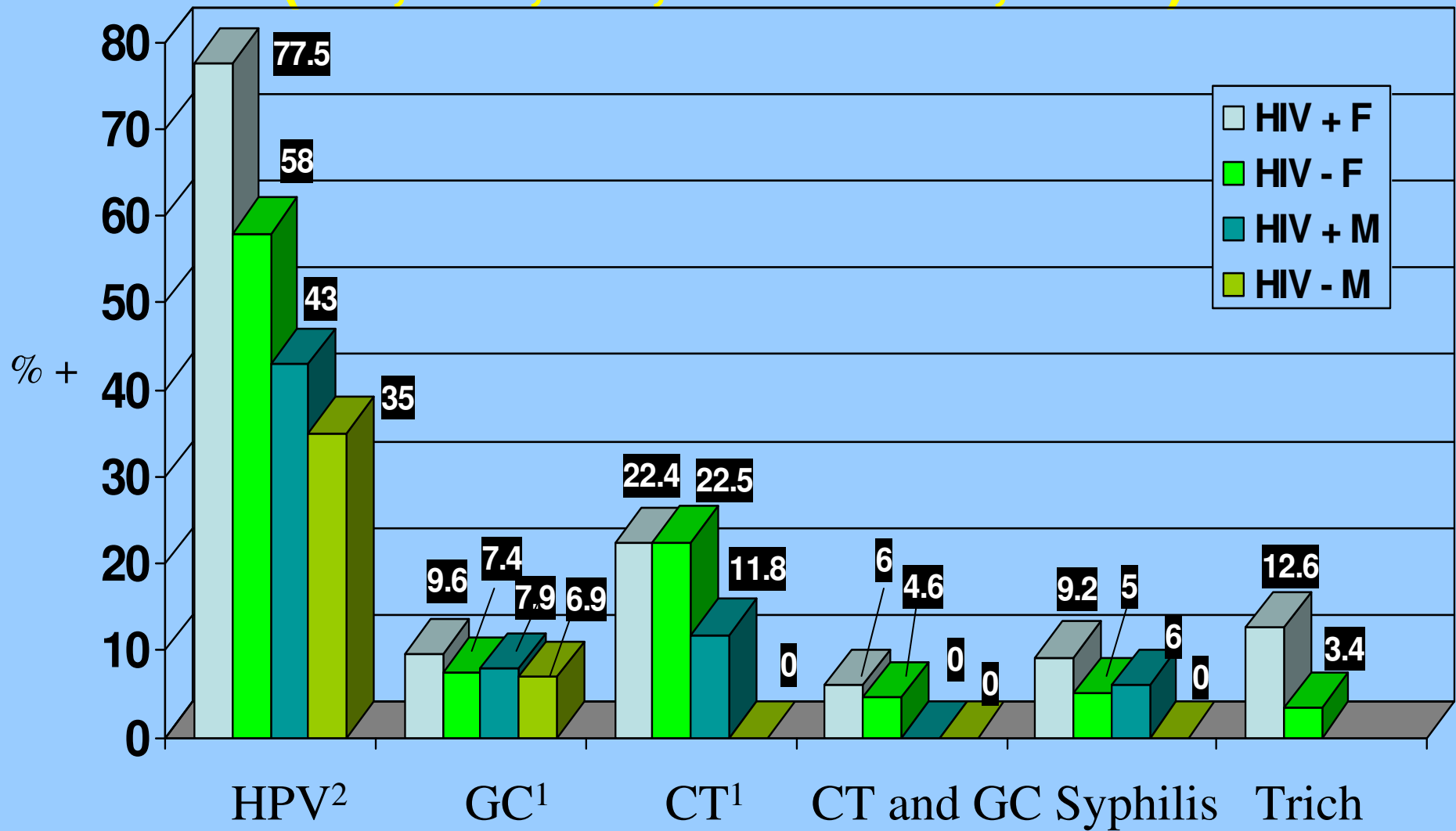
Conclusions, cont'd:

- **The marked elevation in naïve CD8+ cells suggests that adolescents have persistently functioning thymic tissue**
- **The high levels of cytotoxic T-lymphocytes most likely represents an immunologic response to active viral replication**

Final Conclusion:

- **These observations suggest that the immune system of HIV-infected adolescents may be capable of better responses to neo-antigens and cytotoxic T-lymphocyte responses to HIV, compared to either younger children or older adults**
- **More studies needed to explore this**

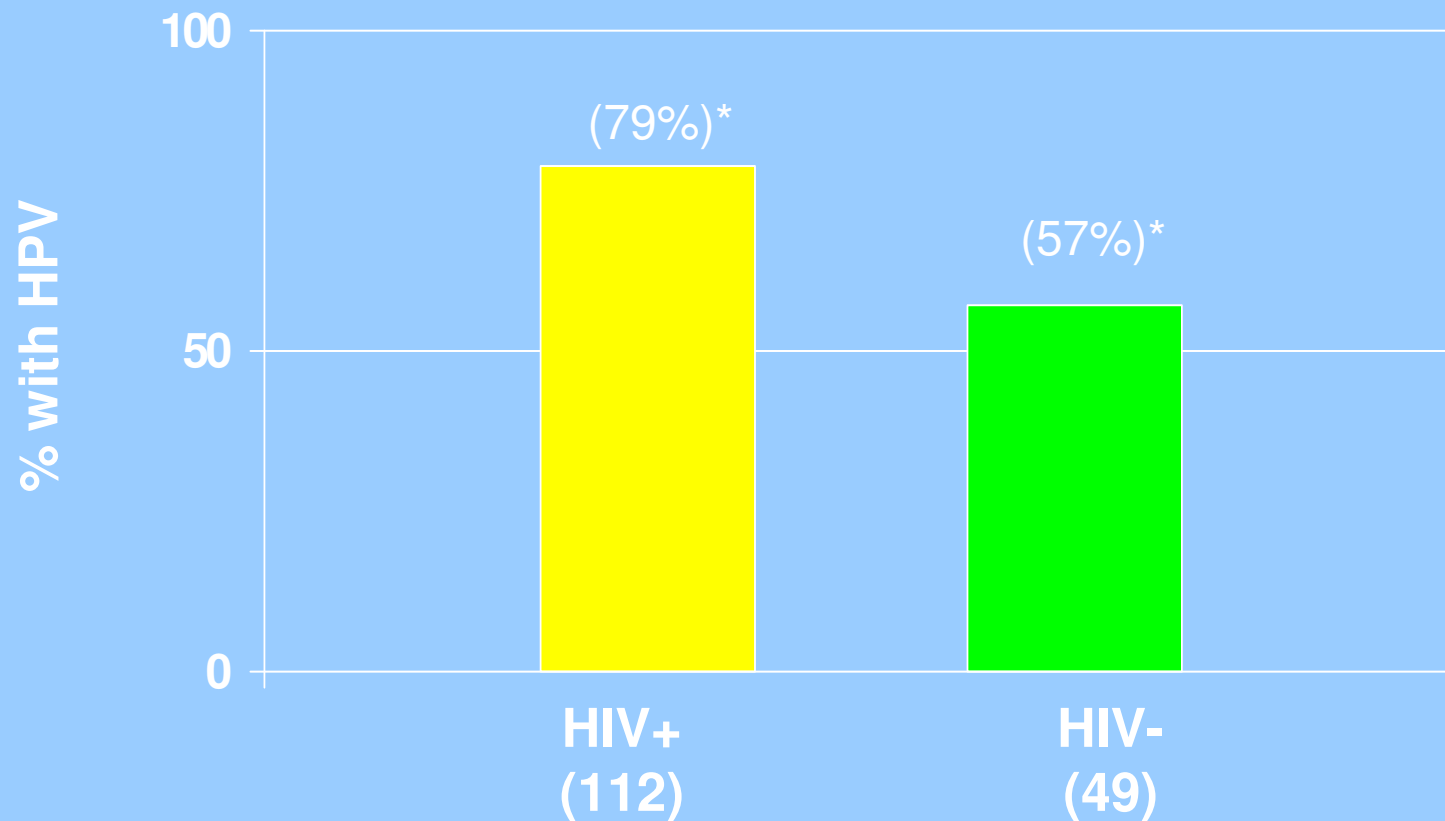
PREVALENCE OF STDs (CT, GC, TV, SYPHILIS, HPV)



¹ includes urine, anus and cervix (females)

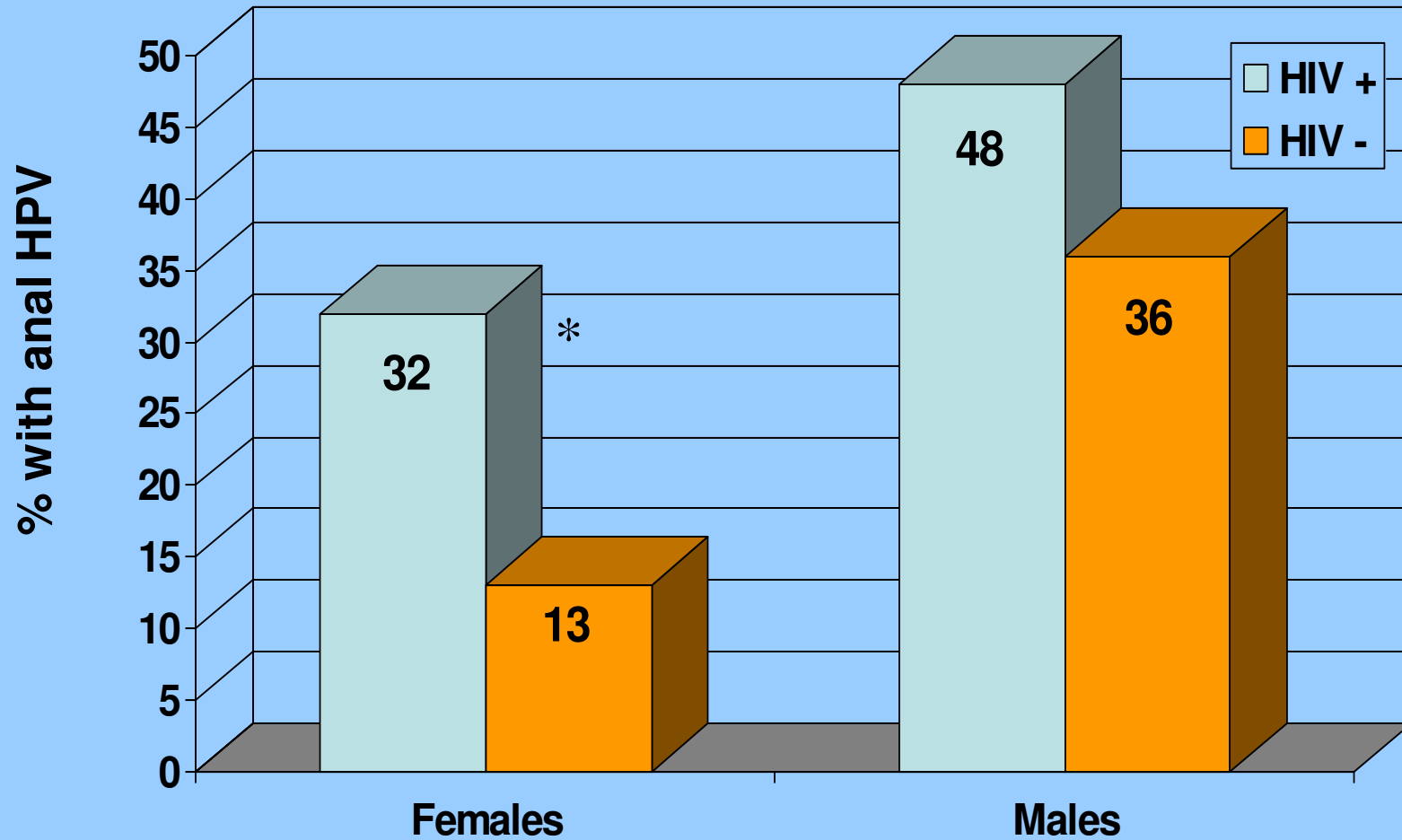
² cervical rates for females, anal rates for males

ASSOCIATION BETWEEN HPV AND HIV STATUS



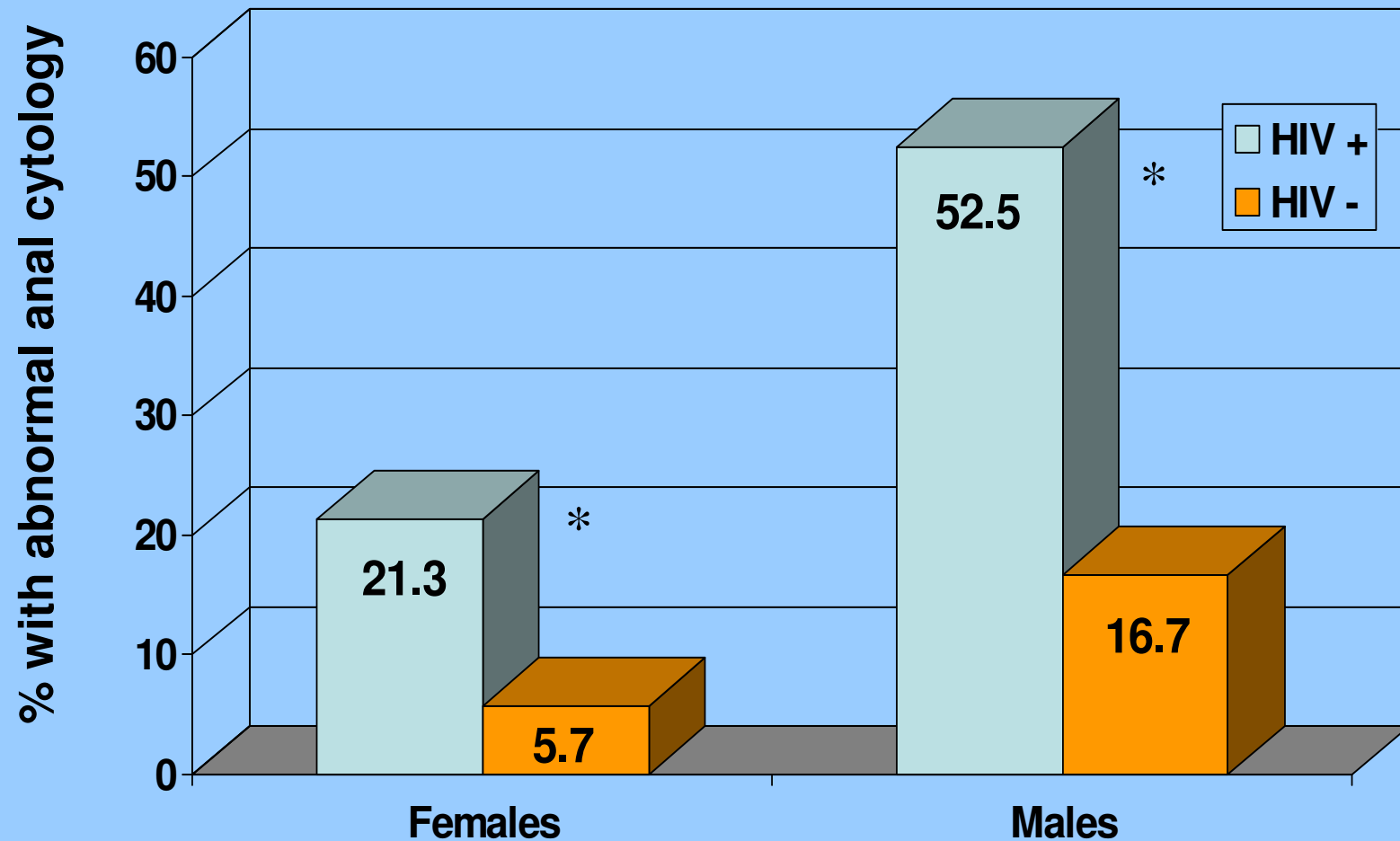
*p < 0.005

ANAL HPV



* $p < 0.01$

ABNORMAL ANAL CYTOLOGY



* $p < 0.01$

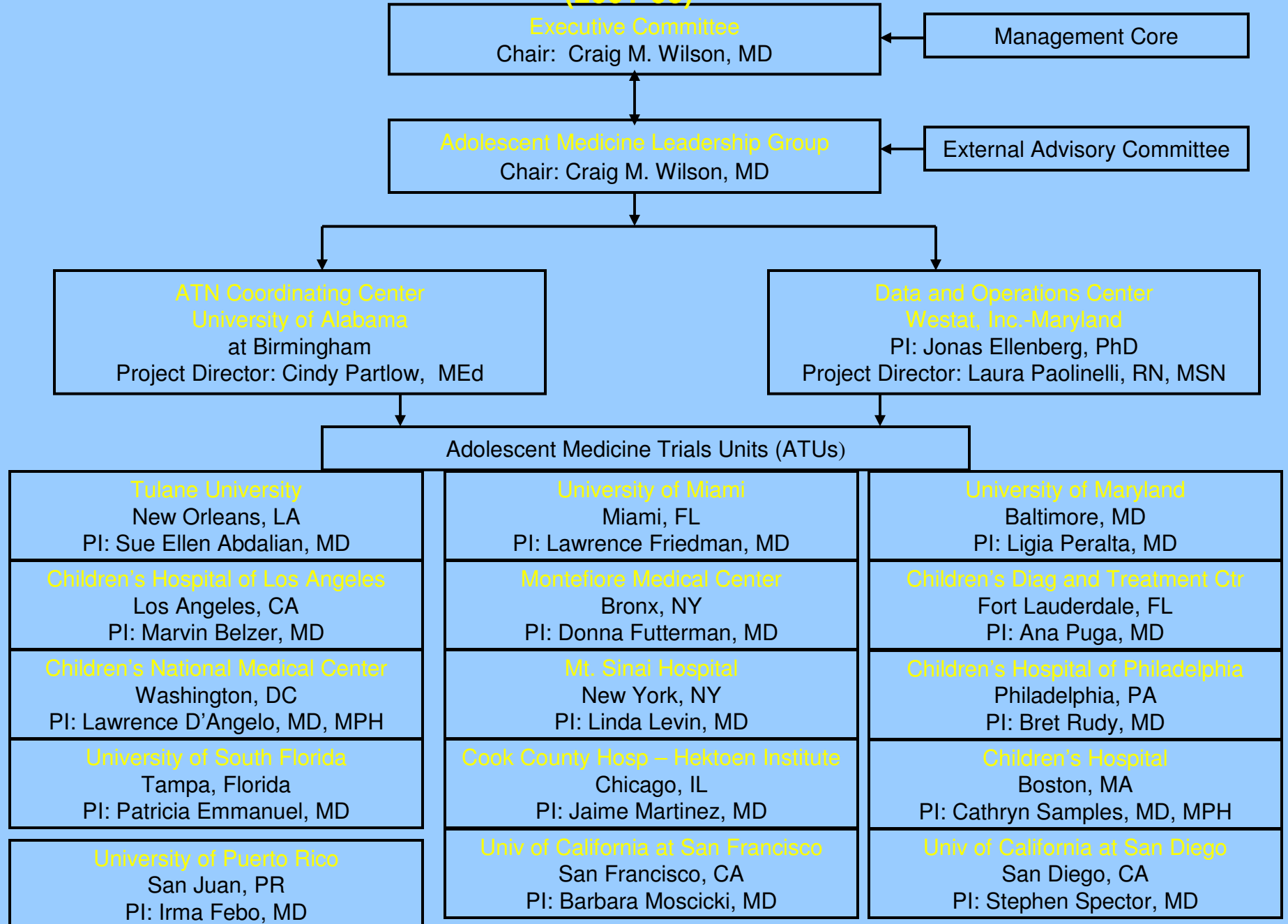
CONCLUSIONS

- **HPV is the most prevalent STI in HIV-infected adolescent males and females**
- **SIL from HPV is a significant problem in HIV infected persons, and is unrelated to CD4 count**
- **Persistence of high-risk HPV types is common in HIV infected women**
- **HIV + women have altered cytologic response to HPV**

CONCLUSIONS

- **HIV infected youth are at high risk for STDs (including CT, GC, trich, syphilis, hepatitis B and C, and CMV), underscoring their continued high sexual risk behaviors**
- **Cervical screening for CT is favorable over urine screening in HIV infected women**

Structural Overview of ATN (2001-06)



ATN 015

Short-Cycle Therapy in HIV-Infected Adolescents

- For 13-24 y/o on HAART with viral suppression following continuous therapy
- “Short-cycle” treatment consists of usual medications Monday-Thursday
- Treatment break Friday-Sunday
- Regular HIV viral load testing, T-cell determinations, chemistries, etc. (weekly, then monthly)
- Rigorous adherence procedures!

ATN 021a/b

Prevalence of Morphologic and Metabolic Abnormalities in HIV [+] and [-] Young Women and Men

- Food frequency questionnaire
- Nutrition and exercise survey
- Body image responses
- Blood tests for glucose tolerance and insulin resistance, with lipid profile
- Vitamin and mineral determinations
- Bone densitometry and lipid distribution measurements by DEXA Scan
- Preliminary results: + and – similar for F and M

ATN 022

A Novel Method to Determine HIV Incidence Among Youth

- For 13-24 y/o with newly identified HIV infection
- Correlation of “detuned assay” method of HIV detection with traditional standard methods (both serum and oral)
- Attempt to date HIV acquisition within 6 months
- Recent sero-converters eligible for substudy ATN 029

ATN 029

Prevalence of HIV Resistance Markers in a Recently Infected Population of Adolescents

- Substudy of ATN 022
- Medication resistance testing performed on subjects with recent HIV infection by detuned assay (within 6 months)
- Genotype and phenotype determinations

ATN 029: Evidence for Transmitted Resistance in ARV-naïve Adolescents and Young Adults

- Recently infected ARV-naïve adolescents (detuned assay)
 - 16–24 years (mean age 19.7 years)
 - Sample from 15 US cities (individual data not yet reported)
- Overall rate of resistance: (genotype; phenotype) 18%; 22%
 - NNRTIs: 15%; 18%
 - PIs: 4%; 6%
 - NRTIs: 4%; 4%
 - 1 subject resistant to all 3 classes of meds

	Male (n=36)	Female (n=19)
African American	58%	42%
Hispanic	21%	25%
White	11%	28%
Other	11%	5%

ATN 023b

Typology of Adherence in Adolescents

- Survey and face-to-face interview concerning compliance with medications
- Belief and personality attributes assessed
- To determine structural and life barriers
- Mental health and substance use factors evaluated
- **Self-efficacy and outcome expectancy interact and correlate with ARV treatment**

ATN 026

Evaluation of HIV-specific CD8+ T-cell Responses and Escape Mutations for Observed Differences in Disease Progression Conferred by HLA Class 1 Alleles

- Continuation of immunologic focus on patients from REACH Study still in care
- F/U testing from REACH Study's serum repository
- Subjects with HLA B*27, B*35, B*53, and B*57 qualified
- Measurement of CD8+ T-cell responses
- Determination of dominant HIV Genotype for resistance
- Medical record review and interview
- Brief PE and routine laboratory testing
- **B*27 and 57 correlate with better prognosis (good CD8 response)**

ATN 053

Post-traumatic Stress Disorder and Risk Behavior in HIV-Positive Female Adolescents

- Qualitative study by interview of HIV-positive female adolescents who have experienced physical and/or sexual abuse
- Goal is to understand the experience of abuse and any relationship to sexual risk behavior in order to inform an intervention that will be conducted later
- For 18-24 y/o females with behaviorally-acquired HIV after the age of 9 years (through heterosexual intercourse or injection drug use), who report a history of sexual and/or physical abuse prior to age 18, and who have engaged in vaginal or anal intercourse

ATN 056

Pharmacokinetics of Once Daily Antiretroviral Therapy Regimens Containing Tenofovir and Atazanavir/Ritonavir in Adolescents and Young Adults

- For 18-24 y/o on stable combination antiretroviral regimen that includes tenofovir plus atazanavir/ritonavir and at least one other active antiretroviral drug
- Pharmacokinetics of tenofovir in combination with atazanavir/ritonavir in HIV-infected adolescents and young adults on stable combination ART
- Estimates the adequacy of using the “standard adult dose” for adolescents and young adults

Other Current ATN Protocols

- 004 Healthy choices
- 020 Identity development in G/B/Q young males
- 024, 025 concerning Hepatitis B vaccine
- 032 “Safer Sex” social network intervention
- 045, 046, 047 concerning life skills, disclosure of diagnosis, and immunologic memory in perinatal adolescents
- 068 Adjustment to newly diagnosed HIV infection
- 061 Early HAART and then de-intensification
- 063 Vitamin D supplementation for Tenofovir
- 071 Neurocognitive functioning

CONNECT



PROTECT[®]

**Youth
Community Resource Directory
Miami-Dade County
2005**

ATN 016

CONNECT TO PROTECT (C2P):
Partnership for Youth Prevention Interventions

**Major effort for community coalitions as
capacity-building around HIV vaccine**

- National Institutes of Health
- National Institute of Child Health and Human Development's *Adolescent Trials Network* Project
- Johns Hopkins University
- University of Alabama
- DePaul University

Overview of what C2P is doing in each ATN city

Phase I (016a)

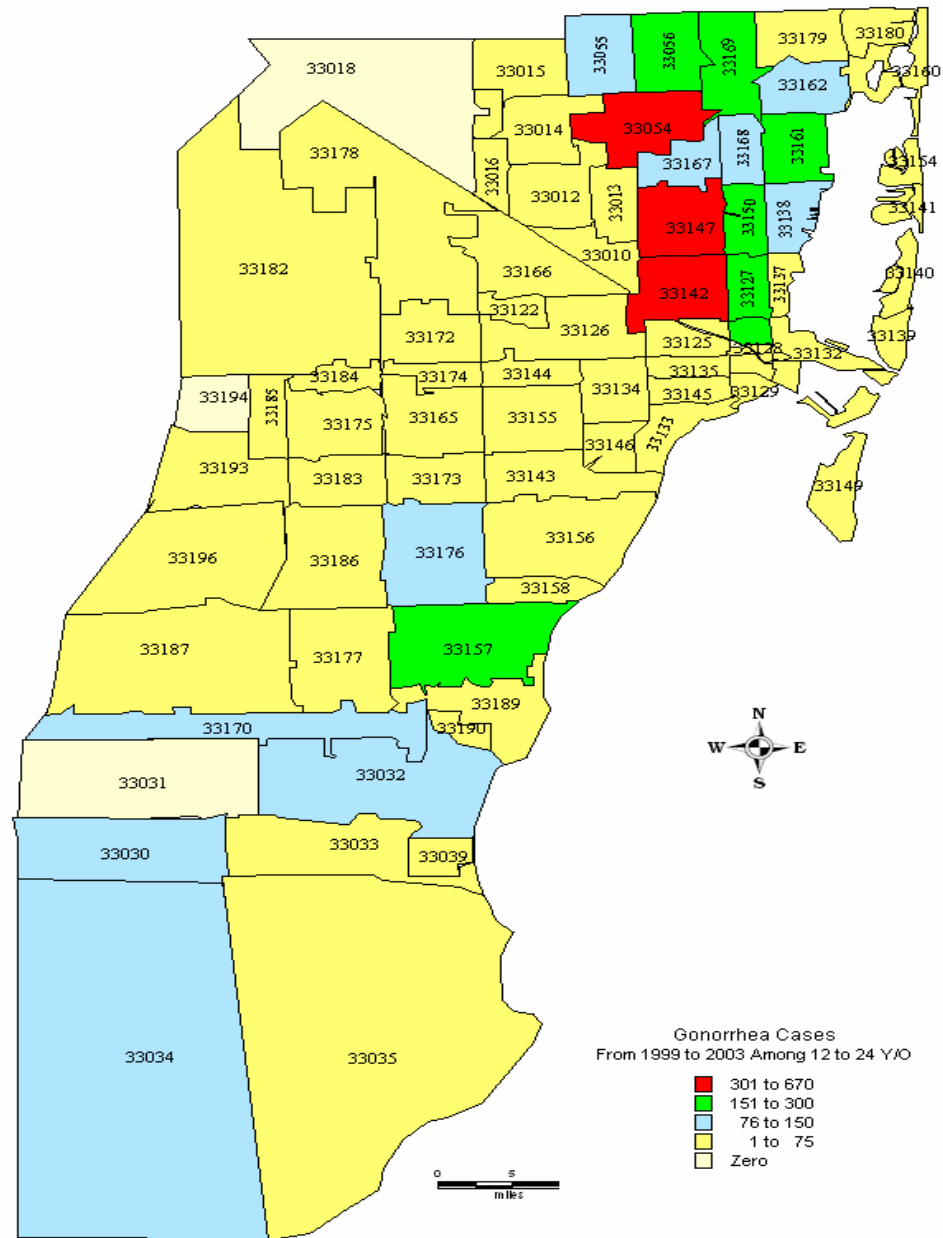
- Gather and map epidemiologic data on youth-specific HIV and STI rates.
- Gather and map epidemiologic data on selected behavioral risk factors among youth.
- Gather and map information about community resources focused on youth and HIV/STIs, as well as other sexual health issues.

Overview of what C2P is doing in each ATN city

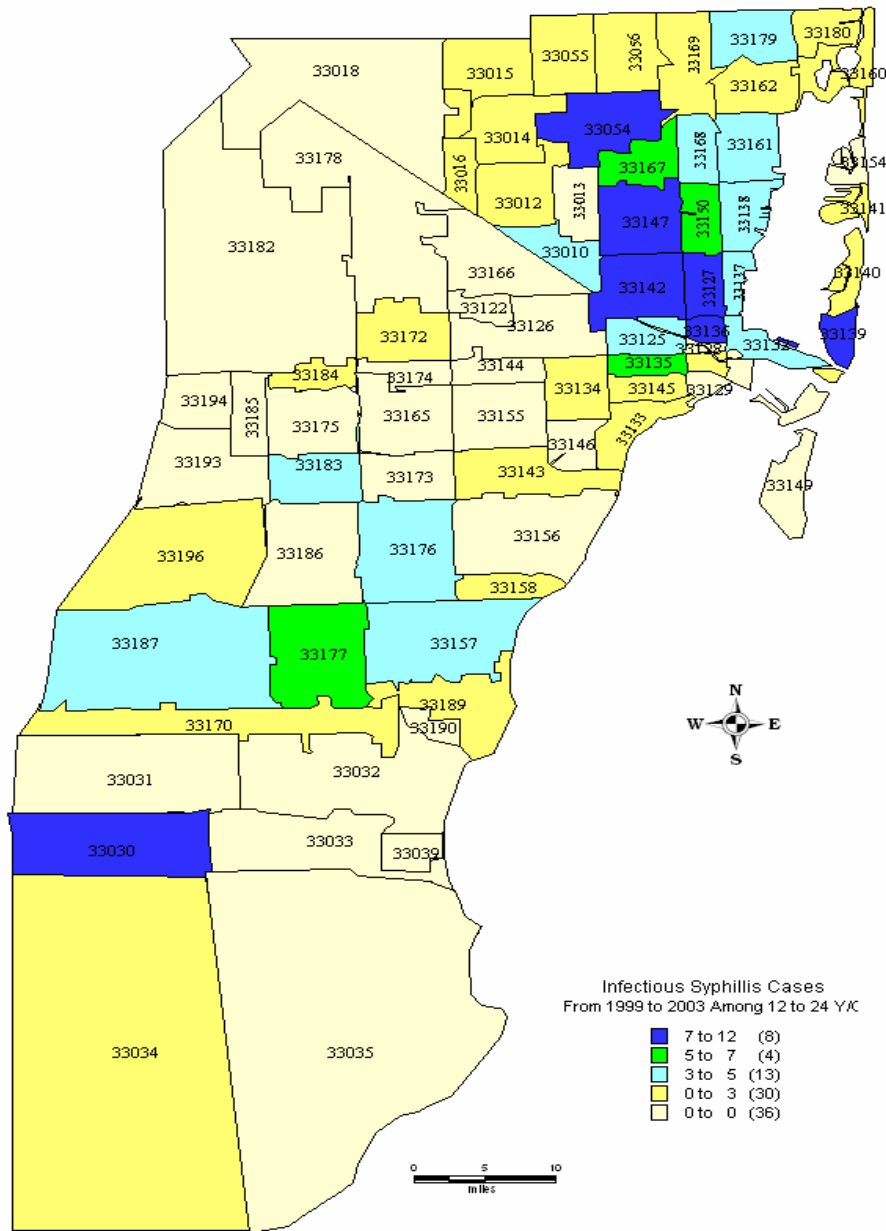
(continued)

- Create a directory of these youth community resources.
- Establish partnerships with community agencies who work with at-risk youth.
- Identify communities' prevention priorities, and then select interventions for **Phase II (016b)**.
- Collect feasibility data for **Phase II (016b)**.

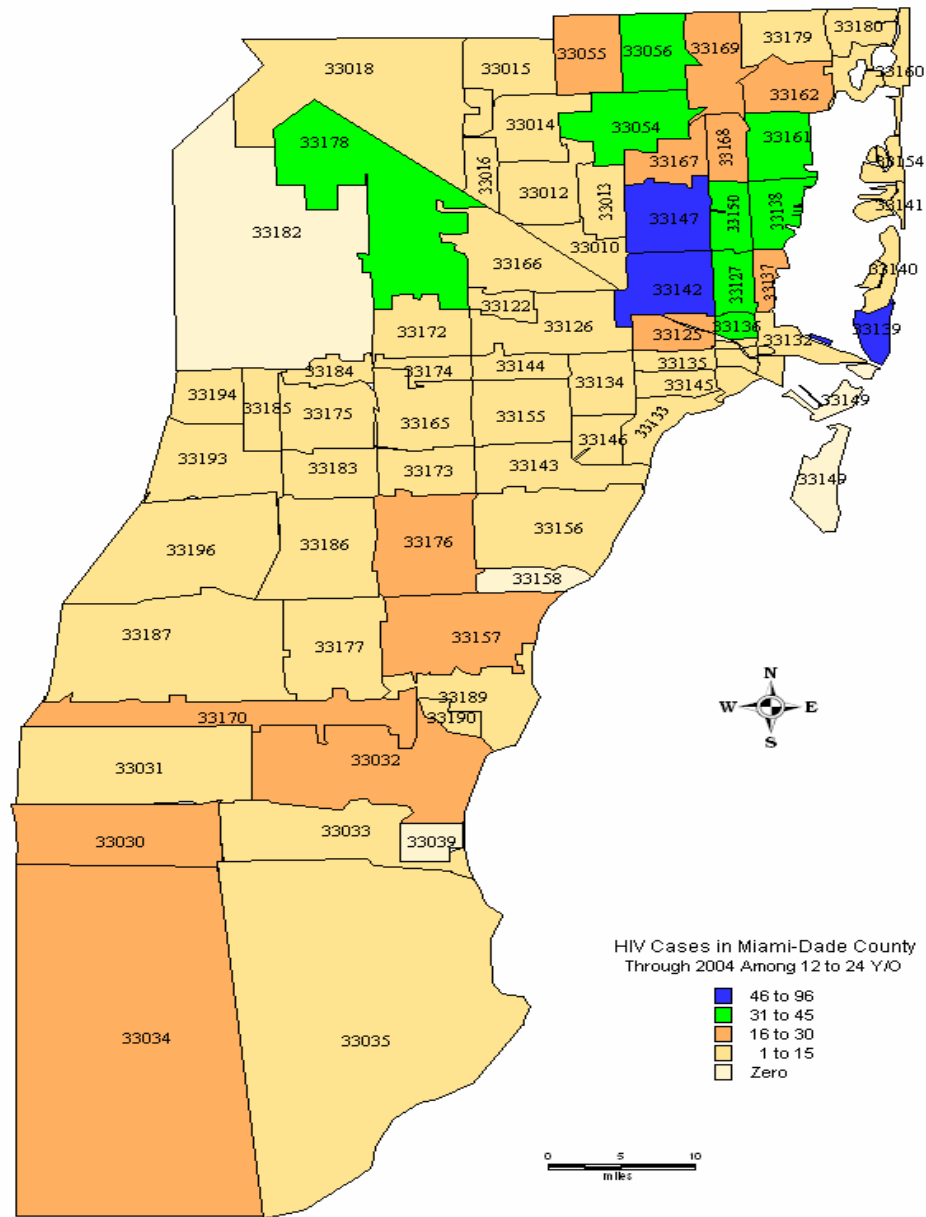
Miami-Dade County Gonorrhea Cases From 1999 to 2003 Among 12 to 24 Y/O by Zip Code
 According to Miami-Dade County Health Department



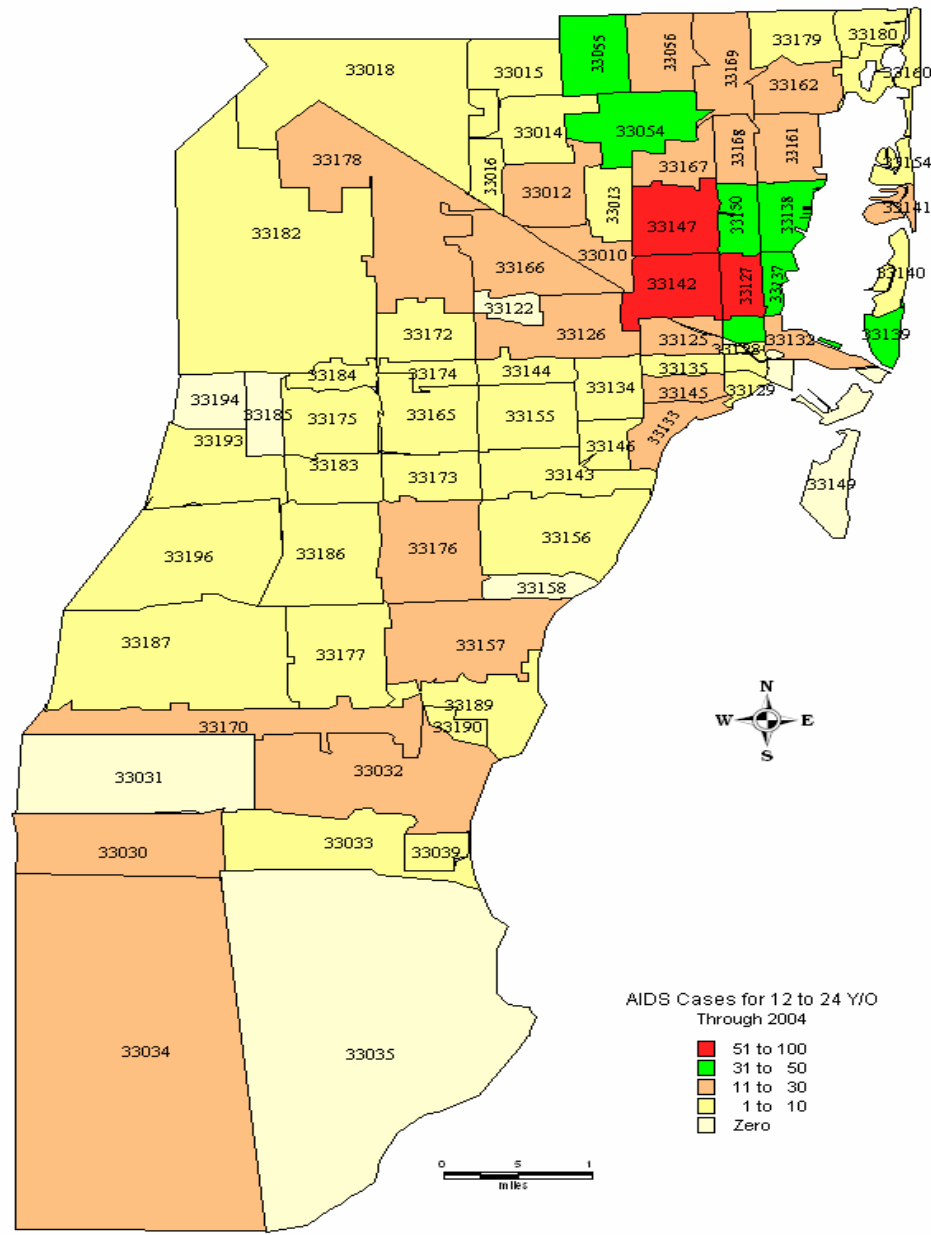
Miami-Dade County Infectious Syphilis Cases From 1999 to 2003 Among 12 to 24 Y/O
by Zip Code According to Miami-Dade County Health Department



Miami-Dade County HIV Cases Through 2004 Among 12 to 24 Y/O by Zip Code
 According to Miami-Dade County Health Department



Miami-Dade County AIDS Cases Among 12 to 24 Y/O Through 2004 by Zip code
 According to Miami-Dade County Health Department



C2P Phase II (016b)

- Do five half-day Working Group meetings
- Perform community assessments
- Identify structural changes needed
- Select interview venues
- Do venue interviews and serosurvey work with youth
- Continue to evaluate data

C2P Phase III (040,041)

- Continue Working Groups
- Do CDC's *PROMISE Intervention* with young females in the local community (other cities targeting young MSMs with *MPOWERment*)
- Begin structural change work with community partners
- Maintain partnerships and monitor progress
- Eventually perform HIV vaccine trials
- Protocols underway

Structural Change Tracks

- Miami-Dade County Public Schools
- Youth Correctional Facilities in Miami-Dade – DJJ & JAC, plus Bay Point School
- Private businesses located in at-risk neighborhoods

Miami-Dade County Public Schools

- Referring students to community health care providers
- Linking students to community prevention programs

Private Businesses

- Education of proprietors around sexual health (ongoing)
- Televised Public Service Announcements
– PSAs
- Condom distribution routes (being done)

Proposed SCOs Targeting Youth Correctional Facilities

By December 2008, the **Department of Corrections (DOC)** will have implemented a policy that all youth being processed at **Juvenile Assessment Center (JAC)** receive HIV/STD prevention information, including where to receive free counseling and testing.

By December 2008, the **Department of Corrections (DOC)** will have implemented a policy that all youth being held in **Department of Juvenile Justice (DJJ)** facilities receive HIV/STD prevention information, including where to receive free counseling and testing.

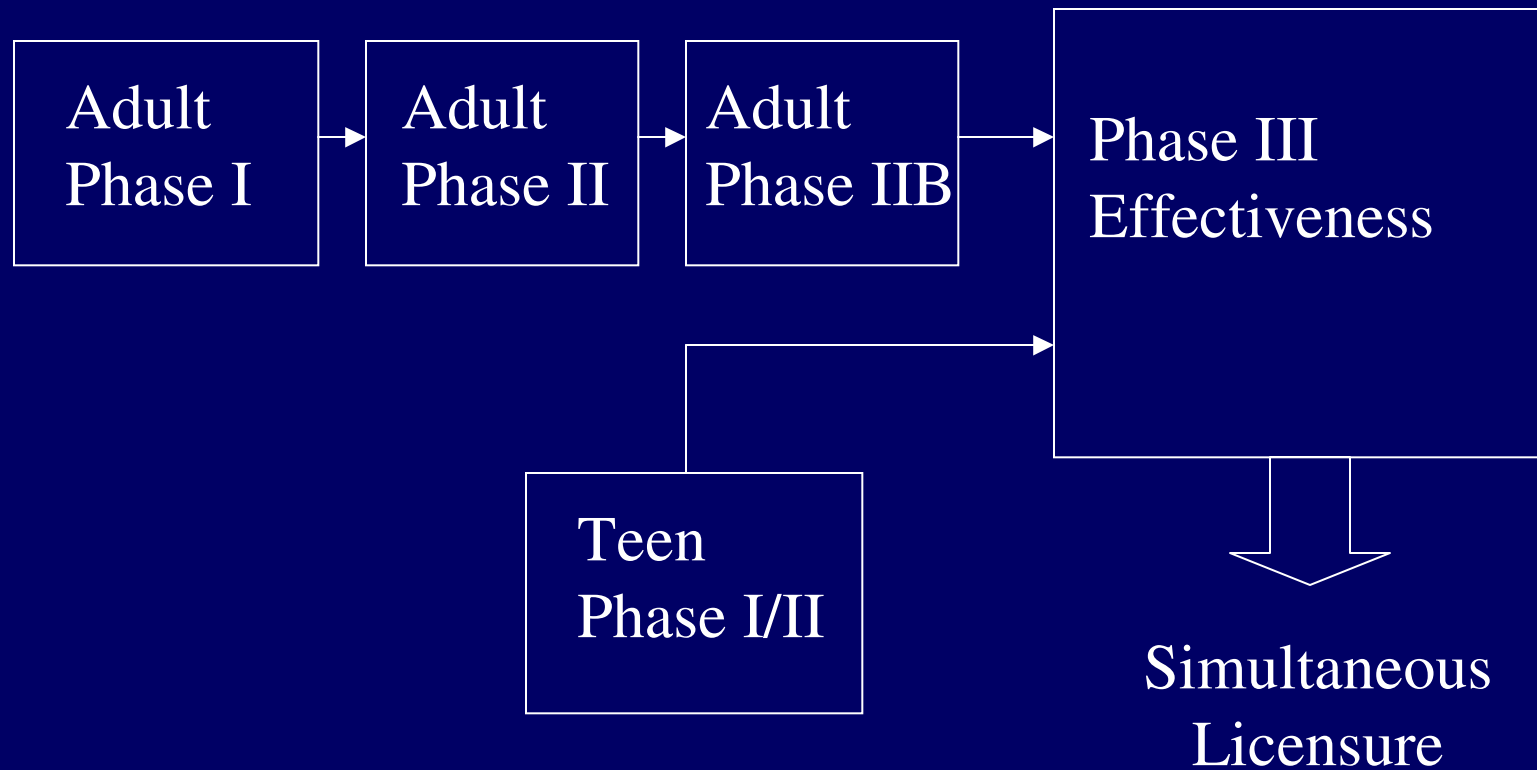
Proposed SCO's Targeting Youth Correctional Facilities

By December 2010, the **Department of Corrections (DOC)** will have implemented a policy that all youth being held at the DJJ receive mandatory on-site HIV/STI counseling and testing opportunity.

ATN-2 Objectives

- Community capacity for HIV vaccine trials for youth
- Enrollment of minors into approved HIV vaccine trials (prevention and therapeutic)
- Youth representation in microbicide trials for prevention of HIV and other STDs
- Other “cutting edge” protocols initially for adults but potentially helpful for youth

Adolescent Research Strategy



ATN-2 Upcoming Protocols

- 039 HIV-infected transgender youth project
- 054 Factors associated with HIV testing and disclosure
- 060 Transitional care for HIV + adolescents
- 064 HPV vaccine
- 065 Treatment readiness measurement tool
- 067 Identifying undiagnosed HIV infection in community
- 069 Reduction of alcohol and marijuana use
- 070 Sexual health intervention for young MSMs
- 073 Assistance with adherence to treatment
- Other yet-to-be-determined PK drug studies, microbicide trials, and vaccine capacity building

Pediatric AIDS Clinical Trials Group IMPAACT, PHACS

- Mostly includes subjects with mother-to-child vertical transmission
- Teenagers often included in general study
- Specific “adolescent initiative” began 1999
- Will orient more towards international work

Research concerning HIV that involves teenagers-

- a) Requires informed consent.
- b) Utilizes special strategies to encourage enrollment and adherence
- c) with study protocols.
- d) Can be exciting and gratifying.
- e) Can be frustrating and tiring.
- f) All of the above.
- g) I'm sorry, I did not learn.

Pediatric ACTG

- 219c Late outcomes
- 245, 390 Combination therapy with advanced disease
- 381 Immune reconstitution
- 1015 Treatment intensification and/or cycling
- 1034 Therapeutic drug monitoring
- 1036 Directly observed therapy
- 1042 Adherence
- 1045 Metabolic outcomes
- 1065 Effectiveness of meningococcal vaccine
- Multiple pregnancy, pharmacokinetic, and vaccination trials

ATN Resources

www.atnonline.org

Adolescent Trials Network website

Citations for:

REACH publications (from beginning)

ATN publications (since inception)

More to come!