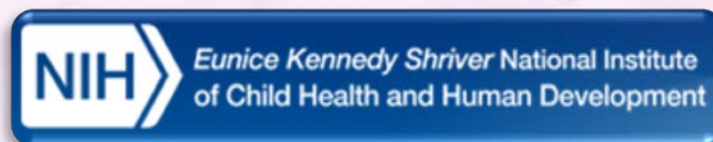
A microscopic image of liver tissue, showing various cells and structures in shades of purple and blue. The image is used as a background for the slide.

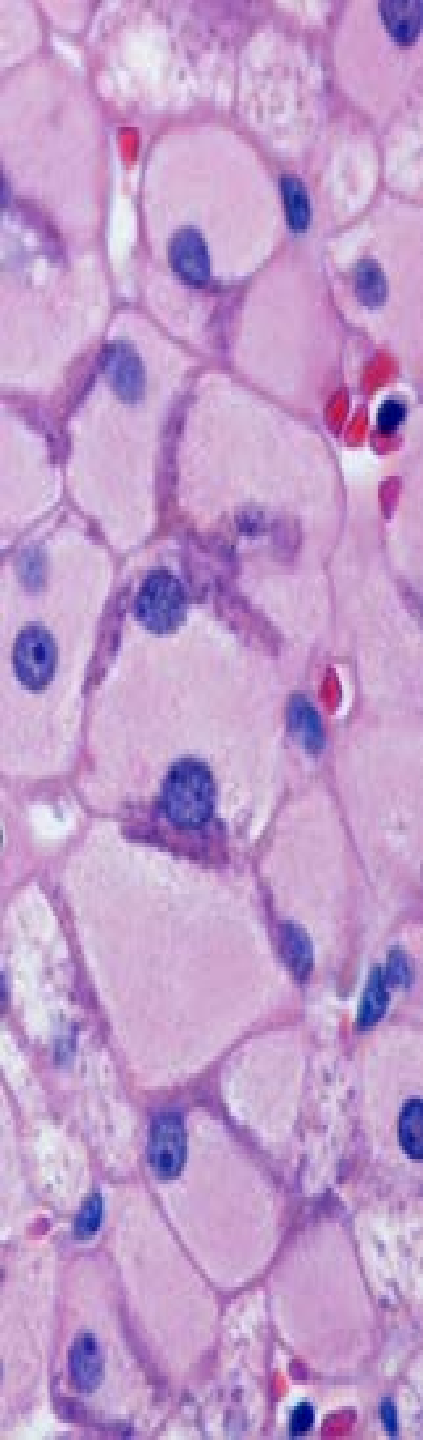
# Prevalence of and Progression to Abnormal Non-Invasive Markers of Liver Disease (APRI and FIB-4) among US HIV-infected Youth

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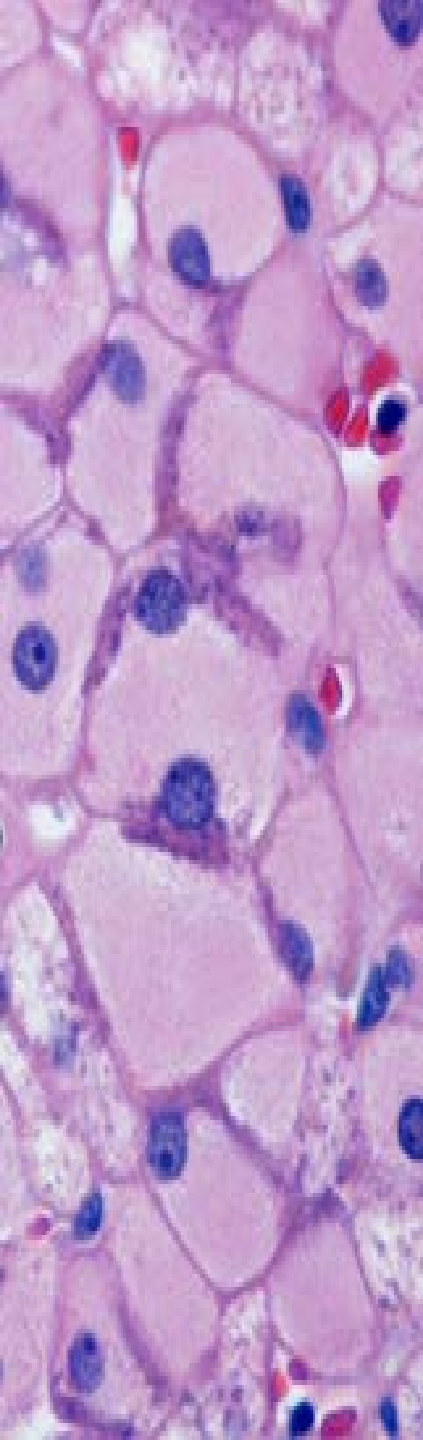
Maternal and Pediatric Infectious Disease Branch





# Background

- HIV infection may contribute to liver disease, *even without* viral hepatitis co-infection
- Potential for ART to also contribute to liver problems
- Non-invasive surrogate markers of liver fibrosis (FIB-4 and APRI) have been investigated and validated in HIV/HCV co-infected adults but have been less studied in children



# Background

- The **FIB-4** index includes age, AST, ALT and platelet count:

$$\text{FIB-4} = \frac{\text{age} \times \text{AST}}{\text{platelet count} \times \sqrt{\text{ALT}}}$$

>1.5 → mild/moderate fibrosis  
>3.25 → advanced fibrosis

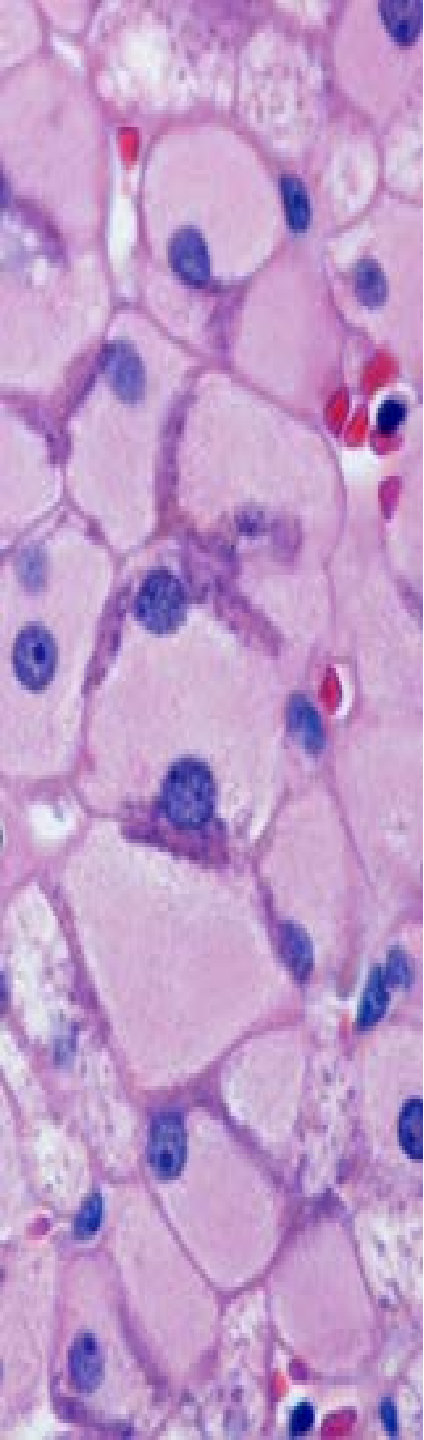
- The **APRI** is the AST-to-platelet ratio index and includes AST, its upper limit of normal and platelet count:

$$\text{APRI} = \frac{\text{AST} / \text{AST ULN}}{\text{platelet count}} \times 100$$

>0.5 → mild/moderate fibrosis  
>1.5 → advanced fibrosis

# Objectives

- To determine how FIB-4 and APRI measures compare between HIV-infected and uninfected youth aged 15-20 years
- Among HIV-infected youth, to determine what are the factors that influence differences in measures
- Characterize how these measures change over time in HIV infected individuals



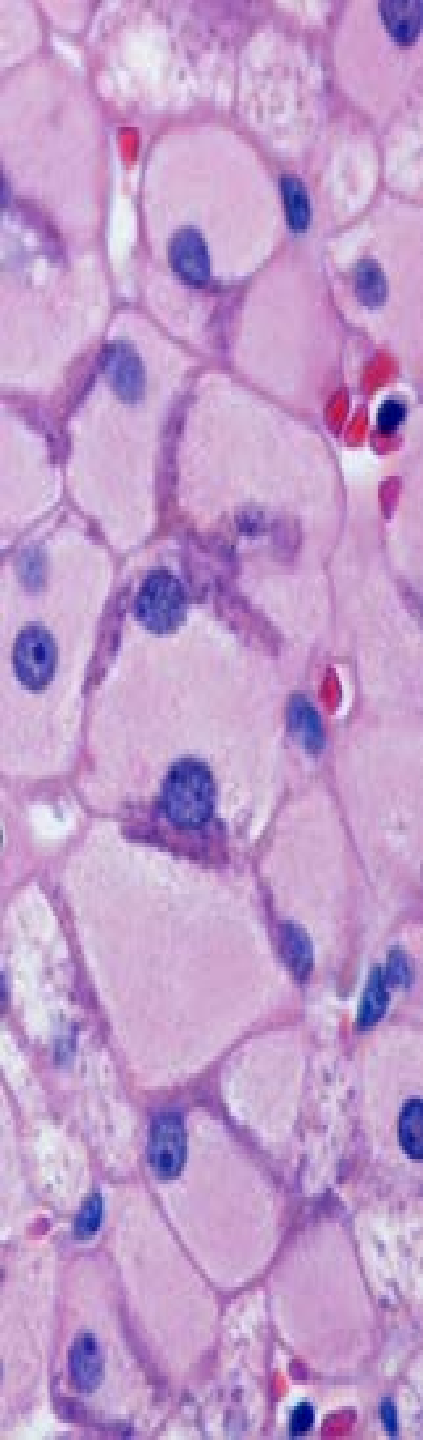


# Methods

- **Reaching for Excellence in Adolescent Care and Health (REACH)** – a prospective observational HIV+ and uninfected youth cohort
  - Sequential behavioral & biomedical assessments and specimen collections from 3/96 – 11/99
  - Non-perinatal HIV only
- **PACTG 219/219C** – prospective multi-center cohort study of HIV and its treatment in infected infants, children and adolescents
  - Serial biomedical assessments from 4/93 – 5/07
  - Perinatal and Non-perinatal HIV
- FIB-4 and APRI measures were evaluated in HIV-**mono-infected** and HIV-**uninfected youth** ages 15-20 years

# Methods

- FIB-4 and APRI measures were compared between HIV-infected and uninfected youth based on single visit
- Within HIV-infected youth with  $\geq 2$  visits
  - Among those with low baseline scores, we estimated and compared incidence rates of progression to higher scores during follow-up
  - Using repeated measures mixed effect linear regression modeling, we estimated longitudinal trends in log transformed scores, adjusting for age, gender, exposure category, and BMI z-score



## Participant Characteristics by Cohort

Characteristic	Total (N=1785)	REACH: HIV uninfected (N=173)	REACH: HIV- infected (Beh) (N=319)	219/C: HIV- infected (Beh) (N=251)	219/C HIV- infected (Peri) (N=1042)
Age at LFT (median, years)	15.6	17.6	17.9	17.9	15.2
Follow up time (median, years)*	2.0	1.4	2.0	1.9	2.1
Sex					
Male	730 41%	38 22%	77 24%	105 42%	510 49%
Female	1,055 59%	135 78%	242 76%	146 58%	532 51%
Race/Ethnicity					
White Non-Hispanic	227 13%	12 7%	10 3%	57 23%	148 14%
Black Non-Hispanic	1,019 57%	106 61%	231 72%	130 52%	552 53%
Other Non-Hispanic	50 3%	12 7%	19 6%	6 2%	13 1%
Hispanic	488 27%	43 25%	58 18%	58 23%	329 32%
Missing	1 0%	0 0%	1 0%	0 0%	0 0%
BMI-Z score (mean)	0.44	0.66	0.74	0.39	0.32
ARV regimen					
Not on ART	396 25%		161 50%	97 39%	138 13%
Non-HAART ART	281 17%		82 26%	28 11%	171 16%
HAART (non-PI)	187 12%		16 5%	60 24%	111 11%
HAART (PI)	748 46%		60 19%	66 26%	622 60%
HIV RNA (median, copies/mL)	2,033		6,600	1,587	1,000
CD4 count (median, cells/μL)	505		487	474	520

\* Among those with at least 2 sequential LFTs

# Cross-Sectional Analysis

## Distribution of Non-Invasive Markers of Liver Disease by Clinical Thresholds

Variable	FIB-4			APRI			Total
	<=1.45	1.45-<3.25	>=3.25	<=0.5	0.5-<=1.5	>1.5	
<b>HIV Status</b>	<i>P* = 0.51</i>			<i>P* = 0.002</i>			
HIV Uninfected	171 99%	2 1%	0 0%	167 97%	4 2%	2 1%	173
HIV Infected	1574 98%	29 2%	9 1%	1409 87%	168 10%	35 2%	1612
<b>Total</b>	<b>1745 98%</b>	<b>31 2%</b>	<b>9 1%</b>	<b>1576 88%</b>	<b>172 10%</b>	<b>37 2%</b>	<b>1785</b>
<b>Cohort</b>	<i>P* = 0.29</i>			<i>P* &lt; 0.001</i>			
REACH HIV Uninfected	171 99%	2 1%	0 0%	167 97%	4 2%	2 1%	173
REACH Behaviorally Infected	317 99%	1 0%	1 0%	298 93%	19 6%	2 1%	319
219/C Behaviorally Infected	244 97%	6 2%	1 0%	212 84%	32 13%	7 3%	251
219/C Perinatally Infected	1013 97%	22 2%	7 1%	899 86%	117 11%	26 2%	1042
<b>Total</b>	<b>1745 98%</b>	<b>31 2%</b>	<b>9 1%</b>	<b>1576 88%</b>	<b>172 10%</b>	<b>37 2%</b>	<b>1785</b>

\* Chi-Square Test

- Univariate analysis for APRI>0.5: males, HIV+, low BMI Z score, low CD4, detectable VL & lack of ART [all p<0.002]
- Adjusted models: For the entire sample, being **HIV-infected** and **male**, and having a **low BMI Z score** independently predicted an **APRI > 0.5** (all p<0.02); among HIV-infected participants, **male sex**, **low CD4 (<350)** and **detectable VL (>400)** were independent predictors of **APRI > 0.5** (all p<0.02)



# Longitudinal Analysis

## Rates of APRI and FIB-4 Progression in ALL HIV-infected Youth During Follow-Up

Marker Threshold	Fibrosis Severity	Total At-Risk	Number with Progression	Percent	Person Years	Incidence per 100 PY (95% CI)
APRI >0.5	mild/mod	1116	176	16%	2347	7.5 (6.5, 8.7)
APRI >1.5	advanced	1256	39	3%	2823	1.4 (1.0, 1.9)
FIB-4 >1.5	mild/mod	1257	46	4%	2822	1.6 (1.2, 2.2)
FIB-4 >2.5	mild/mod	1265	18	1%	2863	0.6 (0.4, 1.0)
FIB-4 >3.25	advanced	1266	9	1%	2871	0.3 (0.2, 0.6)

- On evaluation of progression rates of APRI and FIB-4 by cohort (subgroup), there were no statistically significant associations found

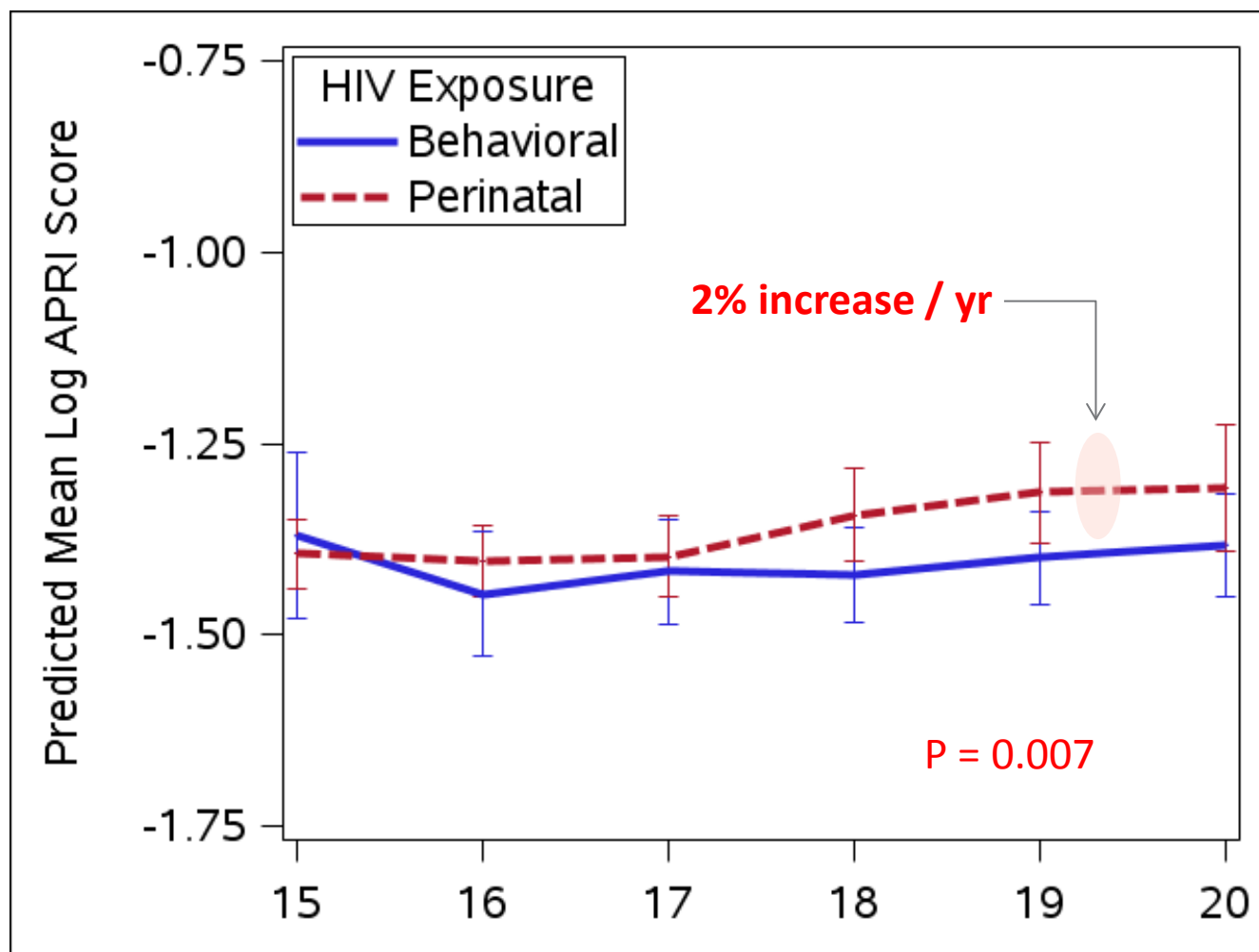
# Longitudinal Analysis (cont'd)

## Rates of APRI and FIB-4 Progression in HIV-infected Youth by **Baseline CD4 Count**

Marker Threshold	CD4 Absolute Count (cells/ $\mu$ L)	Total At-Risk	Number with Progression	Percent	Person Years	Incidence per 100 PY (95% CI)	Incidence Rate Ratio (95% CI)	P-value
APRI >0.5	<350	275	71	26%	571	12.4 ( 9.8, 15.7)	<b>2.14</b> ( 1.58, 2.90)	<0.001
	350 or greater	823	101	12%	1742	5.8 ( 4.8, 7.0)	Reference	- - -
APRI >1.5	<350	344	23	7%	790	2.9 ( 1.9, 4.4)	<b>3.62</b> ( 1.91, 6.85)	<0.001
	350 or greater	891	16	2%	1991	0.8 ( 0.5, 1.3)	Reference	- - -
FIB-4 >1.5	<350	348	28	8%	797	3.5 ( 2.4, 5.1)	<b>3.87</b> ( 2.14, 7.00)	<0.001
	350 or greater	888	18	2%	1984	0.9 ( 0.6, 1.4)	Reference	- - -
FIB-4 >2.5	<350	350	14	4%	814	1.7 ( 1.0, 2.9)	<b>8.64</b> ( 2.84, 26.24)	<0.001
	350 or greater	894	4	0%	2007	0.2 ( 0.1, 0.5)	Reference	- - -
FIB-4 >3.25	<350	350	6	2%	819	0.7 ( 0.3, 1.6)	<b>7.35</b> ( 1.48, 36.42)	0.014
	350 or greater	894	2	0%	2007	0.1 ( 0.0, 0.4)	Reference	- - -

- On evaluation of progression rates of APRI and FIB-4 by **Baseline HIV VL**, there were no statistically significant associations found

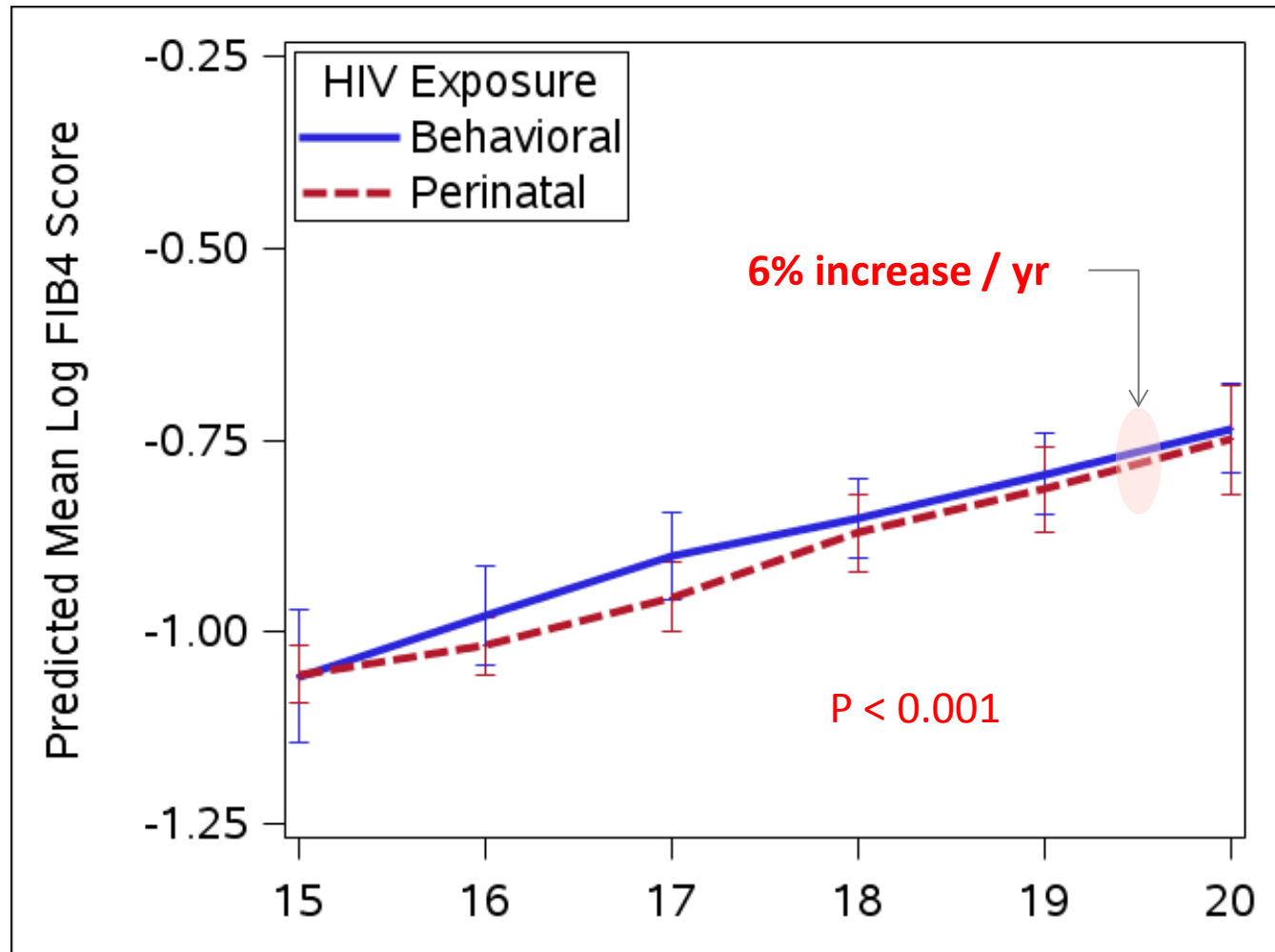
# Predicted Mean Log APRI Score



**Perinatally infected subjects** had significant **2% increase in APRI per year**

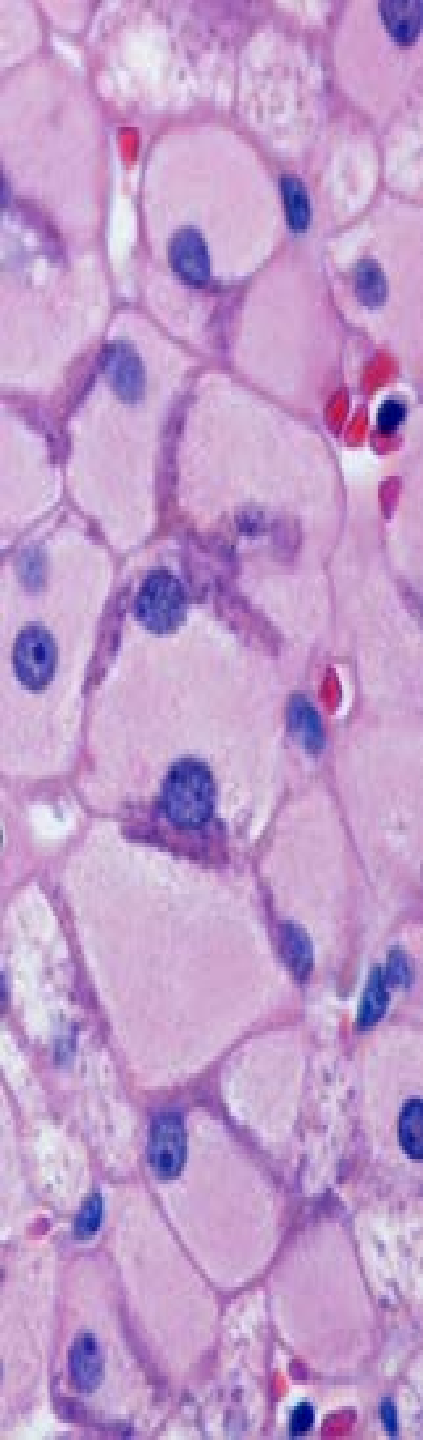
Male gender, CD4 < 350, VL > 400 and those not on ART  
had consistently higher APRI scores over time (p<0.001)

# Predicted Mean Log FIB-4 Score



**All HIV-infected participants** had significant **6% increase in FIB-4 per year**

Male gender, CD4 < 350, VL > 400 and those not on ART had consistently higher FIB-4 scores over time (p<0.001)

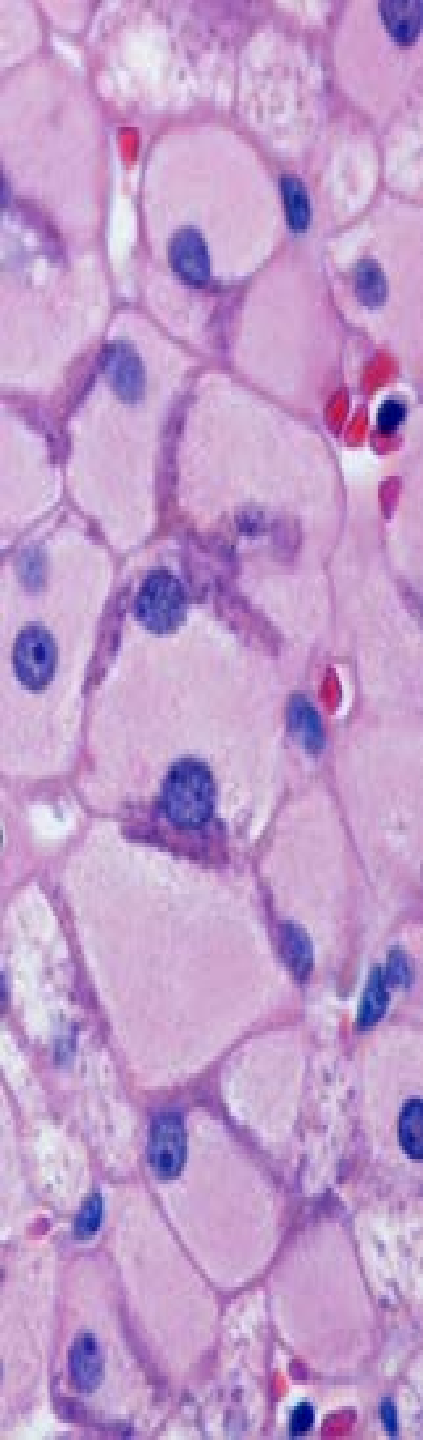


# Limitations

- No liver biopsy available
- FIB-4 experience limited to adults
- Cohort and age effects of data abstraction adjusted for but may still have residual unmeasured confounding

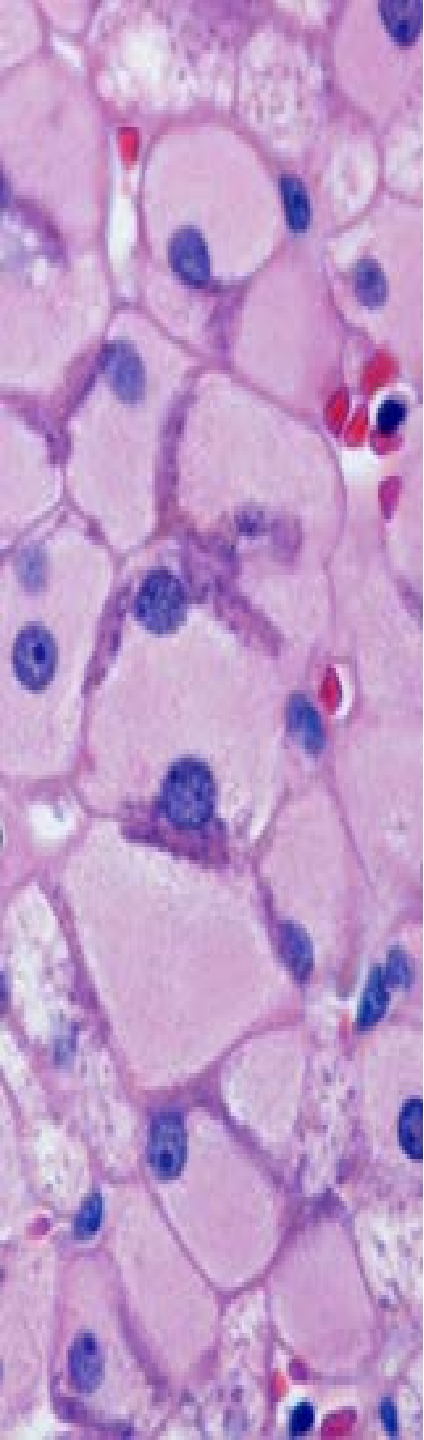
# Conclusions

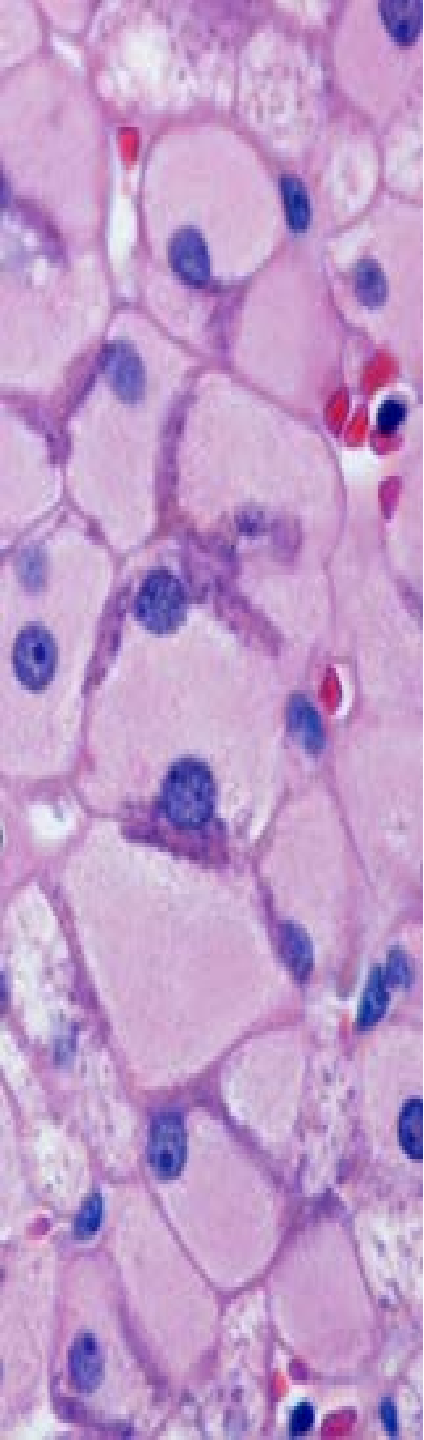
- The mean APRI and FIB-4 scores were higher among HIV-infected youth and remained so after adjustments
- Among HIV infected youth, progression to values suggesting subclinical fibrosis was common
  - IRs for APRI comparable to pediatric studies of younger children
  - Lower baseline CD4 counts predictive 2-8 x higher IRR (APRI & FIB-4)



# Conclusions

- Differences in score trajectories over time
  - APRI significantly increased by **2%** per year among perinatally infected only
  - FIB-4 significantly increased by **6%** per year among all HIV infected
  - Male gender and features of poor HIV control (low CD4, detectable VL , not on ART) had consistently higher APRI and FIB-4 scores over time





# Implications

- Validation analysis between FIB-4 and APRI for this age group using clinical disease staging and progression is underway
- More research needed on non-invasive markers in youth, particularly aging up perinatally infected adolescents
  - Liver stiffness assessment
  - Novel biochemical markers
  - Validation with biopsy



# Acknowledgments

- Funding: **NICHD** (IMPAACT, PHACS, ATN, REACH), **NIAID** (IMPAACT, PHACS)
- Collaborators
  - REACH
    - **Craig Wilson – PI**
  - IMPAACT
    - **Brooks Jackson - PI**
  - NICHD
    - **Rohan Hazra**
    - **Lynne Mofenson**
  - Harvard School of Public Health
    - **PHACS Leadership**
  - Quest Labs
    - **Bill Meyer**

