ATN 110: An HIV PrEP Demonstration Project and Phase II Safety Study for Young Men who Have Sex with Men in the United States

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Background

- Blinded and open label studies among MSM support the efficacy of TDF/FTC for HIV prevention
- In the US, gay/bisexual/MSM ages 13-24 are hardest hit by HIV epidemic
  - 18-24 year old MSM not well-represented in PrEP safety or efficacy studies in US
  - No PrEP data available on adolescent MSM to date
- Additional safety and behavioral data, as well as implementation data, in youth are needed to support a PrEP indication
- Paired PrEP studies:
  - ATN 110 (ages 18-22); data presented here
  - ATN 113 (ages 15-17); data expected 2016
Primary Objectives

• To provide additional safety data regarding FTC/TDF (Truvada®) use among HIV-uninfected YMSM, ages 18-22.

• To examine acceptability, patterns of use, rates of adherence and measured levels of drug exposure when YMSM are provided open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from prior studies.

• To examine patterns of sexual behavior when YMSM are provided a behavioral intervention as well as open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from prior studies.
Inclusion Criteria

• Age 18-22
• Self-reports evidence of high risk for acquiring HIV, including at least one of the following in the last 6 months:
  – Condomless anal intercourse with an HIV-infected male partner or a male partner of unknown HIV status;
  – Anal intercourse with 3 or more male sex partners;
  – Exchange of money, gifts, shelter, or drugs for anal sex with a male partner;
  – Sex with a male partner and has had a STI;
  – Sexual partner of an HIV-infected male with whom condoms were not consistently used; or
  – At least one episode of anal intercourse where the condom broke or slipped off
• Tests HIV antibody negative at time of screening
Study Flow

1. Pre-Screening Survey (venue-based or online)
   - Ineligible or refuse survey

2. In-person screening visit (IC and screening labs)
   - Ineligible based on labs

3. Baseline Visit (review labs & VL)
   - Behavioral Intervention (3MV or PCC)

4. Week 0 – Dispense PrEP

5. Follow-up Visits (weeks 4, 8, 12, 24, 36, 48)
   - HIV Seropositive Visits
   - Extension Phase Visits

6. Week 48: Evaluate for EPH
ATN 110 Study Sites
Consort Diagram

- Approached for Pre-screening (N = 2,186)
  - Refused pre-screening: 921
  - Pre-screened ineligible: 865

- Pre-screened eligible (n=400)
  - Refused study participation: 123

- In-person Screening Visit (n=277)
  - HIV-positive: 11 (4.4%)
  - No show for visit: 27
  - Other reasons: 39

- 200 Enrolled

- 99 Assigned to 3MV
  - 33 Pre-DC
    - LTFU (19)
    - W/D consent (7)
    - Moved (3)
    - VL detect (1)

- 101 Assigned to PCC
  - 25 Pre-DC
    - LTFU (16)
    - W/D consent (3)
    - Moved (4)
    - VL detect (1)

Other reasons:
- Unable to locate (7)
- Proteinuria (5)
- ≥ gr2 hepatobiliary (5)
- Other chronic disease (3)
- Acute Hep B (1)
- Bone fracture (1)
Baseline Demographics

- Mean age: 20.18
- Sexual Identity:
  - Gay: 77.8%
  - Bisexual: 13.7%
- Highest grade completed:
  - High School: 33.8%
  - Some college: 45.5%
- Not currently working: 30.1%
- Ever kicked out: 17.2%
- Ever paid for sex: 28.6%
- Partners in past month: 5
- Condomless sex: 81%
- CRAI w/last partner: 58%
- Any positive STI test: 22%
Safety

• 25 discontinued PrEP but stayed on study
  – Primarily personal choice/decision or side effects (predominantly GI symptoms)

• 3 adverse events were deemed related to study drug
  – Grade 3 nausea
  – Grade 3 weight loss
  – Grade 3 headache

• DXA data currently being analyzed (collected at baseline, 24 and 48 weeks on all participants)
HIV Incidence

- 4 seroconversions through week 48
- HIV incidence = 3.29 per 100 person-years
- No drug resistance found
STI Diagnoses

- Rectal Gonorrhea
- Rectal Chlamydia
- Syphilis
- Any STI

Baseline vs. Week 24 vs. Week 48
Sexual Behavior

Baseline

WK 4

WK 8

WK 12

WK 24

WK 36

WK 48

Male partners

CRAI last partner

Condom broke RAI

Referred for PEP
Adherence: TFV-DP (fmol/punch) via DBS and Dosing Estimates

- Green: >700 (4 or more days)
- Yellow: 350-699 (2-3 days)
- Orange: <350 (<2 days)
- Red: BLQ
Adherence: Median TFV-DP by Race/Ethnicity
Adherence and Sexual Behavior

• Participants that reported engaging in condomless sex had consistently higher levels of TFV-DP ($p=0.005$)
  – Remained consistent over course of the study.

• Similarly, participants who reported CRAI with last partner demonstrated higher TFV-DP levels over course of the study
  – Trend not statistically significant
Conclusions

• ATN 110 successfully identified and engaged YMSM who would be appropriate for PrEP.
  – Previously undiagnosed HIV+ youth were linked to immediate care at youth-focused sites

• PrEP was well tolerated with minimal adverse events

• STI diagnoses were high at baseline and remained constant over time

• HIV incidence rate was high compared to PrEP arms in other open label trials
  – Given high number of incident STIs, would likely be much higher in the absence of PrEP
  – Those that seroconverted had undetectable drug levels
Conclusions

• Participants who reported condomless sex had higher levels of TFV-DP
  – Thus, those that are most susceptible to HIV infection may also be most likely to be adherent

• Adherence was good overall, but varied by race/ethnicity
  – Consistent with recent research highlighting lack of exposure to HIV prevention interventions by BYMSM
  – CALL TO ACTION for more in-depth understanding of the historical, societal, behavioral and attitudinal barriers to PrEP access and adherence among those most impacted in the US – black/African-American young MSM

• Adherence decreased for all participants as study visits decreased in frequency, regardless of race/ethnicity
  – Youth may need enhanced visit schedules or more frequent interactions (in-person or via mobile technology)


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Introduction

• In the U.S., new HIV infection rates are highest among adolescent young men who have sex with men (YMSM)\(^1\)
• PrEP with Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) taken daily is highly effective in adult MSM\(^2\)
• Bone loss is a primary toxicity of TDF when used for either HIV treatment\(^3\) or PrEP\(^4\); infants exposed to TDF in utero have lower BMC\(^5\)
• Peak bone mass is typically achieved in early adulthood and is an important predictor of fracture risk later in life.
• Thus, there is heightened concern about the use of TDF for HIV prevention in adolescents prior to attainment of peak bone mass.

Peak bone mass is achieved during early adulthood
Adolescent Trials Network (ATN) 110

- Open-label PrEP demonstration study to examine patterns of use and adherence and expand safety data among YMSM
- Enrolled 200 at-risk HIV-negative YMSM, ages 18-22 years, at 12 urban sites in U.S.
- 48-week study
- All participants offered PrEP (daily TDF/FTC) plus behavioral risk reduction interventions, sexual health and adherence counseling, STI testing/treatment, condoms
- Primary results presented at IAS 2015 (Hosek et al.)
• DXA scans of hip, spine, and whole body at baseline, weeks 24 and 48; analyzed centrally
• Drug levels measured at baseline and weeks 4, 8, 12, 24, 36, 48
• Dosing frequency extrapolated from tenofovir diphosphate (TFV-DP) concentrations in red blood cells from dried blood spots; $T_{1/2} \approx 17$ days
• Bone results in seroconverters (N=4) censored beginning with date of seroconversion
• Hip results in one participant censored due to interference from implants
Baseline Data (N=200)

- Median age: 20 years (range 18 - 22)
- Median BMI: 23.6 kg/m² (range 17.3 - 58.9)
- Black/African American: 46.5%
- Latino: 26.5%
- Decided to take PrEP at outset: 98.3%
**Low BMD Z-Scores\(^1\) at Baseline**

<table>
<thead>
<tr>
<th>Region</th>
<th>Median (range)</th>
<th>% ≤ -2.0(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>-0.50 (-3.5 to +2.6)</td>
<td>8.1%</td>
</tr>
<tr>
<td>Hip</td>
<td>-0.34 (-3.0 to +2.9)</td>
<td>6.1%</td>
</tr>
<tr>
<td>Total body</td>
<td>-0.40 (-3.0 to +3.0)</td>
<td>3.7%</td>
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Low bone mass previously reported in HIV-negative at-risk men in other PrEP and cross-sectional studies\(^3\)

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1) *Z*-scores: standard deviations around a mean of zero adjusted for age and race/ethnicity.
2) ISCD criterion for low bone mass for age (Lewiecki Bone 2003)
3) Mulligan CID 2012, 2015; Liu PLoSOne 2013; Grijsen JID 2013
Changes from Baseline in BMD (ITT; medians)

% Change in BMD

Wilcoxon signed rank test: * P ≤ 0.001; ** P = 0.02
TFV-DP Concentrations (fmol/punch) Classified as Extrapolated Dosing Frequency

TFV-DP levels (fmol/punch) in red blood cells from dried blood spots used to classify dosing frequency (tablets/week) using estimates developed for adult MSM in iPrEx OLE (Grant Lancet 2014)
Percent Change in Spine and Hip BMD from Baseline to Week 48 Correlated with TFV-DP Exposure

**Spine**
- Spearman correlation: -0.381
- *P* < 0.0001

**Hip**
- Spearman correlation: -0.376
- *P* < 0.0001
Percent Change from in Spine BMD from Baseline to Week 48 Linked with TFV-DP Exposure

Highly protective (>700 fmol/punch)
Median % change in BMD by TFV-DP levels

Significance of change vs. baseline: * P≤0.05; ** P<0.001 (Wilcoxon signed rank)
Bone Fractures

- Pre-study: 88 bone fractures in 53/200 (26%) of participants
- On-study: 8 bone fractures in 5 participants:
  - 2 “slamming fingers in a door or knocking against a solid object”
  - 1 motor vehicle accident
  - 1 fall
  - 1 fight
- No participants had Z-scores ≤ 2.0
Caveats

• Open-label study; no pre-defined control group
• DXA measures areal bone density; considered less accurate during growth, particularly in the hip
• DXA norms for this age group also subject to criticism
Summary/Conclusions

• As previously observed in healthy adult and adolescent at-risk men, bone mass is lower than expected in YMSM

• After 48 weeks, changes in hip and spine BMD were negatively correlated with the magnitude of TFV exposure; bone loss in participants with TFV-DP in the range considered to be highly protective in adults (>700 fmol/punch) was significantly greater than in those with drug levels below the limit of quantitation

• Although the BMD losses were generally modest, their occurrence before attainment of peak bone mass in young men who already have low bone mass may increase their risk of fragility in adulthood

• Follow-up will determine whether and to what extent bone losses are reversible following discontinuation of PrEP
Overall Conclusions

• ATN 110 successfully identified and engaged YMSM who would be appropriate for PrEP.
• PrEP was well tolerated with minimal adverse events
• As previously observed, bone mass is lower than expected in YMSM
  – After 48 weeks, changes in hip and spine BMD negatively correlated with TFV exposure;
  – Bone loss in participants with TFV-DP >700 fmol/punch was significantly greater than in those with levels BLQ
• Although modest, BMD loss before attainment of peak bone mass in young men who already have low bone mass may increase their risk of fragility in adulthood
• Follow-up underway to determine whether and to what extent bone losses are reversible following discontinuation of PrEP
Overall Conclusions

• STI diagnoses were high at baseline and remained constant over time

• HIV incidence rate was high compared to PrEP arms in other open label trials
  – Demonstrated ATN’s access to key risk population

• Those most susceptible to HIV infection (e.g. condomless sex) may also be more likely to be adherent
Overall Conclusions

• Complexities that underpin adherence underscored
  – Variance by R/E consistent with recent research highlighting lack of exposure to HIV prevention interventions by BYMSM
    • NEED more in-depth understanding of the historical, societal, behavioral and attitudinal barriers to PrEP access and adherence among those most impacted in the US – black/African-American young MSM
  – Adherence decreased for all participants as study visits decreased in frequency, regardless of R/E
    • Youth may need enhanced visit schedules or more frequent interactions (in-person or via mobile technology)
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ATN 110 Study Volunteers