Pre-Exposure Prophylaxis (PrEP) Initiative: Open Label Extension

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for the iPrEx study team.

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Grant et al, Melbourne, July 22, 2014;
Grant et al, *Lancet Infectious Diseases*, published online July 22, 2014

Background

- PrEP with oral FTC/TDF, or TDF, prevents HIV acquisition.[1-4]
- Oral FTC/TDF PrEP is approved by the US FDA; the CDC and WHO have issued recommendations for MSM.[5-6]
- PrEP uptake has been slow -- only 2317 patients filled prescriptions for FTC/TDF PrEP in the US between 1/2012 and 9/2013; almost half were women.[7]
- Adherence and sexual practices during PrEP implementation may differ compared with blinded placebo-controlled trials.
- Demonstration projects are needed to optimize PrEP delivery and to assess impact.

1. Grant NEJM 2010; 2. Baeten NEJM 2012; 3. Thigpen NEJM 2012; 4. Choopanya Lancet 2013; 5. US Public Health Service. CDC 2014; 6. WHO Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations, July 2014; 7. Mera HIV Drug Therapy in the Americas Conference, Rio de Janeiro, Brazil.

iPrEx Open Label Extension (OLE) Aims

- Provide post-trial access in accordance with the Declaration of Helsinki and Good Participatory Practices
- Identify demographic and behavioral characteristics associated with PrEP uptake and adherence
- Confirm the effectiveness of PrEP uptake and adherence in a setting more like clinical practice
- Learn what happens to sexual practices when people know that they are receiving effective PrEP
- Validate convenient markers of long-term PrEP use

Clinical Procedures

- Former participants of PrEP trials who were alive and HIV antibody negative at the end of the trials were eligible for this analysis; HIV infected persons were followed as well.
- All were men or transgender women who have sex with men.
- Visits at weeks 0, 4, 8, 12, then every 12 weeks for a total of 72 weeks.
- PrEP was offered at enrollment if HIV seronegative and there was no acute viral syndrome.
- PrEP could be started through week 48 and stopped any time.
- People were encouraged to start or stop PrEP when desired.
- All were followed regardless of PrEP choice.

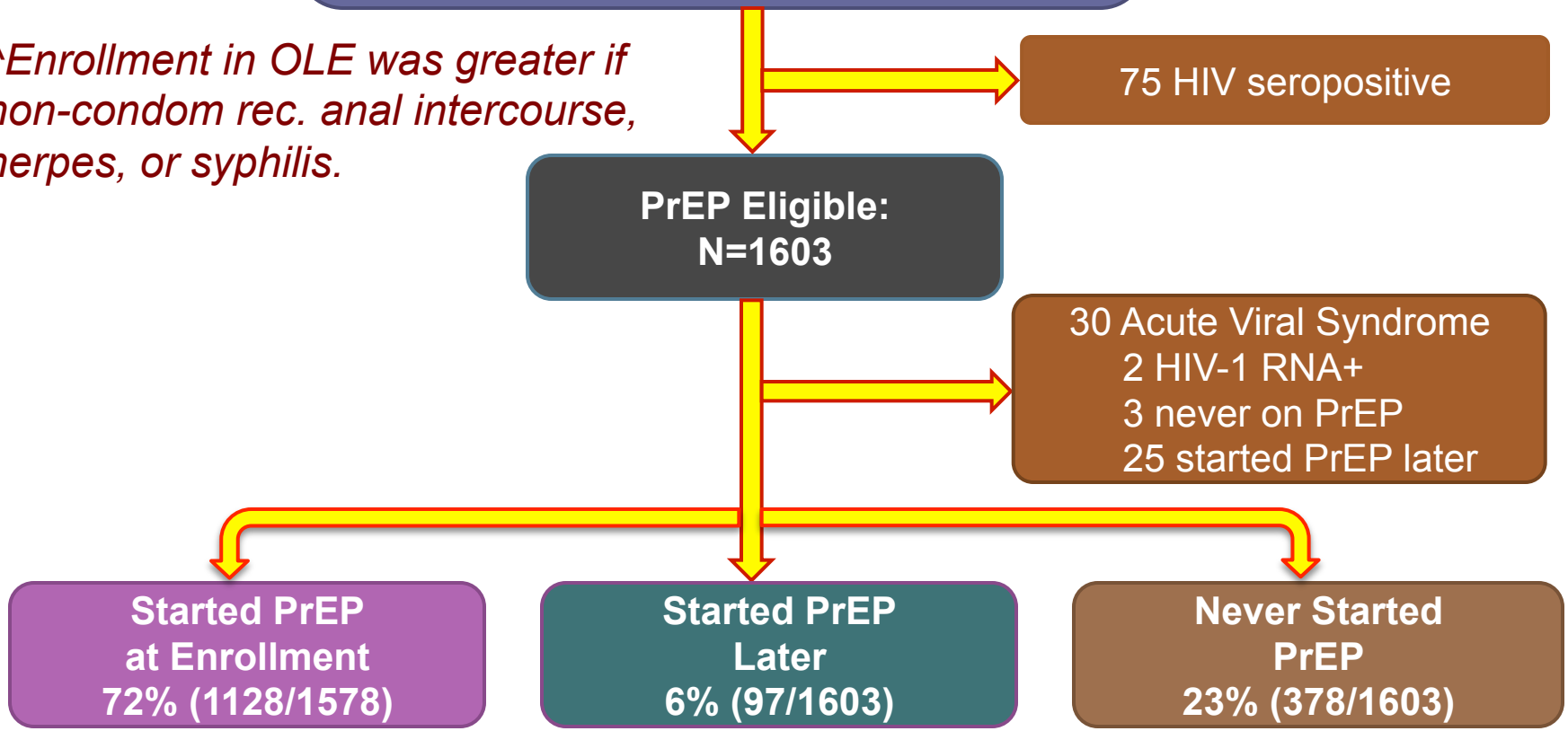
Visits from Jun 2011 to Dec 2013

Sites	11
Total enrolled in OLE	1770
PrEP Eligible	1603
Average age	28

Study flow (HIV uninfected only)

Trial	*Enrolled/OLE Eligible^*	*%*
iPrEx	1526/2336	65%
ATN 082	46/68	68%
US Safety Study	106/271	39%
Total	**1678/2680**	**62%**

^Enrollment in OLE was greater if non-condom rec. anal intercourse, herpes, or syphilis.



Grant Melbourne 2014; Grant *et al*, *Lancet Infectious Diseases*, published online July 22, 2014

PrEP Uptake

	% Of Cohort	% PREP Uptake	Uptake P Value
Non-condom Receptive Anal Intercourse			0.003
No	68%	75%	
Yes	32%	81%	
HSV Seropositive			0.03
No	87%	75%	
Yes	13%	77%	

No difference in PrEP uptake by age, education, transgender, prior randomized group or use of alcohol, methamphetamine, or cocaine.

Grant Melbourne 2014; Grant et al, *Lancet Infectious Diseases*, published online July 22, 2014

Reasons Given For Not Wanting PrEP:

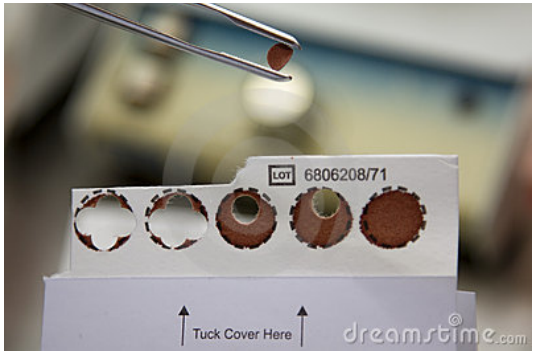
CASI at OLE enrollment, check all that apply, N=373

Reason Given for Declining PrEP	%
I am concerned about side effects from the pills	50%
I don't want to take a pill every day	16%
I don't like taking pills	13%
I can avoid HIV in other ways	14%
I am concerned that people will think that I am HIV positive because I am taking Truvada	7%
I am concerned that people will know that I have sex with men and/or trans people because I am taking Truvada	3%

Reasons did not differ by prior randomized assignment to active vs. placebo.

Grant Melbourne 2014; Grant et al, *Lancet Infectious Diseases*, published online July 22, 2014

Tenofovir diphosphate in Dried Blood Spots

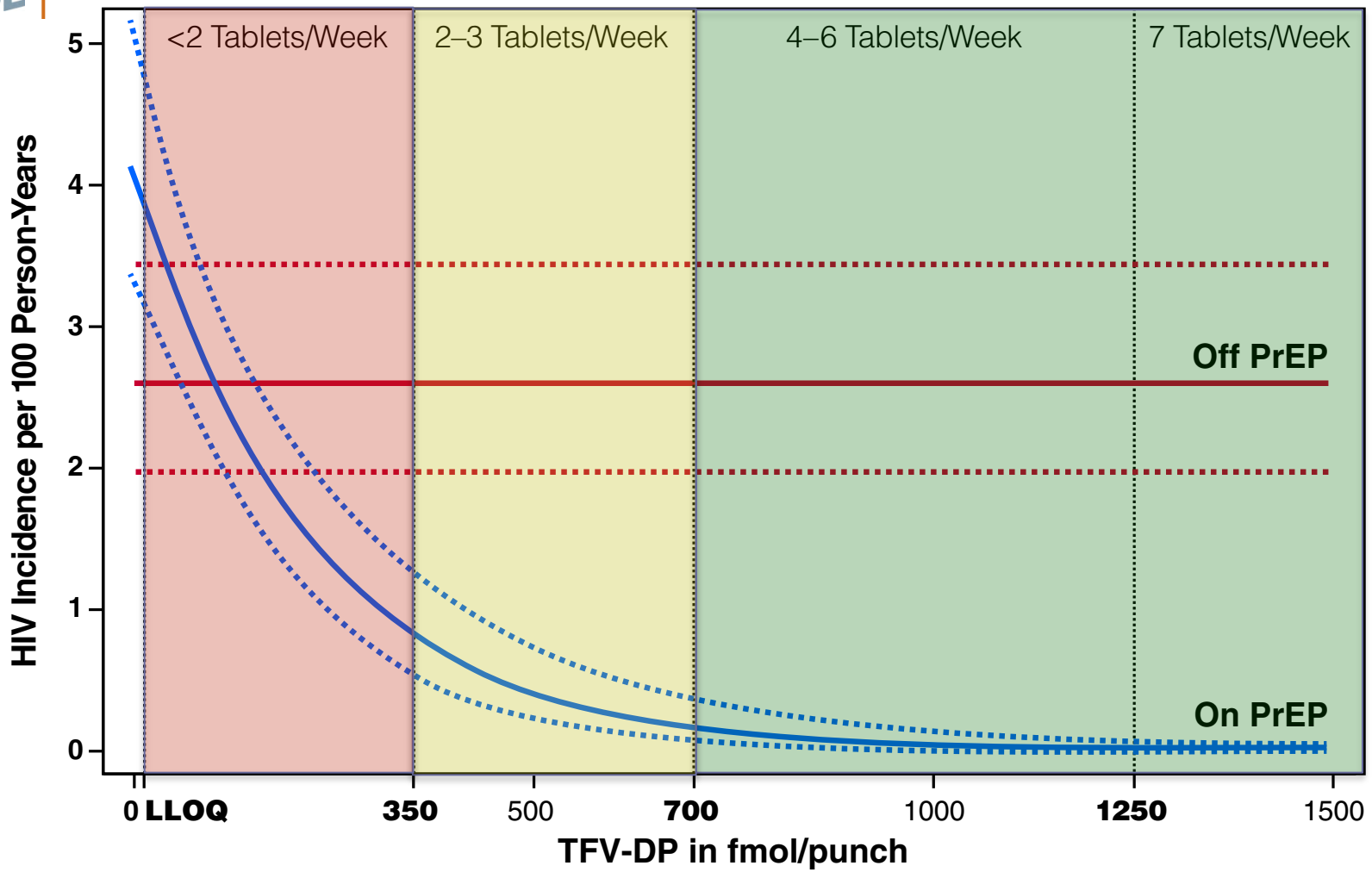


- Tenofovir diphosphate (TFV-DP) accumulates in RBCs, and can be measured in dried blood spots.
- $T_{1/2}$ 17 days.
- Accumulates 25-fold, providing wide dynamic range for estimating dosing;
  - Single dose detectable for >4 weeks.
- Dosing is estimated using information regarding accumulation and decay from a pharmacokinetic study of daily dosing for 30 days.[1]
- Testing was performed in all seroconverters on PrEP and a random sample (27%) of seronegatives.

TFV-DP (fmol/ punch)	Dosing Interpretation
≥1250	daily dosing
700 to 1249	4-6 doses/wk
350 to 699	2-3 doses/wk
<350	< 2 doses/wk

1. Castillo-Mancilla. 2012 AIDS Res Hum Retroviruses (PMID 22935078)

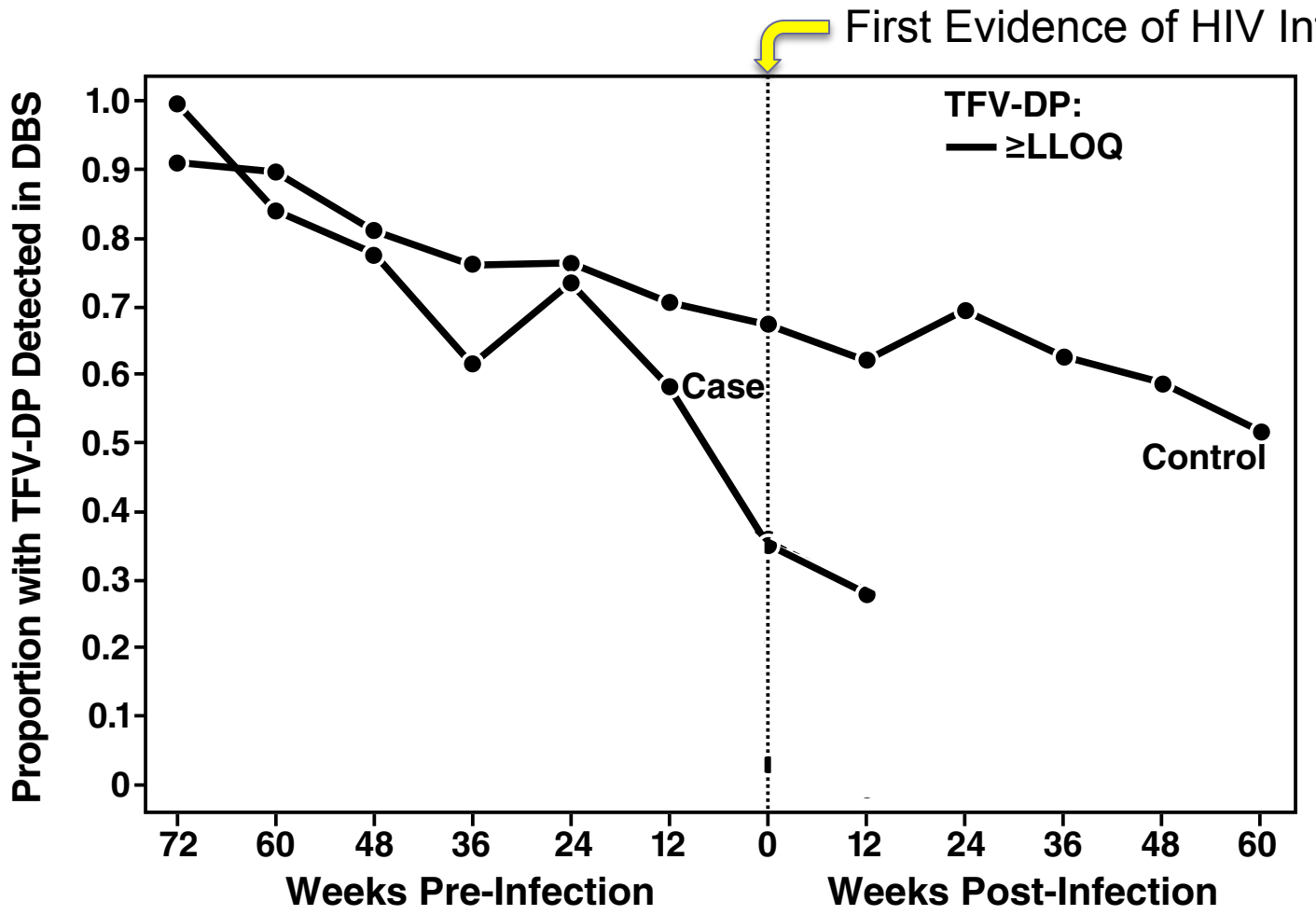
HIV Incidence and Drug Concentrations



Follow-up %	**26%**	**12%**	**21%**	**12%**
Risk Reduction	**44%**	**84%**	**100%**	**100%**
95% CI	**-31 to 77%**	**21 to 99%**	**86 to 100% (combined)**	

Grant Melbourne 2014;
Grant et al, *Lancet Infectious Diseases*, published online July 22, 2014

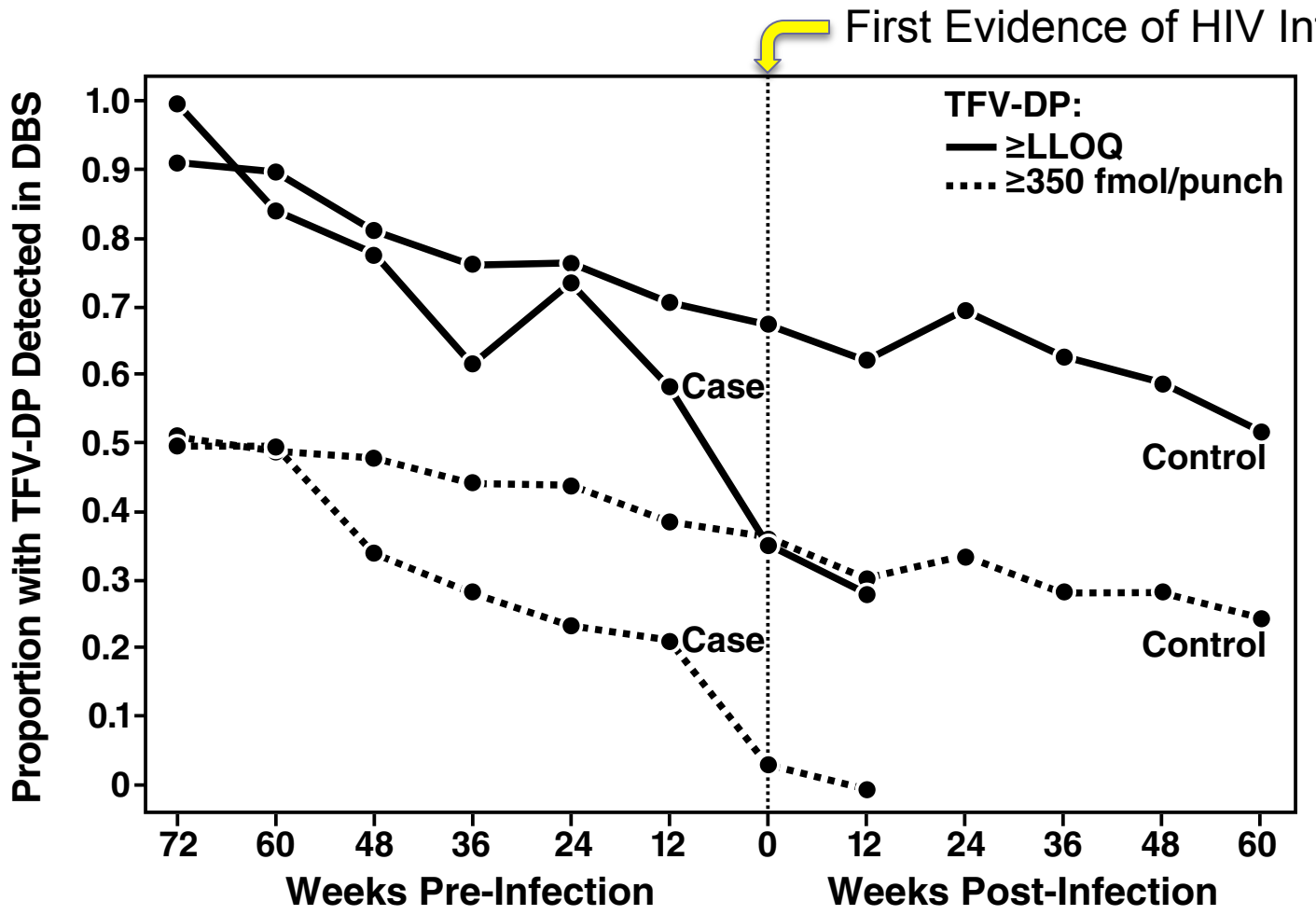
Any TFV-DP in DBS over time



N =												
Control:	380	1306	1647	1396	1489	1441	1338	768	386	266	171	44
Case:	8	22	22	24	24	26	28	7				

Grant Melbourne 2014; Grant et al, *Lancet Infectious Diseases*, published online July 22, 2014

Clinically Significant TFV-DP in DBS



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HIV Incidence by Study Period

Group	Randomized Phase Events / PY Incidence (95% CI)	Gap Phase Events / PY Incidence (95% CI)	Open Label Extension Events / PY Incidence (95% CI)
No Active PrEP	83 / 2113 **3.9** (3.1 to 4.8)	79 / 2076 **3.8** (3.0 to 4.7)	13 / 499 **2.61** (1.5 to 4.5)
FTC/ TDF	48 / 2124 **2.3** (1.7 to 3.0)		28 / 1530 **1.83*** (1.3 to 2.6)

*HIV incidence on PrEP in OLE was:

49% lower than off PrEP after adjusting for baseline sexual risk,
53% lower than during the placebo arm of the randomized phase,
51% lower than during the gap in study phases.

Grant et al, *Lancet Infectious Diseases*, published online July 22, 2014

Correlates of Drug Concentrations In Dried Blood Spots

Predictor of Drug Concentration	Adjusted OR	P Value
Non-condom Receptive Anal Intercourse at entry	1.69	<0.0001
≥ 5 sexual partners in the past 3 months	1.57	<0.0001
Known HIV Positive Partner	1.40	0.03
Age		
18-24	Ref	
25-29	1.08	0.19
30-39	2.02	0.0002
40+	3.16	<0.0001
Education		
Less than secondary	Ref	
Secondary	1.89	<0.0001
Post-secondary	2.40	<0.0001
Transgender	0.72	0.02

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Alcohol and Substance Use and Drug Concentrations in Dried Blood Spots

	Adjusted OR	P Value
Alcohol ≥5 drinks a day on drinking days	0.81	0.07
Cocaine use in the past 30 days	1.07	0.60
Methamphetamine use in the past 30 days	0.78	0.42

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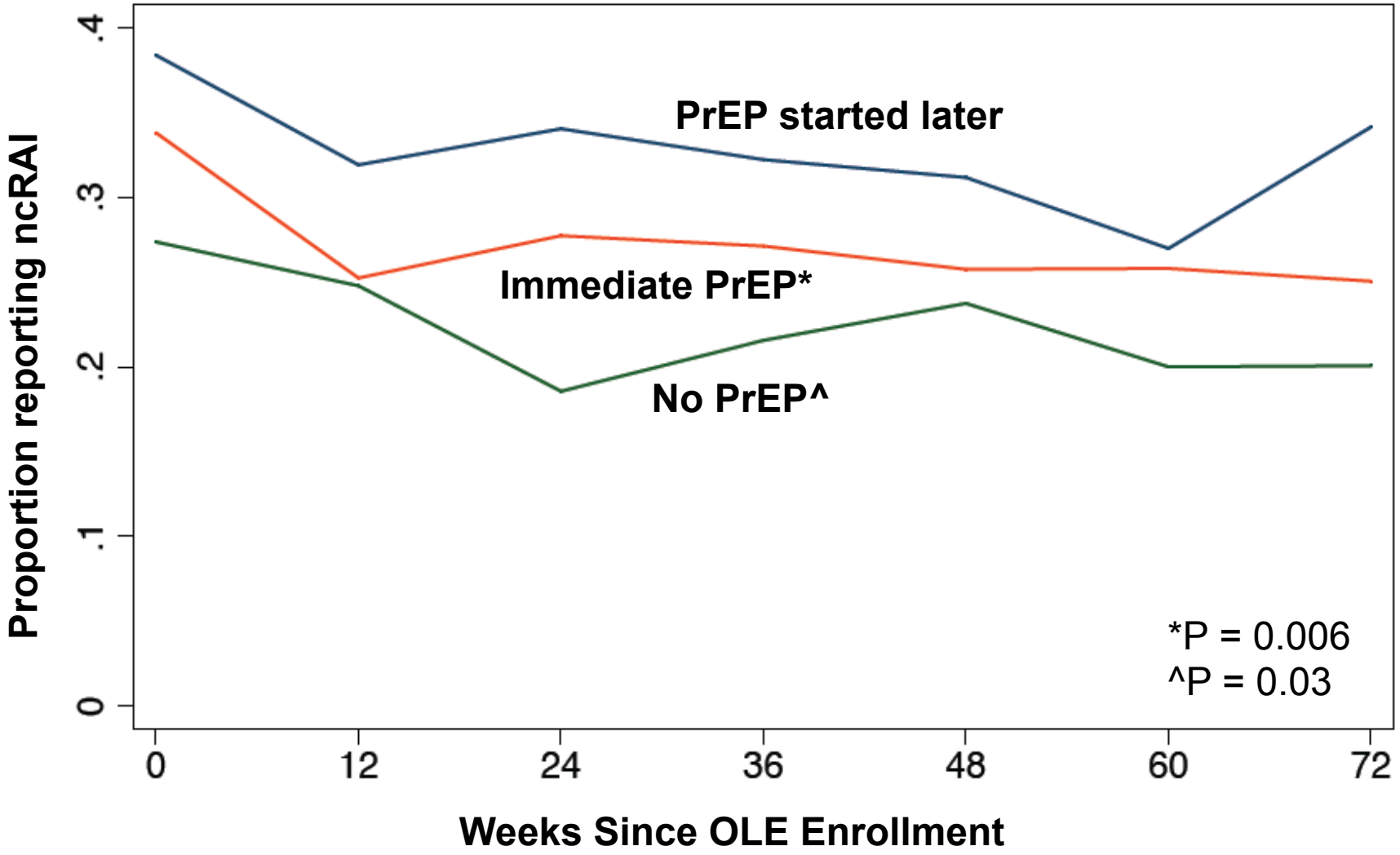
Non-Condom Receptive Anal Intercourse (ncRAI)

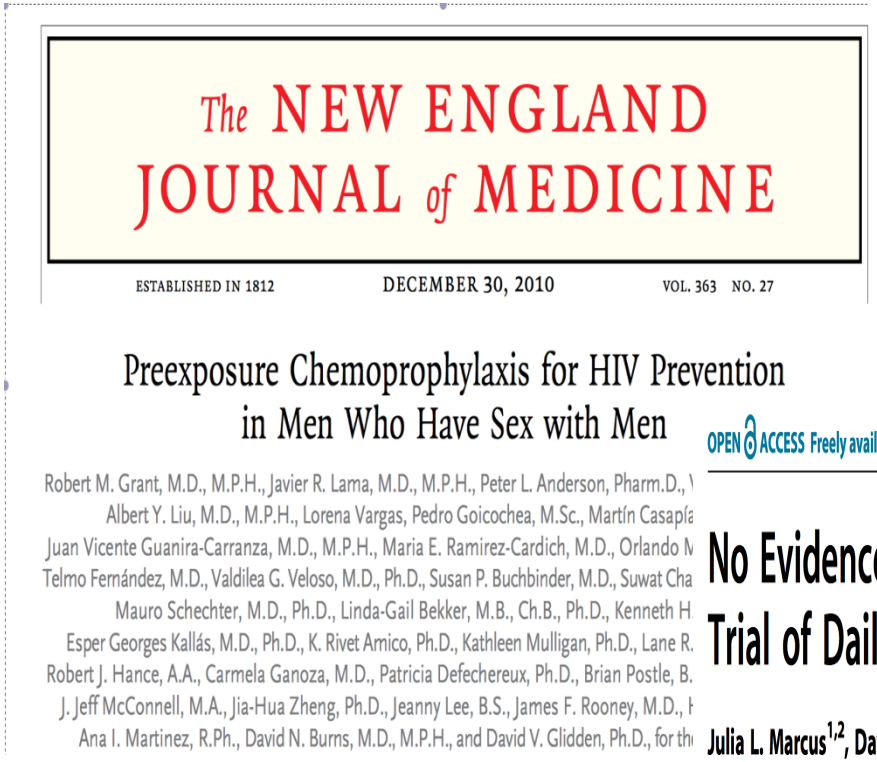


Sex on PrEP

Qualitative findings from the iPrEx Open Label Extension (OLE) in the US

Kimberly Koester, Rivet Amico, Albert Liu, Vanessa McMahon, Sybil Hosek, Kenneth Mayer, Robert Grant

PREP USE AND RISK COMPENSATION



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Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

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OPEN ACCESS Freely available online PLOS ONE

No Evidence of Sexual Risk Compensation in the iPrEx Trial of Daily Oral HIV Preexposure Prophylaxis

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SAMPLE

- Conducted 60 IDIs with PrEP users from April-September 2012
  - Boston *n* = 19
  - Chicago *n* = 21
  - San Francisco *n* = 20
- Mean age = 36 years old
- 51% white; 43% black, 6% other

*All names associated with quotes are pseudonyms

SEX PRACTICES BEFORE & AFTER TAKING PREP

- Prior to taking PrEP, condom use ranged from routine ---> never
- Once on PrEP, the majority did not report significant sexual behaviors changes
  - Younger participants increased condom use
- PrEP use, in most cases, did not lead to increased condomless sex
- PrEP use did lead to decreased stress, fear, guilt

THE HIV ANXIETY IS GONE

At the beginning of the interview I said HIV scared me. Even when I was being safe it scared me. I don't want to say it doesn't scare me, but I think it scares me less now, if that makes any sense? . . . There's a certain amount of comfort that comes from knowing that I'm taking this regularly. . . **So, in general, the anxiety, the HIV anxiety, is gone. I won't say it's gone-gone. But it's not in the front of my head as it used to be, where I was obsessively worried about it while sex was happening.** Darrell, 51 year old African American

USING PREP PROVIDES A RESPITE FROM THE ON-GOING, UNDERLYING THREAT OF HIV

I don't have the background stress that I did before and that's about it. It's not like I'm going out and being like, "ooh, bareback now. I'm protected. It's fine." **It's so, so not the case. …I just didn't have the overwhelming stress and fear and guilt that I would have had before.**

Seth, 29 year old, White

PARTICIPANTS EXPRESSED A THEORETICAL DESIRE FOR INCREASED SEXUAL ADVENTURE BUT THIS DID NOT PLAY OUT IN REALITY

The funny thing is I wanted to let myself be a little more open to doing something while taking somebody home and it didn't happen. We ended up having safe sex anyway.

I thought this was going to have a bigger effect on the way I had sex than it has. I kind of just didn't change my habits very much except just feeling a little less worried.

Conclusions of iPrEx OLE

- PrEP uptake is high across a broad range of demographic groups when provided free of charge by experienced PrEP providers.
- Sexual risk was associated with…
  - Higher retention between the randomized phase and OLE,
  - Greater PrEP uptake, and
  - Greater adherence.
- Adherence has to be good, not perfect:
  - Risk reduction 84% (95% CI: 21 to 99%) with 2-3 tablets/week,
  - Risk reduction 100% (95% CI: 86 to 100%) with ≥4 tablets/week.
- PrEP fails if people stop while still at risk for HIV.
- PrEP use makes sex feel safer, often with surprising results:
  - Relationship goals may emerge,
  - More discussion of other STIs,
  - More planning for safety in calm moments.
- More information is needed about adherence and PK in TGW.


This work was made possible
by the participants
and their communities
who believed that research
could improve their lives