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

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Grant et al, WAC 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

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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.

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Visits from Jun 2011 to Dec 2013

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

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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.

75 HIV seropositive

PrEP Eligible: N=1603

30 Acute Viral Syndrome
2 HIV-1 RNA+
3 never on PrEP
25 started PrEP later

Started PrEP at Enrollment 72% (1128/1578)

Started PrEP Later 6% (97/1603)

Never Started PrEP 23% (378/1603)

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

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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.

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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.

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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)

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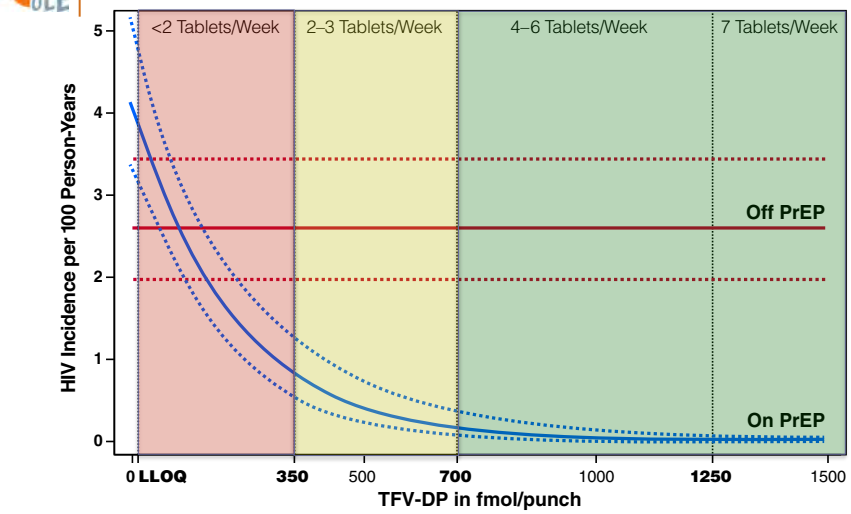
HIV Incidence and Drug Concentrations



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

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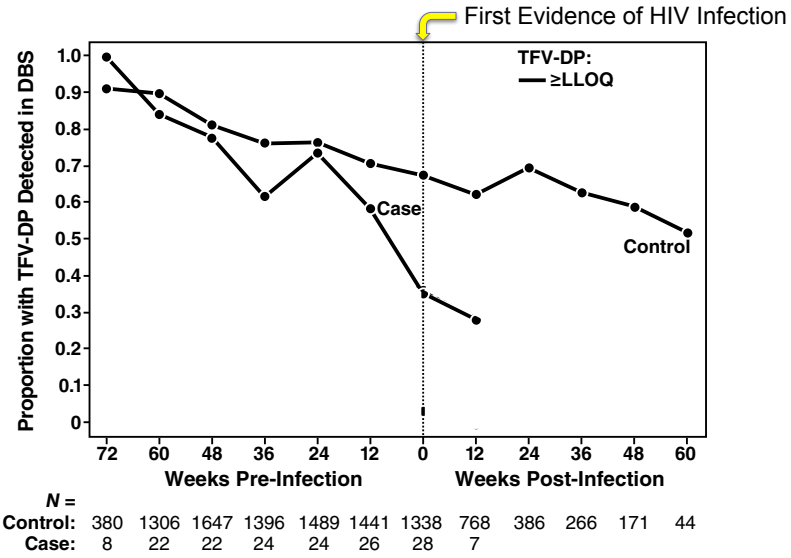
Any TFV-DP in DBS over time



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

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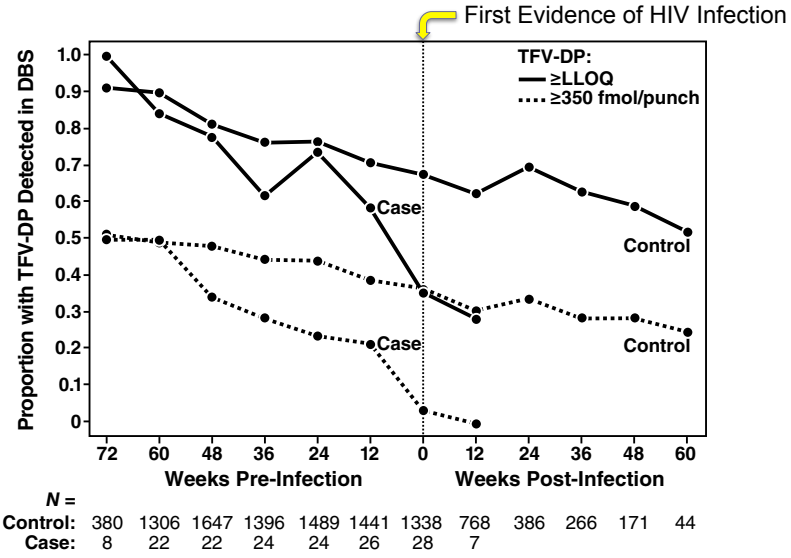
Clinically Significant TFV-DP in DBS



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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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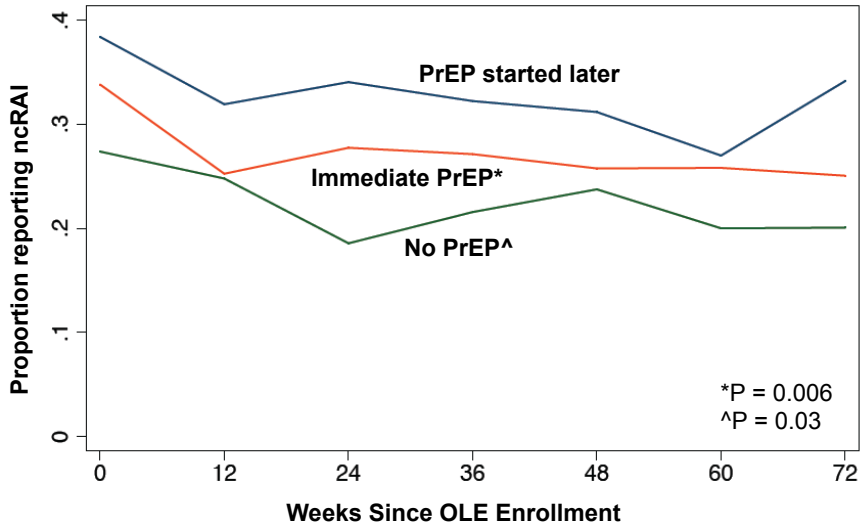
Non-Condom Receptive Anal Intercourse (ncRAI)



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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.
- More information is needed about adherence and PK in TGW.
- Tenofovir diphosphate concentrations in DBS are convenient markers of long term average PrEP use that correlate strongly with PrEP protection.

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