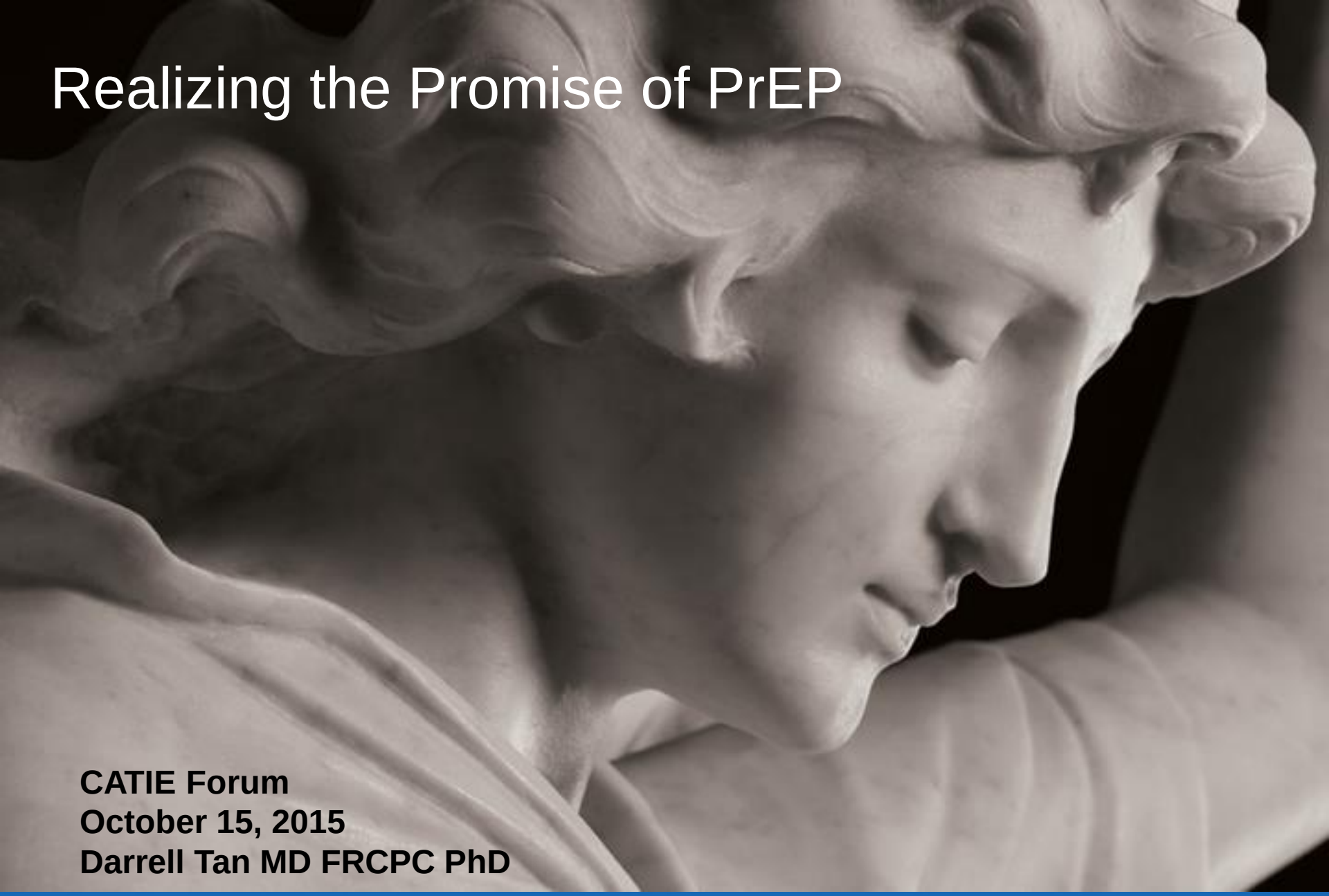
Realizing the Promise of PrEP



CATIE Forum
October 15, 2015
Darrell Tan MD FRCPC PhD

Learning objectives

- To review existing data regarding the efficacy, effectiveness, and main clinical concerns about PrEP
- To propose a roadmap to broader PrEP implementation, including key challenges and opportunities for PrEP to achieve its public health potential in Canada
- To provide examples of work already underway in Canada and the U.S. that can inform the road ahead

The NEW ENGLAND JOURNAL of MEDICINE

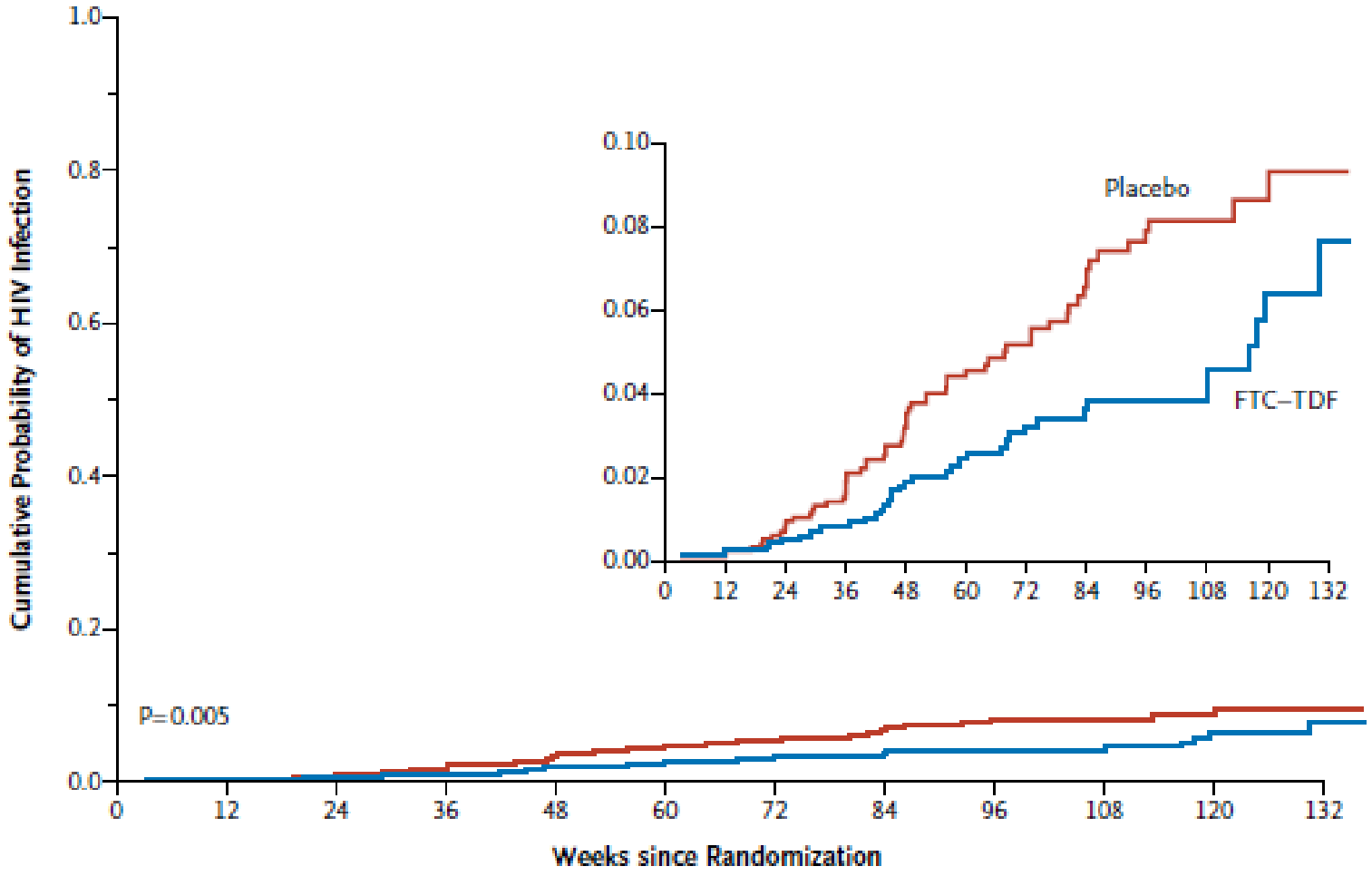
ORIGINAL ARTICLE

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

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H.,

- 2499 MSM / transgender F in 6 countries
  - USA, Peru, Ecuador, Brazil, Thailand, S Africa
- Randomized to daily TDF/FTC vs placebo
- Followed for 3324 person-years (median 1.2y)
- All received package of HIV prevention services
  - HIV testing, counseling, STI testing/treatment, condoms

NEJM 2010;363:2587



No. at Risk												
Placebo	1248	1194	1108	1005	852	647	546	444	370	258	137	60
FTC–TDF	1251	1188	1097	988	848	693	558	447	367	267	147	65

Figure 2. Kaplan–Meier Estimates of Time to HIV Infection (Modified Intention-to-Treat Population).

The cumulative probability of HIV acquisition is shown for the two study groups. The efficacy of preexposure prophylaxis with emtricitabine and tenofovir disoproxil fumarate (FTC–TDF) was 44%, as compared with placebo (P= 0.005). The inset graph shows a more detailed version of the overall graph up to a probability of 0.10.

PrEP Trials Have Shown Efficacy in MSM, Heterosexual Men and Women, and IDUs

Trial	Population/Setting	Intervention	HIV Infections, n		Reduction in HIV Infection Rate, % (95% CI)
			PrEP	Placebo	
iPrEX[1] (N = 2499)	MSM, transgender women, 11 sites in US, South America, Africa, Thailand	TDF/FTC	36	64	44 (15-63)
Thai IDU[4] (N = 2413)	Volunteers from 17 drug treatment centers in Thailand	TDF	17	33	49 (10-72)
TDF2[3] (N = 1219)	Heterosexual males and females in Botswana	TDF/FTC	9	24	62 (21-83)
Partners PrEP[2] (N = 4747)	Serodiscordant couples in Africa	TDF	17	52	67 (44-81)
		TDF/FTC	13		75 (55-87)

1. Grant RM, et al. N Engl J Med. 2010;363: 2587-2599. 2. Baeten JM, et al. N Engl J Med. 2012;367:399-410. 3. Thigpen MC, et al. N Engl J Med. 2012;367:423-434. 4. Choopanya K, et al. Lancet. 2013;381:2083-2090.

July 16, 2012: FDA Approval

U.S. Department of Health & Human Services

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FDA NEWS RELEASE

For Immediate Release: July 16, 2012
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves first drug for reducing the risk of sexually acquired HIV infection

Evidence-based approach enhances existing prevention strategies

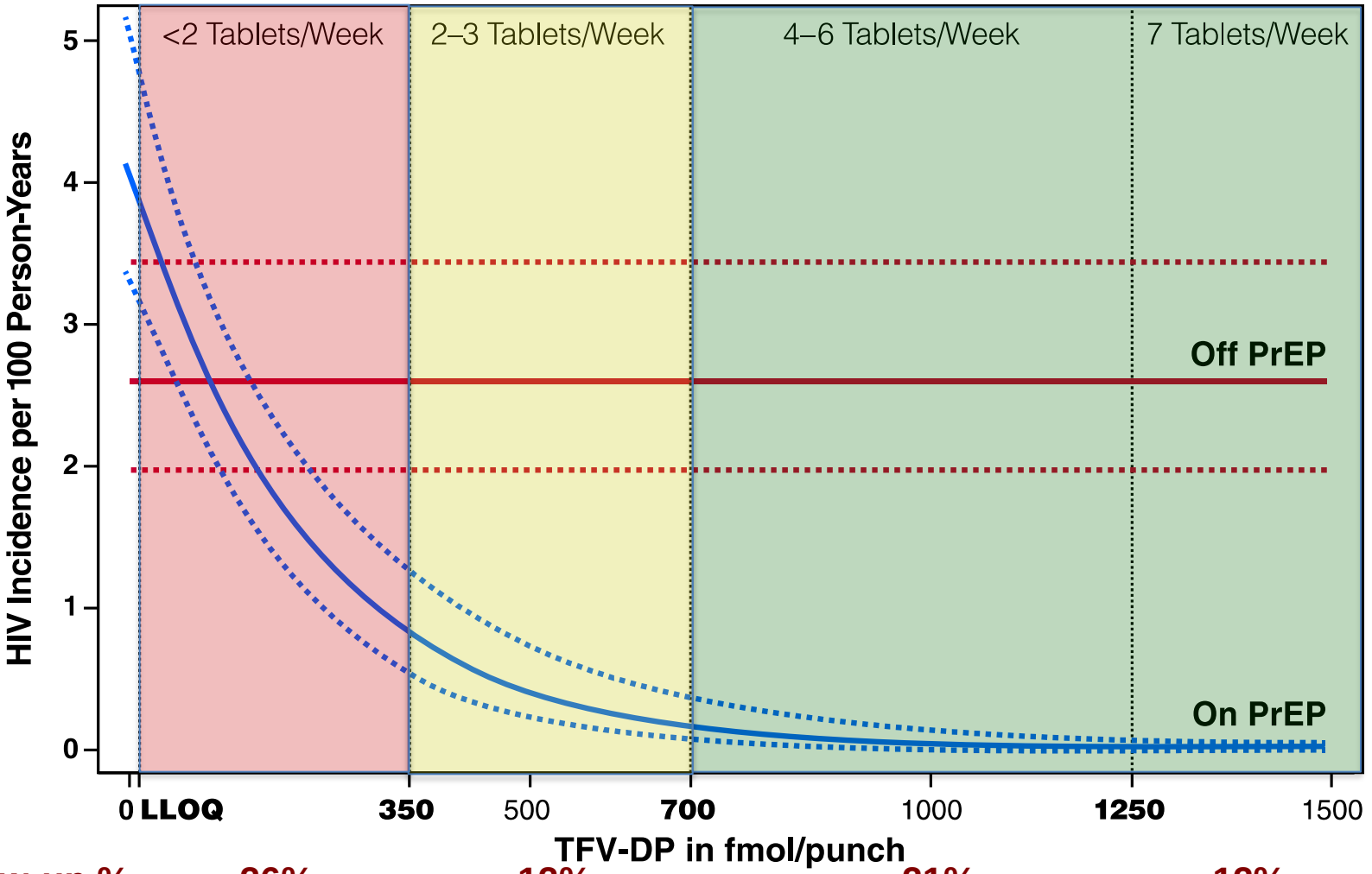
Today, the U.S. Food and Drug Administration approved Truvada (emtricitabine/tenofovir disoproxil fumarate), the first drug approved to reduce the risk of HIV infe uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners. Truvada, taken daily, is to be used fo

Concerns about PrEP:
1. Adherence / Efficacy
PrEP (like ART) works, but only if you take it!

Study	Blood Samples With TFV Detected, %	HIV Protection Efficacy in Randomized Comparison,%
Partners PrEP[1]	81	75
TDF2[2]	80	62
Thai IDU[4]	67	49
iPrEx[3]	51	44
FEM-PrEP[5] and VOICE[6]	< 30	No HIV protection

1. Baeten JM, et al. N Engl J Med. 2012;367:399-410. 2. Thigpen MC, et al. N Engl J Med. 2012;367:423-434. 3. Grant RM, et al. N Engl J Med. 2010;363:2587-2599. 4. Choopanya K, et al. Lancet. 2013;381: 2083-2090. 5. Van Damme L, et al. N Engl J Med. 2012;367:411-422. 6. Marrazzo J, et al. CROI 2013. Abstract 26LB.

iPrEx OLE: Efficacy as a function of drug concentrations in MSM

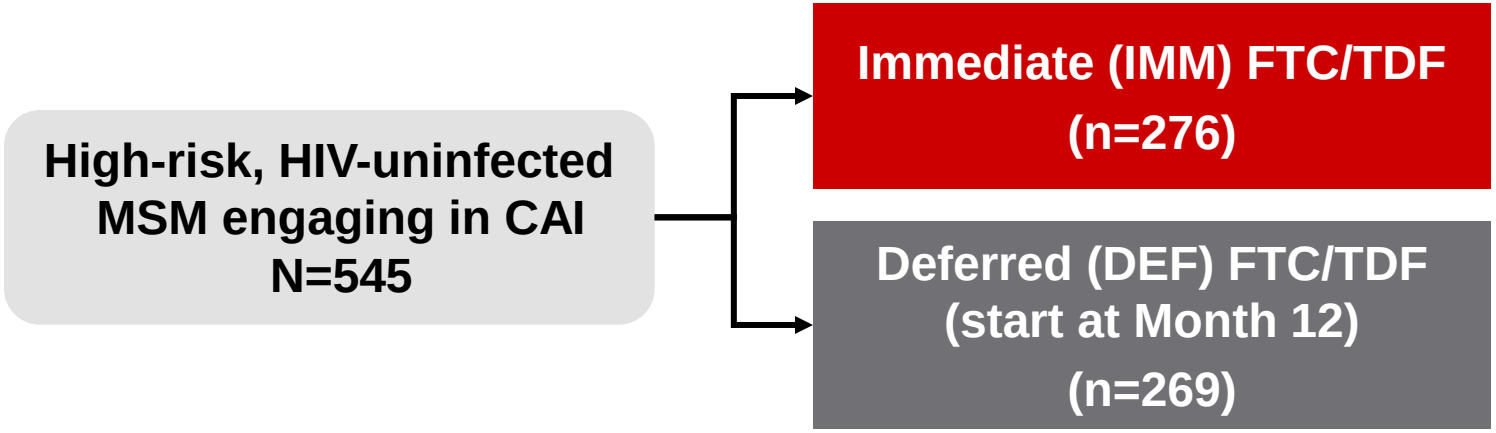


Follow-up %	**26%**	**12%**	**21%**	**12%**
Risk Reduction	**44%**	**84%**	**100%**	**100%**
95% CI	**-31 to 77%**	**21 to 99%**	**86 to 100% (combined)**	

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

Study Design

Randomized, multicenter, open-label pilot study in the UK



Primary endpoint: HIV seroconversion between randomization and Month 12

Secondary endpoints: Safety, adherence, sexual behavior, resistance development

Oct 2014: the PROUD Trial Steering Committee announced that participants on the deferred arm of the study, who had not yet started PrEP, would be offered the opportunity to begin PrEP ahead of schedule

CAI: Condomless anal intercourse
All subjects received comprehensive HIV prevention services, including condoms, risk-reduction counseling, testing and treatment for sexually transmitted infections, and HIV pre- and post-test counseling

Results

HIV Incidence

Group	Infections, n	Follow-up (PY)	Incidence/100 person-years (90% CI)
Overall	22	453	4.9 (3.4-6.8)
Immediate	3	239	1.3 (0.4-3.0)
Deferred	19	214	8.9 (6.0-12.7)

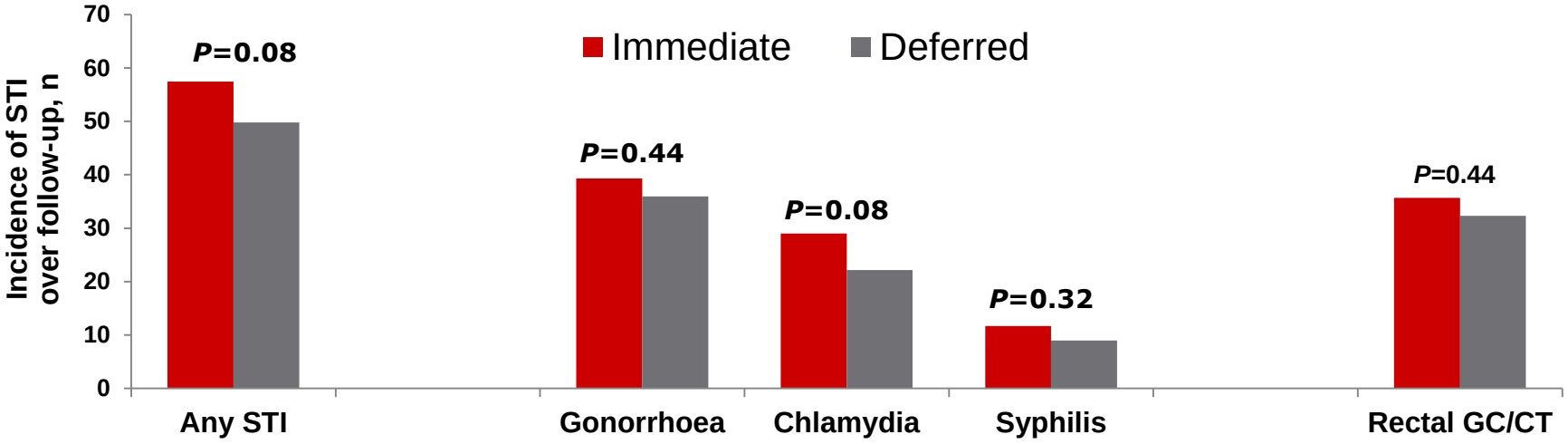
- FTC/TDF prescribed to IMM participants covered 86% of days in follow-up
- Use of post-exposure prophylaxis by arm:
  - IMM: 13 subjects (5%); 15 prescriptions
  - DEF: 83 subjects (31%); 174 prescriptions

86% (90% CI 58-96%) Risk Reduction *P*=0.0002

Number needed to treat=13 (90% CI: 9-25)

Concerns about PrEP:
2. Risk compensation – sexually transmitted infections

Anal sex partners in past 90 days, median (IQR)	Baseline, n=539		Month 12, n=349	
	IMM	DEF	IMM	DEF
Total	10.5 (5-20)	10 (4-20)	10 (3-24)	8 (3-15)
Condomless receptive	3 (1-5)	2 (1-5)	3 (1-8)	2 (1-5)
Condomless insertive	2.5 (1-6)	3 (1-7)	3 (1-8)	3 (1-6)



No significant differences in STIs between the deferred and immediate arms

McCormack S, et al. CROI 2015; Seattle, WA. #22LB

Study Design

High-risk, HIV-uninfected MSM
N=400

- Condomless anal sex with ≥2 partners within 6 months
- eGFR > 60 mL/min

Double-blind, randomized

"On-demand" FTC/TDF treatment

All participants received a package of preventative measures:

- counselling
- repeated HIV testing
- screening & treatment for other STIs
- HBV vaccination
- condoms and gel

"On-demand" FTC/TDF placebo

"On-demand" regimen constitutes:

- **2 FTC/TDF or 2 placebo 2 - 24 hrs prior to sexual intercourse exposure**
- **1 FTC/TDF or placebo 24 hrs and then 48 hrs after first intake**

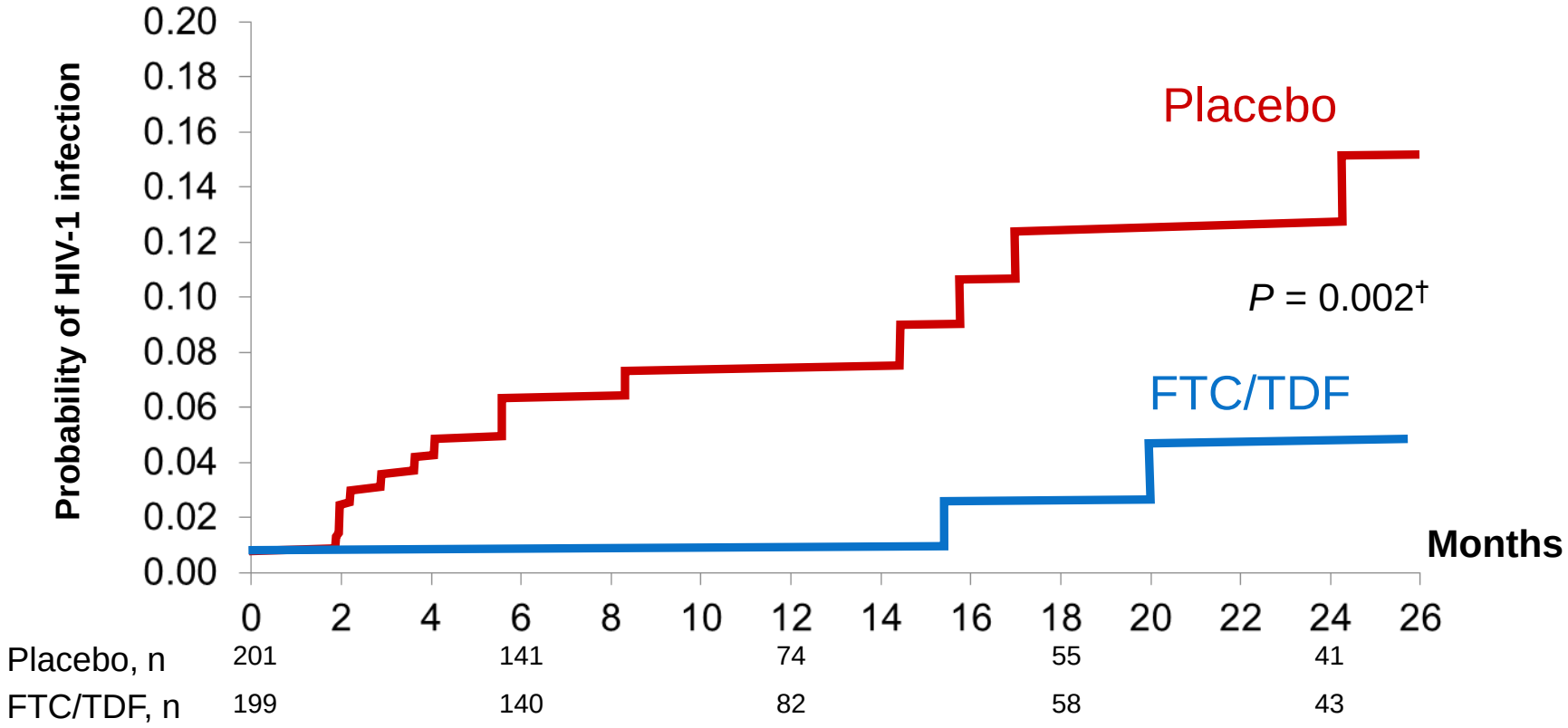
Primary endpoint: HIV seroconversion

Secondary endpoints: Sexual behavior, safety events, adherence

Oct. 2014, the DSMB recommended that the placebo arm be discontinued and patients be offered switching into the treatment arm.

Molina J, et al. CROI 2015; Seattle, WA. #23LB

Kaplan-Meier Estimates of Time to HIV-1 Infection*



86% relative reduction (95% CI: 40-99, *P*=0.002)

16 subjects infected (PBO=14; FTC/TDF=2)

Number need to treat: 18 for 1 year to prevent 1 HIV infection

*mITT Population
†Log-rank test

Molina J, et al. CROI 2015; Seattle, WA. #23LB

Concerns about PrEP: 3. HIV Drug Resistance

‡

Study	Infected on Study		Unrecognized Baseline Infections[d]	
	Infected, *n*	**Resistant to FTC or TDF, *n***	**Infected, *n***	**Resistant to FTC or TDF, *n***
iPrEx[1]	100 (36 on FTC/TDF, 64 on placebo)	None	10 (2 on FTC/TDF, 8 on placebo)	**2** on FTC/TDF (M184V/I); 1 on placebo (M184V)*§
Partners PrEP*[2]	103 (21 on FTC/TDF, 30 on TDF, 52 on placebo)	**3** on FTC/TDF (2 M184I/V, 1 M184I/V + K65R); **1** on TDF (M184I/V); 2 on placebo (M184I/V)†	18 (4 on FTC/TDF, 8 on TDF, 6 on placebo)	**2** on FTC/TDF (M184V); **1** on TDF (K65R/K70E)
TDF2[3]	33 (9 on FTC/TDF, 24 on placebo)	1 on placebo (K65R <1%)†	3 (1 on FTC/TDF, 2 on placebo)	**1** on FTC/TDF (K65R, M184V, A62V)
FEM-PrEP[4]	68 (33 on FTC/TDF, 35 on placebo)	1 on placebo (M184V)*; **4** on FTC/TDF (M184V/I)‡	5 (1 on FTC/TDF, 4 on placebo)	None
VOICE[5]	312	**1** on FTC/TDF (M184V/I)	22	**2** on FTC/TDF (M184V)

8 / 129 = 6.2% **6 / 16 = 37.5%**

* Using ultra-deep sequencing

† Transmitted (primary) resistance can occur independent of PrEP, which likely explains resistance in the placebo arm

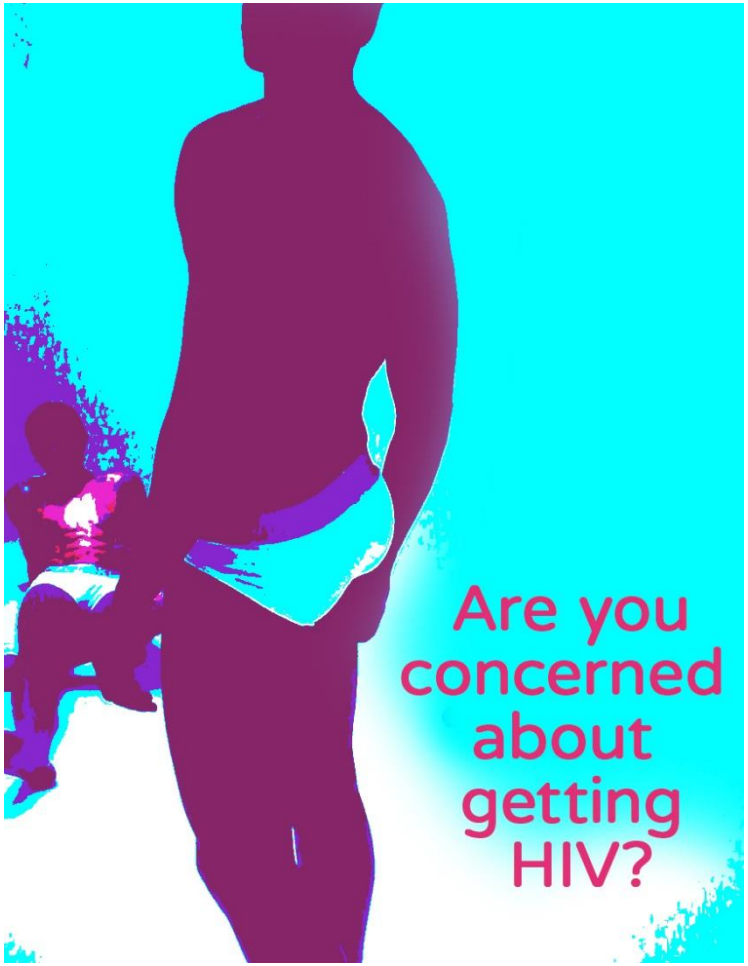
‡ 1 probable and 2 possible transmitted resistance; 1 uncertain timing of infection (HIV RNA detectable at first follow-up visit)

§ Infection + incomplete suppression of replication by FTC/TDF selects resistance; transmitted (primary) resistance can occur, independent of PrEP, which likely explains resistance in the placebo arm

1. Grant R, et al. N Engl J Med 2010;30:2587-99
2. Lehman D, et al. CROI 2014; Boston. #590LB
3. Thigpen M, et al. N Engl J Med 2012;367:423-434
4. Van Damme L, et al. N Engl J Med 2012;367:411-422
5. Parikh, et al. CROI 2014; Boston. #594

PREPARATORY-5

"Canada's first demonstration project of open-label, oral TDF/FTC-based PrEP"



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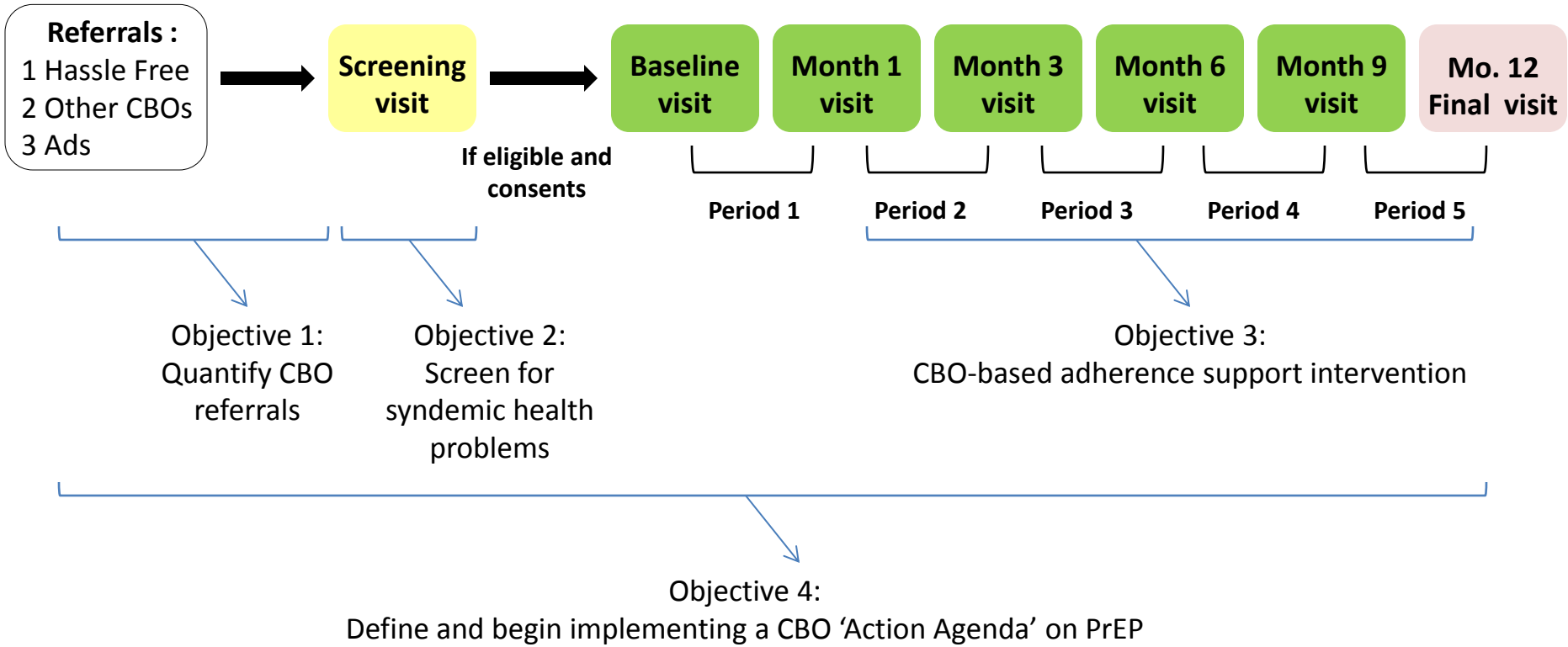
PREPARATORY-5 Trial

- 1-year 'Demonstration Project' in 50 gbMSM
  - Acceptability, adherence, tolerability, toxicity, HIV, STIs
  - Point-of-care HIV testing
- High demand continuing well after enrollment complete
- Community-based research objectives



Summary: What we know about PrEP in late 2015

- PrEP is very **effective** at preventing HIV in gbMSM, IDU and heterosexual men & women when used consistently & correctly
- **Intermittent** PrEP use may be a possibility in select circumstances, but current recommendations are for daily PrEP only
- PrEP is **safe** and well **tolerated**
- Careful monitoring for **STIs** and HIV drug **resistance** is important

A roadmap for delivering PrEP at scale

ACCESS

CANDIDATES

PROVIDERS

INTEGRATION

MONITORING & RESEARCH

1. Widespread public ACCESS to PrEP

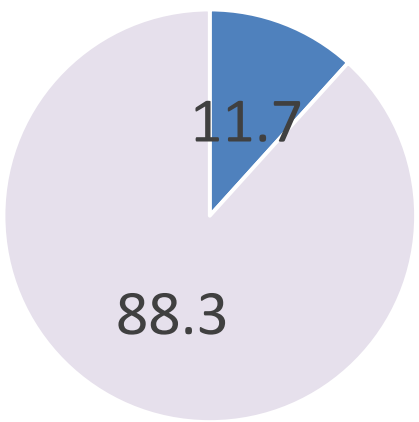
- Health Canada regulatory approval
  - All prescribing in Canada is currently off-label
  - Application submitted August 2015
  - Will greatly facilitate: coverage, policies, programs
- Public coverage
  - Cost is $883.03 CAD / month
  - Almost all current users using private insurance
  - Position of private payers unclear
  - Truvada® patent ends July 2017
  - Financial assistance program?

2. Strategies for identifying PrEP CANDIDATES

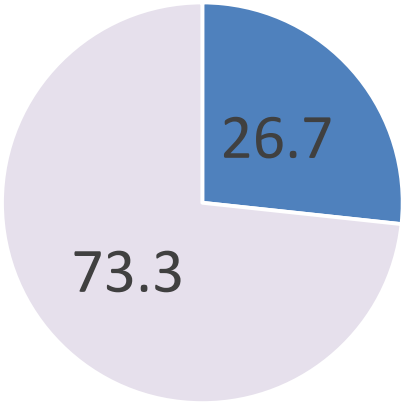
- A) Patient-initiated
  - Need for community awareness
- B) Provider-initiated
  - Clinicians and/or service providers
- C) Public health-initiated?
  - In response to new diagnoses

Increasing community awareness

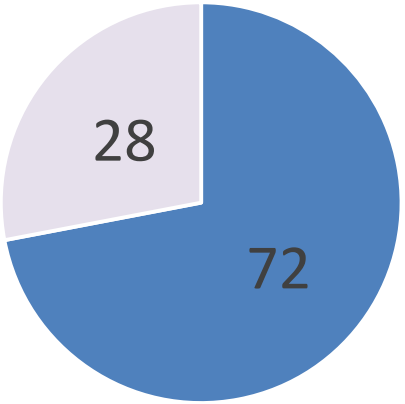
Proportion of MSM at HFC aware of PrEP



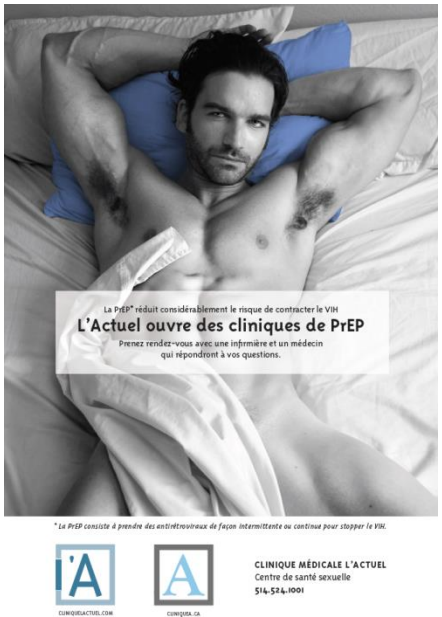
Feb-Jul 2010



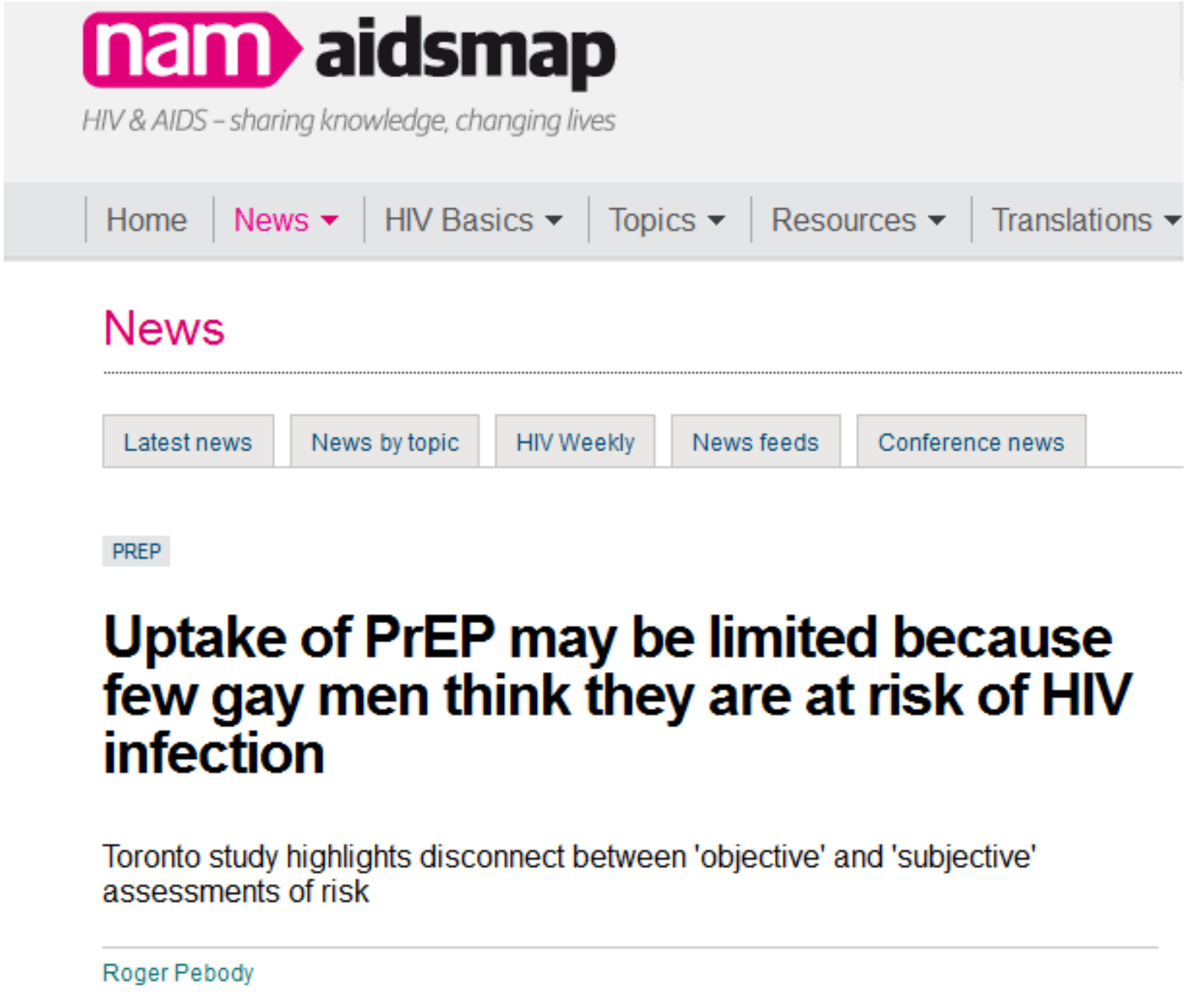
Apr-Jun 2013



Nov 2014-Apr 2015



2. Pathways for identifying PrEP candidates



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PREP

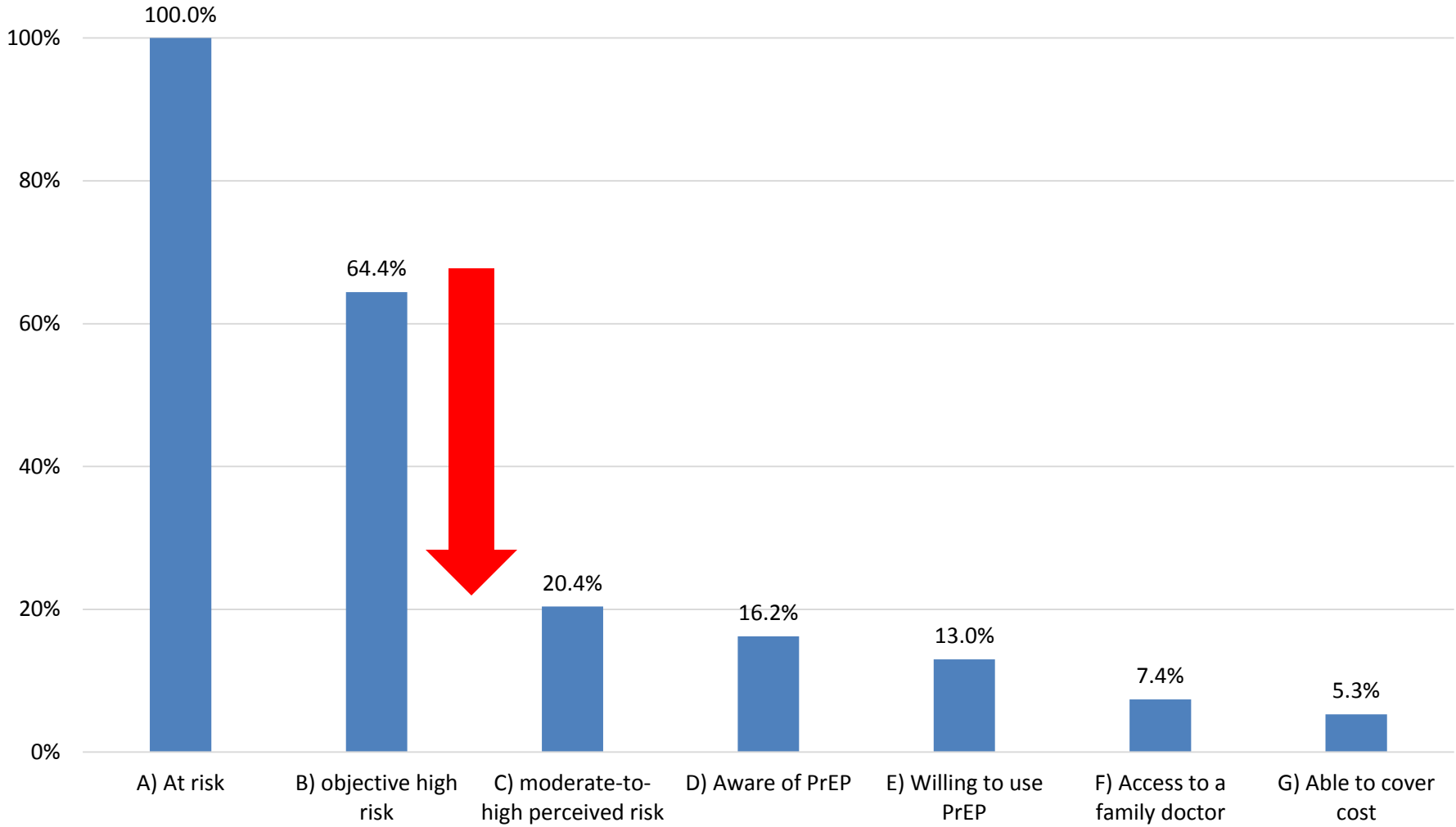
Uptake of PrEP may be limited because few gay men think they are at risk of HIV infection

Toronto study highlights disconnect between 'objective' and 'subjective' assessments of risk

Roger Pebody

Hypothetical 'PrEP Cascade'

n=420 MSM at Hassle Free Clinic



3. Knowledgeable, culturally competent PrEP PROVIDERS

- “I went through a sort of like bad part five years ago. I was just feeling lots of anxiety and I knew it was because I was gay, but I’d try to spin it off to something else... So I went to my doctor and I was like, “I think I know why I’m so anxious all the time.” And she’s like, “Why?” And I was like, “I’m gay.” And then she was like, “I know lots of people that are becoming gay now.” And I was like, “Oh, okay.” And so it just reminded me that a lot of doctors are not really well versed with dealing with people who are gay. And it didn’t come from a bad place from her, I just think it came from ignorance and that’s why I never felt comfortable talking to her about anything else.”

Decentralized delivery by trained clinicians

- Awareness among most clinicians remains low
- PrEP delivery is straightforward, but time-consuming
  - Proper STI screening, adherence counseling, timing of appointments vs Rx renewals, addressing syndemics…
- Nurses
  - Public health / sexual health clinics
- Primary care providers
  - Directories of knowledgeable, gay-friendly MDs
- Resources for clinicians
  - Clinical practice guidelines
  - Phone lines

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PLOS | ONE

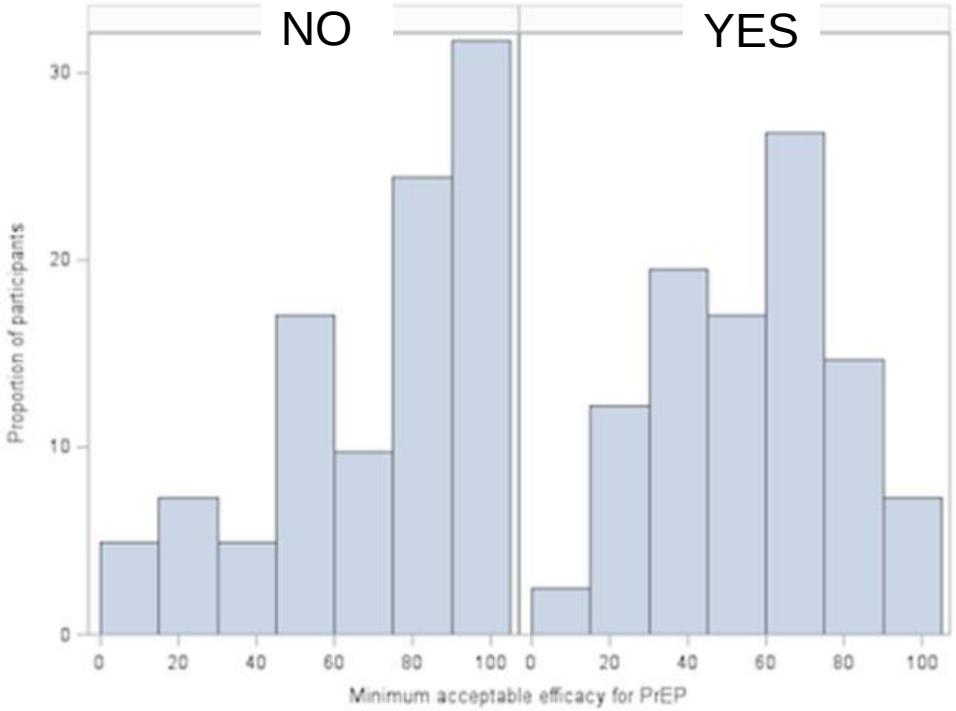
Preparing for PrEP: Perceptions and Readiness of Canadian Physicians for the Implementation of HIV Pre-Exposure Prophylaxis

Malika Sharma[1], James Wilton[2], Heather Senn[3], Shawn Fowler[4], Darrell H. S. Tan[1,3,4,5]*

1 Division of Infectious Diseases, University of Toronto, Toronto, Ontario, Canada, **2** Canadian AIDS Treatment Information Exchange, Toronto, Ontario, Canada, **3** Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, **4** Hassle Free Clinic, Toronto, Ontario, Canada, **5** Division of Infectious Diseases, St Michael's Hospital, Toronto, Ontario, Canada

Minimum level of HIV prevention efficacy respondents thought necessary for regulatory approval, stratified by current opinion on whether PrEP should be Health Canada approved

No:
Median (IQR)
75% (50-90%)



Yes:
Median (IQR)
50% (40-70%)

PLoS One 2014;e105283

4. INTEGRATION with other HIV prevention & health services

- Combination prevention programs
  - Biomedical (eg. PEP, STIs, vaccines…)
  - Behavioural (eg. condoms, adherence…)
  - Mental health (eg. mood, substance use…)
  - Social (eg. housing, employment…)

- Comprehensive care out of PrEP clinic
- Linkage models

l'Actuel CENTRE D'EXCELLENCE VIH · ITS · HÉPATITES

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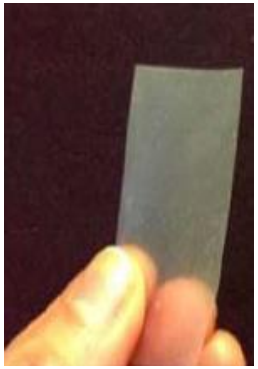
5. Embedded MONITORING and RESEARCH

- Comprehensive monitoring & evaluation
  - Minimum data set – cohort study
  - Administrative data
- Embedded research
  - Biomedical, clinical, behavioural, public health, social
  - Readiness for future prevention technologies

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  - Garfield Durrant
  - Jeff Goldman
  - Derek Manis
  - Ricky Rodrigues
  - Jonathan Ross
  - Richard Utama

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The End