THE FENWAY INSTITUTE

Microbicides and Antiretroviral Therapy

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Infected Genital Leukocytes and Cell-Associated Virus Transmission

October 19th, 2013

Why Chemoprophylaxis Post-HPTN 052?

- Only few MSM and IDU in HPTN 052, so effectiveness of TasP not fully understood
- HIV incidence has not ↓ in England and Denmark, despite access (Birrell, 2013; Audelin, 2013)
- <1/3rd of PLHIV globally are now on treatment; full access will take years
- Not all PLHIV want to start meds with high CD4 counts, and virologic suppression rates vary
- Serostatus awareness is limited among many
- HIV stigma limits willingness to disclose
- Not either/or; models suggest some synergy

PrEP works, but adherence is critical

Study	Efficacy overall	Drug detected overall	Estimated Risk reduction with drug detection
iPrEx	**42%**	**~50%**	**92%**
Partners PrEP	**67-75%**	**82%**	**86% (TDF)** **90% (FTC/TDF)**
TDF-2	**62%**	**80%**	**78%**
Fem-PrEP	**No efficacy**	**26%**	**"adherence too low to assess efficacy"**
VOICE	**No efficacy**	**29%**	**" "**

PrEP Concerns

- **Risk Compensation:** not seen in trials
- **Renal insufficiency**: rare, reversible

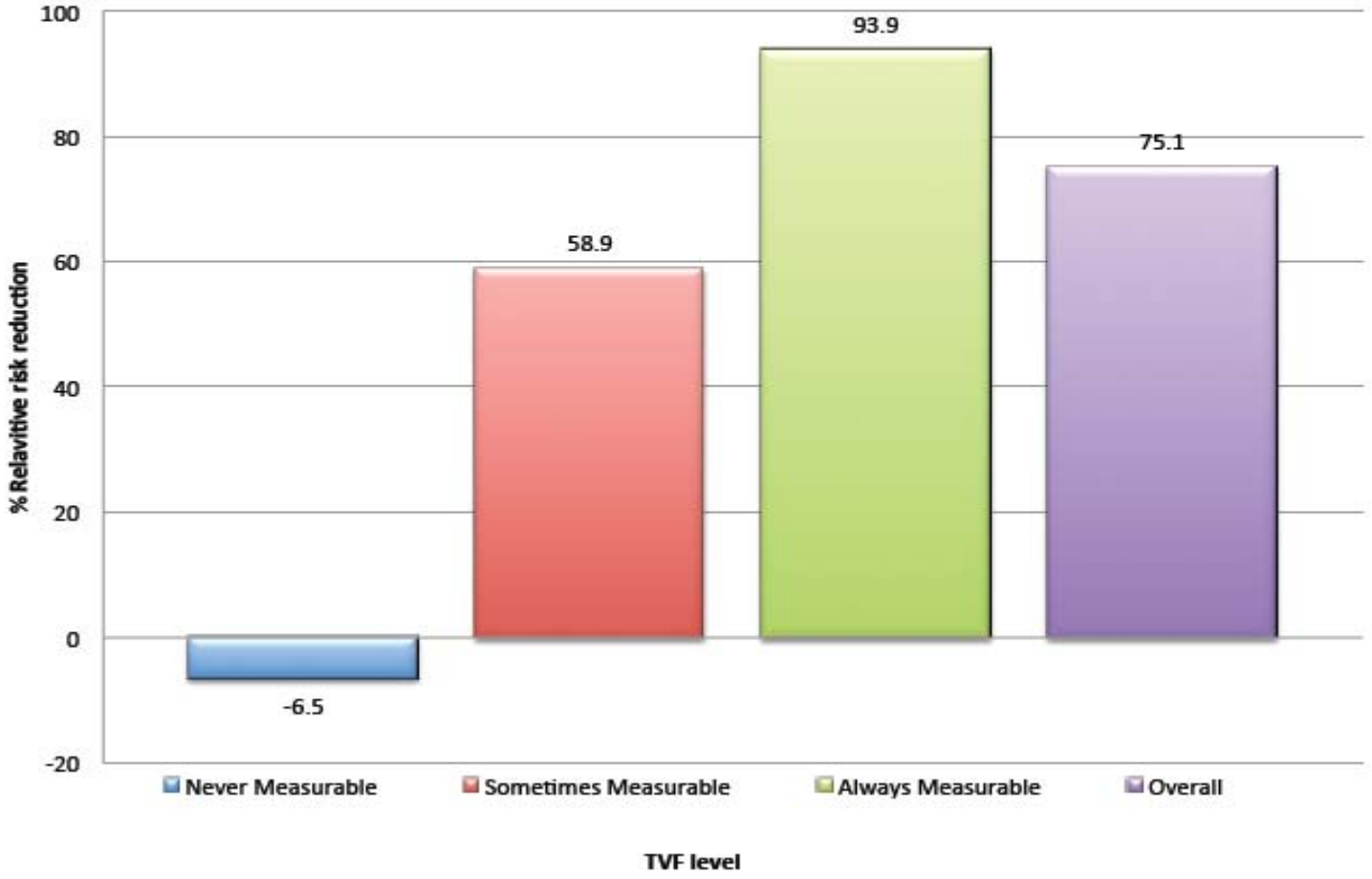
  -but pts had to have normal function for trials
- **Bone demineralization:** statistically significant, not clinically significant at 18 months, **needs f/u**
- **Transmission of resistance**

  -Only in pts started on PrEP with acute HIV

  -All but 1 case 184V (XTC R, less fit virus)

But it is early, and ongoing monitoring needed

Relative risk reduction in acquiring HIV infection (compared with placebo) based on plasma TFV concentrations (Partners PrEP)



Improving Adherence Results in Exceedingly High Levels of Protection

- Partners PrEP adherence sub-study
- 1,147 couples in Uganda: those whose three-month pill use dropped below 80% received enhanced counseling which included problem-solving
- Sub-study also included unannounced home visits; pill use measurement by MEMSCAP
- At the end of the study, 14 participants became HIV-infected, none randomized to TDF/FTC

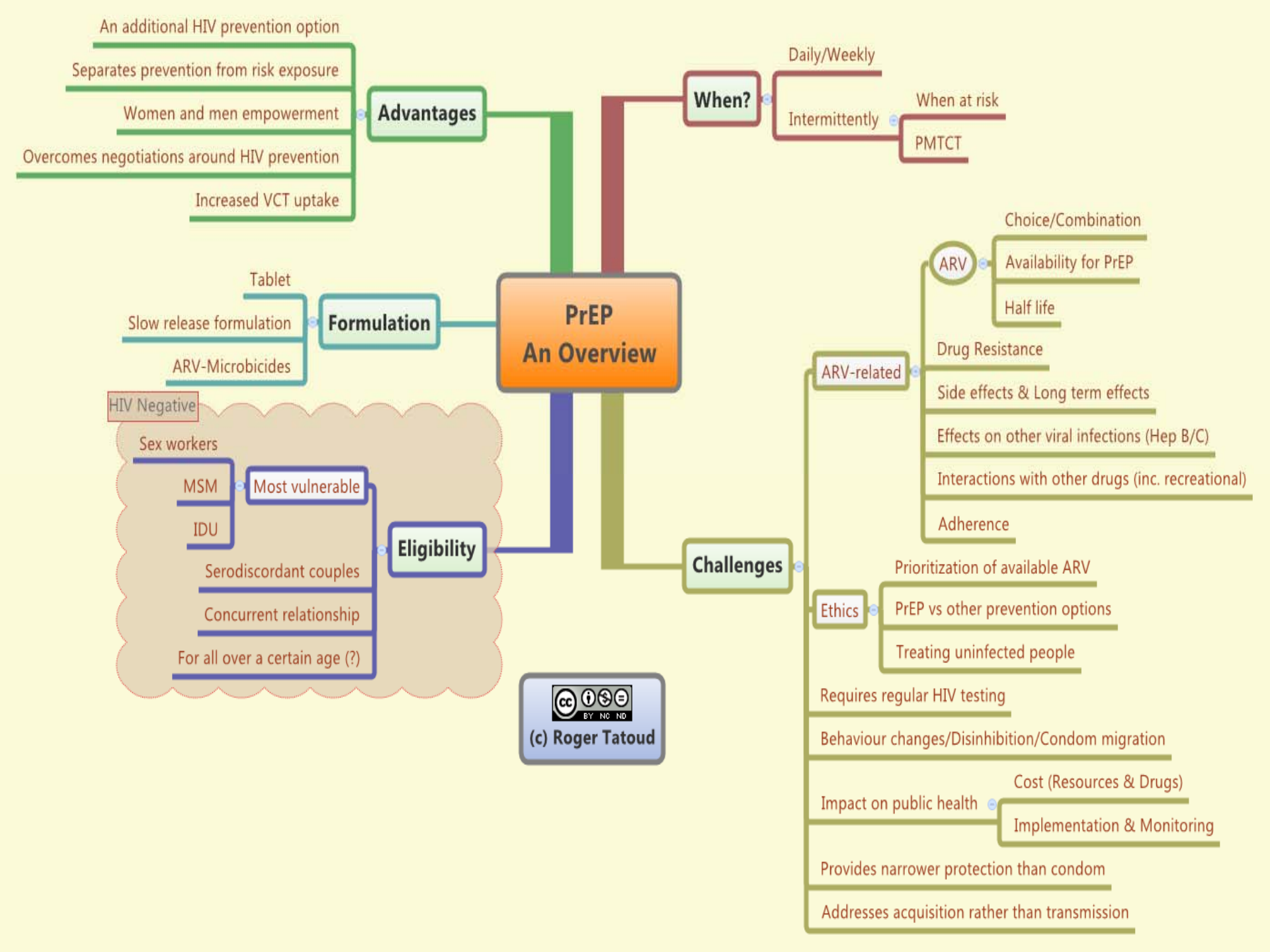
(Haberer, PLoS Medicine, 2013)

Correlates of Drug Detectability in iPrEX

- 179 samples from 7 sites were evaluated after Wk 24 visit
- Overall detection rate
  - TFV-DP: 50%
  - FTC-TP: 62%

Parameter	n	Drug Detected, %
US vs non-US		
▪ US	34	97
▪ Non-US	145	50
Age		
▪ ≥ 25 yrs	101	73
▪ < 25 yrs	78	44
Recent reported sex		
▪ URAI	49	76
▪ Sex, not URAI	107	59
▪ No sex	23	35

Anderson P, et al. Sci Trans Med, 2012


PrEP
An Overview
Advantages
An additional HIV prevention option
Separates prevention from risk exposure
Women and men empowerment
Overcomes negotiations around HIV prevention
Increased VCT uptake
When?
Daily/Weekly
Intermittently
When at risk
PMTCT
Formulation
Tablet
Slow release formulation
ARV-Microbicides
Eligibility
HIV Negative
Sex workers
MSM
IDU
Most vulnerable
Serodiscordant couples
Concurrent relationship
For all over a certain age (?)
Challenges
ARV-related
ARV
Choice/Combination
Availability for PrEP
Half life
Drug Resistance
Side effects & Long term effects
Effects on other viral infections (Hep B/C)
Interactions with other drugs (inc. recreational)
Adherence
Ethics
Prioritization of available ARV
PrEP vs other prevention options
Treating uninfected people
Requires regular HIV testing
Behaviour changes/Disinhibition/Condom migration
Impact on public health
Cost (Resources & Drugs)
Implementation & Monitoring
Provides narrower protection than condom
Addresses acquisition rather than transmission
(c) Roger Tatoud

Key scientific and implementation science questions for PrEP

Topic	Key questions
Priority populations	Who should be prioritized for PrEP? What are key PrEP messages, and how best to disseminate?
Uptake	What is level of interest in PrEP? Who will want PrEP? How to increase uptake in those who need it most?
Adherence	How will PrEP be used? (adherence, persistence) How to start/stop PrEP safely? What are effective strategies to increase PrEP adherence?
Sexual behavior	How will sexual practices change while taking PrEP? What are best approaches to minimize risk compensation?
Safety	What is long term safety of PrEP? (renal, bone) What is optimal HIV testing strategy and frequency?
Delivery	Where are PrEP delivery systems best located? How best to support PrEP providers?
Impact	How can cost-effectiveness of PrEP be maximized? How should PrEP be prioritized with other prevention strategies?

Baeten, Haberer, Liu et al JAIDS 2013

Ongoing and Planned PrEP Trials and Demonstration Projects, as of August 2013

Trial/project	Sponsor/funder	Type/Category	Location	Population	Design/Key questions	Status
Partners Demonstration Project	Led by a team of scientists from Kenya, Uganda and the US; funded by NIMH/NIH, USAID and BMGF	Demonstration Project	Kenya, Uganda	Serodiscordant couples	Evaluates HIV prevention preferences among approximately 1,000 HIV serodiscordant couples, adherence to PrEP and ART and interface of reproductive health priorities and ART-based prevention. Will implement PrEP as "bridge" to ART, providing PrEP to HIV-negative partner when HIV-positive partner is not yet on ART due to ineligibility based on country guidelines or personal decision.	All four sites open and enrolling as of August 2013; results expected in 2016.
LVCT and SWOP	Implemented by national partners in each country in collaboration with the World Health Organization, UNAIDS, O'Neill Institute of Georgetown University, London School of Hygiene and Tropical Medicine, Imperial College London; funded by Bill & Melinda Gates Foundation	Demonstration Project	Kenya	Young women, female sex workers and MSM	Aims to introduce PrEP into combination prevention interventions targeting young women, female sex workers and MSM. Formative research underway to assess consumer perceptions and identify potential barriers and opportunities related to introduction. Outcomes include criteria for PrEP indication among young women and a menu of interventions for target populations, including PrEP and feasible delivery options.	Formative research in planning phase; feasibility study report results likely in December 2013.
Nigerian National Agency for the Control of AIDS		Demonstration Project	Nigeria	Serodiscordant couples	Evaluates the effectiveness of various models for the delivery of PrEP and TasP as part of a combination prevention strategy for 1,200 heterosexual, serodiscordant couples. Couples will be recruited from facilities that provide prevention of vertical transmission, ART and other services. Study sites include Plateau, Edo and Cross River State. Study findings will be used to inform the scale-up of PrEP and TasP as part of a comprehensive national HIV-prevention package.	Formative discussions underway. No start date for demonstration project.
Wits Reproductive Health and HIV Institute		Demonstration Project	South Africa	Female sex workers	Aims to assess whether oral PrEP and TasP can be rolled out within a combination prevention and care approach tailored to the needs of 605, both HIV-positive and negative, female sex workers age 18 and older. Study sites include Hillbrow and Waterval Boven.	Expected start date of February 2014, with expected completion September 2016.
Durbar (DMSC) and Ashodaya Samithi		Demonstration Project	India	Female and transgender sex workers	Aims to assess the potential introduction of PrEP among female and transgender sex workers. The project includes sex workers part of the Durbar Mahila Samanwaya Committee (DMSC), a brothel-based sex work project in Sonagachi, and also the Ashodaya Samithi project, a CBO for street-based sex workers based in Mysore.	Feasibility study underway from May to September 2013, with results expected in October 2013.
The Demo Project	National Institute of Allergy and Infectious Diseases of the NIH	Demonstration Project	US (Miami, Florida; San Francisco, California; and Washington, DC)	MSM and transgender women	Aims to enroll 300 HIV-negative MSM and transgender women at City Clinic, while a sister project in Miami will enroll 200 participants in a PrEP regimen. Whitman Walker Clinic in Washington, DC, will also be a site, aiming to enroll approximately 100 participants.	Started October 2012. Expected completion by August 2014.
East Bay Consortium/ CRUSH (Connecting Resources for Urban Sexual Health)	California HIV/AIDS Research Program of the University of California	Demonstration Project	US (East Bay, California)	Young MSM of color	Aims to test and link young MSM of color to sexual health services; enhance and evaluate engagement and retention strategies for HIV-positive young MSM of color; and engage and retain HIV-negative young MSM of color in sexual health services, including PrEP.	Started in December 2012.

PrEP Demo Projects in the US

Study	Population (N)	Study design	Sites	Timeline
iPrEx OLE (Open Label Extension)	300 MSM /trans women enrolled in iPrEx RCT	Open-label daily FTC/TDF for 72 weeks	San Francisco Boston Chicago	Full enrolled; results 2014
Demo Project	600 MSM/trans women	Open-label daily FTC/TDF for 48 weeks	San Francisco Miami Washington DC	Enrollment Q3 2013, results 2015
CCTG 595	700 MSM/trans women	Open-label daily FTC/TDF for 48 weeks; Randomized to SMS support vs. SOC	San Diego Long Beach, LA Torrance	Enrollment Q2 2013, results 2016
PATH-PrEP	375 MSM/trans women	Open-label daily FTC/TDF for 48 weeks for high risk ; PEP for low risk	Los Angeles	Enrollment April 2013, results 2017
CRUSH	150 young MSM of color, high risk women	Open-label daily FTC/TDF	Oakland	Pilot phase: Q1 2013; expanded phase: Q4 2013
ATN 110 and 113	300 young MSM age 15-22	Open-label daily FTC/TDF for 48 weeks	All 14 ATN sites in US	Enrollment Dec 12, results Q4 2014
HPTN 073	225 Black MSM	Open-label daily FTC/TDF for 48 weeks	Washington DC, LA, Chapel Hill	Enrollment June 2013, results 2017
SPARK	~300 MSM and trans women	Open-label daily FTC/TDF; will evaluate PrEP messages and SMS	New York	Enrollment Q4 2013

Strategies to improve PrEP delivery and adherence

New PrEP drugs and dosing strategies

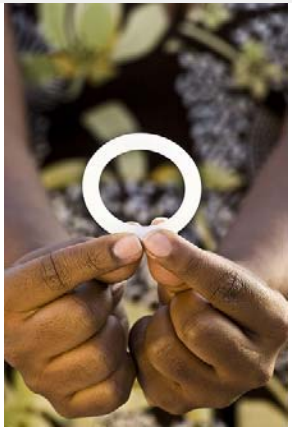
NEXT PrEP
AN HPTN/ACTG STUDY

HPTN 067 ADAPT

Novel adherence strategies

Alternative delivery systems and formulations

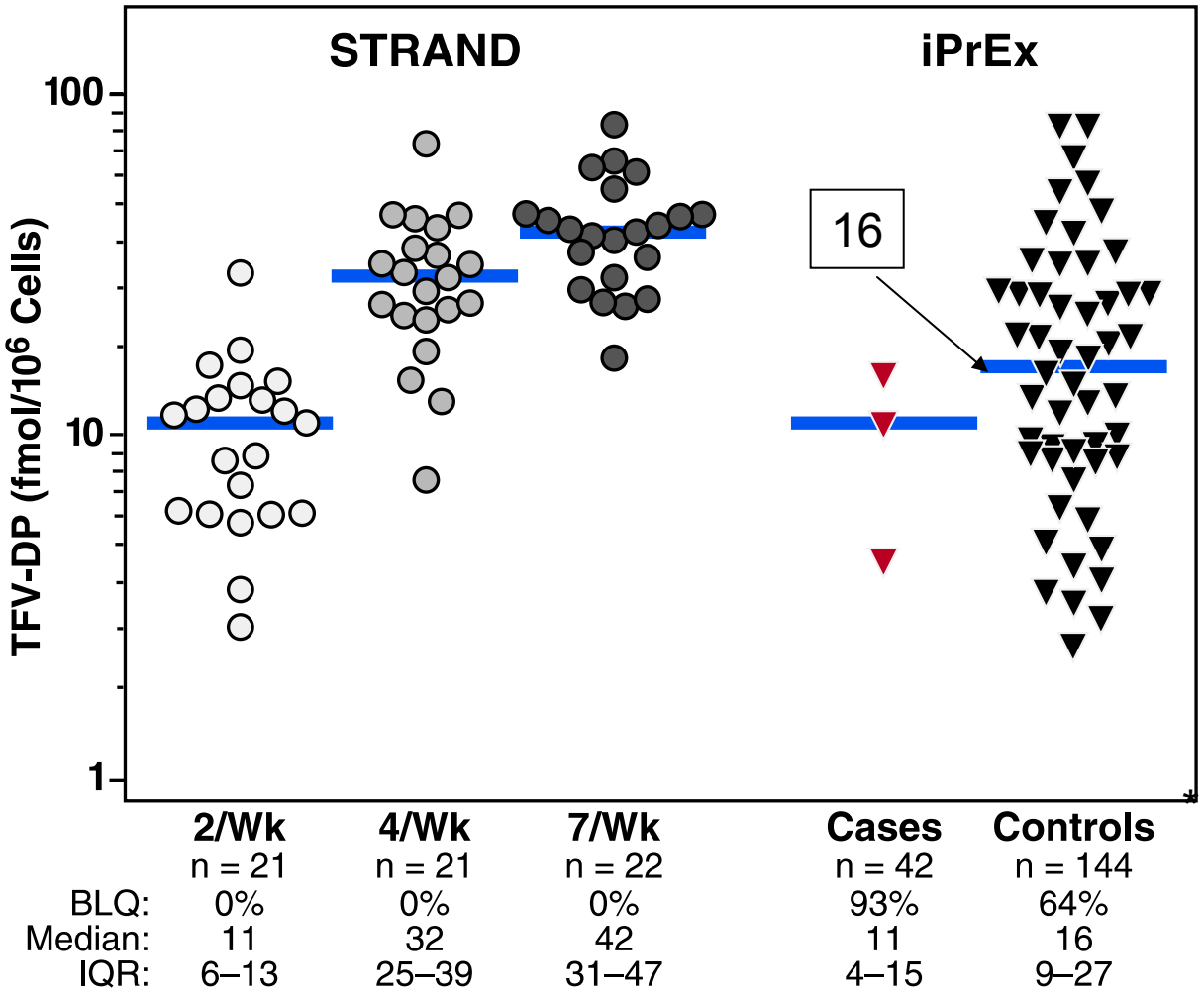
Rectal Microbicides: MTN-017 (TFV rectal gel)



Intra-vaginal rings: ASPIRE (Dapivirine)

Injectable PrEP: HPTN 076 (TMC278) HPTN 077 (GSK744)

TFV-DP Concentrations in IPrEx and STRAND



Regression analysis in iPrEx: 90% reduction in HIV acquisition when TFV-DP>16 fmol/10^6 cells

Predicted risk reduction:
76% with 2 pills / week
96% with 4 pills / week
99% with 7 pills/ week

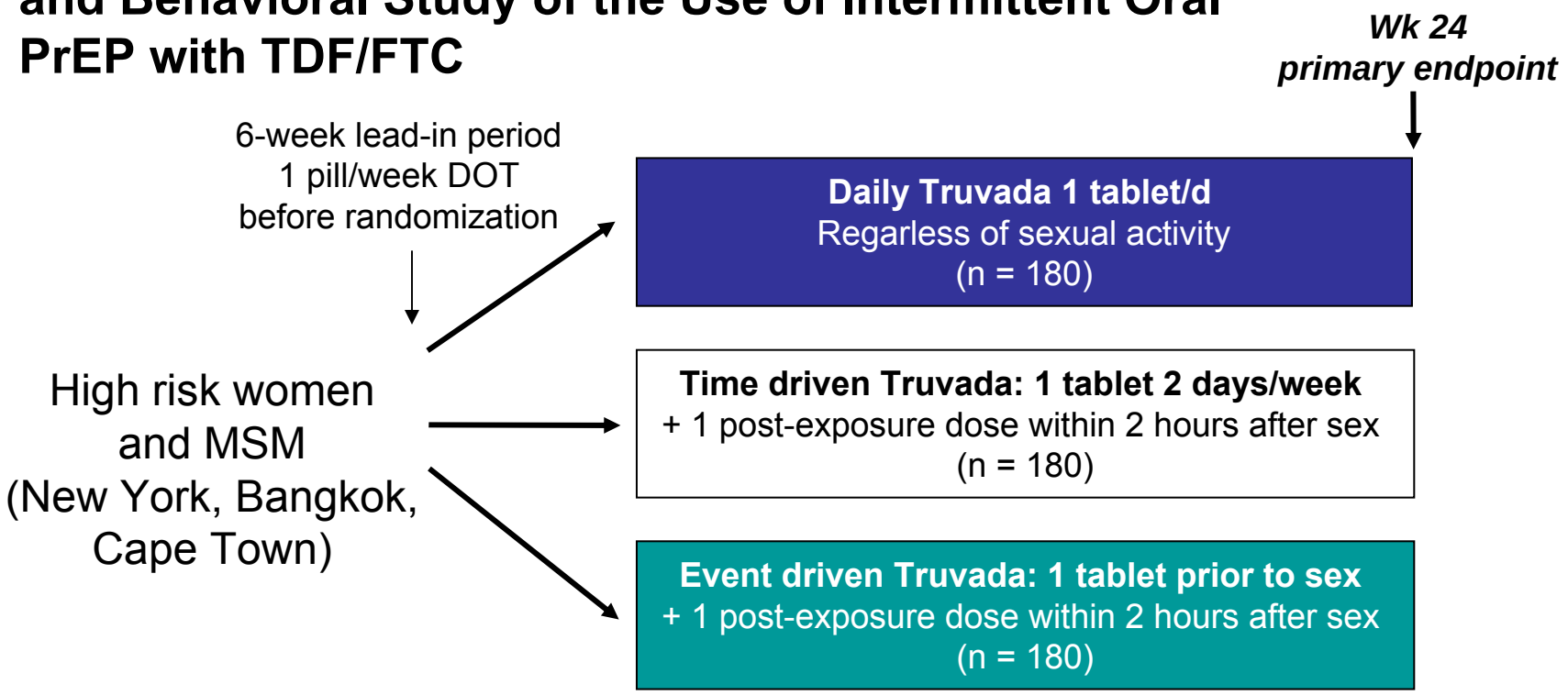
* Visit when HIV was first discovered

Anderson *et al, Science Translational Medicine* 2012 4:151ra125

HPTN 067/ADAPT

(Alternative dosing to augment PrEP pill taking)

Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral PrEP with TDF/FTC

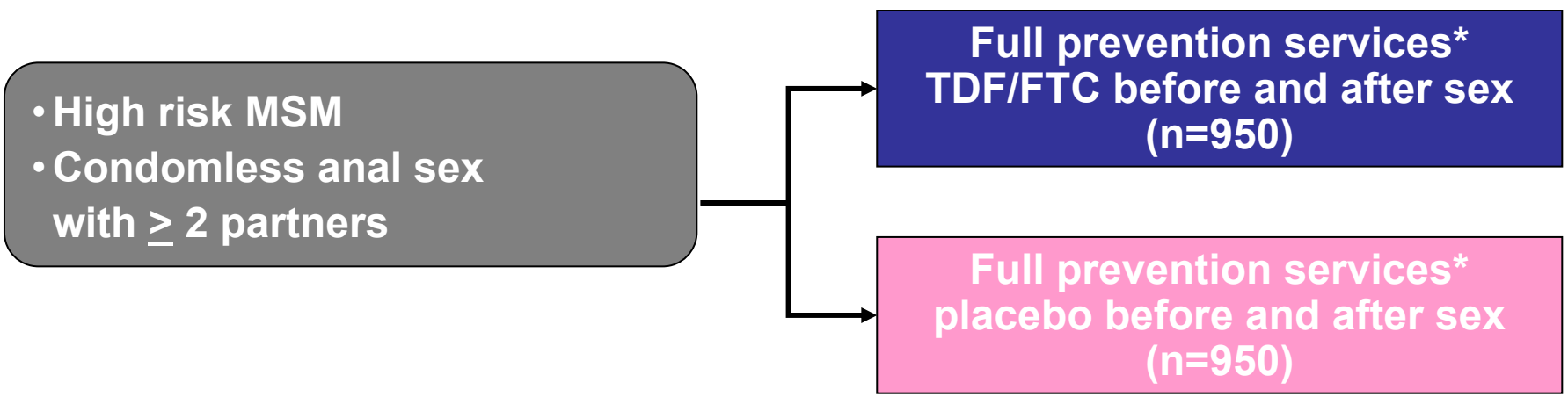


Primary Objective: Is intermittent vs. daily dosing associated with equivalent coverage of sex events, lower number of pills used and decreased side effects

R. Grant, F. Van Griensven, et al.

IPERGAY
Study Design

Effectiveness of "on demand" PrEP
Randomized placebo-controlled trial

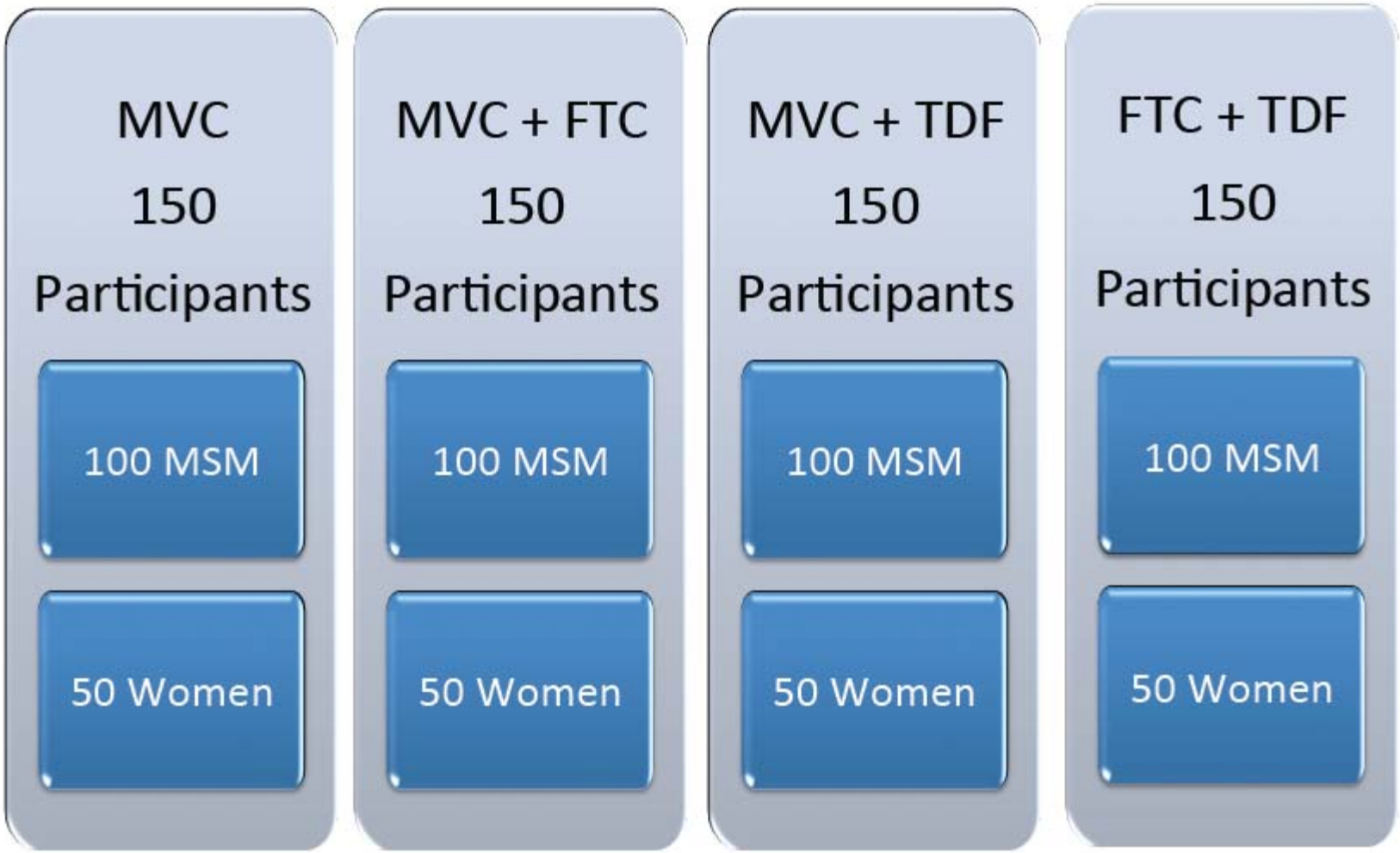


- Counseling, testing for STI, condoms, vaccination, PEP
- Primary endpoint : HIV infection, 64 events expected
- Incidence of HIV-infection: 3%PY, 50% efficacy, ~ 2000 pts

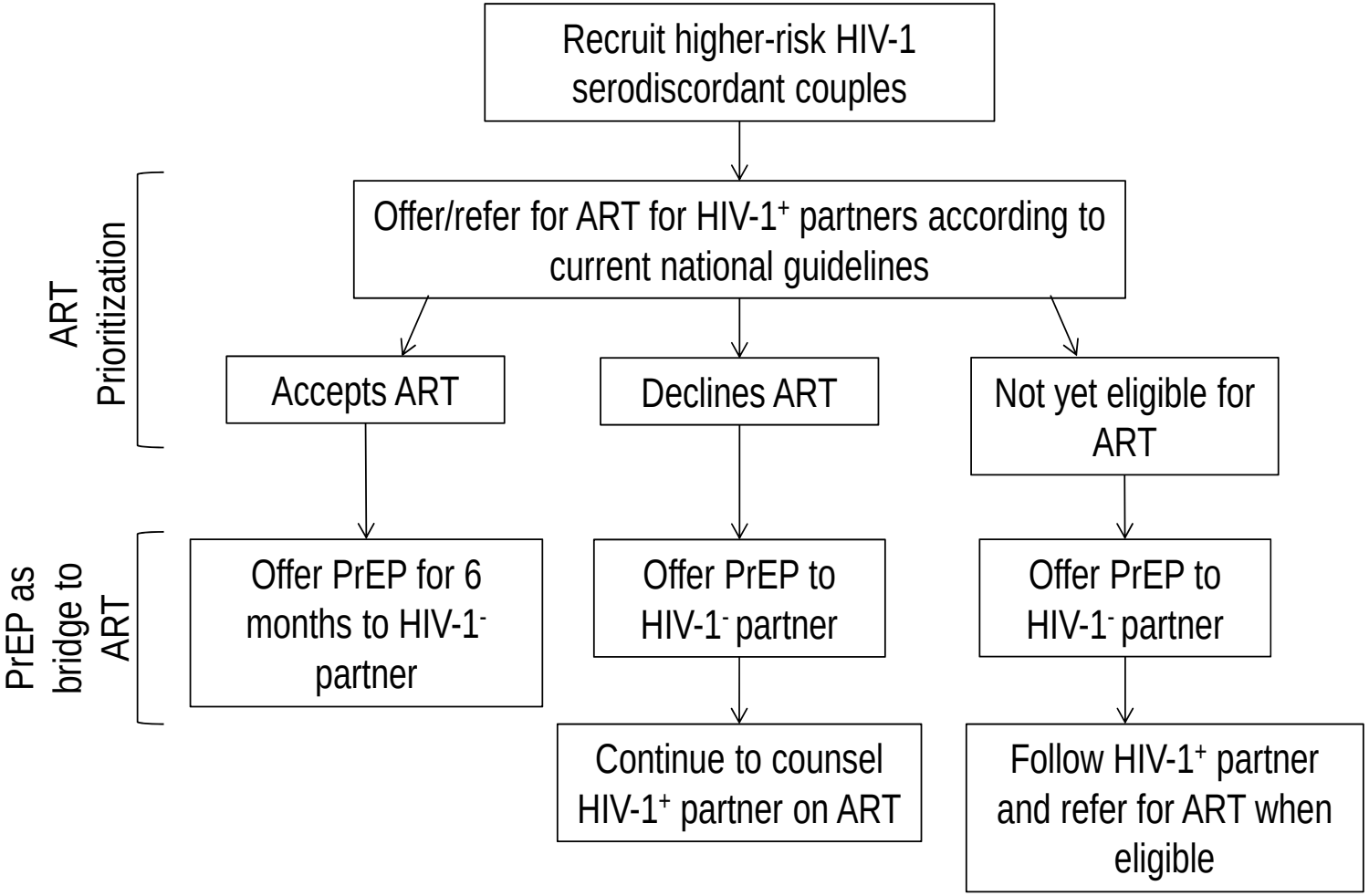
anrs
AGENCE NATIONALE DE RECHERCHES SUR LE SIDA
NATIONAL AGENCY FOR AIDS RESEARCH

the CTN
CIHR Canadian
HIV Trials Network

www.ipergay.fr


MVC
150
Participants
100 MSM
50 Women
MVC + FTC
150
Participants
100 MSM
50 Women
MVC + TDF
150
Participants
100 MSM
50 Women
FTC + TDF
150
Participants
100 MSM
50 Women

Partners Demonstration Project: optimizing PrEP & ART for prevention

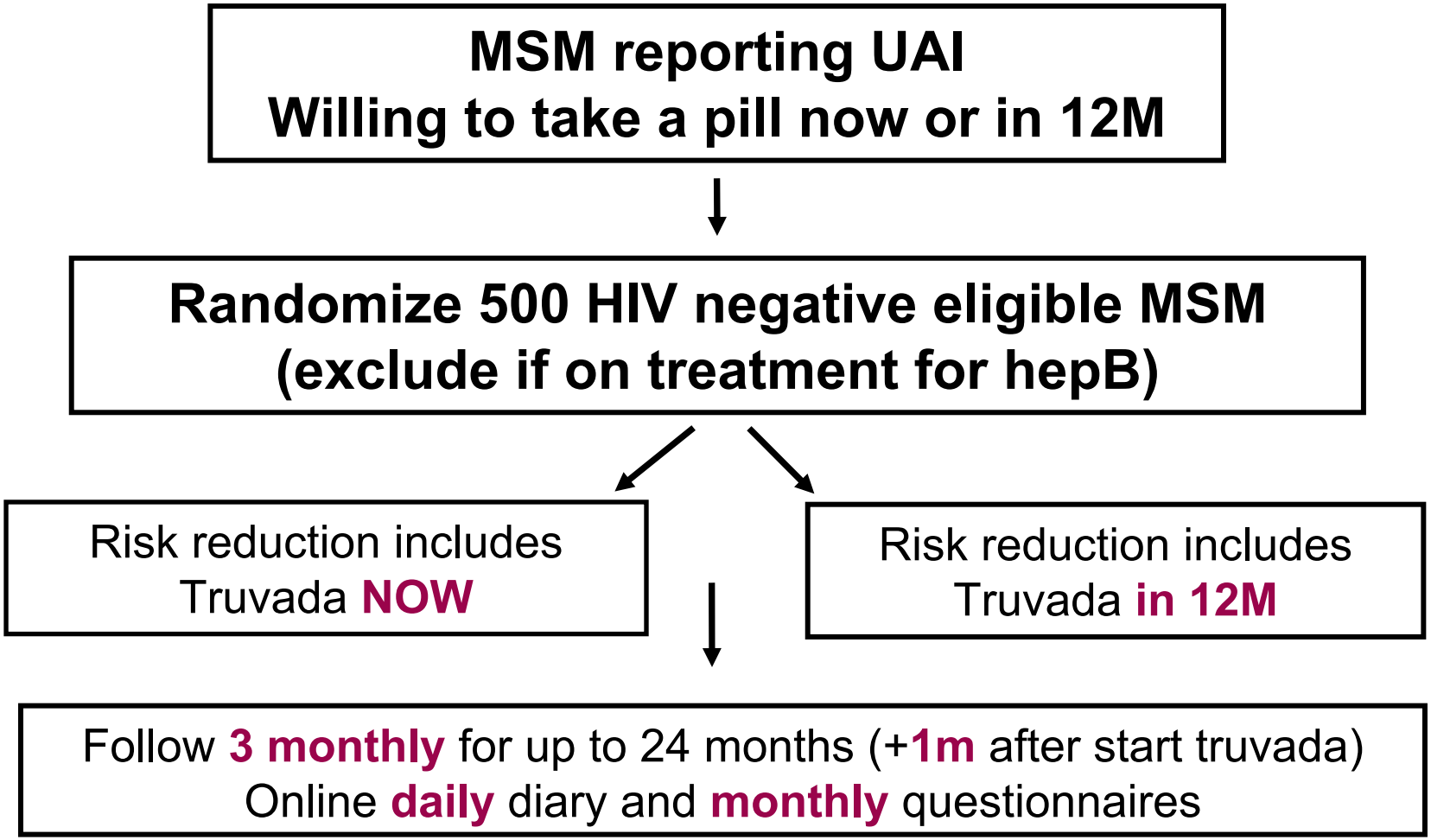


Timeline: late 2012 to mid 2016

Adolescent PrEP

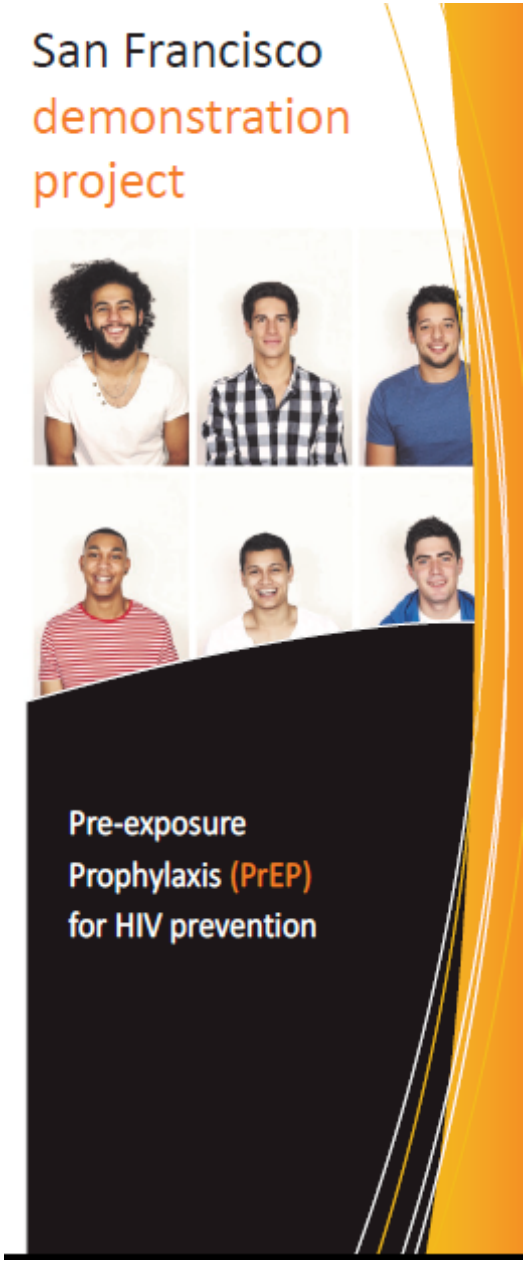
- ATN 082 enrolled 68 young MSM
- 70% agreed to take PrEP
- Of PrEP users, blood levels indicate about 50% adherence, comparable to self-report
- Lots of psychosocial issues reported
- ATN 110 and 113: open label TDF-FTC plus either group (Many Men, Many Voices) or individual intervention (Personal Cognitive Counseling)
- ATN 110: 18-12 yo; ATN 113: 15-17 yo

PROUD Pilot


MSM reporting UAI
Willing to take a pill now or in 12M
Randomize 500 HIV negative eligible MSM
(exclude if on treatment for hepB)
Risk reduction includes Truvada NOW
Risk reduction includes Truvada in 12M
Follow 3 monthly for up to 24 months (+1m after start truvada)
Online daily diary and monthly questionnaires

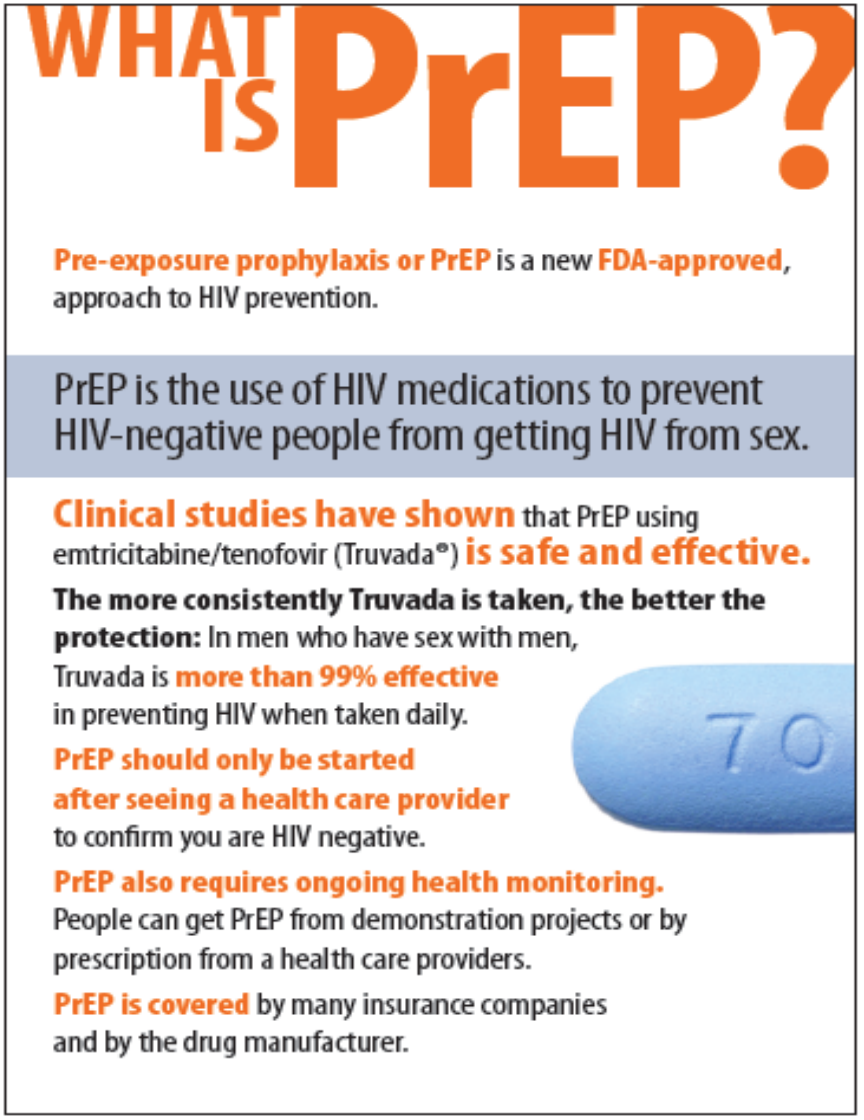
The SFDPH Demo Project

- NIAID-funded PrEP Demonstration Project in 600 MSM and transgender women
  - STD clinics in SF, Miami; CHC in DC
- Key objectives:
  - Assess PrEP uptake, adherence, resistance, and sexual behaviors in real-world setting
  - Determine staff and space needed for PrEP delivery
- Study procedures:
  - Provide TDF/FTC PrEP for 48 weeks
  - Study visits at 1 month, then quarterly
  - Safety monitoring (HIV, Cr) at each visit
  - Integrated risk reduction and adherence



SF Demo: Integrated Counseling (Liu et al)

- Education about pill use
- People who use PrEP more consistently have higher levels of protection against HIV
- Potential side-effects
  - Bloating, soft/more frequent stools, nausea
- Missed Doses
- Developing a routine
- Discussing PrEP with others
- Stopping and restarting PrEP



Some *preliminary* impressions (Al Liu)…

Social benefits

- Decreased anxiety
- Increased communication/disclosure
- Increased intimacy / trust
- Increased sense of community / self-efficacy
- Increased sexual pleasure

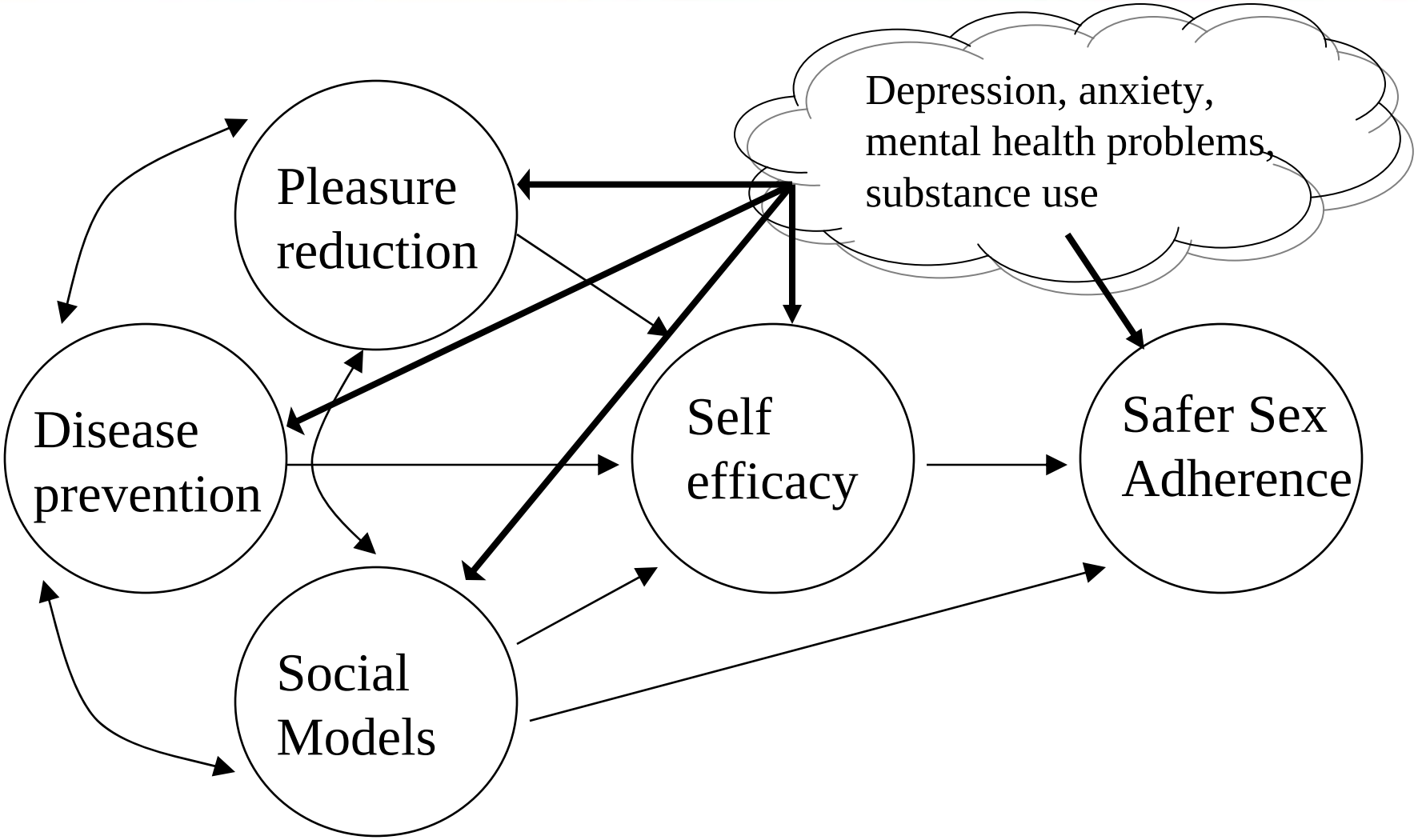
Social harms

•Stigma – HIV / risky behavior

•Negative health provider encounters

- **Anxiety about accessing PrEP after Demo Project**

Social Cognitive Model



Wulfert, Safren, et al., 1999; Journal of Applied Social Psychology

Project PrEPare (Fenway)

• Modeled after “Life-Steps,” (Safren et al) ART adherence intervention

•Modular intervention: 4 weekly visits with nurse and 2 booster sessions.

•Intervention content:

- CBT-oriented adherence problem-solving
- Brief motivational interviewing
- Identification of barriers and solutions
- Sexual risk-reduction strategies

Optional modules:

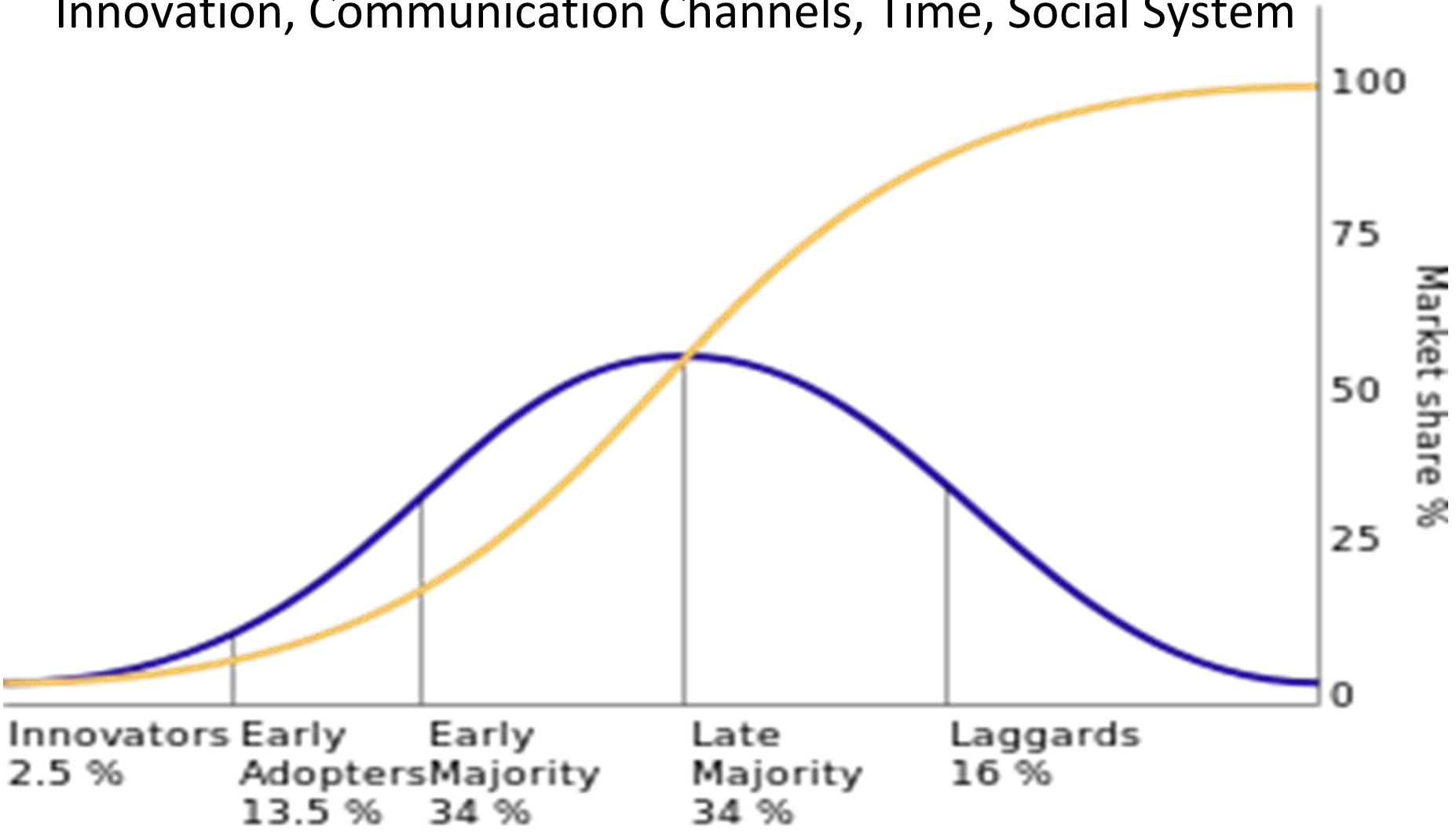
- Mental health and substance use issues

Adherence to PrEP was measured daily via Wisepill, and sexual risk taking was assessed by text messages (Lester, 2010)

Diffusion of Innovations

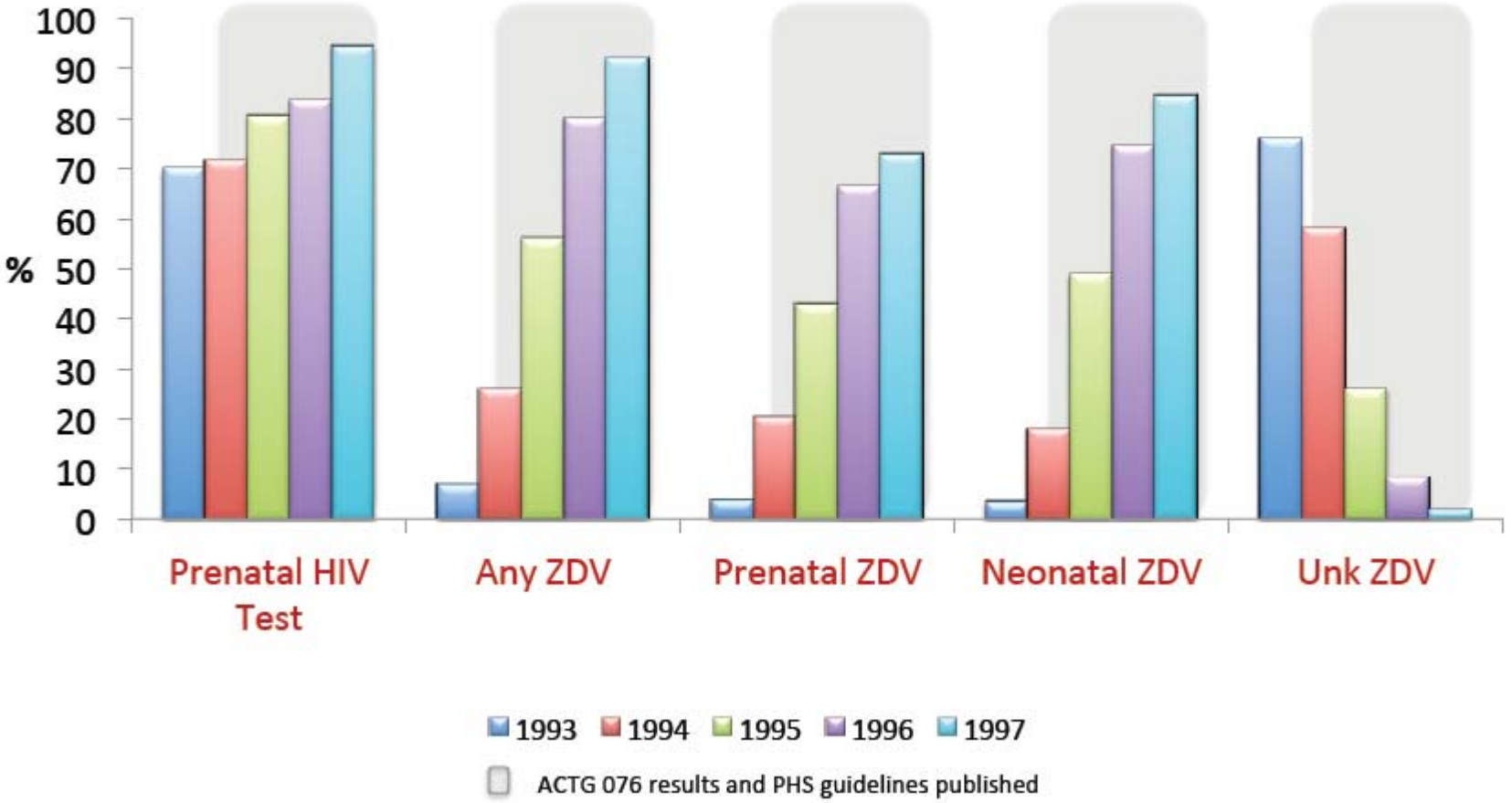
(Everett Rogers, 1962)

Innovation, Communication Channels, Time, Social System



Uptake of ZDV for perinatal prevention

(in 18 states with HIV surveillance)



Source: Lindegren et al., JAMA 1999; 282-531-38

PrEP Attitudes and Uptake

- Manhunt survey pre/post iPrEX

  -4,825 MSM:46 states and 5 Canadian provinces

  -Less than 20% heard of PrEP

  -Less than 1% had used PrEP

  -Majority were interested, depending…..

- Massachusetts MD survey post-CAPRISA

  -Most had heard of CAPRISA 004

  -Some knew that PrEP studies were underway

  -Many concerns about risk compensation, resistance, cost

Krakower et al, PLoS ONE, 2012; White et al, AIDS Pt Care and STDs, 2012

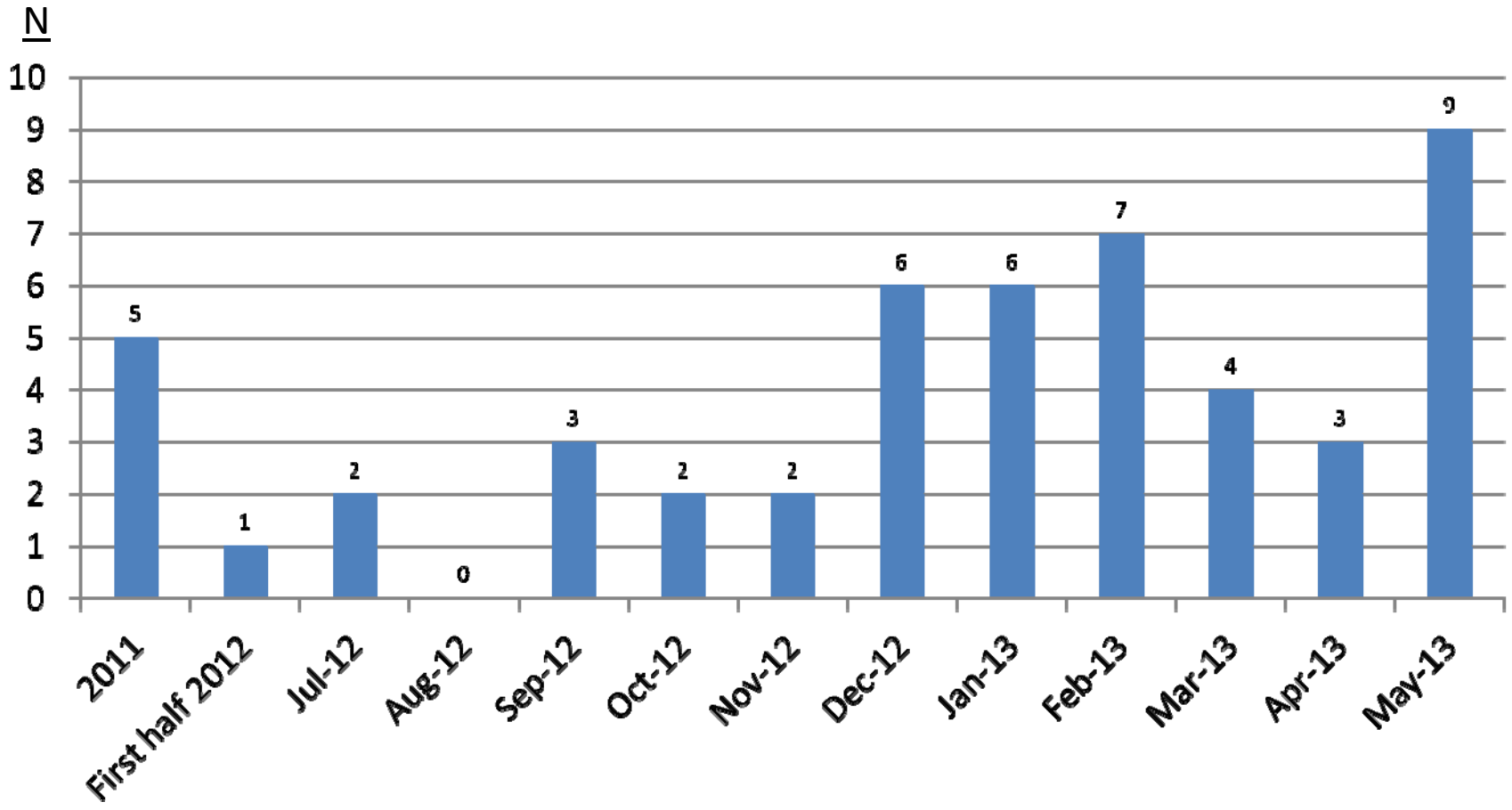
PrEP Use in the US, 2013

(Mera et al, ICAAC, 2013)

- Pharmacy record review (55% of US pharmacies)
- 1,774 pts on PrEP between 1/11 and 3/13
- 53% in 1st half of 2013: increase utilization?
- Median age: 37 y.o. 13.6% <25 y.o.
- Women 47.7% of users
- 49 states; 700 cities; largest N in the South
- Only 37% of PrEP providers also prescribed HAART
- Only 12% of prescribers were ID docs
- Did not capture those in trials (more MSM)

Non Trial PrEP Use at Fenway Health

Dates of Initiation (N=50)



To implement PrEP successfully, it will be essential to engage practicing clinicians

REVIEW | Annals of Internal Medicine

What Primary Care Providers Need to Know About Preexposure Prophylaxis for HIV Prevention

A Narrative Review

Douglas Krakower, MD, and Kenneth H. Mayer, MD

As HIV prevalence climbs globally, including more than 50 000 new infections per year in the United States, we need more effective HIV prevention strategies. The use of antiretrovirals for preexposure prophylaxis (PrEP) among high-risk persons without HIV is emerging as one such strategy. Randomized, controlled trials have demonstrated that once-daily oral PrEP decreased HIV incidence among at-risk men who have sex with men and African heterosexuals, including serodiscordant couples. An additional randomized, controlled trial of a topical pericoital antiretroviral microbicide gel decreased HIV incidence among at-risk heterosexual South African women. Two other studies in African women did not demonstrate the efficacy of oral or topical PrEP, raising concerns about adherence patterns and efficacy in this population.

The U.S. Food and Drug Administration (FDA) Antiviral Drugs Advisory Committee reviewed these studies and additional data in May 2012 and voted to advise the approval of oral tenofovir–emtricitabine for PrEP in high-risk populations. On 16 July 2012, the FDA recommended that this combination medication be approved for use as PrEP in high-risk persons without HIV. Patients may seek PrEP from their primary care providers, and those receiving PrEP require monitoring. Thus, primary care providers should become familiar with PrEP. This review outlines current knowledge about PrEP as it pertains to primary care, including identifying persons likely to benefit from PrEP; counseling to maximize adherence and reduce potential increases in risky behavior; and monitoring for potential drug toxicities, HIV acquisition, and antiretroviral drug resistance. Issues related to cost and insurance coverage are also discussed. Recent data suggest that PrEP, combined with other prevention strategies, holds promise in helping to curtail the HIV epidemic.

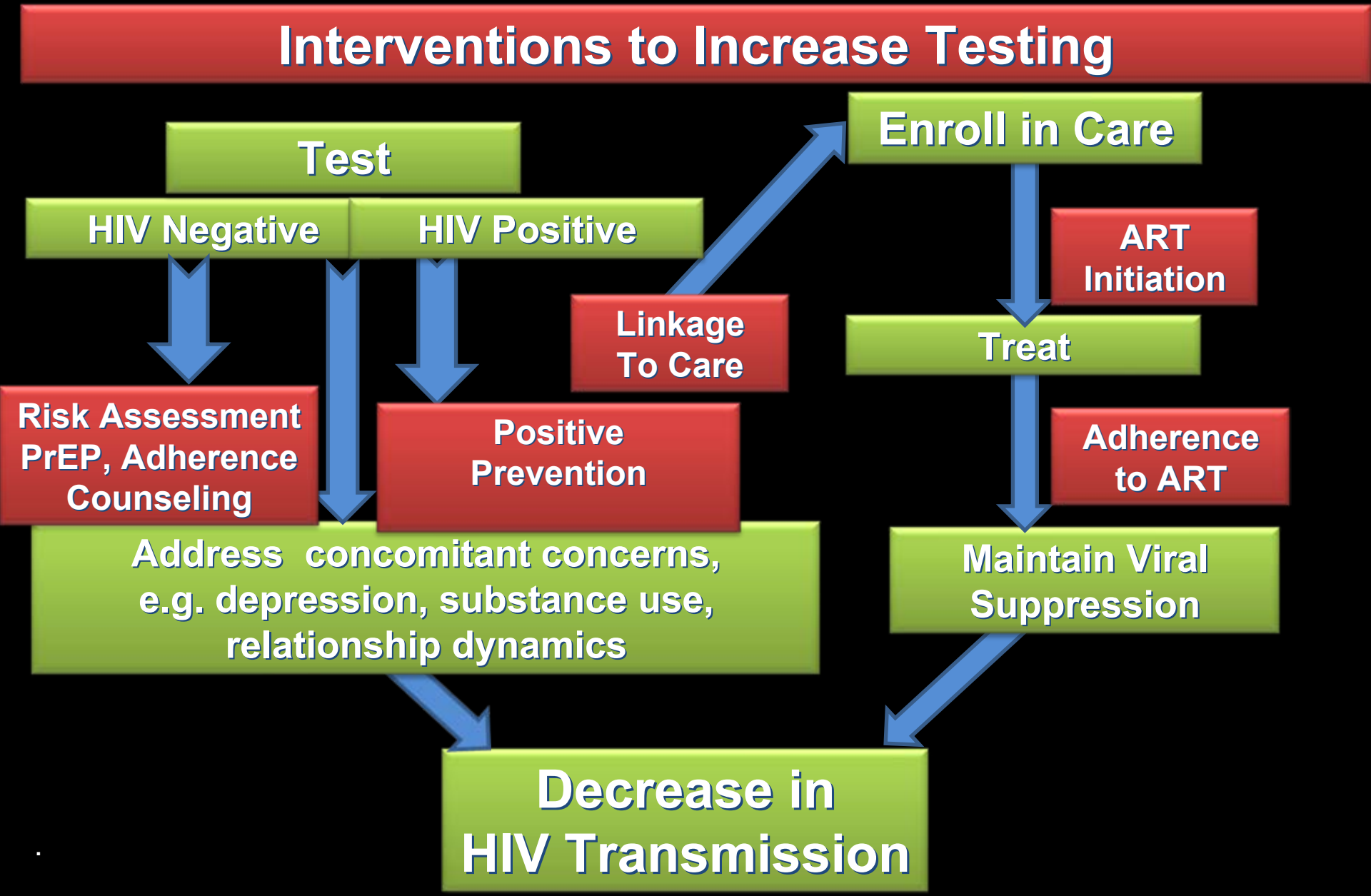
Ann Intern Med. 2012;157:490-497. www.annals.org
For author affiliations, see end of text.
This article was published on www.annals.org on 22 July 2012.

Purview paradox

Practical issue number one is that the people who are going to be prescribing these drugs in theory, who are going to be in the best position, are going to be primary care providers with little or no HIV experience.
–Male, Hospital-based

I think that the idea of adding to what I just did this morning and adding a discussion with my patients about what is their likelihood of having sexual encounters with patients who are HIV-infected, and then on top of that trying to prescribe and get approved medication like Truvada or some other pre-exposure prophylaxis… I just can't imagine it working in the hands of a primary care doctor.
–Female, Hospital-based

Combination Antiretroviral Prevention



Immunoprophylaxis: VRC01 IV or subQ

Dose Groups		VRC01 administration schedule in months (days)											
Group	N	0	0.5 (14)	1 (28)	1.5 (42)	2 (56)	2.5 (70)	3 (84)	3.5 (98)	4 (112)	4.5 (126)	5 (140)	5.5 (154)
1	20	VRC01 40mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV	
2	20	VRC01 40mg/kg IV				VRC01 40mg/kg IV				VRC01 40mg/kg IV			
3	20	VRC01 40mg/kg IV	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC
	4	placebo IV	placebo SC	placebo SC	placebo SC	placebo SC	placebo SC	placebo SC	placebo SC	placebo SC	placebo SC	placebo SC	placebo SC
Total	64	Intravenous (IV) doses administered in 100 mL of normal saline over 1 hr Subcutaneous (SC) doses administered in the minimum volume at 15 mL/hr using an SC infusion pump											

Thank You

Fenway Clinical, Epidemiological and Behavioral Research Teams

Fenway Medical Department

Slim and Quarraisha Abdool Karim

Jared Baeten

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Susan Buchbinder

Connie Celum

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NIAID, NIMH, NIDA, NICHD, CDC, HRSA, Mass DPH, Gilead

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