

Ongoing PrEP Studies: Timelines & Lessons Learned

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Can a pill (or a gel) prevent HIV?



- ... in women and in men
- ... in Africa, Asia, Americas, and the rest of the world
- ... by all routes of HIV transmission among adults



Outline

- Review the status of current PrEP studies
 - Particular emphasis on those studies potentially reporting results in the next year
- Lessons learned in current PrEP studies
- Thinking ahead
 - What we will and will not know from current studies



Status of Current PrEP Studies



Ongoing and Planned Efficacy Trials of PrEP



7 efficacy studies, up to 13 countries

20,000+ participants



CDC PrEP Studies

Location	Population	PrEP Intervention	Status
United States <i>phase II study</i>	400 men who have sex with men	TDF	<ul style="list-style-type: none">• Enrollment began February 2005• Fully enrolled• Results late 2009/early 2010 (safety & risk behavior)

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Thailand (Bangkok Tenofovir Study)	2400 injection drug users (~20% women)	TDF	<ul style="list-style-type: none">• Enrollment began June 2005• ~95% enrolled• Results 2010-2011• Interim efficacy review October 2009

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Botswana (TDF2 Study)	2400 heterosexual men and women	FTC/TDF	<ul style="list-style-type: none"> • Enrollments began March 2007 • <50% enrolled • Results 2011-2012

CAPRISA 004

Location	Population	PrEP Intervention	Status
South Africa <i>phase II study</i>	900 high-risk women	Vaginal TDF gel (coitally-dependent)	<ul style="list-style-type: none">• Enrollments began July 2007• Fully enrolled• One interim efficacy review completed; results expected 2010

Funder: USAID, FHI, CONRAD

iPrEx

Location	Population	PrEP Intervention	Status
Brazil Ecuador Peru South Africa Thailand United States	3000 men who have sex with men	FTC/TDF	<ul style="list-style-type: none">• Enrollments began July 2007• ~2300 enrolled• Results expected 2010-2011• Interim efficacy review November 2009

Funders: US NIH + BMGF

Partners PrEP

Location	Population	PrEP Intervention	Status
Kenya Uganda	3900 HIV serodiscordant couples	TDF FTC/TDF	<ul style="list-style-type: none">• Enrollments began July 2008• >2600 enrolled• Results expected Q4 2012

Funder: BMGF (to University of Washington)




PARTNERS PrEP STUDY

FEM-PrEP

Location	Population	PrEP Intervention	Status
Kenya South Africa <i>Site development ongoing (Malawi, Tanzania, Zambia)</i>	3900 high-risk, heterosexual women	FTC/TDF	<ul style="list-style-type: none">• Enrollments began May 2009• ~250 enrolled so far• Results potentially 2012

Funders: USAID + BMGF (to FHI)

VOICE

Location	Population	PrEP Intervention	Status
Uganda Zimbabwe <i>Site development ongoing (Malawi, South Africa, Zambia)</i>	4200 heterosexual women	TDF FTC/TDF Vaginal TDF gel (5 arm study: including oral and vaginal placebo groups)	<ul style="list-style-type: none">• Enrollments began September 2009 !!!• Results potentially 2012 

Funder: US NIH (through MTN)

Similarities and differences in the design of PrEP efficacy trials

- HIV seroconversion is primary endpoint = event-driven trials
 - Studies continue until a pre-defined number of endpoints is achieved
(*sample size an estimate of # needed to achieve those endpoints*)
- Safety is co-primary endpoint
- Trials assessing whether PrEP will have 50-70% efficacy
 - Larger trials will have confidence bounds to ensure excluding low efficacy (<25-30%)
- Seroconverters followed for ≥ 1 yr, for CD4, HIV-1 RNA, resistance testing
- Each trial is testing PrEP in a unique way
 - Population: IDUs, heterosexual, MSM
 - Agent: TDF, FTC/TDF, topical TDF
 - Location: Africa, Americas, Asia



Lessons Learned



Lesson #1: High expectations

- PrEP faces high expectations
 - Because of the potential for high efficacy for HIV prevention
 - Because of the challenges of implementation (cost, safety monitoring, HIV resistance)



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Funders, governments, global agencies, communities are watching these trials closely



Lesson #2: Slipping timelines

- Most PrEP trials have faced substantial delays – starting later than anticipated and moving more slowly than hoped



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We owe it to our participants, their communities, the funders (and ourselves) to conduct these studies as efficiently as possible.



Timelines

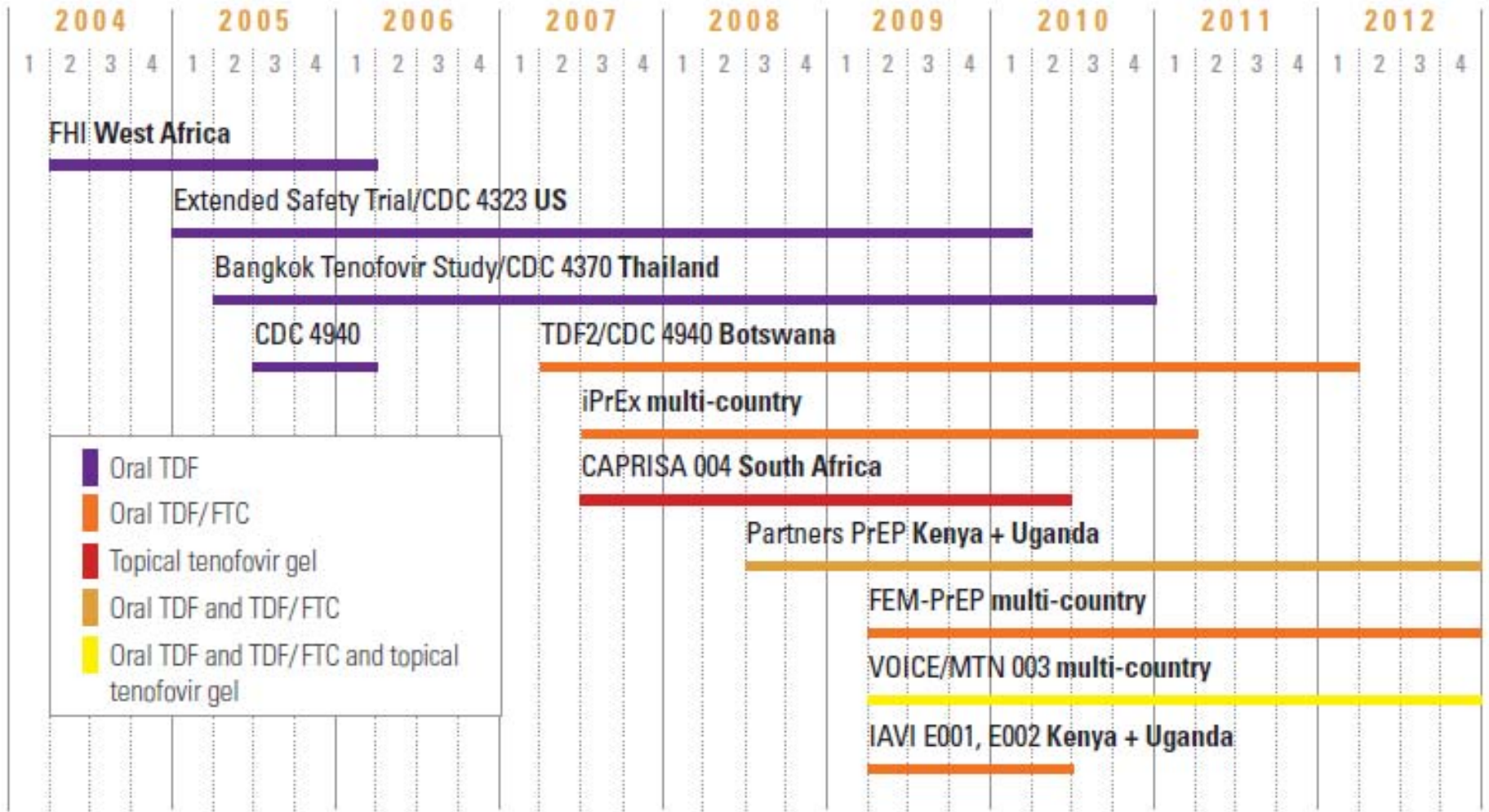


Figure: AVAC
<http://www.avac.org/ht/a/GetDocumentAction/i/3302>



Timelines

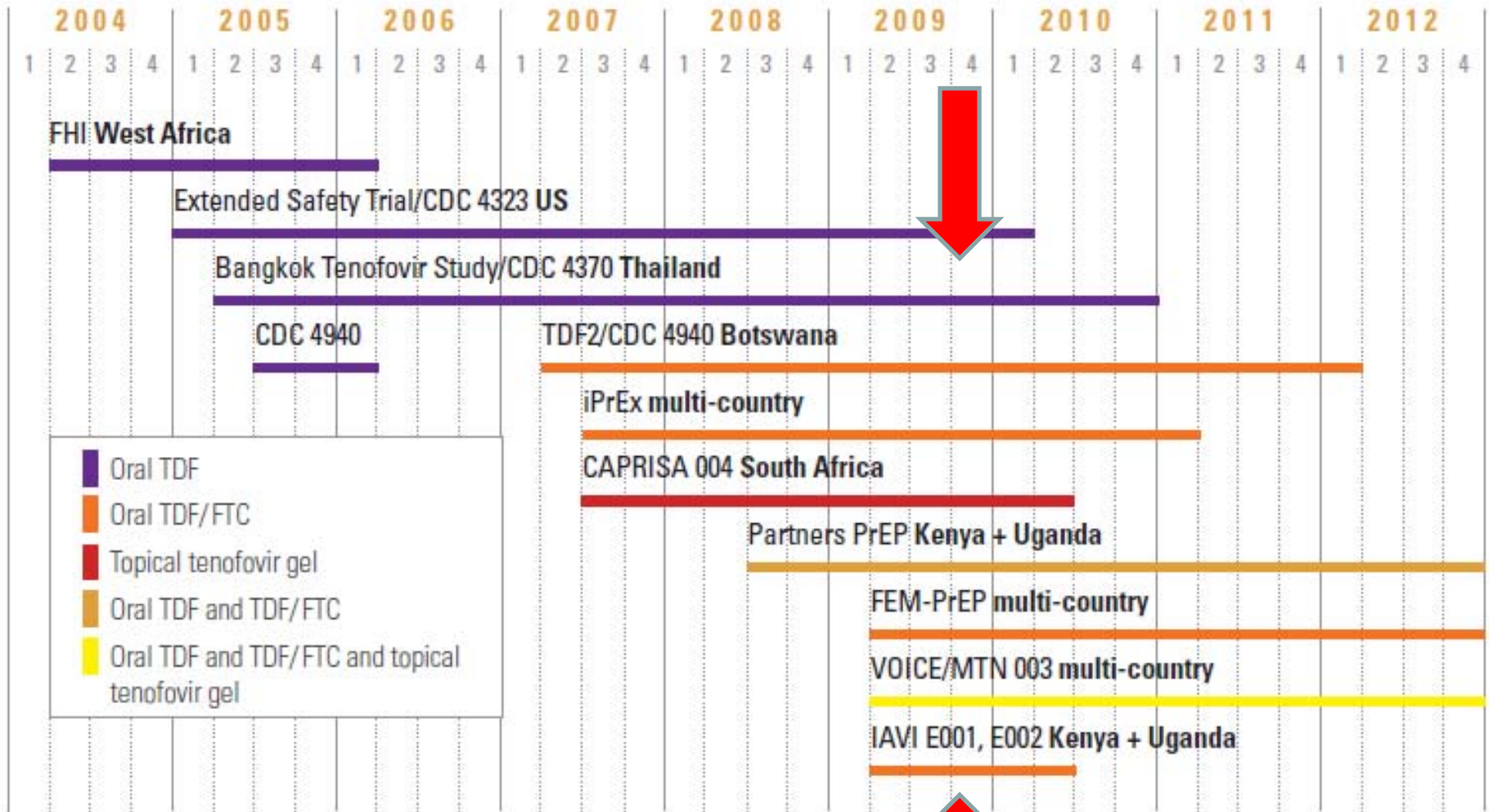


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Lesson #3: Lower HIV incidence

- Sufficient HIV incidence in study populations is required to measure efficacy (*endpoint driven trials*)
- Several PrEP trials have needed to expand their sample size in the face of lower than expected HIV incidence



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Declining incidence in communities and intensive prevention services in trials might lower incidence but do not reduce the necessity of these studies



Lesson #4: Co-enrollment

- Different PrEP studies are operating in parallel in countries and in communities
 - Kenya, Malawi, South Africa, Uganda, Zambia
- Co-enrollment is a risk to safety of study participants *(if taking double dose TDF)* and integrity of trial results *(if taking TDF from one trial and placebo from another)*



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We have to work together to ensure that our drive to enroll high numbers does not blind us to this risk & that systems are in place to detect co-enrollments



Lesson #5: Complex trials

- **Complex start-up and study procedures**
 - Monthly visits for HIV testing, study drug provision, safety assessment, adherence and risk-reduction counseling
 - Quarterly lab testing
 - Compounding numbers of visits
 - Multi-layered regulatory review & approvals



Everything is important, all at once

Recruitment

Retention

Adherence

Sample collection

Staff morale

Community

Referral partners

Etc. Etc. Etc.

QA/QC

Regulatory

Safety

Space

Study drug

Contraception

Communications



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The teams conducting these studies are the best in the world – ongoing PrEP trials have demonstrated the expertise of study sites and the dedication of participants



Lesson #6: Maintaining Adherence

- High adherence to study product is essential to know if PrEP works for preventing HIV
 - And adherence has been challenging in some HIV prevention trials
- Accurate, honest assessment of adherence helps us to understand the challenges to taking PrEP
 - Including understanding the possibilities of pill dumping and pill sharing



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Can we maintain high adherence, high attention to adherence, & optimize accurate reporting of adherence, in the midst of other priorities?



Lesson #7: Engage communities

- To engage the community & a wide range of stakeholders:
 - Ethical conduct of research, HIV testing & prevention
 - PrEP – rationale and ongoing studies
 - Relationship of PrEP to ART for HIV+
 - PrEP and HIV resistance – what is known, what is being learned in the trials
 - Planning for implementation
- PrEP is as much about *treatment* as it is about *prevention*



Community engagement



Community turn-out for Kabwohe initiation – September 2008



Lesson #8: Resistance is key

- Stakeholder concerns about resistance must be recognized
 - HIV treatment has been revolutionized by ARVs
 - Resistance is the primary concern of regulators, providers, and communities
 - Messaging regarding resistance is essential



Lesson #9: Clear communications

Clear and honest messages regarding PrEP and resistance, safety, behavior change, and costs of implementation must continue & require re-ënforcement.

Just one pill a day to keep virus away

BUYEKEZWA MAKWABE

SEXUALLY active people could end up choosing to pop a pill every morning to ward off HIV infection.

That is if a worldwide study on the pre-exposure prophylaxis (PrEP) drug Truvada as a preventative measure proves to be a success.

The research combines a preventative pill, counselling and the use of condoms by “high risk” individuals in the sex trade or unsteady, dysfunctional and risky relationships.

While countries like Botswana are studying the impact this has on heterosexual couples, South Africa is studying its efficacy on high risk, sexually active HIV-negative men who have sex with other men.

The Desmond Tutu HIV Centre at the University of Cape

immediately because an antiviral is on board.”

PrEP is a therapy taken to prevent, rather than to treat, an infection or illness and Truvada (a combination of two HIV treatment drugs — tenofovir and emtricitabine) is already being used to treat people with HIV infection.

Research done by the institution showed 10% of men who engaged in sex with other men were infected and 35% in townships. UNAids research showed there were 4.3 million new HIV infections worldwide in 2006.

Bekker said South Africa was a country that continued to see an increase in new HIV infections.

She said men who had sex with other men were a vulnerable group and while studies were done on heterosexual couples, this group had received little attention, especially in Africa.

Of the 3 000 men having sex with other men worldwide that will take part in the study, 200 will come from Cape Town — Khayelitsha, Guguletu, Mitchells Plain, Retreat, Sea Point and Green Point.

“Our recruitment is in the greater Cape Town area. We are

HIV in SA: key facts

- People with HIV: 5.5 million
- Proportion of population (over the age of two) with HIV: 10.8%
- Pregnant women with HIV: 29.1%
- Babies infected with HIV every year: about 60 000 (born with HIV and



Lesson #10: We are all in this together

- Ongoing PrEP studies are interwoven and interdependent
 - Challenges affecting one trial affect all
 - Important & helpful to share lessons & successful strategies
 - Partners PrEP and VOICE are ‘sister’ studies
 - Similar approach to efficacy, safety, and resistance could allow combined analyses of more rare issues (safety, resistance) that neither could do alone



Partners PrEP Team



UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER



2008 PARTNERS PREP MEETING
SPEKE RESORT MUNYONYO - KAMPALA, UGANDA

Thinking Ahead



Anticipating results from other PrEP trials

UNAIDS / CDC / GCM stakeholders meeting

Kampala, March 2009

- Consensus for need for multiple trials of PrEP, to ensure confidence in efficacy estimates and efficacy across populations
- Strong consensus that positive efficacy results in one trial, or two, should not halt other trials
 - Particularly necessary to understand safety and efficacy in women & in African populations
 - *(Arguably, important to understand safety and efficacy in multiple African populations, given differences in HIV-1 clade [potential K65R for clade C], and to give broadest possible demonstration in anticipation of implementation)*



What we will learn from current PrEP trials

- If positive results (≥ 2 studies), will have proof of concept
 - i.e., TDF and/or TDF/FTC = effective as PrEP *in populations studied*
- Will be some understanding of relationship of adherence to efficacy
 - Adherence biomarkers (plasma, PBMCs) may be key
- Will have excellent information on 1-3 year safety
 - Among those with normal renal, liver & hematologic function
- Will have some information about resistance with PrEP
 - But, anticipating few breakthrough infections with resistance
- Will be able to detail the impact of PrEP on behavioral risks
 - In context of intensive prevention provided in trials



What we'll want to know about PrEP: safety & adherence

- Safety
 - Other populations: pregnant & breastfeeding women, adolescents
 - Resistance – frequency, persistence, potential spread in communities
- Adherence
 - Long-term adherence, adherence in “real world”
 - Intermittent dosing – efficacy and adherence?
- Safety & efficacy of other classes of ARVs for PrEP

CCR5 inhibitors (e.g., maraviroc)

TMC278 (injectible?)



What we'll want to know about PrEP: sexual behavior if PrEP efficacious

The Next Condom Conundrum

Why use a rubber when you can just pop a pill? That's what HIV-negative guys across the country are asking themselves -- and their doctors.

ADVOCATE.COM

January 2009

- How much will people increase their risks if they feel protected by PrEP?
- How much will that reduce effectiveness of PrEP ?
- How to target to highest risk, clearly message about efficacy yet stress partial protection of PrEP?



While waiting for efficacy results, preparing for PrEP implementation

- Targeting to those at highest risk
 - *Discordant couples?*
 - *Behaviorally high-risk MSM, heterosexual women and men?*
- Frequency of HIV & safety testing in persons on PrEP
 - Balancing feasibility, costs & need to minimize PrEP exposure after HIV infection
- Population surveillance for ART resistance
- Extensive stakeholder & community preparation about concept of PrEP
- Who will pay? For how long?



Partners PrEP Team

- **UW Coordinating Center**
Connie Celum (PI), Jared Baeten (Co-Chair and Medical Director)
Linda Barnes (Program Manager), Deborah Donnell (Protocol Statistician), Justin Brantley, Jeanne Conley, Amy Dao, Carlos Flores, Harald Haugen, Renee Heffron, Jim Hughes, Erin Kahle, Johanna Karas, Becky Karschney, Lara Kidoguchi, Meighan Krows, Matt Leidholm, Jai Lingappa, Toni Maddox, Amalia Magaret, Julie McElrath, Allison Mobley, Susan Morrison, Nelly Mugo, Andrew Mujugira, Vikram Nayani, Patrick Ndase, Apollo Odika, Hilda O'Hara, Dana Panteleeff, Alice Rose, Marothodi Semanya, Heena Shah, Calvin Tran, Richard Wang, Ellen Wilcox, Christy Wilson
- **Sites**
 - Eldoret, Kenya (Moi Univ, Indiana Univ): Edwin Were (PI), Ken Fife (PI), Cosmas Apaka
 - Jinja, Uganda (Makarere U, UW); Patrick Ndase (PI), Elly Katabira (PI), Paul Muwanguzi
 - Kabwohe, Uganda (KCRC): Elioda Tumwesigye (PI), Stephen Asiimwe
 - Kampala, Uganda (Makarere U): Elly Katabira (PI), Allan Ronald (PI), Edith Nakku-Joloba
 - Kisumu, Kenya (KEMRI, UCSF): Elizabeth Bukusi (PI), Craig Cohen (PI), Josephine Odoyo
 - Mbale, Uganda (TASO, CDC): Jonathan Wangisi (PI), Christine Nabiryo (PI), Akasiima Mucunguzi
 - Nairobi, Kenya (U Nairobi, UW): James Kiarie (PI), Carey Farquhar (PI), Grace John-Stewart (PI), Harrison Tamooch, Freda Kinoti
 - Thika, Kenya (U Nairobi, UW): Nelly Mugo (PI), Kenneth Ngure
 - Tororo, Uganda (CDC, TASO): Jim Campbell (PI), Jordan Tappero (PI), Aloysious Kakia
- **DF/Net:** Lisa Ondrejcek, Darryl Pahl, Richard Berman, Gavin Radkey
- **CLS:** Wendy Stevens, Charlotte Ingram, Mumtaz Booley, Feroza Bulbulia, Nombulelo Gqomane, Jan van den Heuvel
- **ClinPhone**
- **Gilead (study drug):** Jim Rooney, Rich Clark, Abboud Habr, Farideh Said
- **Bill & Melinda Gates Foundation (study funder):** Renee Ridzon, Stephen Becker
- **HIV discordant couples who test, screen, & participate**



Thank you, and we wish you a very
successful first year in VOICE!



PARTNERS PrEP STUDY