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# Partners in Prevention

## Challenges, Characteristics, & Lessons Learned in a Clinical Trial among HIV Discordant Couples

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Institute of Medicine  
Methodological Challenges in HIV Prevention Trials  
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# Interventions to Prevent HIV Transmission

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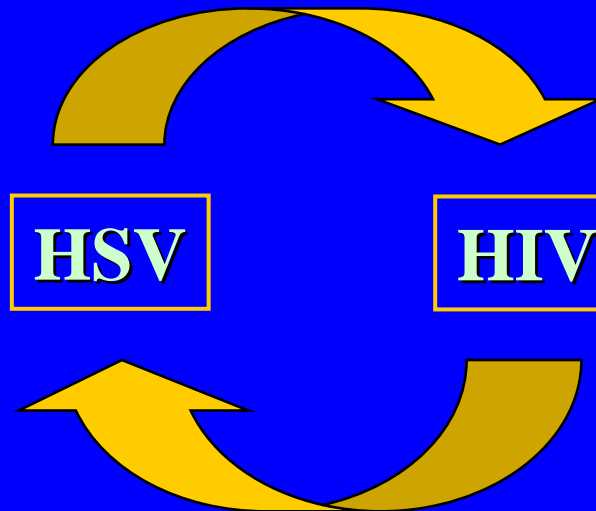
- Most HIV transmissions in Africa occur in HIV discordant couples unaware of their HIV discordancy
- HIV+ persons not on HAART
- HAART likely reduces HIV transmission
  - However, drug toxicities, resistance, costs unlikely to increase its use for HIV prevention for those with higher CD4 counts
- Behavioral interventions have limited impact
- Need a biologic intervention to reduce HIV transmission in persons not on HAART
  - Will stimulate more people to learn their HIV status
  - HSV-2 & male circumcision are possible strategies

# HSV-2 and HIV interactions

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Increased HIV susceptibility & infectivity

- HSV-2 ↑ risk of acquiring HIV 2-3 fold

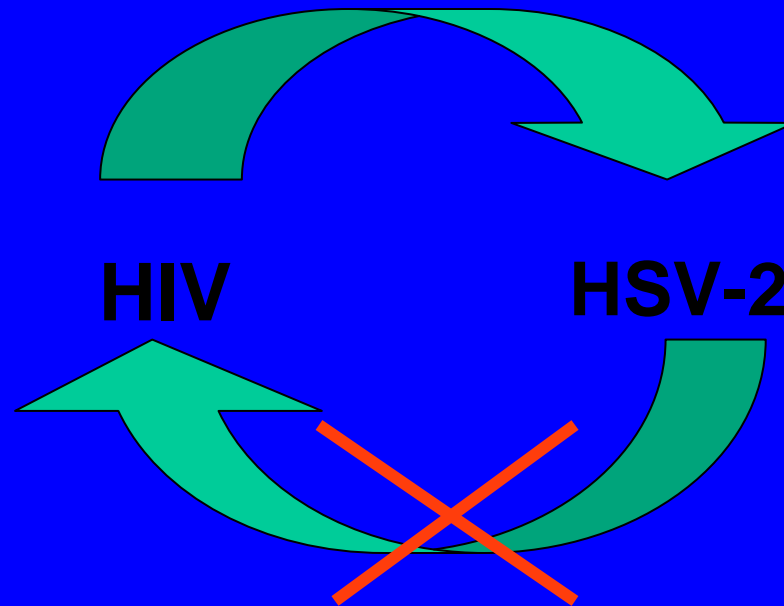


- HSV-2 ↑ HIV levels in plasma & genital tract
- HSV-2 risk of HIV transmission (Rakai)

Increased frequency & duration of GUD

# HSV-2 suppression and HIV

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## Effect of HSV-2 suppression on HIV

- ↓ HIV levels in plasma & genital tract
- ↓ symptomatic herpes, ↓ HSV shedding

## Need to know re HSV-2 suppression on

- HIV acquisition
- HIV transmission

# HSV-2 Suppression to Prevent HIV Transmission

**3300** HIV- discordant couples with HIV+ partner also HSV 2-coinfected



Randomize HIV/HSV-2 + persons w/ CD4  $\geq$ 250



Acyclovir 400 mg twice daily



Placebo twice daily



Follow couples for 1-2 years

**1° endpoint: HIV infection in HIV-negative partner**  
(estimated 4% in placebo arm)



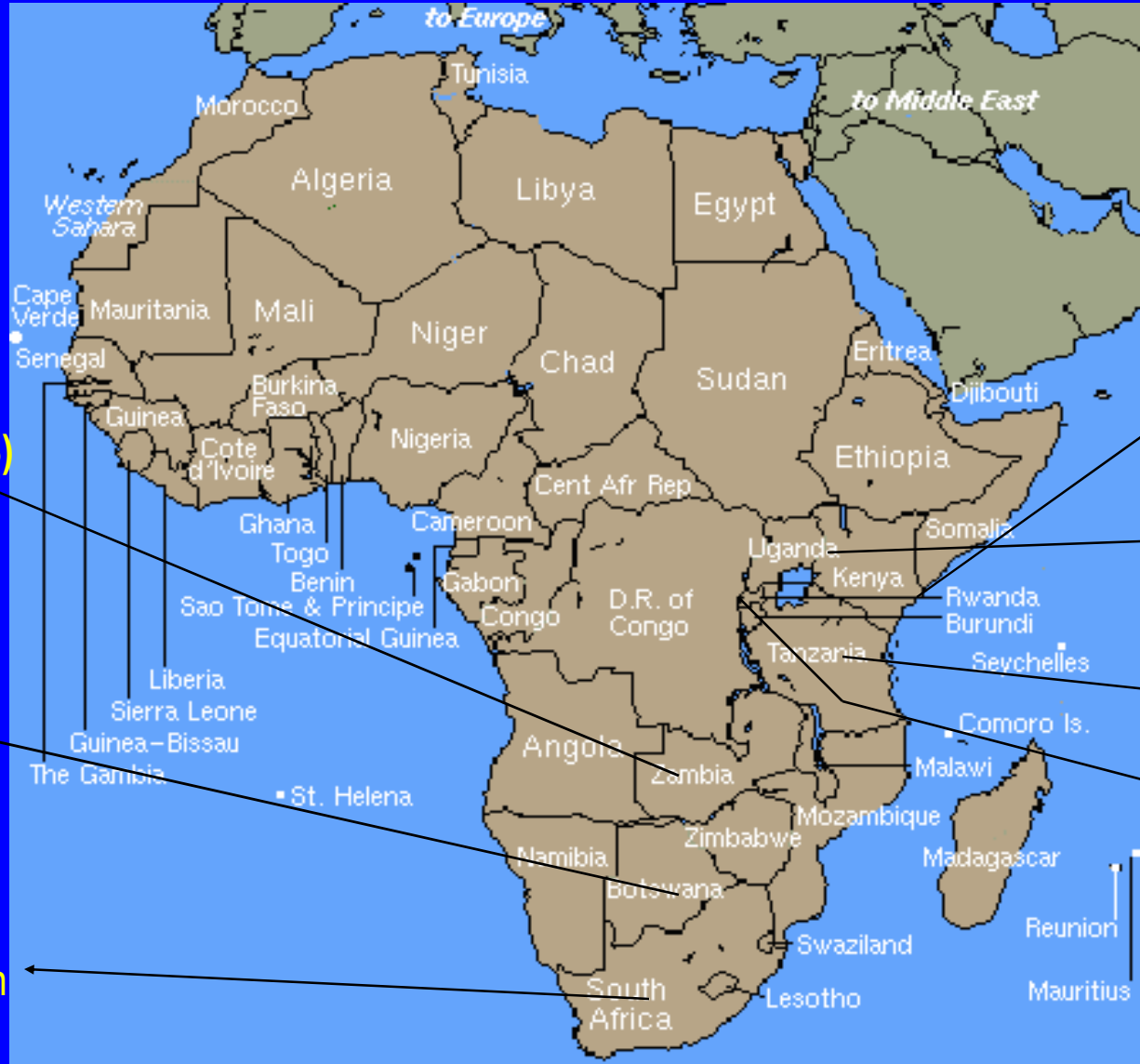
# Partners in Prevention Objectives

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- Primary objective: Assess HIV transmission to HIV-neg partners
  - Hypothesis: HSV-2 suppression will ↓ HIV transmission by 50%  
(in context of prevention services & bacterial STI treatment)
- Secondary Objectives: Effect of HSV-2 suppression on ...
  - ◆ HIV levels in blood and genital tract and CD4 count
  - ◆ Incidence of asymptomatic & symptomatic genital herpes
  - ◆ Changes in sexual behavior
  - ◆ Incidence of herpes zoster (shingles)
  - ◆ Will assess per-contact transmission rates for covariates (gender, HIV levels, CD4, circumcision, STIs)



# 14 Sites for HSV-HIV Transmission Trial



Lusaka, Kitwe,  
Ndola, Zambia (3)

Gaborone,  
Botswana

Soweto, Orange  
Farm, Cape Town  
SA (3)

Nairobi, Thika  
Eldoret, Kisumu  
Kenya (4)

Kampala, Uganda

Moshi, Tanzania

Kigali, Rwanda



# HIV discordant couples: Significance & additional challenges

- HIV transmission in Africa often occurs within HIV discordant couples in stable partnerships
- For each couple in which one partner is HIV-positive, ~50:50 chance their partner is HIV-discordant
- However, most couples are not aware of their HIV discordancy
  - ◆ HIV disclosure by HIV+ is low (~ 20%) due to stigma
  - ◆ Men are reluctant to be tested for HIV
  - ◆ Small proportion (~10%) test for HIV as couples
- Requires large community outreach & VCT collaborative effort



# Prevention trials with couples to reduce infectiousness are the most challenging!

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- Deliver intervention to the infected & follow the susceptible for transmission
  - ◆ Requires twice the participants & visits
- When submitted grant Jan 2003, limited experience with recruiting HIV discordant couples
- Sites found effective recruitment strategies
  - ◆ Have exceeded total HIV discordant couples published in the literature (2000) over 20 years



# What did we expect about recruitment?

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- We expected:
  - ◆ Discordant couples are highly prevalent, given HIV prevalence in sites and prior data
  - ◆ May have screened to enrolled ratios of 15 to 30:1:
    - If HIV prevalence is 10%, screen 10 couples to find a couple where one partner is HIV-positive
    - 50:50 chance their partner is HIV-negative
    - Thus, may need to screen 20 couples to find an HIV discordant couple
  - ◆ Anticipated cohort characteristics
    - Cohabiting HIV-discordant couples
    - Asymptomatic HIV+ partner, given CD4 >250
    - Regular sex partners
    - There may be regional differences in study cohort
    - Local recruitment factors may impact on characteristics

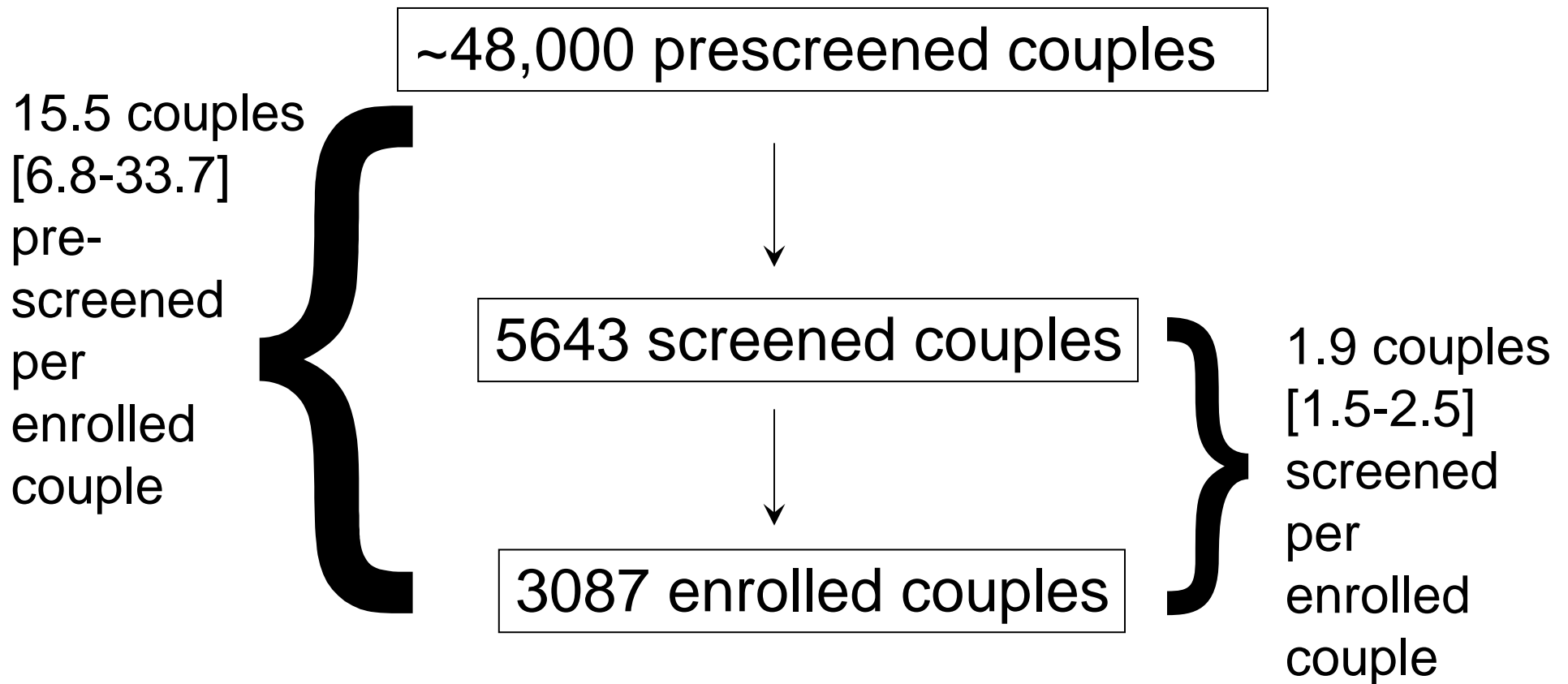
# Recruitment challenges & resourceful strategies



Drama group in market, Kisumu, Kenya

- May 2005: enrolled 100<sup>th</sup> couple
- Jan 2006: enrolled 1000<sup>th</sup> couple
- Feb 15, 2007: enrolled 3000<sup>th</sup> couple
- April 30, 2007: enrolled ??<sup>th</sup> couple

# Prescreening/screening ratio



# Demographics, Clinical and Behavioral Characteristics



# Index Demographics

Demographic Feature	Study Total (N/%)	Regional Total by site N or median% (Range)	
		E. Africa	S. Africa
Total Enrollment	3031	1939 (153-445)	1092 (74-303)
Female	67%	70% (53-86)	70% (62-76)
Age Group			
18-20	3	3% (1-7)	3% (0-6)
21-25	15	14% (6-25)	14% (1-18)
26-30	24	23% (19-30)	23% (18-30)
31-35	25	22% (18-29)	24% (18-26)
36+	34	31% (25-41)	39% (24-46)
Unknown	0	0% (0-1)	0% (0-1)
Married to partner	75%	94% (42-100)	35% (11-100)
Time living w/ partner (yr)	5	6	5
Any monthly income	36%	40% (28-65)	24% (8-60)
Two enrolled partners	16, <1%	11, <1%	5, <1%

# Clinical Characteristics

Clinical Feature	Index			Partner		
	Study median	By site		Study median	By site	
		N or median% (Range)			N or median% (Range)	
		E. Africa	S. Africa		E. Africa	S. Africa
CD4 - median	461	469 (461-560)	461 (412-475)	---	--	--
GUD 3 mo	23%	25% (7-38)	17% (9-32)	10%	7% (3-21)	9% (1-14)
GUD exam	4%	4% (1-8)	4% (1-7)	1%	2% (0-3)	1% (0-4)
Circ (men)	33%	63% (13-97)	13% (0-79)	53%	80% (28-98)	39% (13-85)
HSV-2 pos	--	--	--	57%	57% (44-70)	56% (48-63)
Syndromic STI Diagnosis (enrollment)						
Urethritis	1%	--	--	2%	--	--
GUD	9%	--	--	3%	--	--
Herpes	9%	--	--	9%	--	--
Vaginitis	35%	--	--	37%	--	--
Cervitis	15%	--	--	13%	--	--
PID	8%	--	--	9%	--	--

# Index Behavioral Characteristics (N=2928)

Feature	Female			Male		
	Total	Regional Total		Total	Regional Total	
		E. Africa	S.Africa		E. Africa	S. Africa
# participants	1973	1231	742	954	629	325
Sex acts w/ study partner (past mo)	4	4 (3-8)	4 (4-8)	4	3 (3-5)	4 (3-6)
# times w/ condom (past mo)	3	3 (2-7)	3 (2-8)	3	3 (1-5)	3 (2-6)
# other partners (past mo)	1	1 (0-7)	1 (0-6)	3	5 (0-27)	2 (1-4)

# Retention, Adherence and Pregnancy



# Retention Characteristics

Retention (% complete among expected)	Index			Partner		
	Study Total	Regional totals median % (range)		Study Total	Regional totals median % (range)	
		E. Africa	S. Africa		E. Africa	S. Africa
Total enrolled	2929	1859	1070	2940	1869	1071
@ 1 mo/3 mo	97%	97 (94-99)	97 (94-100)	98%	97 (93-100)	96 (93-99)
@ 6 mo	94%	95 (91-98)	93 (91-100)	93%	94 (90-99)	92 (87-98)
@ 12 mo	93%	92 (91-98)	94.5 (88-98)	91%	90 (85-98)	93 (86-100)

# Adherence Characteristics

Adherence Feature	Study Total	Regional Total	
		E. Africa	S. Africa
Total doses taken	1,463,526 (90%)	90% (88-93)	92% (87-92)
Visits with drug dispensed	96%	97% (96-98)	97% (93-99)
Visits with >75% doses taken	93%	93% (91-96)	94% (86-96)
Visits with $\geq 6$ consecutive missed doses	4%	3% (0-8)	3% (2-8)
Visits with <u>any</u> missed doses	14%	12% (7-25)	11% (7-17)

# Impact of Pregnancy

Participant	Study Median Preg Rate/pyr f-u	Regional Median Preg Rate (w/ site range)	
		E. Africa	S. Africa
Index	15%	15% (3-18)	15% (2-31)
Partner	23%	23% (9-86)	21% (7-33)

## Impact on study drug:

- Total months study drug prescribed: 23,928
- Total months off study drug due to pregnancy: 918 (3.8%)
  - May be indicative of high miscarriage and/or abortion rate

# Contraceptive Use

Type	Female Index			Female Partner		
	Study Median %	Regional Total Median (site range)		Study Median %	Regional Total Median (site range)	
		E. Africa	S. Africa		E. Africa	S. Africa
None	31%	17% (1-70)	15% (2-58)	32%	25% (0-67)	20% (0-59)
Oral	5%	4% (1-5)	6% (0-16)	4%	3% (0-4)	9% (5-14)
IUD	1%	0% (0-5)	0% (0-4)	2%	3% (0-9)	0% (0-4)
Injectable	14%	12% (9-16)	21% (2-31)	11%	9% (7-15)	13% (5-31)
Condom	48%	62% (18-72)	41% (13-84)	46%	58% (10-87)	33% (12-74)
Surgery	4%	3% (1-6)	5% (0-7)	3%	1% (0-9)	4% (1-17)
Other	2%	2% (0-6)	0% (0-13)	4%	6% (0-12)	0% (0-17)

# Summary: HIV Discordant Couples Enrolled

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- High prescreened-to-enrolled ratio
- Enrolled long-term couples, recently identified as HIV discordant
  - ◆ 2/3 of index participants are female
- Cohort characteristics similar between region except:
  - ◆ Marriage rates and partner income higher in E. Africa
  - ◆ Male circumcision rates higher in E. Africa
  - ◆ Higher rates of condom use in E. Africa
- Clinical trial performance indices good over first year
  - ◆ Retention high 1st yr – may anticipate ‘study fatigue’ in 2<sup>nd</sup> year
  - ◆ Adherence high but need to repeatedly counsel study ppts and monitor
  - ◆ High pregnancy rates but relatively low impact on missed study drug

“It’s not over until it’s over”  
Yogi Berra

- Applies to clinical trials as well as baseball

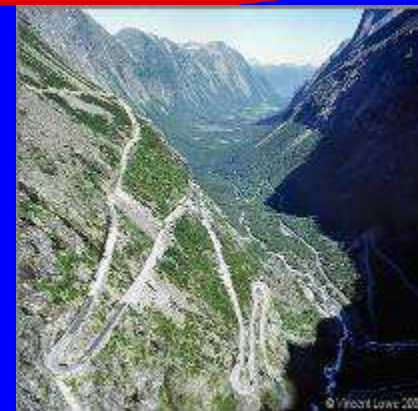
# Global Health Impact of HSV-2 Interventions on HIV Transmission

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- Of possible biologic interventions for HIV prevention, HSV-2 has great applicability
  - Relevant to men & women, up to 60% of HIV-negative & 80% of HIV-positive persons globally
  - Generic, safe drug (acyclovir) available & on Essential Drugs List
- Partners in Prevention could have big global health impact
  - Easier to scale up HSV-2 suppression for HIV+ persons, 80% of who are HSV-2+ where HIV care programs exist
  - For HIV- persons with 50% HSV-2 prevalence, will need serologic testing, integration into VCTs
  - Coverage is critical to eventual global health impact

# Partners in Prevention: Lessons Learned relevant to HIV Prevention Trials

- Challenges of HIV discordant couples trials can be met
- Sites are extremely motivated & invested
  - ◆ Believe in the hypothesis being tested
  - ◆ Additional benefits of providing couples' counseling & sensitizing communities to HIV discordancy
- Required infrastructure development, close partnering with sites, intensive community collaborations to recruit HIV discordant couples, & site resourcefulness
- Important to identify experienced senior site investigator & motivated junior investigator



# Partnerships are key to success

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- Between sponsor and PI
- Between PI and site PIs
- Among site PI and site staff
  - ◆ Recruitment, adherence and retention is everyone's job
- Across sites
  - ◆ Sites are extremely valuable resource to each other
- Between sites and community in which they are working & recruiting
- Between study participants and site staff

# **“It takes a big village to design & implement clinical trials”: Thanks to our Partners in Prevention**

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- Jai Lingappa—Medical Director and co-investigator
- Anna Wald & Larry Corey – co-Investigators
- Linda Barnes – Fiscal and Program Manager
- Nelly Mugo – Regional Director eastern Africa
- Andrew Mujugira – Regional Director southern Africa
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- Carlos Flores & Christy Wilson – Administrative support
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- Margaret Warner-Lubin – Clinical Operations Manager
- Ellen Wilcox— Protocol Specialist
- Dila Perera – Site coordinator
- Jim Hughes & Amalia Meier, PhD – Biostatisticians
- Lynda McVarish- Data Manager
- DF Net
- Clinical Lab Services, Univ of Wits
- **All investigators & staff members at the 14 sites**
- **All HIV-discordant couples screened and enrolled**

# A trial is only as strong as its sites: Partners in Prevention Site Investigators

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Nairobi, Kenya (Kenyatta Nat'l Hosp): James Kiarie, Carey Farquhar,  
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# Thank you to the study participants

## Lusaka 039 Participant Support Group

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