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A Study to Prevent Infection with a Ring for Extended Use

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MTN microbicide trials network

MTN-020 / ASPIRE

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Overview

- Background and rationale
- Design and objectives
- Timelines
- Optimizing implementation

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Background and Rationale

Antiretrovirals for HIV protection

- Right drug

(safe, effective, potent)

- Right place

(sufficient concentrations at site of exposure)

- Right time

(present when exposed, user-independent adherence)

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Tenofovir-based PrEP for HIV prevention: success and challenges

- During the past two years, large studies of oral and topical tenofovir-based PrEP have demonstrated efficacy for HIV protection:

Trial	PrEP regimen	Population	Reduction in HIV risk
CAPRISA 004	Peri-coital tenofovir gel	Women	39%
iPrEx	Daily oral FTC/TDF	Men who have sex with men	44%
TDF2	Daily oral FTC/TDF	Young heterosexuals	62%
Partners PrEP	Daily oral TDF and FTC/TDF	HIV serodiscordant couples	67% (TDF) 75% (FTC/TDF)

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Truvada® for HIV prevention

FDA Approves First Medication to Reduce HIV Risk

"It is still better to prevent HIV than to treat a life-long infection of HIV."

Deborah Birnkrant, director of the
Division of Antiviral Products, US FDA,
16 July 2012

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Tenofovir-based PrEP for HIV prevention: success and challenges

- However, not all trials of tenofovir-based PrEP have found HIV protection:
  - No efficacy for daily oral FTC/TDF in FEM-PrEP trial and for daily tenofovir gel and daily TDF in VOICE study, both studies of women with high HIV incidence

- Across PrEP studies, adherence is likely an important driver of HIV protection

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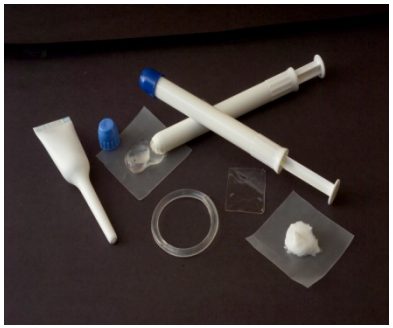
Developing a range of options for antiretroviral-based HIV prevention

Pill



Gel

Vaginal film

Vaginal ring

Injectable

- ✓ Truvada PrEP is critical first proof on a future pathway.
- ✓ Ultimate goals: multiple options, long acting, safe, effective, low cost and user-friendly
- ✓ Maximize choice & optimize effectiveness

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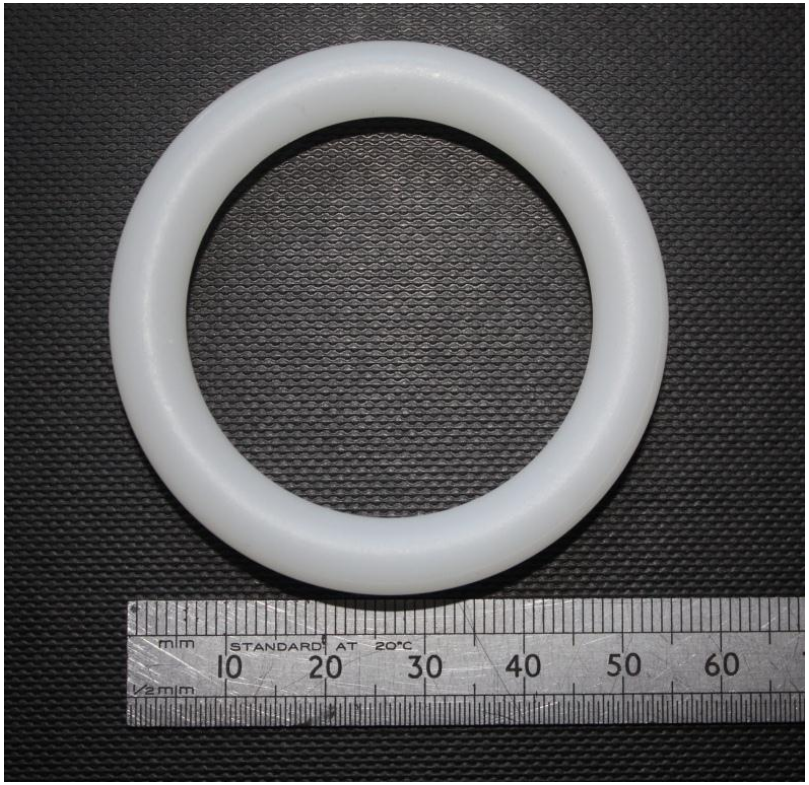
Dapivirine ring

- Dapivirine is a non-nucleoside reverse transcriptase inhibitor
- Flexible ring made of an elastic silicone material
- Measures 56 mm (about 2 ½”) in diameter and 7.7 mm (3/4”) thick
- Designed for 28-day use
- International Partnership for Microbicides (IPM) providing both the placebo ring and the dapivirine ring for the study



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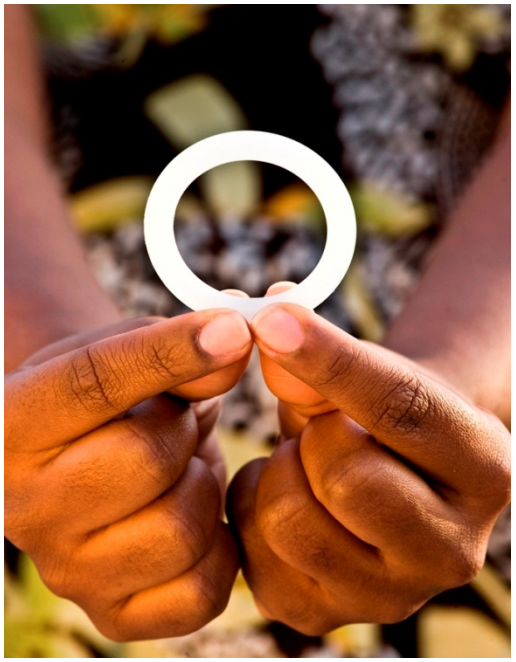
Dapivirine ring for HIV prevention

- Dapivirine ring has shown safety and acceptability in phase I and phase II trials *but its large-scale safety and its effectiveness for HIV protection are unknown*

- MTN-020, in concert with the entire dapivirine package, will provide strength of evidence to support potential licensure



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Study Design and Objectives

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- **A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women**

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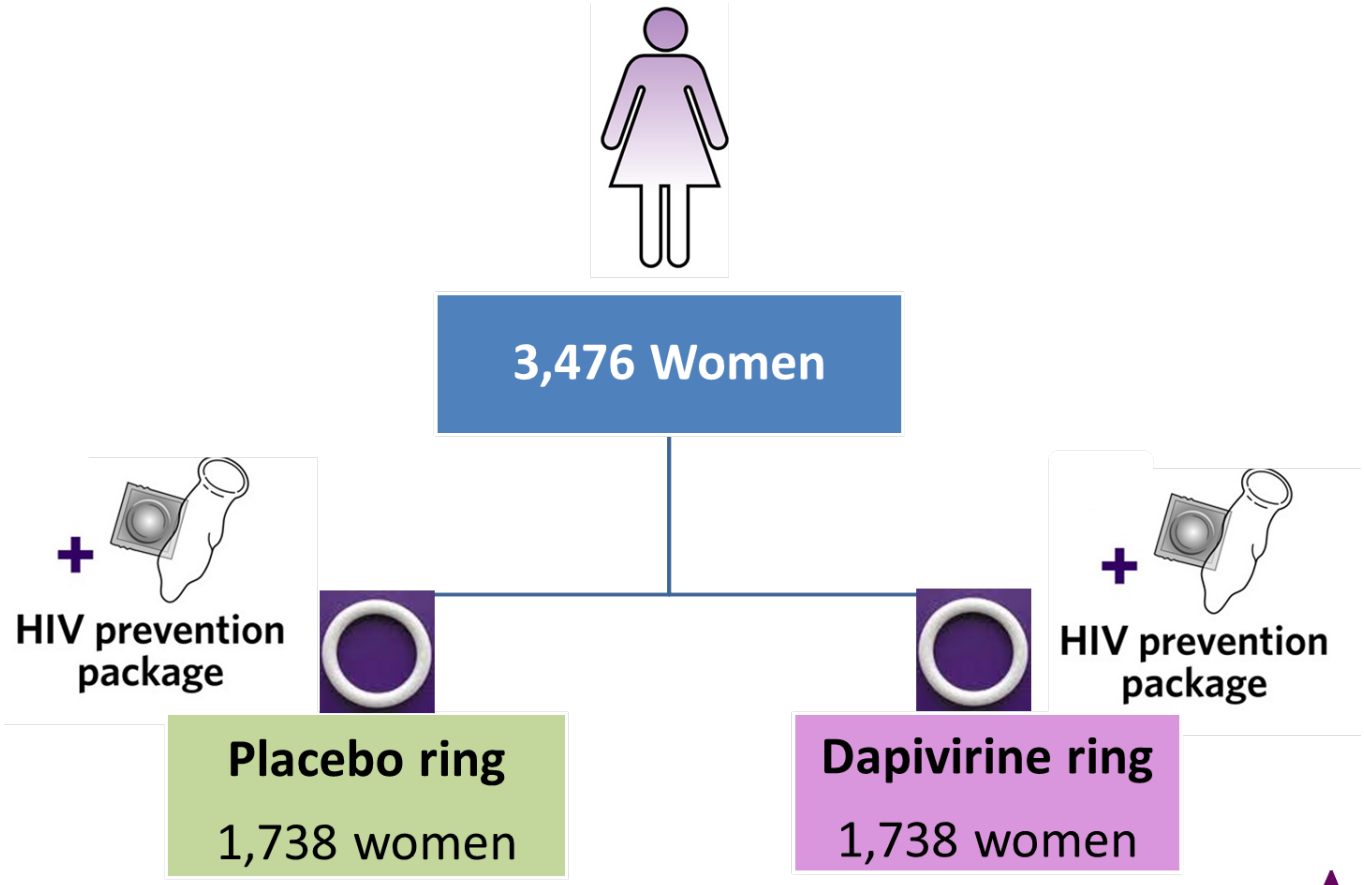
ASPIRE Study Design



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Design

- N=3476 (~4400 person-years)
  - sexually active, HIV-uninfected women who are non-pregnant, contracepting, aged 18-45 years
- Accrual over approximately 12 months, with total study duration approximately 24 months
  - Designed so that all participants will achieve 12 months on study product
- Monthly follow-up
  - HIV testing, contraceptive counseling/provision, safety monitoring

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Objectives

PRIMARY

- Safety and effectiveness for HIV-1 prevention

SECONDARY

- Acceptability, adherence, resistance, PK/PD

EXPLORATORY

- Genital microenvironment, adherence vs. PK, delayed seroconversion

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Protocol

- Version 1.0 : DAIDS approval 27 September 2011
- LoA#01 (7 November 2011)
  - Timing of pelvic exam schedule, samples to be collected and tests to be completed on vaginal samples
  - Clarification on collection of plasma and testing for CD4 and HIV PCR after seroconversion
  - Approved at all sites
- LoA #02 (19 April 2012)
  - Allows for continuation of vaginal procedures in pregnant women
  - Clarifies timing of vaginal fluid collection, plans for collection of used rings for testing
  - Addition of in-depth interviews and focus group discussions (subset of sites)

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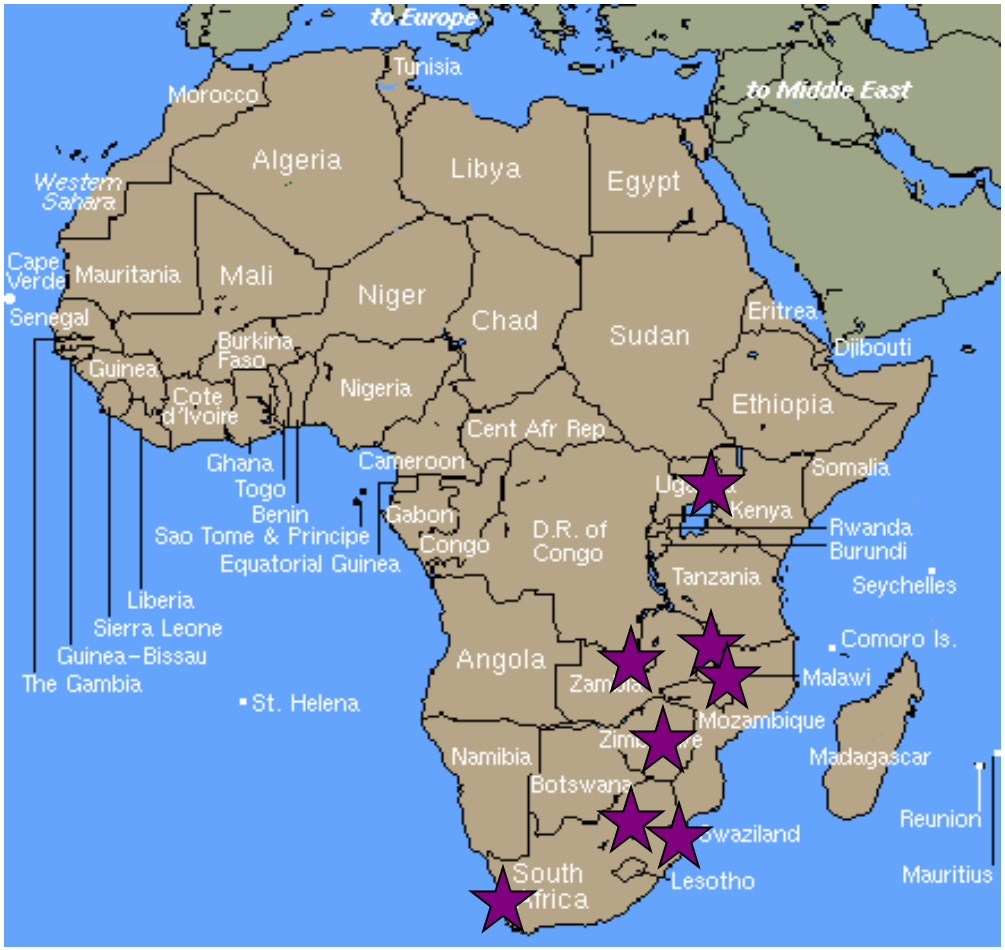
Proposed sites



Blantyre
Lilongwe
Malawi

Cape Town
Durban (7 sites)
Johannesburg
South Africa

Kampala
Uganda

Lusaka
Zambia

Harare (3 sites)
Zimbabwe

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Timelines

ASPIRE to date

- January - March 2011
  - Concept approved by MTN Executive Committee
  - Protocol Consultation Meeting with Site Investigators
- May – July 2011
  - NIAID SWG, PSRC
- September 2011
  - v1.0 to sites for IRB submission
- October 2011
  - Community Consultation, Operational Walk-Through
- January 2012
  - DSMB protocol review
- June, July 2012
  - First site training (Cape Town), first activation (Kampala)
- August 21, 2012
  - First enrollment (Kampala)

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Site activations

Site	Date of activation	Site	Date of activation
MA – Blantyre	**APPROVALS PENDING**	SA – MRC/Verulam	28 AUG 2012
MA - Lilongwe	**APPROVALS PENDING**	SA – MRC/Umkomaas	28 AUG 2012
SA – Cape Town	4 SEP 2012	SA – WRHI	POISED
SA – CAPRISA eThekwini	13 SEP 2012	UG – Kampala	19 JUL 2012
SA – MRC/Botha's Hill	28 AUG 2012	ZA – Lusaka	**APPROVALS PENDING**
SA – MRC/Chatsworth	28 AUG 2012	ZI – Seke South	POISED
SA – MRC/Isipingo	28 AUG 2012	ZI – Spilhaus	POISED
SA – MRC/Tongaat	28 AUG 2012	ZI – Zengeza	POISED

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Enrollments (27 SEP 2012)

Site	First enr	# scr	# enr	scr:enr ratio
SA – Cape Town	19 SEP 2012	5	3	1.7
SA – CAPRISA eThekwini		1	0	-
SA – MRC/Botha's Hill	10 SEP 2012	39	14	2.8
SA – MRC/Chatsworth	11 SEP 2012	27	11	2.5
SA – MRC/Isipingo	19 SEP 2012	13	4	3.3
SA – MRC/Tongaat	17 SEP 2012	25	5	5.0
SA – MRC/Verulam	13 SEP 2012	33	8	4.1
SA – MRC/Umkomaas	14 SEP 2012	26	13	2.0
UG – Kampala	21 AUG 2012	52	35	1.5
TOTAL		**221**	**93**	**2.4**

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Timeline

2011	• Initiate site IRB and regulatory approval process
2012	• IRB/regulatory approvals, trainings, enrollments begin Q3
2013	• Enrollments and follow-up continue
2014	• End of participant follow-up
2015	• Results

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Clinical development program for dapivirine for HIV prevention

- To date, 25 phase I/II trials of dapivirine (in oral, gel, and ring form) have been conducted
- Trials have demonstrated high safety for topical dapivirine
- Agency reviews (FDA/EMA) have permitted move to efficacy evaluation
- In parallel to MTN-020, IPM will conduct IPM 027 – focus on extended safety plus efficacy

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MTN-020 and IPM 027

	MTN-020	IPM 027
Design	endpoint driven	fixed time
No. of participants	3,476	1,650
Randomization	1:1	2:1
Age	18-45 yrs	18-45 yrs
Product use period	Until end of study (12-24 months)	24 months fixed
Person-years follow-up (all / Dapivirine Vaginal Ring)	4,396 / 2,198	3,150 / 2,100
HIV-1 seroconversions	120	80
Power for 50% effect	97%	83%

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Key Considerations for Optimization of Implementation

Operational Focus = The Big Five

Accrual

Adherence

Retention

Data Quality and Timeliness

Clinical and Laboratory Participant Safety

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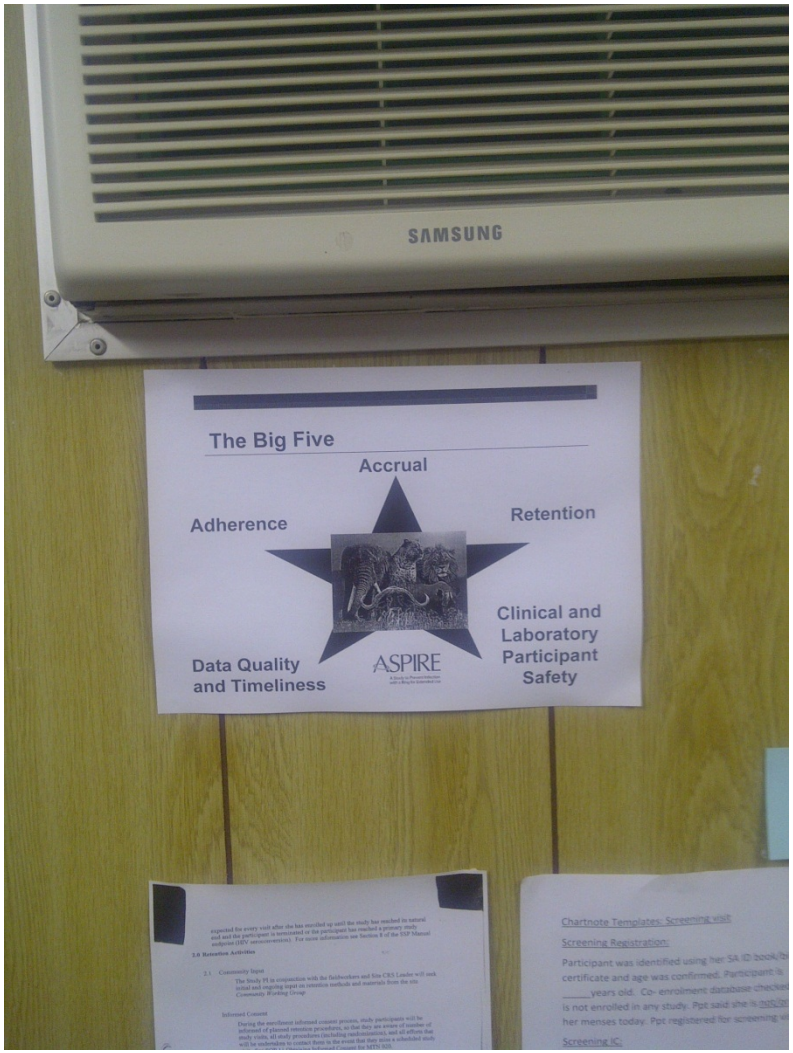
Umkomaas


SAMSUNG
The Big Five
Accrual
Adherence
Retention
Clinical and Laboratory Participant Safety
Data Quality and Timeliness
ASPIRE
Chartnote Templates: Screening visit
Screening Registration:

Operational efficiencies (1)

- Accrual
  - Modest sample size = achievable number of recruitments
  - Enrollment goal = those who will return as scheduled for follow-up

- Follow-up
  - Streamlined data collection and study procedures = reduced time spent in clinic
  - Allowances for efficiencies for individual women – protocol provisions for extra ring dispensing and off-site visits

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Operational efficiencies (2)

- Retention
  - Focus from day one from participant one : resource and attention allocation will be critical
  - *No retention = no adherence*

- Provision of services on-site
  - Contraception : expanding method mix and convenience – Contraceptive Action Team efforts
  - Partner HIV testing, STI evaluation/referral

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Operational efficiencies (3)

- Focus on efficiencies
  - Coordination within oversight team: FHI360, Regional Physician, PPD

- Communications
  - Weekly protocol team management calls (W, 6 AM Pacific)
  - Weekly priority emails from FHI360 to sites – collating protocol team priorities; biweekly calls
  - Monthly team calls = site-driven exercises – sharing experiences
  - Listservs : cross-site communications/sharing

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Numbers that matter

- 3476 = total number of women enrolled
- >95% = retention, product distribution
- 100% = attention to data quality, safety

Everything else flows from these

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IT TAKES A TEAM

MTN microbicide trials network

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National Institutes of Health

Statistical Center for HIV/AIDS Research & Prevention
SCHARP

fhi360

Malawi College of Medicine – JHU Research Project

WRHI

CIDRZ

MRC South Africa

CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

UNC Project - Malawi

International Partnership for Microbicides

University of Zimbabwe, School of Medicine

Desmond Tutu HIV Foundation

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