

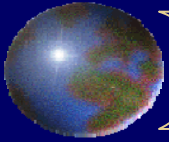


HSV interventions to control HIV

Impact of HSV-2 suppressive therapy on HIV incidence and infectivity in HSV-2 seropositive women: a randomised controlled trial in Tanzania

Deborah Watson-Jones, John Changalucha, Helen Weiss, Clare Tanton, Mary Rusizoka, Kathy Baisley, Dean Everett, Kokugonza Mugeye, Tim Clayton, David Ross, Richard Hayes

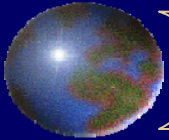
African Medical & Research Foundation (AMREF), Mwanza, Tanzania
National Institute for Medical Research, Mwanza
Wellcome Bloomsbury Centre for Clinical Tropical Medicine,
London School of Hygiene & Tropical Medicine



Aims of trial in Mwanza

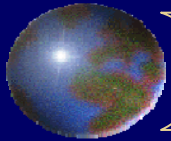
To determine if HSV-2 suppressive therapy with aciclovir twice per day reduces:

1. HIV incidence in HIV-negative women at high risk of HIV in Tanzania
2. HSV-2 and HIV viral shedding in women dually infected with HIV and HSV-2
3. HIV plasma viral load in dually-infected women



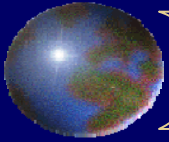
Design of Trial

- Randomised, double-blind, placebo-controlled trial
- Oral aciclovir 400mg b.d. vs placebo
- Cohort of women working in bars etc.
- 12-30 months follow-up
- HIV+ & HIV- women followed in same cohort



Study sites

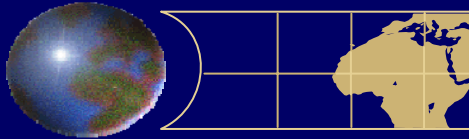




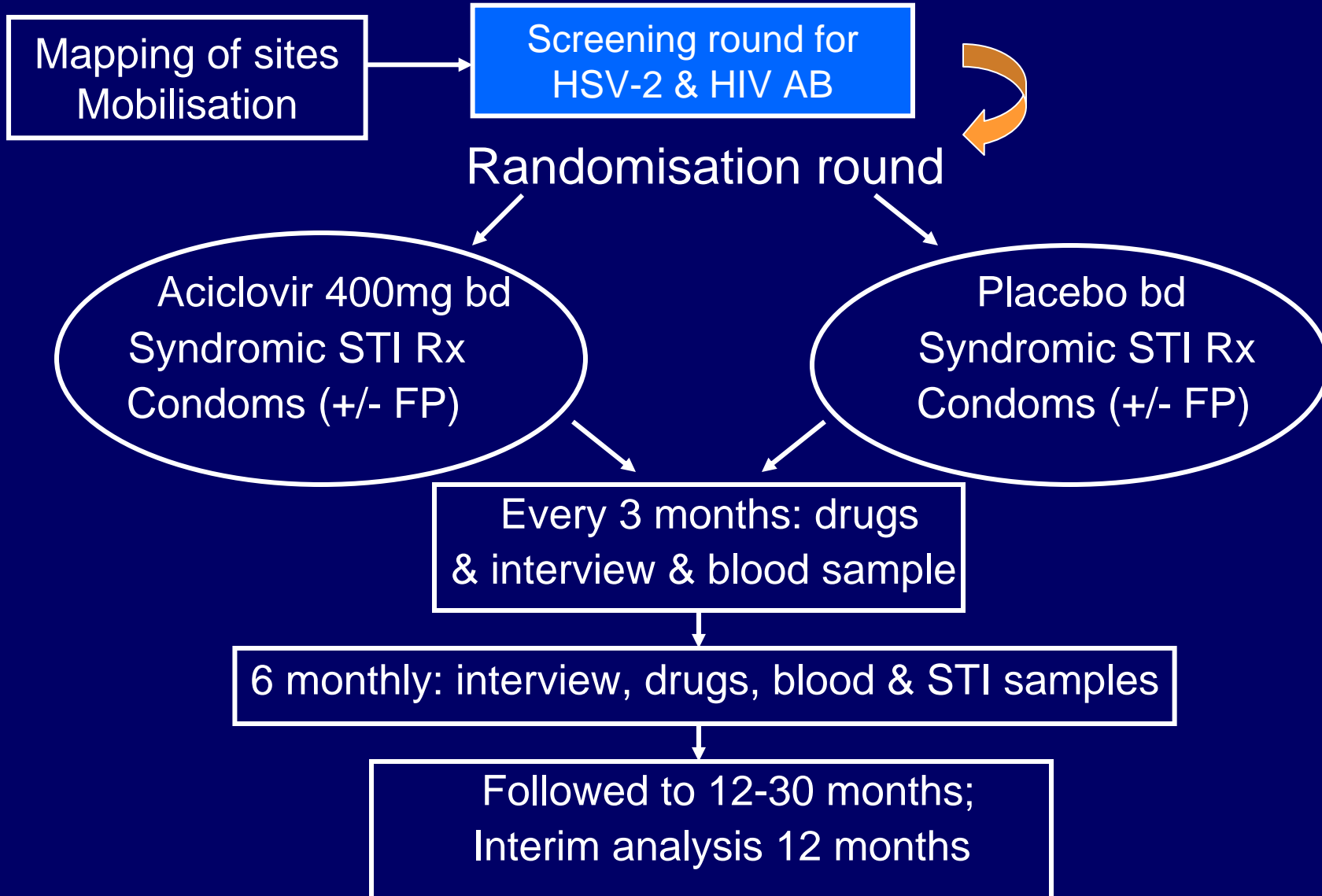
Study population

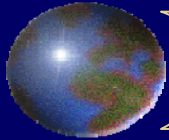
Women working in bars,
guesthouses etc, & local
food vendors & local
brew-sellers

- opportunistic sex work
- “core group” at high HIV risk



Study design





Sample size

Initial sample size:

80% power for 50% reduction in HIV incidence (7.5 per 100pyr overall)
40% reduction in HIV RNA shedding

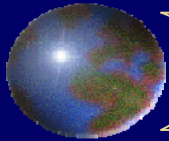
600 HIV seronegative women; 400 HIV seropositive women

However, due to

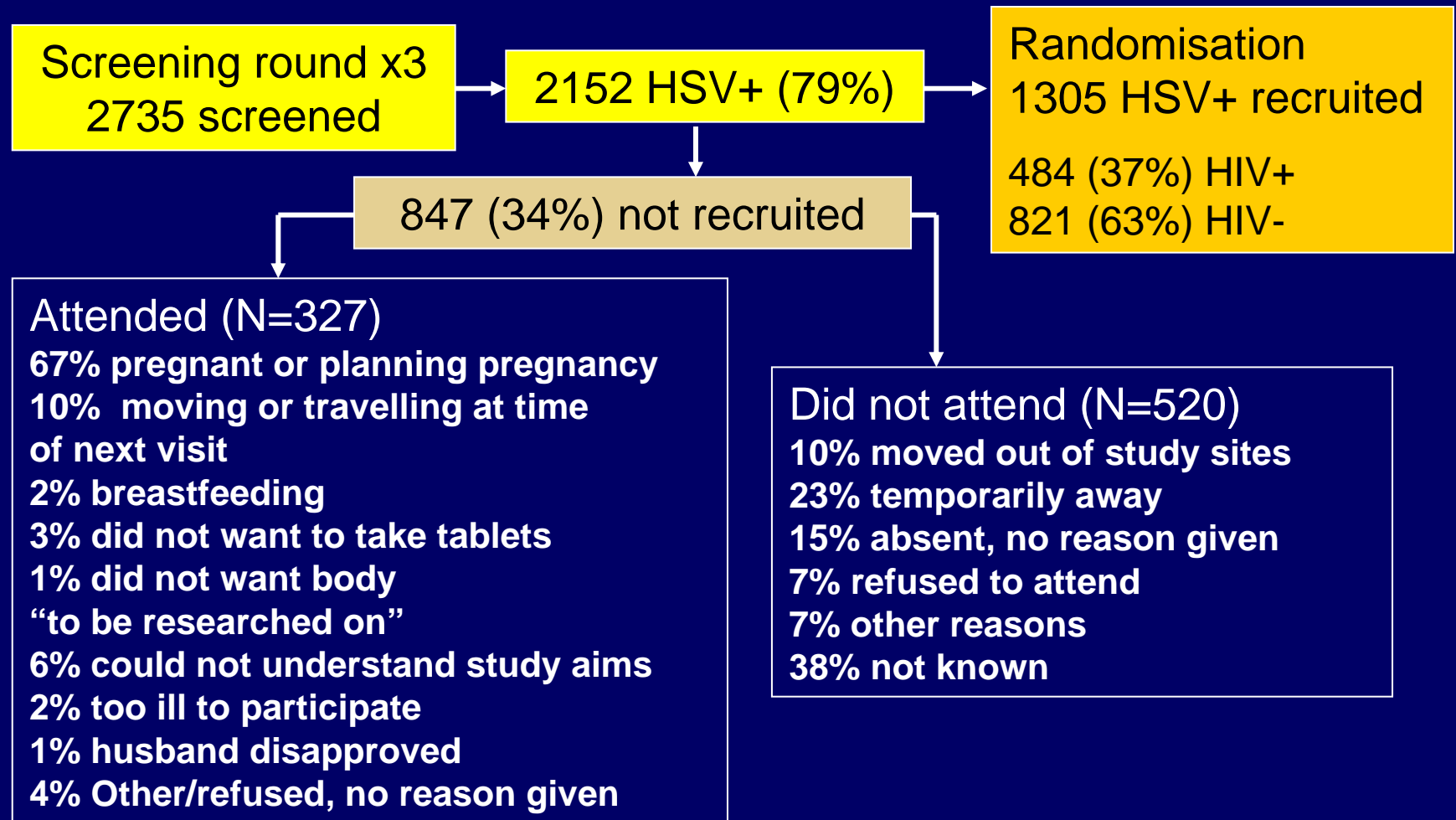
- lower than expected HIV incidence (4.5 per 100 pyr overall)
- higher rate of loss due to pregnancy & other reasons (25%)

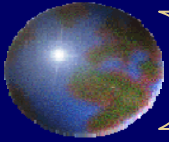
Follow up extended to 30m for enrolled & additional 300 women recruited in 2005 & followed for 12 months

→ 821 HIV seronegative women; 484 HIV seropositive women enrolled



Cohort enrolment



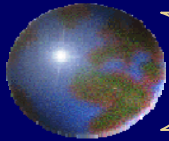


Recruitment

- HSV+ women
- Aged 16-35 yr
- Interview
- Pregnancy test
- Blood: HIV, syphilis
HIV viral load
- Examination & STD samples:
 - Bacterial vaginosis, candidiasis, *N gonorrhoeae*, *C trachomatis*, *T vaginalis*
 - Cervico-vaginal lavage (HIV & HSV shedding)

Not eligible if:

- pregnant/planning pregnancy
- epilepsy
- breastfeeding
- travelling at next appointment
- unable to understand study procedures
- significant illness



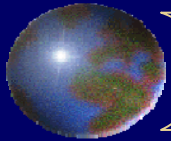
Recruitment

- 3 phases of enrolment

703 enrolled Phase I

298 enrolled Phase II

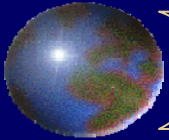
304 enrolled Phase III
(followed for 12 months)



Trial procedures

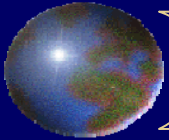
	E	3m	6m	9m	12m	15m	18m	21m	24m	27m	30m
Interview	√	√	√	√	√	√	√	√	√	√	√
Tablets	√	√	√	√	√	√	√	√	√	√	
Examination	√		√		√		√		√		√
STI samples	√		√		√				√		√
CVL	√		√		√				√		√
PVL	√		√		√		√		√		√
CD4			√*		√*				√***		√
Syndromic STI care	√	√	√	√	√	√	√	√	√	√	√
FP & VCT	√	√	√	√	√	√	√	√	√	√	√

* Phase 3 women only ** phase 2 women only



Clinical care

- VCT, condoms, syndromic STI care, FP
- Pregnancy test at FU if suspect pregnancy or late LMP
- Pregnant women withdrawn from trial tablets but could stay in for follow-up
 - Pregnant HIV+: transport & overnight accomodation for PMTCT in Mwanza
- Basic care for minor conditions (malaria, diarrhoea etc).
- Referral; Hospitals, VCT support services; ART clinic

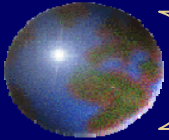


Adherence follow-up

- Adherence support visit 3-4 wk later
- Tablet counting
- Counselling & support

Urine analysis

- Random urine samples tested for ACV metabolites
 - between booked visits (6m & 9m)
 - at 6m booked visit



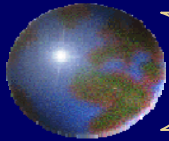
Outcomes

HIV acquisition study:

- HIV incidence

Shedding study:

- Prevalence & quantity of:
 - cervico-vaginal HIV-1 RNA (log copies/ml)
 - cervico-vaginal HSV-2 DNA (HIV+ & HIV-) (log copies/ml)
- Plasma HIV-1 RNA load (log copies/ml)



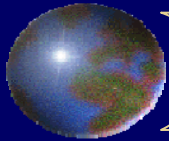
Follow up of cohort

	HIV neg <u>N (%)</u>	HIV pos <u>N (%)</u>
Completed follow-up (attended)*	651 (79%)	321 (66%)
Withdrawn from tab & did not attend final visit	57 (7%)	86 (18%)
On tablets & did not attend final visit **	113 (14%)	77 (16%)
<i>Phase 1 & 2 on tablets to 30m</i>	<i>346 (56%)</i>	<i>199 (52%)</i>
<i>Phase 3 on tablets to 12 m</i>	<i>155 (76%)</i>	<i>75 (74%)</i>
<i>Total completed on tablets***</i>	<i>501 (61%)</i>	<i>274 (57%)</i>

* includes women on tablets & women who stopped tablets but attended final visit

** includes all defaulters who miss other visits & final visit & women who did not agree to extend from 24 to 30m

** total women who reached final visit & were still taking tablets



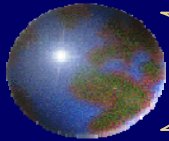
Follow up for MITT analysis HIV negative

Main analysis will be modified intent-to-treat, with women censored at earliest of:

- HIV seroconversion
- First positive pregnancy test
- End of trial or last visit seen

Point of censoring	N (%)	Median time Yrs (IQR)
End of trial	458 (56%)	2.54 (1.00-2.57)
HIV seroconversion	57 (7%)	0.66 (0.36-1.70)
Pregnancy*	166 (20%)	0.96 (0.48-1.71)
Last visit seen*	140 (17%)	0.48 (0.00-1.45)
Total	821 (100)	1.52

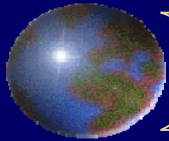
* Included one woman who died in each group



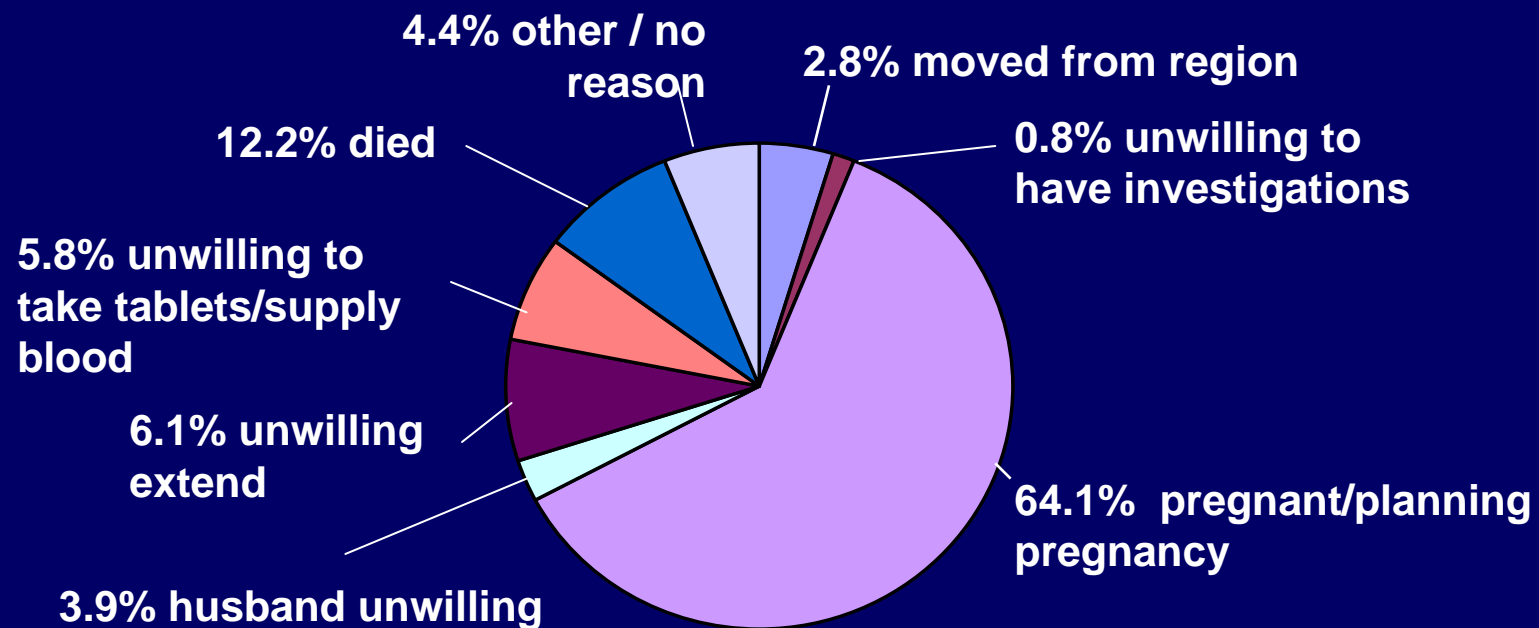
Follow up for MITT analysis HIV-positive

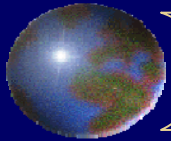
Point of censoring	N (%)	Median time Yrs (IQR)
End of trial	274 (57%)	2.54 (1.01-2.57)
Pregnancy*	63 (13%)	0.94 (0.48-1.56)
Death	45 (9%)	0.95 (0.25-1.44)
Last visit seen	102 (21%)	0.93 (0.28-1.99)
Total	484	1.98

* Includes 3 women who died after pregnancy



Reasons for withdrawal from trial tablets (N=362; 28%)

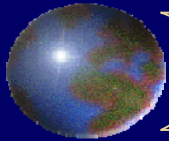




Severe adverse events

	HIV negative N=821		HIV positive N=484		Total	
	N	%	N	%	N	%
Women with SAE (Number of Events)	86 (95)	10.5	111 (147)	22.9	197 (242)	15.1
Death	2	0.2	48*	9.9	50	3.8
Life-threatening illness	15	1.8	60	12.4	75	5.8
Hospitalisation	89	9.7	93	19.2	173	13.3
Persistent disability	1	0.1	1	0.2	2	0.2
Congenital abnormality	0		0		0	

* Including 5 who died after stopped study tablets

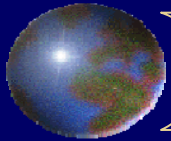


Adherence (tablet counts)

Adherence ¹	N	%
<25%	20	1.5
25–49%	42	3.2
50–74%	227	17.4
$\geq 75\%$	950	72.8
Unknown ²	64	4.9
Total	1305	100

¹ Censored at earliest of date of first positive pregnancy, or date of last follow-up

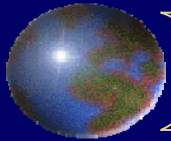
² Women who did not attend after randomisation round



Characteristics of seroconverters

	Seroconverters	HIV-	p
No. (%)	66	-	-
Incidence rate	4.5 per 100 pyr*	-	-
Median age at screening (IQR)	26 (23-30)	28 (23-32)	0.23
Married	29.6%	28.9%	0.92
Bar worker	9.3%	12.8%	0.45
Irregular condom use during FU	95.6%	97.0%	0.58
Blood Tx/injections during FU	31.5%	24.1%	0.23
Paid sex using FU	77.8%	51.5%	<0.001
GUD during FU	3.7%	2.0%	0.38
Vaginal discharge during FU	59.3%	48.6%	0.13

* Preliminary – seroconverters still being confirmed

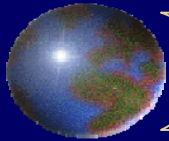


Pregnancy during trial

	N	%
6 m	33	2.7
12 m	30	2.6
18 m	23	2.9
24 m	25	3.4
30 m	12	1.8
Overall prevalence	254	19.5

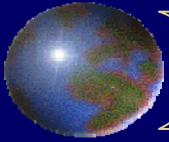
1 Includes all women who became pregnant, regardless of reason for withdrawal.

2 Denominator is women still in study (on treatment, or withdrawn & agreed to follow-up), & not already pregnant



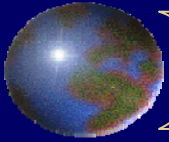
Reported problems

Commonly reported problem	%
Had to travel during study	7.8
Difficult not getting pregnant	3.1
Hid participation from partner	3.1
Partner did not like	2.9
Concerned about aspect of study	2.6
Wanted to get pregnant	2.5
Not paid enough	1.8
Became sick after entered	1.5
Difficult remembering to take tablets	1.4
'Other'	5.7



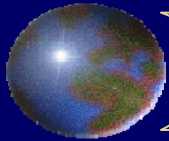
Challenges

- Pregnancy
- Adherence
- HIV incidence
- Large study area
 - Mobile team
 - Round trip ~500-700 km
mainly rough roads &
involves ferry crossing
 - Some sites no mobile
phone coverage



Conclusions

- Able to recruit into trial despite challenging environment & study population
- Study population able to understand trial concepts
Repeated explanations through multiple channels
- Good follow-up; withdrawals due to pregnancy
- Adherence complex to monitor
- Support between rounds very important



Co-investigators & Collaborators

Co-investigators HIV acquisition study	Deborah Watson-Jones, Richard Hayes, John Changalucha, David Ross
Co-investigators HIV/HSV shedding study	Deborah Watson-Jones, Clare Tanton, Helen Weiss, John Changalucha, Richard Hayes
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Funding	The Wellcome Trust; MRC; DFID
HSV team	Pascal Ama, Mariam Barabara, Mary Biseko, Felician Fidel, Hildegrade Fidelis, Juliana Fulla, Beatrice Kamala, Joseph Kihayi, Christina Kanyankole, Humphrey Komba, Pascal Maganga, Leocardia Mmary, Fabian Msakwa, Adrophina Mutagulwa, Crescential Mutungi, Merciana Mwanusi, Joseph Mzugu, Ennegrace Nkya, Hashim Omary, Mary Rusizoka, William Rudibuka, Simon Sichwale, Richard Sungwa

