Regional Physician - International Site Support Model

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Annual MTN Meeting

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Challenges of doing efficacy trials

- Getting microbicide product through to licensure
  - Resources aren't limitless hence may not have benefit of second trial with positive findings
  - Strength of evidence required for licensure from single positive trial often requires a false +ve rate in the range of 0.0005 – 0.005 (two-sided p-value 0.001 – 0.01)
- Recruitment
  - Need to target high risk women (powers up your study, narrows your CI)
- Retention
  - impacts your efficacy estimates
- Poor study product adherence will lower efficacy levels
  - ITT analysis
  - PP analysis- challenge of incorporation of post-hoc data into analysis (propensity score analysis)

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Role Overview in Regional Physician model

- Close relations & regular access to sites
  - Work with sites to address major trial implementation challenges (recruitment, retention, product adherence, etc).
  - Ensure assessment & provision of site-specific training needs (Research methodology, HIV/AIDS care etc)
- Coordination of Regional Trainings
  - Promote cross-site sharing of information regarding implementation challenges & successes (cross-site visitation trainings)
  - MTN Regional training May 2006 (roll out HPTN 035-A, MTN 015 & HPTN 035 refresher training)
- Provide insights to MTN CORE & sites, regarding status of trial implementation o a site-specific level
  - Generation of consolidated reports (pools mthly reports from CL, SCHARP & FHI)

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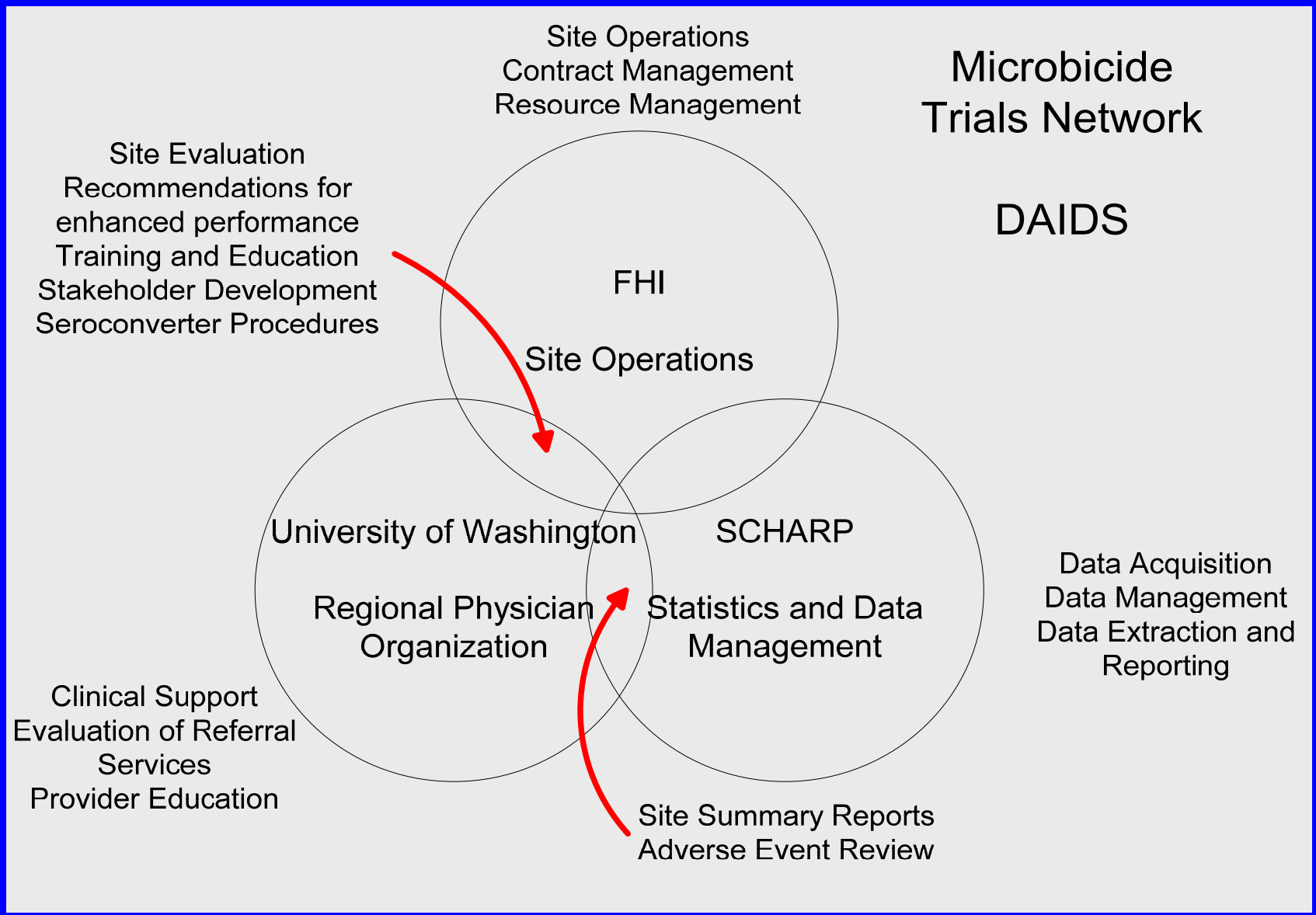
Future Integration of Roles



Consolidated Reports (Deducted version)

Recruitment

The site has maintained a steady accrual rate since May 2005 and as of February 16, 2007 the site had enrolled 502 women. This represents 83.7% of targeted accrual at the site. The site is commended for this enrollment performance. At the current enrollment rate of 23.7 participants per study month, we are confidence that the site will be able to meet its accrual target by the end of July 2007

Study Product Adherence

The rate of gel use among non-condom sex acts at the site is 80% (excluding those on product hold). This is slightly lower than the cross-site rate of 81%. However, 161 of the 438 non-condom acts without Gel use (37%) occurred at site. Gel use is especially important among non-condom sex acts if targeted study end-points are to become plausibly achievable.

- *The site should review potential impediments to enhanced gel use particularly among non-condom sex acts and mould gel adherence messaging around common reasons for non condom use in order to further reduce non-condom acts without gel use.*

Retention

The site has maintained retention rates above the cross-site average for most study months and is therefore highly commended for this achievement despite their large client load. However, the site's retention rates fall short of the protocol specified retention target of 95% per year.

- *To achieve targeted retention rates, continued efforts through counseling messages and exploring potential impediments for participants honoring visit schedules, is needed.*

Data Management

With a cumulative QC rate per 100 records of 4.9, and 4.1 for January of 2007, site has continued to provide high quality data despite the large number of participants enrolled. The site has a lower QC rate than the target rate of 5.0 (per data mgt SOP) and the cross-site average of 5.5 to date. However, for both Dec 2006 & January 2007 mean days to fax in CRF's stood at 9.4 and 5.9 days respectively, higher than target of 5 days.

- *The site should let SCHARP know if they are experiencing any technical difficulties with faxing in forms.*

Laboratory & Repository

The site has no major outstanding laboratory issues. The site has completed validation of the ProbeTec and has submitted all its proficiency panels.

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Product Adherence (wk prior to q-terly)	
%age of vaginal sex acts with condom	1318 (62%)
%age of acts with Gel use	1566 (73%)
%age of gel use with condom acts	904 (42%)
%age of non-condom acts with Gel use	662 (80%)
%age of acts without both gel & condom use	161 (8%)

Report date	6- Feb, 2007

Comments

Although the site's percentage of non-condom acts with Gel use is closer to the cross-site average of 81%, because of the large number of enrollees at the site, it contributed the greatest number of non-condom sex acts without Gel use (161 non-condom acts missed Gel) compared to 438 acts across all.

The site needs to constantly review common reasons for non-condom adherence & mould your gel adherence messaging around such reasons in order to decrease non-condom acts without Gel use.

Characteristics of Enrolled Participants	
Married to partner	219 (94%)
Participant lives with partner	217 (94%)
Partner/husband has > one known wife/partner	17 (7%)
Sure that partner has only one partner/wife	165 (71%)
Do not know if partner/husband has other partners	50 (22%)
Participants with > one sexual partner in prior 3 months	0%

Report date	6-Dec-06

Comments

Cross-site marriage rate is 56% compared to site's 94%. Fewer women at the site (7%) are in known polygamous relations compared to cross-site average of 14%, yet a higher percentage (71%) are sure of being the only partner to their husband/spouse compared to 53% overall. 0% of women at the site have had more than one sexual partner in past 3 months compared to 4% across all sites.

- *Need to reconsider strategies which may enhance recruitment whose risk profile is less certain in regard to their partners' & their sexual behavior, i.e. need to test the microbicide candidate among women who will need it should it be efficacious.*

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Application of lessons learned HPTN 035 to future effectiveness trials – (1)

- Recruitment
  - Benefits from a periodic external, objective assessment
  - Definition of accrual period and/or targets determines extent to which desired recruitment categories are targeted
  - How do we enhance risk profile for women accrued on to effectiveness trials?

    Risk criteria are typically broad
    - Zimbabwe/Malawi – HIVNET 016A
    - Zambia - ? Young women regardless of marital status
    - Uganda – MOH survey
    - S. Africa – may vary by province
    - Relatively high baseline HIV prevalence among screened

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It may seem pretty easy, but getting on top of the game implies preparation even for least of tasks

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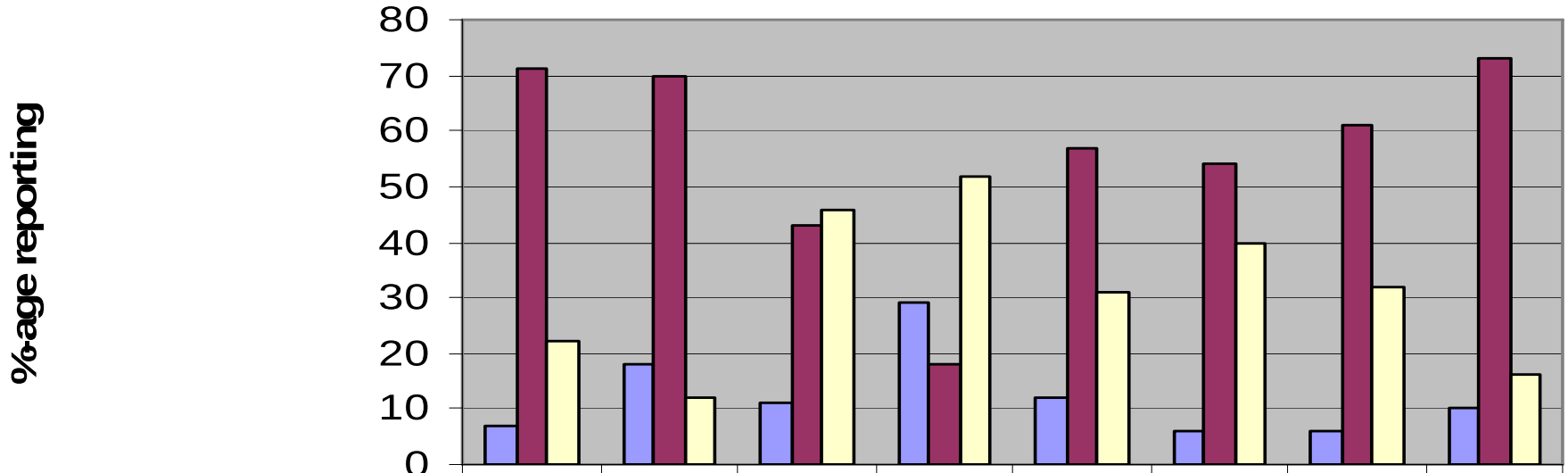
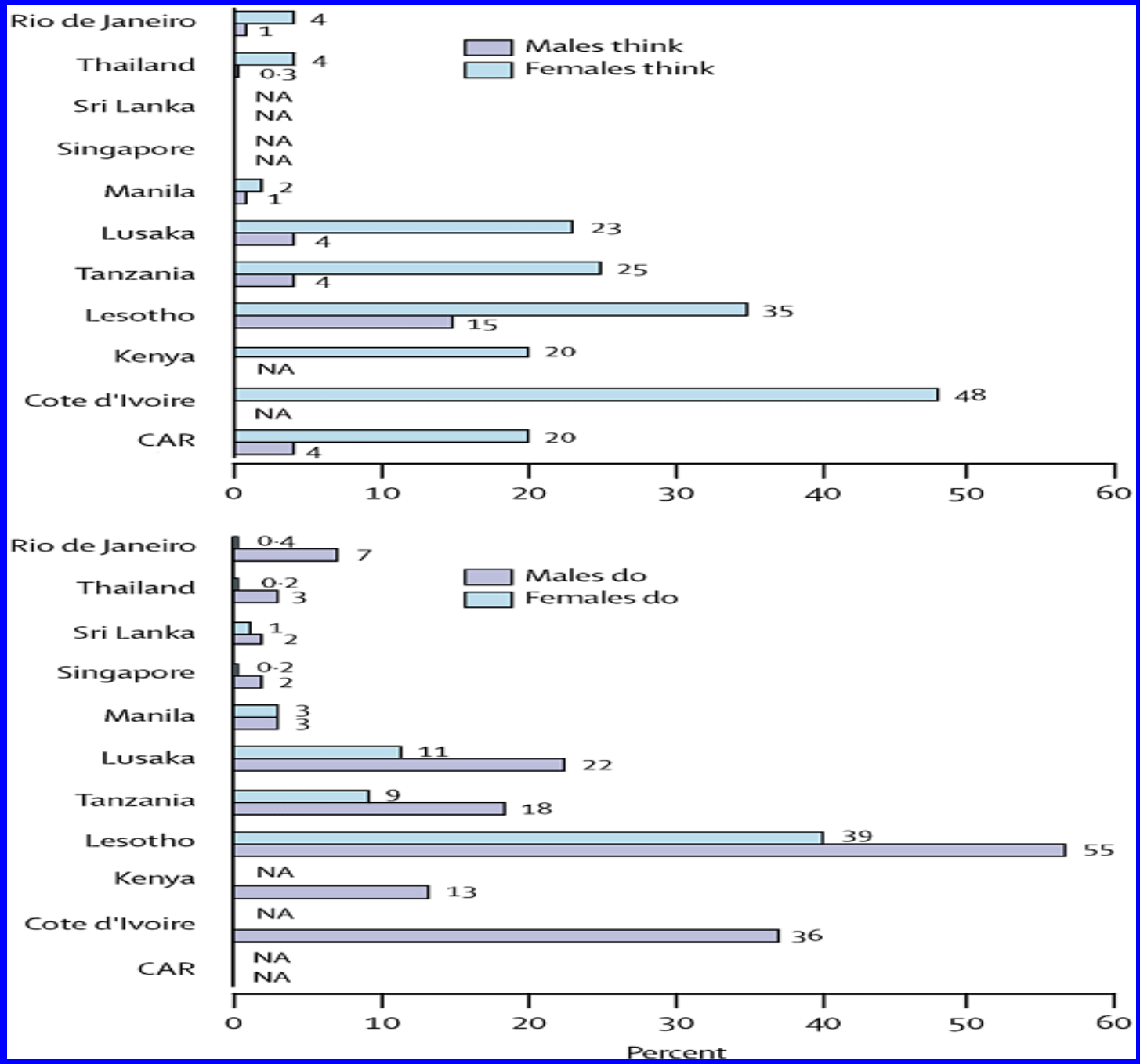
Does the male partner behavior define a woman's risk to HIV Infection? (Role of concurrent sexual partnerships)

Perception of relationship risk among HPTN 035 participants



	1	2	3	4	5	6	7	8
> 1 wife/partner	7	18	11	29	12	6	6	10
1 partner	71	70	43	18	57	54	61	73
Don't know	22	12	46	52	31	40	32	16

Sites



D. Halperin,
Lancet, Vol 364
Issue 9428, pgs 4-6

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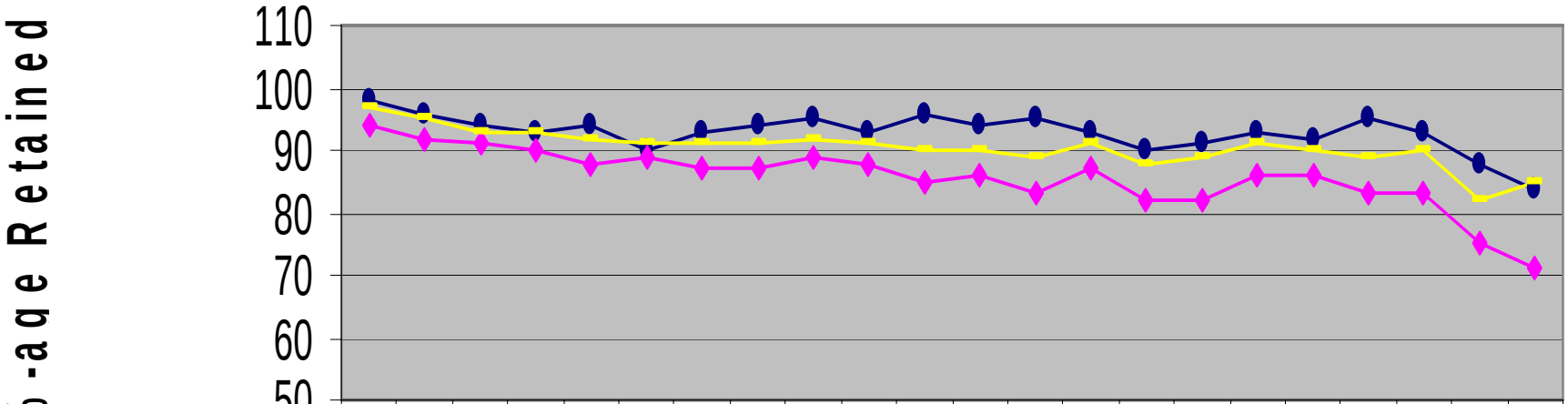
Application of lessons learned HPTN 035 to future effectiveness trials – (2)

- Retention
  - Retention in one site benefits from a shared understanding of strategies & lessons learned across other sites
  - Need to anticipate retention challenges: holiday, planting seasons, disclosures issues, client needs etc
  - Clinic flow operations can also benefit from outside review to help optimize staff time & reduce inefficiencies in participant flow
  - NOT ALL RETENTION CHALLENGES IMPROVED BY THE ABOVE

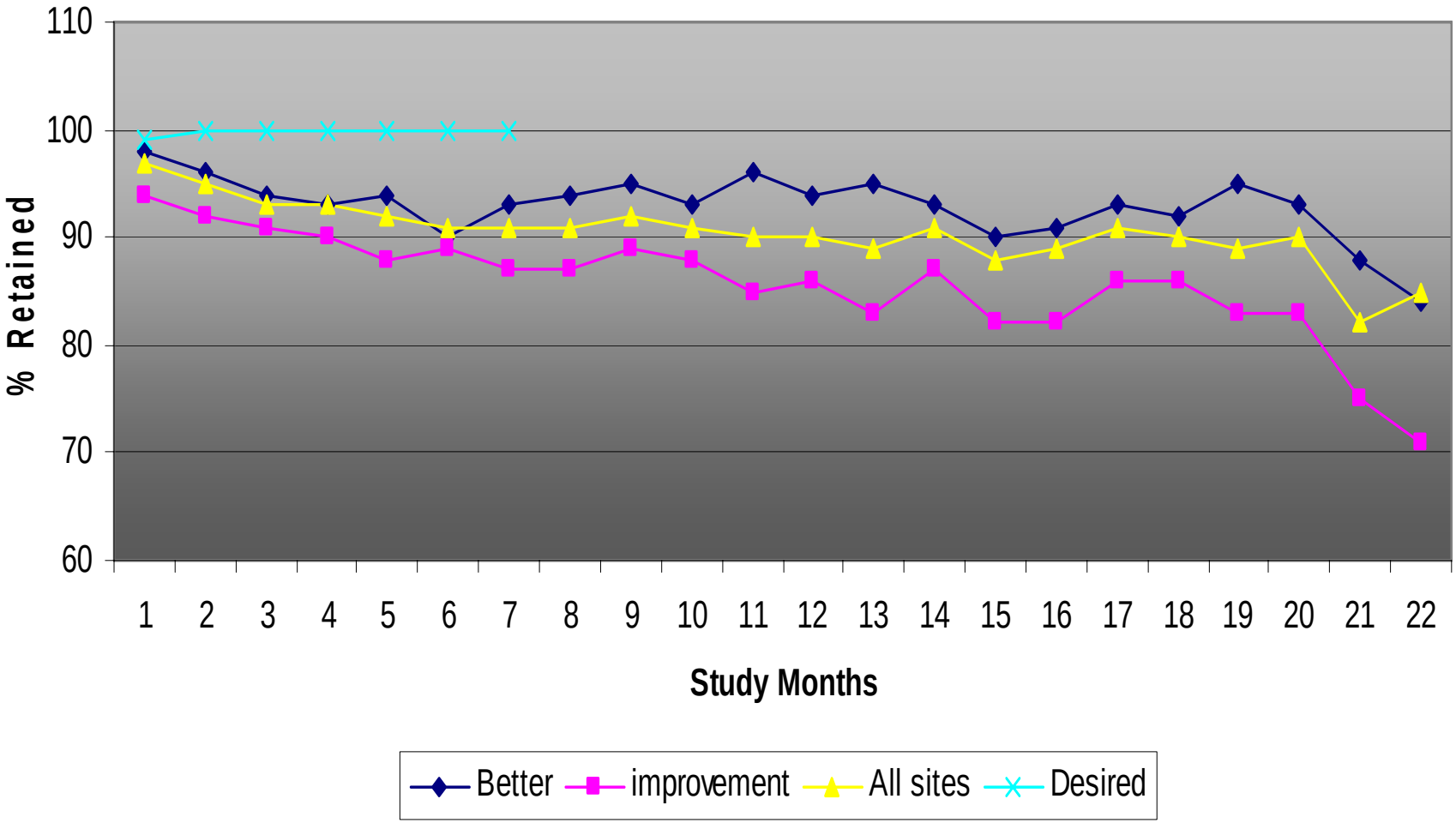
Retention across sites as of Feb 3, 2007 report



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Better	98	96	94	93	94	90	93	94	95	93	96	94	95	93	90	91	93	92	95	93	88	84
improvement	94	92	91	90	88	89	87	87	89	88	85	86	83	87	82	82	86	86	83	83	75	71
All sites	97	95	93	93	92	91	91	91	92	91	90	90	89	91	88	89	91	90	89	90	82	85

Study Months

Retention Rates across sites (as of Feb 3, 2007 report)



- Successful retention strategies at one site may seem similar to those used at another site, yet different
- Peer educator model in Lusaka may be worthy trying in highly mobile population

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Application of lessons learned HPTN 035 to future effectiveness trials – (3)

- Study drug Adherence; Challenge with self-reported data
  - Fine line between getting what participants perceive you want to hear & getting what actually happens
  - Need to constantly engage site staff regarding adherence messaging (no standard approach given variability in circumstances impacting adherence)
- Evidence that we can still do better in product adherence
  - Site's post sero-conversion experiences "Self-confessed non-adherence"
  - Key is how to get staff use such negative experiences to enhance adherence counseling
  - ? Experiences from the Caraguard trial

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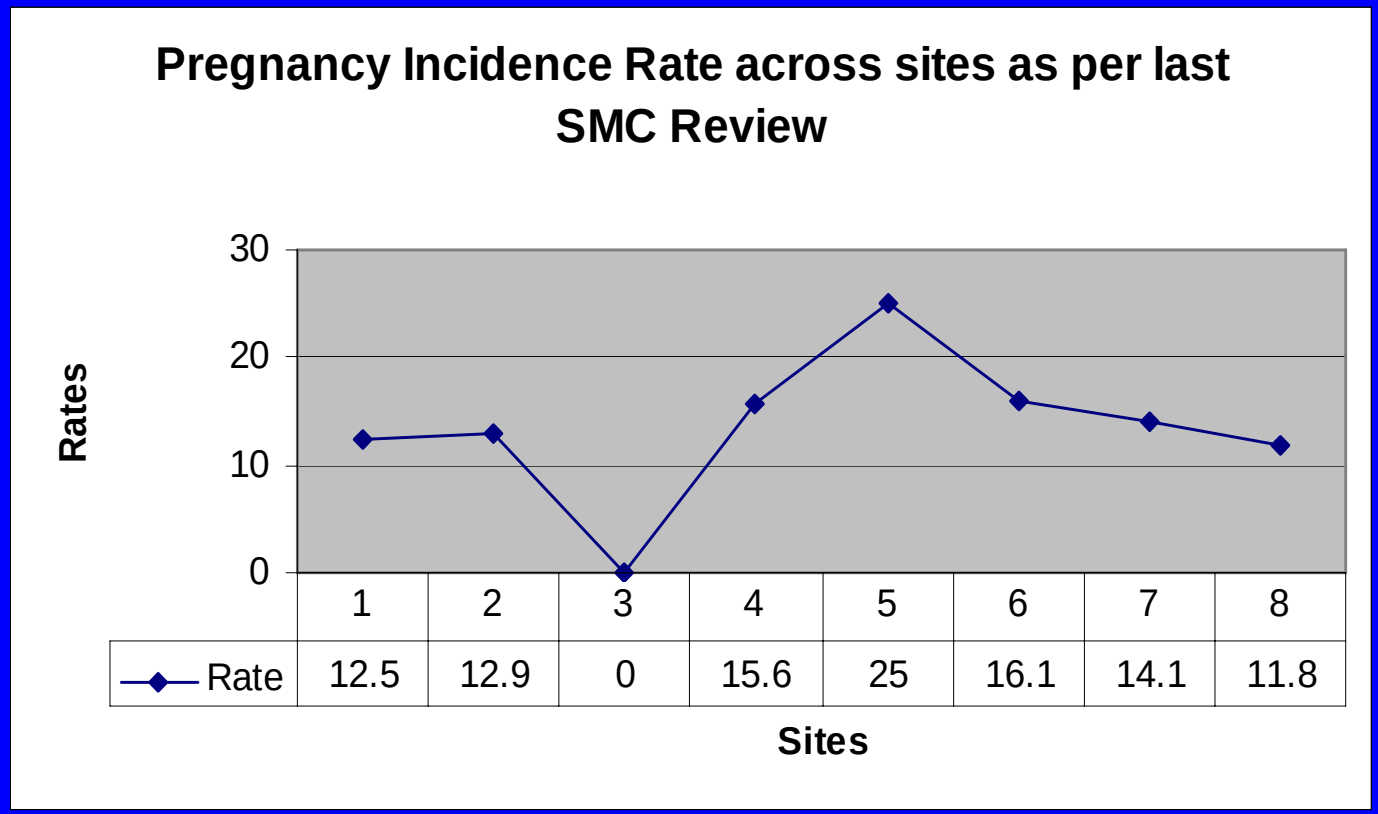
Study product adherence (ctd)

- Impact of non-adherence on efficacy assessment & future availability of a microbicide product on market;
  - Real potential to shelve otherwise acceptably effective products (ITT analysis)
  - Even with Per protocol analysis, its resource intensive to adjust for info obtained post-hoc (developing propensity scores)

Application of lessons learned HPTN 035 to future effectiveness trials – (4)

Pregnancy rates

- Risk of infection changes with pregnancy (sexual activity, time on study product, unprotected sex lowered) (Wes Rountree at M2006)



Summary

- Regular outside review of recruitment, retention, product adherence & other implementation aspects critical
- Promotion of inter-site collaboration (including inter-site personnel visitation & workshops) based on site-specific strengths & weaknesses is key to addressing implementation challenges
- Need to work regularly work with sites (asking right questions positively engages at all levels of implementation)

Benedete Nakayima in her 70's lost 6 daughters & 5 sons to HIV

Photo/ Farhana Haque Rahman/ Human rights watch website