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Recruitment of Female Sex Workers in HIV Prevention Trials: Can Efficacy Endpoints Be Reached More Efficiently?

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- HIV epidemic remains significant public health burden with estimated:
 - **36.7 million** people living with HIV in 2015
 - **2.1 million** new infections in 2015
- HIV prevention successes:
 - **Preventing mother-to-child transmission:** 70% reduction since 2001
 - **Medical male circumcision:** ~60% efficacy
 - **Treatment as prevention:** ~96% efficacy
 - **Daily pre-exposure prophylaxis (PrEP):** 38%-75% efficacy

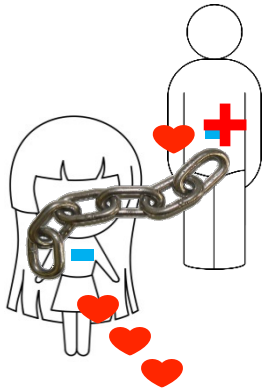
- New biomedical modalities for HIV prevention are currently tested
 - Long-acting injectable (HPTN 083, HPTN 084)
 - Broadly neutralizing antibodies (HPTN 081, HPTN 085)
 - HIV multi-dose vaccine (HVTN 702)
- RCT design typically assumes a common effectiveness at all levels of HIV risk
- RCTs of HIV biomedical interventions often enroll participants with nonuniform HIV exposure, including people never exposed to HIV.
- In this group an effective intervention cannot demonstrate an effect which result in attenuation of observed treatment efficacy

- Female sex workers (FSW) are disproportionately infected with HIV. Within sub-Saharan Africa:
 - HIV prevalence among FSW is nearly 40%
 - Annual HIV incidence among FSW ranges from 0.9% in Burkina Faso to 9.8% in Zimbabwe
- Given their considerable risk of HIV acquisition, FSW would clearly benefit from effective prevention interventions
- Despite FSW being at high risk for HIV acquisition, few recent HIV prevention trials have purposely enrolled FSW
- Enrolling participants with higher and more consistent exposure to HIV, such as FSW, will affect the results of future HIV prevention trials

- To explore the extent to which enrolling different proportions of FSW may reduce the expected duration of trials and improve efficacy estimates
- To compare scenarios in which FSW have a high volume of clients and consistent condom use (e.g. professional FSWs) with scenarios in which FSWs practice sex work less frequently with fewer clients (e.g. part time FSWs).
- To investigate the importance of retaining FSWs in the trials with long follow-up periods. We study the influence of higher loss-to-follow-up rates in FSWs on trial duration and observed efficacy.

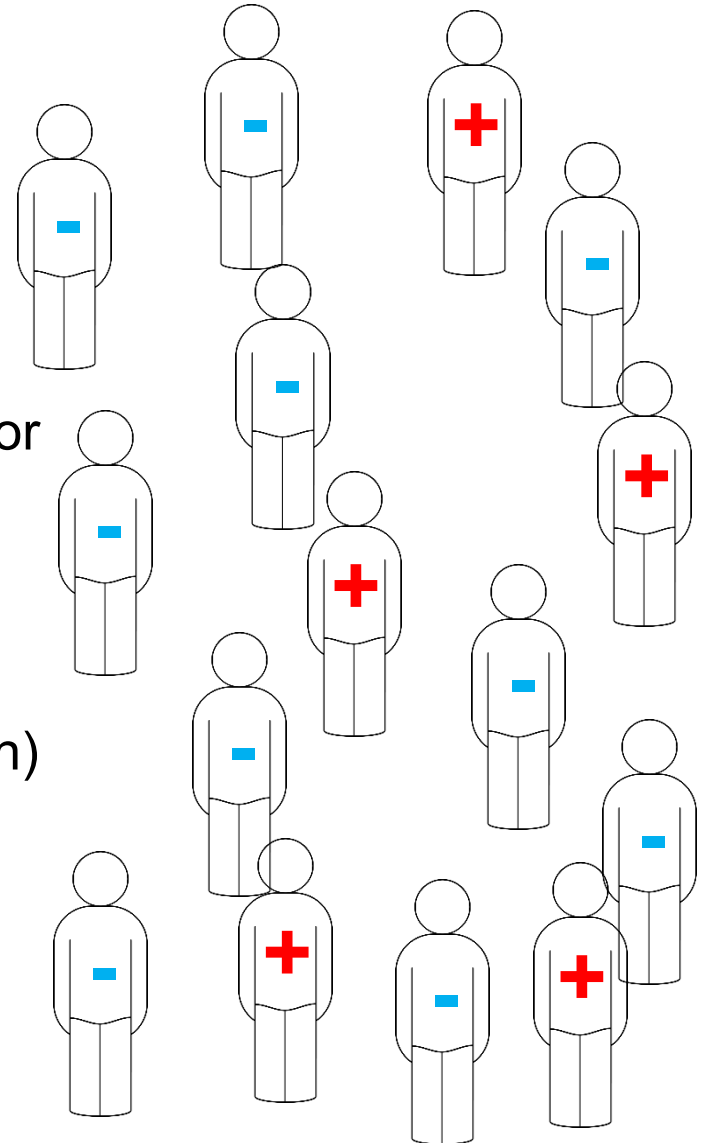
- Stochastic individual-based mathematical model simulates RCT of HIV prevention in HIV-uninfected women.
- 3600 women are enrolled over a one-year period and randomized in a 1:1 ratio to active or placebo arms
- The primary design of interest was an event-driven trial, i.e., a trial that concludes when 120 infections have occurred
- The women were divided into three categories:
 - FSW,
 - low-risk non-FSW and
 - high-risk non-FSW
- Presented results are based on 1000 simulations per scenario

Model development



Probability to acquire HIV depends on:

- the type of the act (vaginal or anal)
- the use of condom
- partner's HIV stage and ART status
- PrEP protection (by regimen)

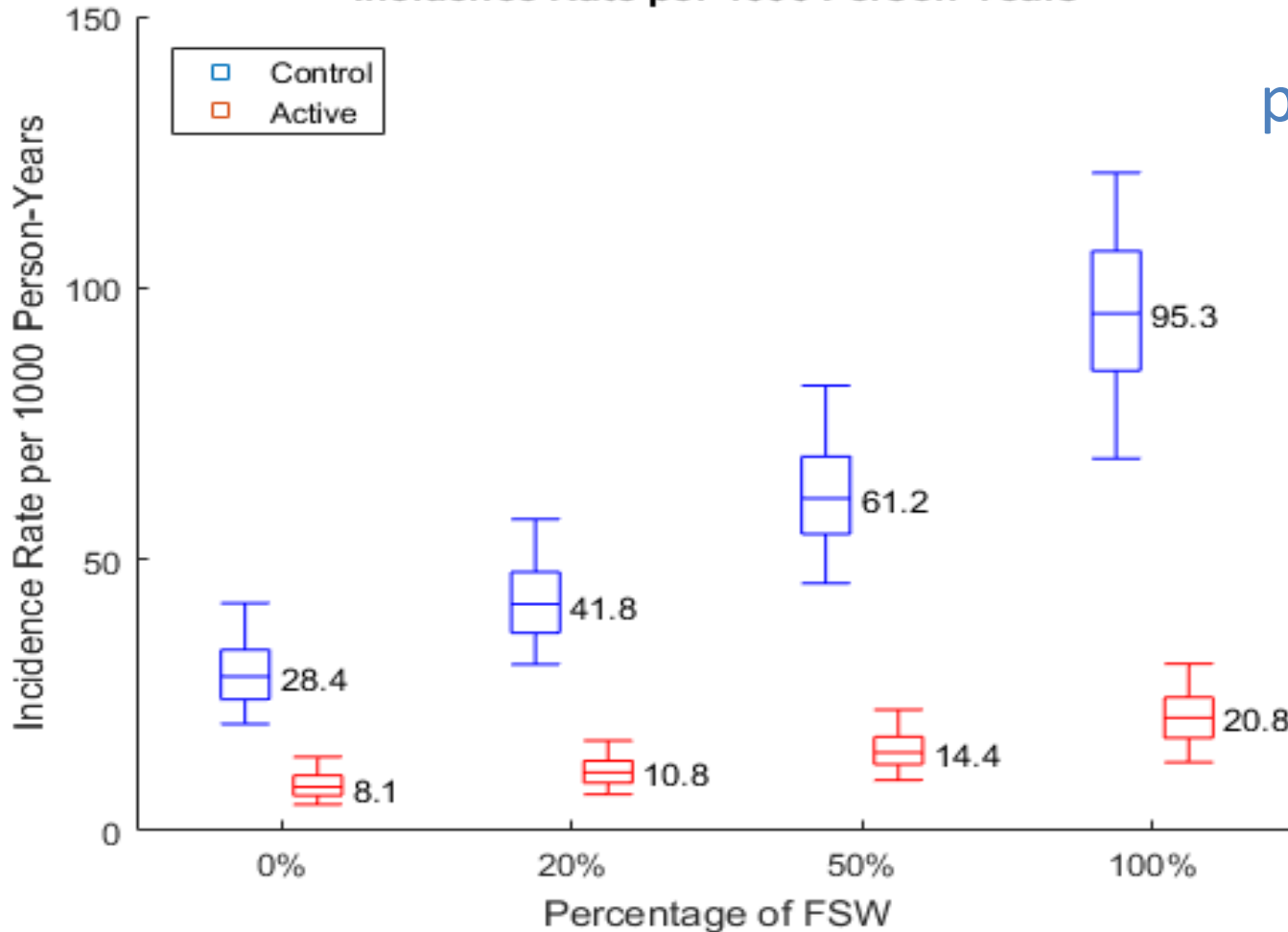


- HIV prevention:
 - **Main: 80% efficacy** in reducing the HIV acquisition risk per act
 - **Alternative: 50% efficacy** in reducing the HIV acquisition risk per act.
- Proportions of FSW enrolled in the trial:
 - **0%, 20%, 50% and 100%**
- Loss-to-follow-up rates (annually) among FSW
 - **5%, 10%, 20% and 50%**

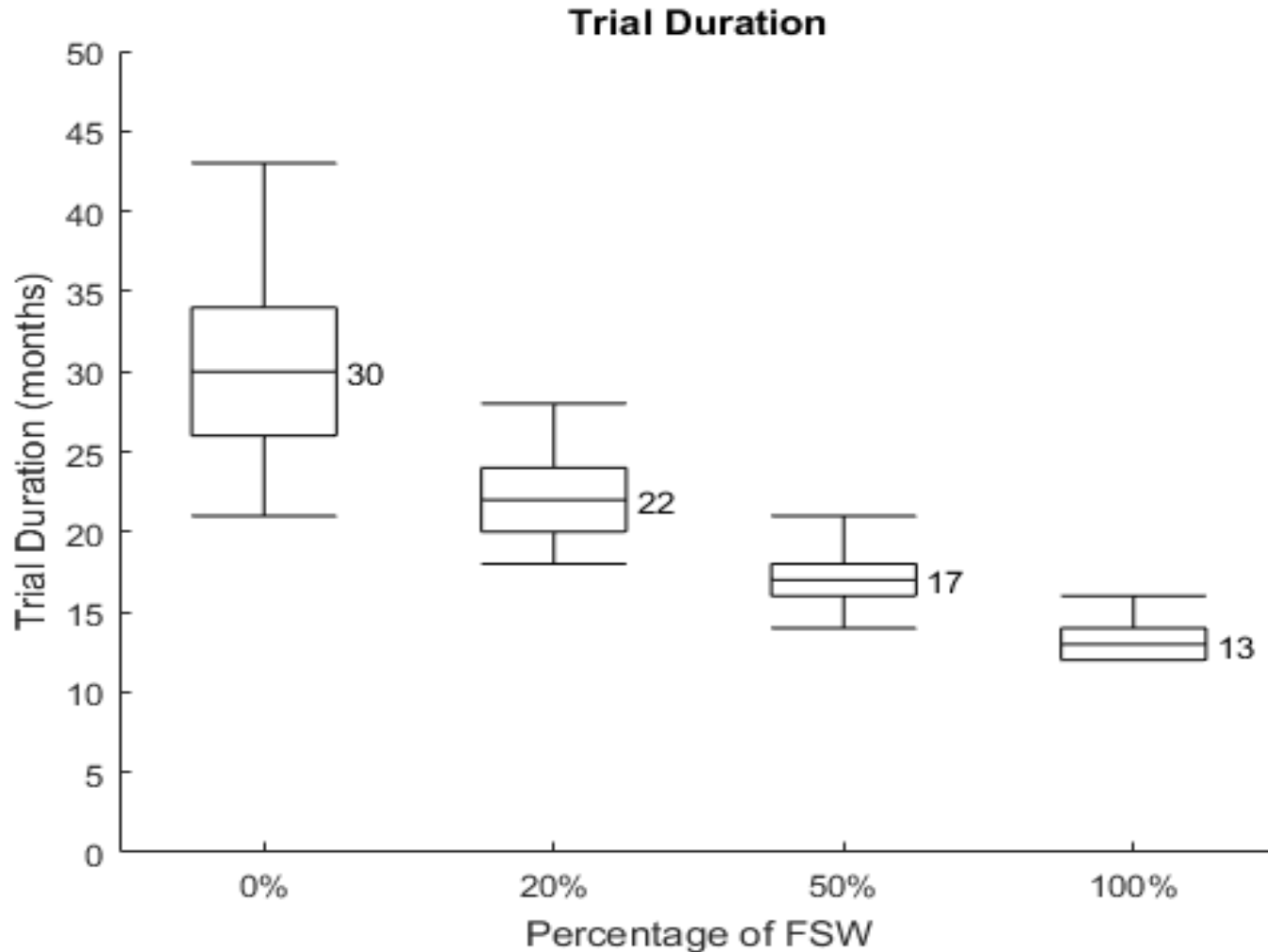
Observed Efficacy = $1 - \text{HIV incidence rate in active arm} / \text{HIV incidence rate in control arm}$

Impact of FSW enrollment on HIV Incidence

Incidence Rate per 1000 Person-Years

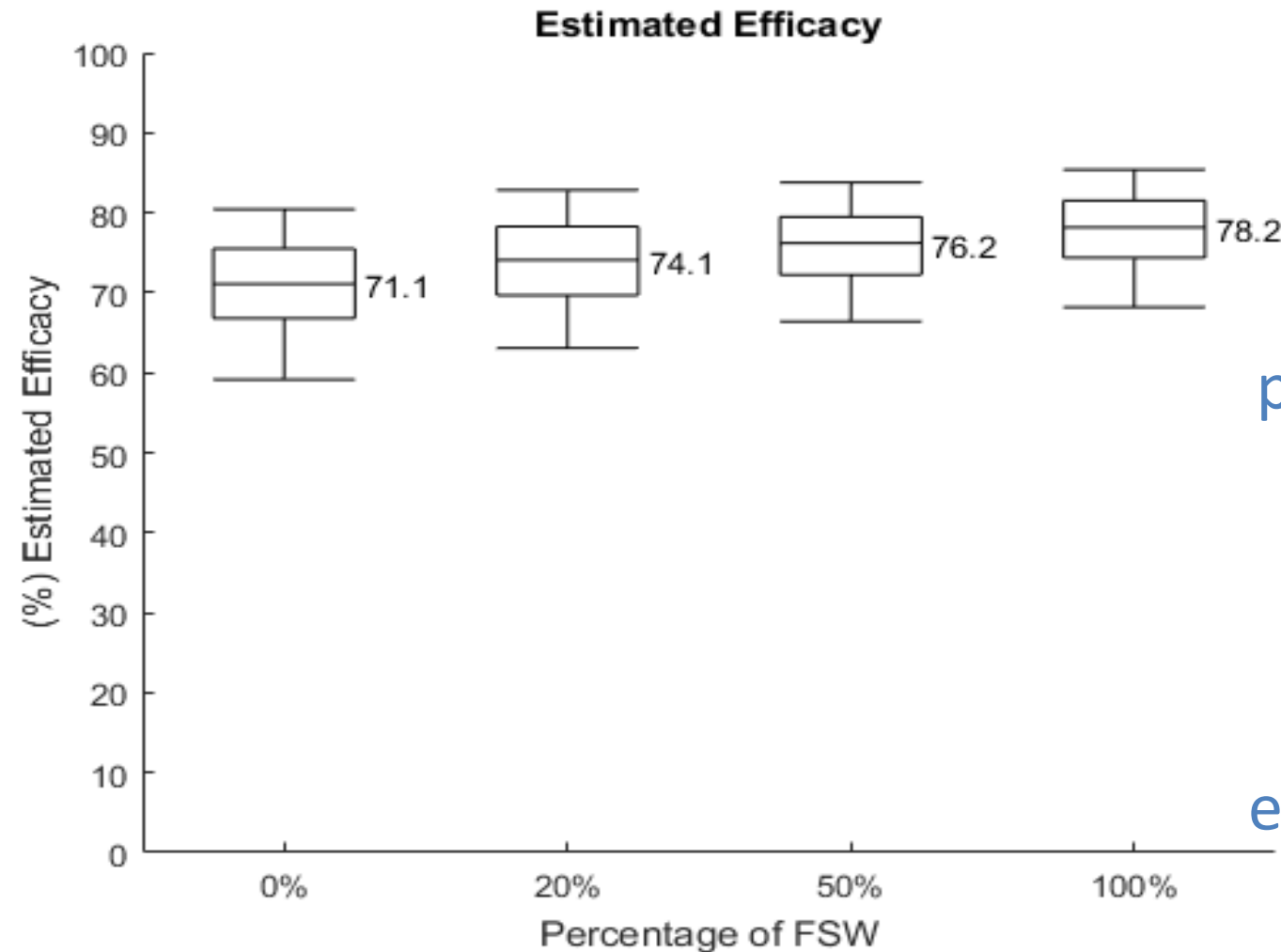


Enrolling professional FSW participants resulted in increasing HIV incidence rates



Enrolling professional FSW participants substantially reduced the expected trial duration

Impact of FSW enrollment on estimated efficacy in RCTs

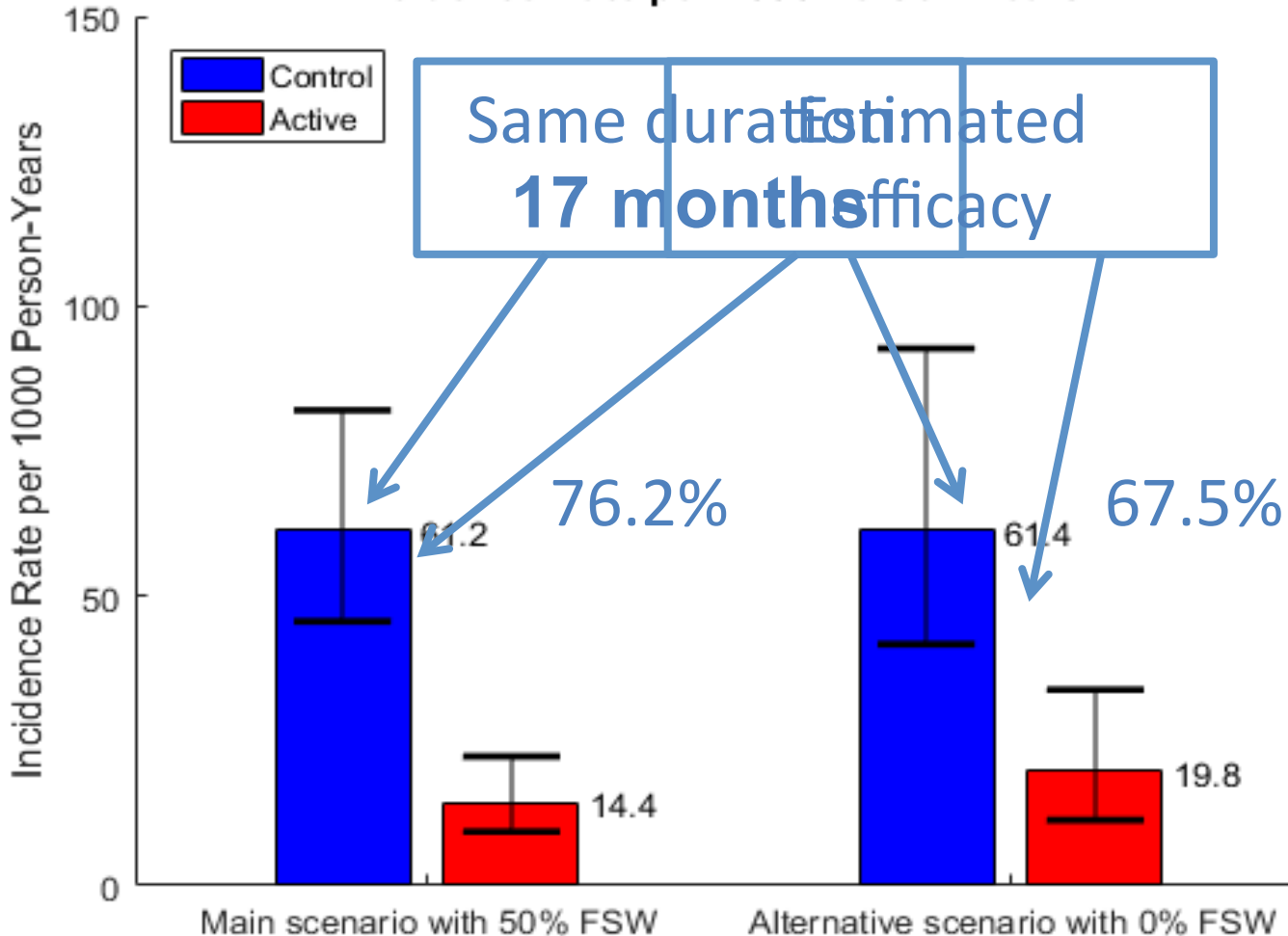


Enrolling professional FSW participants is reducing the extent to which efficacy estimated in RCTs underestimates the true efficacy

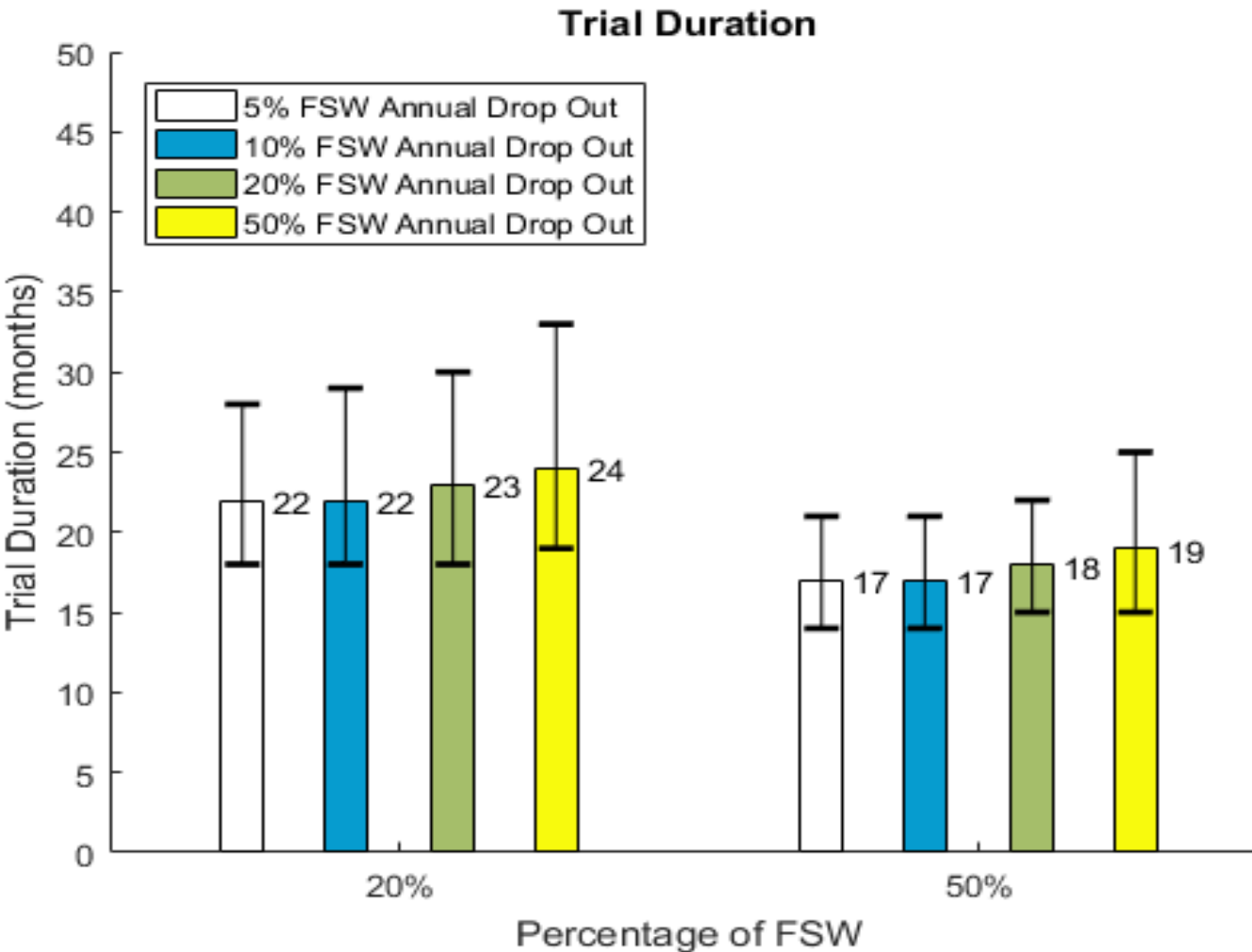
Impact of FSW enrollment on estimated efficacy in RCTs

Differences in estimated efficacy can't be attributed to higher HIV incidence among FSW

Incidence Rate per 1000 Person-Years



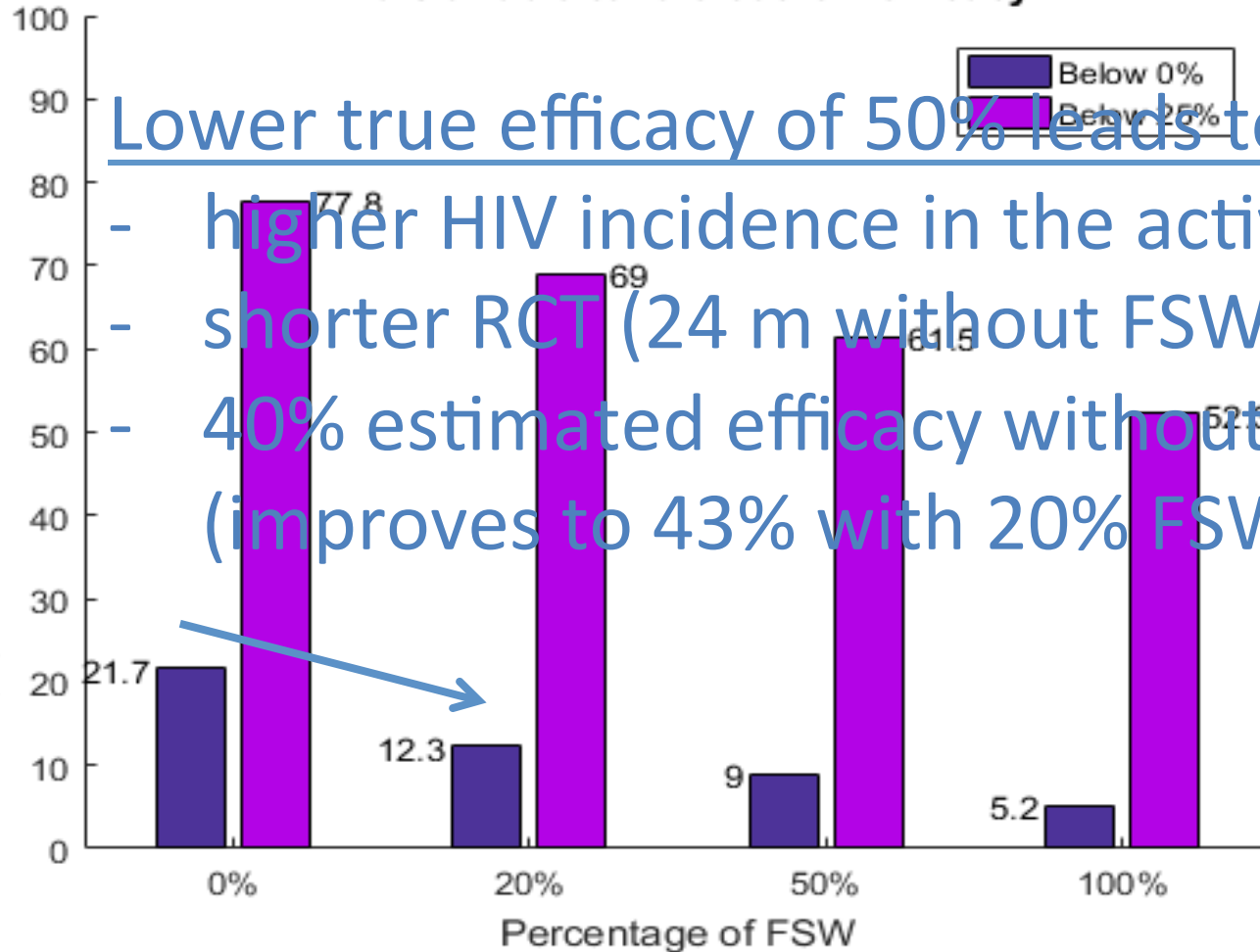
How important is it to retain FSW in the trial?



Higher dropout rates among FSW participants is expected to make the trial up to 2 months longer. Estimated efficacy was essentially unaffected.

What if the true efficacy is lower?

Trials unable to rule out low efficacy



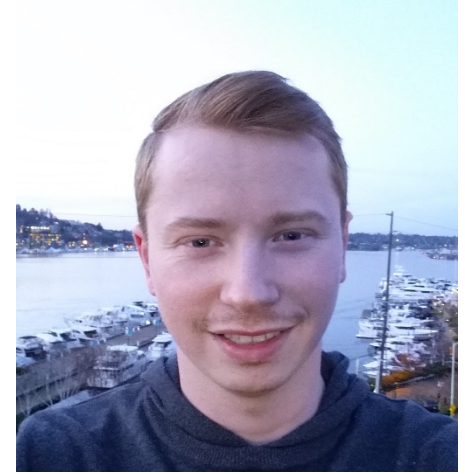
Lower true efficacy of 50% leads to:

- higher HIV incidence in the active arm
- shorter RCT (24 m without FSW)
- 40% estimated efficacy without FSW
(improves to 43% with 20% FSW enrolled)

43% reduction in the likelihood for inconclusive trial if 20% FSW are enrolled

- Despite the potential logistical challenges of recruiting and retaining FSW, trialists should revisit the idea of enrolling FSW in settings where HIV incidence among FSW is higher than among non-FSW.
- Our analysis suggests that enrolling FSW would increase HIV incidence, reduce trial duration and improve estimates of the true efficacy per sex act, even if the annual dropout rate among FSW participants is high.

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