



Predicting the individual-level effectiveness of daily and non-daily PrEP based on study results from HPTN 067 ADAPT

Dobromir Dimitrov

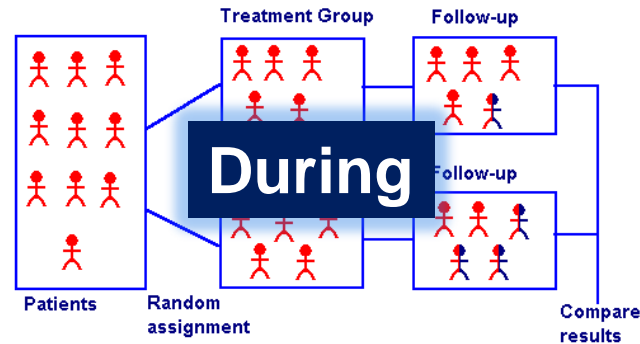
Fred Hutchinson Cancer Research Center

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- A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral PrEP
- Evaluate the feasibility of intermittent dosing of PrEP regimen among HIV-uninfected MSM/TGW and WSM at high risk of acquiring HIV infection (178 MSM/TGW in Bangkok, 179 MSM/TGW in New York and 179 WSM in Cape Town)
- Pill taking is informed by an electronic dispensing device (Wisepill™) that recorded each opening
- Treatment regimen:
 - daily dosing
 - time-driven dosing (2 per week + within 2h after sex)
 - event-driven dosing (within 2d before + within 2h after sex).



Before



After

Trial endpoints: Total number of pills taken, Sex acts coverage

Analysis of coverage data by arm and site



Connect coverage data with PrEP efficacy per act
Model development
Model calibration

Model development
Model calibration

Modelling: predict HIV incidence reduction by arm and site

Effectiveness analysis
estimate HIV incidence reduction

Sex coverage per protocol

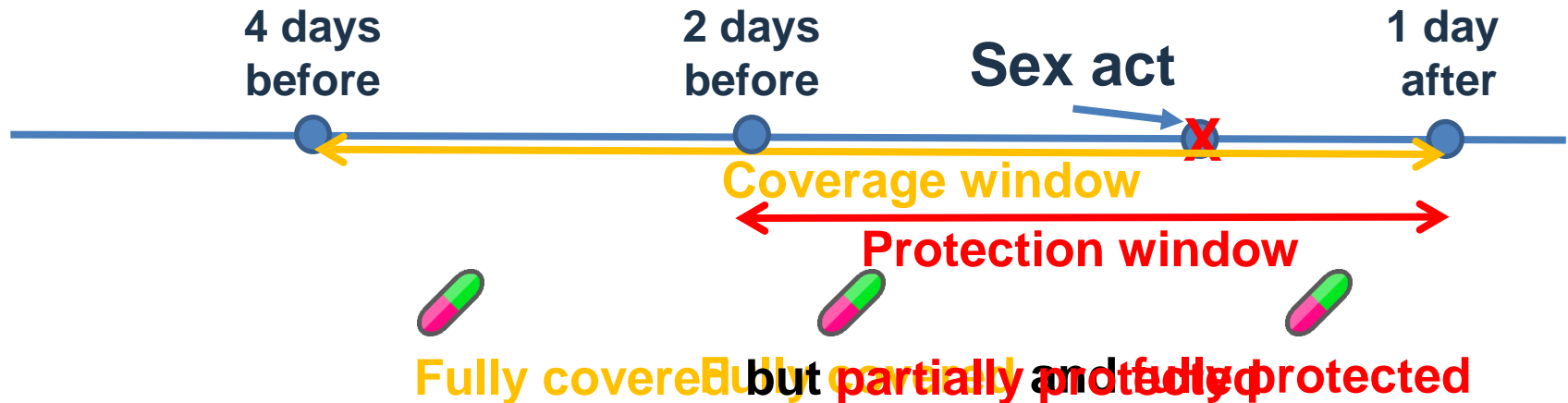
- Sexual activity is based on weekly interviews by phone or in person, i.e., entirely based on self-reported data
- Pill taking is informed by an electronic dispensing device that recorded each opening
- Sex coverage was defined as follows:
 - Fully covered acts - pills taken **within 4 days before** and **1 day after** an act.
 - Partially covered acts - only before or after pill is taken
- This definition guarantees that all sex acts are fully covered with all 3 treatment regimens (daily, time-driven, event-driven) assuming perfect adherence



- iPrEx analysis suggests that PrEP is protective for MSM even if taken only twice a week (Anderson et al., Sc.Trans.Med. 2012). Non-daily regimens of PrEP also showed efficacy (McCormack, Lancet 2016; Molina, CROI 2015) when used by MSM
- Trials testing daily PrEP on women suggest strong dependence on adherence and less forgiveness for missed doses (Baeten, NEJM 2012; Van Damme, NEJM 2012, Marrazzo, NEJM 2015)
- Later studies suggest that women need more frequent PrEP dosing than men to protect against HIV (Cottrell, JID 2016)
- HPTN 067 definition of coverage is unlikely to provide protection for women
- Sex acts covered by this definition are unlikely to be equally protected even for MSM

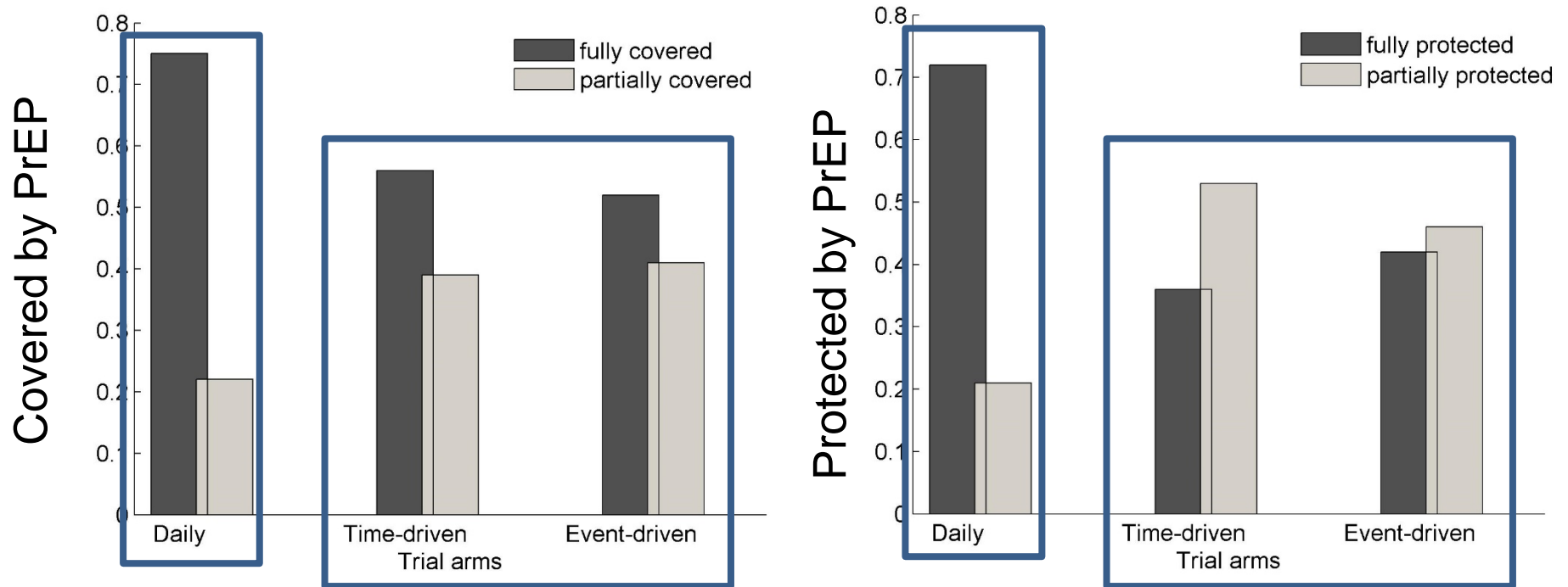
Modified definition: PrEP Protected sex acts

- We define sex acts to be protected by PrEP as follows:
 - Fully protected acts - pills taken **within 2 days before** and **1 day after** an act. This definition is more restrictive than the definition used in the trial protocol.
 - Partially protected acts - only before or after pill is taken



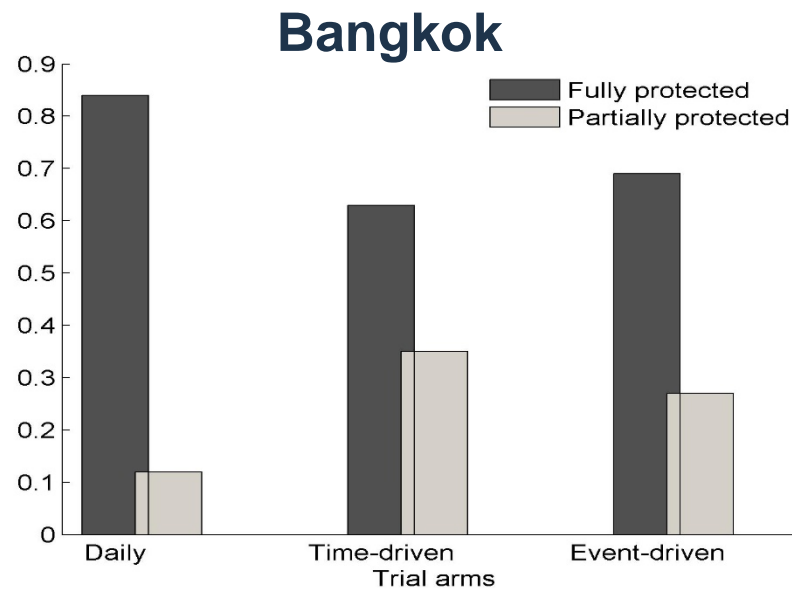
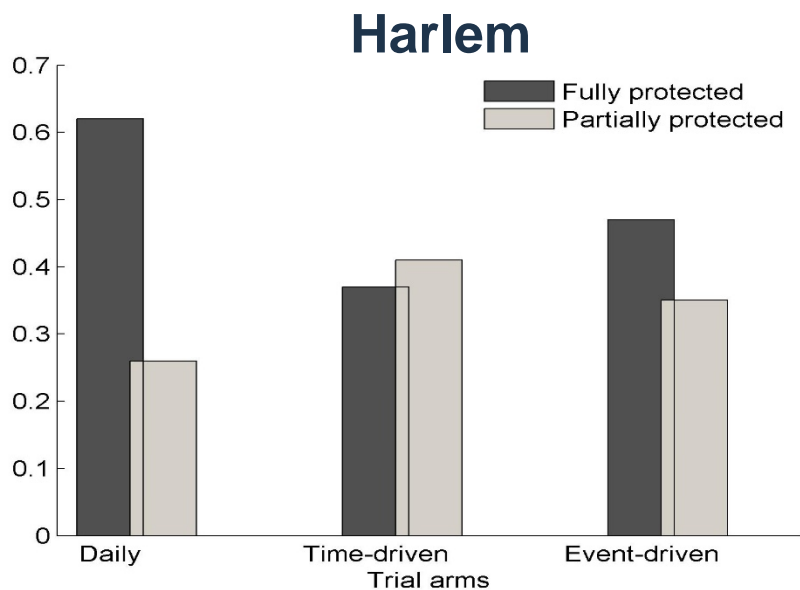
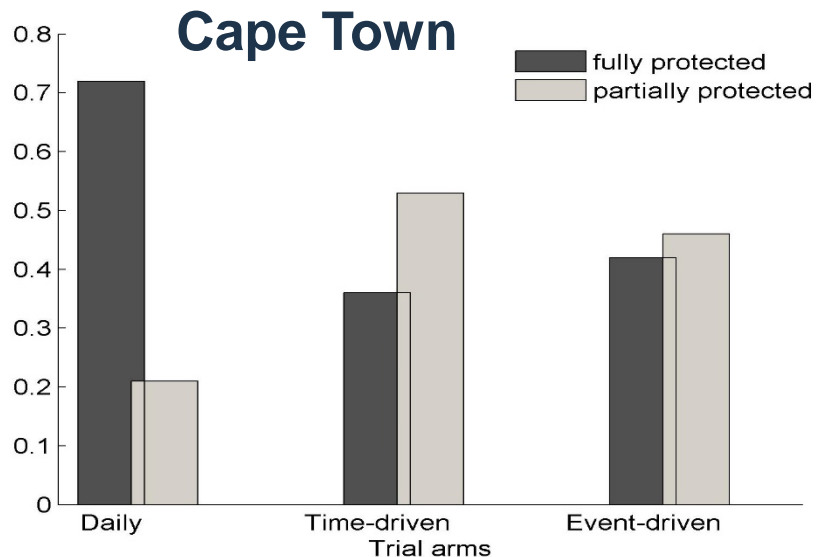
Protected vs. covered sex acts

- Difference in distribution of covered and protected sex acts based on data from Cape Town site



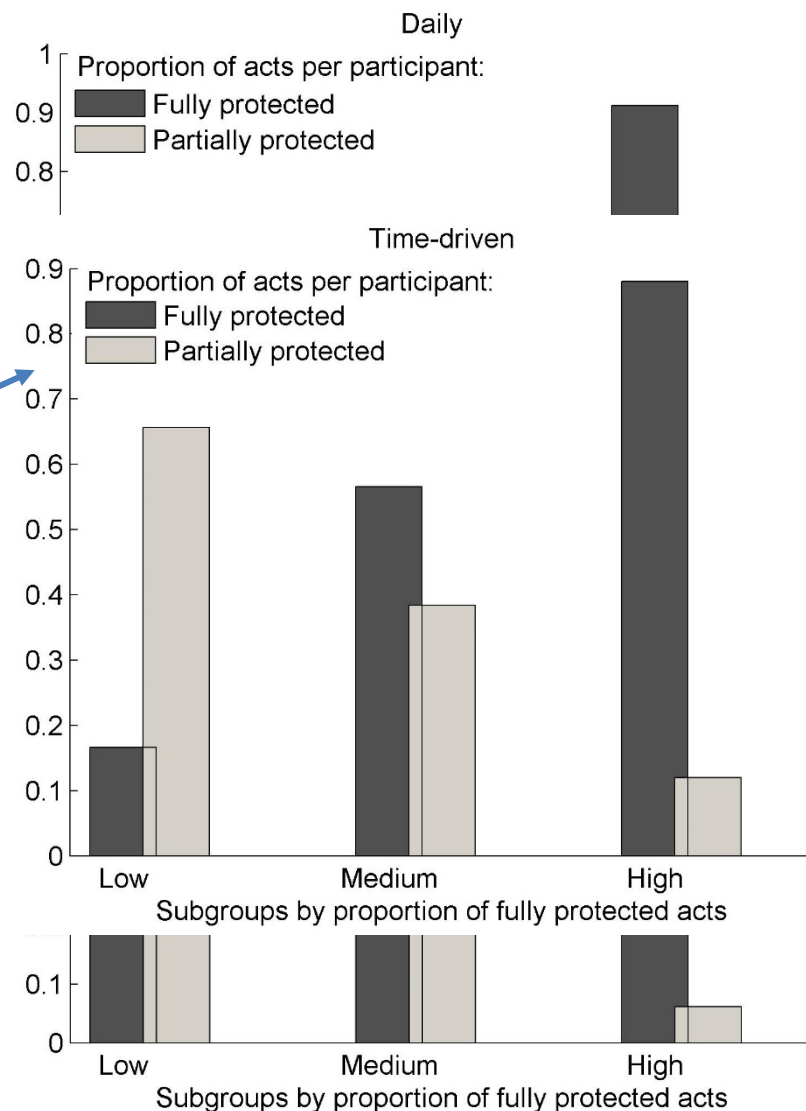
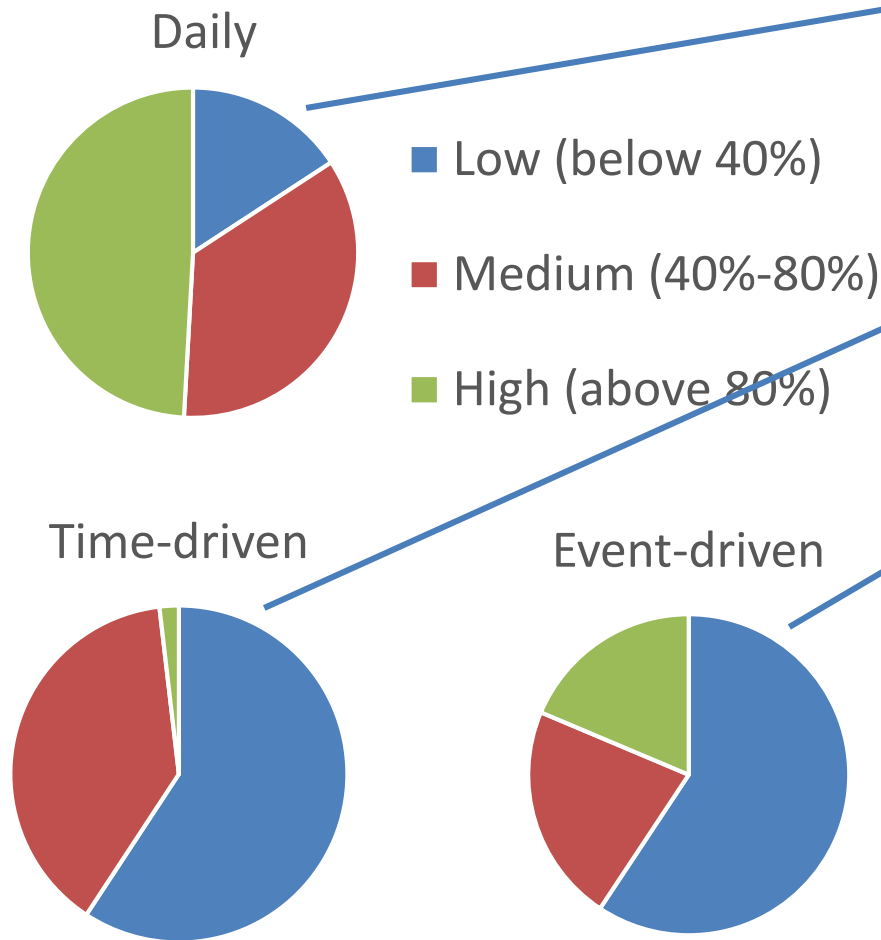
Small differences in the daily arms: **Significant differences in the non-daily arms:**
 >70% fully covered (56-20% tested) fully protected than fully covered
 >20% partially covered (10-15% tested) partially protected than covered

Protected acts by site and arm

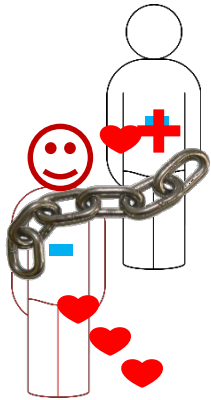


Distribution of protected sex acts based on data from HPTN 067

Division of Cape Town participants by % of fully covered acts:

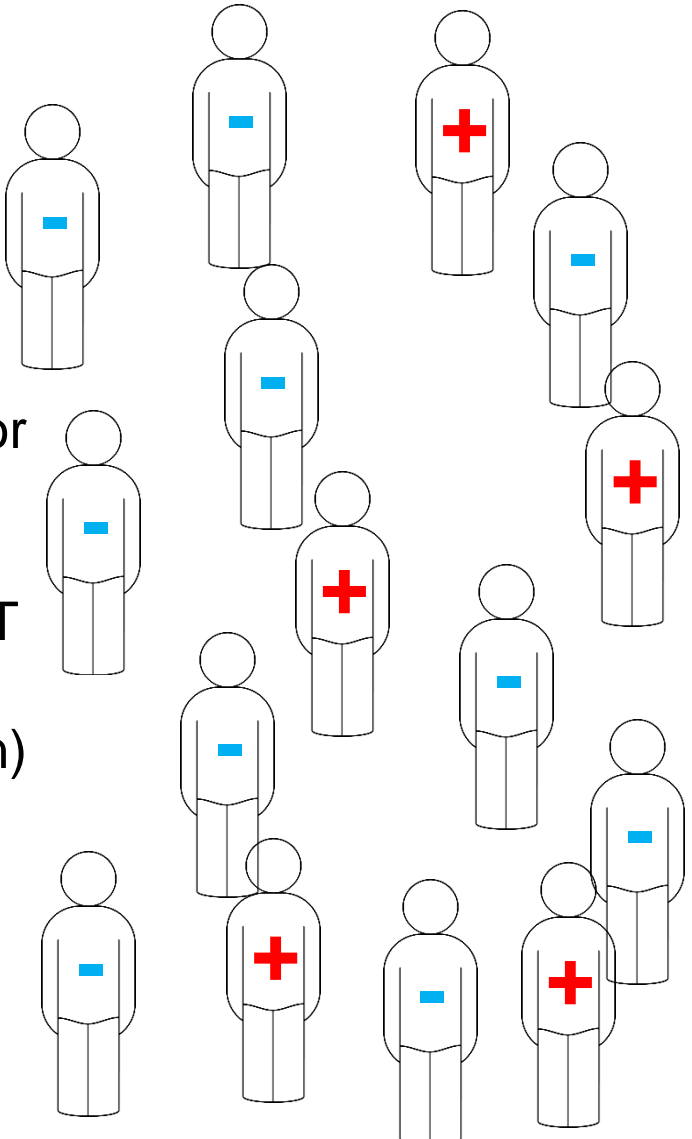


- Stochastic individual-based mathematical model simulates HIV acquisition among a cohort of uninfected individuals.
- Participants are assigned in 2 risk groups with number and type of current partnerships based on data from Cape Town, New York and Bangkok.
- For each PrEP regimen the cohort is followed for 1 year under 2 distinct scenarios:
 - PrEP is used and the distribution of sex acts protected by PrEP is based on data from HPTN 067 by site and arm.
 - PrEP is not used
- Presented results are based on 1000 simulations per scenario



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)



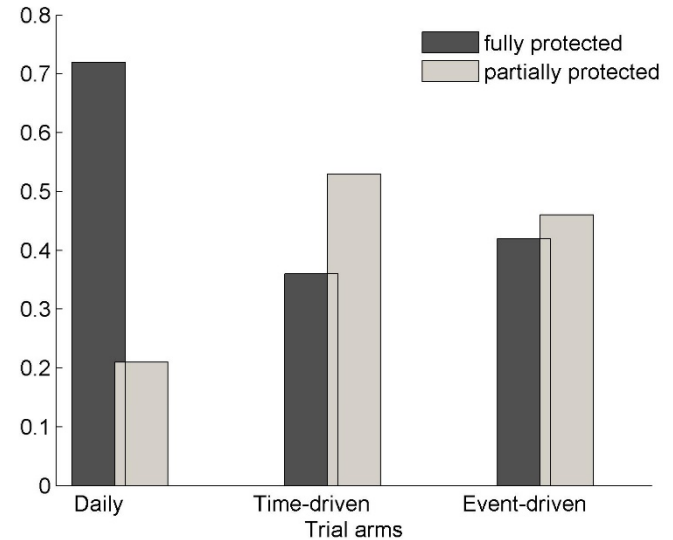
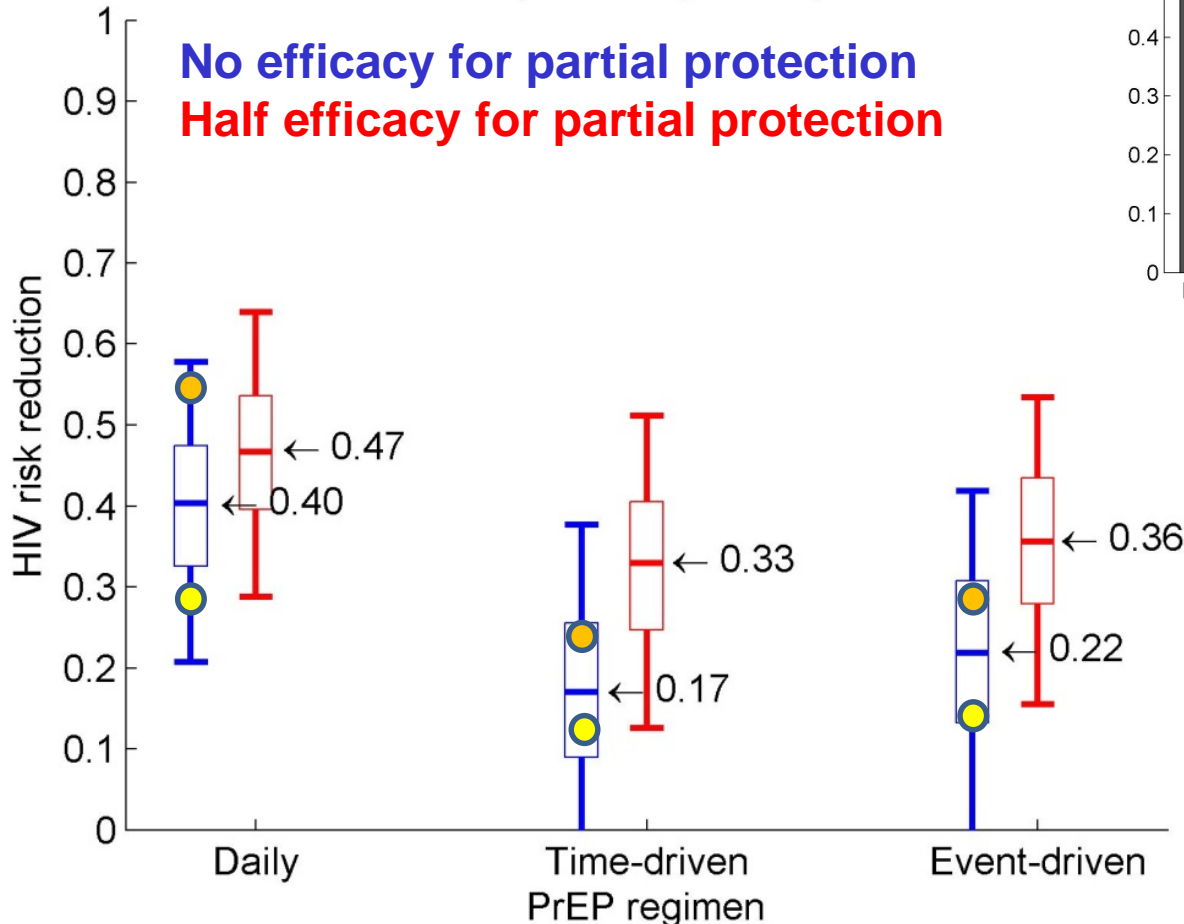
Rates of initiation and dissolution of partnerships, frequency, type, and protection of sexual acts are calibrated for Cape Town, New York and Bangkok.

- PrEP protection:
 - **90% efficacy** in reducing the HIV acquisition risk per fully protected acts for MSM.
 - **70% efficacy** in reducing the HIV acquisition risk per fully protected acts for women.
- Scenarios on partially protected acts:
 - **No PrEP efficacy** retained for partially protected acts
 - **Half of the PrEP efficacy** retained for partially protected acts

$$\text{Effectiveness} = 1 - \frac{\text{HIV incidence rate with PrEP}}{\text{HIV incidence rate without PrEP}}$$

Cape Town (women)

No efficacy for partial protection
Half efficacy for partial protection

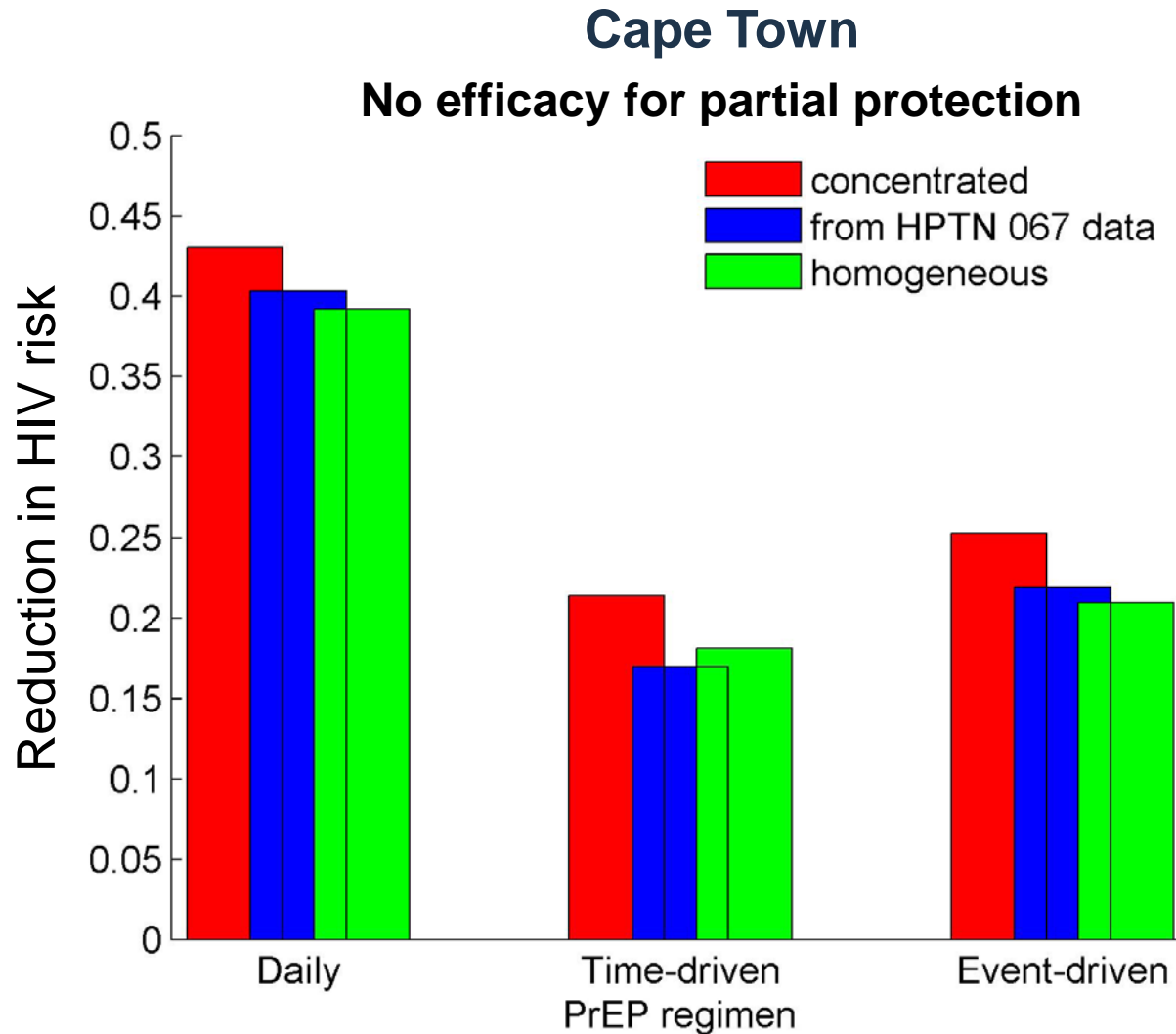


Key assumption:
70% efficacy per fully protected act

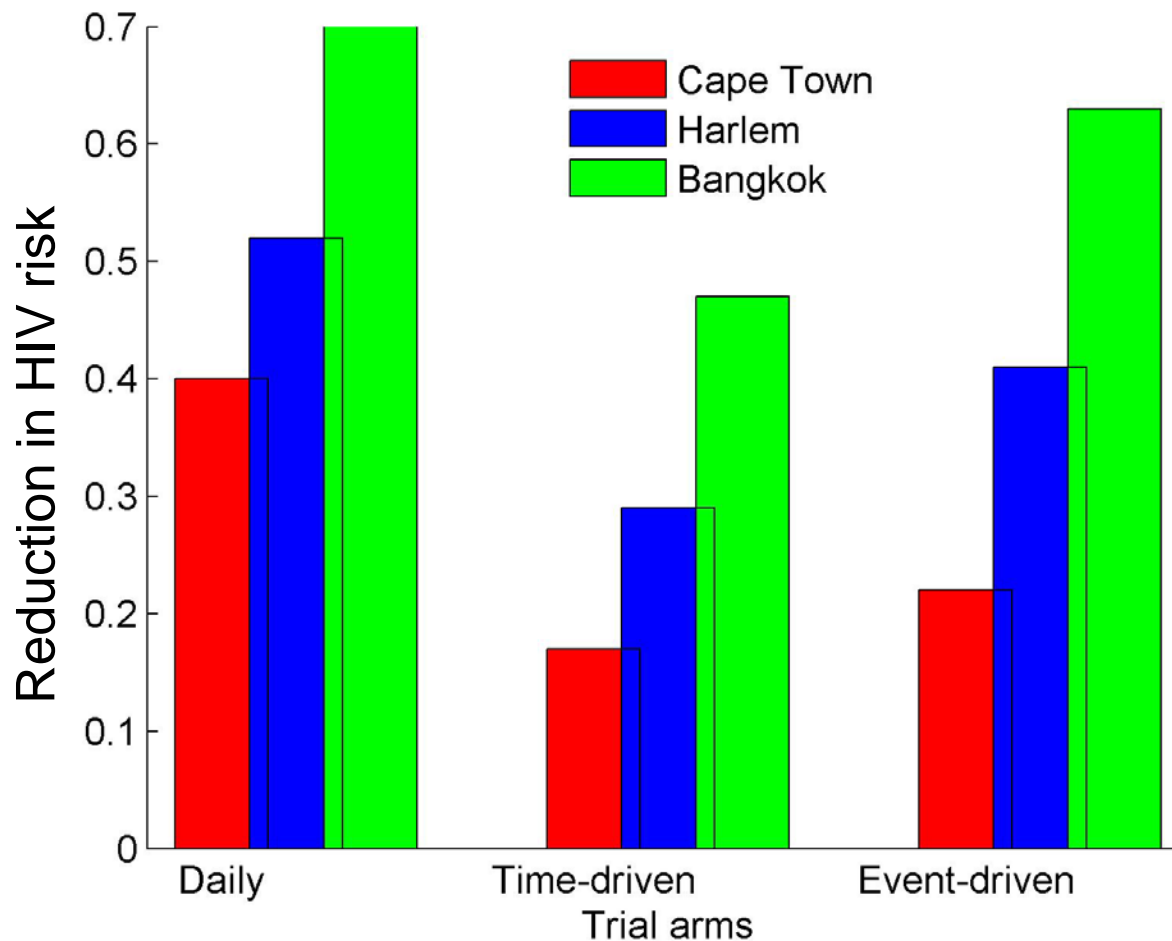
Alternatives:
50% efficacy

90% efficacy

How important is the distribution of protected sex acts?



No efficacy for partial protection



Summary

- Non-daily PrEP is unlikely to be as effective as daily PrEP in reducing HIV incidence among females in South Africa and among MSM in USA and Thailand due to higher proportion of sex acts protected with daily use.
- The analysis of the three sites suggests that PrEP will be most effective among MSM in Thailand and least effective among women in South Africa
- Uncertainty in the PrEP efficacy associated with non-daily regimens should be further investigated to provide more reliable estimates of effectiveness

Acknowledgements

Daniel Wood



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