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Injectable cabotegravir for HIV prevention – status and updates

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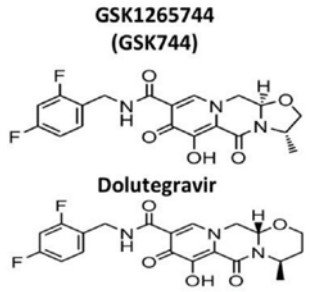
University of the Witwatersrand
MTN Regional Meeting, Cape Town, September 2019

Outline

- Rationale: injectable cabotegravir for PrEP
- Phase II study updates
- Phase III study updates
- Lessons learned

Cabotegravir



- Integrase inhibitor
- LA formulation is low solubility crystalline drug suspended in aqueous vehicle for intramuscular injection
- High genetic barrier to resistance and long half life makes it favourable for PrEP
- HIV treatment studies (with rilpivirine) demonstrate potent anti-HIV activity and high resistance barrier
- NHP studies demonstrate high levels of protection against rectal, vaginal, parenteral or penile SHIV challenges

Source: Andrews, 2014; Radzio, 2015; Andrews, 2015; Andrews, 2017; Dobard, 2018

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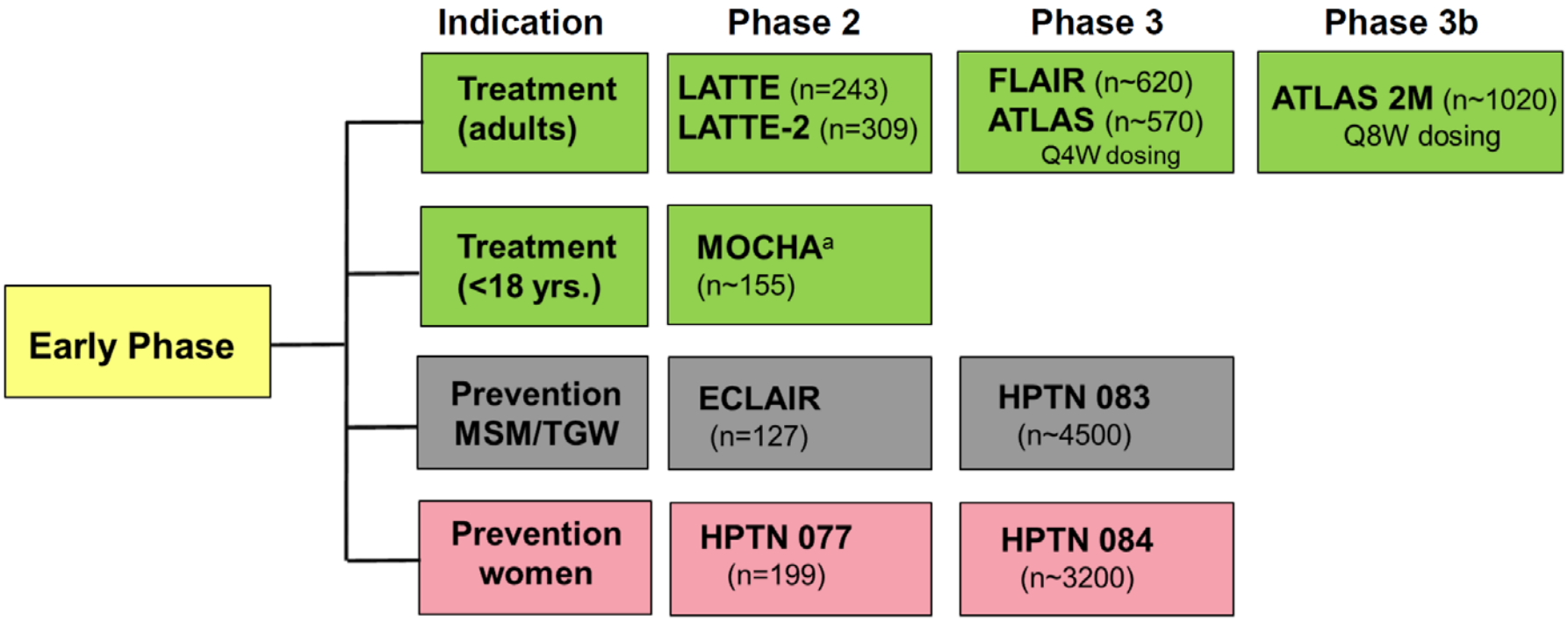
CAB LA development programme



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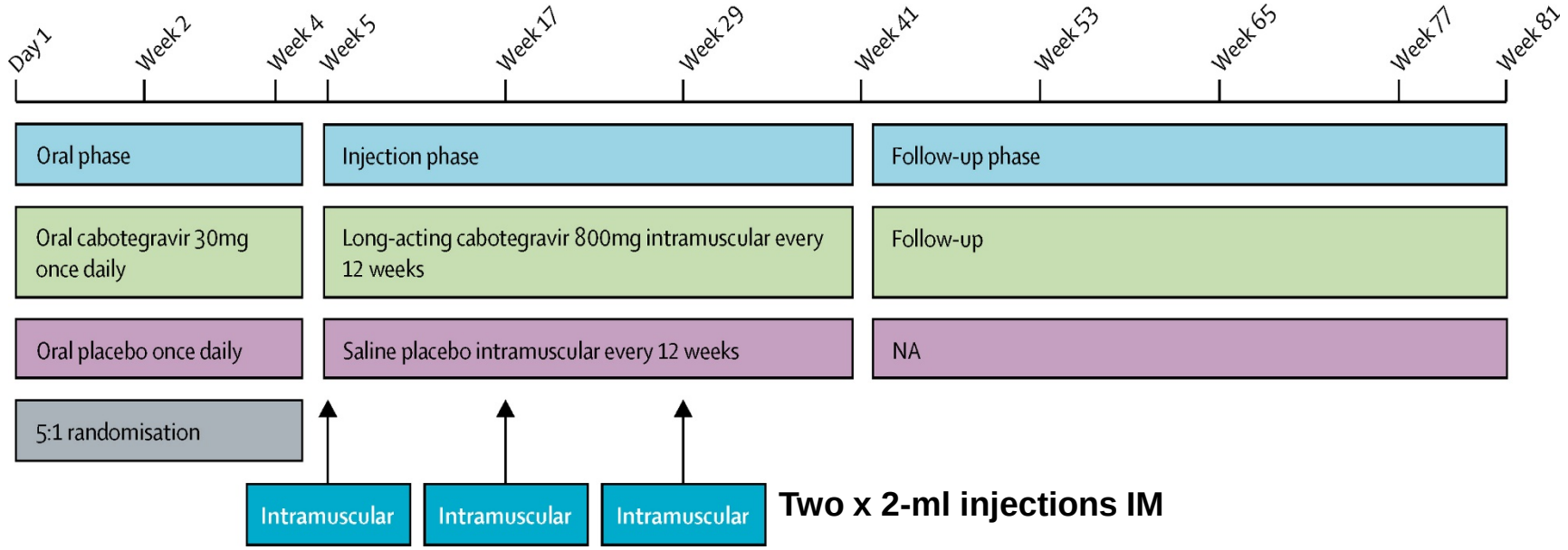
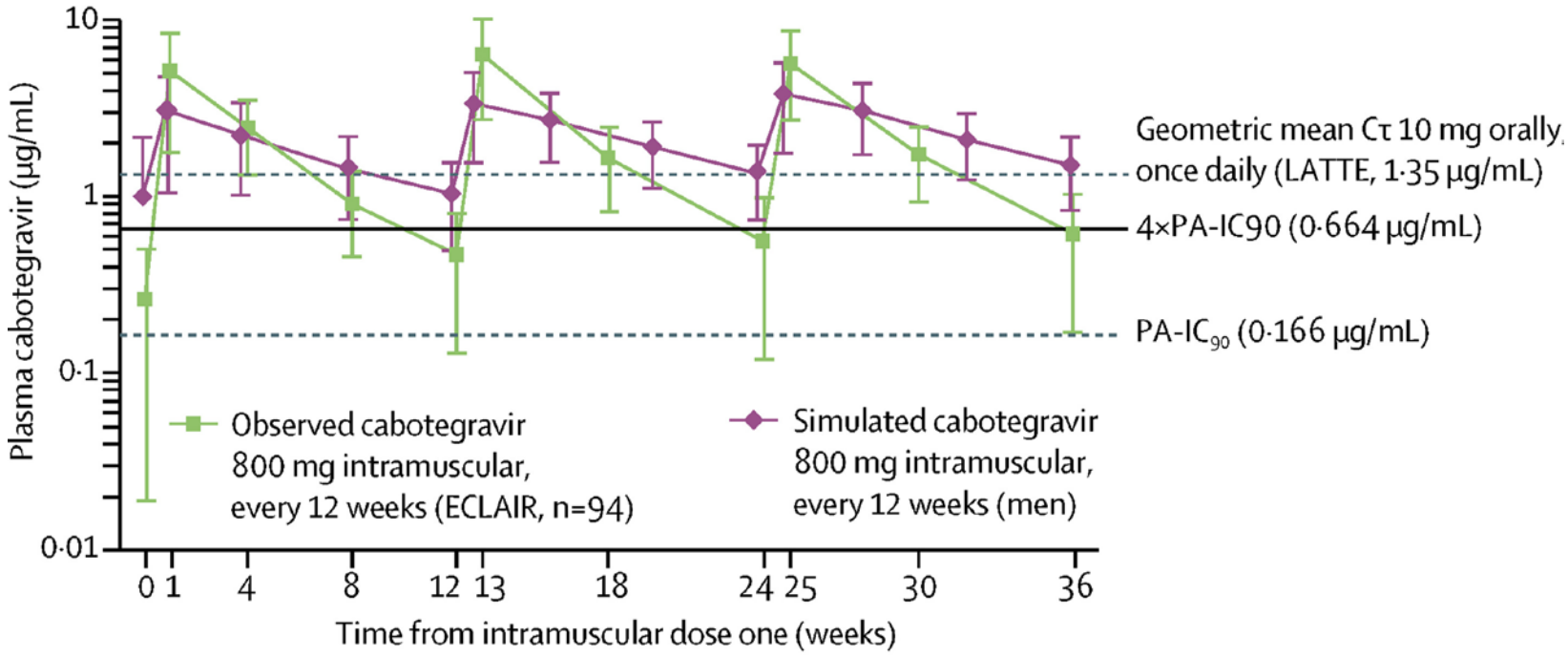
CAB LA Phase II – ECLAIR

Objective: To evaluate the safety and tolerability of the injectable agent in HIV uninfected US men.



Markowitz et al, Lancet HIV 2017.

ECLAIR: predicted vs. observed CAB LA PK



Only 30-37% achieved target concentrations ≥ 4 X PAIC90

Markowitz et al, Lancet HIV 2017

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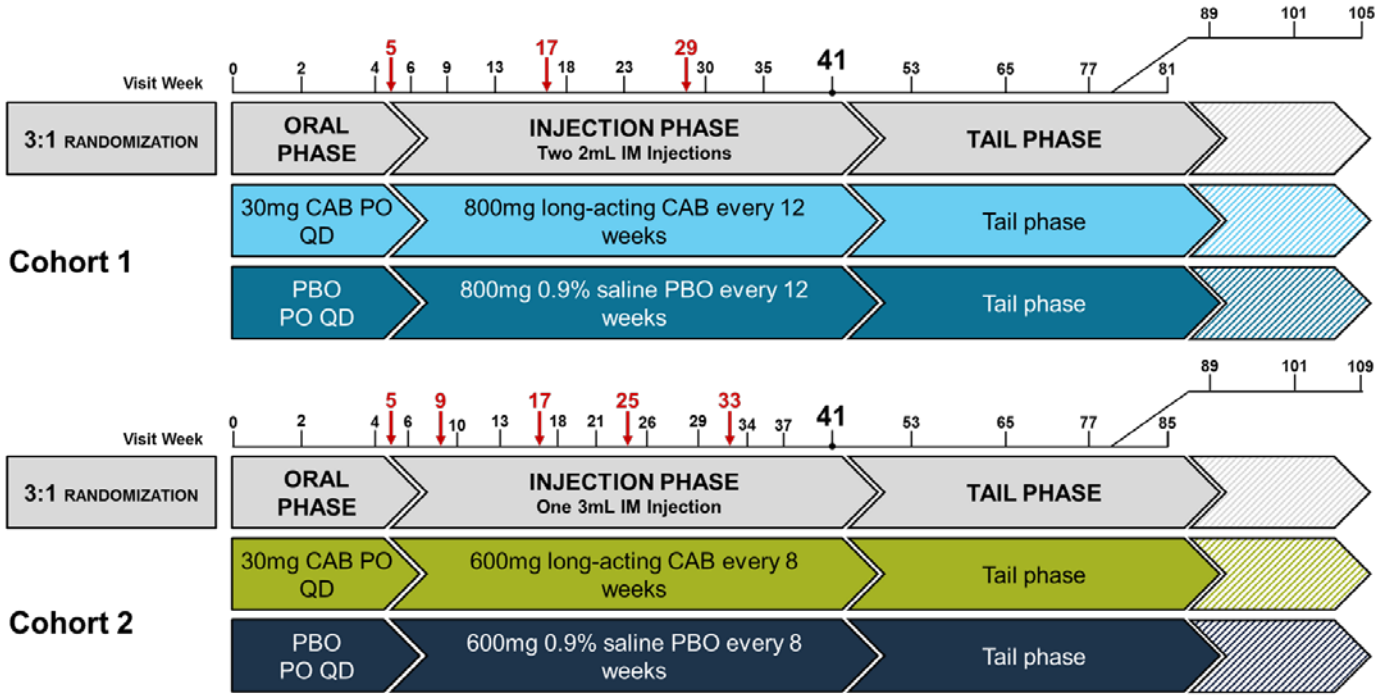
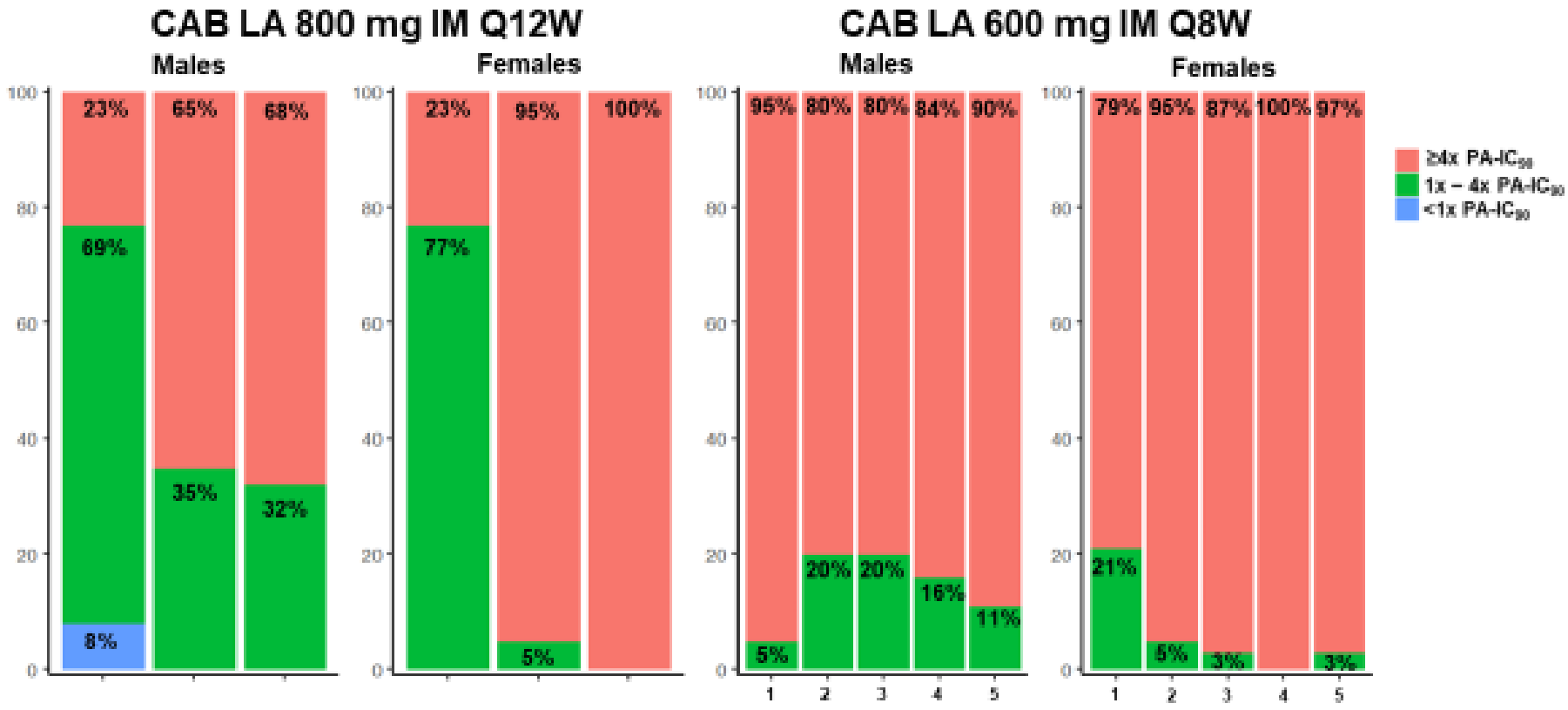
CAB LA Phase II – HPTN 077

Objective: To evaluate the safety, tolerability, and pharmacokinetics of CAB LA in healthy, HIV-uninfected males and females.



Landovitz, Plos Medicine 2018.

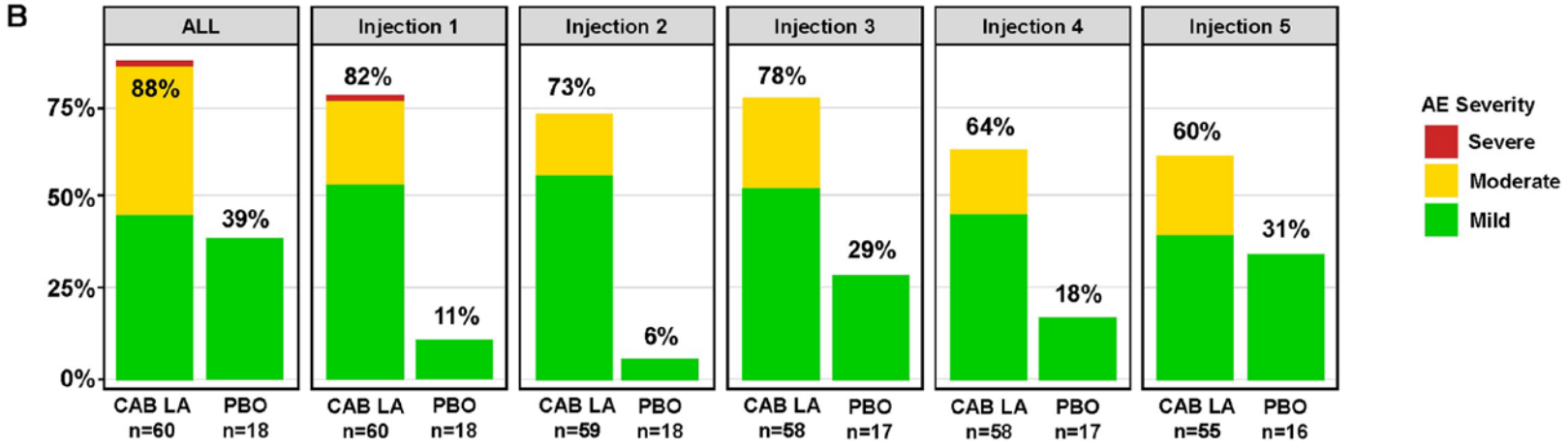
HPTN 077: CAB LA Cτ following each injection



Landovitz, PLoS Medicine 2018

CAB LA Ph II: safety and acceptability

HPTN 077: proportion reporting any Injection site reactions



- Ph II acceptability studies show high preference for injection vs. pills
  - despite ISR because of convenience and perceived adherence advantage
  - Very few discontinuations d/t ISR
- In 077, injection preference increased with time and was higher in non-US sites (95%)

Landovitz, 2018; Kerrigan, 2018; Murray, 2018; Tolley, R4P 2018

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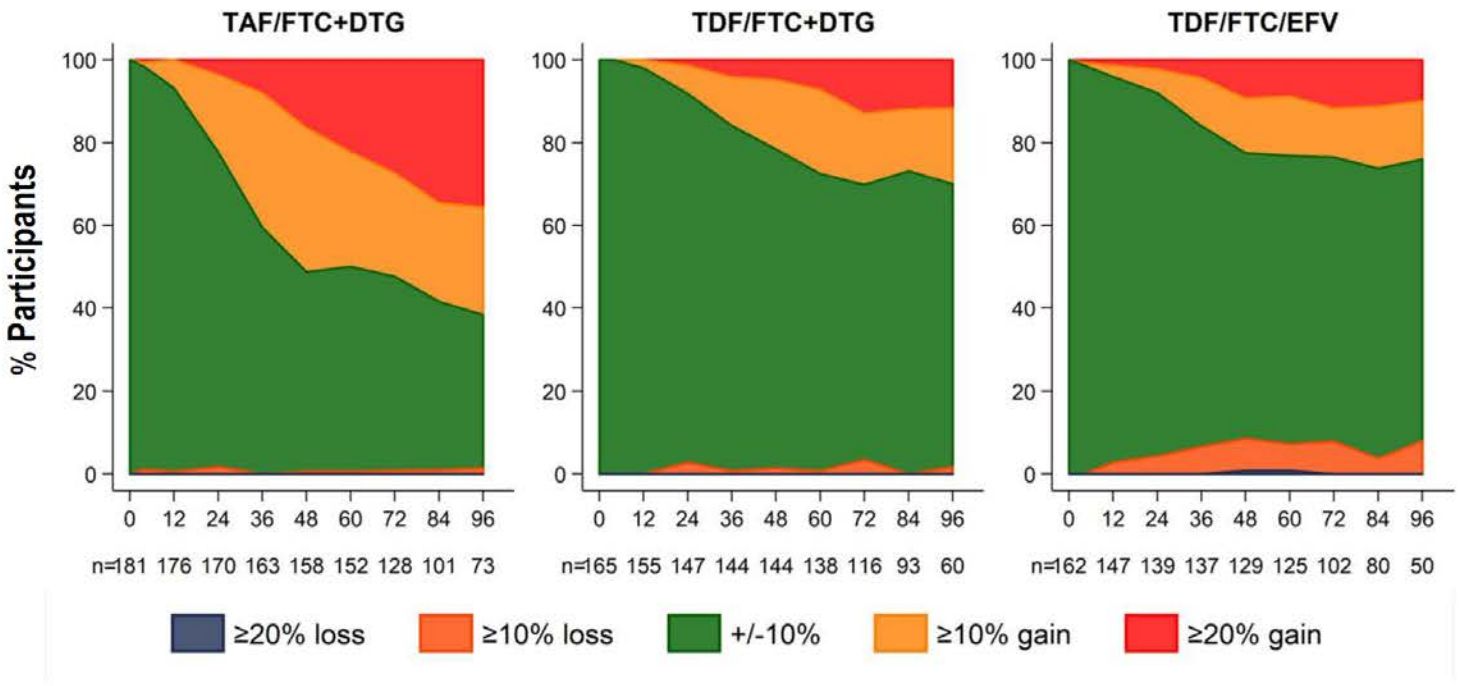
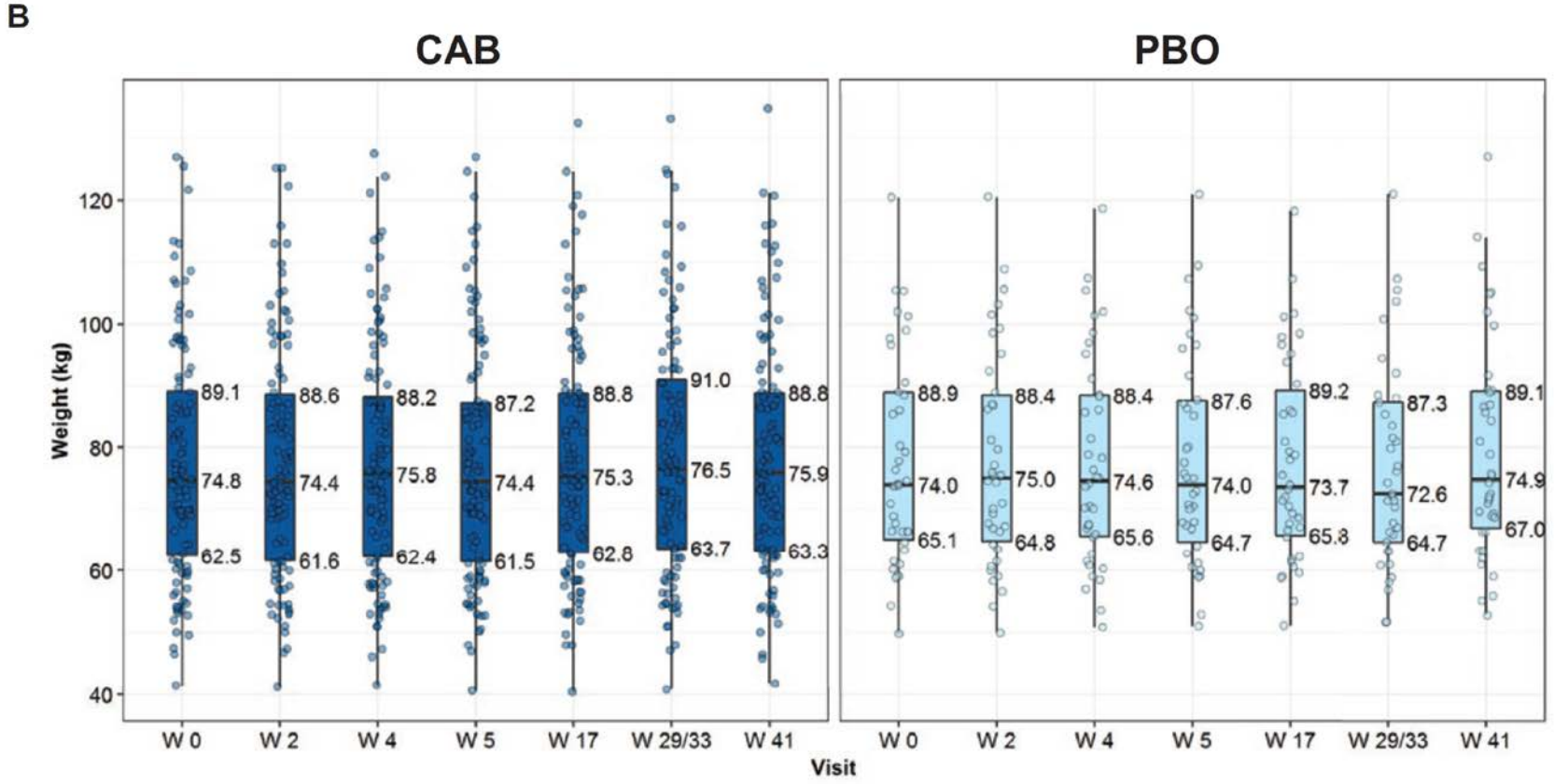
ADVANCE: Percentage change in weight over time: women



Weight gain more severe in female patients, and with lower CD4+ counts and higher viral loads

Moorhouse, IAS 2019; Venter, NEJM 2019

HPTN 077: No differences in weight gain

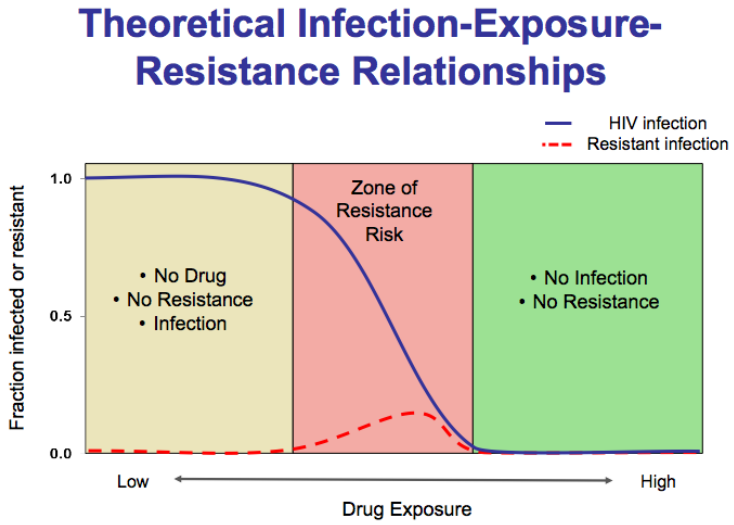


- Distributions did not vary by race, sex at birth, BMI category, smoking status or geographic region

Landovitz, CID 2019

CAB LA - the PK tail

- When administering agents with long t1/2 in non-removable method
- May have prolonged sub-therapeutic tail; great concern for poorly adherent



Markowitz, Lancet HIV 2017; Slide modified from John Mellors, FDA 2012

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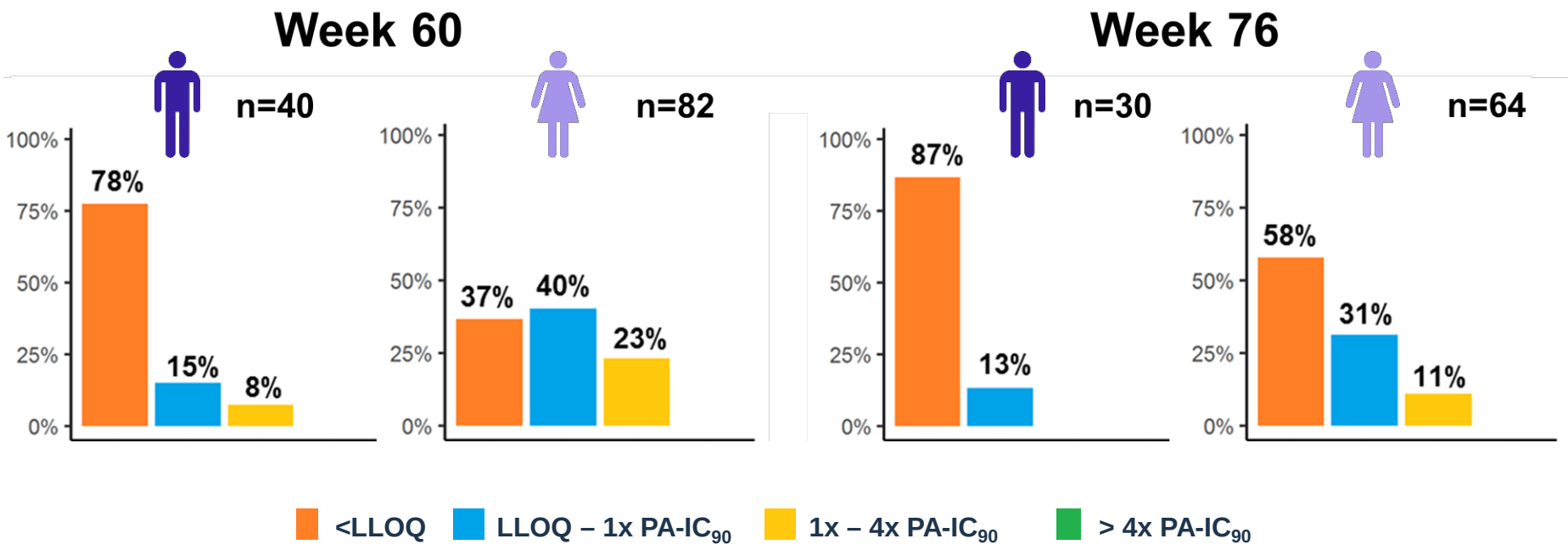
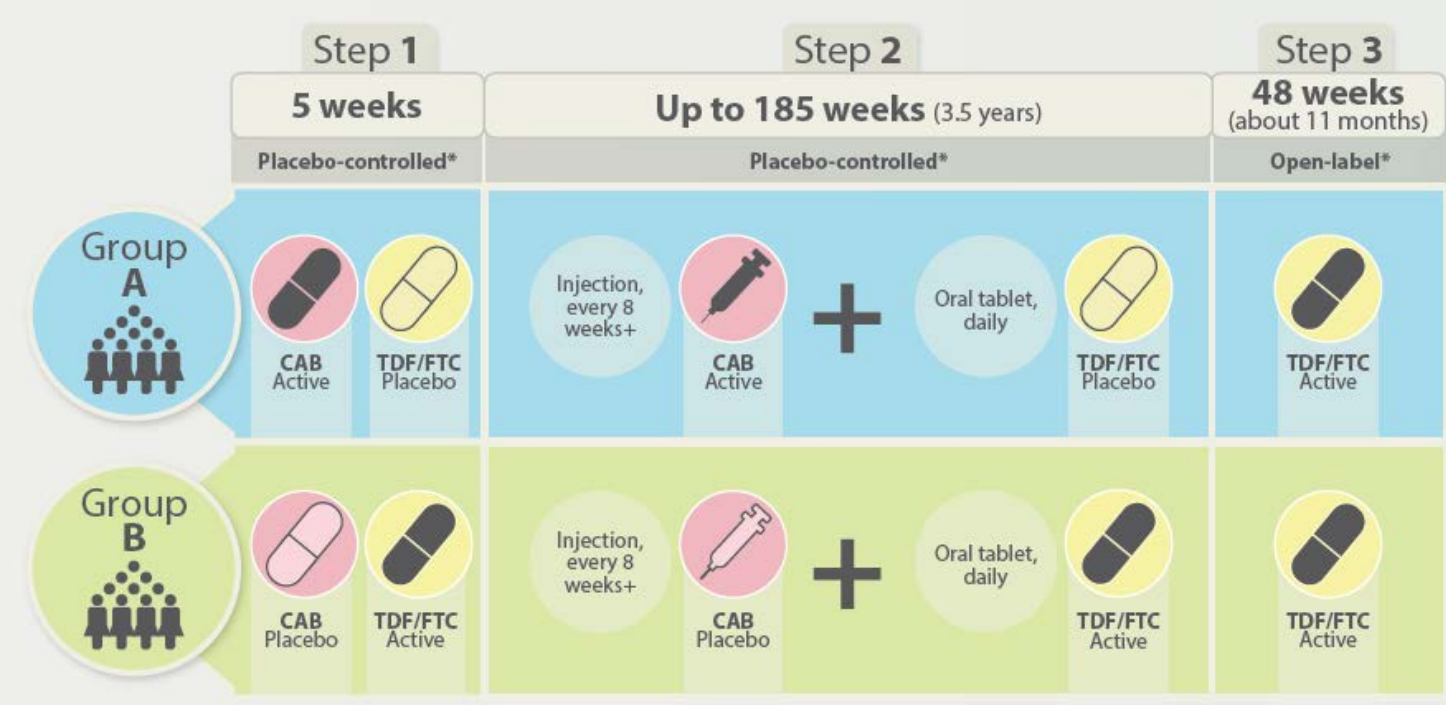
HPTN 077: CAB LA PK tail



Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.

HPTN 083 and 084: Phase III for CAB LA PrEP

Objective: To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084)



Primary outcome: HIV incidence

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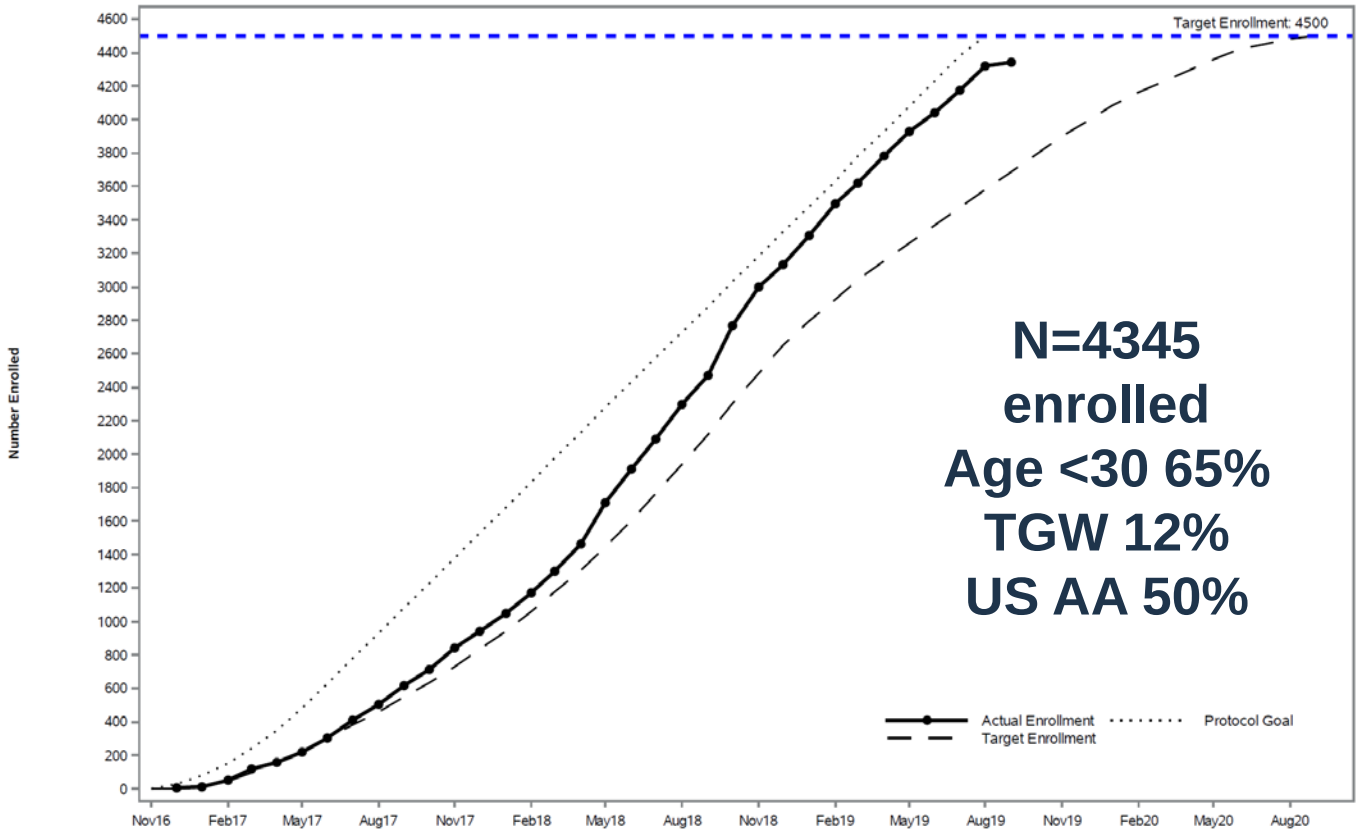
HPTN 083 – enrolment progress

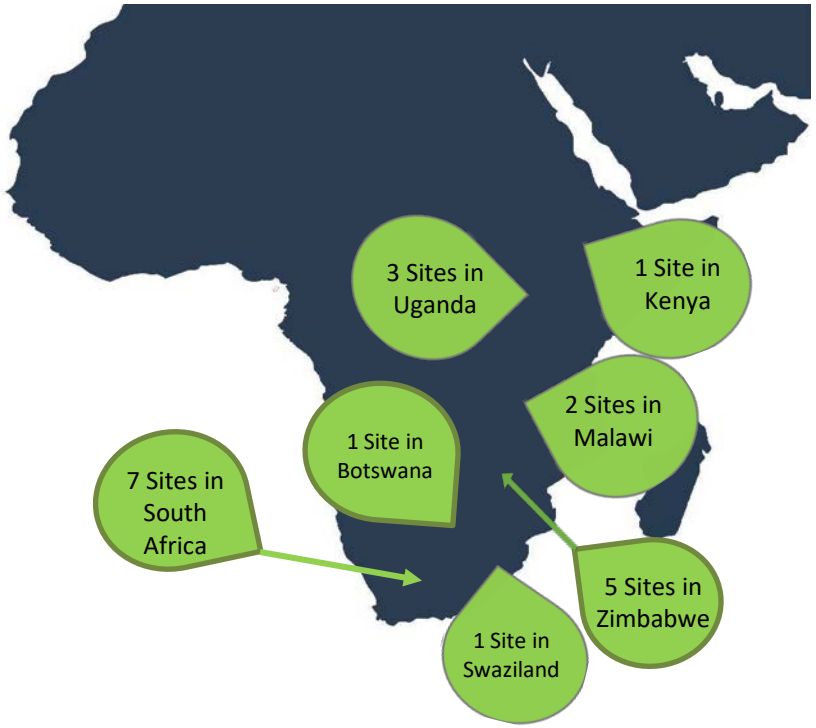


43 sites across USA, S. America, Asia, Africa

HPTN 084 - study Population

3,200 women who have sex with men

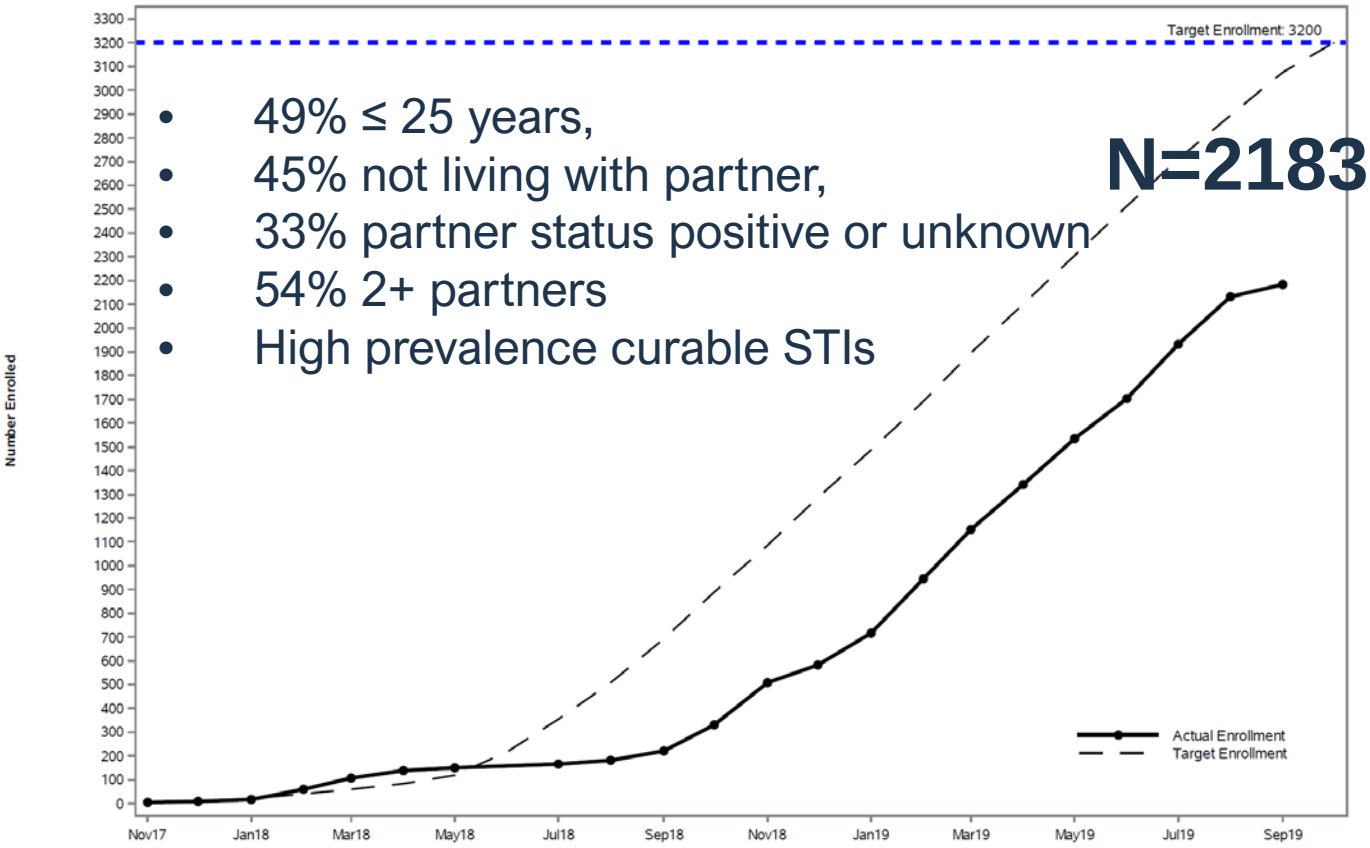
- Female
- HIV negative
- Age 18-45 years
- Sexually active (vaginal intercourse twice in past 30 days)
- **Modified VOICE Risk Score 3**
- Not pregnant or breastfeeding
- No previous enrollment in vaccine trial and no co-enrollment in other HIV prevention trials
- No contraindications to either agent



HPTN 084 – enrolment progress

- 49% ≤ 25 years,
- 45% not living with partner,
- 33% partner status positive or unknown
- 54% 2+ partners
- High prevalence curable STIs

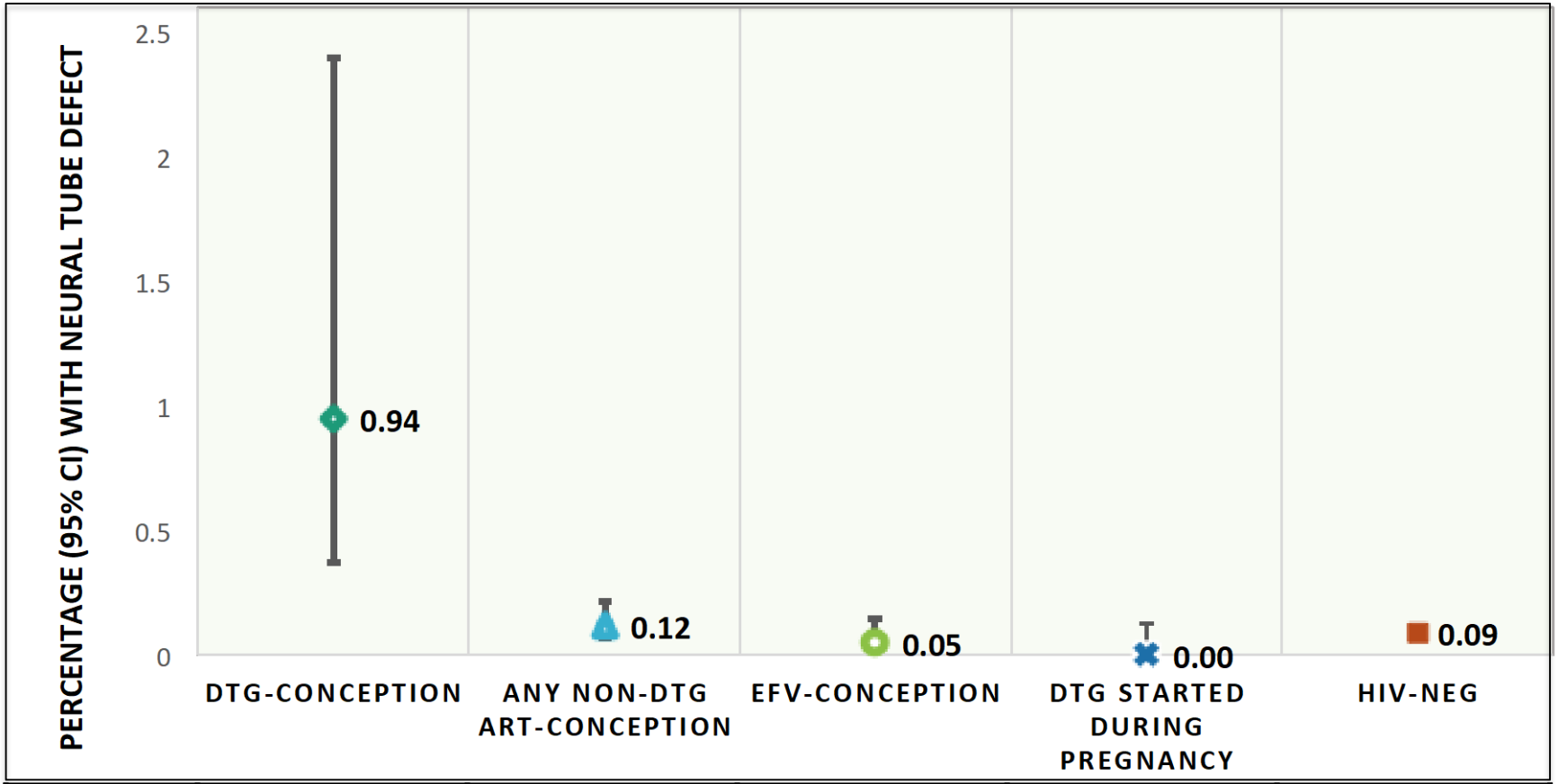
N=2183



https://atlas.scharp.org/cpas/files/HPTN/084/%40files/hptn_084_enrollment_graph.pdf

NTD Prevalence Difference by Exposure

: Zash, IAS 2018



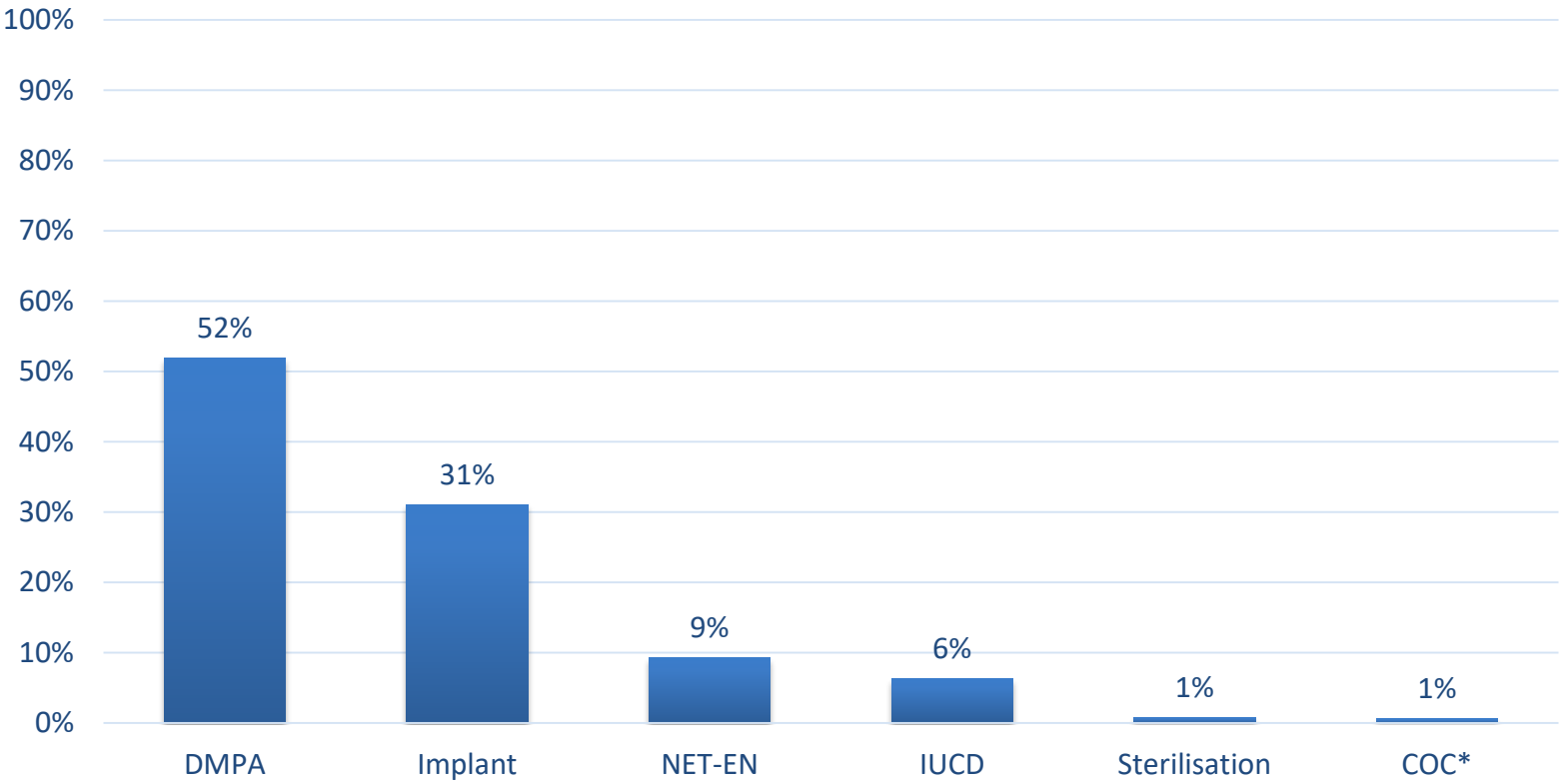
NTDs/Exposures	4/426	14/11,300	3/5,787	0/2.812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	**ref**	**-0.82% (-0.24%, -2.3%)**	**-0.89% (-0.31%,- 2.3%)**	**-0.94% (-0.35%, -2.4%)**	**-0.85% (-0.27%, -2.3%)**

CAB LA in women of reproductive potential

- HPTN 084 protocol modified LOA #3
  - Require women to be on a long-acting contraceptive at enrolment
  - No evidence of drug-drug interactions with contraceptives
    - Will expand the dataset to include data on DMPA, NET-EN and etonorgestrel
  - Target pregnancy incidence <3%

- For those that become pregnant
  - Unblinding at confirmed pregnancy visit
  - Referral for early ultrasound and follow up
  - Plan for co-enrolment in a protocol to assess CAB PK in breastmilk and infant plasma

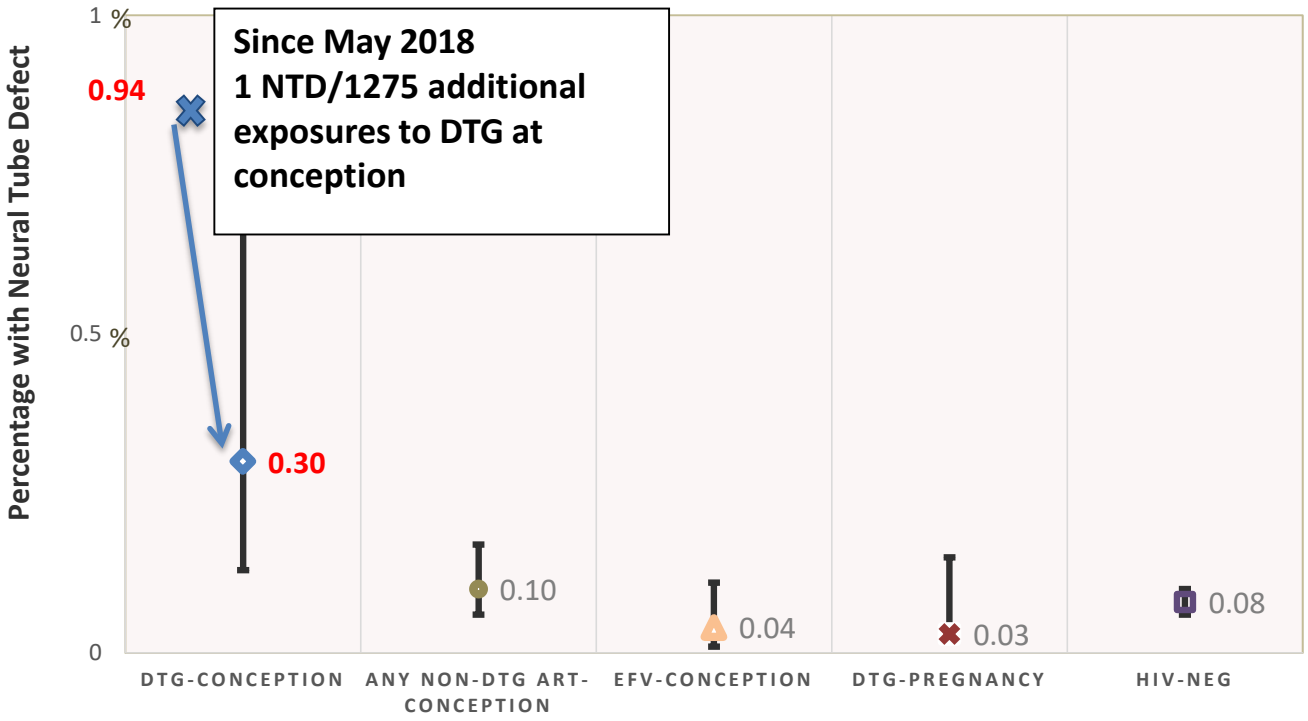
Contraceptive use at most recent visit
(n=2145)



**COC users all transitioned to TDF/FTC*

Source: SCHARP report, 9 SEPT 2019

NTD Prevalence by Exposure



NTDs/Exposures	5/1683	15/14792	3/7959	1/3840	70/89372
% with NTD (95% CI)	0.30% (0.13, 0.69)	0.10% (0.06, 0.17)	0.04% (0.01, 0.11)	0.03% (0.0, 0.15)	0.08% (0.06, 0.10)
Prevalence Difference (95% CI)	**ref**	**0.20% (0.01, 0.59)**	**0.26% (0.07, 0.66)**	**0.27% (0.06, 0.67)**	**0.22% (0.05, 0.62)**

Zash, IAS 2019

What have we learned

- >6,500 ppl across diverse geographies enrolled in these trials

- High risk i.e. PrEP eligible
- Injections appear highly acceptable
- Stigma observed with oral PrEP (and ART) still present in many communities
- Risk factors that shape HIV e.g. gender-based violence, alcohol and substance use, STIs are highly prevalent
  - Influence participation and need for services

What have we learned

- 2nd generation trial with two active products
  - More complex design
  - Consideration of AE attribution
  - Need to be attentive to effects of long acting product
    - Needed if effective?
  - Effects on conventional HIV testing algorithms
    - Need for new approaches
    - Education of health care providers and participants

Next steps

- Protocol revisions for both trials underway
- Addition of adolescent sub-studies
- Complete trials and plan for success
  - Learn lesson from oral PrEP introduction
  - E.g. Biopic initiative to consider questions that can be addressed in current trials or trials post-licensure
  - Future products

ACKNOWLEDGEMENTS

Participants, communities and CABs
Trial staff
Network partners
SMC, DSMB

Partners and funders

Viiv Healthcare

Bill & Melinda Gates Foundation

Division of AIDS, National Institutes of Health

The HIV Prevention Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068619, UM1AI068613, UM1AI1068617), with co-funding from the National Institute of Mental Health, and the National Institute on Drug Abuse, all components of the U.S. National Institutes of Health.