Challenges and Opportunities in HIV Preexposure Prophylaxis: The 2021 Update

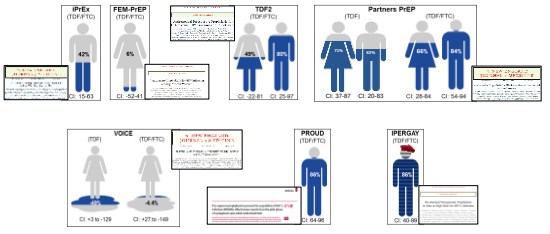
Raphael J. Landovitz MD MSc
Professor of Medicine
University of California Los Angeles
Center for Clinical AIDS Research & Education
Los Angeles, California

Financial Relationships With Commercial Entities

Dr Landovitz has served as on scientific advisory boards for Gilead Sciences, Inc, and Merck & Co., Inc, and has received honoraria from Roche, Inc, and Janssen Pharmaceuticals. (Updated 05/14/21)

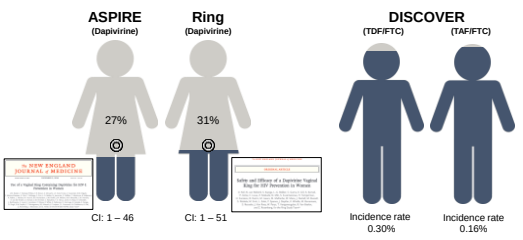
Slide 2 of 37

Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials



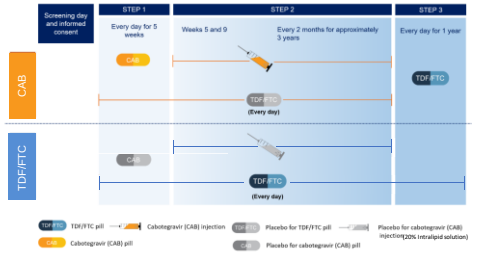
Slide 3 of 37 Landovitz RJ et al. AIDS 2020, #OAXLB0101

"PrEP 2.0": Trials of Novel PrEP Agents



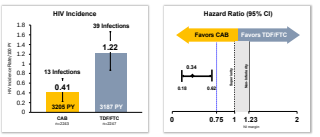
Slide 4 of 37 Landovitz RJ et al. AIDS 2020, #OAXLB0101

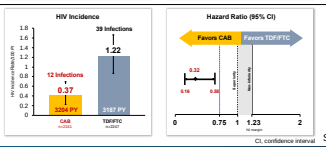
HPTN 083 Study Design



Slide 5 of 37 Landovitz RJ et al. AIDS 2020, #OAXLB0101

HIV Incidence: CAB vs. TDF/FTC

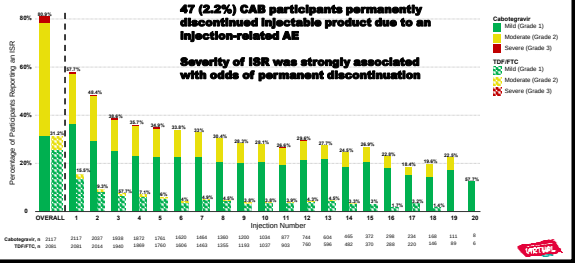




CI, confidence interval

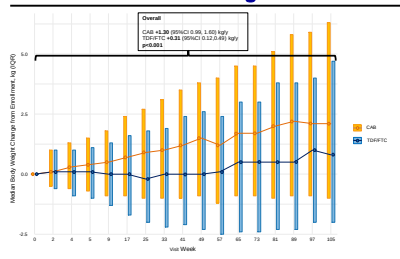
Slide 7 of 37

Injection Site Reactions



Changes in Weight

Median of changes from baseline (IQR)





Cabotegravir Is Not Associated With Weight Gain in Human Immunodeficiency Virus–uninfected Individuals in HPTN 077

HPTN 077: Over 41 weeks

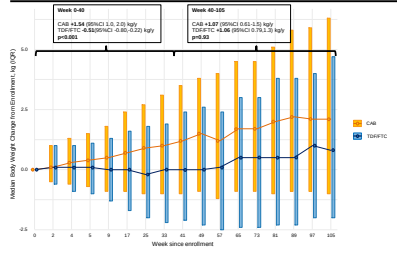
CAB **+1.48** (95%CI 0.15, 2.8) kg/y
PBO **+1.57** (95%CI -1.35,4.49) kg/y
p=0.95

Landovitz RJ et al. CID 2019.

 Landovitz RJ et al. AIDS 2020, #OAXLB0101

Changes in Weight

Median of changes from baseline





Cabotegravir Is Not Associated With Weight Gain in Human Immunodeficiency Virus–uninfected Individuals in HPTN 077

HPTN 077: Over 41 weeks

CAB **+1.48** (95%CI 0.15, 2.8) kg/y
PBO **+1.57** (95%CI -1.35,4.49) kg/y
p=0.95

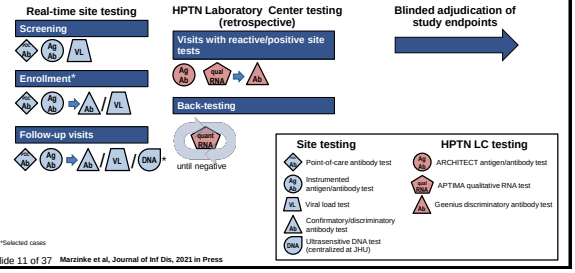
Landovitz RJ et al. CID 2019.

 Landovitz RJ et al. AIDS 2020, #OAXLB0101

And then we observed something unexpected…

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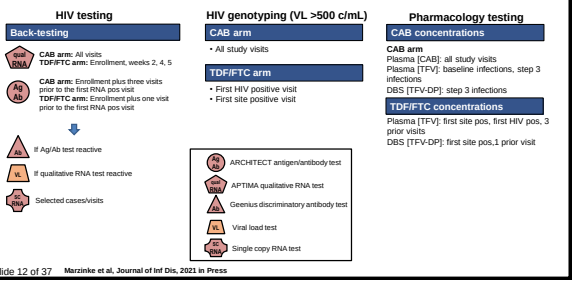
Pre-specified HIV Testing



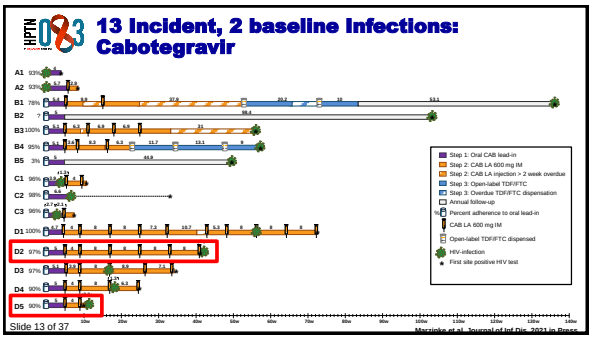
*Selected cases

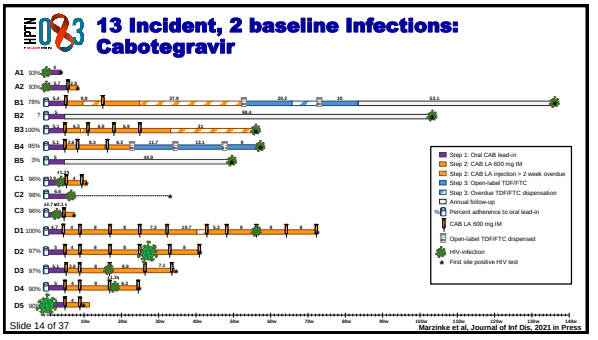
Slide 11 of 37 **Marzinke et al, Journal of Inf Dis, 2021 in Press**

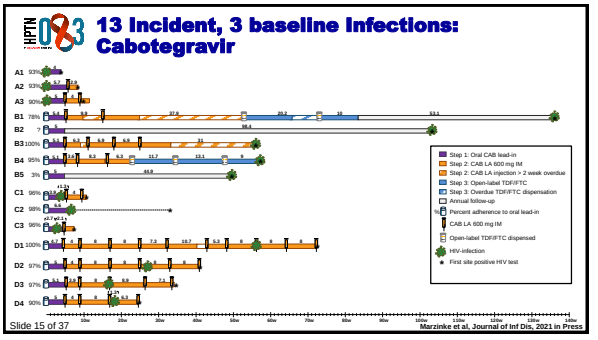
Extended HPTN LC Testing



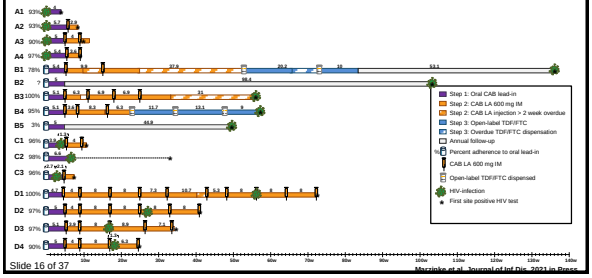
Slide 12 of 37 **Marzinke et al, Journal of Inf Dis, 2021 in Press**


HPTN 083
13 Incident, 2 baseline Infections:
Cabotegravir
A1 93%
A2 93%
B1 78%
B2 ?
B3 100%
B4 95%
B5 3%
C1 96%
C2 98%
C3 96%
D1 100%
D2 97%
D3 97%
D4 90%
D5 90%
Step 1: Oral CAB lead-in
Step 2: CAB LA 600 mg IM
Step 2: CAB LA injection > 2 week overdue
Step 3: Open-label TDF/FTC
Step 3: Overdue TDF/FTC dispensation
Annual follow-up
Percent adherence to oral lead-in
CAB LA 600 mg IM
Open-label TDF/FTC dispensed
HIV-infection
First site positive HIV test
Slide 13 of 37
Marzinke et al, Journal of Inf Dis, 2021 in Press


HPTN 083
13 Incident, 2 baseline Infections:
Cabotegravir
A1 93%
A2 93%
B1 78%
B2 ?
B3 100%
B4 95%
B5 3%
C1 96%
C2 98%
C3 96%
D1 100%
D2 97%
D3 97%
D4 90%
D5 90%
Step 1: Oral CAB lead-in
Step 2: CAB LA 600 mg IM
Step 2: CAB LA injection > 2 week overdue
Step 3: Open-label TDF/FTC
Step 3: Overdue TDF/FTC dispensation
Annual follow-up
Percent adherence to oral lead-in
CAB LA 600 mg IM
Open-label TDF/FTC dispensed
HIV-infection
First site positive HIV test
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Marzinke et al, Journal of Inf Dis, 2021 in Press


HPTN 083
13 Incident, 3 baseline Infections:
Cabotegravir
A1 93%
A2 93%
A3 90%
B1 78%
B2 ?
B3 100%
B4 95%
B5 3%
C1 96%
C2 98%
C3 96%
D1 100%
D2 97%
D3 97%
D4 90%
Step 1: Oral CAB lead-in
Step 2: CAB LA 600 mg IM
Step 2: CAB LA injection > 2 week overdue
Step 3: Open-label TDF/FTC
Step 3: Overdue TDF/FTC dispensation
Annual follow-up
Percent adherence to oral lead-in
CAB LA 600 mg IM
Open-label TDF/FTC dispensed
HIV-infection
First site positive HIV test
Slide 15 of 37
Marzinke et al, Journal of Inf Dis, 2021 in Press

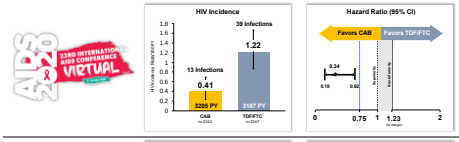
12 Incident, 4 baseline infections: Cabotegravir

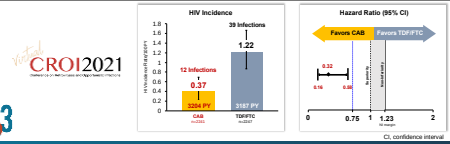


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Marcinko et al. Journal of Inf Dis. 2021 in Press

HIV Incidence: CAB vs. TDF/FTC



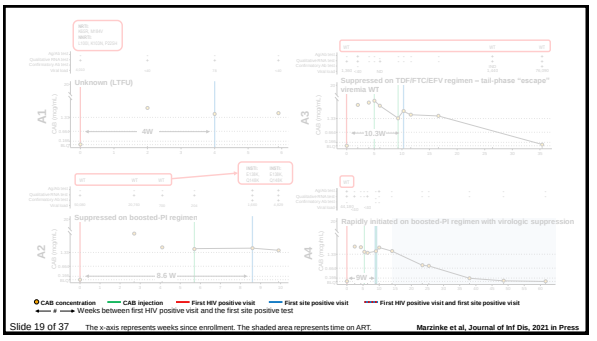


CI, confidence interval

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CAB arm, Group A
HIV positive at study enrollment

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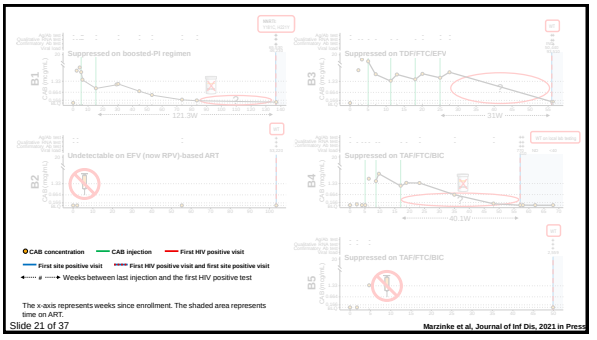
Slide 19 of 37

The x-axis represents weeks since enrollment. The shaded area represents time on ART.

Marzinke et al, Journal of Inf Dis, 2021 in Press

CAB arm, Group B
No recent CAB exposure

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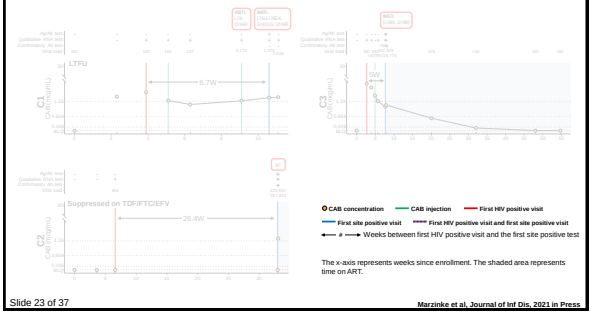
The x-axis represents weeks since enrollment. The shaded area represents time on ART.

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Marzinke et al, Journal of Inf Dis, 2021 in Press

CAB arm, Group C
Infected during the CAB oral lead-in period

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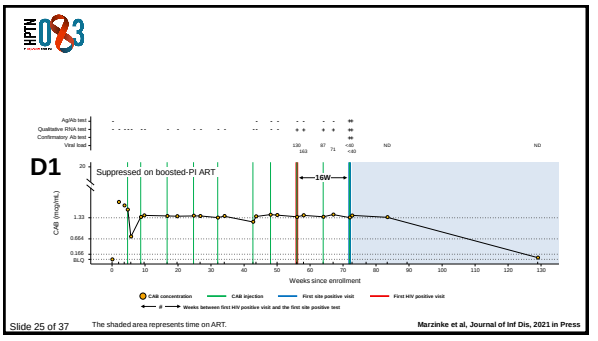


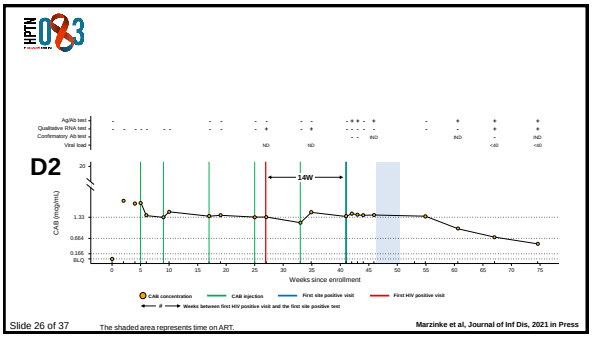
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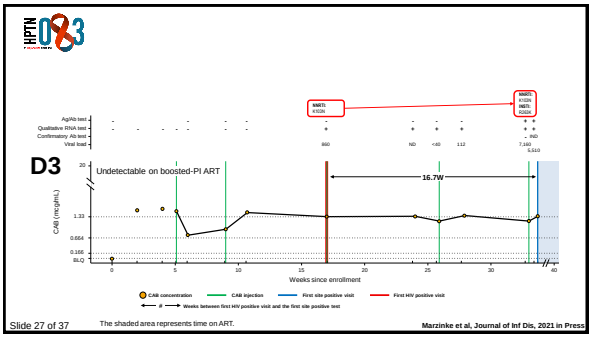
Marzinke et al, Journal of Inf Dis, 2021 in Press

CAB arm, Group D
Infected in the setting of on-time CAB injections

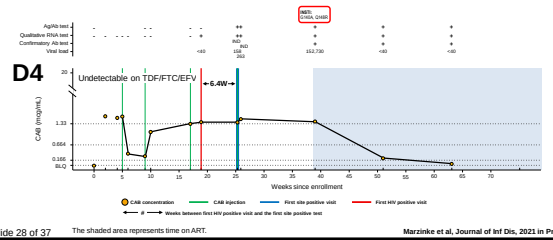
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HPTN 083
Ag/Ab test
Qualitative RNA test
Confirmatory Ab test
Viral load
130
160
97
71
<40
<40
ND
ND
D1
Suppressed on boosted-PI ART
16W
CAB (mcg/mL)
20
1.33
0.664
0.166
BLQ
0
10
20
30
40
50
60
70
80
90
100
110
120
130
Weeks since enrollment
CAB concentration
CAB injection
First site positive visit
First HIV positive visit
Weeks between first HIV positive visit and the first site positive test
Slide 25 of 37
The shaded area represents time on ART.
Marzinke et al, Journal of Inf Dis, 2021 in Press


HPTN 083
Ag/Ab test
Qualitative RNA test
Confirmatory Ab test
Viral load
ND
ND
IND
IND
<40
<40
D2
14W
CAB (mcg/mL)
20
1.33
0.664
0.166
BLQ
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
Weeks since enrollment
CAB concentration
CAB injection
First site positive visit
First HIV positive visit
Weeks between first HIV positive visit and the first site positive test
Slide 26 of 37
The shaded area represents time on ART.
Marzinke et al, Journal of Inf Dis, 2021 in Press


HPTN 083
Ag/Ab test
Qualitative RNA test
Confirmatory Ab test
Viral load
M46I
K103N
M46I
K103N
M46I
K103N
860
ND
<40
112
IND
7,160
5,010
D3
Undetectable on boosted-PI ART
16.7W
CAB (mcg/mL)
20
1.33
0.664
0.166
BLQ
0
5
10
15
20
25
30
40
Weeks since enrollment
CAB concentration
CAB injection
First site positive visit
First HIV positive visit
Weeks between first HIV positive visit and the first site positive test
Slide 27 of 37
The shaded area represents time on ART.
Marzinke et al, Journal of Inf Dis, 2021 in Press

A Cautionary Tale



The shaded area represents time on ART.

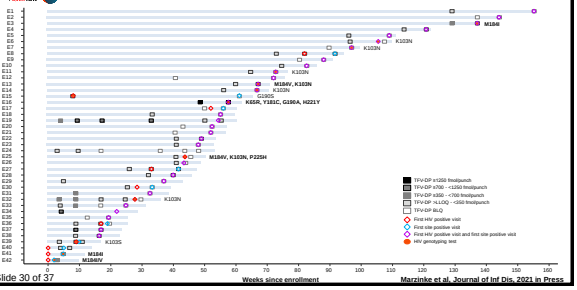
Marzinke et al, Journal of Inf Dis, 2021 in Press

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TDF/FTC arm

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39 Incident, 3 Baseline Infections: TDF/FTC



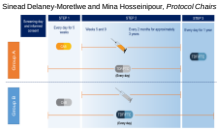
Marzinke et al, Journal of Inf Dis, 2021 in Press

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CAB-LA vs. daily oral TDF/FTC for Women in Sub-Saharan Africa

Sinead Delaney-Moretlwe and Mina Hosseinipour, *Protocol Chairs*

- **Primary Objective: Reduce HIV Incidence** (superiority, double blind, double dummy design)
- Endpoint-driven trial (HIV infection) – monitored by NIAID DSMB every 6 months
- Est. study duration: enrollment 24 months; follow-up up to 4.5 years
- N=3200 at 20 sites in Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe



Start Nov 2017
Blinded Study halted by DSMB November 2020

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HPTN HIV Prevention Trials Network

Primary outcome: HIV incidence

40 infections over 3892 person-years
Pooled HIV incidence 1.03 (0.73, 1.4) per 100 person-years

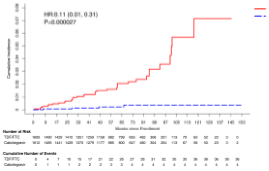
	CAB	TDF/FTC
HIV infections	4	36
Person-years	1,953	1,939
HIV incidence (95% CI)	0.2 (0.06, 0.52)	1.86 (1.3, 2.57)

Wald test z statistic – 4.20, efficacy stopping bound (z scale) – 3.61

Slide 32 of 37 Delany-Moretlwe S, et al. R4P 2021, Abstract LB1479

HPTN HIV Prevention Trials Network

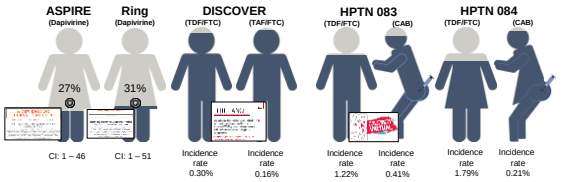
Cumulative HIV incidence – ITT



*Women in the CAB group had an **89% lower risk of HIV infection,** compared to TDF/FTC group*

Slide 33 of 37 Delany-Moretlwe S, et al. R4P 2021, Abstract LB1479

"PrEP 3.0": Trials of Novel PrEP Agents



And now in Phase 3 clinical trials: Monthly oral islatravir, and injectable Lenacapavir (every 6 months, subcutaneous)

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Conclusions

- **Both agents highly effective for HIV prevention**
- **The PrEP regimen containing CAB-LA was superior to a daily oral regimen of TDF/FTC in HPTN 083 and HPTN 084**
  - **CAB-LA was generally well tolerated despite injection site reactions**
- **1/4, 0/5, 2/3, and 2/4 Acute (Prevalent), Distant from CAB, Oral-lead-in, and On-time injection participants developed INSTI resistance**
  - **Tail phase seroconversion did not result in INSTI resistance**
  - **Breakthrough at high and expected CAB concentrations resulted in INSTI resistance**
- **CAB is the first long-acting injectable agent to demonstrate robust HIV prevention efficacy – others are coming – better diagnostics needed!**

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Acknowledgements

Sponsor

- U.S. National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), and the National Institute of Child Health and Human Development (NICHD) all components of the U.S. National Institutes of Health (NIH)
- Additional funding from ViiV Healthcare

HIV Prevention Trials Network (HPTN)

- Laboratory Center (Johns Hopkins University)
- Statistical Center for HIV/AIDS Research and Prevention (SCHARP), Fred Hutchinson Cancer Research Center
- Leadership and Operations Center, FHI 360
- HPTN Leadership

Pharmaceutical Support

- ViiV Healthcare
- Gilead Sciences, Inc.

HPTN 083 Study Team

Community Program Managers Community Educators & Recruiters, CAB Members

Our 43 Sites in 7 countries

...and our Study Participants!

Questions? Email rlandovitz@mednet.ucla.edu or @doc_in_a_box

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Question-and-Answer Session