The powers and perils of DBS testing for PrEP

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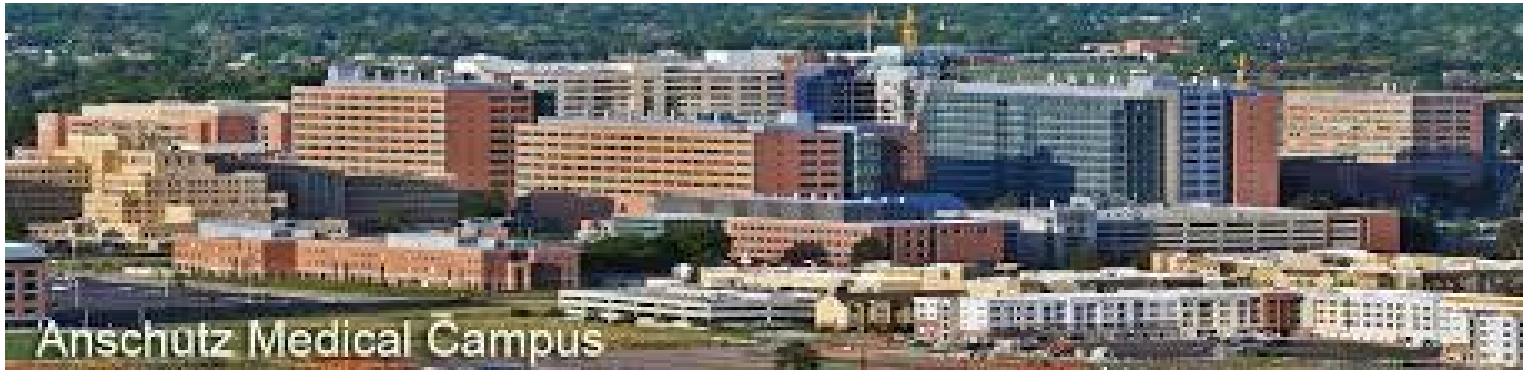

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What is DBS?

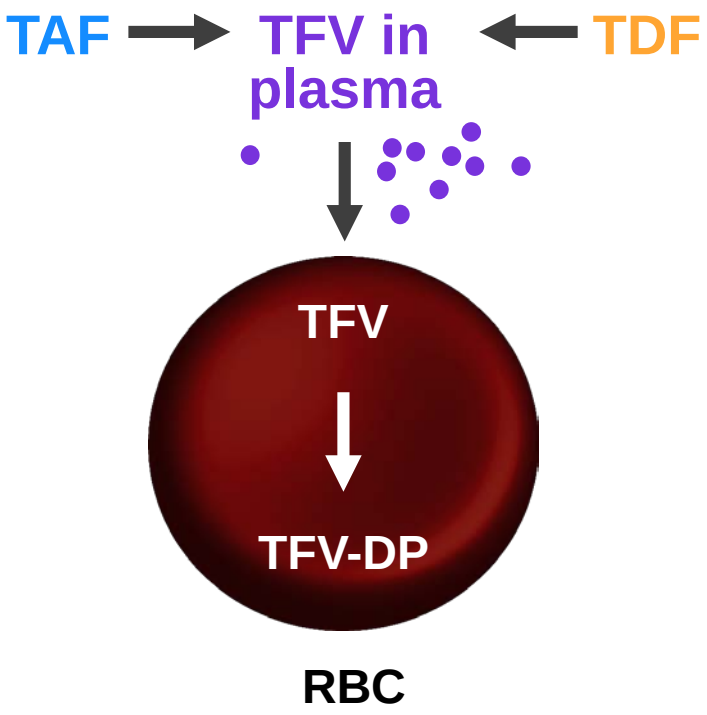
- Intracellular (RBC) tenofovir-diphosphate (TFV-DP) measured using dried blood spots (DBS)
  - emtricitabine-triphosphate (FTC-TP) and lamivudine-triphosphate (3TC-TP) in the same DBS

- Measurements are used to assess adherence to TDF or TAF-based therapies

Selected studies using DBS for adherence

- MTN 034, 042
- HPTN 082, 083, 084
- HVTN (AMP), 703, 704
- IMPAACT 2009
- iPrEx OLE, ATN110/113, DISCOVER

TFV-DP in DBS is a unique Adherence Biomarker

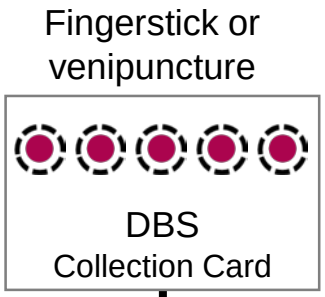


Key: TFV-DP Half Life in RBC ~17–20 days

- DBS provides an objective measure of average adherence during the prior ~6-8 weeks; analogous to Hgb-A1C for glucose

Bushman LR, et al. J Pharm Biomed Anal. 2011;56:390-401; Durand-Gasselin L, et al. AAC 2007;51:2105-11; Castillo-Mancilla, J. 2012 AHRH.

Process: TFV-DP in DBS for Adherence



Analysis
LC-MS/MS

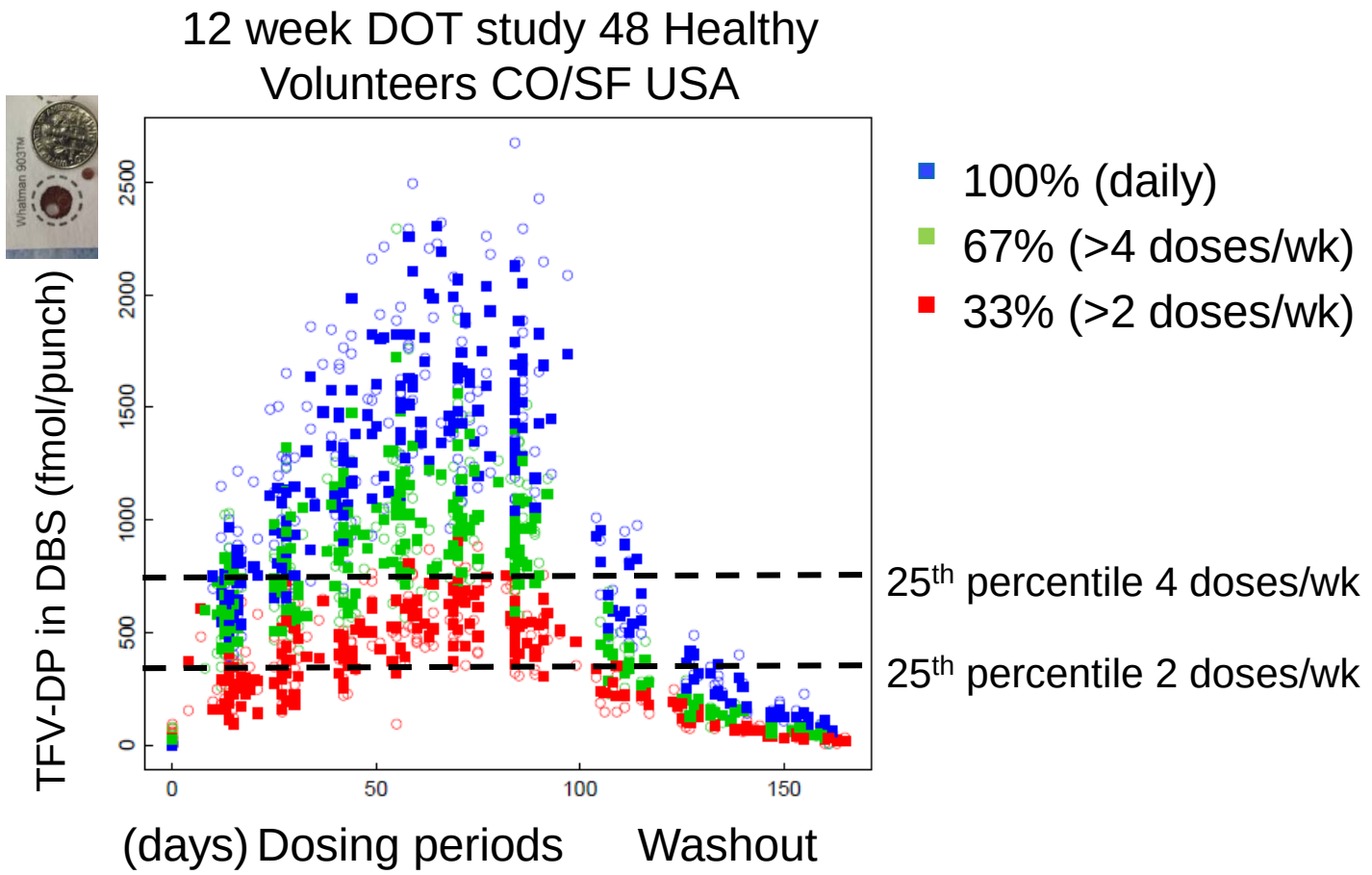
TFV-DP level
fmol/punches

Directly
observed dosing
PK studies

Interpretation	DBS TFV-DP, fmol/punch(es)	
	TAF	TDF
≥4 doses/wk	≥900	≥700
2–3 doses/wk	450–899	350–699
<2 doses/wk	<450	<350

Zheng JH, et al. J Pharm Biomed Anal 2016;122:16-20. Castillo-Mancilla JR. AIDS Res Hum Retroviruses. 2013 Feb;29(2):384-90. Anderson PL. Antimicrob Agents Chemother. 2018.; Yager J. Abstract 0463. 2019 CROI.

DBS thresholds, F-TDF



Anderson PL, et al. 2018. AAC. (PMID 29038282)

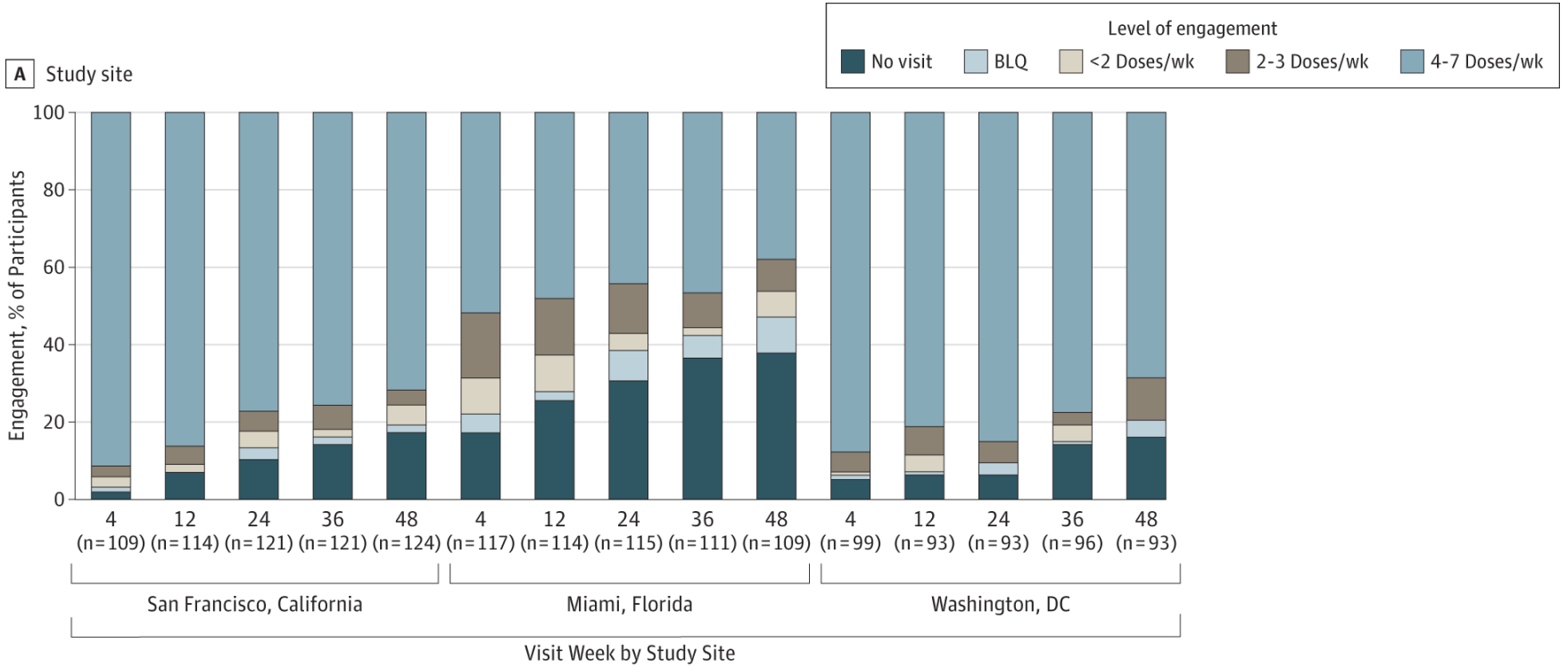
Power: Gradients of adherence with DBS

Steady-state TFV-DP (fmol/punch)	Adherence Interpretation
≥700	≥4 doses/wk
350 to 699	2-3 doses/wk
< 350	< 2 doses/wk

Pre-steady-state TFV-DP (<8 weeks) can be divided by $1 - e^{-0.04 * \text{Rx day}}$

Brooks K. 2018. CP&T (PMID 30178462)

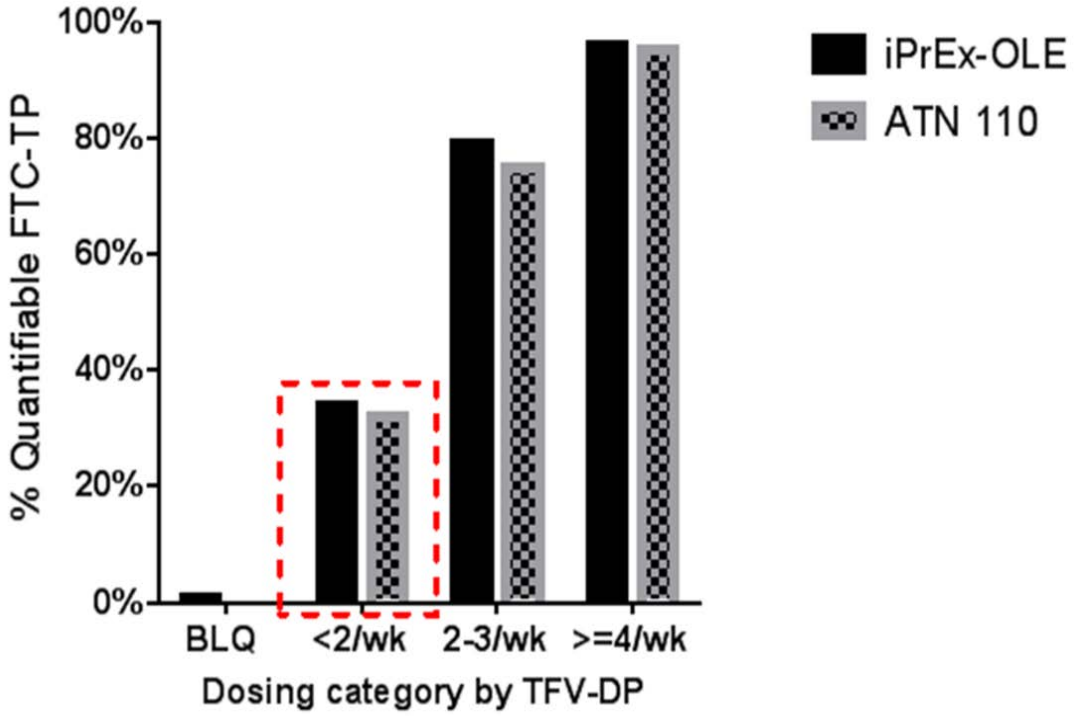
Power: DBS for interpreting PrEP engagement



Liu A. JAMA Intern Med 2016.

Power: deciphering white coat dosing

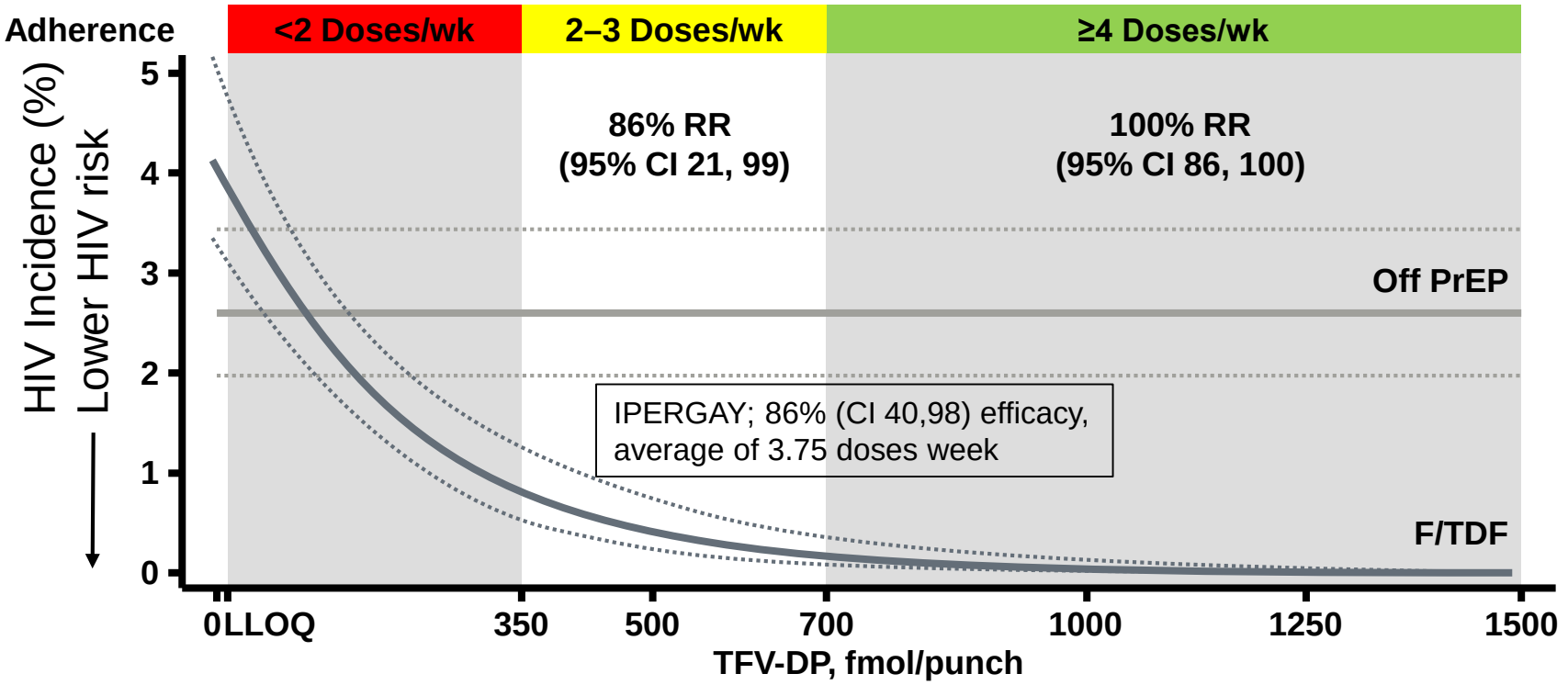
- FTC-TP short half-life like plasma TFV
- ~30% with TFV-DP <2 tab/wk had FTC-TP suggesting white coat dosing.



N=445

Castillo-Mancilla Antimicrob Agents Chemother. 2016 Aug 29.

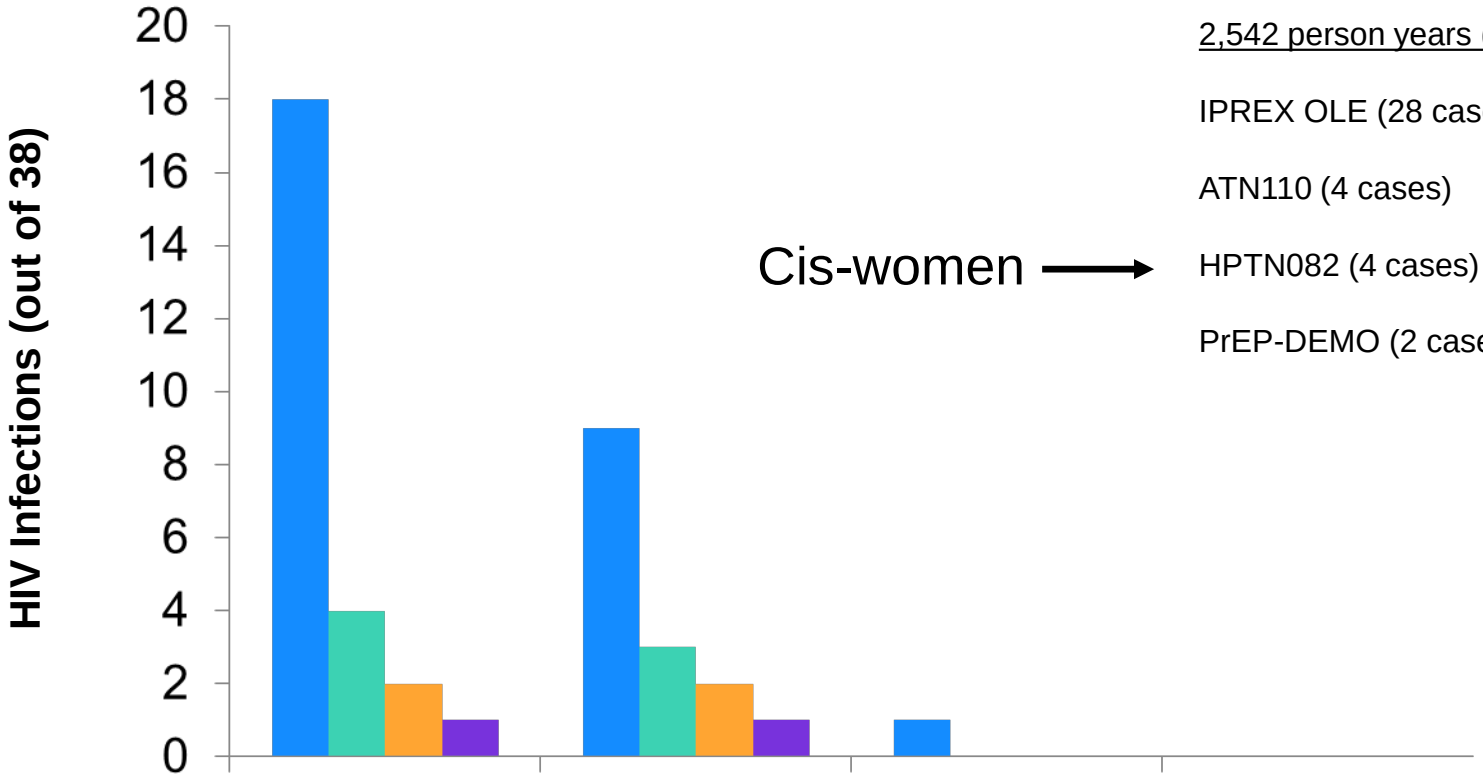
Power: DBS & HIV Risk Reduction in iPrEx OLE



In event-driven dosing (IPERGAY) 86% efficacy in MSM with 3.75 doses/wk

Grant RM, et al. Lancet Infect Dis. 2014;14:820–9. JM Molina, NEJM 2015 Dec 3;373(23):2237-46

Power: consistent adherence-response



DBS (fmol/punch)	BLQ	BLQ - 349	350-699	≥700
Adherence	No dosing	< 2 doses/wk	2-3 doses/wk	≥4 doses/wk
HIV risk reduction (OLE) (95% CI)		44% (-31,77)	84% (21,99)	100% (86, 100)

Grant. Lancet Infect Dis. 2014 Sep;14(9):820-9. AY Liu JAMA Intern Med. 2016 Jan 1;176(1):75-84.
Hosek. JAIDS 2016 Sep 13; Molina. NEJM 2015 Dec 3;373(23):2237-46. Anderson, STM 2012 (PMID 22972843); Celum C et al. IAS 2019; 21-24 July 2019, Mexico City, Mexico.

Peril: Cannot decipher dosing patterns

Hypothetical dosing calendar

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Sex		O					O							O		O			O				O			O			O		O			O				O			O				O			O														
Adher-ence		X	X	X		X	X							X	X	X			X	X	X		x	x		x	X		x	X		X	X	x			X	x	X		X	x	X			x	X	X	X												

PK Sample

PK Sample

TFV-DP in DBS …
~2-3 dose/wk over
last 6-8 weeks

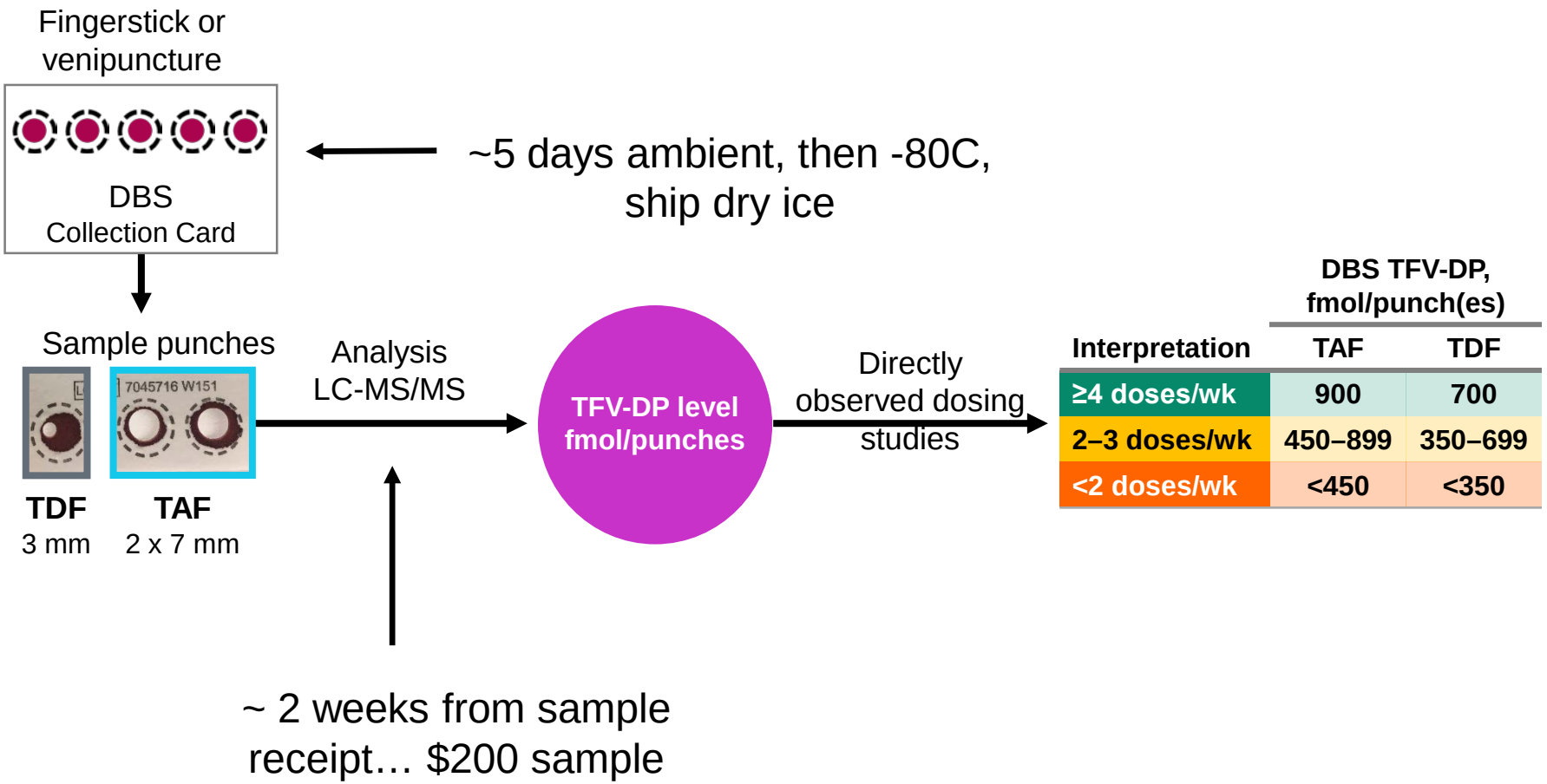
(FTC-TP + and -)

Peril: PK from USA healthy volunteers

12 week DOT study 48 Healthy Volunteers CO/SF USA → Normal HCT, Only 17% African descent…

Anderson PL, et al. 2018. AAC. (PMID 29038282)

Peril: Storage, Turnaround Time and Cost



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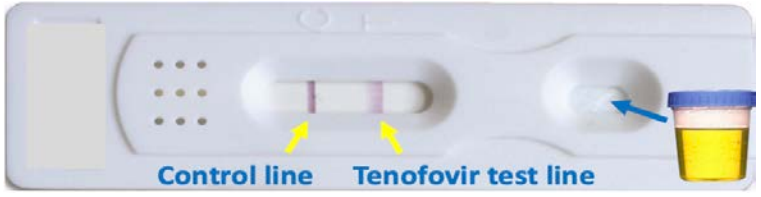
Future: Point of care

- Here for TFV in urine
  - UCSF (Gandhi/Alere-Abbott)
  - Ursure (https://www.ursureinc.com/)



- TFV-DP in RBC (blood)
  - CAVP/Purdue

Summary

Powers

- Gradients of adherence
- Hgb A1C-like interpretation
- Immune to white coat
- Strongly linked to outcomes
- Collection cheap/easy

Perils

- PK variability
- No dosing patterns
- -80C storage/dry ice ship
- Not POC and $$ (LC-MS)

Thank you!!

- Participants, colleagues, funders, the CAVP – special thanks to Lane Bushman, J Kiser, J Castillo-Mancilla

- JJ Kiser
- LR Bushman
- J Castillo-Mancilla
- JH Zheng
- L Ellison
- K Brooks
- C Mchugh
- And past and present members of the CAVP

- DV Glidden
- RM Grant
- A Liu