Innovative Measures of Adherence: What is in a drop of blood?

Jose Castillo-Mancilla, MD
Associate Professor
Division of Infectious Diseases
University of Colorado

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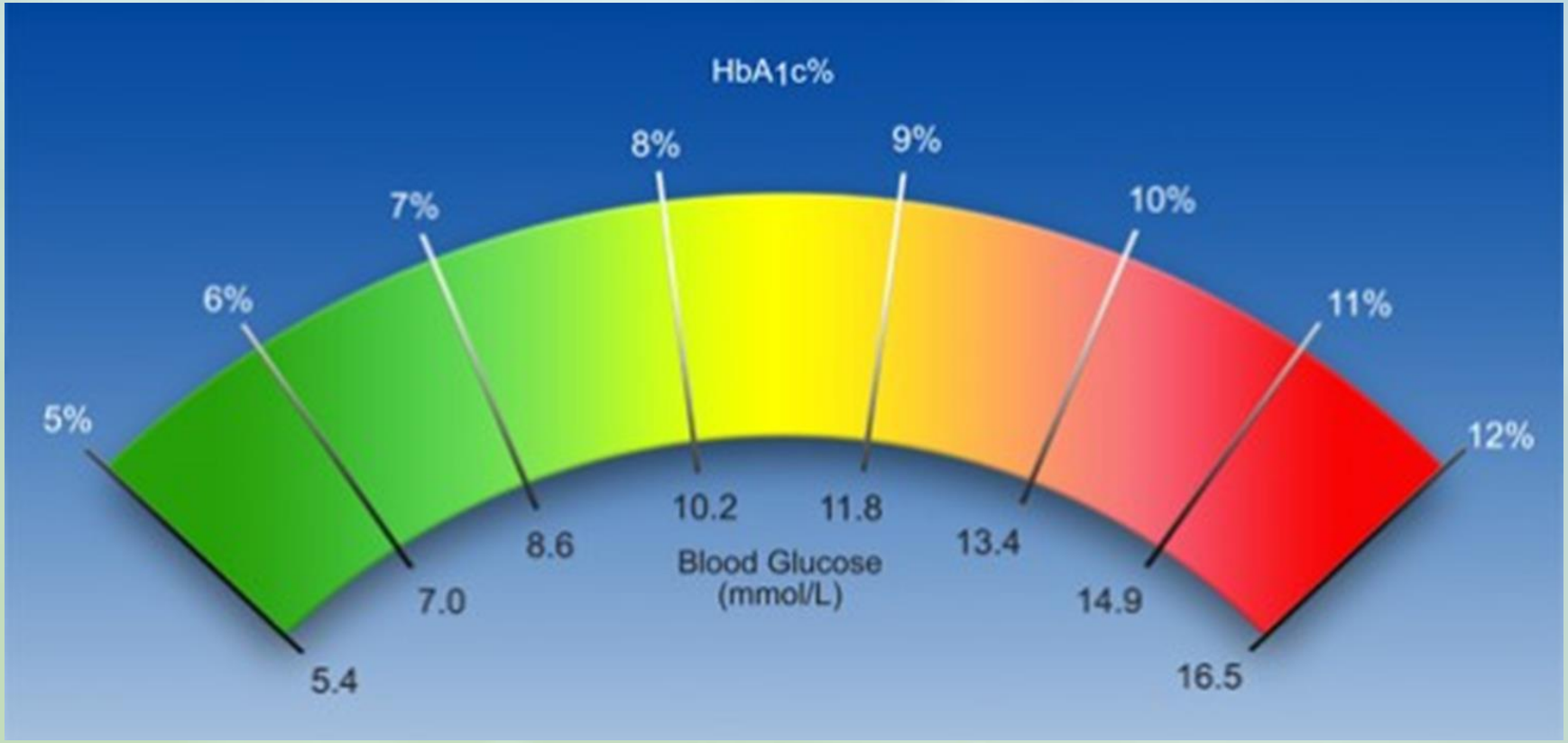
Outline

- Pharmacology of antiretrovirals in dried blood spots.
- Data on the use of dried blood spots to quantify adherence ART.
- Challenges and future directions.

Cumulative Adherence

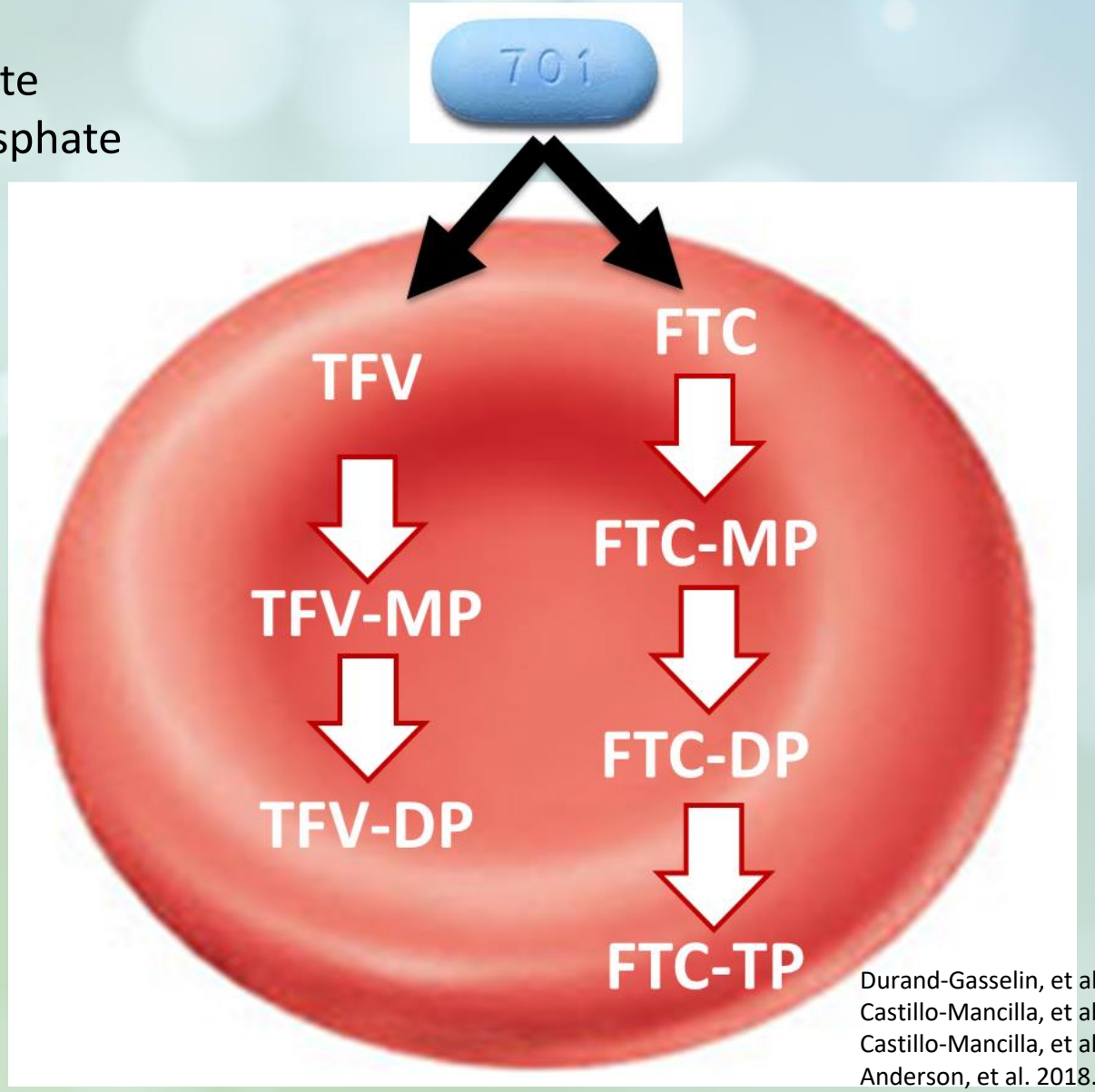
- Which is a better predictor of diabetes outcomes?
  - Fasting morning glucose vs. HbA1c



Sacks, et al. 2011. Diabetes Care (PMID 21270207).

TFV-DP and FTC-TP in RBC and DBS

TFV-DP: tenofovir diphosphate
FTC-TP: emtricitabine triphosphate



Cumulative Adherence

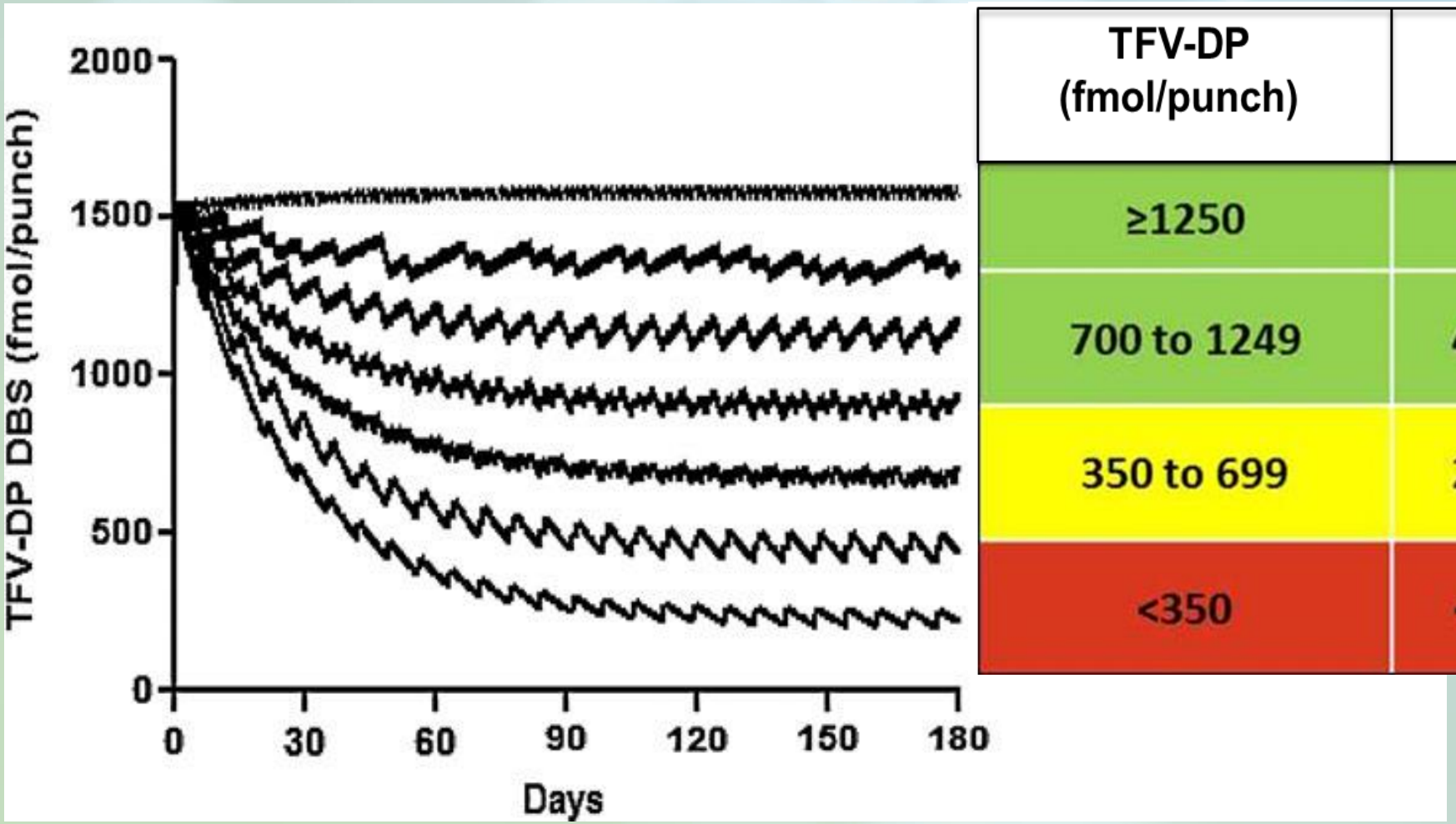
17-day half-life

Recent dosing

35-hr half-life

Durand-Gasselin, et al. 2007. AAC (PMID 17438052).
Castillo-Mancilla, et al. 2013. AIDS Res Hum Retroviruses (PMID 22935078).
Castillo-Mancilla, et al. 2015. AAC (PMID: 27572401).
Anderson, et al. 2018. AAC (PMID 29038282).

TFV-DP in DBS: adherence gradient



TFV-DP (fmol/punch)	Adherence Interpretation
≥1250	7 doses/wk
700 to 1249	4-6 doses/wk
350 to 699	2-3 doses/wk
<350	< 2 doses/wk

- Model confirmed using directly-observed therapy.

Castillo-Mancilla, et al. 2013. AIDS Res Hum Retroviruses (PMID 22935078).
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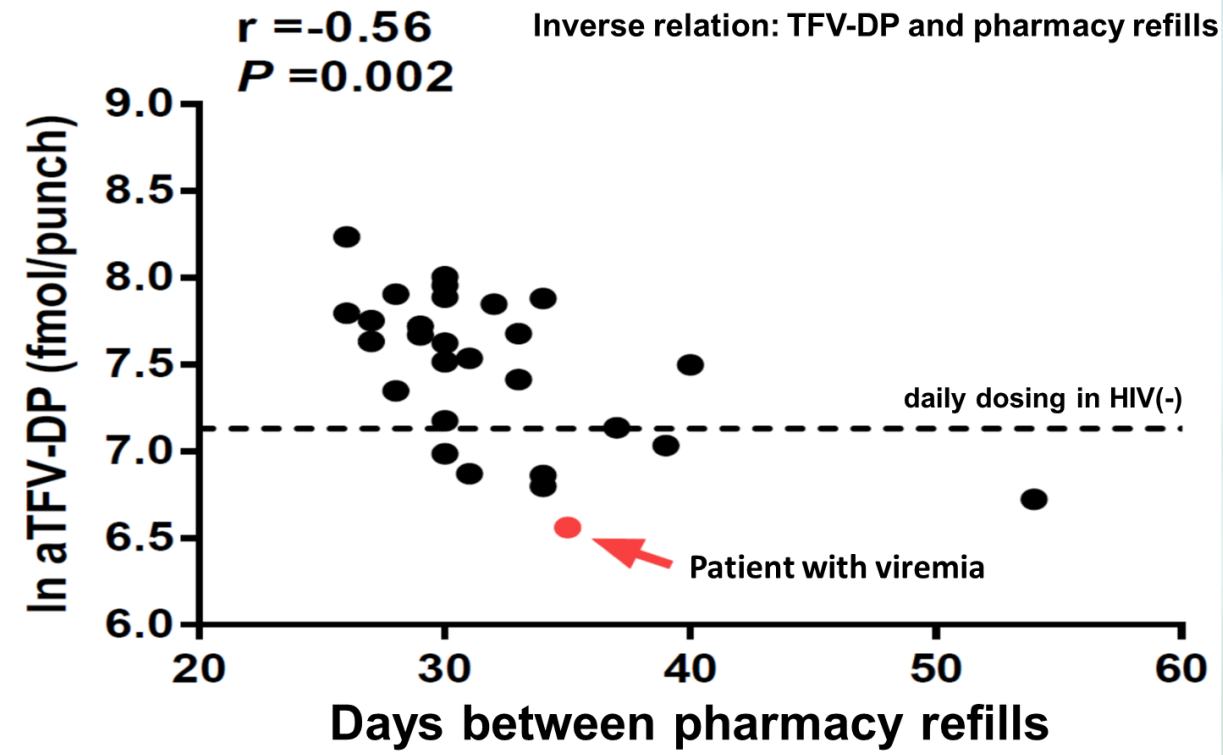
TFV-DP in HIV



United States

Correlation of TFV-DP$_{adj}$ with % Wisepill openings in previous 28 days:

Exclude 6 participants with significant TFV-DP$_{adj}$ but sustained absence of Wisepill openings

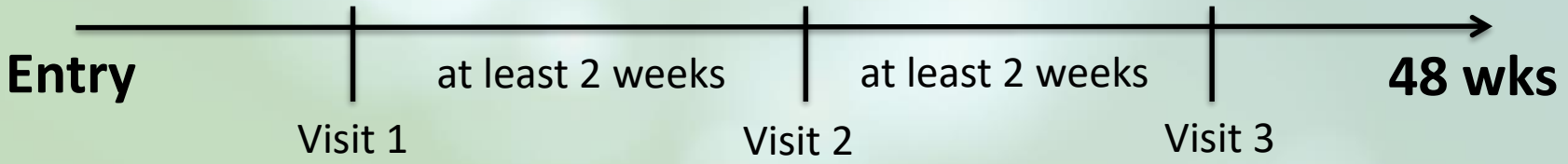
	All participants (N=29)			Participants excluded (N=23)		
	N (data points)	*r*	*p*	N (data points)	*r*	*p*
All visits	142	.348	<.001	**112**	**.510**	**<.001**

South Africa

Castillo-Mancilla, et al. 2014 AIDS Res Human Retroviruses (PMID 25328112).
Warne, et al. 2015 IAPAC. Abstract #241.

TFV-DP in HIV

- How do TFV-DP concentrations in patients with HIV infection compare to uninfected volunteers?
- What is the association of TFV-DP in DBS and viral suppression?
- DBS in a prospective clinical cohort of patients with HIV infection on TDF-based therapy (NCT02012621).
  - Clinic visit where routine HIV VL was collected.



Enrollment: June 2014-July 2017

Castillo-Mancilla, et al. 2018 CROI. Abstract #25.

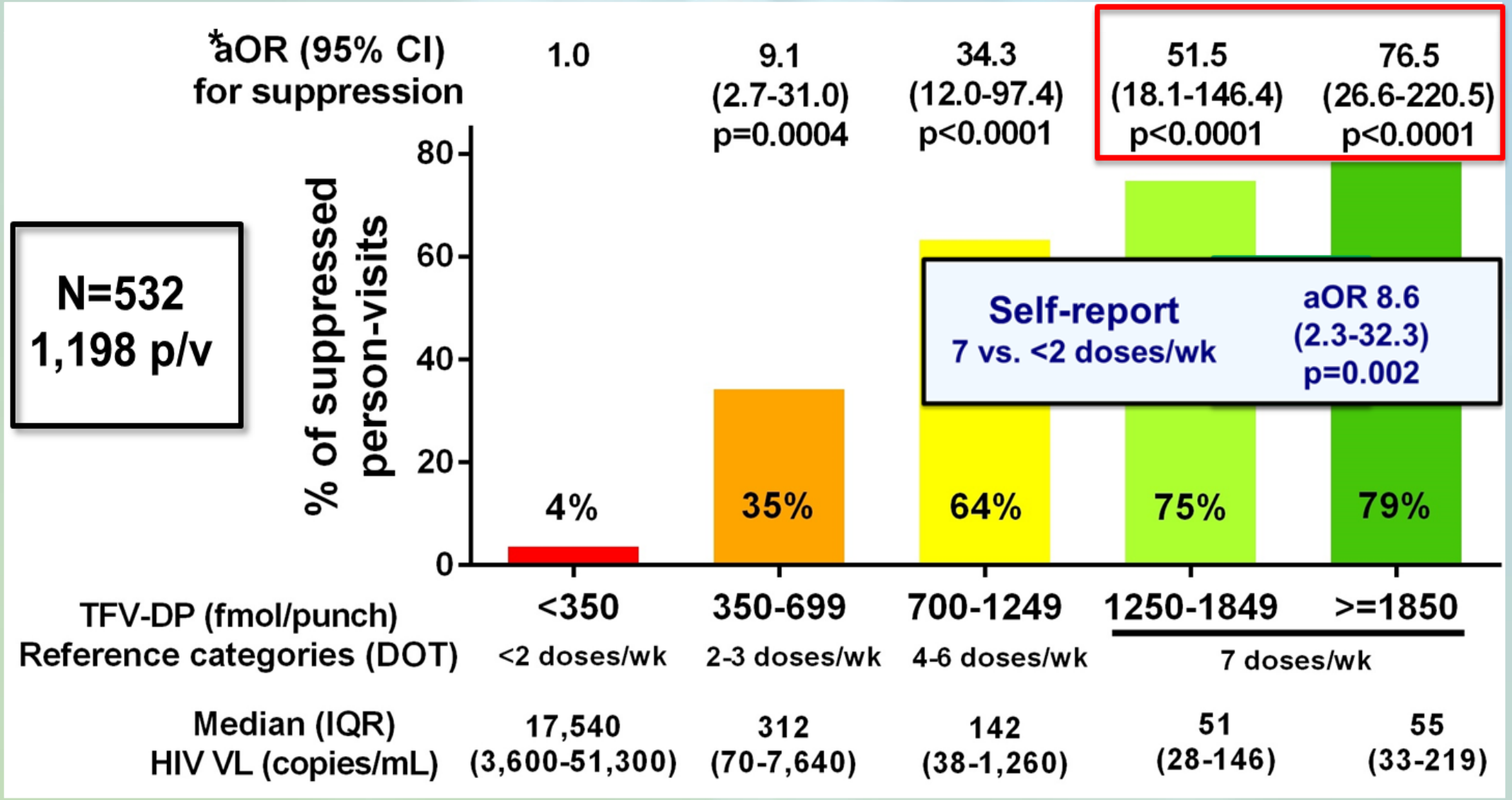
TFV-DP in HIV

Variable	TFV–DP (fmol/punch) GM (95% CI)	P–value
Viremic	1021 (917, 1138)	<0.0001
Suppressed	1728 (1601, 1865)	

Race, BMI, ART class, use of booster all influenced drug concentrations

Castillo-Mancilla, et al. 2018 CROI. Abstract #25.

TFV-DP in HIV: suppression



*Adjusted for age, gender, race, BMI, serum creatinine, CD4⁺ T-cell count, ART class, duration of ART and dosing category

Castillo-Mancilla, et al. 2018 CROI. Abstract #25.

Challenges/Limitations

- Adherence measures limited to TFV/FTC based regimens.
  - New data on 3TC-TP also quantifiable in DBS.
- Requires a specialized laboratory for analysis.

Schauer AP, et al. 2018. JPBA (PMID: 29100029)

Future Directions

- Extend current research into TAF-based therapy.
- Prospective application in routine clinical practice:
  - Early intervention to prevent viral rebound and treatment failure
  - Prompt identification of treatment toxicity?
  - Point of care testing and assay availability (R01 AI122298)
- Quantification of adherence and exposure in the virally-suppressed patient.
- Can TFV-DP in DBS complement other adherence measures?

Acknowledgments

#ADHERENCE2018

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uchealth

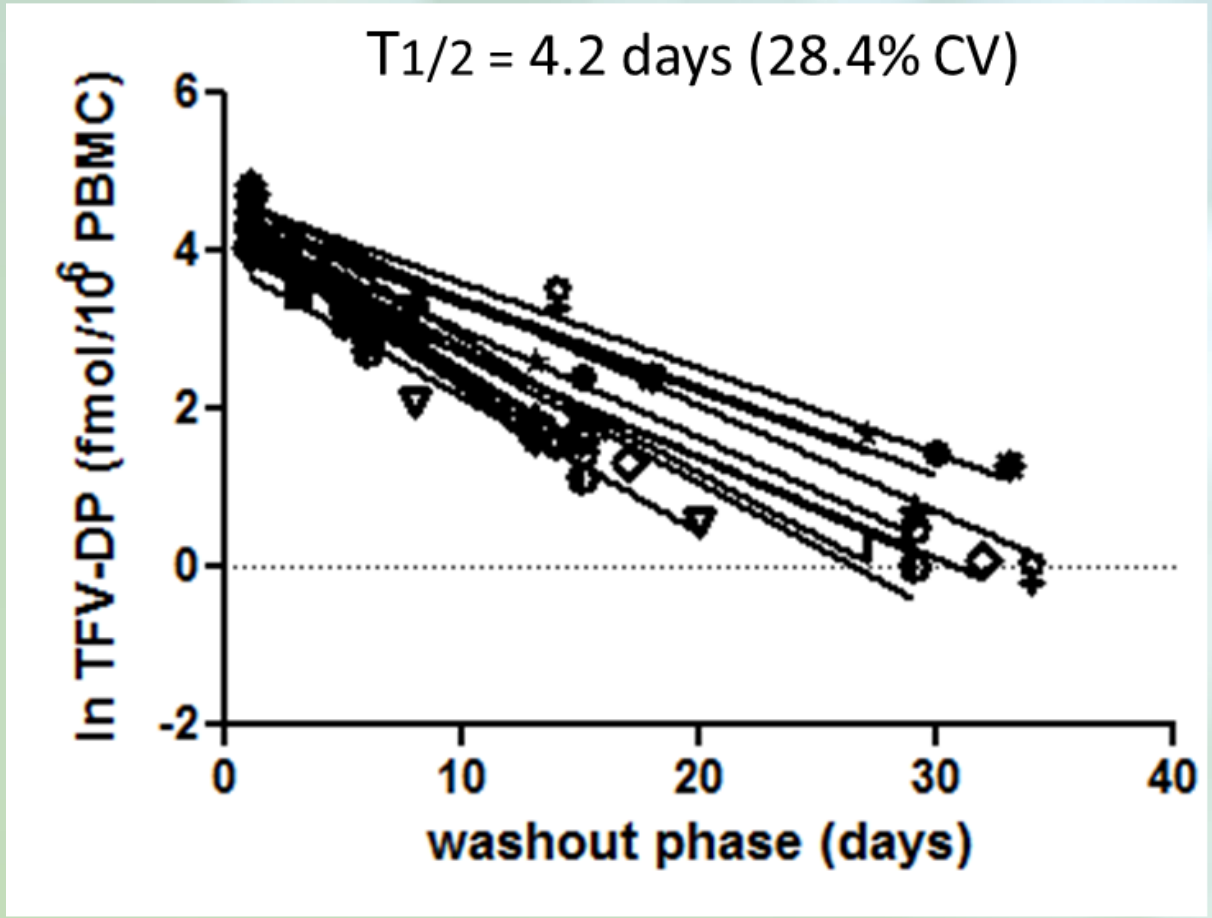
Thank you!

jose.castillo-mancilla@ucdenver.edu

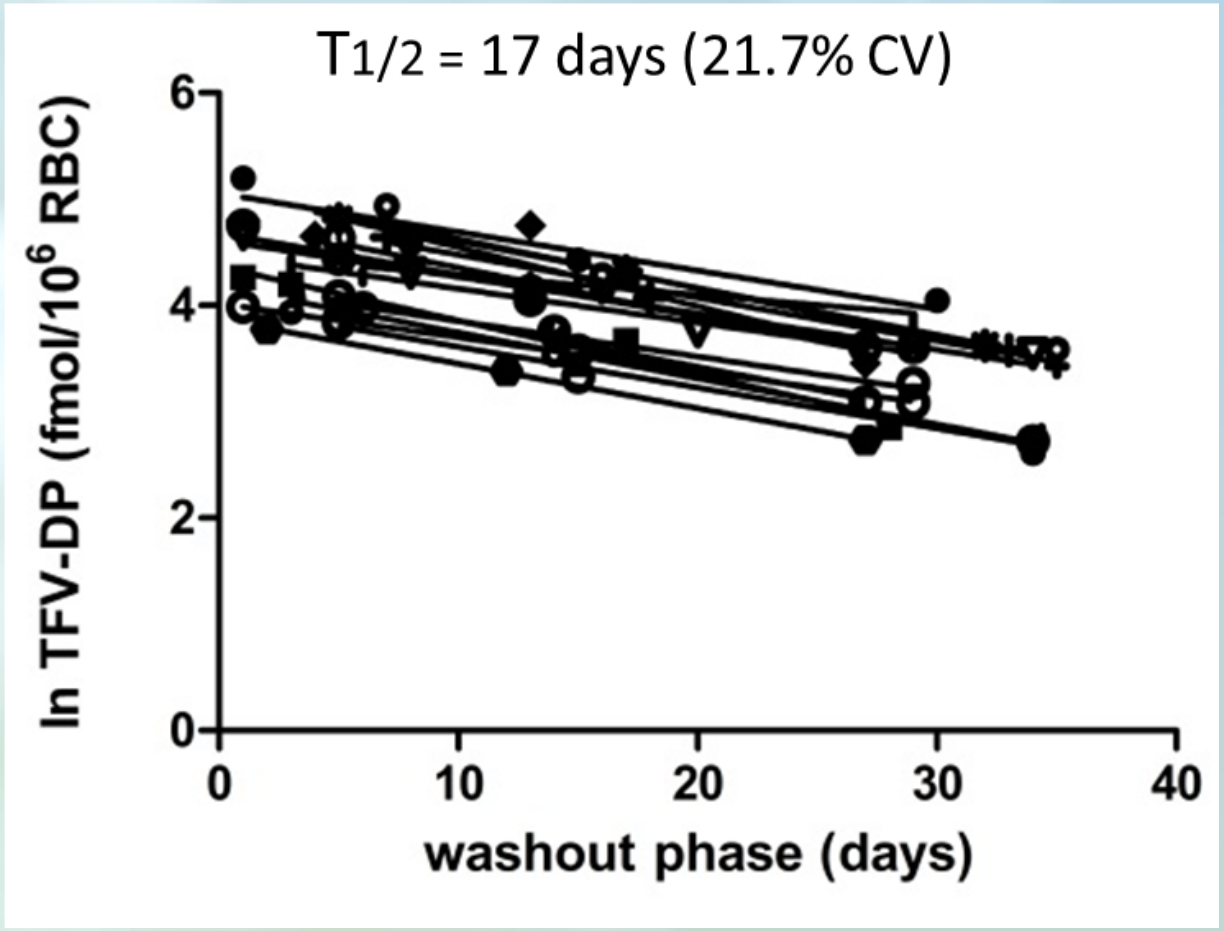
Backup Slides

TFV-DP half-lives RBC vs PBMC

PBMC



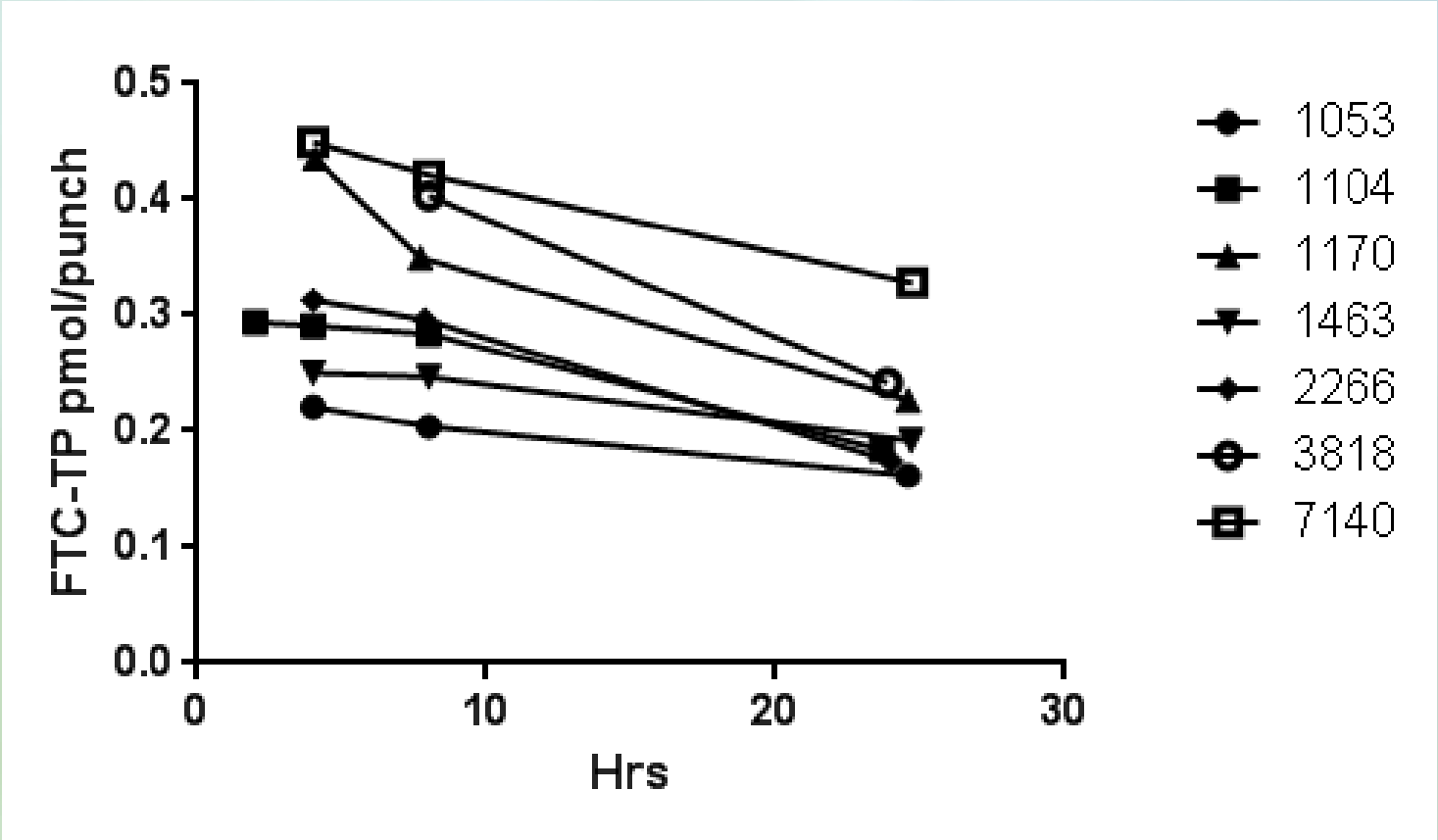
RBC



Castillo-Mancilla, et al. 2013. AIDS Res Hum Retroviruses (PMID 22935078).

FTC-TP in DBS informs recent dosing

- Terminal phase:
  - T ½= 31 (22-52) hrs.



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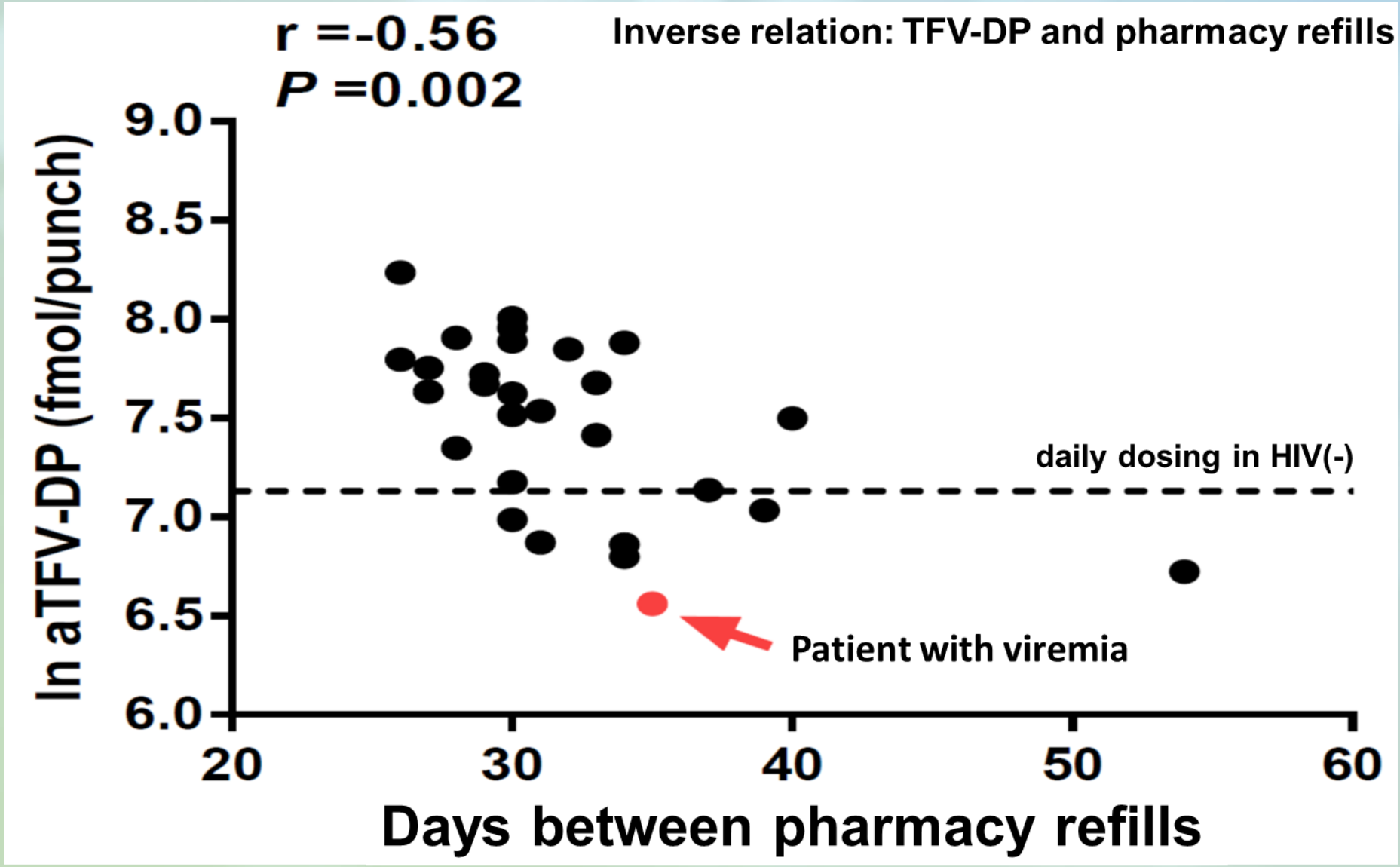
TFV-DP in HIV



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TFV-DP in HIV

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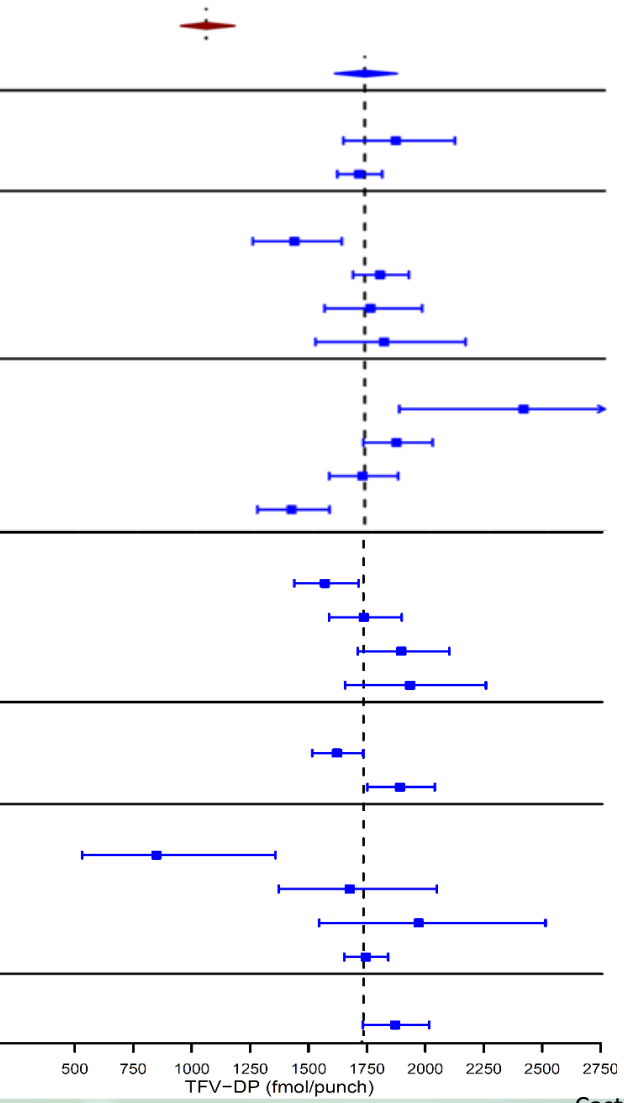
TFV-DP in HIV

Variable	TFV-DP (fmol/punch) GM (95% CI)	P-value
Viremic	**1021 (917, 1138)**	**<0.0001**
Suppressed	**1728 (1601, 1865)**	
Sex		
Female	1860 (1637, 2112)	Ref
Male	1704 (1611, 1802)	0.22
Race		
Black	1428 (1251, 1630)	Ref
White	1793 (1678, 1916)	0.003
Hispanic	1752 (1557, 1972)	0.02
Other	1810 (1518, 2157)	0.03
BMI (Kg/m^2)		
<18.5	2404 (1875, 3082)	Ref
18.5–25	1863 (1722, 2017)	0.06
25–30	1718 (1577, 1870)	0.01
30–50	1416 (1271, 1578)	0.0002
ART		
NNRTI-based	1563 (1432, 1707)	Ref
INSTI-based	1729 (1580, 1892)	0.12
b/PI-based	1890 (1704, 2095)	0.006
Multiclass	1927 (1650, 2252)	0.02
Booster		
No	1614 (1508, 1727)	Ref
Yes	1884 (1745, 2033)	0.003
Time on ART		
<1 month	842 (525, 1351)	Ref
1–3 months	1669 (1365, 2042)	0.009
3–6 months	1964 (1539, 2507)	0.002
>6 months	1738 (1646, 1834)	0.003
3m SR Adher		
100%	1863 (1726, 2010)	



Castillo-Mancilla, et al. 2018 CROI. Abstract #25.

FTC-TP in HIV

TFV-DP (fmol/punch)	FTC-TP	
	Quantifiable n (%)	BLQ n (%)
<350	3 (15)	17 (85)
350-699	21 (66)	11 (34)
700-1249	88 (85)	15 (15)
>1250-1849	153 (98)	3 (2)
≥1850	190 (99)	2 (1)

aOR (95% CI) for viral suppression: 7.3 (4.4-12.1); p<0.0001