Utility of Dried Blood Spot-Derived ARV Biomarkers as an Objective Measure of Treatment Adherence in South Africa

Patricia Warne, Reuben Robbins, Peter Anderson, Hetta Gouse, John Joska, Cheng-Shiun Leu, Yoliswa Mtingeni, Michelle Henry, Javier Lopez Rios, José Castillo-Mancilla, Bruce Levin, Claude Mellins, Robert Remien

HIV Center, NYS Psychiatric Institute and Columbia University; University of Cape Town; University of Colorado

HIV CENTER for Clinical and Behavioral Studies
at the New York State Psychiatric Institute and Columbia University

INTRODUCTION

- Objective measures of ART adherence should
  - impose minimal burden on patients/research participants and on healthcare systems;
  - be usable in a range of settings;
  - **be valid and reliable;**
  - **provide information to facilitate timely intervention and clinical management.**

MONITORING ARVs IN BLOOD

- Strengths:
  - Direct evidence of drug ingestion
  - Acceptability
- Limitations:
  - Short plasma $t_{1/2}$ of parent drugs → snapshot of very recent ingestion
  - Sampling and processing constraints
- Tenofovir-diphosphate (TFV-DP)
  - $t_{1/2}$ in RBCs = 17 days → drug ingestion over a longer period

MONITORING ARVs IN BLOOD

- Assay of TVF-DP from dried blood spots (DBS)
  - Sampling advantages
  - Characterized in “high-resource” clinical research settings in the US among HIV– research participants and among HIV+ patients.*

* Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, Fernandez C, Langness J, Kiser JJ, Bushman LR, Anderson PL. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Research and Human Retroviruses*. 2013;29(2):384-390.

Castillo-Mancilla JR, Searls K, Caraway P, Zheng JH, Gardner EM, Predhomme J, Bushman LR, Anderson PL, Meditz AL. Tenofovir diphosphate in dried blood spots as an objective measure of adherence in HIV-infected women. *AIDS Research and Human Retroviruses*. 2015;31(4):428-432.

GOAL OF THIS STUDY

We explored the utility of this assay as a measure of ART adherence in a real-world, low-resource clinic setting in South Africa.

How do DBS-derived TFV-DP levels relate to

- ARV adherence as determined by an EMD (i.e., Wisepill openings)?
- ARV adherence as determined by self-report?

PARTICIPANTS (N=29)

- HIV+ patients enrolled in an RCT of *Masivukeni,* a multimedia adherence intervention being evaluated in public HIV care clinics in Cape Town.
- Initiated a once-daily ART regimen containing tenofovir (TFV) in the past 1-2 months (e.g., Atroiza, Odimune).

METHODS: PROCEDURES

- 5 monthly visits
- Blood draw by venipuncture for DBS.
- Self-reported adherence in past month:
  4 questions adapted from Wilson et al.
- Daily Wisepill output (as part of parent study)
- R300/study visit

METHODS: DBS AND ASSAYS

- Blood samples (25 µl) from venipuncture pipetted onto Whatman 903 ProteinSaver cards, air dried, and stored at -80^{o}C.
- Shipped to University of Colorado on dry ice for assay in the Anderson laboratory.
- 3 mm punches extracted and assayed for TFV-DP by LC/MS/MS.*

* Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, Fernandez C, Langness J, Kiser JJ, Bushman LR, Anderson PL. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Research and Human Retroviruses*. 2013;29(2):384-390.

METHODS: DATA ANALYSIS

- % Wisepill adherence (openings) in 28 days prior to DBS sampling:

$$\frac{\text{\# days device opened}}{\text{\# days device detected as active}}$$

- Pre-steady-state TFV-DP levels (fmol/punch) were adjusted to steady-state ($TFV\text{-}DP_{adj}$) assuming a 17-day half-life in RBCs.

- $TFV\text{-}DP_{adj}$ levels were log-transformed, and Pearson correlations were calculated.

RESULTS: SAMPLE CHARACTERISTICS (1)

- Demographics:
  - 90% women, 100% Black African
  - Mean age: 30 years (SD±5.25)

- ***Time on ART*** at pilot study Visit 1:
  Mean: 32 days; Median: 29 days;
  Range: 23-52 days

- % Wisepill openings over ***entire study:***
  Mean: 76%; Median: 84%; SD: 25%

- % Wisepill openings in the ***4 weeks previous to each study visit:***
  Mean: 74%; Median: 90%; SD: 34%

RESULTS: SAMPLE CHARACTERISTICS (2)

DBS tenofovir-diphosphate (TFV-DP) levels (fmol/punch)

	Mean	Median	Range	SD
Castillo-Mancilla et al. (2015)* HIV+ women on ART (US)		1,874	706-3,776	

* Castillo-Mancilla JR, Searls K, Caraway P, Zheng JH, Gardner EM, Predhomme J, Bushman LR, Anderson PL, Meditz AL. Tenofovir diphosphate in dried blood spots as an objective measure of adherence in HIV-infected women. *AIDS Research and Human Retroviruses*. 2015;31(4):428-432.

RESULTS: SAMPLE CHARACTERISTICS (2)

DBS tenofovir-diphosphate (TFV-DP) levels (fmol/punch)

	Mean	Median	Range	SD
Castillo-Mancilla et al. (2015)* HIV+ women on ART (US)		1,874	706-3,776	
TFV-DP$_{adj}$ all time points	**1,013**	**939**	**0-3,623**	**489**

* Castillo-Mancilla JR, Searls K, Caraway P, Zheng JH, Gardner EM, Predhomme J, Bushman LR, Anderson PL, Meditz AL. Tenofovir diphosphate in dried blood spots as an objective measure of adherence in HIV-infected women. *AIDS Research and Human Retroviruses*. 2015;31(4):428-432.

RESULTS: SELF-REPORTED ADHERENCE

At least 98% of the time, participants reported excellent – if not "perfect" – adherence to their HIV meds in the past month:

- 0 days missing one or more doses
- Always or almost always taking meds "as supposed to"
- Excellent or very good job taking meds "as supposed to"
- Taking their meds as "about the same as usual"

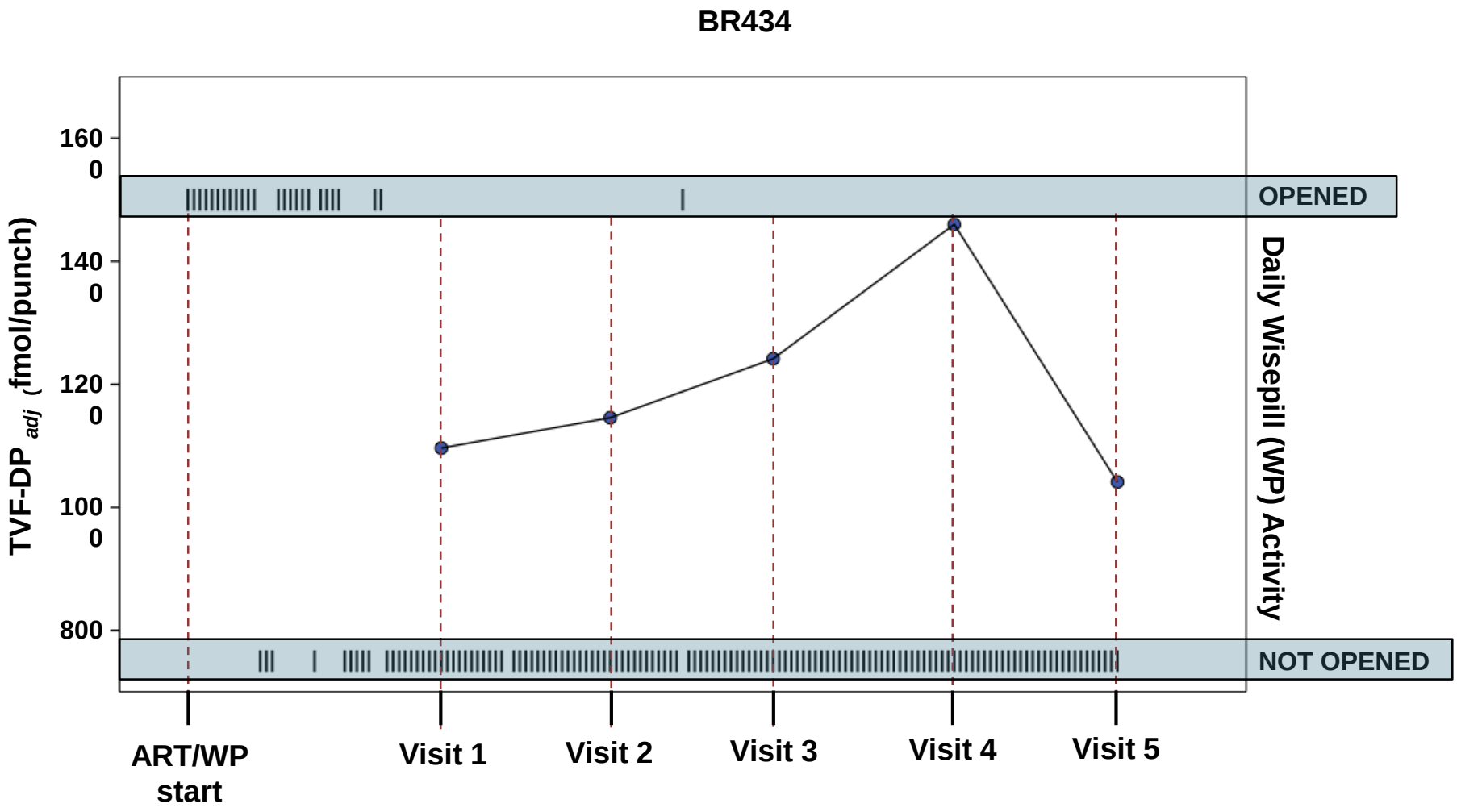
RESULTS:
TFV-DP and WISEPILL

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

ALL PARTICIPANTS

	r	*p*
All visits (142 data points)	.348	<.001

RESULTS:
TFV-DP and WISEPILL (cont'd.)



RESULTS: TFV-DP and WISEPILL (cont'd.)

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**

CONCLUSIONS and AREAS FOR FUTURE RESEARCH

- Determining associations between DBS-derived TFV-DP levels and ART adherence was hampered by problems in Wisepill use in at least 20% of our sample.
- These device-use problems might not have been recognized without the TFV-DP assay results.

CONCLUSIONS and AREAS FOR FUTURE RESEARCH

- Larger studies are needed to understand the strengths and limitations of DBS ARV anabolite assays and EMDs as clinically meaningful objective measures of adherence.
  - Are moderate correlations between TFV-DP levels and % Wisepill openings due to use of the device, intra-individual PK variability, or both?
  - Can drug anabolite assays overcome the confounder of EMD adherence – i.e., by measuring actual medication ingestion rather than device use?

CONCLUSIONS and AREAS FOR FUTURE RESEARCH

- Our sample (which was, overall, relatively adherent to Wisepill use) has a lower median TFV-DP level than the US sample. Is this due to
  - Genetic variation among patients/populations?
  - Exposure to other medical conditions/drugs?
  - Use of generic medications?
- Does the assay need to be “calibrated” for different populations?

CONCLUSIONS and AREAS FOR FUTURE RESEARCH

- A DBS-based assay of TFV-DP has potential as a tool for monitoring adherence and helping patients manage their HIV disease.
  - How will providers interpret/use assay results?
  - Can assay results be used to motivate adherence among patients?
  - How should results be framed? How will patients understand/act on feedback?
  - How would point-of-care or home-testing versions of the assay be used?

CONCLUSIONS and AREAS FOR FUTURE RESEARCH

- Could DBS ARV anabolite assays have advantages over standard clinical markers (e.g., CD4+ cell counts, viral load) in detecting adherence problems?
  - Can the assay predict the development of viral breakthrough/viremia due to non-adherence?
  - How much advanced warning of viral breakthrough/viremia could regular (e.g., monthly) use of this assay give?

ACKNOWLEDGMENTS

HIV Center, NYSPI and Columbia University

Robert H. Remien, Ph.D.
Patricia Warne, Ph.D.
Reuben Robbins, Ph.D.
Claude Ann Mellins, Ph.D.
Javier López-Rios, B.A.
Cheng-Shiun Leu, Ph.D.
Bruce Levin, Ph.D.

University of Cape Town

John Joska, M.B.Ch.B.
Hetta Gouse, Ph.D.
Michelle Henry
Yoliswa Mtigeni

University of Colorado

Peter L. Anderson, Pharm.D.
José Castillo-Mancilla, M.D.

National Institute of Mental Health

Administrative Supplement to "Masivukeni: A Multimedia ART Adherence Intervention for Resource-Limited Settings (R01-MH95576-03S1; PI: Robert H. Remien, Ph.D.)

NIMH Program Officer: Michael Stirratt, Ph.D.

HIV Center for Clinical and Behavioral Studies (P30-MH43520; Center Director and PI: Robert H. Remien, Ph.D.)

HIV CENTER for Clinical and Behavioral Studies
at the New York State Psychiatric Institute and Columbia University