Adherence in Oral PrEP & Microbicides

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Outline

1. Product adherence optimization and need for better measures.
2. Types of quantitative measures:
   - EMS: Electronic Event Monitoring Systems
   - IEM: Ingestion/Insertion Event Markers
   - Markers of other behaviors: sexual exposure
   - Other “smart”/ “objective” measures of use
3. Point of entry for targeted interventions
4. Understanding (Non-) adherence

Note: “objective” = respondent-independent

Selected oral PrEP & microbicide trials (Africa)

Name	Population	Estimated Adherence		
		Self report	CPC	Drug level (in subset)
TDF2	557 ♀ & 662 ♂	94%	84%	80%
Partners PrEP	4758 sd ♀/♂ couples	98%	97%	82%
Fem-PrEP	2120 ♀	95%	85%	<40%
VOICE	5029 ♀			
TDF		90%	87%	30%
Truvada		91%	92%	29%
TFV gel		91%	86%	25%

Ambia (review) 2013; Baeten (review) 2013; van der Straten 2012; Baeten CROI 2013; Marrazzo CROI 2013

1. Adherence Optimization

Definition: Adherence (in trials) = participant's use of study product as instructed

The key to understanding adherence, like any scientific phenomena, is to accurately measure it.

Measurement is intrinsically embedded in the goal of adherence optimization

Adherence Optimization

- **Why measure adherence?**
  - Explain trial results/interpret findings
  - Entry point for adherence intervention
  - Outcome to evaluate interventions
  - Target appropriate populations for future trials
- **Why understand adherence behavior?**
  - Explain use/non-use in individuals
  - Identify modifiable behaviors
  - Tailor and optimize interventions

IOM 2008 Report Recommendation 5-1

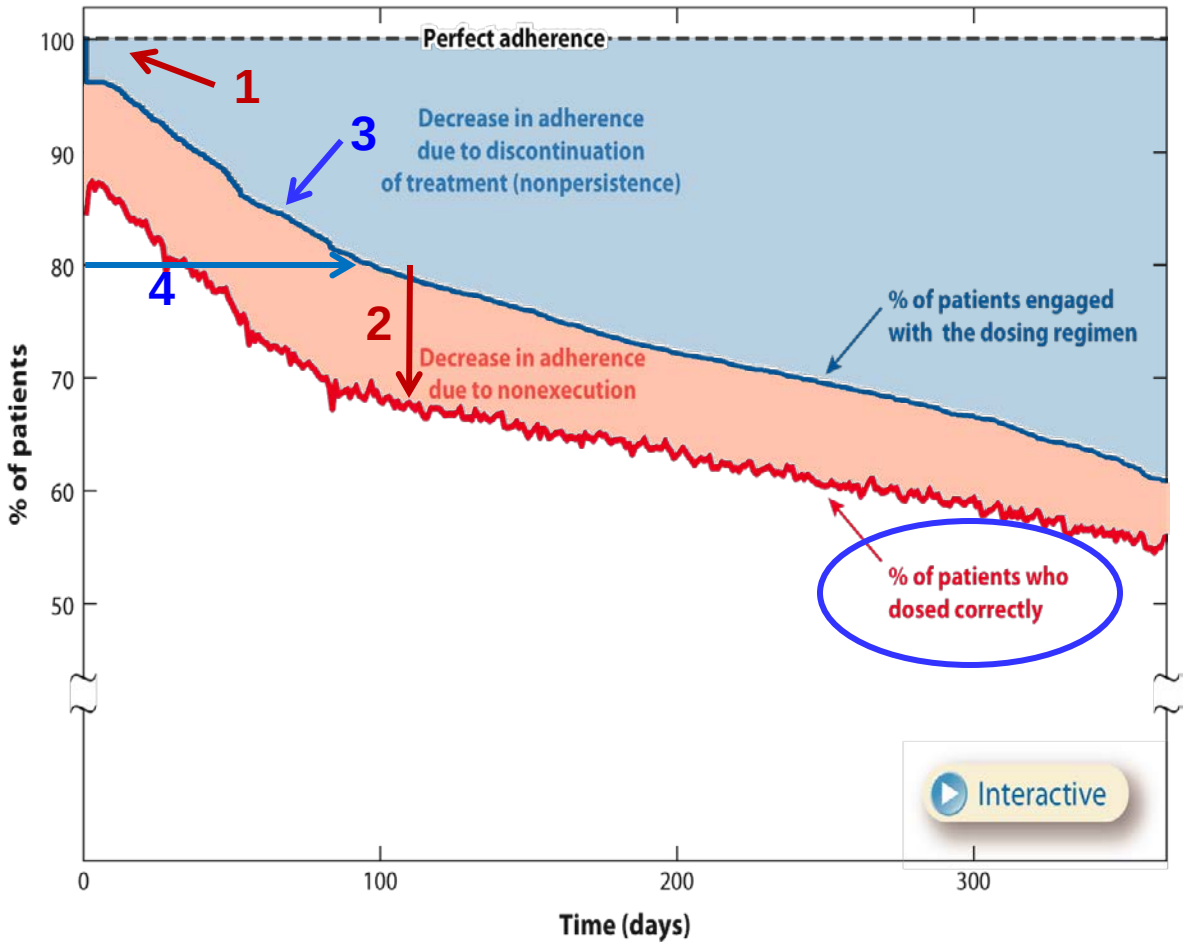
"Because simple measures of adherence can mask substantially different underlying adherence problems, investigators should develop and use adherence measures that can capture different adherence patterns over time."

Source: IOM Methodological Challenges in Biomedical HIV Prevention Trials, 2008 Report

Dimensions of adherence

- Initiation (1)
  Time point for 1st dose
- Execution (2)
  Actual = Instructed dosing
- Discontinuation (3)
  Time point for last dose
- Persistence (4)
  Period between initiation and discontinuation

Adherence parameters in ~17K ppts; 95 studies



Sources: IOM report 2008; Blaschke et al., Ann.Rev.PT 2012; van der Straten et al., CHAR 2012

Adherence measures selection: focus on objectives

Critical characteristic of measure	1. Explain trial results	2. Inform adherence intervention
High accuracy	X	X
Low participant burden/invasiveness	X	X
Simple and low cost to implement	X	X
Minimize opportunity for manipulation		X
Minimize Hawthorne effect*	X	
Allows for real-time feedback		X

* *This includes minimizing adding new procedures or behaviors associated with doing the measurement*

See: Deschamps et al., 2006

Dosing, delivery and measurement

	Dosing & Delivery Method			
	Intermittent		Continuous/Long acting	
	Gel, Tablet, etc…		Ring	Injectables
Dimensions of Adherence	Time-driven	Event-driven		
Initiation	DOI	x	DOI	DOI
Execution	x	x	x	(na)
Discontinuation	x	x	x	DOI
Persistence	x	x	x	DOI
Other behaviors critical to adherence measurement				
Visit attendance	x		x	x
Sexual exposure		x		

Methods:
User-dependent
User-independent

DOI: Directly observed/supervised insertion /ingestion /injection at the study clinic

X= accurate measurement is needed

2. Types of quantitative measures

EMS: Electronic Event Monitoring Systems

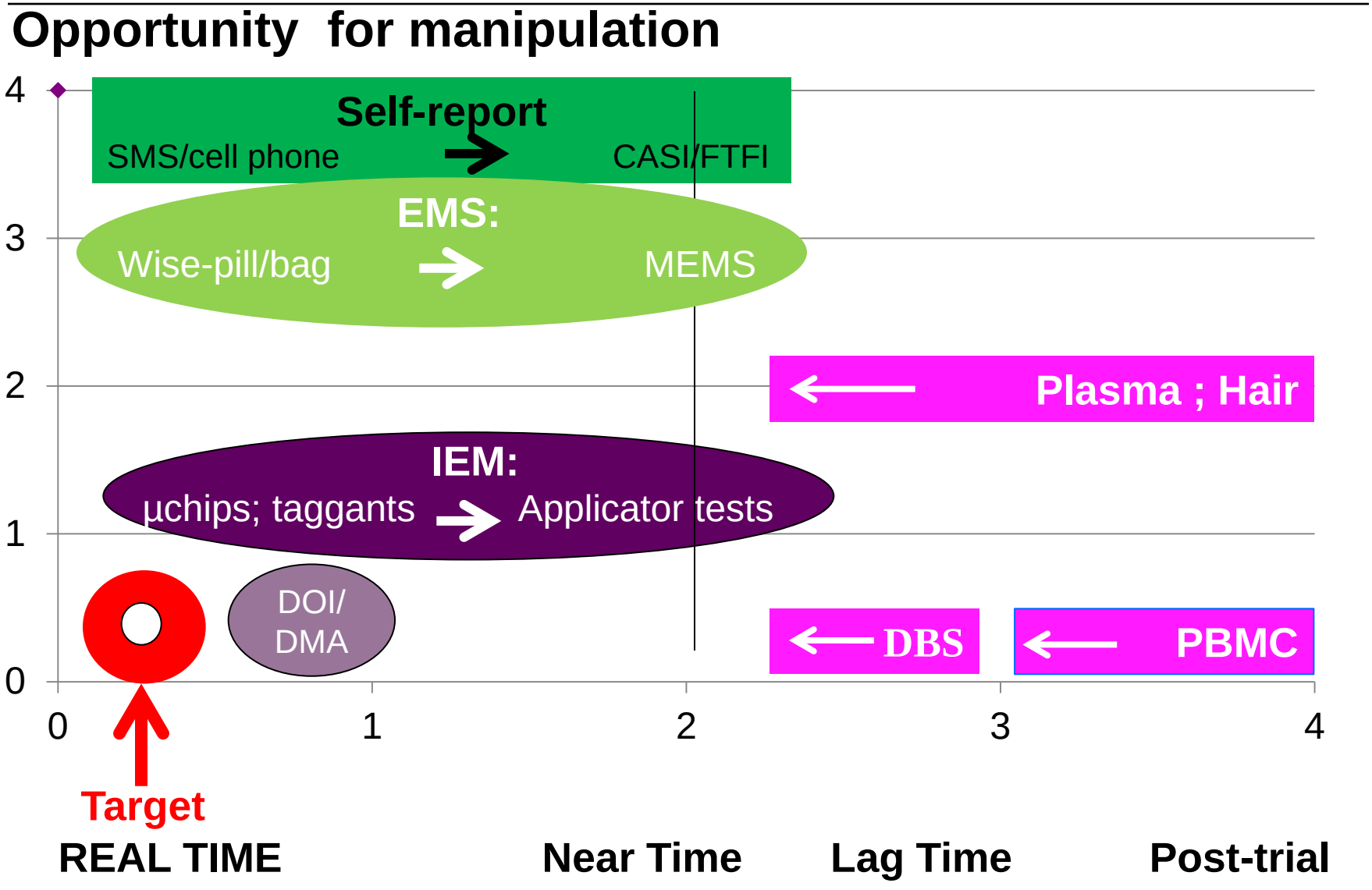
- AEB: Adherence execution behavior
  - MEMS: bottle, jar
  - Wisepill
  - Wisebag
  - Strip package monitor
  - Electronic Trace Sheet Monitor

IEM: Insertion* Event Markers

- AEB:
  - Applicator tests
    - DSA
    - UVA
    - VIRA
- Combination:
  - Dual-marker applicator test
- Direct measures of use
  - Taggant/ Breath test
  - Ingested µchip
  - Adherence sensors

* Ingestion / Insertion / Injection

Trade-offs between measures

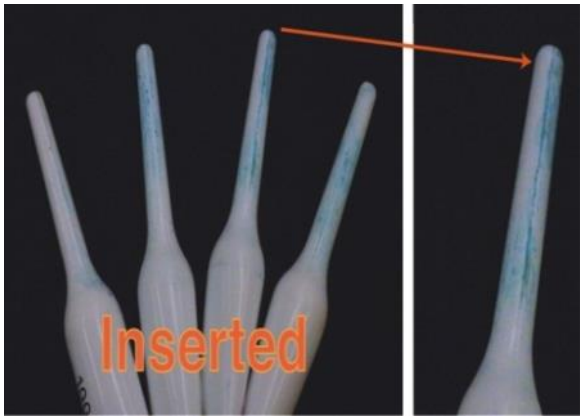


EMS: Event Monitoring Systems

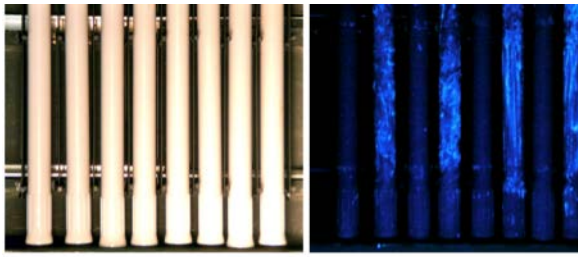
- Strengths:
  - Not product specific
  - Provides date & time stamp
  - Real-time monitoring (or near-time)
  - Blinding maintained
- Accuracy?
  - Pocket dosing (underestimation)
  - Curiosity events (overestimation)
  - Can be manipulated
- Weaknesses:
  - Adherence execution behavior (indirect)
  - ? Burden (opening, storage, disposal)
  - Cost

IEM: Applicator Tests

- Strengths:
  - Usable for any drug in gel applicator
  - Blinding maintained
  - Low tech
- Accuracy
  - May depend on applicator type
  - Assessors' skills
  - Less likely to be manipulated
- Weaknesses:
  - Participant and staff burden
  - Adherence execution behavior
  - No date and time stamp
  - Cannot monitor real-time (near time?)



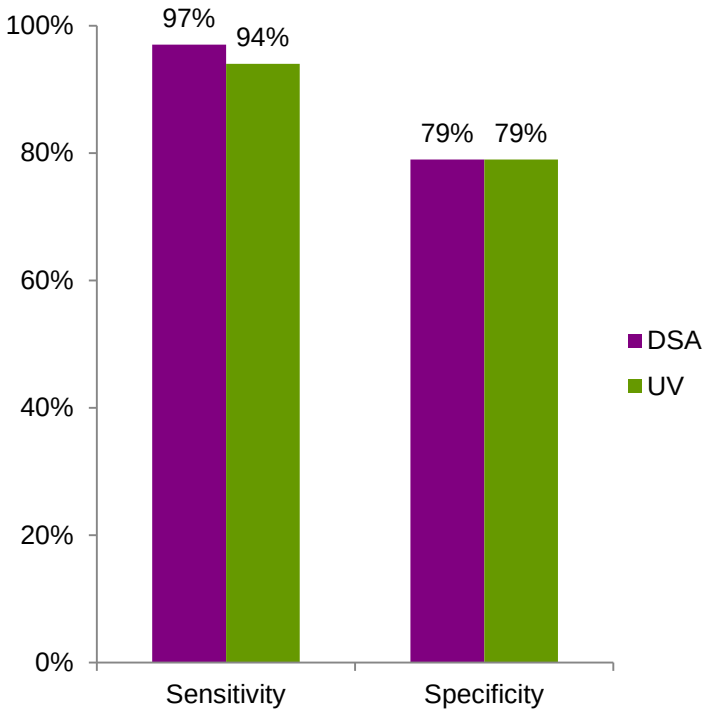
Dye Stain Assay


UV Light

Katzen et al., 2011 Moench et al., 2012

Applicator test studies, Bronx NY

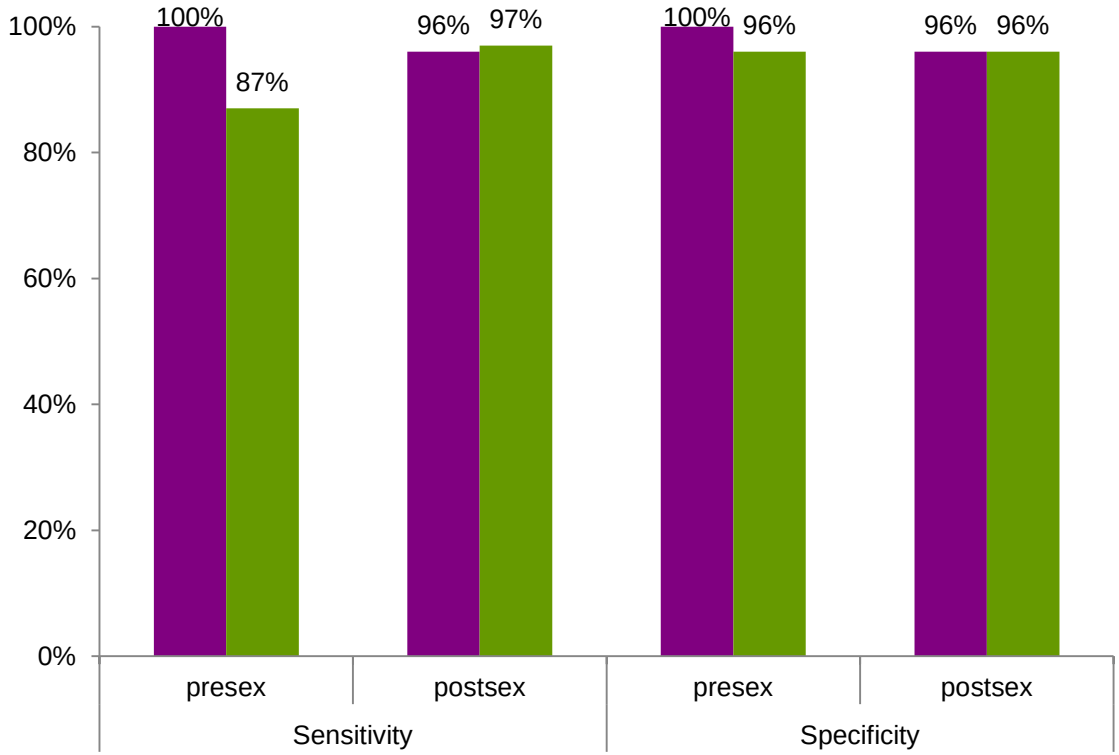
Study1: ♀ daily gel use (N=39)



van der Straten et al., STD in press 2013

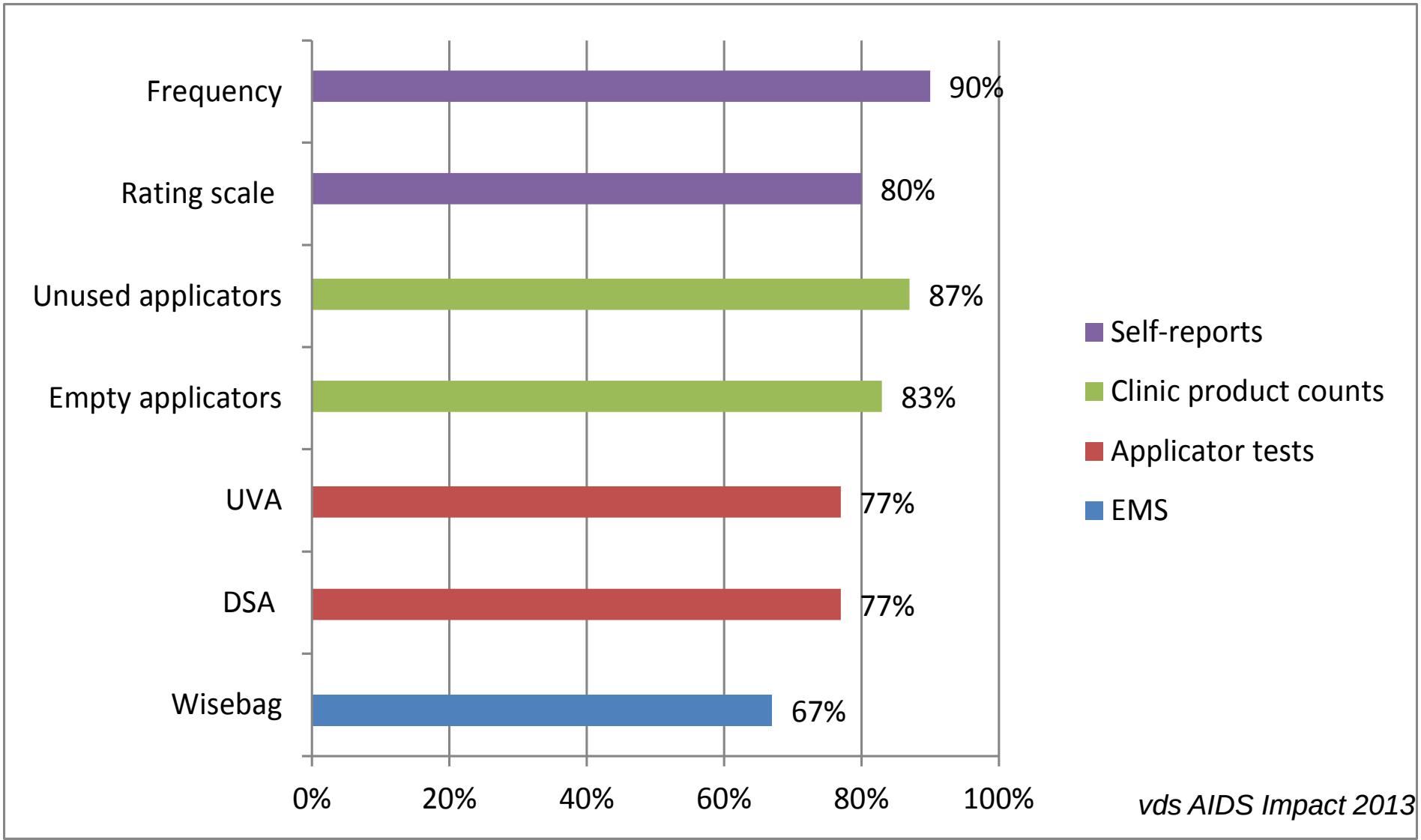
Study2: Couple BAT24 use (N=15)

Postsex RSID as biomarker of semen exposure



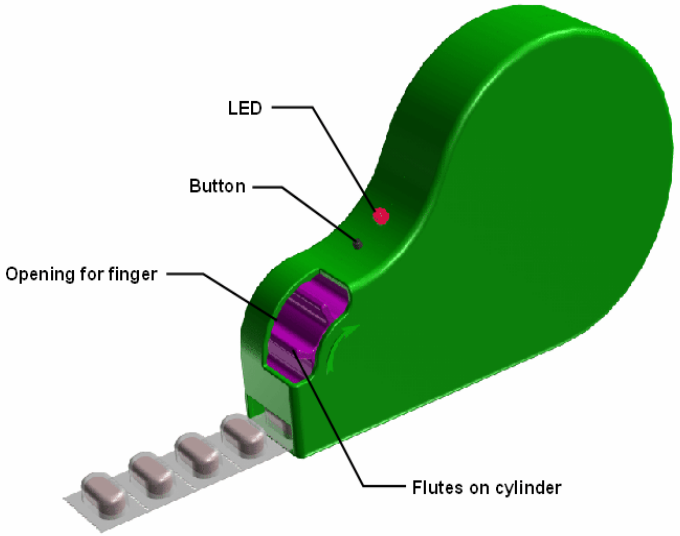
Keller et al., STD in press 2013

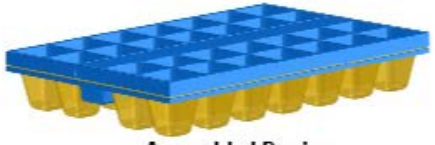
Median adherence over 30 days per various measures (N=39)



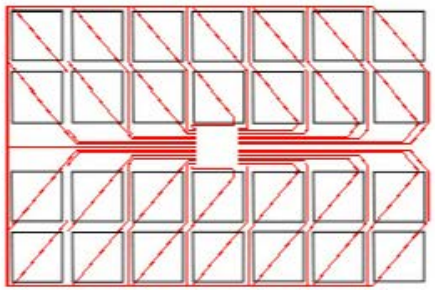
Other “SMART” tools:

Cypak blister packs

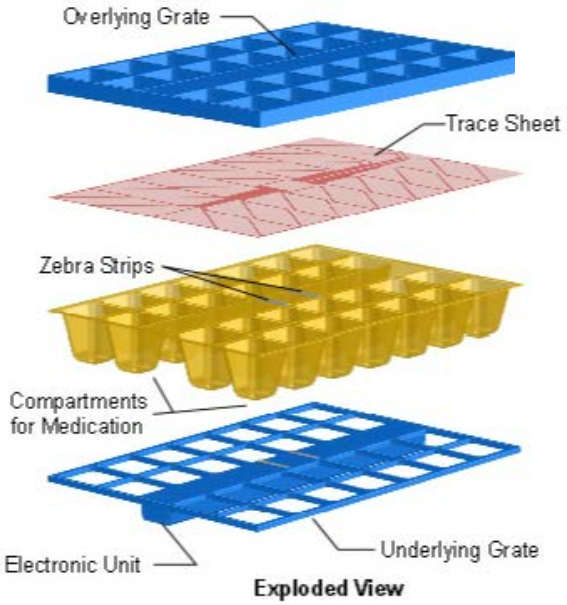




Assembled Device



Top View of Trace Sheet



Exploded View

http://www.medicationmonitors.net./

Ingestible event marker (Proteus):

- Ingestible microchip sensor device, activated upon ingestion
- Disposable body patch transmits to Bluetooth device
- >14,000 IEM ingestions recorded in adherence trials
- Positive detection accuracy of 99.3%, no adverse events

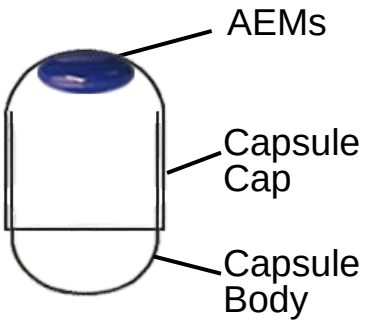
PHOTO: PROTEUS DIGITAL HEALTH

http://proteusdigitalhealth.com/

SMART® Adherence System

SMART® Medication

GRAS **flavorant** incorporated into a capsule as adherence-enabling markers (AEMs), generate exhaled drug ingestion markers (EDIMs)



Patient / Study Participant

Participant at home exhales into SMART® device

SMART® Device

Breath analysis proves ingestion; wirelessly reports adherence in real-time

Better Outcomes

Monitored call-back within minutes to participants who miss doses

Slide: courtesy of D. Dennis; Xhale, inc. 2012

Adherence monitoring of rings

- Ring adherence:
  - Ring are new, raise some concerns
  - Removals: sex, menses, to clean…
- ASPIRE MTN020:
  - Visual inspection @ return visit
  - Plasma drug PK (blinded)
  - Vaginal swab PK
  - Biofilm on rings (lab stage)
  - Residual drug in rings

SMART Diaphragm

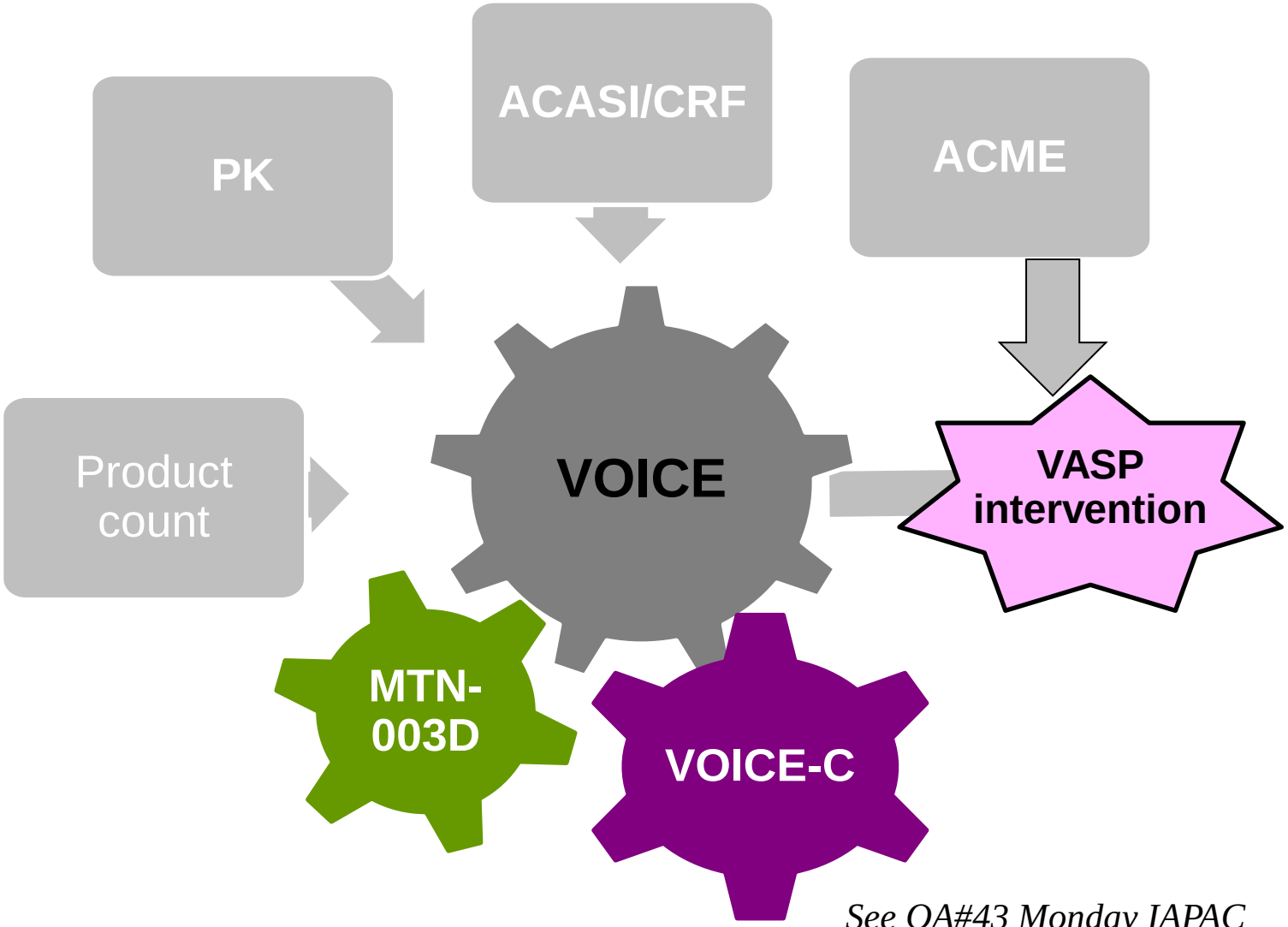
- Device can detect preterm birth earlier than current methods (in pilot phase)
- Measures collagen changes in the cervix
  - Electrodes to measure impedance
  - LED and photodiode to measure fluorescence
- Other adaptations possible: add sensors to a ring to monitor ring use. E.g. T^{o} monitor; pH sensor

L. Rand, personal communication 2013; Etemadi et al., 2013

3. Point of entry for targeted PrEP interventions

- **REAL time**: reminder tools+ targeted counseling
  - Wisepill/Wisebag
  - Other EMS with real-time signaling
  - IEM like breath taggants linked to “smart” system
- **NEAR time:** targeted counseling
  - MEMS
  - Unanounced Product Count
  - Applicator tests (e.g. VIRA, UVA)
- **Lagged time:**
  - Drug Level
  - Applicator tests (e.g DSA, combination tests)

4. Understanding (non-) adherence: VOICE and Ancillary Activities



See OA#43 Monday IAPAC

Summary/Conclusion

1. Adherence measurement
   - Objective measures can help interpret trial results
   - With accurate measures, we can:
     - Evaluate interventions to optimize adherence
     - Identify correlates of adherence (or its components)
     - Test and compare useability/utility of measures
   - Better measures should continue to be developed
     - Low cost and for use on site
     - Minimize burden to staff and participants
     - Able to distinguish the 4 components of adherence
     - Allow monitoring outside of trial setting

Summary/Conclusion (con't)

2. Understand adherence behavior:
   - Explain use/non-use in different populations
   - Identify modifiable factors to optimize adherence
   - Identify which component of (non-) adherence is most problematic
   - Tailor and optimize interventions
   - Develop more user-friendly products and dosage

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