# PREP Adherence Measurement

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Harvard Global Health Institute

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# PREP Adherence

- Achilles heel of biomedical prevention
- Measurement challenge: relationship between product and sexual exposure.
- New conceptual frameworks to enhance intervention effectiveness

# Interpretation of PrEP Adherence Requires Knowing Pattern of Dosing and Sexual Exposure

## Regimen: Monday, Friday and After Sex

| Day | M | T | W | Th | F | Sa | Su | M | T | W | Th | F | Sa | Su | M | T | W | Th | F | Sa | Su |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | | | | | | x | | | | x | | x | x | x | | | | | | x | x |
| Scheduled Dose | x | | | | x | x | | x | | x | | x | x | x | x | | | | x | x | x |
| Actual Dose | x | | | | x | x | | x | | | | | | | x | | | | | | |
| Adherence | | | | | | | | | | | | | | | | | | | | | |

Adherence 15/21 days = 71%

| Day | M | T | W | Th | F | Sa | Su | M | T | W | Th | F | Sa | Su | M | T | W | Th | F | Sa | Su |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | | | | | | | | | | | | | | | | | | | | | |
| Scheduled Dose | x | | | | x | | | x | | | | x | | | x | | | | x | | |
| Actual Dose | | | | | | | | | | | | | | | | | | | | | |
| Adherence | | | | | | | | | | | | | | | | | | | | | |

Adherence 0/21 days = 0%

Adherent  Nonadherent

# Measuring Adherence

Subjective Measures

- Patient interview
  - Pill recognition
  - 3, 4, 7, 30 day patient report
  - Visual-analog scale
  - Rating scale
  - Computer assisted self interview (CASI)
  - Telephone assisted

Objective Measures

- Electronic monitoring
- Unannounced pill count
  - Home or usual place of residence
  - Telephone *a la Kalichman*
- Pharmacy refill
- Drug/biomarker levels
  - Plasma
  - Cervical/vaginal lavage
  - Hair
  - Breath
  - Chips/lasers/magnets
- Mucosal applicator staining

AIDS Behav
DOI 10.1007/s10461-007-9261-4

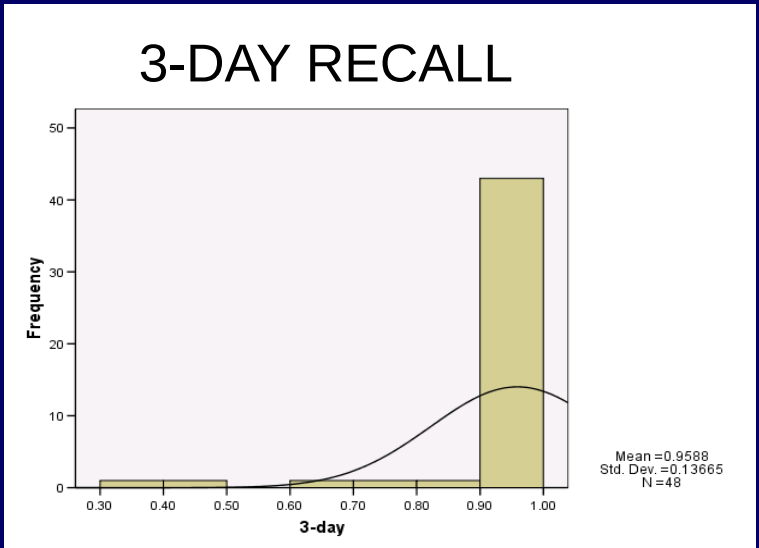
ORIGINAL PAPER

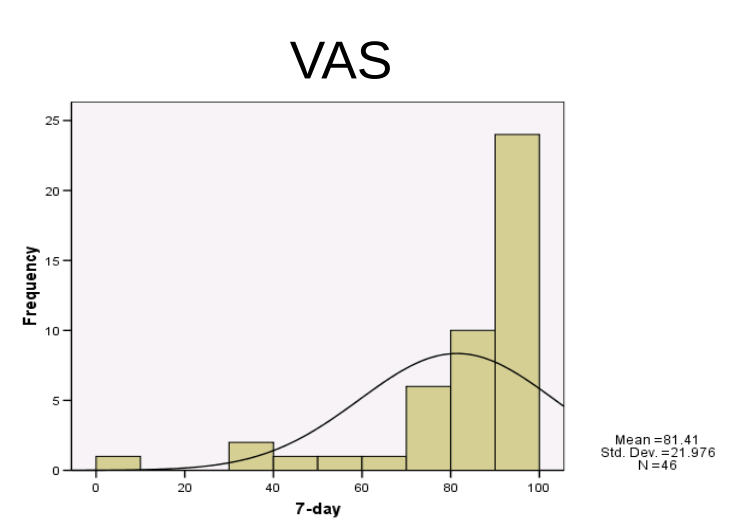
# Optimal Recall Period and Response Task for Self-Reported HIV Medication Adherence

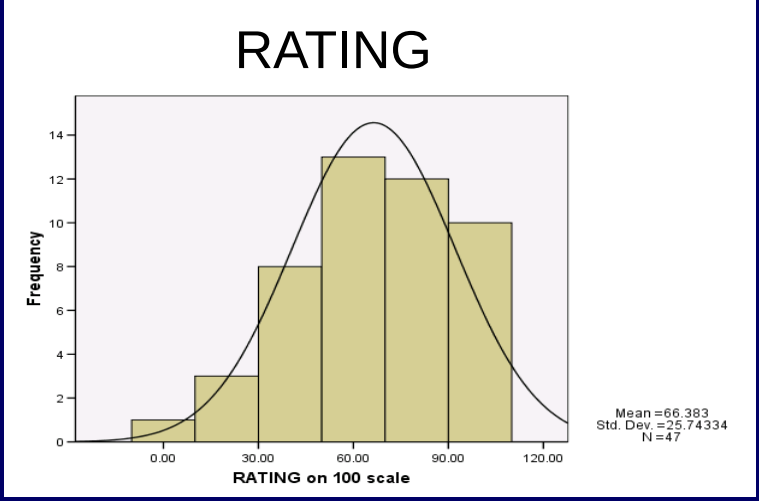
Minyi Lu · Steven A. Safren · Paul R. Skolnik · William H. Rogers · William Coady · Helene Hardy · Ira B. Wilson

Received: 2 October 2006 / Accepted: 15 May 2007

# Distribution of Response Items




**Rating: *Rate* your ability to take all your medications as prescribed" (6 categories: very poor, poor, fair, good, very good, and excellent**

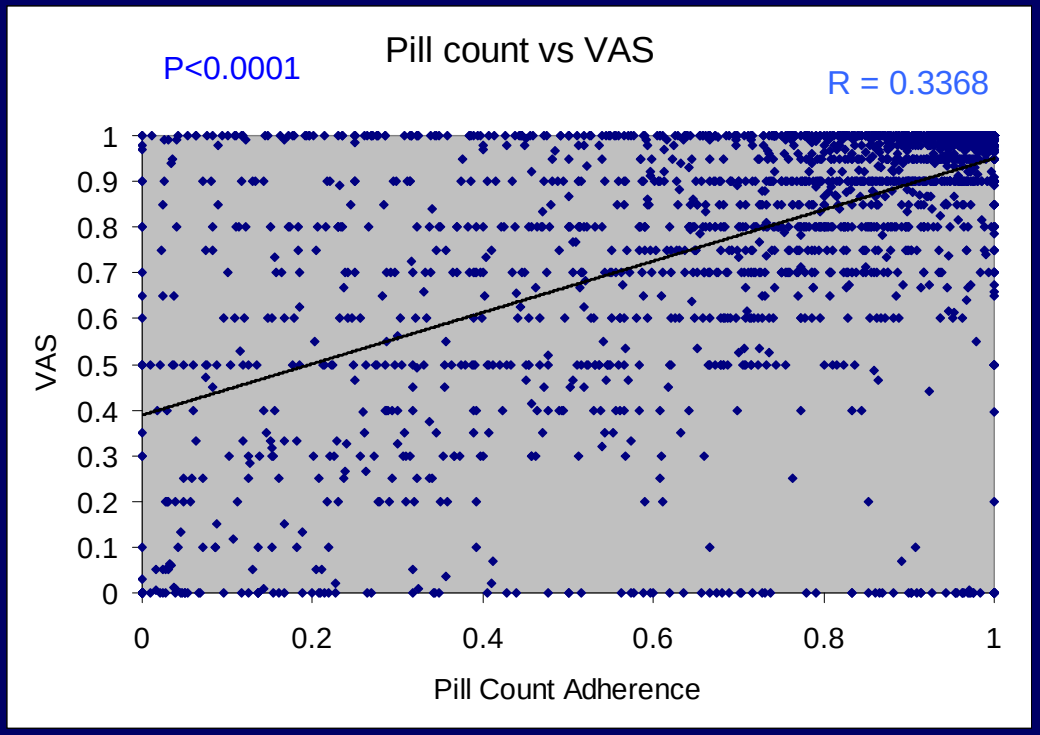
# IPREX Positive and Negative Predictive Value of Dedtectable Drug by Level of Self-reported Adherence Rivet Amico et al CROI 2011

| | Self-report Interview | Self-report CASI | Pill count | MPR | % |
|---|---|---|---|---|---|
| | N=179 | N=179 | N=179 | | N=179 |
| None missed (≥100%) PPV | 68% | 62% | 59% | >=1.25 PPV | 75% |
| 80-99% PPV | 58% | 66% | 64% | 1.0 – <1.25 PPV | 42% |
| >50-79% PPV | 64% | 43% | 56% | >0.50 – <1.0 PPV | 39% |
| <=50% NPV | 88% | 78% | 85% | <=0.50 NPV | 100% |
| Missing (or don't know) NPV | 81% | 83% | | | |

# Patient Interview vs Unannounced Pill Count

## 4729 observations in 345 patients (Bangsberg unpublished)

**30 Day Visual Analog Scale**




**Unannounced Home Pill Count**

# Self report

- Pros
  - Inexpensive
  - Monitors all medications
  - Can detect patterns
- Cons
  - Social desirability
  - Remembering what you forgot
  - Ceiling effect
  - Limited precision

# Interactive Voice Response/SMS Text

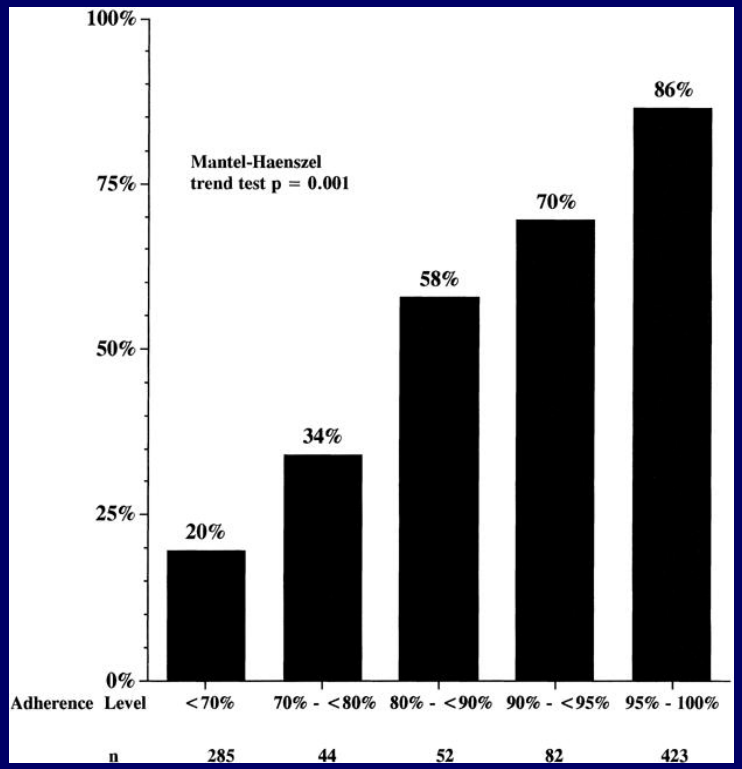
- Daily alcohol use, condom, and other frequent behavior *(Barta, AIDS Care, 2007, Rose JGIM 2010, Midanick Drug ETOH Rev 2010; Schroder Curr HIV/AIDS 2009)*
- Challenges confirming identify, does not remove social desirability bias *(Chang AIDS Patient Care STDS, 2008; Curioso BMC 2007; Abayomi Afr J Med Sci 2006,Haberer, AIDS Beh 2010)*

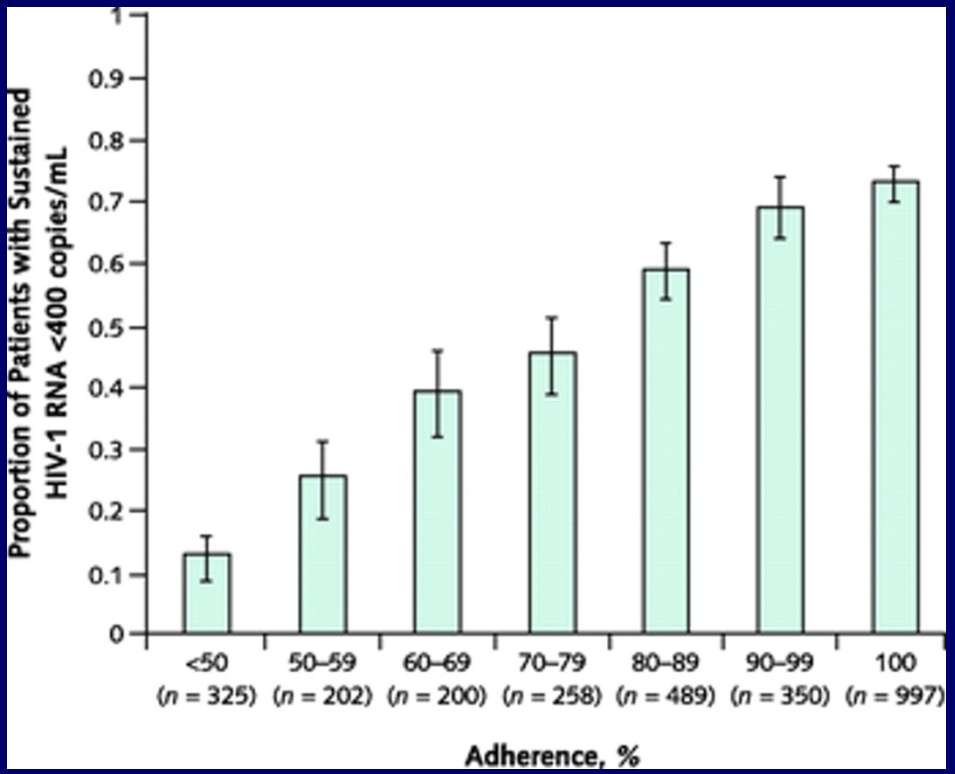
# Phone-based data collection

- Pros
  - Potential for use in remote areas
  - Automated and scalable
  - Potential for reduced social desirability bias
  - Allows for frequent data collection
  - IVR useful for illiterate participants
  - SMS convenient, popular with youth
- Cons
  - Requires cell phones and tech infrastructure
  - Subject to network availability
  - Initial start-up costs plus on-going fees
  - Technical literacy
  - Confirming correct patient identity in settings of shared/borrowed phones

# Pharmacy Refill Adherence Predicts Viral Suppression

## Gross Pharmacoepi 2005, Grossberg J Clin Inv 2004




Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. J Acquir Immune Defic Syndr. 2000 Apr 1;23(4):360-1.

**Nachega, J. B. et. al. Ann Intern Med 2007;146:564-573**

# Pharmacy Refill

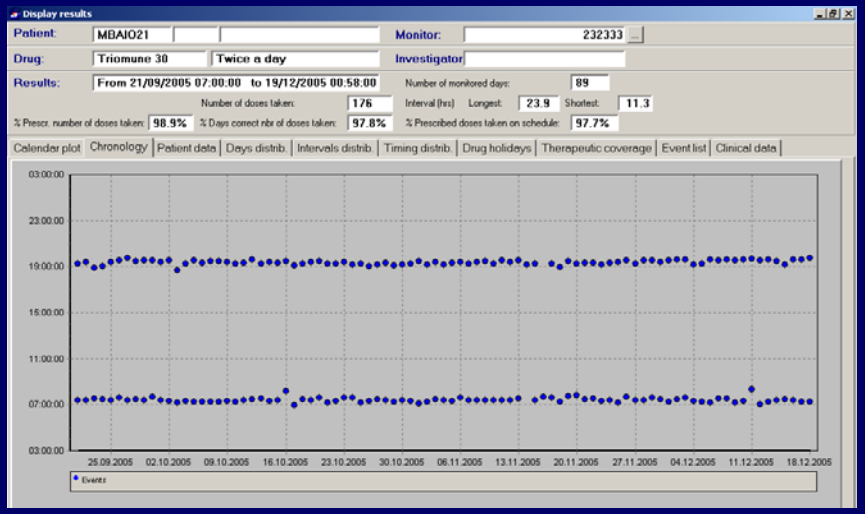
Strength

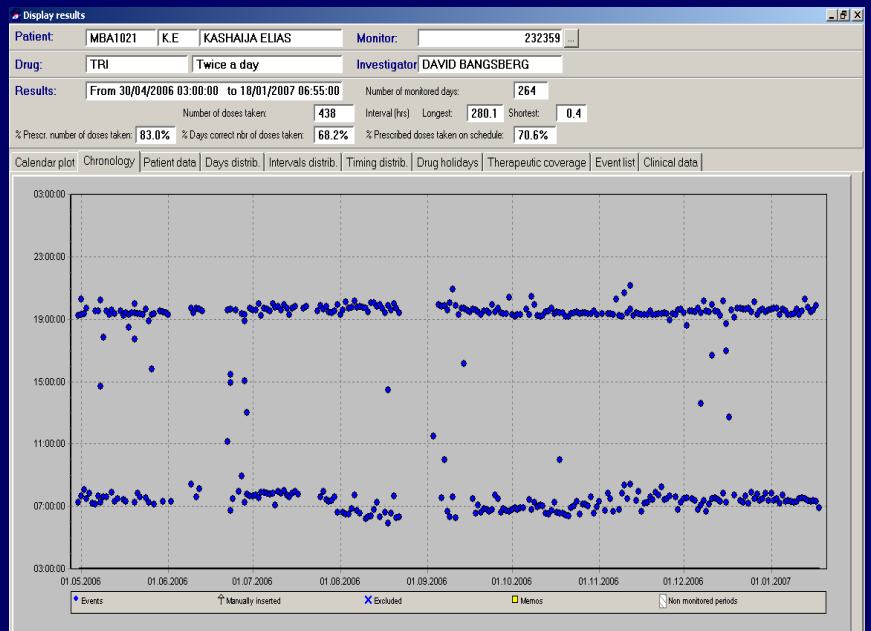
- Inexpensive
- Multiple meds
- Pill box organizer compatible
- Feasible in RLS

Weakness

- No patterns
- Detects maximum possible adherence
- Multiple medication sources jepordizes accuracy (Acri Aids Beh 2010)
- Pill take back in RLS

# Electronic Monitoring MEMS


Maier and Bangsberg PLOS March, 2006

# Real-time Adherence Monitoring Systems

Bangsberg JID 2008:3:272-8

Bangsberg and Deeks Ann Int Med;2010:152:54-6;

WISEPILL DISPENSER

PATIENT CELLPHONE

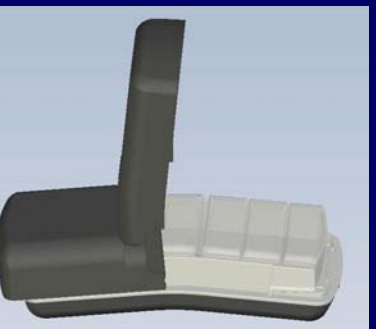
CAREGIVER CELLPHONE


**MESSAGE SENT WHEN DISPENSER IS OPENED**

**SMS**

WISEPILL CLIENT Report

WISEPILL WEB SERVER



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Entebbe
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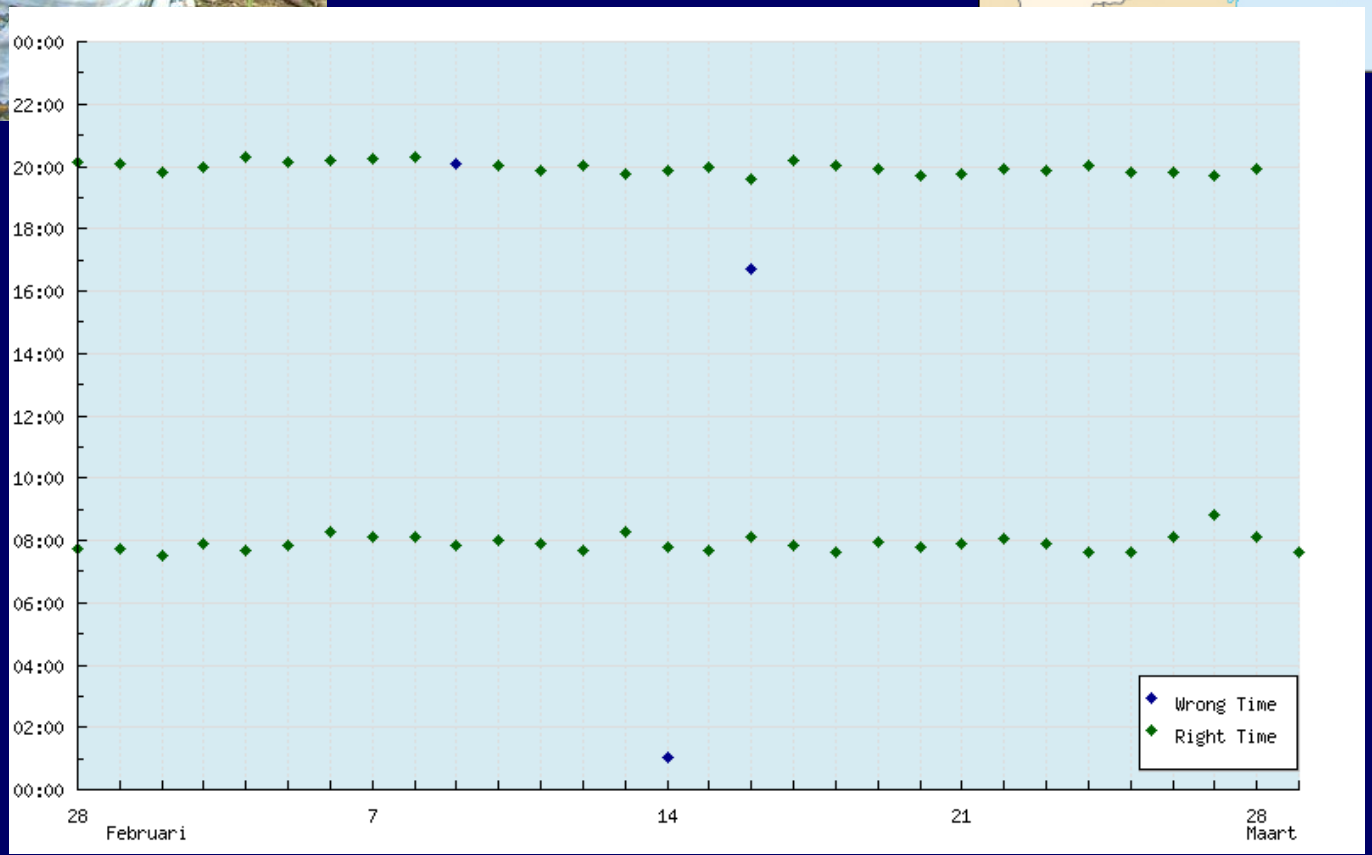
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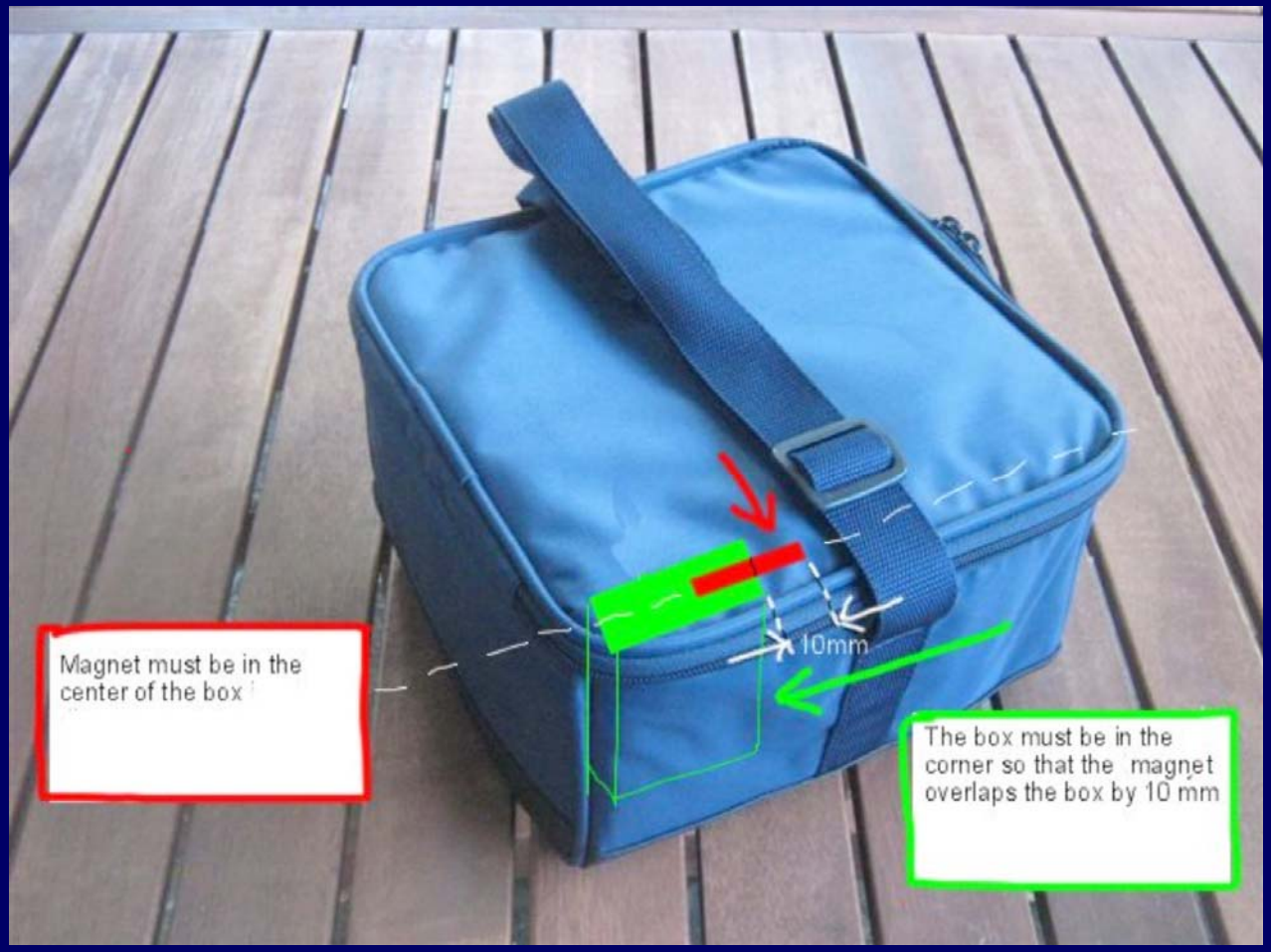
# Measuring Adherence to Microbicide Applicators Using Electronic Containers



# Electronic Monitoring

Strengths

- Precision
- Adherence patterns
- Real-time monitoring facilitates resolution of missed dose/device nonuse and intervention

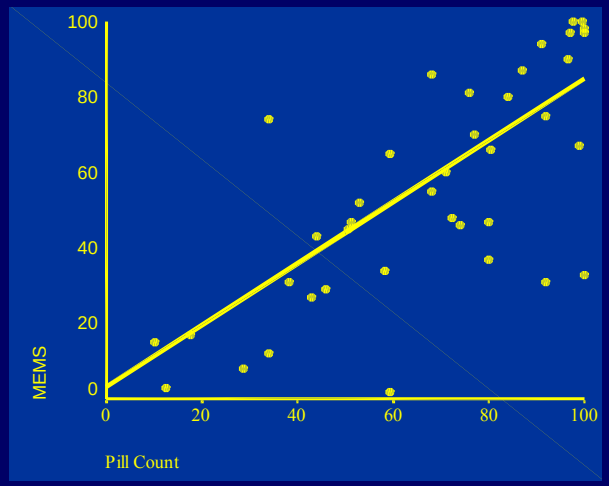
Weaknesses

- Nonadherence to meds or device?
  - Pocket doses
  - Curiosity events
  - Discontinuation
- Multiple bottles
- Pill box organizer compatibility
- Expense
- Loss/technical failure
- Power supply
- Pill capacity

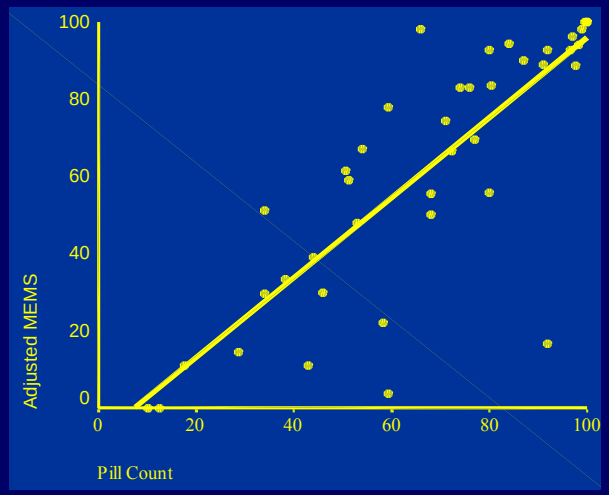
# Unannounced Home Pill Count


A 24 B
NONFICTION
327
327-328
A 25 B
NONFICTION
329-340
340-341

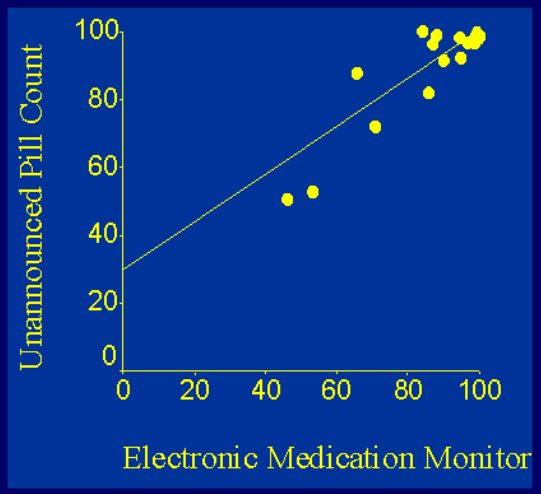
# MEMS vs. Unannounced Pill Count Adherence




Unadjusted MEMS (SF)

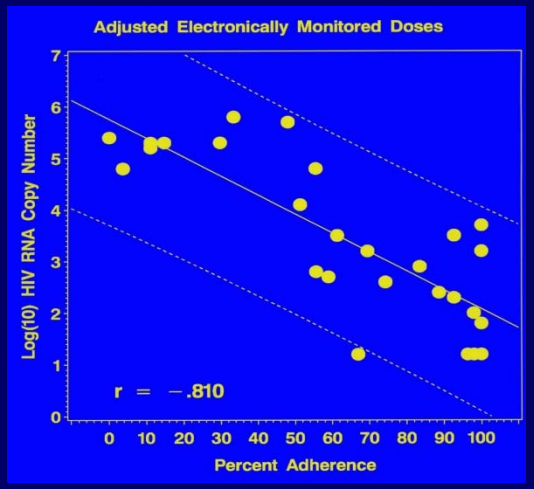



Adjusted MEMS (SF)

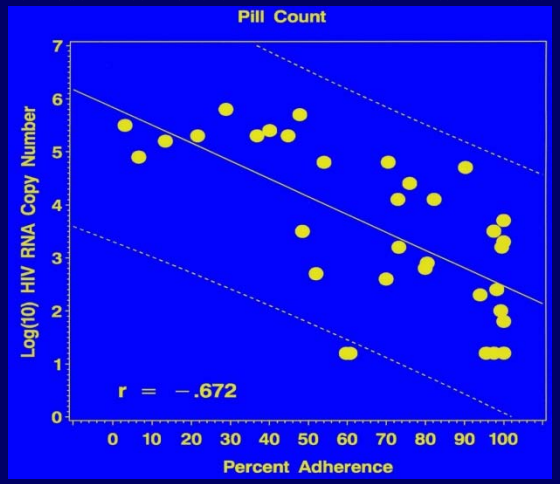



Adjusted MEMS (Uganda)

# MEMS/Unannounced Pill Count vs HIV Viral RNA




**MEMS**




**Unannounced Pill Count**

Bangsberg DR, et al. AIDS. 2000;14:357

Bangsberg et al AIDS and Behavior 2001:5:275-281

Oyugi et al JAIDS 2004 36:1100

# Telephone Assisted Unannounced Pill Counts

- Mobile phone-based unannounced pill counts compared to home-base pill counts in the US *(Kalichman JGIM 2008 and HIV Clin Trials, 2008)*
  - interclass correlation for the number of pills counted = 0.990-0.997, $p<0.001$
  - Kappa coefficient for adherence levels = 0.94
  - Does not increase adherence over time (*Kalichman in press*)

# Unannounced Pill Count

Strength

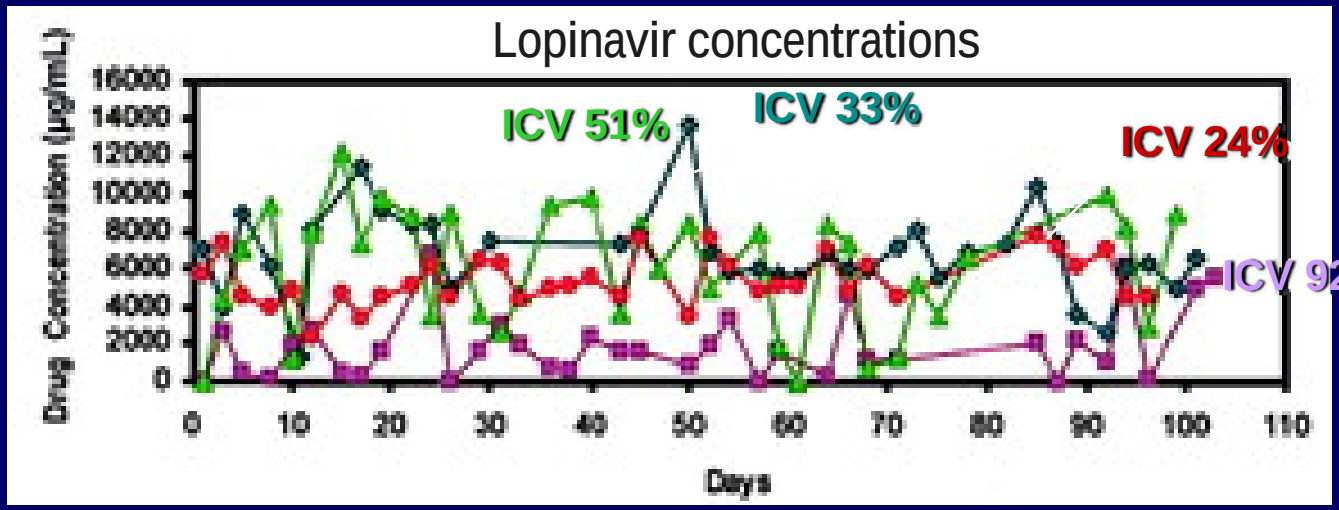
- Precise “average” adherence per month
- Multiple meds
- Consistent with pill box organizers
- Little differential missing data bias

Weakness

- Resource/personnel intensive
- Disclosure/privacy
- Pharmacy “take-back” in RLS

# Drug Levels

Nettles et al. Marked intraindividual variability in antiretroviral concentrations may limit the utility of therapeutic drug monitoring.CID. 2006 April 15;42(8):1189-96




Drug levels highly variable in suppressed patients (Nettles et al)

- 10 pts on HAART (≥3 months) - undetectable viral loads
- HIV RNA and drug level 3x/week same time/dose each day
- Intra-individual coefficients of variation 43% PI and 26% NNRTIs

# Drug Levels

Liechty et al. Are untimed drug levels useful predictors of adherence behavior? AIDS 2004:18:127

- 83 patients with drug level and concurrent unannounced pill count
- Drug levels poorly associated with unannounced pill count
- Absent drug level confirms <60% adherence
- High drug level does not confirm >60% adherence

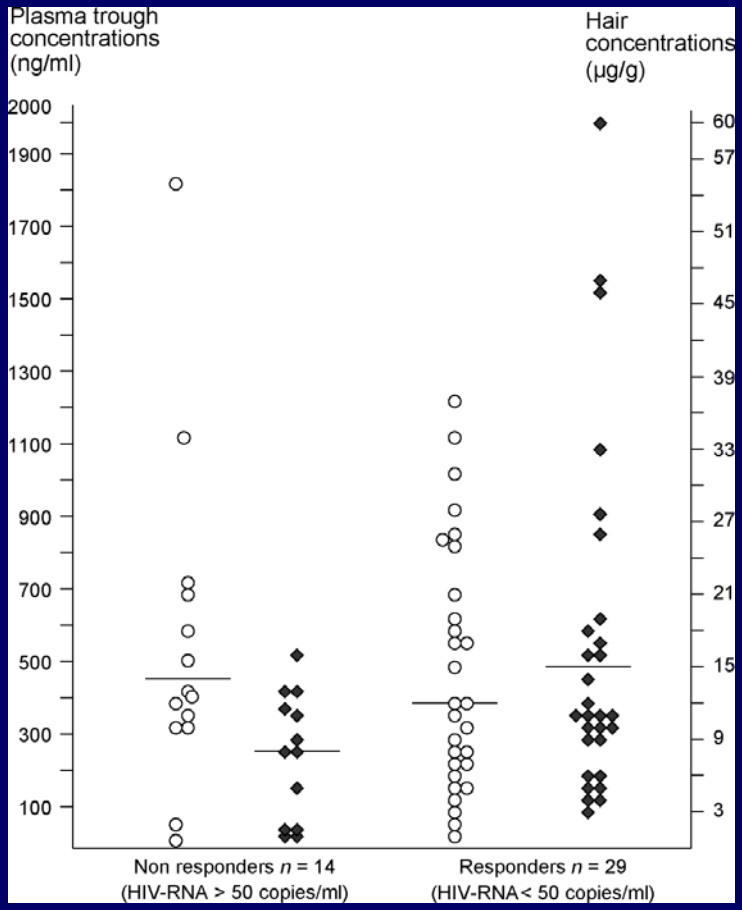
# White Coat Compliance Limits Therapeutic Drug Monitoring

Podsadecki et al HIV Clin Trials. 2008 Jul-Aug;9(4):238-46

- 190 pts on LPV/TNF/FTC with MEMS adherence for 96 weeks.
- PK collected for 768 visits
- Perfect adherence only in prior 3 days for 31% of PK visits

# ARV Levels in Hair
# Indinavir in hair vs plasma

- 43 pts on ~4 mo of IDV HAART
- Models with sex, baseline PI-naïve status, starting viral load, levels – only hair levels associated with virological success (OR 3.88 (1.01-14.94) – not plasma
- Analogous to Hgb A1C



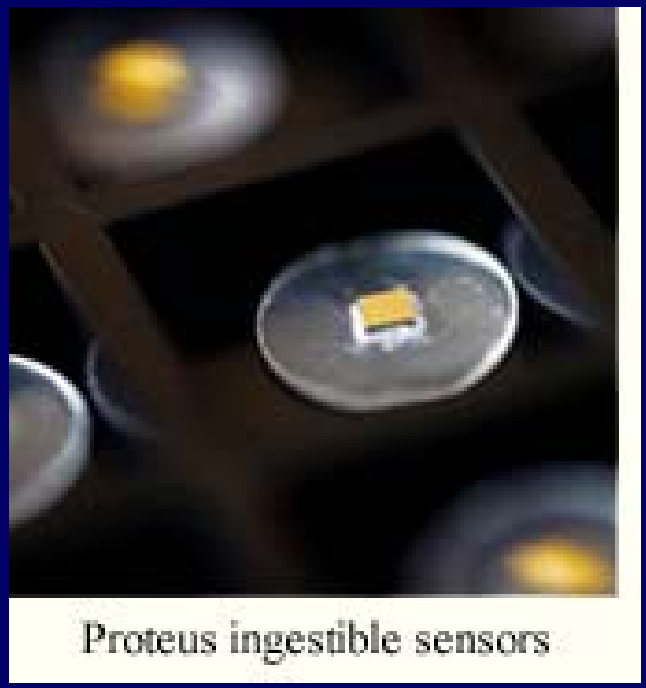

Duvall. AIDS 2007

# Drug Levels

- Pros
  - Objectively confirms ingestion
  - Accommodates multiple medications
- Cons
  - Conflation of biologic and behavioral variability
  - Little information on pattern of adherence
  - Subject to white-coat compliance

# Ingestible event markers*

- Metabolite detection
- ID-Cap
- MagneTrace
- ChipSkin
- Smart System
- Wristwatch



Proteus ingestible sensors

*Term coined by Jessica Haberer

# Ingestible Event Markers

- Pros
  - May confirm ingestion depending on strategy
  - Allows for tracking of individual medications
  - Accommodates multiple medications

- Cons
  - Requires a detection device and adherence to the adherence monitoring strategy
  - Requires collaboration with drug manufacturers
  - Potential concern about technology at the patient level

# Near Perfect Early Adherence to Antiretroviral Pre-Exposure Prophylaxis (PrEP) Against HIV Infection Among HIV-Serodiscordant Couples as Determined by Multiple Measures: Preliminary data from the Partners PrEP Study

**CROI 2011**

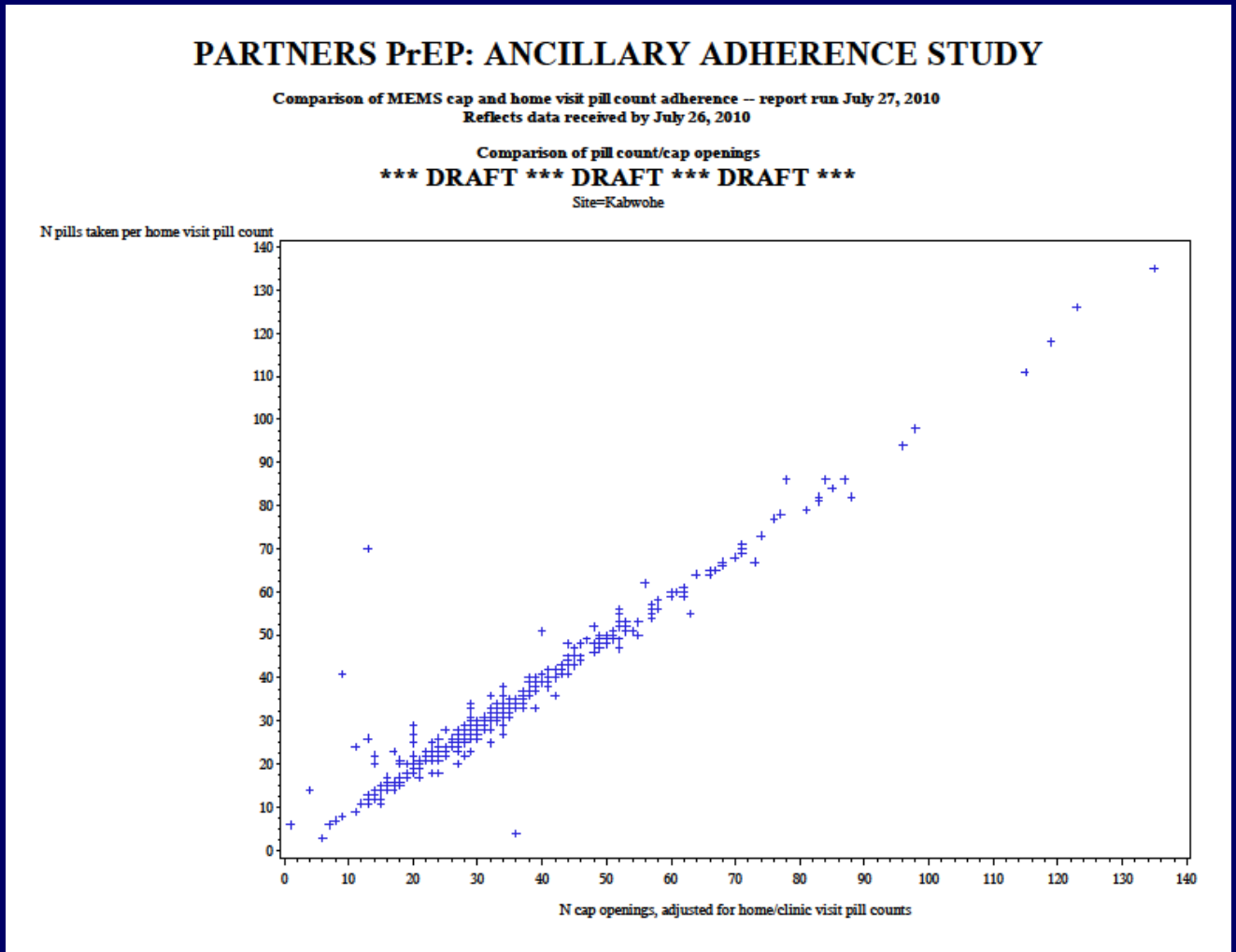
Jessica Haberer, Jared Baeten, Connie Celum, Elioda Tumwesigye[3], Elly Katabira, Meighan Krows, Lara Kidoguchi, Deborah Donnell, Andrew Mujugira, David Bangsberg

N=544

| | |
|---|---|
| Clinic-based pill counts | 99.6% (IQR 96.1-100.9) |
| MEMS | 101.9% (IQR 97.4-104.7) |
| Unannounced pill counts | 99.1% (IQR 97.2-100.0) |

**Additional measure: random home drug level in index and partner**

# Unannounced Pill Count vs MEMS in in Partners PREP Study



# Safety and adherence to intermittent Emtricitabine/Tenofovir for HIV pre-exposure prophylaxis (PrEP) in Kenya and Uganda

**Mutua, Sanders, Kamali, Kibengo, Mugo, Anzala, Grosskurth, Haberer, Bangsberg D, Barin B, Vooijs D, Verlinde C, Rooney, Fast, Berkley, Priddy**

**IAS 2010**

| Group | Dosing Schedule | Kenya (MSM/FSW) | Uganda (DC) |
|---|---|---|---|
| Daily | Fixed | 79% [61-95] | 96% [86-100] |
| Intermittent | Fixed | 75% [61-93] | 79% [68-82%] |
| | Post-coital | 0% [0-33] | 40% [30-67] |
| | Post-coital within 2 hrs | 100% [100-100] | 100% [100-100] |

# Using an Interactive Short Message Service (SMS) data collection system in an HIV Pre-Exposure Prophylaxis clinical trial in Uganda and Kenya

**Kamali , Mark, Haberer, Sanders, Mutua, Kibengo, Mugo, Anzala, Grosskurth, Burin, Bangsberg, Rooney, Lima, Fast, Berkley, and Priddy**

**IAS 2010**

| Response Rate (%) | | Daily FTC/TDF or placebo | Intermittent FTC/TDF or placebo | Total |
|---|---|---|---|---|
| **Kenya (n=68)** | Median (Unadjusted) | 23.3 | 30.2 | 24.7 |
| | Median (Adjusted for major SMS outages) | 27.8 | 35.7 | 29.4 |
| **Uganda (n=72)** | Median (Unadjusted) | 74.6 | 74.6 | 74.6 |
| | Median (Adjusted for major SMS outages) | 80.3 | 80.3 | 80.3 |

# HPTN 069

PI: Gulick; Protocol Co-chari Mayer and Wilken

**A Phase II Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Adherence of Maraviroc (MVC), Maraviroc + Emtricitabine (MVC+FTC), or Tenofovir/Emtricitabine (TDF/FTC) For Pre-Exposure Prophylaxis (PrEP) To Prevent HIV Transmission in At-Risk Men Who Have Sex with Men**

- **Adherence Measures:**
  - **Wisepill**
  - **Daily SMS of sexual exposure over 3 30 day assessments: Week 0-4, 20-24 and 44-48.**
    - **How many times did you have sex in the last 24 hours? 2) (if yes)**
    - **How many of these times did you use a condom?**
  - **Summary measure: % adherent sex acts dosing within 24 before/after exposure**
  - **Drug levels: blood, hair, and rectum**

# Conclusions

- Subjective
  - Memory limitation, social desirability
  - Ceiling effect
  - Qualitative over quantitative
  - Patterns and barriers
- “Objective” measures improve precision with tradeoffs in acceptability and cost
- Technological advances will increase feasibility of real-time monitoring and adherence case management to proactively prevent treatment failure

# Summary

- Participant report has unavoidable limitations
  - Memory limitation, social desirability
  - Ceiling effect
  - Qualitative over quantitative
  - Patterns and barriers
- Emerging methods and strategies improve precision and discrimination
- Wireless technology is appealing for the real-time information
- Detecting timing of dosing relative to sexual exposure remains a challenge

# Recommendation for Optimal PREP Adherence Measurement Today

- Real-time wireless container monitoring
- Daily SMS/IVR detection of sexual exposure over defined windows of observation, supplemented by timeline follow-back calendar recall
- Supplemented by random home-based plasma/cervical vaginal lavage drug levels.

# What's Love Got to Do With It?


**Courtesy Fran Priddy IAVI**

# Thanks to

- Jessica Haberer
- Connie Celum, Jared Baeten and team
- Fran Priddy
- Trip Gulick, Ken Mayer, Tim Wilkins
- Rivet Amico
- Norma Ware