



MASSACHUSETTS
GENERAL HOSPITAL

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HARVARD
MEDICAL SCHOOL

Adherence Monitoring - State of the Science and Future Innovations

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Conflicts of Interest

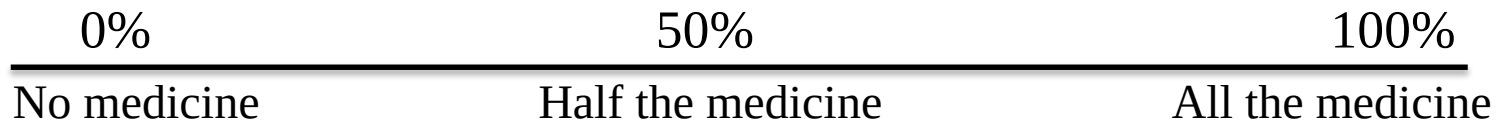
- I am/have been a paid consultant for the International AIDS Vaccine Initiative, the World Health Organization, and FHI 360
- I receive funding from NIMH, NIAID, and the Gates Foundation
- I partner with several technology companies, but receive no financial support from them

Outline

- Commonly used adherence monitoring measures
- Innovations in adherence monitoring
- Recommendations of what to use when and why

Self-reported adherence

- Standard assessment in clinical practice, trials, studies
- Formats
 - Doses missed or taken
 - Interruptions (e.g., consecutive doses missed)
 - Percent/visual analog scale



- Rating scales (poor, fair, good, etc)
 - Frequency (rarely, sometimes, often, always, etc)
- Recall periods typically 3, 7, or 30-days
- Interview in person or by phone, computer assisted (ACASI)

Memory and adherence

- We tend to remember specific events for a few days (e.g., breakfast)
- Beyond that, we remember patterns
(Wilson, Cur HIV/AIDS Rep, 2009)
- Goal with self-report is to “pull people off the ceiling”



Self-reported adherence

Pros

- Easy to collect
- Inexpensive
- Compatible with pill boxes

Cons

- Inaccuracy due to social desirability bias
- Infrequent data collection may lead to recall bias
- Differential response bias common
- Difficult to get patterns

Pill counts

- Mode of collection
 - Announced at clinic, pharmacy, or study visits
 - Unannounced
 - Home (*Bangsberg, AIDS, 2000*)
 - Phone (*Kalichman, HIV Clin Trials, 2008*)
- Percent adherence = $\frac{\text{pills dispensed} - \text{pill count}}{(\text{pills/day}) * (\# \text{ days})}$



Clinic-based pill counts

Pros

- Relatively easy to collect
- Inexpensive
- Compatible with pill boxes

Cons

- Inaccuracy due to social desirability bias (pill dumping)
- No patterns
- Potential for Hawthorne effect

Unannounced pill counts

Pros

- More likely to be truly objective
- Compatible with pill boxes

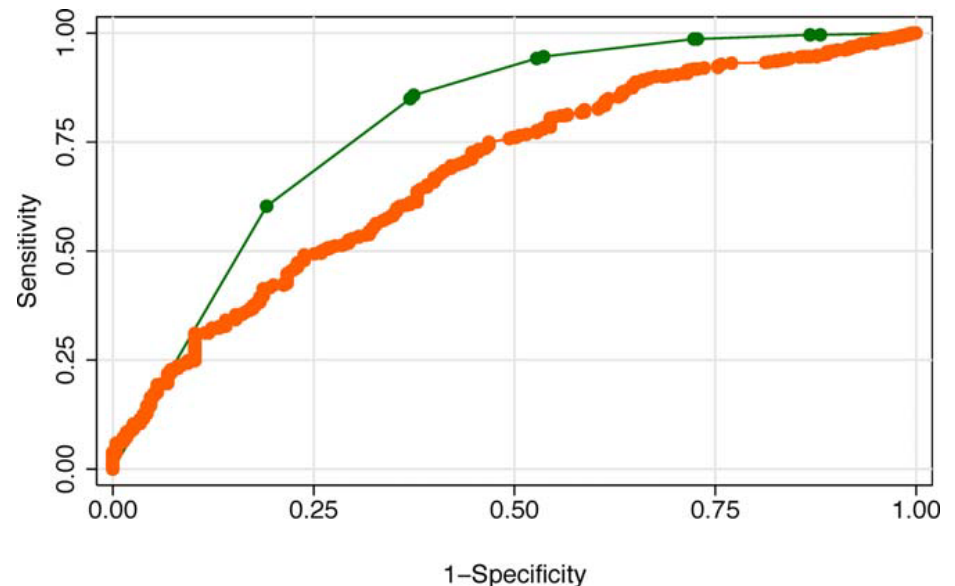
Cons

- May be logistically challenging and resource intensive
- No patterns



Pharmacy refill

- Percent adherence (medication possession ratio) =
$$\frac{\text{\# days (months) drug dispensed}}{\text{\# days (months) between the first and last dispensing}}$$
- Better predictor of viral suppression than CD4 count
(*Bisson, PLoS Med, 2008*)



Pharmacy refill

Pros

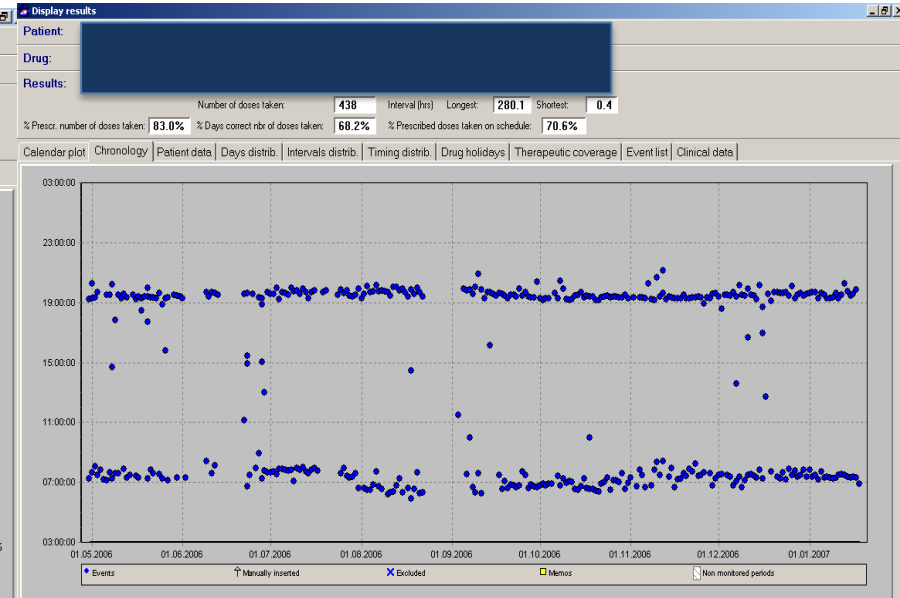
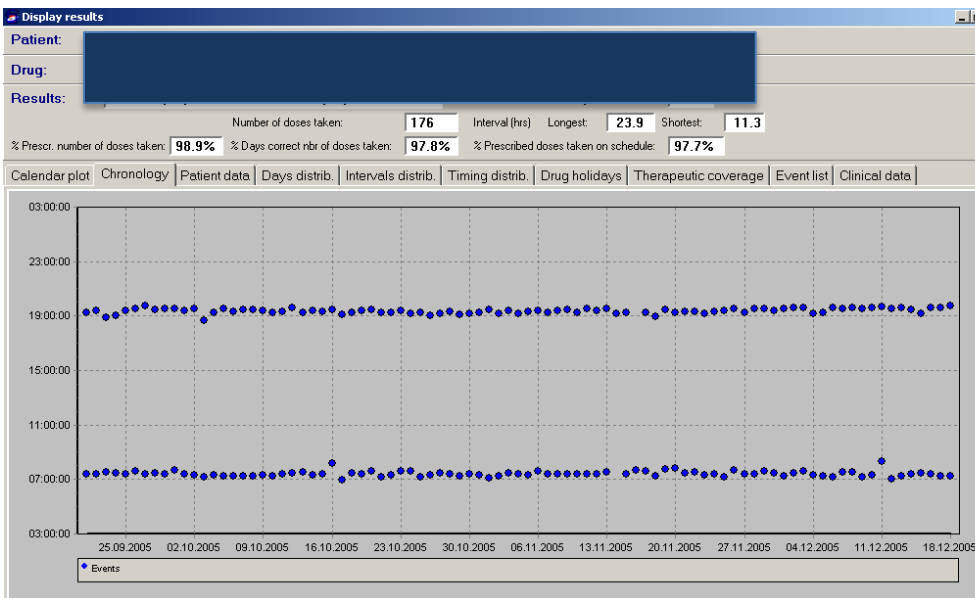
- Relatively inexpensive
- Potentially feasible in resource-limited settings
- Compatible with pill boxes

Cons

- Can be difficult to implement
- Only assesses maximal predicted adherence

Medication Event Monitoring System (MEMS)

- Used in >200 studies for >25 years
- Date-and-time stamp for each opening/closure
- Data downloaded via USB cable



Electronic monitoring

Pros

- Likely most objective measure of behavior
- Provides patterns of adherence

Cons

- Curiosity openings and pocket doses
- Requires adherence to the adherence measurement
- Potential for Hawthorne effect
- Expensive
- Not compatible with pill boxes

Drug levels

- May be performed in
 - Plasma
 - Peripheral blood mononuclear cells (PBMC)
 - Red blood cells (RBC)
 - [Hair]
- Provide periodic, summary measures of varying time periods

Drug levels

Pros

- Objective
- Distinguish adherers from non-adherers
(*Donnell, JAIDS, 2014*)

Cons

- Potential for Hawthorne effect
- Expensive
- Require specialized lab capacity
- Subject to biological and behavioral variation
- Blunt measure (*Liechty, AIDS, 2004*)



HIV/RNA

Pros

- Objective
- Indicate adequate adherence

Cons

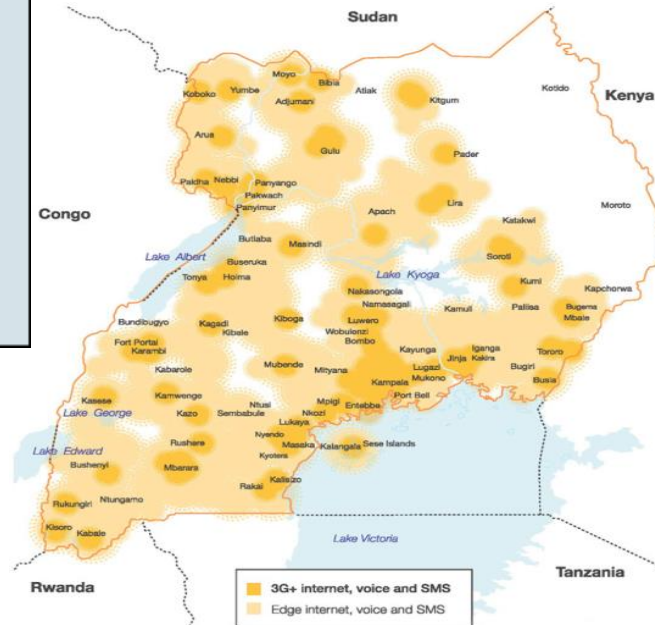
- Expensive
- Typically done infrequently
- Does not reveal adherence challenges that may ultimately lead to viral failure

Cell phones

Cell phones are nearly ubiquitous



stay in touch with over 1,000,000 people
across Uganda on the best network at the best rates



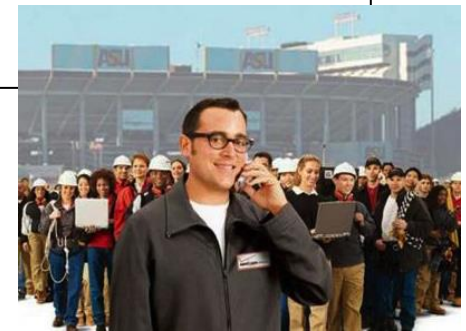
Cell phones

Pros

- SMS and IVR
- Convenient
- Frequent data collection
- Relative anonymity

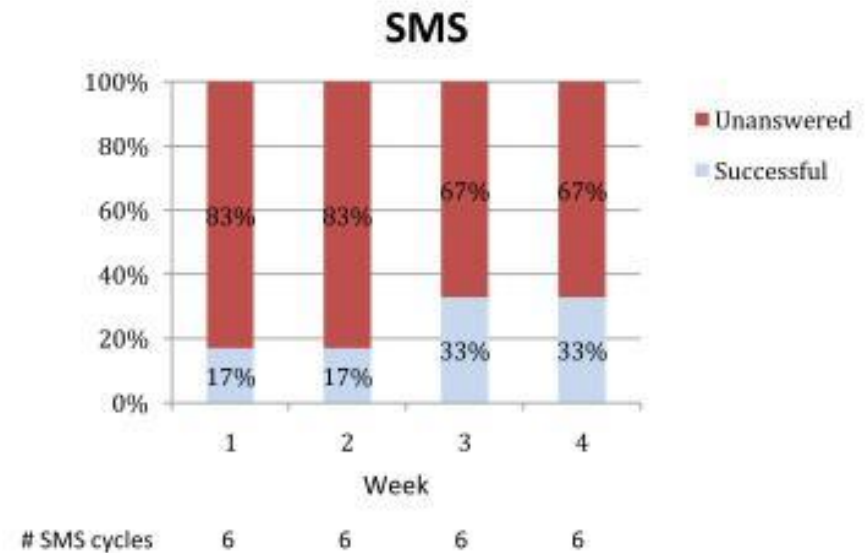
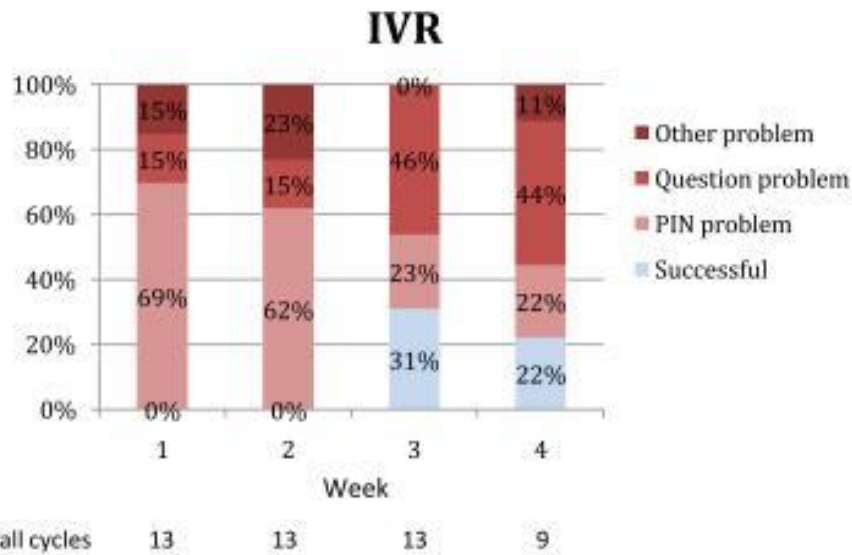
Cons

- “Can you hear me now?”
- Variable understanding of expected responses
- Literacy
- Shared phones
- Low battery, powered off
- Participant availability
- Cost



Feasibility

- Study of weekly IVR/SMS queries of missed doses of ART among in southwestern Uganda



(Haberer, AIDS Behav, 2010)

More on feasibility

- 75% of US participants (N=44) retained in a 90-day daily IVR survey of sexual behavior; 97% of surveys completed (*Schroeder, Curr HIV/AIDS Rep, 2009*)
- Mean 50% weekly IVR reports completed by US substance users (N=50) (*Tucker, AIDS Patient Care STDS, 2013*)
- Response rates for daily SMS on PrEP adherence/sex
 - 74% for couples in Uganda (*Kibengo, PLoS One, 2013*)
 - 23% for MSM and FSW in Kenya (*Mutua, PLoS One, 2012*)

Getting easier

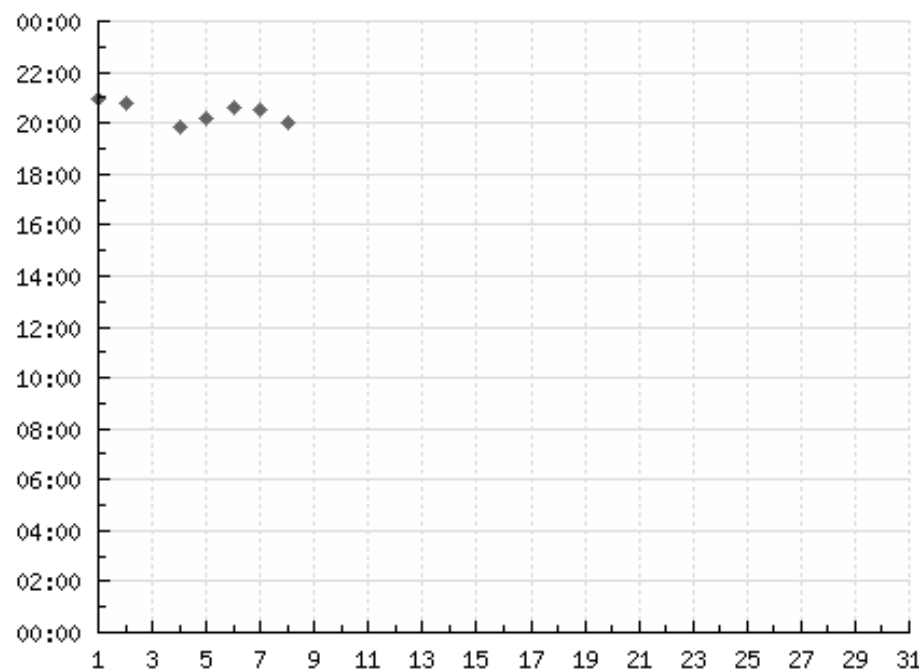
- Successful responses
 - Weekly queries of missed doses among adults and children in southwestern Uganda (*Haberer, AIDS, 2013*)
 - ~85% by SMS
 - ~70% by IVR
 - Periodic daily queries of PrEP adherence and sexual behavior in Uganda and Kenya
 - ~75% by SMS (*Haberer, poster #316*)
- Differences: just-in-time training, accounting for anticipated problems and difference in phones

Wireless electronic adherence monitors



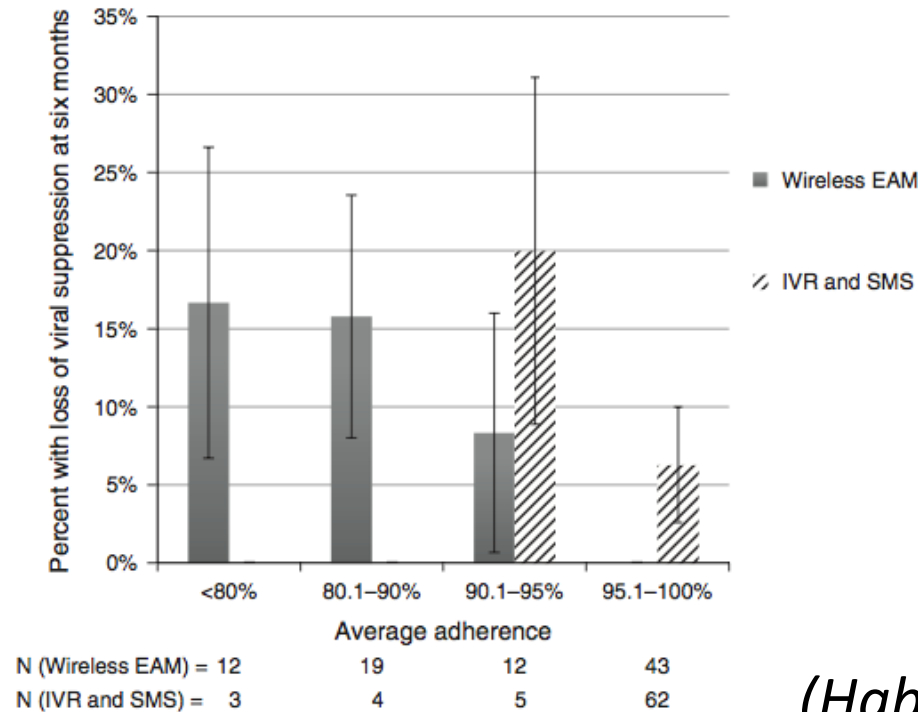


Real-time data



Validity

- Wisepill and IVR/SMS-report in southwestern Uganda



(Haberer, AIDS, 2013)

- Loss of viral suppression was associated with wireless EAM ($p=0.02$), but not IVR/SMS-report ($p=0.54$)

Acceptability and the Hawthorne effect

- Wisepill currently involved in 25+ studies
- Wisepill acceptability varies by setting
 - High in Uganda (*Haberer, AIDS Behavior, 2010*) and South Africa/Wisebag for gel applicators (*van der Straten, AIDS Behav, 2013*)
 - Mixed in China/concern for unintended disclosure (*Bachman, AIDS Res Treat, 2013; Sabin Abstract #369*)
- Greater adherence with Med Signals compared to control ($p < 0.001$); (*Ryder, Am Geriatr Soc Mtg, 2008*)

Detection of viremia in real time

- 447 individuals on ART in southwestern Uganda
(R01MH098744; PI: Bangsberg)
- Routine HIV RNA every 4 months
- Adherence lapses >48 hours investigated
- HIV RNA determined during the adherence lapse

	Univariable	Multivariable
	OR (p)	OR (p)
Duration of lapse (days)	1.27 (p=0.004)	1.27 (p=0.025)
Duration of viral suppression (years)	0.71 (p=0.071)	0.53 (p=0.007)
30 day adherence (10% increments)	0.75 (p=0.035)	0.81 (p=0.19)
Baseline viral load (at ART start) /1000	0.99 (p=0.55)	--
Regimen - NVP	(ref)	(ref)
EFV	0.20 (p=0.020)	0.06 (p<0.001)

(Haberer, CROI 2013)

Considerations with wireless electronic adherence monitors

Everything with MEMS plus

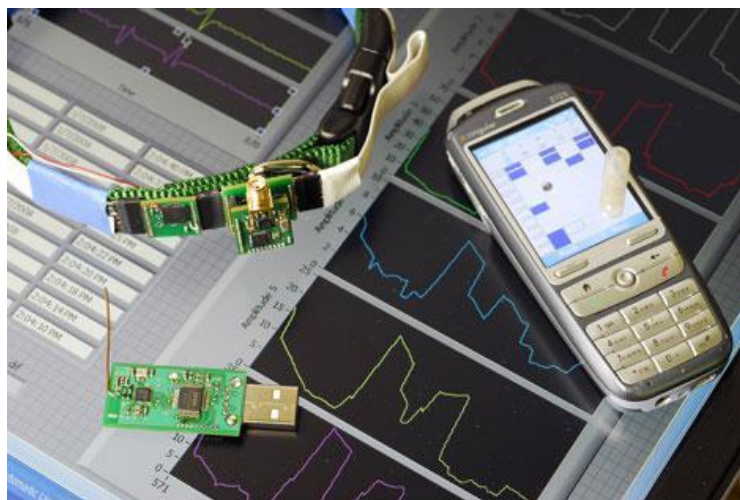
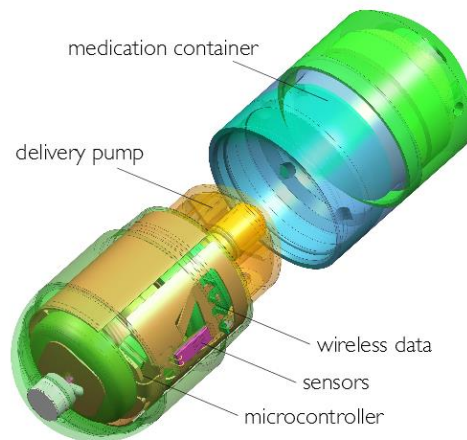
Pros

- Capacity for real-time data/intervention
- Reduced data loss

Cons

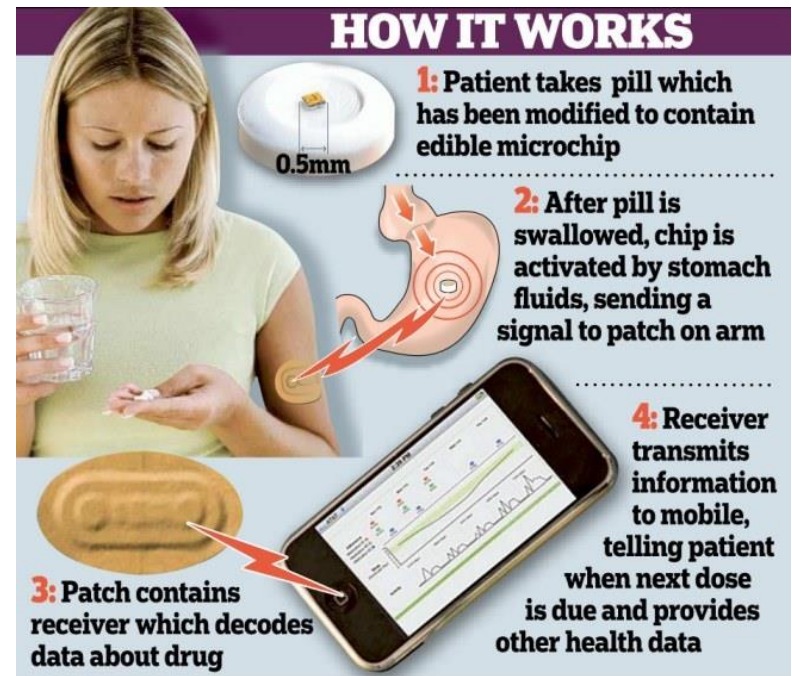
- Cost
- Increased data management
- Cellular reception
- Batteries, SIM cards
- Potential for unintended disclosure
- Hawthorne effect may be high

Ingestion event monitors



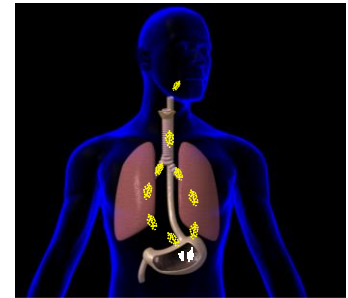
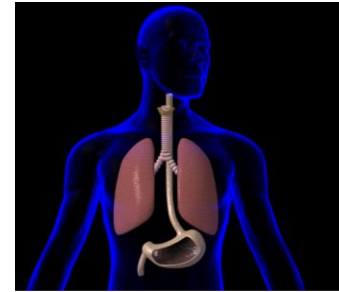
Edible tracers

- Helius
- Intellicap
- MagneTrace
- Helius (Proteus Digital Health)
 - Sensitivity 97%, specificity 98% compared to DOT (*Au-Yeung, Wireless Health, 2010*)
 - Feasible for 4-weeks of monitoring in 28 US individuals with mental health disorders (*Kane, J Clin Pschy, 2013*)
 - Accurate/feasible for TB treatment in US (N=30) (*Belknap, PLoS One, 2013*)
 - Also monitors heart rate, temperature, activity



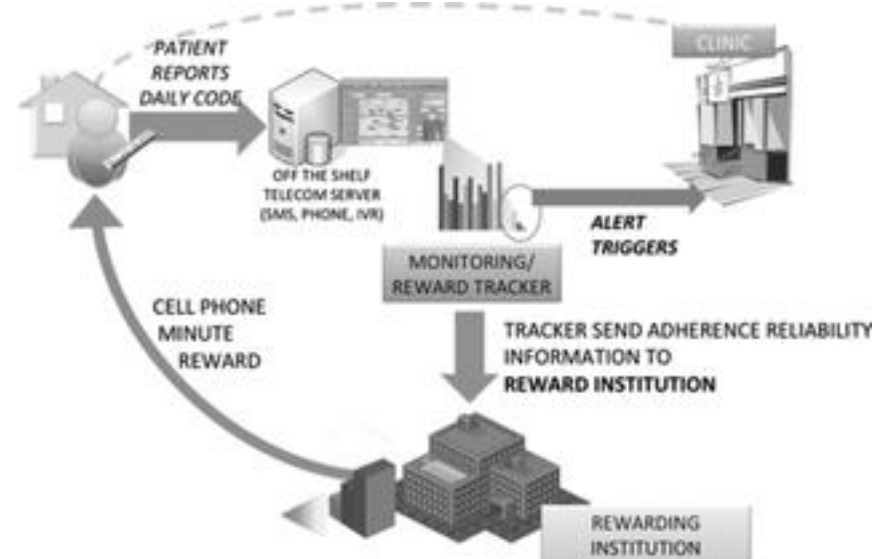
Taggants

- Drugs marked with an inert detectable taggant
- Adherence measured through breath test
- Xhale
 - Reminders sent to breathe into the device
 - Taggant recorded and transferred via USB for adherence management
- Ester taggants for vaginal gel use shown to be feasible among 8 US women (*Morey, J Clin Pharm, 2013*)



Metabolite detectors

- Adhere.IO (a.k.a. XoutTB)
- “Behavioral diagnostic”
- Urine metabolite
- Text in unique code with incentive for response
- Evaluated in Pakistan



Ingestion event monitors

• Pros

- Objective documentation of ingestion
- Detect adherence patterns
- Real-time data

• Cons

- Requires adherence to an adherence monitor
- May be disconcerting ethically
- Logistics of repackaging or use of 2nd pills
- Limited publications



Google Glass?



Will we be able to watch people taking their medication every day?

Drug levels in hair



Photo courtesy of M. Gandhi

- Surpassed any other predictor of virologic outcomes in WIHS; Hair ATV in the highest quintile had OR 59.8 (*Gandhi, Clin Infect Dis, 2011*)
- Phase 1 PK study showed 76% increase in hair level per 2-fold dose increase in frequency of dosing (*Liu, PLoS One, 2014*)
- Acceptability largely high, although challenges seen with some populations (*Olds, submitted; Hickey JAIDS 2014*)

Drug levels in hair

• Pros

- Simple to collect
- Store at room temperature
- Process in central lab
- Summary measure of adherence over time

• Cons

- Cost of processing
- No patterns
- Metabolism may be variable
- Potential challenges with sample collection

Ethics of novel adherence monitoring strategies

- Privacy
- Confidentiality
- Autonomy
- Dependence
- Ancillary care obligations

R21AI108329 (PI: Haberer, Eyal)

Recommendations

- Choice of measure depends on resources and goals (*Williams, AIDS Behav, 2012*)
 - Easy of use
 - Expense
 - Capacity
 - Goals of measurement
- Self-report is too unreliable to be your only measure
- Drug levels or HIV RNA do not provide enough information about behavior to be your only measure

Recommendations

- Use multiple measures, including 1+ objective measures
- “I have no money, but really want to know about adherence...”
 - Pharmacy refill, if closed system
 - Consider reprioritizing funds
 - Consider objective measures in at least a subset

Recommendations

- Real-time monitoring makes sense when you need data in real-time
- Ingestion event monitors aren't ready for prime time, but may be a viable tool in the future

Acknowledgments

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