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Actionable Adherence Monitoring: Technological Methods to Monitor and Support Adherence to Antiretroviral Therapy

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Abstract

Purpose of Review: Current digital technologies being used for "actionable adherence monitoring"; that is, technologies that can be used to identify episodes of non-adherence to ART in a timely manner such that tailored interventions based on adherence data can be provided when and where they are needed most.

Recent findings: Current digital communication technologies used to monitor ART adherence include electronic adherence monitors (EAM); digital ingestion monitors; cellular phones; and electronic pharmacy refill tracking systems.

Summary: Currently available real-time adherence monitoring approaches based on cellular technology allow for the delivery of interventions precisely when and where they are needed. Such technology can potentially enable significant efficiency of care delivery and impact on adherence and associated clinical outcomes. Standard digital advances, such as automated reminders in EAM and electronic pharmacy records, may also achieve improvements with relative lower cost and easier implementation. Future research is needed to improve the functionality of these approaches, with attention paid to system-level issues through implementation science, as well as acceptability and ethical considerations at the individual level.

Keywords

actionable adherence monitoring; HIV/AIDS; antiretroviral therapy; real-time electronic adherence monitoring; digital ingestion monitoring; cellular phones; electronic pharmacy refill

Introduction

Of the approximately 36.7 million people worldwide living with HIV, 20.9 million were accessing antiretroviral therapy (ART) by June 2017 [1]. Although this figure is a major increase from 7.7 million people in 2010, access to treatment alone is insufficient to meet

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Conflict of Interest

Kate M. Bell declares no conflict of interest.

Human and Animal Rights and Informed Consent

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UNAIDS 90–90–90 targets calling for rapid scale-up of engagement in HIV care to end the epidemic by 2030 [2]. Sustained adherence to ART is critical for achieving and maintaining the viral suppression that allows individuals living with HIV to lead healthy, productive lives and reduce the risk of HIV transmission to others [3, 4]. The level of adherence required to achieve optimal immune function and viral suppression varies depending on regimen and duration of viral suppression [5]; however, consistent dosing over time is necessary to realize the benefits of ART [6, 7]. For most people living with HIV, however, adequate adherence to sustain viral suppression over a lifetime remains a major challenge. Even patients with typically excellent adherence will likely experience treatment interruptions due to disruptions in their daily routine, relapse of substance use or mental illness, or simple pill fatigue [8]. Accurate, feasible, and acceptable methods for adherence monitoring are needed so that support can be provided when needed.

Typical methods to monitor ART adherence include structured patient interviews (also known as self-report), pill counts, and pharmacy refill, which are often associated with overestimates of adherence when compared to more objective measures, thus potentially leading to undetected nonadherence [9]. Furthermore, these methods are employed on an intermittent basis, usually when individuals present to facilities for care, such that missed doses are detected several weeks to months after they occur. Any necessary adherence interventions may therefore not be initiated prior to viral replication, which can lead to treatment failure and drug resistance. This delay may contribute to limited improvements in adherence with many interventions over time [10].

The objective of this commentary is to summarize current digital technologies being used for “actionable adherence monitoring” [11]. That is, these technologies can be used to identify episodes of non-adherence to ART in a timely manner such that tailored interventions based on adherence data can be provided when and where they are needed most. We reviewed the current literature through a search of PubMed and Google Scholar, as well as reviewed ongoing trials through ClinicalTrials.gov. “Adherence” is defined here as medication initiation (i.e., taking the first dose); execution (i.e., taking each subsequent dose as prescribed); and persistence (i.e., continuing therapy without prolonged gaps in, or cessation of treatment) [12]. While we primarily focus on the use of technology for measuring adherence to ART, we also draw from other relevant lessons learned from measuring adherence to medication for other illnesses, such as tuberculosis. Current digital communication technologies used to monitor ART adherence include electronic adherence monitors (EAM); digital ingestion monitors; cellular phones; and electronic pharmacy refill tracking systems (Table 1) [13].

Electronic Adherence Monitors (EAM)

Standard Electronic Adherence Monitors—The first well-known EAM was the Medication Event Monitoring System, or MEMS. Developed over 25 years ago, this monitor consists of a specialized bottle cap that contains a microelectronic switch, a clock, and a memory chip. The cap fits on multiple standard and large-sized medication bottles. Each opening and closing of the MEMS cap records a time and date stamp that is stored and later downloaded to a computer via a USB cable [14]. Other standard EAM have included Med

eMonitor [15] and Medsignals [16]. These devices allow assessment of dose-by-dose pill taking behavior, providing patterns of adherence. These patterns are particularly important for ART, as consecutive missed doses greatly increase the risk for viremia compared to occasional missed doses [17, 18]. Standard EAM are also simple to use, typically with a long-lasting battery life.

A review and meta-analysis of traditional EAM interventions in 79 randomized controlled trials (RCTs) of multiple medical conditions showed that feedback to patients about their dosing patterns was the largest factor in influencing adherence behavior [19]. Day-to-day dosing patterns can be used to inform counseling sessions, so that appropriate interventions can be applied in appropriate circumstances—an approach called "data-informed counseling" [20]. For example, a counselor can use motivational interviewing techniques [21] to understanding what happened on specific days when the monitor indicated no pills were taken. This information can then be used to ideally prevent similar situations in the future.

These important data, however, can only be accessed for analysis when an individual comes into a clinic, thus introducing a delay between knowledge of the lapse(s) and potential intervention. Another significant limitation of the MEMS cap is that it can only be used with a single bottle preventing the ability to monitor multiple medications with a single dose [14]. Device non-use or mis-use can also lead to misclassification bias[20]ndividuals may remove multiple pills at one time for later dosing (called "pocket dosing"), resulting in falsely low adherence estimates. Additionally, individuals may open the monitor without taking medication (called "curiosity openings"), resulting in falsely high adherence estimates [22].

Recently, reminders have been added to a standard EAM and studied for the treatment of tuberculosis, as an alternative and potential improvement on directly observed therapy [23]. An RCT in China compared EAM with audio reminders for delayed or missed doses alone, scheduled SMS alone, and EAM with reminders plus scheduled SMS, compared to a control of standard care [24]. Clinicians also reviewed data at monthly follow-up visits to provide data-informed counseling. The study found that EAM with audio reminders improved adherence in TB patients with or with scheduled SMS reminders; SMS reminders alone did not [24]. While encouraging, battery problems were common, and clinicians did not always follow-up on non-adherence. A low-cost version of this type of EAM is being rolled out for treatment of multidrug resistant TB in India [25]; similar devices could be considered for ART delivery.

Real-time Electronic Adherence Monitors—Real-time EAM function similarly to standard EAM, but are equipped to transmit data to a central server via cellular networks. These devices thus allow for real-time monitoring between routine clinic visits and the potential for delivery of adherence interventions precisely when they are needed. Real-time EAM can be linked to a variety of means of communication, such as live phone calls, text messages, and/or emails, through which data-informed counseling or other interventions can be delivered. The intervention can be sent to the patient directly, as well as to friends and family members ("social supporters"), health-care providers, and/or researchers [14]. Some real-time EAMs also have built in audio and/or visual reminders. The wide availability of

cellular networks globally makes real-time electronic dose monitoring a feasible and promising tool to measuring and responding to medication nonadherence [26–28]. Acceptability is generally high, although concerns have been found in marginalized populations for whom the device may result in unintended disclosure of HIV status [29, 30]. While real-time EAM exhibit several advantages over traditional EAM, several challenges remain. The need to keep the cellular phones and/or EAM charged with electricity, gaps in available network coverage, and low education and literacy levels in many target populations all limit the potential impact of these interventions [31]. Real-time EAM also have the same challenges of device non-use and misuse, as noted above for standard EAM.

Evidence on the impact of real-time EAM and associated interventions is mixed. An RCT in China that combined SMS reminders triggered by delayed or missed doses with data-informed counseling found significantly improved ART adherence, particularly among those with suboptimal (less than 95%) adherence at baseline [29]. A similarly designed study in South Africa found SMS reminders reduced duration of the non-adherence, but did not significantly improve overall adherence or viral suppression [32]. Unlike the trial in China, however, the trial in South Africa enrolled participants at ART initiation, so baseline adherence was unknown. Data-informed counseling was also provided to participants in both the control and intervention arm. Neither study was powered for impact on viral suppression. In another South African study, short-term use of real-time EAM with reminders for delayed or missed doses plus intensive counseling was assessed for patients failing second line ART and compared with historical controls with intensive counseling alone; the benefit in adherence and viral suppression was modest [33].

Another RCT in Uganda tested both scheduled (daily for one month, followed by weekly for two months) reminders and reminders triggered by delayed or missed doses combined with real-time EAM; counseling was not informed by the EAM data [5]. This trial found improved adherence and a decrease in treatment interruptions only with scheduled reminders. Participants reported the importance of the SMS reminders in establishing a habit of adherence and additionally saw the SMS as an extension of care from the clinic [34]. In this study, SMS notifications of missed or delayed doses were also sent to family or friends who knew the participant's HIV status and had provided social support in the past. This aspect of the intervention, however, showed no clear benefit. Complexities of relationship dynamics, lack of guidance in providing support, and lack of resources to provide support were cited as potential explanations of this finding [35].

Importantly, the act of monitoring with EAM itself can function as an intervention (i.e., the Hawthorne effect) [36], which may be stronger in real-time versus standard EAM [37]. Participants from the above-noted trial in Uganda indicated they improved their adherence specifically because they knew they were being actively watched [34]. This type of motivation was seen as encouragement, not punitive. None of the trials with real-time EAM have included controls without monitoring, because of the need for comparable adherence outcomes. Large studies powered for viral suppression could answer this question, but have not yet been conducted.

Another important limitation to standard and real-time EAM has been cost, confining both technologies primarily to the research realm. Recent developments, however, have produced low-cost versions of both technologies, including options for audio and SMS-based reminders, that are currently undergoing study for both HIV (K24MH114732) and TB (ISRCTN35812455). This work has the potential to make adherence-informed care a reality in clinical practice. Importantly, the 2017 update of the WHO's "Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care," recommends digital medication monitors as a suitable "adherence intervention" and EAM is being rolled out as standard of care for drug-susceptible TB patients in China [38].

Digital Ingestion Monitoring

An innovative approach to monitoring involves, an ingestible sensor attached to a gelatin capsule to be taken alongside the medication of interest or embedded in the medication itself. When the sensor comes in contact with gastric acid after swallowing, a signal is sent to a receiver patch on the skin that then connects to a mobile-phone-based user interface via Bluetooth technology. This information can then be seen through a central server by individuals, social supporters, healthcare providers, and/or researchers. The system further allows direct correlation between drug ingestion, health-related behaviors such as physical activity, and physiological response (e.g. heart rate, sleep quality, and blood pressure) [39]. Clinical studies began ten years ago and over 20,000 device ingestions have been evaluated for safety and performance. Results demonstrate that the device is safe and is an accurate measure of medication adherence as compared with directly observed therapy [40].

Like EAM, ingestion monitors provide a day-to-day pattern of adherence that can be used for data-informed counseling or paired to SMS and other interventions. Unique to ingestion monitors, however, is the ability to confirm actual pill ingestion. This information may be particularly relevant for pharmacokinetic studies, as well as for clinical trials in which the assessment of efficacy can be greatly impacted by adherence [29]. Experience to date has included treatment of schizophrenia [41], diabetes [42], hypertension [43] and anti-tuberculosis treatment [40]. Trials are also ongoing for ART (NCT02797262), and HIV pre-exposure prophylaxis (PrEP) (NCT02891720). Limitations to ingestion monitoring include the complexity of the system in which any failure results in the loss of adherence data, as well as cost. Acceptability in initial studies has been good [40, 43], although the technology has been described as "creepy" in the popular media [44]. It is also not yet clear if the positive view of monitoring that has been seen with EAM [34] will extend to ingestion monitoring as well or if concerns will arise with long-term use. The US Food and Drug Administration recently approved the use of an ingestion monitor for aripiprazole, a treatment of schizophrenia, so important clinical data will be forthcoming [45].

Self-Reported Adherence Monitoring through Mobile Phones

As noted above, widespread appeal of cellular phones [46] and availability of cellular networks has resulted in much excitement for mobile phone-based adherence *interventions* (without EAM), many of which have been shown to improve adherence for ART [47] and treatment of other chronic conditions [48]. Mobile phones, however, may also be used for *monitoring* purposes; platforms include live calls, interactive voice response such as

recorded messages with automated response options, SMS, and smart phone applications. Individuals may provide self-report of taken or missed doses on a daily or other periodic basis, or perform and report their own pill counts [49]. Mobile phones may also collect other relevant information for their care, such as adherence challenges or clinical questions; these "ecological momentary assessments" allow for determination of context dependent and dynamic adherence patterns [50]. Data may be used to inform providers and researchers of adherence and/or for self-monitoring and self-management [51, 52]. Some limitations to self-reported adherence by mobile phone are similar to those of standard self-report. That is, individuals may overestimate their adherence due to social desirability or recall bias [53], although ecological momentary assessments may mitigate the latter. Individuals may also forget to document their pill taking behavior, prioritize other activities, and/or be unable to report due to technical challenges as described above. Literacy also may be a concern with text message-based reporting.

An early pilot study of caregivers of children living with HIV in Uganda showed poor completion rates for both SMS and IVR-based reports, primarily due to forgotten personal identification numbers, although acceptability was very high [54]. Additionally, adherence reported through SMS and IVR was uniformly high and did not correlate with viral suppression in that study. More recent research has involved SMS-based self-reports for PrEP. Two studies of PrEP use among serodiscordant couples in East Africa showed high acceptability for this measure [13, 55, 56], although accuracy is unknown. These studies also collected SMS reports of sexual behavior, which can be used to determine if PrEP is being used when the individual is at risk of HIV exposure (a concept known as prevention-effective adherence) [57]. One of these studies found increased adherence with reports of condomless sex within the serodiscordant couple [56]. Importantly, participants in the above-noted study indicated that the SMS queries served as reminders and supported their adherence [58]. Further research is needed in this area.

A recent pilot study in the US combined many features of mobile phones to monitor and support adherence among individuals with HIV and substance use [59]. Specifically, this study used mobile phone-reported pill counts to assess a smartphone-based intervention that provided tailored reminders, feedback on app use, and education, as well as collected ecological momentary assessments, as an adjunct to directly observed treatment and adherence counseling [60]. This intervention was found to be usable and feasible, but did not improve adherence compared to a control that received directly observe treatment and adherence counseling alone.

In the area of tuberculosis treatment, a novel system mobile phone-based system called 99DOTS has been developed as another alternative to standard directly observed therapy [59]. In this system, individuals are issued TB medications in blister packs wrapped in a custom envelope. When a dose is dispensed, a hidden phone number is revealed on the inner envelope flap, prompting the patient to place a toll-free call to indicate a dose taken. 99DOTS is being rolled out for standard anti-TB treatment in multiple states in India and studies on accuracy and clinical impact are forthcoming [23]. Applications to ART may warrant consideration.

Electronic Pharmacy Records

Nearly all clinical settings record dispensing of ART. Pharmacy records provide an objective measure of drug availability and are already a part of many national monitoring and evaluation frameworks [61]. Importantly, pharmacy refill adherence outperforms self-reported adherence in predicting HIV outcomes [62]. Moreover, many clinics routinely use pharmacy records to identify individuals who are not retained in care at that facility [63]. Tracking systems, often involving community health workers in person or via mobile phones, then try to determine if the individual has been seen elsewhere or died, or if he/she is truly out of care. While often effective, these systems are inefficient in terms of time and human resources when they are paper-based.

Electronic pharmacy databases are the standard of care in developed settings and are being seen in resource-limited settings as well [64]. Electronic versions have been shown to be feasible and accurate compared to paper and cohort reports in Malawi and South Africa [63, 65], and importantly allow for automated triggering of tracking and contact efforts. In a study conducted in Haiti, an ART failure risk score was developed from electronic pharmacy records and linked to alerts for clinical follow-up [66].

Importantly, electronic pharmacy records build upon routine clinical engagement and existing infrastructure that can be readily scaled. As a limitation, however, they are blunt in that they provide only maximal predicted levels of adherence. Patterns of adherence are limited to the time interval in which the ART is dispensed, typically one to three months or even longer. The benefits of real-time intervention as noted above are therefore not achievable.

Common Considerations

Targeted and tailored/differentiated care over time—With all of the above technologies, a common goal is to optimize identification of individuals struggling with adherence and provide the interventions they need to achieve sustained viral suppression. At the same time, individuals with high adherence can also be identified and resources that would have been used unnecessarily to support them can be directed to those in need. In recent years, ART delivery models have explored various models to provide this type of differentiated care [67]. While potentially challenging to implement individualized care in settings driving by algorithmic public health models, the technologies presented in this article may facilitate the process through automated systems. For example, in settings that are achieving the 90–90–90 goals for ART delivery, adherence support can be directed to the 10% who are not achieving viral suppression. In settings where more individuals are struggling with adherence, technology can increase the reach of interventions through more efficient delivery.

Moreover, few studies have assessed ART adherence over the long-term. Although many studies report high levels of adherence and viral suppression among those in care, we do not know how most will do as their ART extends into its second or third decade or beyond. In a meta-analysis of up to two years of follow-up, one-third of individuals had viral suppression

[68]. Automated, digital technologies may be useful for scalable, long-term monitoring to ensure continued progress in the fight against the HIV epidemic.

'Active' versus 'passive' adherence monitoring—Some digital adherence measurement tools require more active participation by the patient than others, which may influence measurement accuracy. SMS self-report requires the most effort, in that an individual must act to demonstrate his or her adherence. Electronic adherence monitoring and digital ingestion systems do not necessitate action per se. However, the former requires use of the monitor, whereas the later requires patients to wear a patch and, in some cases, carry a cell phone. Electronic pharmacy record tracking is the most passive approach and requires no active participation by the patient beyond routine care engagement.

Ethical considerations of moving adherence monitoring out of the clinic—Many technologies take adherence monitoring from the clinic into the lives of individuals living with HIV. While technology is becoming pervasive globally, consideration is needed as to how it may impact key ethical concerns. Monitoring, for instance, may affect privacy of HIV status, confidentiality of health-related information, autonomy in choosing how to manage HIV infection, and trust of healthcare providers and researchers [69]. Monitoring also raises questions about when to act on detected nonadherence [70], as resources are typically limited. The high degree of acceptability seen in most studies is encouraging, yet ethical concerns have been raised relating to the "biomedical big brother" nature of digital ingestion monitoring, as well as the potential for insurance companies to incentivize use [44, 71]. Normative guidance specifically addressing these ethical concerns will be important as these technologies are introduced into clinical care.

Conclusions

Current digital communication technologies hold great promise for improving ART delivery and impact. Real-time approaches based on cellular technology (i.e., real-time EAM, digital ingestion monitoring, and mobile phone-based monitoring) provide the capacity necessary to deliver interventions precisely when and where they are needed, potentially enabling significant efficiency of care delivery and impact on adherence and associated clinical outcomes. Standard digital advances, such as automated reminders in EAM and electronic pharmacy records may also achieve similar advances with relative lower cost and easier implementation. Future research is needed in improving the functionality of these approaches, with attention paid to system-level issues through implementation science, as well as acceptability and ethical considerations at the individual-level.

An estimated 17.2 million people are currently living with HIV and not accessing ART. As efforts continue to expand to identify those with HIV infection and help them access ART, novel and innovative approaches will be needed to ensure consistent ART adherence. Improvements are needed in many areas of adherence intervention, including counseling, education, health systems, and social determinants of health [29]. The technologies described in this article can enable alignment of these interventions with those in need, thereby promoting optimal individual health for all who are living with HIV and moving us closer toward ending HIV transmission.

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Table 1.

Strengths, limitations, potential advances, and other considerations for actionable adherence monitoring tools that can be used for targeted and tailored support

Monitoring Tool	Example Technologies/Devices	Strengths	Limitations	Potential advances/Considerations	Published and Registered Ongoing Studies
Electronic Adherence monitors (EAM)	• MEMS • Wisepill • Wisebag • evriMED 500/1000 • AdhereTech • GlowCaps • MedMinder • MedSignals • Sensemedic Smart • Tell-Me-Box	• Ability to provide day-to-day patterns that better predict the risk of virologic failure compared to average adherence [16,17] and enable data-informed counseling (ref) • Ability in some EAM to target and tailor care based on real-time pill taking behavior [18, 19, 20] • Wide availability of cell networks in many target populations [25–27] • Some EAM offer reminders and/or send phone calls; emails; or SMS to patient, friends, family, health care providers,	• Currently most devices are expensive and resource-intensive • Technical challenges (e.g. battery failures, gaps in available network coverage) • Low literacy level in target populations [30] • Concerns in marginalized populations for whom the EAM device may result in unintended disclosure of HIV serostatus [28,29]	• Further development needed to improve aspects of the technology and reduce cost for use at scale • Act of monitoring with EAM can function as an intervention (i.e. Hawthorne effect) [35, 33]	Published studies: [6, 16–20, 22, 23, 28, 31–33] Registered Ongoing Studies involving ART, PrEP and TB: NCT03086655, NCT02915367, NCT02611362, NCT02573376, NCT01817621, NCT01790373

Monitoring Tool	Example Technologies/Devices	Strengths	Limitations	Potential advances/Considerations	Published and Registered Ongoing Studies
		and/or researchers			
Digital ingestion systems	• Proteus Digital Health Feedback System	• Ability to confirm pill ingestion • Direct correlation between drug ingestion, health-related behaviors such as physical activity, and physiological response (e.g. heart rate, sleep quality, and blood pressure) [37] • Results demonstrate device is safe and accurate measure of adherence as compared to directly observed therapy [38] • Potential for systems to be paired with SMS and other interventions	• Currently expensive and resource intensive • Technical challenges (e.g. battery failures, gaps in available network coverage) • Feasibility and acceptability in resource limited settings and longitudinal use are unknown	• Ability to confirm pill ingestion may be informative for pharmacokinetic studies and clinical trials in which assessment of efficacy can be impacted by adherence [28]	Published studies: [37–42] Registered Ongoing Studies: NCT02891720, NCT02797262, NCT02968576, NCT02800655
Cell phones/SMS (self-report)	• mSurvey • 99DOTS	• Easy and relatively inexpensive to collect • Can collect health-related ecological momentary assessments, as well as	• Difficult to assess patterns of adherence • Low literacy level in target populations	• SMS reporting may decrease social desirability due to relative anonymity • Ability to collect data frequently may reduce recall bias	[14, 22, 43–45, 50–52, 54–55]

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Monitoring Tool	Example Technologies/Devices	Strengths	Limitations	Potential advances/Considerations	Published and Registered Ongoing Studies
		adherence, for relevant context [46] • Can send reminders and/or phone calls; emails; or SMS to patient, friends, family, health care providers, and/or researchers • May help overcome recall bias through frequent reporting			
Electronic pharmacy records		• Excellent measure of ART initiation and persistence • Leverages existing infrastructure [57] • Outperforms self-reported adherence in predicting HIV outcomes [58] • Can be used to track those who are not retained in care [59] • Does not require active participation	• Can only be used with patients engaged in care • Limited to maximal predicted adherence, not pill-taking behavior or ingestion • Many existing pharmacy systems are not optimized for tracking	• Great potential for increasing the efficiency and reach of tracking systems currently based on paper records	[57–59, 66, 62]

Monitoring Tool	Example Technologies/Devices	Strengths	Limitations	Potential advances/Considerations	Published and Registered Ongoing Studies
		by individual taking ART			