Methods for Assessing the Adherence to Medical Devices

Leah M. Johnson, Stephanie L. Swarner, Ariane van der Straten, and Ginger D. Rothrock
Contents

About the Authors i
Acknowledgments ii
Abstract ii
Introduction 1
Adherence to Medication: Perspectives and Challenges 1
Methods for Assessing Adherence to Medications Delivered Via
Conventional Routes 2
Direct Methods for Assessing Adherence 2
Indirect Methods for Assessing Adherence 2
Medical Devices That Deliver Drugs 3
Stationary Medical Devices 3
Patient-Accessible Medical Devices 3
A New Opportunity: Assessing Adherence of Medical Devices 4
Case Study: Assessing Adherence to Vaginal Rings
for HIV Prevention 5
Pre-Exposure Prophylaxis (PrEP) for HIV 5
Vaginal Rings for HIV PrEP 5
Assessing Adherence of Vaginal Rings 6
Conclusions and Future Outlook 7
References 8

About the Authors
Leah M. Johnson, PhD, is a research chemist at RTI International, where she leads a variety of research and development projects involving advanced materials for applications in both the health and the energy industries.

Stephanie L. Swarner, BS, is a materials engineer at RTI International. She develops polymeric materials for a variety of medical device technologies.

Ariane van der Straten, PhD, MPH, is an RTI Fellow and director of the Women’s Global Health Imperative group. She is a global leader in investigating the acceptability of and adherence to new biomedical technologies for HIV prevention.

Ginger D. Rothrock, PhD, is the director of the Advanced Materials and Systems Integration group at RTI. She is responsible for business development and technical leadership in the areas of advanced materials and manufacturing for commercial sectors.
Abstract

Assessing patient adherence to medication is necessary to distinguish between nonadherence and inferior drug efficacy, which is crucial to avoid poor clinical outcomes. Adherence measurements pose various challenges, because many methods rely on subjective assessments or slow and costly measurements, which are infeasible in resource-poor settings. Recent developments of new medical devices for delivery of medications requires additional considerations in adherence. In this report, we propose that medical devices may serve a dual-functional purpose: to deliver the drug(s) and monitor adherence. We provide an illustrative case study that involves assessing the adherence of vaginal rings for delivery of antiretroviral drugs for pre-exposure prophylaxis (PrEP) of HIV.

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Introduction

Effective medical interventions for preventing or treating a disease require that patients adhere to the prescribed medication regimen. A recent upsurge in the development of medical devices has provided new routes for delivery of medications. Medical devices may offer advantages over conventional drug delivery (e.g., oral pills) by providing localized treatment, reducing systemic toxicity, and delivering drugs otherwise incompatible with oral formulations. Continued progress of medical devices, however, will require novel approaches for monitoring adherence in ways that accommodate users by remaining inconspicuous and burden free.

We propose a new approach for measuring patient adherence to medical devices. By using the material integral to the drug delivery device itself, a signaling mechanism can inform clinicians about the degree of device use. We foresee that an adherence monitoring system integral to a drug delivery device will support medical providers in deciphering device use during clinical trials. The monitoring system could also help patients by providing feedback to users who unknowingly misuse their devices or can alert users of counterfeit devices. To understand this concept, we first explore the current landscape for monitoring adherence to orally delivered medications. A discussion of medical devices follows, with emphasis on an RTI International case study involving a vaginal ring drug delivery device with the potential to report the level of patient adherence through a simple change in color.

Adherence to Medication: Perspectives and Challenges

Strategies for medical interventions often require multiple steps: assessing a condition or disease risk, prescribing adequate therapy or preventive strategy, and correlating patient outcomes with the prescribed treatment. The effectiveness of these tactics requires adequate support from health care systems, proper communication from physicians to clarify the intervention strategy, and patients’ adherence to the prescribed plan. The term adherence—referred to as adopting and following a medical regimen by a patient as prescribed—has largely replaced the term compliance, which implies a passive obedience to medical instruction (Brown & Bussell, 2011; Jimmy & Jose, 2011). The medical community recognizes the overall importance of adherence; it is often described as the Achilles’ heel in bridging treatment plans with successful outcomes.

A measurement of adherence is required to understand the efficacy of drug treatments or medical regimens. Without this measurement, making a clear distinction between drug efficacy and drug misuse is nearly impossible, ultimately leading to poor clinical outcomes. For example, the persistence of a disease may result from low efficacy of a drug or from low adherence, so identifying the cause is crucial for success in the public health sector. The ability to understand adherence also reveals numerous opportunities for the medical community to examine behaviors in specific populations and customize treatment plans for overall improvements to health care and successful outcomes of patient care.

To address adherence, providers and patients must consider many challenges. Such challenges may originate from patients, physicians, or the health care system (Brown & Bussell, 2011), and can take a considerable toll on medical outcomes. Patient-related challenges often result from a combination of low motivation, low health literacy, forgetfulness, economics, or a burdensome regimen. Other obstacles can involve inadequate contact with a physician or complex health care systems. Because adherence to medical regimens depends on many factors (e.g., treatment type, disease category, patient circumstances), the reported nonadherence rates correspondingly vary. In one report by the World Health Organization (WHO), approximately 50 percent of patients with chronic diseases did not adhere to medical therapy in developed countries (World Health Organization, 2003). Nonadherence has also been shown to be a particular challenge in prophylactic strategies for disease prevention (Van Damme et al., 2012).

Many strategies are intended to improve patient adherence, such as promoting patients’ health literacy, improving patient-to-physician communication, and developing better electronic health records (Brown...
& Bussell, 2011). Despite these efforts, nonadherence is still prominent in various circumstances, necessitating new actions for improved solutions. This existing need for accurate adherence measures will likely grow along with continued advancements in medical technologies and therapies.

**Methods for Assessing Adherence to Medications Delivered Via Conventional Routes**

Various methods exist for evaluating adherence to medications delivered via conventional routes (i.e., enteral, parenteral). The method selected is often contingent on costs, available resources, and ease of execution. In general, the approaches for measuring adherence involve two broad categories: direct methods and indirect methods (Jimmy & Jose, 2011; Osterberg & Blaschke, 2005).

**Direct Methods for Assessing Adherence**

Direct methods often involve assays that measure the drug, related metabolite, or marker in the biological fluids of the patient. For example, direct methods have been employed to analyze adherence to antihypertensive treatment using urine samples (Tomaszewski et al., 2014) and adherence to antiretroviral medications using plasma (Duong et al., 2001). High-burden direct methods include supervised dosing, which is used in high-risk circumstances such as treatment for tuberculosis (Chang, Leung, & Tam, 2004) or treatment of narcotic addictions (Amass, 2001). Although generally considered more accurate than indirect methods, direct assessments are often plagued by high costs, slow implementation, differences in biomarker metabolism among patients, and the burden in measuring adherence over extended time intervals.

**Indirect Methods for Assessing Adherence**

Indirect methods typically use information obtained from patients through questionnaires, self-reports, or patient diaries, which has shown utility for overseeing treatment programs and managing clinical studies (Chesney et al., 2000; Mannheimer et al., 2002). Although indirect methods are commonly used, patient-reported data can have errors because of this approach's subjectivity. Alternative indirect approaches depend on tracking patients’ medication use, such as rates of prescription refills, pill counts, and electronic monitoring devices. These medication tracking methods strive for more objective analysis than patient-reports might provide, but they still remain subject to patient cooperation. For example, office-based pill counts during antiretroviral therapy may overestimate adherence levels (Liu et al., 2001).

Medication event monitoring systems (MEMS) are another leading indirect approach for monitoring adherence to oral medications. MEMS have a microprocessor to record the handling of a medication bottle in an effort to correlate bottle manipulation to the levels of drug ingestion. MEMS have been used to evaluate adherence in various cases, including antibiotic regimens (Kardas, 2007), immunosuppressive medications for renal transplant recipients (Russell et al., 2006), medication for patients with schizophrenia (Diaz et al., 2001), antiretroviral therapy (Deschamps et al., 2004), and HIV pre-exposure prophylaxis (PrEP) (Haberer et al., 2013). Although an effective tool, MEMS monitor an adherence-implementation behavior (opening the medication bottle) and thus fail to capture information concerning the actual patient intake of the drug, which may involve improper dosing or intentional discarding of medications.

Recent developments for measuring adherence of oral medications have leveraged technologies from fields outside health care. For example, Proteus Digital Health developed an integrated-circuit microsensor to measure ingestion of medicine and adherence in real time (Hafezi et al., 2015). By correlating the ingestible sensor embedded within a tablet with a wearable patch, information is obtained not only about adherence but also about physical activity and physiological responses (e.g., heart rate, blood pressure, sleep content). However, the patch (worn on the torso) must be replaced weekly.
Medical Devices That Deliver Drugs

The rapid progress in biomedical technologies has resulted in an upsurge of novel medical devices that deliver drugs to prevent or treat many medical conditions. Medical devices that deliver drugs typically comprise biocompatible polymeric materials that controllably release drugs over time. Drug delivery medical devices can provide localized continuous treatment, reduce systemic toxicity, improve patient compliance, and deliver drugs that are incompatible with oral formulations. These medical devices fall into two categories: stationary and patient-accessible.

Stationary Medical Devices

Stationary medical devices that deliver drugs are implanted in the body by a medical professional and are not designed for removal by the patient. For example, a solid implant for long-acting contraception (Espey & Ogburn, 2011) is an FDA approved stationary device currently available on the US market. Notably, the stationary devices can be removed by a medical professional, but otherwise remain in place to release drugs over time.

Patient-Accessible Medical Devices

Alternatively, many medical devices are patient-accessible, that is, the patient can control the device (i.e., use, place, remove) without medical provider oversight. Examples of patient-accessible drug delivery devices (Table 1) can include transdermal patches, muco-adhesive films, ocular devices, vaginal rings, and intraoral devices (Ranade & Cannon, 2011). Many patients value the autonomy these patient-controlled drug delivery devices provide; they enable patients to manage their personal health and, in many cases, help patients avoid clinical office visits for removal or insertion of devices, which reduces cost and inconvenience.

Table 1. Examples of patient-accessible drug delivery devices

<table>
<thead>
<tr>
<th>Route of delivery</th>
<th>Device type</th>
<th>Medical condition</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal patch</td>
<td>ADHD (Anderson &amp; Scott, 2006; Wilens et al., 2008)</td>
<td>Methylphenidate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoking Cessation (Jorenby et al., 1999)</td>
<td>Nicotine, bupropion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hormone Replacement (Vehkavaara et al., 2000)</td>
<td>Estrogen</td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>Contact lenses</td>
<td>Overactive Bladder (Bakshi, Bajaj, Malhotra, Madan, &amp; Amrutiya, 2008)</td>
<td>Oxybutynin</td>
</tr>
<tr>
<td></td>
<td>Ocular Inflammation (Kim &amp; Chauhan, 2008)</td>
<td>Dexamethasone, timolol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glaucoma (Peng, Burke, Carbia, Plummer, &amp; Chauhan, 2012)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Dry powder inhaler</td>
<td>Asthma (Raphael, Taveras, Iverson, O’Brien, &amp; Miller, 2016)</td>
<td>Albuterol</td>
</tr>
<tr>
<td></td>
<td>Nebulizer</td>
<td>Ventilated Patients (Manthous, Hall, Schmidt, &amp; Wood, 1993)</td>
<td>Albuterol</td>
</tr>
<tr>
<td></td>
<td>Metered dose inhaler</td>
<td>Chronic Obstructive Pulmonary Disease (Mouloudi, Katsanoulas, Anastasaki, Hoing, &amp; Georgopoulos, 1999)</td>
<td>Albuterol</td>
</tr>
<tr>
<td>Intravaginal</td>
<td>Vaginal ring</td>
<td>Contraception (Sivin et al., 2005)</td>
<td>Neostosterone, ethinylestradiol</td>
</tr>
<tr>
<td></td>
<td>HIV Prevention (Devlin, Nuttall, Wilder, Woodsong, &amp; Rosenberg, 2013)</td>
<td>Dapivirine</td>
<td></td>
</tr>
<tr>
<td>Intranasal</td>
<td>Pressurized aerosol</td>
<td>Rhinitis (Thorsson, Borgå, &amp; Edsbäcker, 1999)</td>
<td>Budesonide</td>
</tr>
<tr>
<td></td>
<td>Mechanical pump</td>
<td>Smoking Cessation (Sutherland, Russell, Stapleton, Feyerabend, &amp; Ferno, 1992)</td>
<td>Nicotine</td>
</tr>
</tbody>
</table>

ADHD = Attention-deficit/hyperactivity disorder.
A New Opportunity: Assessing Adherence of Medical Devices

Because stationary devices (e.g., drug-eluting cardiovascular stents), are permanent or remain in place for a designated time, adherence measurement is not necessary. Conversely, patient-accessible medical devices are available to the user, which raises the possibility of unintentional or intentional misuse of the device. Misuse, in turn, can hinder physicians’ ability to determine the level of patient adherence. Just as with traditionally delivered medications, if patients use drug delivery devices incorrectly (driven by technical or social factors), the disease may persist or inaccuracies in determining drug efficacy may result.

We believe that a unique opportunity exists for measuring the adherence of drug delivery devices that are patient-accessible, such as those in Table 1, by exploiting the materials integral to the device or applicator. In other words, configuring many medical devices may serve two simultaneous functions: to deliver the drug itself and to monitor adherence. Specifically, the device material that houses the drug can also house an integral monitoring system that measures adherence by responding to environmental stimuli (Figure 1). This monitoring system can be designed for simplicity, allowing an understanding of adherence at point-of-care settings or by the patient.

To our knowledge, this concept has not been implemented in any practical way for drug delivery devices and shows very limited use in the health field. In some examples, reports have described a removable orthodontic aligner containing an integrated color-changing compartment that fades with use to measure patient adherence to the dental appliance (Schott & Göz, 2011; Tuncay, 2009). Visually based notifications in medical devices have been used to measure factors other than adherence, such as identifying urinary tract infections via a color-changing strip in “smart diapers” (Gael, Gael, & Gael, 2001) and sensing glucose levels using color-based indicators in ocular inserts and diagnostic contact lens (Alexeev, Das, Finegold, & Asher, 2004).

Exploiting fully this novel design of medical devices as a dual-functional apparatus (i.e., drug delivery vehicle and adherence monitoring system) requires that certain parameters be met. Most crucial is that the adherence monitoring system must remain independent of the device’s drug delivery function; that is, the monitoring feature exists solely to reveal adherence information, and it must not interfere with drug release. In addition, to be useful as an adherence monitor, the devices must not undergo extensive biodegradation during the duration of drug delivery and adherence monitoring. Finally, the adherence monitoring feature must be biocompatible and robust so that it can withstand long-term use safely and does not provide opportunity for patient or user interference.

Numerous designs can achieve an integral monitoring system and depend on the materials and arrangement of the device. For instance, optical differences resulting from chemical, physicochemical, or physicomechanical changes occurring with the device over time could be used for adherence measurements. As another example, technologies associated with color-changing biosensors for diagnostic devices could be leveraged in this arena.
Case Study: Assessing Adherence to Vaginal Rings for HIV Prevention

In the following section, we describe a case study performed at RTI International showing that vaginal ring (VR) medical devices change color on the basis of time of exposure to vaginal environments simulated in a laboratory setting. The color change could be used to monitor adherence of VRs to better understand efficacy of this device for HIV prevention.

Pre-Exposure Prophylaxis (PrEP) for HIV

Recent advances in preventive strategies for HIV include PrEP, in which HIV-negative individuals receive antiretroviral (ARV) drugs to prevent infection (Choopanya et al., 2013; Grant et al., 2010). With proper adherence by patients, the PrEP approach has shown high efficacy in preventing the acquisition of HIV. Understanding adherence levels is fundamental for the success of PrEP: patients must correctly follow the regimen to ensure adequate levels of the ARV drug are present in the body at the time of potential HIV exposure (Amico, Mansoor, Corneli, Torjesen, & van der Straten, 2013).

Results from PrEP clinical trials revealed that the choice of method for measuring adherence is critical (van der Straten, Montgomery, Hartmann, & Minnis, 2013; van der Straten, Van Damme, Haberer, & Bangsberg, 2012). The FEM-PrEP clinical trial involving a daily pill (i.e., tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) co-formulation, named Truvada™) resulted in differences of reported adherence levels based on the technique used for the measurement. For example, 95 percent of women self-reported they had “usually” or “always” taken the daily pill, whereas measurements of the drug as a marker of use showed that fewer than 40 percent of the HIV-uninfected women had detectable levels of recent pill use at visits (Van Damme et al., 2012). Similar and highly discrepant results regarding adherence levels occurred with the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial, which assessed daily oral TDF, daily oral TDF-FTC, and 1% tenofovir vaginal gel for PrEP (Marrazzo et al., 2015). Although self-report is simple and low cost, it has yielded inflated adherence estimates in these and several other trials compared with biological measures of use.

Conversely, directly assessing drug levels is costly, invasive (requires collection of biological specimens), and labor intensive. Additionally, this approach cannot be conducted in real time. An improved method of measurement, as compared with self-report or plasma sampling that resolved discrepancy of adherence levels would be highly valuable to researchers, patients, and clinicians.

Vaginal Rings for HIV PrEP

To date, successful approaches for PrEP delivery involved a daily oral pill, topical gels, films, vaginal rings (VRs), and more recently, long-acting injections. The myriad PrEP delivery options accommodate various preferences of the recipients, ultimately supporting the likelihood of adherence. In particular, the VR drug delivery option holds great promise for PrEP by offering women a simple, low-burden regimen that eliminates the need to administer the drug before intercourse (e.g., vaginal gels) or to perform a daily action (e.g., take a pill every day).

VRs are torus-shaped, flexible drug delivery devices consisting of biocompatible silicone or thermoplastic material embedded with one or more ARV drugs (Figure 2) (Friend, 2011). Once positioned within the vagina, the VR remains stationary during the sustained release of the ARV drug with time, typically over 1 month. Because VRs are patient-accessible devices, the user controls both insertion and removal, if needed.

Figure 2. A vaginal ring drug delivery device prepared at RTI International

This simulated device (without drug) consists of silicone and a color-based indicator.
Results from two recent Phase III clinical trials for PrEP-based VR (i.e., The Ring Study, led by the International Partnership for Microbicides [IPM] and ASPIRE [A Study to Prevent Infection with a Ring for Extended Use], funded by the US NIH-and conducted by the Microbicide Trials Network) showed promising results for preventing HIV in women (Baeten et al., 2016; Nel et al., 2016). Overall, the Ring Study showed a risk reduction of HIV infection by 30.7 percent in comparison to placebo, whereas the ASPIRE study showed a lowered occurrence of HIV infection by 27 percent in comparison to placebo. These studies also reported an important relationship between adherence and efficacy: data suggested that HIV protection was higher in participants with greater adherence. For example, post hoc analysis showed efficacy of HIV-1 protection at 56 percent, and a rate of adherence at 70 percent in women over 21 years of age (Baeten et al., 2016).

During these clinical trials, clinicians explored women's VR use by measuring plasma levels of drug and residual drug in the VR. Many reasons could explain why women might remove their VRs: request from partners, discomfort, or misunderstanding of proper use. Based on the divergent adherence levels reported and the limitations of drug monitoring, a more objective and easy measurement technique will benefit assessment of adherence in these types of studies.

**Assessing Adherence of Vaginal Rings**

RTI designed an approach based on the principle of a dual-functional medical device. Our aim was to design a VR that reveals adherence levels while simultaneously maintaining the capability to deliver an ARV drug. Our approach involves a quantitative test that measures the extent of ring use based on a definitive, easy-to-interpret visual signal originating from the VR device.

Specifically, we designed a VR that can change color depending on the exposure to low pH conditions naturally present in healthy vaginal environments (e.g., typically pH=4.2) (Owen & Katz, 1999). This smart VR can determine the amount of time the ring was present in this low pH environment and respond by changing color; thus, it produces an easily observable signal change that allows users and clinicians to determine VR use.

Preliminary studies by RTI investigators revealed the ability to generate VRs that respond to environment pH differences. To accomplish this testing strategy, we employed biocompatible-grade silicone polymer formulations containing a bromocresol green indicator (Figure 3A). The bromocresol green pH indicator transitions color at a pH range of 3.8 to 5.4, which reflects the range of pH in vaginal environments. Immersion of the VR in simulated vaginal fluid produced distinct color change over the course of 7 days with the ability to detect a color change within approximately 3 days (Figure 3A). Moreover, the corresponding red, green, blue values (Figure 3B) enable analysts to assign numerical values to the colored rings, for example, by using an open-source software program, Image J, a free image-processing software provided by the National Institutes of Health (NIH). These proof-of-concept studies demonstrate the capability to generate

![Figure 3](image-url)
silicone VR materials that change appearance based on environmental stimuli (e.g., pH) and offer a new, practical adherence measurement technique.

Our advances show technology feasibility, demonstrating the ability to prepare in-house VRs that change color based on exposure to simulated vaginal environments. To advance this system further, we are considering additional factors. For instance, owing to the potential variability in pH of vaginal environments that differ with age, health status, and sexual activity (exposure to semen), further studies will capture adherence information from differing environmental pH levels and different markers. We will also evaluate the release rates of the drug from these smart devices to ensure that the monitoring system does not interfere with medication release.

The development of the VR, as described in this case study, supports the ongoing need to advance various PrEP methods for women. A major consideration is that women are more vulnerable to heterosexual transmission of HIV than men, owing to the combined effects of biological makeup and social circumstances, particularly in developing countries. For example, in South Africa, the prevalence of new HIV infections in women was reported as four times higher than the prevalence in men for those between 15 and 24 years of age (Shisana et al., 2014). By providing women an additional PrEP option that delivers drug continuously over a month, VR devices may help prevent HIV in women.

Importantly, the ability to monitor VR usage and assess adherence levels through an easy color-monitoring system can assist investigators in evaluating VR efficacy. A color-changing VR accommodates straightforward analysis of VR adherence at the point of care without reliance on expensive, cumbersome diagnostic techniques. Furthermore, as described in Figure 1, self-monitoring devices can serve both clinicians and users of the device. For VRs, the monitoring feature could be designed to include additional beneficial information, such as the amount of drug remaining in the ring (i.e., suggesting adequate drug released for HIV protection) or an understanding of the quality of the VR (e.g., that the VR is not counterfeit).

Conclusions and Future Outlook

The medical community recognizes that understanding patient adherence to medications is critical for success in disease prevention and management. Knowledge of adherence is particularly important during clinical trials, where great financial and human resources are committed for determining the efficacy and safety of products. Without critical adherence information, study data could be inaccurate or misinterpreted, which in turn could lead to excessive costs, incorrect interpretation of drug safety and efficacy, and, in extreme cases, injury to participants.

On the basis of ongoing development and implementation of new patient-controlled drug delivery devices, we see an emerging need to understand adherence during future device development. Although many device technologies are in their infancy, rapid advances will require an understanding of adherence as many of these technologies progress through clinical trials, demonstration projects, and real-world implementation. For example, a variety of patient-accessible drug delivery devices, including transdermal patches, contact lenses, and VRs, may benefit from monitoring systems that accurately determine adherence levels while posing little or no burden to the user. Similar to oral medications, novel drug delivery systems require a full understanding of adherence in an unobtrusive, easy, and cost-effective manner.

Our case study presents a new platform for VRs with monitoring systems integral to the device that can reveal use. This type of VR monitoring system may improve adherence with a new tactic that can remind users and enhance their cooperation. For instance, with oral medications, strategies such as calendar pillboxes, blister packaging, and electronic devices with built-in dose-memory functions can help patients raise and maintain their adherence levels. Similarly, the capability for women to understand their VR device via a simple color-change may enable greater adherence levels. We anticipate that the ability to leverage new drug delivery technologies for
additional functions, such as monitoring adherence levels, will improve the prevention and management of numerous health conditions, ultimately benefiting both patients and the medical community.

References


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