Development of a Multi-Method Tool to Measure ART Adherence in Resource-Constrained Settings: The South Africa Experience

Gavin Steel
Jude Nwokike
Mohan P. Joshi

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Rational Pharmaceutical Management Plus Program
Center for Pharmaceutical Management
Management Sciences for Health
4301 North Fairfax Drive, Suite 400
Arlington, VA 22203 USA
Phone: 703-524-6575
Fax: 703-524-7898
E-mail: rpmplus@msh.org
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About RPM Plus
Rational Pharmaceutical Management (RPM) Plus Program works in more than 20 developing and transitional countries to provide technical assistance to strengthen pharmaceutical and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning and in promoting the appropriate use of health commodities in the public and private sectors.

Abstract
As antiretroviral medicines become increasingly available and affordable for the treatment of eligible patients more attention is rightly being focused on issues related to rational use particularly adherence. Ensuring adherence to antiretroviral therapy (ART) treatment is one of the key strategies that will delay emergence of resistant strains of the virus and ensure durability of the present regimens. Health care workers are not easily able to identify patients who may or may not adhere to treatment; formal measurement of adherence provides an opportunity for identifying patients who may require adherence support measures.

The USAID-supported Management Sciences for Health RPM Plus Program is providing technical assistance and support to South Africa’s Department of Health (DOH) in the Comprehensive HIV and AIDS Care, Management and Treatment Plan for the development of strategies for adherence monitoring and measurement. The collaboration between the DOH and RPM Plus led to the development of a multi-method adherence assessment tool based on previously validated elements including self-report, visual analogue scale, pill identification test, and pill count. The use of this tool is expected to standardize adherence measurement in ART clinics and facilitate comparison of adherence rates and adherence support measures across facilities, thus leading to identification of support measures that are associated with higher adherence rates. This technical report provides an overview of ART adherence measurement and describes the process of developing the multi-method adherence assessment tool in South Africa.

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Key Words and Terms
HIV/AIDS, adherence, antiretrovirals (ARVs), adherence monitoring, adherence assessment, adherence support measures, antiretroviral therapy (ART)
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<td>acquired immunodeficiency syndrome</td>
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<td>ART</td>
<td>antiretroviral therapy</td>
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<td>ARV</td>
<td>antiretroviral</td>
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<td>CASI</td>
<td>Computer-Assisted Self-Interviewing</td>
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<td>DOH</td>
<td>South Africa Department of Health</td>
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<td>DOT</td>
<td>directly observed treatment</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>MEMS</td>
<td>Medication Event Monitoring System</td>
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<td>MSH</td>
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<td>Rational Pharmaceutical Management Plus (Program) [MSH]</td>
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<tr>
<td>TDM</td>
<td>therapeutic drug monitoring</td>
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<td>USAID</td>
<td>U. S. Agency for International Development</td>
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<tr>
<td>VAS</td>
<td>visual analogue scale</td>
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<td>WHO</td>
<td>World Health Organization</td>
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INTRODUCTION

Sub-Saharan Africa is the epicenter of the HIV/AIDS epidemic accounting for 24.7 million or 63 percent of all persons infected with HIV. Sub-Saharan Africa is the epicenter of the HIV/AIDS epidemic accounting for 63 percent of all persons infected with HIV. The increasing affordability of the ARVs among other things has dramatically facilitated the scaling up of antiretroviral therapy (ART) programs worldwide and in South Africa. Given the recent global efforts towards expanding access and availability of ARVs, the case for adherence is even more relevant as HIV is highly mutable and requires lifelong treatment. As obstacles to access are being dismantled, attention is increasing focused on adherence to treatment. Adherence has long been considered a key element towards reducing the likelihood of the emergence and spread of drug-resistant pathogens. Due to cross-resistance, the virus can become resistant to an entire class of ARVs thereby rendering that class ineffective not just for the individual but also for the society. Some studies indicate that as much as one in five people newly infected with HIV have been infected with treatment resistant virus. And we have gone this route before; resistance has primarily resulted in the loss of use of chloroquine and sulfadoxine-pyrimethamine as the cornerstone for the management of malaria. With tuberculosis treatment, global surveillance data indicate overall prevalences for resistance to any of the four drugs at 12.6 percent and 2.2 percent for multidrug resistance.

Literature is sparse on the burden of nonadherence to ARV treatment such as the increased health care costs, effects on human resource productivity, disruption of families and communities, and morbidity and mortality in developing countries. However, it is well understood and documented that HIV/AIDS requires near perfect adherence to obtain successful treatment outcomes. Recent studies have estimated the required level of adherence for sustained virological suppression to be about 95 percent. Evidence-based data from developing countries regarding ART adherence rates, predictors, and the effectiveness of support interventions are limited. The implication is that there is urgent need for systematic data collection and analysis to estimate the prevalence of nonadherence and to make strong evidence-based recommendations on the best ways to improve medication adherence. The first step will include the development and standardization of adherence measurement tools. Using this tool to measure adherence will ensure that adherence reports across treatment facilities are comparable, and using it to identify the nonadherent patient will help trigger support measures to promote adherence. Adherence interventions have been shown to be cost-effective strategies which payers can accommodate. Evidence of cost effectiveness of adherence interventions to improve outcomes in diabetes, hypertension, and asthma are

5 There are several articles and studies on the cost of nonadherence to other chronic diseases.
readily available in the literature.\textsuperscript{6} In a U.S. cross-site evaluation, the cost of HIV medication adherence support interventions with moderate efficacy costing about $100/month have been estimated to meet a cost-effectiveness threshold.\textsuperscript{7}


How Common Is Nonadherence?

"Drugs don't work if people don't take them."8 Nonadherence is a global problem and has been seen in all diseases. According to WHO, adherence to long-term therapies in chronic illnesses averages 50 percent in developed countries.9 In developing countries, the rates are thought to be even lower. It is undeniable that many patients experience difficulty in following treatment recommendations. In ART, the literature reports similar adherence difficulties; adherence to ARVs varies between 37 and 83 percent, depending on the drug under study.10 Several studies have shown varying levels of adherence: more than 10 percent of patients report missing one or more medication doses on any given day, and more than 33 percent report missing doses in the past two to four weeks.11 It is estimated that 50 percent of prescriptions filled are not taken correctly. It is important to note that nonadherence includes not taking medications at prescribed time intervals and non-compliance to dosing instructions regarding dietary or fluid intake.12

The earlier apprehension over lower levels of ART adherence in the developing countries has not been justified and there is substantive evidence that adherence in developing countries are comparable to that in developed countries.13 In the Cape Town AIDS cohort study that evaluated 289 patients accessing treatment between January 1996 and May 2001, 63 percent of patients maintained adherence of 90 percent or greater.14 In the Khayelitsha project,15 one of the early ARV pilots in government health facilities that aimed to demonstrate the feasibility of antiretroviral therapy at primary health care level, 90 percent of patients were considered to be highly adherent, meaning that they take at least 95 percent of their medicines. There are, however, challenges to maintaining this impressive, though not optimal, performance; adherence wanes over time, learned behaviors change over time and long-term adverse effects can lead to nonadherence. So nonadherence remains a major concern as the ART programs scale up and as more patients are expected to remain on this life-long therapy, these necessitate the need for the development of additional interventions to maintain optimal adherence.

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8 C. Everett Koop, former U.S. Surgeon General
15 WHO, Médecins sans Frontières South Africa, the Department of Public Health at the University of Cape Town, and the Provincial Administration. of the Western Cape, South Africa. 2003. Antiretroviral therapy in primary health care: experience of the Khayelitsha programme in South Africa : case study. Geneva: WHO.
Why Measuring Adherence Is Important

Adherence to treatment is critical to obtain full benefits of ART including maximum and durable suppression of viral replication, reduced destruction of CD4 cells, prevention of viral resistance, promotion of immune reconstitution, and slowed disease progression. With an effective regimen that is fully suppressive to viral replication, nonadherence is the single most important factor that can lead to viral resistance. WHO\textsuperscript{16} recommends that accurate assessment of adherence is necessary for effective and efficient treatment planning. Decisions to change recommendations, medications, and/or communication style to promote adherence depend on valid and reliable measurement of adherence. Without formal assessment, providers are unlikely to accurately identify adherent and nonadherent patients, missing the opportunity for reinforcement and constructive interventions respectively. If adherence is below optimal and drug levels are low, viruses continue to replicate. HIV is highly adaptive to viral-suppressing pressures and can rapidly mutate to develop resistance. Another reason why adherence is important is that HAART may still improve CD4 cell levels despite ongoing viral replication because the mutant viruses which emerge are less fit and less destructive than wild-type HIV.\textsuperscript{17}

Paterson’s et al\textsuperscript{18} pioneer study established that up to 95 percent adherence is necessary for HIV viral suppression. The study linked the relationship between adherence and viral load (VL); as adherence decreased, VLs increased sharply in a dose-response effect. The study was able to conclude that greater adherence levels were associated with greater reduction in VLs. Generalizing Paterson’s findings to the less developed countries may require taking the following gaps into consideration—small number of patients; only protease inhibitors patients studied; patients did not have formal institution-based adherence education, and MEMScap, which is not easily available in developing countries, was used. However, other studies have confirmed Paterson’s study and the relation between adherence and treatment outcomes; there is evidence that for every 10 percent decrease in adherence, there is a 16 percent increase in HIV-related mortality.\textsuperscript{19}

Therefore, adherence needs to be measured in clinical settings. Accurate and reliable measures of adherence and better understanding of both barriers and facilitators of adherence are needed to help clinicians identify patients who need assistance with their pill taking, to design and evaluate effective interventions to enhance adherence, and to interpret the role of adherence in evaluating clinical outcomes and making treatment decisions.\textsuperscript{20} Measuring adherence to ART is even more challenging due to evolving evidence that different classes of ARVs may require difference adherence levels to sustain virological suppression. The responses seen in the different class-specific adherence-resistance relationships indicates that there may be differences in the manner the HIV responds to different levels of adherence.

\textsuperscript{16} WHO. 2003. Adherence.
However, in general, the current ARVs do not provide adequate therapeutic coverage (non-forgiving) when patients intermittently forget to adhere. Levels of adherence that had historically been regarded as “good enough” for other chronic diseases has been found not to be good enough for ART. “Good enough” adherence (sub-optimal adherence to suppress viral replication) may predispose to a situation where drug pressure selects resistant virus. To be in a position to identify adherence problems (irrespective of which class of ARV patients are on) and develop interventions to improve it, adherence measurement is fundamental and improved tools need to be developed to assess adherence.

Attributes and Challenges of a Good Measurement

The measurement of adherence of patients to treatment has been a major challenge because of the subjective and private nature of pill taking behavior in ambulatory patients. These challenges are compounded by the fact that adherence is not only affected by patient behavior alone but also by health system, socioeconomic, disease-related, and drug-related factors. Tools employed for the measurement of adherence should meet basic psychometric standards of acceptable reliability and validity. Quantitative assessment of adherence using reliable tools has been a challenge with disease management. However, active research in this area has blossomed by the importance of adherence in determining drug exposure, efficacy of new agents, and treatment outcomes.

The ideal adherence measurement tool should be non-invasive, simple to use, sensitive, specific, and predictive of nonadherence. The tool should be able to collect data that is: multidimensional in terms of being able to record not just dose taken or missed but also other dosing instructions like food, time of dosing and concurrent use with other medicines and categorical in terms of continuous in number of pills taken as against dichotomous in expressing pills taken or not taken.

The metrics used to describe adherence should cover the following areas—

<table>
<thead>
<tr>
<th>Metric</th>
<th>Derivation</th>
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<tr>
<td>Percent Adherence</td>
<td>Ratio (number of pills taken/number of pills prescribed)</td>
</tr>
<tr>
<td>Percent Adherent Dosing Days</td>
<td>Ratio (number of days dose taken/number of days of dosing)</td>
</tr>
<tr>
<td>Therapeutic Coverage</td>
<td>Ratio (time spent with inefficacious drug concentrations/time on therapy)</td>
</tr>
<tr>
<td>Frequency of Drug Holidays</td>
<td>Frequency of ≥3 days without drug intake</td>
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Currently, there is no adherence measurement tool with all of the above attributes so no single measurement strategy has been deemed optimal for the measurement of adherence.

**Currently Available Tools**

Currently available methods for adherence assessment can be grouped into two categories—

- Direct and objective measures
  - Directly observed treatment (DOT)
  - Therapeutic drug monitoring (TDM)
  - Biomarkers
  - Medication Event Monitoring System (MEMS)
- Indirect measures
  - Pharmacy records
  - Self-report (including Computer-Assisted Self-Interviewing [CASI])
  - Pill count (PC)
  - Visual analogue scale (VAS)
  - Pill identification test (PIT)

The DOT method has health care workers directly administer medicines to patients. This method confirms adherence since the health care worker observes the patient taking the medicine.\(^27\) The DOT is an objective way of measuring adherence. Farmer et al\(^28\) recommend that DOT can be highly effective in settings of great privation as long as there is sustained commitment to uninterrupted care that is free to the patient. Conversely, there are opinions that DOT requires extensive costs, can be stalled by stigma, erodes patients’ privacy, is paternalistic, and may require complex logistics for a life-long treatment like HIV/AIDS. There are concerns that costs and utility may make the large-scale use of DOT in the resources-limited settings almost impractical. There were experiences with DOT in treating tuberculosis but those experiences can not be extrapolated to HIV/AIDS because of issues of stigma and the huge cost that will be required for the administering of DOT in a chronic, life-long disease like HIV/AIDS.

TDM involves measuring drug levels in the blood. TDM is not being used routinely to measure adherence because its use is limited to the protease inhibitor classes. In some ARVs, such as nucleoside reverse transcriptase inhibitors (NRTI), blood levels may not directly infer levels inside HIV-infected cells. However, other laboratory markers like the mean corpuscular volume can be measured for zidovudine and stavudine. The expense related to conducting therapeutic drug measurements is also prohibitive for routine use in developing countries. Biomarkers can be used to monitor adherence by adding secondary non-toxic medicines to indicate that active primary medicine was taken. An example is adding riboflavin to medication and checking the level of riboflavin in the urine—availability of riboflavin in the urine allows the conclusion that the active drug was administered. The use of biomarkers has also met some challenges, chiefly the cost involved in its large scale implementation of all classes of ARVs.


The cost challenges faced by the previously mentioned tools are same for the electronic tools. The MEMS is considered by many to be the current state-of-the-art method of evaluating adherence, largely because adherence is most predictive of clinical outcome when measured with this methodology.29,30 MEMS contain an electronic device fitted to pill containers which records the removal of the cap. It is increasingly being used in the packaging industry31 and is reliable in recording dosing histories of ambulatory patients. This electronic tool contains microcircuitry which can be integrated into product packaging that may include medicine bottle caps, blister packages, and even nebulizers. Removal of the cap or tampering is detected and recorded, and therefore provides a proxy for the removal of a dose and consequent ingestion. The advantages of this method are that it correlates well with virologic outcomes and that data is available in a computer accessible format, allows more detailed view of nonadherence patterns.32 Some challenges to the MEMS include patients opening the bottle but not taking a pill, patients decanting pills, measuring only one medication at a time, being unavailable for blister packs, and cost.

Some of the indirect electronic measures of adherence are also difficult for use in developing countries due to infrastructure constraints. An example of this is using pharmacy records as a proxy of adherence for CASI. This cannot be easily implemented for routine data collection on adherence since it depends on information technology which is not universally available in most resource-limited countries. Patients collecting their medications regularly on a due date are assumed to be adhering to treatment. An effective record-keeping system is essential for pharmacy records to serve as a reliable proxy of adherence. Features of pharmacy records as a proxy for the measuring adherence include that the method can generate a refill list and flag patients not reporting for refills. The limitations of using pharmacy records include that they serve only as proxy of ingestion of medicine, require patient to use the same pharmacy each time, and may require electronic tracking.33

Other indirect methods of measuring adherence (self-report, PC, VAS, and PIT) have the potential for use in resource-limited settings. Patient self-report of adherence is routinely used in assessing adherence both in clinical trials and in routine clinic settings. The self-report method has been validated and shown to predict virological response.34-36,37,38,39,40

31 MEMS became commercially available in 1987.
However, there is also evidence that self-report may overestimate adherence even when questions are asked in a non-judgmental manner.\textsuperscript{41} While self-reporting is easy to use, it is vulnerable to fabrications, to the dynamics of provider-patient relationship and may overestimate adherence. Whether pill counting is a sensitive tool for the measurement of adherence is controversial. In some studies, pill count has been found to predict response to ART,\textsuperscript{42} particularly when conducted with no advanced warning. However, in some others studies it has been shown to be liable to pill dumping, white-coat adherence,\textsuperscript{43} fabrication, and manipulation.

VAS is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be measured directly.\textsuperscript{44} For the measurement of adherence, the patient is asked to place a mark somewhere along the line from 0 to 10 that best describes their adherence to the prescribed ARVs. VAS is a simple tool for uncovering adherence and has the potential for use in resource-constrained settings. The reliability and validity of the VAS has been demonstrated,\textsuperscript{45-47} though measurement errors can still occur. PIT is a novel method of detecting low adherence. PIT involves inviting patients to distinguish the pills in their regimen from a display of ARVs, including two “twin pills” that are similar but not identical.\textsuperscript{48} Other models of this method involve the inclusion of other adherence-related questions for the patient to respond. These questions are constructed to provide further evidence that the patient has a good understanding of how to take the prescribed medicines. The features of PIT include reliability, particularly at the initial phase of treatment; correlation with validated self-report adherence measure; loss of sensitivity in treatment experienced patients; and being a remote marker of actual pill intake.

\section*{Evidence for Multi-Method Approach}

Though some of the adherence measurement tools have been validated to be sensitive in measuring adherence, the majority of the tools currently used cannot meet all the features of an ideal tool. Hence, there is no gold standard in the measurement of adherence. This has led...
to the recommendation of a multi-method approach that combines feasible self reporting and reasonable objective measures as the current state-of-the-art in measurement of adherence behavior.\textsuperscript{49} The multi-method tool can include self-report and different combinations of other tools including pill count, PIT, VAS, electronic methods, and drug levels.\textsuperscript{50,51,52} The RPM Plus review identified simple self-report questionnaires, pill counting, and VAS as the best potential adherence measurement tools for resource-limited settings. In settings where these tools have not been tested and calibrated, a multimodal adherence measurement tool is recommended.\textsuperscript{53}

### Measurement as a First Step Towards Intervention

Adherence measurement provides an opportunity to reinforce the adherent patient and to flag patients that require support to improve adherence. Without formal assessment of adherence the opportunities for interventions are lost. The measurement of adherence including the history of dosing is therefore the first step towards the design and implementation of interventions to improve adherence. Costs involved in developing and applying adherence measurement and intervention strategies are justified by the gains in preserving future treatment options. Goldie et al\textsuperscript{54} showed that interventions that reduced virologic failure rates by 10 percent increased the quality-adjusted life expectancy by 3.2 months, whereas those that reduced the failure by 80 percent increased the quality-adjusted life expectancy by 34.8 months, as compared with standard care. In patients with advanced disease and those with lower levels of baseline adherence, even very expensive interventions, if moderately effective, would yield cost-effectiveness estimates that compare favorably with other interventions in HIV/AIDS disease.

Other research on costs of delivering adherence interventions over the first year of patient support indicate a median direct annual cost of 420 U.S. dollars (USD) (range USD 60–700) per patient; 66 percent of this was attributed to staffing but also included USD 72 per annum for patient incentives. It is claimed that the absolute cost of adherence interventions appear to be relatively low—slightly less than that of a genotype test.\textsuperscript{55} The cost involved in the implementing a multi-method tool to measure adherence in resource-limited setting is therefore hoped to be justified as a subcomponent of the costs of adherence interventions which have been shown to be cost-effective.

\textsuperscript{49} WHO. 2003. Adherence.


Section three of the first edition of the South Africa Department of Health’s National Antiretroviral Treatment Guidelines clearly highlights medication adherence as an essential element to maintain the health benefits provided by ART. Clinicians are required to monitor and evaluate adherence, and respond appropriately. In support of this mandate, the guideline indicates the need for training as a means to ensure patient adherence to ART. The guideline also mentioned pill count and routine patient counseling as some of the strategies to determine medication adherence. Chapter XI of the Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa lists patient adherence as one of the functional elements of the patient information system. Despite the clear articulation of ART adherence measurement and support as an essential program element, details regarding the practice remain undefined.

The RPM Plus project is assisting South Africa’s Department of Health at the national and provincial levels to implement the country’s Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment. Developing a systematic and organized approach to implement adherence measurement and adherence improvement interventions will support the Operational Plan and the National HIV/AIDS Program and provide benefit to patients and ART facilities. In 2005, RPM Plus developed a document, Antiretroviral Therapy Adherence Measurement and Support in South Africa: Initial Activities from July 4 to 26, 2005, containing a proposal on “improving treatment outcomes and preventing resistance to antiretrovirals by enhancing adherence to antiretroviral therapy.” The proposal aimed at the improvement of patient adherence to ARV regimens by providing ART facility staff with tools to collect, analyze, and use information, longitudinally, that will enable them to make well informed decisions about adherence support measures for their patients. The proposal was presented to the National Department of Health (NDoH), U.S. Agency for International Development (USAID) and other key stakeholders at the following forums—

- July 12, 2005—Presented to USAID South Africa
- July 18, 2005—Presented to the NDOH’s HIV directorate’s treatment and support team
- July 21, 2005—Presented to the Eastern Cape HIV and AIDS Director
- July 26, 2005—Presented at the National HIV Directorates Meeting

The proposal planned to address issues related to adherence to ART in the following systematic and organized sequential steps—

1. Develop an instrument to record medication adherence
2. Pilot test the tool

3. Develop database and data management system for adherence measures

4. Implement nationwide adherence measurement

5. Provide ART adherence updates from lessons learned about successful interventions

Following these consultations, the NDoH and USAID approved for the implementation of activities contained in the proposal. It is hoped that RPM Plus, working closely with USAID and other key stakeholders under the leadership of NDoH, will be able to deliver on the critical elements of the proposal and contribute to improved ART health outcomes. The following sections describe the efforts made in implementation of the previously mentioned steps.

1. Develop an Instrument to Record Medication Adherence

The challenges to developing and adopting an adherence measurement tool include—

- Providing evidence about the utility of adherence measurement
- Identifying a measure that meets desired but realistic features and benefits
- Adapting that measure to the peculiarities of the setting where it will be used

The evidence of the utility of adherence measures can be summarized in this WHO statement, “measurement of adherence provides useful information that outcome-monitoring alone cannot provide, but it remains only an estimate of a patient’s actual behavior…without formal assessment, providers are unlikely to accurately identify adherent and non-adherent patients, missing the opportunity for reinforcement and constructive interventions respectively.”

The desire to know what patients do with their prescribed regimens or to understand patient drug-taking behavior dates back to Hippocrates. Ignorance about patient adherence behavior can partially be attributed to providers’ paternalistic perspective and misconceptions that patients are to be blamed for nonadherence. Some of the traditional ways of ensuring that patients have adhered to the prescribed regimen include the use of directly observed treatment and the administration of injections. To measure adherence in an ambulatory ART patient in resource-constrained settings, there is a need for an adherence measurement tool with the following features and benefits—

- Objective in measuring adherence
- Internal consistency
- Positive predictive value
- Suitable for use at routine ART clinics in resource-constrained environments (e.g., simple, nonelectronic, and quick to administer)

To identify available adherence assessment tools that meet these criteria or develop an evidence-base for the development of a tool in the event that such tool could not be identified, RPM Plus conducted a systematic review on adherence measurement.

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Adoption of a Multi-Method Tool

RPM Plus developed a draft tool which was a multi-method adherence assessment form based on previously validated elements including self-report, VAS, PIT, and pill count. The self-report was based upon the Morisky Medication Adherence Scale. Based on the WHO recommendations and the findings from the RPM Plus review of literature (presented at the 26th International AIDS Conference Toronto, Canada, in August 2006 [Annex 1]), the multi-method adherence assessment tool was adopted for further development, adaptation, and implementation in South Africa.

RPM Plus presented a plan to pilot the tool to the Eastern Cape DOH (HIV Directorate, Pharmaceutical Services, and East London Health Complex). The planned activity was shared with the Eastern Cape HIV pharmacists’ quarterly meeting held in East London. The pilot protocol was also submitted to the East London Health Complex Ethics Committee. The Committee provided approval for the work.

2. Pilot Test the Tool

The pilot test was conducted in ART clinics at two hospitals. After receiving an orientation on the use of the tool the participating ART pharmacists at Cecilia Makwane Hospital (CMH) administered the tool in 800 patient contacts. A series of feedback discussion sessions were held involving the participating pharmacists where each element of the form was revised based on this preliminary experience. These revisions primarily addressed patient acceptability and integration of the administration of the tool with the clinical activities of the pharmacists. The revised tool and an associated evaluation tool on the usability was then tested in 440 patient contacts from CMH and Rustenburg Wellness Clinic. This experience revealed that administering the tool took on average five minutes and that the administering pharmacists were of the opinion that the tool was useful in their care of ART patient in the majority of contacts. Furthermore patient characteristics such as language and level of education did not impact upon the usability of the tool. Minor revisions were made to the tool based on these findings and recommendations obtained from the administering pharmacists from the two hospitals. The overall results obtained from this experience indicated the following benefits of the tool—

- Level of effort required to administer it was acceptable for routine use in busy ART clinics
- The tool was user-friendly and can be used by both pharmacists and middle level health care workers

Validation with MEMS

The next part of the pilot consisted of validation of the multi-method tool through comparison with MEMS as the proxy objective measure. The MEMS used for the validation contained a

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61 WHO. 2003 Adherence
medication bottle cap with a micro-switch, a clock, and memory that records the occurrence and time of each bottle opening. This enables continuous assessment of what patients do with prescribed medicines where opening the medicine bottle is regarded as a proxy for actually taking the medicines. In this way a profile of presumed medication taking behavior can be compiled. The MEMS data was used to validate each element of the adherence assessment tool using the Spearman’s coefficient of correlations test. An interim analysis of the data involving 33 patients was performed with a final analysis planned for a later date. Pill dumping whereby the patient intentionally removes doses from the container to appease the clinical staff that they are adherent was suspected in 18 percent of patients.

Each element of the tool tended to overestimate the adherence of the patient; however, the assessment using the multi-method tended to underestimate adherence of the patient when compared with the MEMS observations. It is felt that by under estimating adherence the multi-method approach would likely identify more patients that require adherence improvement measures and hence would protect against the emergence of resistance in those patient that would otherwise be missed if individual components were used on their own as they tended to overestimate adherence. Limitations of this interim analysis are the sample size and the fact that the distribution of patients was not uniform in terms of level of adherence because two-thirds of the patients (66 percent of the 33) were those with high levels of adherence. These interim results were presented both in South Africa and at the American Public Health Association conference in November 2006 (Annex 2). However, the correlations between the multi-method approach and MEMS are sufficiently strong to suggest that a national pilot program would be appropriate in order to use the tool in a more diverse set of environments. It is envisaged that further experiences obtained from this national pilot may provide sufficient grounds for wider implementation. The multi-method tool now called the “Patient Adherence Record” (Annex 3).

3. Develop Database and Data Management System for Adherence Measures

It is planned that the multi-method adherence assessment tool will be completed by health care workers when medicines are refilled. Health care workers will therefore need to be conversant with the use of the tool. To facilitate the process for widespread use of the Patient Adherence Record, RPM Plus has developed a guideline called “Instructions for Completing Patients Adherence Record” (Annex 4). The use of this guideline and brief (one hour) training is thought to be adequate for acquiring necessary skills for administering the tool on patients.

RPM Plus is working with the NDOH to have the Patient Adherence Record included in the patient case file so it will be accessible for use and review by all providers who attend to the patient. This will ensure that any provider attending to the patient has an overview of the patient’s adherence status and can subsequently plan referrals and/or interventions based on that. It will be possible to maintain a longitudinal record of a particular patient’s adherence profile in the case file. Individual patient adherence records will be used in obtaining the facility’s average monthly adherence record. RPM Plus is in discussions with the NDOH to finalize plans for the collection of these aggregate and longitudinal data.
4. Implement Nationwide Adherence Measurement

At the invitation of the NDOH, RPM Plus presented the final form of the Patient Adherence Record to the National/Provincial Meeting on Comprehensive HIV & AIDS Management and Treatment Plan on May 31, 2007 (Annex 5).

At the end of the meeting, the NDOH suggested that RPM Plus collaborate with the department for immediate nationwide implementation of the Patient Adherence Record.

5. Provide ART Adherence Updates from Lessons Learned About Successful Interventions

It is hoped that as soon as implementation experiences are obtained, RPM Plus will collaborate with NDOH to ensure that health care providers, HIV clinicians, and providers who use the tool are given updates on lessons learned from using the tool and implementation of associated interventions. Under NDOH leadership, MSH/RPM Plus will help develop modalities for planning updates and best practice forums.
ANNEX 1. POSTER PRESENTATION AT THE 26TH INTERNATIONAL AIDS, CONFERENCE, TORONTO, CANADA, AUGUST 13–18, 2006

Analyzing Medication Adherence Measurement Tools in Predicting ART Outcomes in Resource-Limited Settings

J. Nwachukwu, G. Shul, and M. P. Joshi

Management Sciences for Health/National Pharmaceutical Management Plus (MSH/NPM Plus)

Background

Medication adherence to antiretroviral therapy (ART) provides an opportunity to reinforce client behavior and improve treatment outcomes. Although various adherence measurement tools have been validated for accuracy, feasibility, and cost-effectiveness, no systematic reviews of validated tools applicable to resource-limited settings exist. In this study, National Pharmaceutical Management (NPM) Plus Program’s objective was to identify validated adherence measurement tools that can be used in client-documented ART in resource-limited settings.

Methods

Search strategy:

- Search scientific literature databases
- Search for articles published between 1980 and 2008
- Search following search terms: adherence, adherence measurement, assessing adherence, compliance, evaluating adherence, level of adherence measurement, adherence, predicting nonadherence, sensitivity of adherence measures, validity of adherence measures
- Do not consider attributes of measurement such as multidimensional, continuous, and time intervals

Inclusion criteria:

- Validation against an objective measure
- Comparison with objective measures (CD4 or viral load) and/or electronic measures (Medication Event Monitoring System (MEMS))
- Reliability as measured by sensitivity, specificity, and/or positive predictive value
- Studies making reference to feasibility, consistency, and/or reproducibility of results

Note: Studies exclusively using electronic measures were excluded.

Results

- Of the 124 studies found, 97 (80 percent) confirmed self-reporting. Of the self-reporting studies, 60 (88 percent) confirmed their reliability to predict adherence (Figure 1).
- Of 24 studies on pill counting, 21 (81 percent) confirmed their reliability.
- Of 15 studies using visual analog scale (VAS), 11 were confirmed reliable.
- All 15 studies using a multistudy tool demonstrated their reliability.
- Pill identification test, pharmacy refill records, and provider estimate methods had weak sensitivity and low predictive values.

Conclusion

ART programs need reliable monitoring client adherence, but validated measurement tools are lacking in resource-limited settings. Based on this analysis, the study identified simple self-report questionnaires, pill counting, and VAS as the best potential adherence measurement tools for resource-limited settings. In settings where these tools have not been tested and calibrated, a multimodal adherence measurement tool is recommended.

BPM Plus is using these results to develop a multimodal tool for use in ART clinics in South Africa, with possible applications in other resource-limited settings.

Recommendations for the Applicability of Tools for Resource-Limited Settings

- ART programs must reliably monitor client adherence.
- Simple self-reporting, pill counting, and VAS are reliable measurement tools for resource-limited settings.
- In settings where these tools have been tested and calibrated, consider using the proposed algorithm (Figure 1).
- In settings where these tools have not been tested and calibrated, a multimodal adherence measurement tool is recommended.

This poster was made possible through support provided by the U.S. Agency for International Development, under the terms of Cooperative Agreement Number AID-OAA-A-00-09-00014-00. The opinions expressed herein are those of the authors and do not necessarily reflect the views of the U.S. Agency for International Development.
Development of a Multimethod Medication Adherence Assessment Tool Suitable for Antiretroviral Therapy Facilities in Resource-Constrained Settings

Gavin Stewart Steel, Shabir Banoo, Mark Paterson, Heidi Van Rooyen, Jude Nwokike, Mohan P. Joshi, Jean-Pierre Sallet, and Gillian Collett

Purpose

- Successful virological control and prevention of resistance to antiretroviral (ARV) medicines requires near perfect levels of adherence
- Experience with long-term therapies has shown that adherence rates are often suboptimal (50%) and tend to drop off with time
- This study discusses an adherence tool designed for routine clinical use by pharmacists, pharmacist’s assistants, and nurses caring for clients receiving antiretroviral therapy (ART)
Objectives

- To develop an adherence measurement tool suitable for use in ART chronic care in resource-limited settings
- Validate the adherence tool
  - Establish correlation between measures
  - Determine subjective utility
  - Set an objective measure
- Measure and stratify the impact on professional time

Method (1)

- The World Health Organization recommends a multimethod approach when measuring patient adherence
- A literature survey was conducted to identify viable adherence measurement methodologies for routine use in ART clinics*
- Only methods that had been validated and that employed nonelectronic measurement strategies were considered

Method (2)

- The four measures included in the multimethod pilot tool were—
  - Self-report
  - Visual Analogue Scale (VAS)
  - Pill identification test
  - Pill count

- The adherence tool developed was administered to patients presenting for routine follow-up ART care at two South African hospitals.

- After each patient contact, the administering health care worker was asked to rank his or her experience with the tool.

Adherence Measurement Tool (1)

Pilot version
Adherence Measurement Tool (2)

Pilot version

I – Personal Descriptive Demographic data

Please provide the following descriptive data about the patient:

1. Home address

2. Education level

3. Treatment Description

4. Age in years

5. Smoking status

6. Antiretroviral history

II – Level of Effort & Utility

This section describes your views upon the health care worker with the specific patient/client:

1. EASILY

2. Difficult but not a major problem

3. Very difficult

4. Patient/client's willingness to participate in the assessment

5. Patient/client's readiness to comply with the instructions

6. Patient/client's understanding of the instructions

Adherence Measurement Tool (3)

Validation version

Patient Adherence record

Adherence score

Global adherence score

Adherence summary

Adherence percentage

Medication schedule

Medication adherence

Medication adherence summary

Medication adherence percentage

Medication adherence summary
Method (3)

- To provide objective data to validate the tool, the following data was collected in a small cohort (10% of original group)
  - Medication Event Monitoring System (MEMS)
  - Viral load and CD4 count
  - A blinded pill count where patients were randomly assigned to receive an undisclosed quantity of medication
### Results—Feasibility

<table>
<thead>
<tr>
<th>Time</th>
<th>Median 5 minutes, 95% confidence interval between 3 to 15 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of education</td>
<td>73%—no more than a secondary education</td>
</tr>
<tr>
<td>Age of respondents</td>
<td>61%—30 to 60 years</td>
</tr>
<tr>
<td>Language</td>
<td>53%—Xhosa</td>
</tr>
<tr>
<td>Interviewer experience</td>
<td>57%—ranked as “extremely useful” or “useful”</td>
</tr>
<tr>
<td>Administration of questionnaire</td>
<td>46%—ranked as “easy and useful”</td>
</tr>
<tr>
<td>Self-report</td>
<td>45%—ranked as “very useful” or “useful”</td>
</tr>
</tbody>
</table>

Note: N = 440
Correlation of Measures

<table>
<thead>
<tr>
<th>Adherence</th>
<th>MEMS</th>
<th>Self-report</th>
<th>Pill count</th>
<th>VAS</th>
<th>Multi-method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>15%</td>
<td>3%</td>
<td>0</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Medium</td>
<td>18%</td>
<td>21%</td>
<td>19%</td>
<td>21%</td>
<td>36%</td>
</tr>
<tr>
<td>High</td>
<td>66%</td>
<td>76%</td>
<td>81%</td>
<td>76%</td>
<td>56%</td>
</tr>
<tr>
<td>Spearman</td>
<td>r = 0.53</td>
<td>r = 0.52</td>
<td>r = 0.41</td>
<td>r = 0.50</td>
<td></td>
</tr>
</tbody>
</table>

Note: N = 33

Pill Count

- 60% of patients were blinded as to the quantity of medicine dispensed
- Pill dumping occurred in at least 18% of blinded patients as evidenced by a pill count > 100%

<table>
<thead>
<tr>
<th>Difference (MEMS – PC)</th>
<th>Blinded</th>
<th>Non-blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>0 to 10</td>
<td>23%</td>
<td>20%</td>
</tr>
<tr>
<td>0</td>
<td>36%</td>
<td>70%</td>
</tr>
<tr>
<td>&lt;0</td>
<td>9%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Clinical Experience

- All patients were on the same nucleoside reverse transcriptase inhibitor (NRTI)-based regimen—EFV, D4T, and 3TC. Average duration of treatment was 6 to 12 months with 5% on ART one to two years.
- With the aid of the tool adherence was assessed in patients presenting with treatment failure. Of these patients—
  - Two thirds had adherence profiles that merited the introduction of a protease inhibitor-based regimen without further intervention
  - The remaining third required additional adherence support measures prior to introducing protease inhibitors to prevent resistance to this second-line regimen
- High levels of adherence were associated with undetectable viral load while nonadherence levels(<55%) were most likely to present with treatment failure.

Summary (1)

- The interview took an average of 5 minutes
- The tool has been administered by both higher levels as well as mid-level health care professionals.
- In the self-report, Boolean {Yes/No} style responses were recommended above rank order because—
  - 20% of interviewers described the use of the rank order as “difficult.” This percentage was linked to patient’s level of education.
  - Ranking numbers had a weak correlation with MEMS \( r = 0.42 \).
  - Ranking process was time consuming to administer.
Summary (2)

- Of the components of the multimethod tool—
  - Self-reporting had the highest correlation with MEMS and viral load
  - VAS and PIT exhibited a weak positive correlation; however, users indicated that the two components added qualitatively to the overall assessment
  - Pill count may be unreliable in patients who have previously counted pills as they may dump pills

Discussion/Findings (1)

- Preliminary experience confirmed that a Boolean-type response offers a practical alternative in the routine assessment of adherence by self-reporting.
- The adherence assessment tool was widely accepted by health care professionals and did not take too long to administer.
- Nonelectronic methods of adherence assessment were found to be reliable when validated against MEMS.
Discussion/Findings (2)

- A multimethod adherence assessment tool is recommended supported by the following—
  - No single measure was demonstrated to be superior
  - Each individual component overestimated adherence to varying extents
  - Individual tool components identified different types of adherence difficulties in patients with moderate to low levels of adherence
  - Overall adherence rating was conservative and was able to identify more patients who may require adherence support

Recommendations

- A simple, multimethod approach could provide a reliable and user-friendly adherence assessment tool for use in pharmaceutical care of ART patients in resource-constrained settings.
- Adherence assessments should be performed on all ART patients presenting with treatment failure as well as those requiring an adherence step-up intervention.
- Adherence rates and support measures employed should be compared among facilities to identify adherence strategies that will improve patient outcomes and preserve effectiveness of currently available ARVs by preventing antimicrobial resistance.
Acknowledgments

- South African Department of Health
- Staff of the Eastern Cape and North West Department of Health, South Africa
- U.S. Agency for International Development
- U.S. President’s Emergency Plan for AIDS Relief
Patient Adherence Record

Version 1.1

<table>
<thead>
<tr>
<th>Folder No.</th>
<th>Date</th>
<th>/</th>
<th>/</th>
<th>(dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment was initiated on  /  /  Duration of treatment  Months/years

Begin by telling the patient that, "Most people with HIV have many pills to take at different times during the day. Many people find it hard to always remember to take their pills. It is important for me to understand how you are really doing with your medicine. Don’t worry about telling me if you don’t always take all your doses. I need to know what is really happening, not what you think I want to hear."

Self-Reporting

Please mark the client’s response to the following questions.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you sometimes find it difficult to remember to take your medicine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When you feel better, do you sometimes stop taking your medicine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thinking back over the past four days, have you missed any of your doses?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sometimes if you feel worse when you take the medicine, do you stop taking it?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Visual Analogue Scale (VAS)

Ask the client to think back over the past four days and identify the times when he or she either missed a dose or took it at the wrong time. Show the client a copy of this visual analogue scale, or an unmarked enlarged version. While placing your finger on the appropriate place, tell the client that if he or she had taken all medicine doses to point to 10. If the client missed all the doses, he or she would point to 0—in the meantime, you move your finger to 0. Now give the client an opportunity to point out their level of adherence. The health care worker then marks the visual analogue scale. If the scale is marked off at 4, then the percentage adherence would be 40 percent.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>

Score   ____%
Pill Identification Test (PIT)

Ask the client to inspect each container and its contents. He or she should then tell you the name of the medication, number of pills to take per dose, the times he or she takes the medication, and whether there are any additional instructions.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Knows the name (Y/N)</th>
<th>Knows the number of pills per dose (Y/N)</th>
<th>Time the medication is taken</th>
<th>Knows any additional instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Morning (hour)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Evening (hour)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Judged correct (Y/N)</td>
<td></td>
</tr>
</tbody>
</table>

Pill Count

Did the client return the medication containers?

*If yes, check that the client only used medication from this container since the date of their last visit. If leftover medication had been used or an emergency prescription obtained, then the calculation will be invalid—omit and move to Adherence Assessment.

\[
\text{% Adherence} = \frac{\text{Dispensed} - \text{Returned}}{\text{Expected to be taken}} \times 100 = \frac{x}{100} = \%
\]

Adherence Assessment

<table>
<thead>
<tr>
<th>Self-reporting</th>
<th>No to all questions</th>
<th>Yes to 1 question</th>
<th>Yes to 2 or more questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>95% or more</td>
<td>75–94%</td>
<td>Less than 75%</td>
</tr>
<tr>
<td>PIT—Client knows the…</td>
<td>Dose, time, and</td>
<td>Dose and time</td>
<td>Dose only or confused</td>
</tr>
<tr>
<td></td>
<td>instructions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pill count</td>
<td>95% or more</td>
<td>75–94%</td>
<td>Less than 75%</td>
</tr>
<tr>
<td>Overall Adherence</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
</tr>
</tbody>
</table>

Adherence Support Measures

<table>
<thead>
<tr>
<th>Code</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS01</td>
<td>Treatment preparedness</td>
</tr>
<tr>
<td>AS02</td>
<td>Treatment buddy or community health worker</td>
</tr>
<tr>
<td>AS03</td>
<td>Home visit</td>
</tr>
<tr>
<td>AS04</td>
<td>Medication counseling—dosing regimen and</td>
</tr>
<tr>
<td></td>
<td>instructions</td>
</tr>
<tr>
<td>AS05</td>
<td>Medication counseling—show and tell</td>
</tr>
<tr>
<td>AS06</td>
<td>Medication counseling—safety</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>AS07</td>
<td>Life style inventory</td>
</tr>
<tr>
<td>AS08</td>
<td>Medication diary</td>
</tr>
<tr>
<td>AS09</td>
<td>Motivational interviewing</td>
</tr>
<tr>
<td>AS10</td>
<td>Reminder such as a pill box</td>
</tr>
<tr>
<td>AS11</td>
<td>Support groups</td>
</tr>
<tr>
<td>AS12</td>
<td>Printed medication information</td>
</tr>
<tr>
<td>AS13</td>
<td>Personalized printed medication information</td>
</tr>
<tr>
<td>AS99</td>
<td>Other—please specify under notes</td>
</tr>
</tbody>
</table>

**Comments** (Insert comments as needed)

---

**Adherence Improvement Plan** (Include details of plan agreed on with client)

---
Instructions for Completing Patient Adherence Record

Version 1.1

Background

This tool has been designed to assist pharmacists, pharmacy assistants, nurses and doctors in the assessment and monitoring of adherence to long term therapies such as antiretroviral treatment. The adherence record should be retained in the client’s medical records for future reference in planning adherence improvement interventions.

The adherence assessment can be performed routinely. However if this is not possible it is recommended that adherence be assessed whenever a viral load is performed, treatment failure is suspected, adherence problems are suspected, a step-up adherence intervention has been initiated and/or when a change in regimen is being contemplated.

This medication adherence record is a multi-method tool comprised of four components that had been previously validated. This approach has been adopted based upon the WHO recommendation that states, “A multi-method approach that combines feasible self-reporting and reasonable objective measures is the current state-of-the-art in measurement of adherence behavior.”

The four sections of the tool include—

1. Self report
2. Visual analogue scale (VAS)
3. Pill identification test (PIT)
4. Pill count

The tool’s fundamental premise is that the regimen, rather than the individual medicines, is the unit for assessing adherence. Selective adherence to some but not all of the medications in the combination regimen means that the intended benefits of combination therapy (pharmacological synergy) are not achieved, and in the instance of infectious disease, may precipitate resistance.

Basic Methodology

The data elements of this adherence assessment tool must be completed by the health care worker administering the tool and not the client.
Before assessing the client’s adherence levels, it is important to set the scene by informing the client that this assessment is not punitive but rather aimed at helping them achieve optimal adherence. A recommended approach would be to tell the client that:

“Most people with HIV have many pills to take at different times during the day. Many people find it hard to always remember to take their pills. It is important for me to understand how you are really doing with your medicine. Don’t worry about telling me if you don’t always take all your doses. I need to know what is really happening, not what you think I want to hear.”

In the self report, the health care worker guides clients through a series of questions to which they respond yes or no. An adherent client will respond no to all questions. This helps validates responses since ordinarily clients tend to respond yes to any questions posed to them by a health care professional to please them.

A visual analogue scale has been included to verify the verbal responses. In this question, clients are asked to rate their adherence to their medication over the past four weeks. The client then indicates on a graduated scale where they believe their adherence has been during this period.

The pill identification test begins with the health care personnel familiarizing themselves with the last prescription that was dispensed. This is then followed by the client being shown a physical example or photograph of the same brand of the tablet, capsule, or bottle for liquid preparations that the client had been given in the preceding month —this is key. The client then attempts to name the product and describes—

- The number of tablets, capsules, and medicine measures that he or she consumes at each dosing interval.
- The exact time when he or she takes the dose. (As the client describes these times, pay careful attention to the spontaneity of the response and not merely the correctness on the dosing times. Probe for further responses.)
- Additional instructions he or she follows when taking the medication such as remembering to have a meal before taking the dose. (If the client does not provide the correct information use open-ended questions to verify how they take their doses.)

Wait until the client has completed explaining all of the medications in the regimen before providing corrective counseling for any medication that requires it.

In the pill count, the returned medication is counted and the percentage adherence is calculated using the equation provided. Note that the denominator is the amount of medication that the client is expected to have taken and not the amount that was dispensed.

**Detailed Instructions**

<table>
<thead>
<tr>
<th>Folder No.</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>(dd/mm/yyyy)</td>
<td>/</td>
</tr>
</tbody>
</table>
The folder number and date are recorded to allow copies of the form to be kept in the client’s folder. Changes in the client’s adherence can also be monitored over time. Ongoing monitoring of adherence is important as adherence generally tends to decrease with time.

Treatment was initiated on __/__/____ Duration of treatment __________ Months/years

**Self Report**

Clients tend to answer yes to questions posed to them by their health care provider to please them. Based upon this observation, the questions have been designed so that an adherent client gives a no response.

A. Do you sometimes find it difficult to remember to take your medication?  
*This question aims to test whether there are established dosing cues in the client’s daily routine.*

B. When you feel better, do you sometimes take a break from your medication?  
*Clients frequently stop taking their medication when their presenting health problem has been resolved.*

C. Thinking back over the past four days, have you missed any of your doses?  
*Try to get the client to think back over the past few days. It may help to identify a routine daily event such as meals, work, or television programs watched, and enquire about the nature of that event four days previously. For example, ask the client what they had for dinner on Tuesday.*

D. Sometimes if you feel worse when you take the medicine, do you stop taking it?  
*If the presenting health problem has not produced symptoms or the problems have been resolved, and there are bothersome side effects from the medicine, clients find it difficult to rationalize continued adherence.*

**Assessing Adherence**

Count the number of No answers to questions A through D.

- If all 4 answers are No, then the client is classified as being highly adherent.
- If there is 1 Yes answer, then the client is classified as being moderately adherent.
- Where there are 2 or more Yes answers, the client is classified as having low adherence.
**Visual Analogue Scale (VAS)**

Ideally, use a laminated visual analogue scale (ruler) that has been enlarged or the scale on the questionnaire. Whichever form of the scale you use, it is important that you use an **unmarked** one. While placing your finger on 10, tell the client to also point to 10 if he or she had taken all medicine doses. If the client missed all the doses, he or she would point to 0—in the meantime, you move your finger to 0. For a client using the visual analogue scale for the first time, it may help to ask the client to indicate where a theoretical client who managed to take all the doses would point, then to indicate where the theoretical client who had missed all of his or her doses would point. Note that during this demonstration we are using the third person. Now ask the client to think back about the dosing of their medication over the past four days. Having given the client time to reflect ask them to place their finger on the point on the scale (ruler) that best reflects his or her adherence during this time.

![Visual Analogue Scale (VAS)](image)

Now score the percentage on the box as follows if the client chose 4, then the score will be 40 percent.

**Pill Identification Test (PIT)**

Familiarize yourself with the last prescription that was dispensed to the client. Pay careful attention to the brand that was dispensed in order to identify the identical product that the client has been using. Show the client a physical example or photograph of the identical tablet, capsule, or bottle for liquid preparations that he/she was given in the preceding month.

Ask the client to inspect the contents of each container and its contents, and tell you the

- Medication’s name
- Number of pills to take per dose
- The actual times he or she takes the medication
- If there are any additional instructions relating to the medication such as store in a refrigerator, take with food, or avoid other medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Knows the name (Y/N)</th>
<th>Knows the number of pills per dose (Y/N)</th>
<th>Time the medication is taken</th>
<th>Knows any additional instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Morning (hour)</td>
<td>Judged correct (Y/N)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Evening (hour)</td>
<td></td>
</tr>
</tbody>
</table>
**Instructions for Completing Patient Adherence Record**

- In the left hand column under medication, record the medication that has been assessed—feel free to use abbreviations, e.g., 3TC, to reduce the amount of writing.

- Ask the client to provide the name of the medication. Record the response by recording a Y for yes (correct response) and an N for no (incorrect response). If the response is incorrect, teach him or her the name of the medication. Note—the client’s response to this question is not included in the adherence assessment.

- Ask clients how many tablets, capsules, or medicine measures they take in the morning and then in the evening. If their response is correct for both, place a Y in the column; if either or both of the dosing times are incorrect, place an N in the box.

- Now ask the clients to identify the usual time they take their morning and evening doses. Record the actual times in the boxes provided. As the client describes these times, pay careful attention to the spontaneity of the response, not only the correctness of responses in terms of the dosing times. If there is hesitation, it may mean that they are taking their medication at inconsistent times (e.g., 1700h today, then 2000h tomorrow). Explore with the client whether or not it is possible for them to take their medication at a consistent time. This is achieved by taking a brief inventory of their daily activities during a typical week day followed by differences in schedule over weekends. If the times they take the medication are within reasonable limits (one hour) of the dosing interval, place a Y in the column; if incorrect, place an N in the column.

  Example: If the first dose of a 12-hour regimen is taken at 0700h, then ideally the evening dose would be 1900h; however, if the client takes their medication any time between 1800h and 2000h, it is considered acceptable for most medications. If you are uncertain about this, contact a person knowledgeable in pharmacology.

- Where the regimen is associated with a particular additional instruction, ask the client if there is anything special that they have to do when taking the dose such as the need to take the dose before or after a meal. If the client does not provide the correct information use open-ended questions to verify how they take their doses. If correct, place a Y in the column; if incorrect, a N.

Wait until the client has completed providing responses on all of the medications in the regimen before providing corrective counseling for any medication that may be required.

**Example:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Knows the name (Y/N)</th>
<th>Knows the number of pills per dose (Y/N)</th>
<th>Time the medication is taken</th>
<th>Knows any additional instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Morning (hour)</td>
<td>Evening (hour)</td>
</tr>
<tr>
<td>D4T</td>
<td>Y</td>
<td>Y</td>
<td>0715h</td>
<td>2000h</td>
</tr>
<tr>
<td>3TC</td>
<td>Y</td>
<td>Y</td>
<td>0715h</td>
<td>2000h</td>
</tr>
</tbody>
</table>
Pill Count

Did the client bring his or her medication containers back? Yes  No

Calculated percentage adherence

\[
\% \text{ Adherence} = \frac{\text{Dispensed} - \text{Returned}}{\text{Expected to be taken}} \times 100
\]

• If the client returns the container, then check the yes box; and if the client did not, check the no box.

• For those clients who have not returned their medication container, skip the pill count calculation and move directly to the adherence assessment section.

• Check that the client only used medication from this container since the date of his or her last visit. If leftover medication had been used or an emergency prescription obtained, then the calculation will be invalid and should not be completed.

• Record the quantity dispensed during the last visit in the space that says \textit{dispensed}.

• Count the remaining tablets and write it in the space that says \textit{returned}.

• Next count the number of days since the medication has been dispensed. Multiply the number of days by the prescribed number of tablets to be taken in a day. Example: 2 tablets twice daily = 2 x 2 = 4 tablets per day for 27 days = 4 x 27 = 108.

• The percentage adherence is then calculated as the number dispensed minus the number returned which is then divided by the number of tablets the client should have taken.

Example: If 120 were dispensed and the client returned with 17 tablets and the regimen required 2 tablets twice a day to be taken for 27 days, the percentage adherence is—

\[
\% \text{ Adherence} = \frac{120 - 17}{108} \times 100 = 95\%
\]
Instructions for Completing Patient Adherence Record

Adherence Assessment

<table>
<thead>
<tr>
<th>Self-reporting</th>
<th>No to all questions</th>
<th>Yes to 1 question</th>
<th>Yes to 2 or more questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>95% or more</td>
<td>75–94%</td>
<td>Less than 75%</td>
</tr>
<tr>
<td>PIT—Client knows the...</td>
<td>Dose, time, and instructions</td>
<td>Dose and time</td>
<td>Dose only or confused</td>
</tr>
<tr>
<td>Pill count</td>
<td>95% or more</td>
<td>75–94%</td>
<td>Less than 75%</td>
</tr>
<tr>
<td>Overall Adherence</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
</tr>
</tbody>
</table>

Check the results in the columns provided—

- If all the results appear in the same column, e.g., “All No,” “VAS 95% or more,” “Dose, Time, and Instructions,” and the pill count was 95 percent or more, then the overall level of adherence is “High.”

- Although you may not have responses to all the four methods, you can still use this tool. Remember that each one of these measures indirectly assesses adherence but is slightly over or under what the adherence really is. So, the more measures that can be recorded, the stronger the probability that the adherence assessment accurately shows how the client takes medicine. This multi-method approach provides data from different sources that can be compared to assess client adherence (triangulation) to verify the true level of adherence.

- At the very minimum you should record the results of the self report. However, this has a tendency to measure higher levels of adherence than actually happened.

- When the results do not all line up in a single vertical column—
  - If they are spread over two columns, take the adherence level of the right hand column as the estimated adherence.
  - If they are spread over three columns, then use the middle level of adherence.

Example

<table>
<thead>
<tr>
<th>Self-reporting</th>
<th>No to all questions</th>
<th>Yes to 1 question</th>
<th>Yes to 2 or more questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>95% or more</td>
<td>75–94%</td>
<td>Less than 75%</td>
</tr>
<tr>
<td>PIT—Client knows the...</td>
<td>Dose, time, and instructions</td>
<td>Dose and time</td>
<td>Dose only or confused</td>
</tr>
<tr>
<td>Pill count</td>
<td>95% or more</td>
<td>75–94%</td>
<td>Less than 75%</td>
</tr>
<tr>
<td>Overall Adherence</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
</tr>
</tbody>
</table>

Adherence in this client has been recorded as moderate because self report had 1 yes answer.
Note: We record the level of adherence as High, Moderate, or Low instead of as a percentage. The percentage is important in a clinical trial; however, in clinical practice, the question we are trying to answer is whether or not there is sufficient adherence to prevent resistance or whether adherence support interventions are needed.

- If the level of adherence is high, record it in the clinic record and provide the client with reinforcement.

- For moderate levels of adherence, discuss the result with the client and continue to measure adherence levels. If moderate levels of adherence have been observed for three sequential visits, institute an adherence support measure.

- If a low level of adherence or non-adherence has been observed—
  - Refer the client to a pharmacist for a step-up adherence intervention such as motivational interviewing.
  - Monitor CD4 count as per usual and monitor viral load as the client is at risk of developing resistance.

**Adherence Support Measures**

Review the clinic records as well as past adherence assessment records and verify with the clients whether or not they had any additional aids to assist them in remembering to take their medications and record the menu of measures in the boxes provided by checking off the appropriate box. It is likely with any given client that more than one of the measures may have been used.

<table>
<thead>
<tr>
<th>Code</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS01</td>
<td>Treatment preparedness</td>
</tr>
<tr>
<td>AS02</td>
<td>Treatment buddy or community health worker</td>
</tr>
<tr>
<td>AS03</td>
<td>Home visit</td>
</tr>
<tr>
<td>AS04</td>
<td>Medication counseling—dosing regimen and instructions</td>
</tr>
<tr>
<td>AS05</td>
<td>Medication counseling—show and tell</td>
</tr>
<tr>
<td>AS06</td>
<td>Medication counseling—safety</td>
</tr>
<tr>
<td>AS07</td>
<td>Life style inventory</td>
</tr>
<tr>
<td>AS08</td>
<td>Medication diary</td>
</tr>
<tr>
<td>AS09</td>
<td>Motivational interviewing</td>
</tr>
<tr>
<td>AS10</td>
<td>Reminder such as a pill box</td>
</tr>
<tr>
<td>AS11</td>
<td>Support groups</td>
</tr>
<tr>
<td>AS12</td>
<td>Printed medication information</td>
</tr>
<tr>
<td>AS13</td>
<td>Personalized printed medication information</td>
</tr>
<tr>
<td>AS99</td>
<td>Other—please specify under notes</td>
</tr>
</tbody>
</table>

Tick off the corresponding blocks for those adherence support measures that the client has been exposed to. The notes section allows for an expanded description of other interventions or the success or failures of the interventions.
This record allows the pharmacist to decide on adherence support measures in those clients who require an adherence improvement intervention.

### Comments (Insert comments as needed)

The comments section allows the pharmacist to record—

- A more detailed description of any identified adherence barriers
- Counseling points to facilitate incremental counseling
- Any pertinent information that would enrich future adherence counseling or other improvement interventions

### Adherence Improvement Plan (Include details of plan agreed on with client)

This block allows the pharmacist to develop an adherence improvement plans for those clients who require it. It also serves to record planned future interventions for clients who are being actively monitored for the need of additional adherence improvement interventions.
Proposed Implementation of a Multimethod Medication Adherence Assessment Tool to support the “Comprehensive Plan” in South Africa

Gavin Steel, Shabir Banoo and Jean-Pierre Sallet
RPM Plus/MSH
Background

- Successful virological control and prevention of resistance to antiretroviral (ARV) medicines requires near perfect levels of adherence.
- Experience with long-term therapies has shown that adherence rates are often suboptimal (50%) and tend to drop off with time.
- An adherence tool designed for routine clinical use by pharmacists, pharmacist’s assistants, and nurses caring for clients receiving antiretroviral therapy (ART) was developed and tested by RPM Plus.

Objectives

- Prevent antimicrobial resistance.
- Preserve first line therapy effectiveness through sustained high levels of adherence.
- Support NDOH adherence strategy.
Method (1)

- The World Health Organization recommends a multimethod approach when measuring patient adherence
- A literature survey was conducted to identify viable adherence measurement methodologies for routine use in ART clinics*
- Only methods that had been validated and that employed non electronic measurement strategies were considered


Method (2)

- The four measures included in the multimethod pilot tool were—
  - Self-report
  - Visual Analogue Scale (VAS)
  - Pill identification test (PIT)
  - Pill count
- The adherence tool developed was administered to patients presenting for routine follow-up ART care
- After each patient contact, the administering health care worker was asked to rank his or her experience with the tool
# Development of a Multi-Method Tool to Measure ART Adherence in Resource-Constrained Settings

## Patient Adherence Record

### Version 1.1

<table>
<thead>
<tr>
<th>Folder No.</th>
<th>Date of Visit (dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment was initiated on** / / **Duration of treatment** / **years**

Despite having the patient take ART, **“Most people with HIV have many pills to take at different times during the day. Many people find it hard to always remember to take their pills. It is important for me to understand how you are really doing with your medicine. Don’t worry about telling me if you don’t always take all of your doses. I need to know what is really happening, not what you think I want to hear.”**

### Self-Reporting

**Please mark the client’s response to the following questions.**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you sometimes find it difficult to remember to take your medicine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When you feel better, do you sometimes stop taking your medicine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Thinking back over the past four days, have you missed any of your doses?</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Visual Analogue Scale (VAS)**

Ask the client to think back over the past four days and identify the times when he or she either missed a dose or broke it in the wrong time. Show the client a copy of the Visual Analogue Scale or an unmarked unslashed version. While placing your finger on the appropriate place, tell the client that if he or she has taken all medicines, please point to 10. If the client started all the doses, he or she would point to 0—in the meantime, you move your finger to 0. Now give the client an opportunity to point out their level of adherence. The health care worker then marks the visual analogue scale and records the adherence score. The result is noted on 0–10 scale, with the percentage adherence could be 0–99 percent.

### Pill Identification Test (PIT)

Ask the client to inspect each container and its contents. He or she should then tell you the name of the medication, number of pills to take per dose, the times he or she takes the medication, and whether there are any missed doses.

**Medication**

<table>
<thead>
<tr>
<th>Knows the name (VAS)</th>
<th>Knows the number of pills per dose (VAS)</th>
<th>Knows the timing (VAS)</th>
<th>Knows any side effects (VAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pill Count**

Did the client return the medication container?

- Yes
- No

If Yes, check that the client only used medication from this container since the date of their last visit. If the client had obtained an emergency prescription obtained, then the calculation will be adjusted—kept in adherence assessment.

<table>
<thead>
<tr>
<th>% Adherence = Dispensed - Returned</th>
<th>%</th>
<th>X 100 =</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Adherence Assessment

**Self-reporting**

<table>
<thead>
<tr>
<th>VAS</th>
<th>All No answers</th>
<th>1 Yes answer</th>
<th>2 or more Yes answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
<td></td>
<td>%</td>
</tr>
</tbody>
</table>

**PIT—Client Answers Yes**

- Time and Instructions
- Dose and Time
- Dose only

**Pill count**

- 99 to 100
- 71 to 99
- Less than 71

**Overall Adherence**

- High
- Moderate
- Low

### Adherence Support Measures

**Code**

- A501 Treatment adherence
- A502 Treatment buddy or community health worker
- A503 Home visit
- A504 Health education—dosing regimen and instructions
- A505 Medication adherence—draw and tell
- A506 Medication adherence—call
- A507 Life style inventory
- A508 Medication diary
- A509 Medication adherence—teaching
- A510 Reminder such as a pill box
- A511 Support groups
- A512 Printed medication information
- A513 Personalized printed medication information
- A519 Other—please specify under notes

**Notes**

**Comments**

**Adherence Improvement Plan**

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

48
Composite assessment - triangulation

<table>
<thead>
<tr>
<th>Method (3)</th>
<th>To provide objective data to validate the tool, the following data was collected in a small group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Medication Event Monitoring System (MEMS)</td>
</tr>
<tr>
<td></td>
<td>- Viral load and CD4 count</td>
</tr>
<tr>
<td></td>
<td>- A blinded pill count where patients were randomly assigned to receive an undisclosed quantity of medication</td>
</tr>
</tbody>
</table>
### Results—Feasibility

<table>
<thead>
<tr>
<th>Time</th>
<th>Median 5 minutes, 95% confidence interval between 3 to 15 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of education</td>
<td>73%—no more than a secondary education</td>
</tr>
<tr>
<td>Age of respondents</td>
<td>61%—30 to 60 years</td>
</tr>
<tr>
<td>Language</td>
<td>53%—Xhosa</td>
</tr>
<tr>
<td>Interviewer experience</td>
<td>57%—ranked as “extremely useful” or “useful”</td>
</tr>
<tr>
<td>Administration of questionnaire</td>
<td>46%—ranked as “easy and useful”</td>
</tr>
<tr>
<td>Self-report</td>
<td>45%—ranked as “very useful” or “useful”</td>
</tr>
</tbody>
</table>

**Note:** N = 440

### Correlation of Measures

<table>
<thead>
<tr>
<th>Adherence</th>
<th>MEMS</th>
<th>Self-report</th>
<th>Pill count</th>
<th>VAS</th>
<th>Multi-method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>15%</td>
<td>3%</td>
<td>0</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Medium</td>
<td>18%</td>
<td>21%</td>
<td>19%</td>
<td>21%</td>
<td>36%</td>
</tr>
<tr>
<td>High</td>
<td>66%</td>
<td>76%</td>
<td>81%</td>
<td>76%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Spearman:
- Low: $r = 0.53$
- Medium: $r = 0.52$
- High: $r = 0.41$
- Multi-method: $r = 0.73$

**Multi method score:** $r = 0.73$ 95% CI 0.5 – 0.85
Pill Count

- 60% of patients were blinded as to the quantity of medicine dispensed
- Pill dumping occurred in at least 18% of blinded patients as evidenced by a pill count > 100%

<table>
<thead>
<tr>
<th>Difference (MEMS – PC)</th>
<th>Blinded</th>
<th>Non-blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>0 to 10</td>
<td>23%</td>
<td>20%</td>
</tr>
<tr>
<td>0</td>
<td>36%</td>
<td>70%</td>
</tr>
<tr>
<td>&lt;0</td>
<td>9%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Summary (1)

- The interview took an average of 5 minutes
- The tool has been administered by both higher levels as well as mid-level health care professionals.
- In the self-report, “YES/NO” style responses were recommended above rank order because—
  - 20% of interviewers described the use of the rank order as “difficult.” This percentage was linked to patient’s level of education.
  - Ranking numbers had a weak correlation with MEMS \( r = 0.42 \).
  - Ranking process was time consuming to administer.
Summary (2)

- Of the components of the multimethod tool—
  - Self-reporting had the highest correlation with MEMS and viral load
  - VAS and PIT exhibited a weak positive correlation; however, users indicated that the two components added qualitatively to the overall assessment
  - Pill count may be unreliable in patients who have previously counted pills as they may dump pills

Discussion/Findings (1)

- Preliminary experience confirmed that a YES/NO-type response offers a practical alternative in the routine assessment of adherence by self-reporting
- The adherence assessment tool was widely accepted by health care professionals and did not take too long to administer
- Nonelectronic methods of adherence assessment were found to be reliable when validated against MEMS
Discussion/Findings (2)

- A multi-method adherence assessment tool is recommended supported by the following—
  - No single measure was demonstrated to be superior
  - Each individual component overestimated adherence to varying extents
  - Individual tool components identified different types of adherence difficulties in patients with moderate to low levels of adherence
  - Overall adherence rating was conservative and was able to identify more patients who may require adherence support

Proposed Way Forward

- Presentation to National CCMT
- Identify Provincial counterparts and sites in all 9 provinces
- Conduct training
- Conduct follow-up visits
- Quarterly review and reporting to CCMT
- Standardization of adherence assessment for use in patient care
Other RPM Plus adherence support activities

- Down referral
- Advanced adherence counseling skills training
  - Show & tell
  - Motivational interviewing
- HIV/AIDS Pharmaceutical management training

Acknowledgments

- South African Department of Health
- Staff of the Eastern Cape and North West Department of Health, South Africa
- U.S. Agency for International Development
- PEPFAR