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

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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)

CONTENTS

ACRONYMS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
CASI	Computer-Assisted Self-Interviewing
CMH	Cecilia Makwane Hospital
DOH	South Africa Department of Health
DOT	directly observed treatment
HIV	human immunodeficiency virus
MEMS	Medication Event Monitoring System
MSH	Management Sciences for Health
NDOH	National Department of Health
PAHO	Pan American Health Organization
PC	pill count
PIT	Pill identification test
RPM Plus	Rational Pharmaceutical Management Plus (Program) [MSH]
TDM	therapeutic drug monitoring
USAID	U. S. Agency for International Development
VAS	visual analogue scale
WHO	World Health Organization

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.[1] South Africa bears a huge burden of the HIV/AIDS epidemic. About 5.54 million people were estimated to be living with HIV in South Africa in 2005, with 18.8 percent of the adult population (15-49) affected.[2] Initially, challenges for confronting the AIDS epidemic was primarily concentrated on access to antiretroviral (ARV) medicines. 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.[3] 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.[4]

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.[5] 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

[1] UNAIDS. 2006. AIDS Epidemic update. <http://www.unaids.org/en/HIV_data/epi2006/default.asp> (accessed June 1, 2007).
[2] Department of Health. HIV and AIDS and STI Strategic Plan for South Africa 2007-2011. <http://www.doh.gov.za/docs/hivaids-progressrep.html> (accessed June 1, 2007).
[3] Little, S., S. Holte, J. Routy, et al. 2002. Antiretroviral drug resistance among patients recently infected with HIV. N Engl J Med 347:385-394.
[4] Pablos-Méndez, A., M. Raviglione, A. Laszlo, et al. 1998. Global Surveillance for Antituberculosis-Drug Resistance, 1994–1997. N Engl J Med 338(23):1641-1649.
[5] There are several articles and studies on the cost of nonadherence to other chronic diseases.

readily available in the literature.[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.[7]

[6] World Health Organization (WHO). 2003. Adherence to long-term therapies: evidence for action. Geneva: WHO.

[7] Schackman, B.R., R. Finkelstein, C.P. Neukermans, et al. 2005. The cost of HIV medication adherence support interventions: results of a cross-site evaluation. AIDS Care 17(8):927-37.

LITERATURE REVIEW ON MEASURING ADHERENCE

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
[9] WHO. 2003. Adherence.
[10] Stein, M.D., J.D. Rich, J. Maksad, et al. 2000. Adherence to antiretroviral therapy among HIV-infected methadone patients: effect of ongoing illicit drug use. Am J Drug Alcohol Abuse,26:195-205.
[11] Chesney, M.A. 2000. Factors affecting adherence to antiretroviral therapy. Clin Infect Dis 2000; 30 S171–S76.
[12] Paterson, D., S. Swindells, J. Mohr, et al. 2000. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Int Med: 21-30.
[13] Mills, E.J., J.B. Nachega, D.R. Bangsberg, et al. 2006. *Adherence to HAART: A Systematic Review of Developed and Developing Nation Patient-Reported Barriers and Facilitators*. PLoS Med. 3(11):e438.
[14] Orrell, C., D.R. Bangsberg, M. Badri, et al. 2003. Adherence is not a barrier to successful antiretroviral therapy in South Africa. AIDS 17: 1369-75.
[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[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.[17]

Paterson's et al[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.[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.[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.

[16] WHO. 2003. Adherence.
[17] Miller, V., C. Sabin, A. Phillips, et al. 2000. The impact of protease inhibitor containing highly active antiretroviral therapy on progression of HIV disease and its relationship to CD4 and viral load. AIDS 14(14): 2129-2136.
[18] Paterson, D.L., et al. 2000. Adherence. Ann Intern Med.
[19] Hogg, R., B. Yip, K. Chan. 2000. Nonadherence to triple combination therapy is predictive of AIDS progression and death in HIV-positive men and women. Paper presented at the 13th International AIDS Conference, July 9-14, Durban, South Africa.
[20] Wagner, G. 2004. Measuring Instruments and Predictors in Medication adherence in HIV/AIDS. In Medication Adherence in HIV/AIDS edited by Jeffrey Laurence. New York: Mary Ann Liebert, Inc.

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.[21] 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[22] should cover the following areas—

Metric	Derivation
Percent Adherence	Ratio (number of pills taken/number of pills prescribed)[23]
Percent Adherent Dosing Days	Ratio (number of days dose taken/number of days of dosing)[24]
Therapeutic Coverage	Ratio (time spent with inefficacious drug concentrations/time on therapy)[25]
Frequency of Drug Holidays	Frequency of ≥3 days without drug intake[26]

[21] Nunnally, J., and I. Bernstein. 1994. Psychometric theory. 3rd ed. New York, McGraw-Hill.
[22] Kenna, L., L. Labbe, J. Barrett, et al. 2005. Modeling and Simulation of Adherence: Approaches and Applications in Therapeutics. AAPS Journal 07(02):E390-E407.
[23] Cramer, J.A., R.H. Mattson, M.L. Prevey, et al. 1989. How often is medication taken as prescribed? A novel assessment technique. JAMA 261:3273-3277.
[24] Vrijens, B., and E. Goetghebeur. 1997. Comparing compliance patterns between randomized treatments. Control Clin Trials 18:187-203.
[25] Urquhart J. 1994. Role of patient compliance in clinical pharmacokinetics. A review of recent research. Clin Pharmacokinet 27:202-215.
[26] Vrijens, B., E. Tousset , P. Gaillard, et al. 2005. Major features of dose omissions in 87 ambulatory drug trials. Clin Pharmacol Ther 77: 99.

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.

[27] Lanzafame, M., M. Trevenzoli, A. Cattelan, et al. 2000. Directly observed therapy in HIV: A realistic perspective. J Acquir Immune Defic Syndr 25:200-201.
[28] Farmer P., F. Léandre, J. Mukherjee, et al. 2001. DOT-HAART explained: Community-based approaches to HIV treatment in resource-poor settings. ImpActAIDS. *http://www.impactaids.org.uk/farmer.htm*

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 industry[31] 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.[34,35,36,37,38,39,40]

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[29] Bangsberg, D., F. Hecht, E. Charlebois, et al. 2001. Comparing objective methods of adherence assessment: Electronic medication monitoring and unannounced pill count. *AIDS Behav* 2001;5:275-281

[30] Arnsten, J., P. Demas, H. Farzadegan, et al. 2001. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: Comparison of self-report and electronic monitoring. *Clin Infect Dis* 33:1417-1432

[31] MEMS became commercially available in 1987.

[32] Shuter, J. 2004. Measuring adherence. http://www.hivguidelines.org/admin/files/ce/slide-presentations/measuring-adherence.ppt#267,9,Slide 9 (accessed June 1, 2007)

[33] Liu, H., C. Golin, and L. Miller. 2001. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med* 134(10):968-77.

[34] Godin, G., C. Gagne, and H. Naccache. 2003. Validation of a Self-Reported Questionnaire Assessing Adherence to Antiretroviral Medication. *AIDS Patient Care STDs* 17(7):325-332.

[35] Arnsten, J., P. Demas, M. Gourevitch, et al. 2000. *Adherence and viral load in HIV-infected drug users: comparison of self-report and medication event monitors (MEMS).* Abstract no. 69, Seventh Conference on Retroviruses and Opportunistic Infections, January 30-February 2, 2000, San Francisco, CA.

[36] Ferris, D., H. Dawood, M. Chiasson, et al. 2004. *Self-reported adherence to antiretroviral therapy and virologic outcomes in HIV-infected persons in Durban, KwaZulu Natal, South Africa*. Paper presented at XV International AIDS Conference, July 11-16, Bangkok, Thailand.

[37] Haubrich, R.H., S.J. Little, J.S. Currier, et al. 1999. The value of patient reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. *AIDS* 13(9):1099-1107.

However, there is also evidence that self-report may overestimate adherence even when questions are asked in non-judgmental manner.[41] While self-reporting is easy to use, it is vulnerability to fabrications, to the dynamics of provider-patient relationship and may over-estimate 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,[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,[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.[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,[45,46,47] 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.[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.

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

[38] Brown, S., G. Friedland, and U. Bodasing. 2004. *Assessment of adherence to antiretroviral therapy in HIV-infected South African adults.* Abstract B12223 presented at the XV International AIDS Conference, July 11-16, Bangkok, Thailand.
[39] Mannheimer, S., G. Friedland, and J. Matts. 2002. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis* 34:1115-21.
[40] Fletcher, C., M. Testa, R. Brundage, et al. 2005. Four measures of antiretroviral medication adherence and virologic response in AIDS clinical trials group study 359. *J Acquir Immune Defic Syndr* 40(3):301-6.
[41] British HIV Association/Medical Society for the Study of Venereal Diseases (MSSVD). 2002. Guidelines on provision of adherence support to individuals receiving antiretroviral therapy. <http://www.aidsmap.com/cms1032065.asp> (accessed June 1, 2007).
[42] Liu, H., et al. 2001. A comparison study of multiple measures. *Ann Intern Med.*
[43] Feinstein, A.R. 1990. On white-coat effects and the electronic monitoring of compliance. *Arch Intern Med* 150:1377-1378.
[44] N. Crichton. 2001. Journal of Clinical Nursing, 10, 697±706. Blackwell Science Ltd.
[45] Walsh, J., S. Mandalia, B. Gazzard. 2002. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS* 2002 Jan 25;16(2):269-77.
[46] Giordano, T., D. Guzman, R. Clark, et al. 2004. Measuring Adherence to Antiretroviral Therapy in a Diverse Population Using a Visual Analogue Scale. *HIV Clin Trials*. 5(2):74-79.
[47] Maneesriwongul, W., A. Willaims. 2004. *Measuring medication adherence AIDS patients in Thailand: A pilot study*. Paper presented at XV International Conference on AIDS, July 11–16, Bangkok, Thailand.
[48] Parienti, J., R. Verdon, and C. Bazin. 2001. The pills identification test: a tool to assess adherence to antiretroviral therapy. *JAMA* 285(4):412.

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.[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.[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.[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[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.[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.

[49] WHO. 2003. *Adherence*.
[50] Hirschhorn, L., R. Mukherjee, S. Manheimer, et al. 2002. *A multi-method approach to measuring antiretroviral therapy (ART) adherence from the cross-site SPNS adherence collaboration*. Abstract WePeB5819, XIV International AIDS Conference, July 7-12, Barcelona, Spain.
[51] Oyugi, J., J. Byakika-Tusiime, E. Charlebois E, et al. 2004. Measures of Adherence Indicate High Levels of Adherence to Generic HIV Antiretroviral Therapy in a Resource-Limited Setting. *J Acquir Immune Defic Syndr* 36, :5.
[52] Llabre, M., K. Weaver, R. Durán, et al. 2006. A Measurement Model of Medication Adherence to Highly Active Antiretroviral Therapy and Its Relation to Viral Load in HIV-Positive Adults. *AIDS Patient Care STDs* 20(10):701 -711.
[53] Nwokike, J., G. Steel, and M. Joshi. Analyzing medication adherence measurement tools in predicting ART outcomes in resource-limited settings. www.aids2006.org/admin/images/upload/1004.pdf.
[54] Goldie, S.J., A.D. Paltiel, M.C. Weinstein, et al. 2003. Projecting the cost-effectiveness of adherence interventions in persons with human immunodeficiency virus infection. *Am J Med* 115:632-641.
[55] Schackman, B.R., R. Finkelstein, C.P. Neukermans, et al. 2005. The cost of HIV medication adherence support interventions: results of a cross-site evaluation. *AIDS Care* 17(8):927-37.

RPM PLUS ADHERENCE ACTIVITIES IN SOUTH AFRICA

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.[56] 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,*[57] 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

[56] South Africa Department of Health. 2003. *Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa*. (assessed March 14, 2007) <http://www.info.gov.za/issues/hiv/careplan.htm>

[57] Steel, G., M. Joshi, and S. Paige. 2005. *Antiretroviral Therapy Adherence Measurement and Support in South Africa: Initial Activities from July 4 to 26, 2005.* Submitted to the U.S. Agency for International Development by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health.

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."[58]

The desire to know what patients do with their prescribed regimens or to understand patient drug-taking behavior dates back to Hippocrates.[59] 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.

[58] WHO. 2003. *Adherence to long-term therapies: evidence for action*. Geneva: WHO.
[59] Cramer, J.A., and B. Spilker, eds. 1991. *Patient Compliance in Medical Practice and Clinical Trials*. New York: Raven Press Ltd.

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.[60] Based on the WHO recommendations[61] 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 Rusternburg 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

[60] Morisky, D.E., L.W. Green, and D.M. Levine. 1986. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 24:67-74.
[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

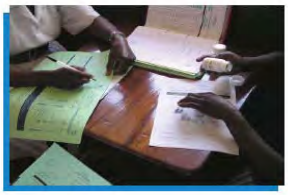
J. Nwokike,* G. Steel,* and M. P. Joshi*

*Management Sciences for Health/Rational Pharmaceutical Management Plus (MSH/RPM Plus)

Background

Formally assessing medication adherence in antiretroviral therapy (ART) provides an opportunity to reinforce client behavior or use constructive interventions to address problems. Although various adherence measurement instruments have been validated for accuracy, dependability, and consistency, no systematic review of validated tools applicable to resource-limited settings exists. In this study, Rational Pharmaceutical Management (RPM) Plus Program's objective was to identify validated adherence measurement tools that can be tested on clients undergoing ART in resource-limited settings.

Methods



Search strategy—

- Examine 15 scientific literature databases
- Search for articles published between 1995 and 2005
- Use the following search terms: adherence, adherence measures, assessing adherence, compliance, evaluating adherence, levels of adherence measuring 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 measure (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 dependability, consistency, and reproducibility of results

Note: Studies exclusively using electronic measures were excluded.

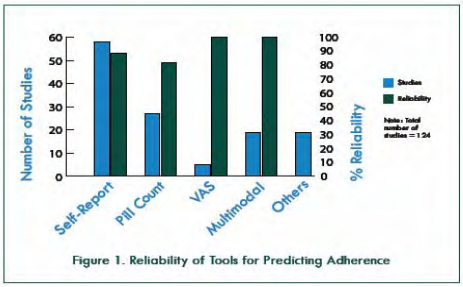


Figure 1. Reliability of Tools for Predicting Adherence

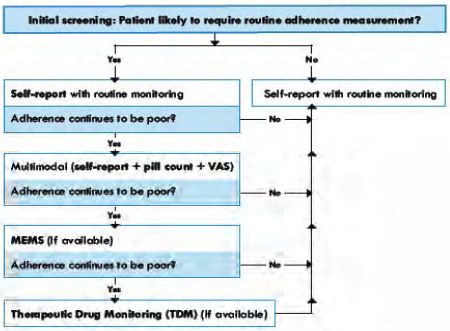


Figure 2. Proposed Algorithm for the Use of Adherence Measurement Tools

Results

- Of the 124 studies found, 57 (46 percent) involved self-reporting. Of the self-reporting studies, 50 (88 percent) confirmed their reliability to predict adherence (Figure 1).
- Of 26 studies on pill counting, 21 (81 percent) confirmed their reliability.
- All five studies using visual analog scale (VAS) were confirmed reliable.
- All 18 studies using a multimodal 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 to reliably monitor client adherence, but validated measurement tools are lacking for resource-limited sites. 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. RPM 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/patient 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 2).
- In settings where these tools have not been tested and calibrated, a multimodal adherence measurement tool is recommended

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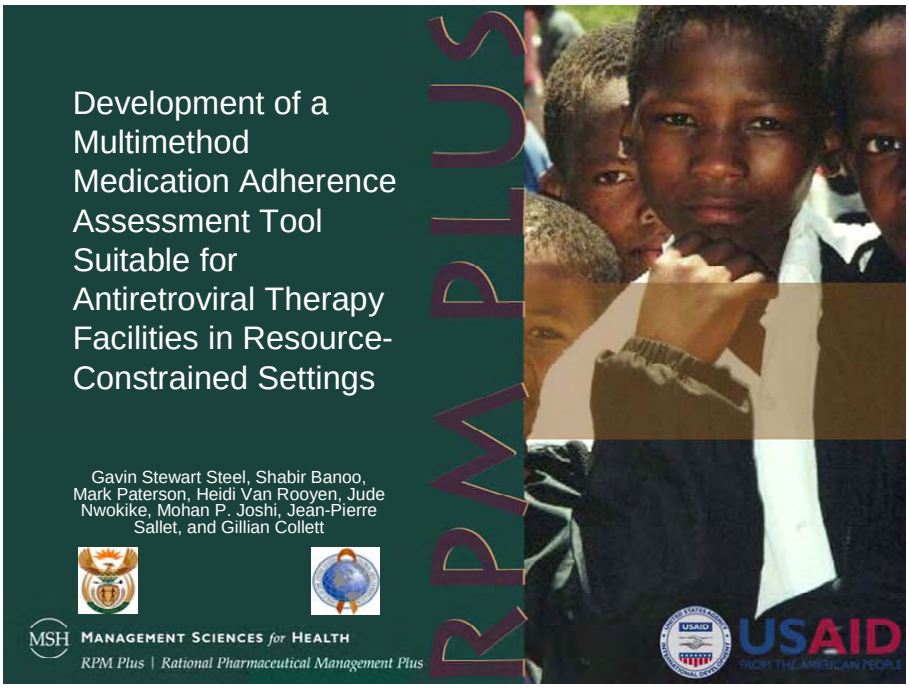
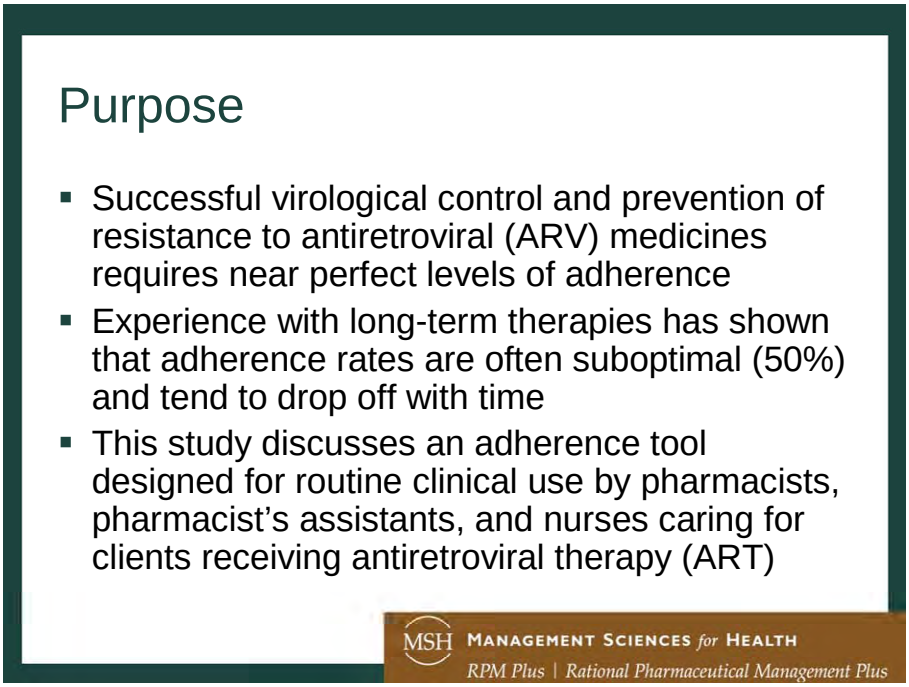
ANNEX 2. PRESENTATION MADE AT THE APHA 134TH ANNUAL MEETING AND EXPOSITION, NOVEMBER 4–8, 2006, BOSTON, MA.





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

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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

* Nwokike, J., G. Steel, and M. Joshi. 2006. *Analyzing Medication Adherence Measurement Tools in Predicting Antiretroviral Treatment Outcomes in Resource-limited Settings* (abstract). The XVI International AIDS Conference. August 13–18, Toronto. <www.msh.org/news_room/events/aids2006_pdf/02_aidsconf2006.pdf>.

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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.

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Adherence Measurement Tool (1)

Pilot version

Start ___ h ___

Patient Adherence record Pilot version

Folder/Clinic No ___ Date ___ Class ART ___

Instructions: Please tick the block with the most appropriate response.

Self report

a) Do you sometimes find it difficult to remember to take your medicine? Yes / No
b) When you feel better do you sometimes stop taking your medicine? Yes / No
c) Thinking back over the past 4 days would you say that you have missed any of your doses? Yes / No
d) Sometimes if you feel worse when you take the medicine, do you stop taking it ? Yes / No

Adherence assessment All No **High** | 1 to 2 Yes **Moderate** | 2 to 4 Yes **Low**

e) When was the last time you missed a dose? Within the last week | 1-2 weeks ago | 3-4 weeks ago | 1-3 months ago | Never

Visual Analogue Scale (VAS)

Circle a number on this line that shows your best guess about how much medicine you have taken over the past 4 weeks. For example, if you took all the medicines without missing even a single dose, circle 10. If on the other hand you did not take the medicines at all during the past 4 weeks, then you would circle 0.

0 1 2 3 4 5 6 7 8 9 10 Score ___ %

Pill identification Test (PIT) Follows instructions Yes / No

Ask the client to inspect each container & its contents and then tell you the name of the medication, number of pills per dose, the times they take the medication and whether there are any additional instructions

Name of Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken: morning	evening	Correct (Y/N)	Knows additional instructions (Y/N)
			h	h		
			h	h		
			h	h		
			h	h		

Pill Count

Did the client bring their medication containers back? Yes / No

Calculated percentage adherence

% Adherence = Dispensed − returned / Expected to be taken X 100 = ___ − ___ X 100 = ___ %

Adherence Support measures

Additional Education	Pill Box	Diary	Lifestyle inventory	New Rx	To Daddy or CHW	Reminder	Motivational interview
Other							

End ___ h ___ Duration ___ min

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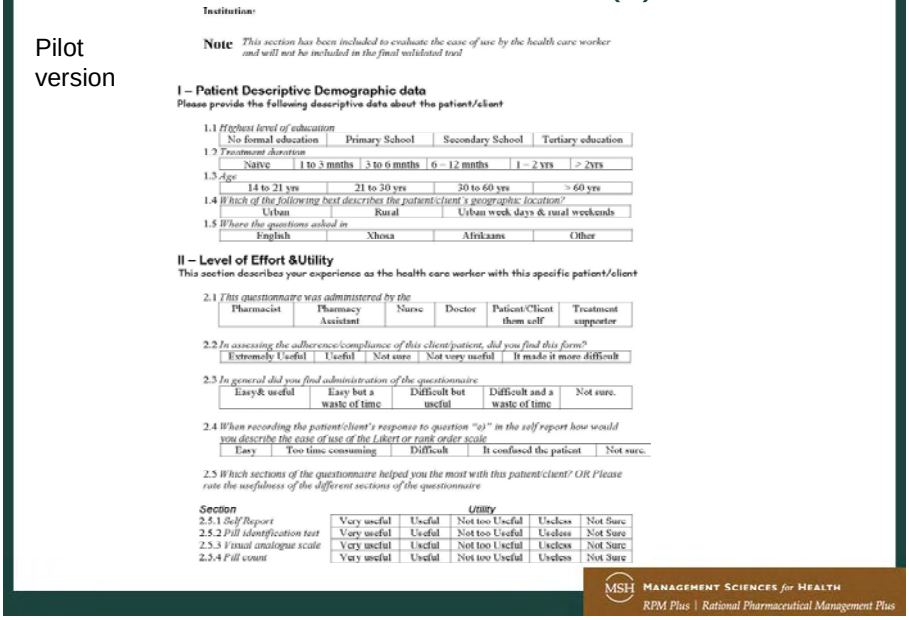
Adherence Measurement Tool (2)

Pilot version



Institution:

Note *This section has been included to evaluate the ease of use by the health care worker and will not be included in the final validated tool*

I – Patient Descriptive Demographic data

Please provide the following descriptive data about the patient/client

1.1 *Highest level of education*

No formal education	Primary School	Secondary School	Tertiary education

1.2 *Treatment duration*

Naive	1 to 3 mnths	3 to 6 mnths	6 – 12 mnths	1 – 2 yrs	> 2yrs

1.3 *Age*

14 to 21 yrs	21 to 30 yrs	30 to 60 yrs	> 60 yrs

1.4 *Which of the following best describes the patient/client's geographic location?*

Urban	Rural	Urban week days & rural weekends

1.5 *Where the questions asked in*

English	Xhosa	Afrikaans	Other

II – Level of Effort &Utility

This section describes your experience as the health care worker with this specific patient/client

2.1 *This questionnaire was administered by the*

Pharmacist	Pharmacy Assistant	Nurse	Doctor	Patient/Client them self	Treatment supporter

2.2 *In assessing the adherence/compliance of this client/patient, did you find this form?*

Extremely Useful	Useful	Not sure	Not very useful	It made it more difficult

2.3 *In general did you find administration of the questionnaire*

Easy& useful	Easy but a waste of time	Difficult but useful	Difficult and a waste of time	Not sure.

2.4 *When recording the patient/client's response to question "a)" in the self report how would you describe the ease of use of the Likert or rank order scale*

Easy	Too time consuming	Difficult	It confused the patient	Not sure.

2.5 *Which sections of the questionnaire helped you the most with this patient/client? OR Please rate the usefulness of the different sections of the questionnaire*

Section	Utility				
2.5.1 *Self Report*	Very useful	Useful	Not too Useful	Useless	Not Sure
2.5.2 *Pill identification test*	Very useful	Useful	Not too Useful	Useless	Not Sure
2.5.3 *Visual analogue scale*	Very useful	Useful	Not too Useful	Useless	Not Sure
2.3.4 *Pill count*	Very useful	Useful	Not too Useful	Useless	Not Sure

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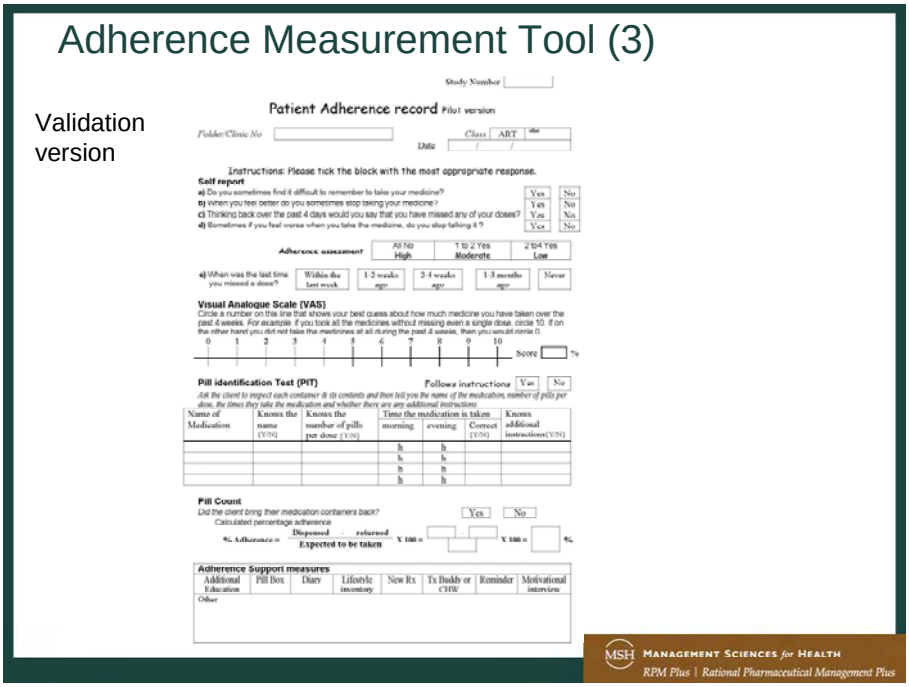
Adherence Measurement Tool (3)

Validation version



Study Number

Patient Adherence record Pilot version

Folder/Clinic No

Date

Class | ART | other

Instructions: Please tick the block with the most appropriate response.

Self report

a) Do you sometimes find it difficult to remember to take your medicine? Yes / No
b) When you feel better do you sometimes stop taking your medicine? Yes / No
c) Thinking back over the past 4 days would you say that you have missed any of your doses? Yes / No
d) Sometimes if you feel worse when you take the medicine, do you stop taking it ? Yes / No

Adherence assessment

All No High	1 to 2 Yes Moderate	2 to4 Yes Low

e) When was the last time you missed a dose?

Within the last week	1-2 weeks ago	2-4 weeks ago	1-3 months ago	Never

Visual Analogue Scale (VAS)

Circle a number on this line that shows your best guess about how much medicine you have taken over the past 4 weeks. For example if you took all the medicines without missing even a single dose, circle 10. If on the other hand you did not take the medicines at all during the past 4 weeks, then you would circle 0.

0 1 2 3 4 5 6 7 8 9 10 Score %

Pill identification Test (PIT) Follows instructions Yes / No

Ask the client to inspect each container & its contents and then tell you the name of the medication, number of pills per dose, the times they take the medication and whether there are any additional instructions

Name of Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken: morning	evening	Correct (Y/N)	Knows additional instructions(Y/N)
			h	h		
			h	h		
			h	h		
			h	h		

Pill Count

Did the client bring their medication containers back? Yes / No

Calculated percentage adherence

% Adherence = (Dispensed − returned) / Expected to be taken X 100 = X 100 = %

Adherence Support measures

Additional Education	Pill Box	Diary	Lifestyle inventory	New Rx	Tx Buddy or CHW	Reminder	Motivational interview

Other

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Adherence Measurement Tool (4)

Validation version

Institution: Overage Yes No

I – Patient Descriptive Demographic data

1.1 Highest level of education

No formal education | Primary School | Secondary School | Tertiary education

1.2 Treatment duration

Naïve | 1 to 3 mnths | 3 to 6 mnths | 6 – 12 mnths | 1 – 2 yrs | > 2yrs

1.3 Age

14 to 21 yrs | 21 to 30 yrs | 30 to 60 yrs | > 60 yrs

1.4 Which of the following best describes the patient/client's geographic location?

Urban | Rural | Urban week days & rural weekends

1.5 Where the questions asked in

English | Xhosa | Afrikaans | Tswana | Zulu | Other

1.6 Was an interpreter used? No Yes

II – Objective measures.

Tx initiated on / / Current regiman

Date	Viral Load	CD_4 count
/ /		

Medication Event Monitoring System - MEMS

Date	am	pm	Adherent
/ /	h	h	

Committee Adherence assessment High Moderate Low

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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 CD_4 count
  - A blinded pill count where patients were randomly assigned to receive an undisclosed quantity of medication

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Assessment of Patient's Adherence by a Pharmacist and Pharmacist's Assistant

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Results—Feasibility

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

Note: N = 440

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Correlation of Measures

Adherence	MEMS	Self-report	Pill count	VAS	Multi-method
Low	15%	3%	0	3%	6%
Medium	18%	21%	19%	21%	36%
High	66%	76%	81%	76%	56%
Spearman		r = 0.53	r = 0.52	r = 0.41	r = 0.50

Note: N = 33

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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%

Difference {MEMS – PC}	*Blinded*	*Non-blinded*
>10	31 %	
0 to 10	23%	20%
0	36%	70%
<0	9%	10%

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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.

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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.

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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

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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.

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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

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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.

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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

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ANNEX 3. PATIENT ADHERENCE RECORD

Patient Adherence Record

Version 1.1

Folder No.	Date (dd/mm/yyyy) / /

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."*

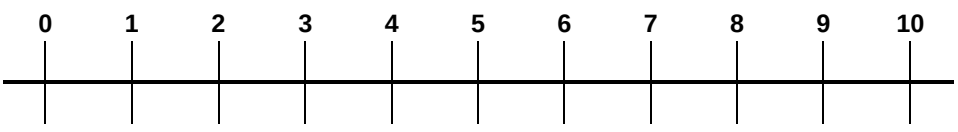
Self-Reporting

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

Question	Yes	No
Do you sometimes find it difficult to remember to take your medicine?		
When you feel better, do you sometimes stop taking your medicine?		
Thinking back over the past four days, have you missed any of your doses?		
Sometimes if you feel worse when you take the medicine, do you stop talking it?		

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.



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.

Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken			Knows any additional instruction
			Morning (hour)	Evening (hour)	Judged correct (Y/N)	

Pill Count

Did the client return the medication containers? Yes* No

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.

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

Adherence Assessment

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

Adherence Support Measures

Code			Notes
AS01	Treatment preparedness		
AS02	Treatment buddy or community health worker		
AS03	Home visit		
AS04	Medication counseling—dosing regimen and instructions		
AS05	Medication counseling—show and tell		

AS06	Medication counseling—safety		
AS07	Life style inventory		
AS08	Medication diary		
AS09	Motivational interviewing		
AS10	Reminder such as a pill box		
AS11	Support groups		
AS12	Printed medication information		
AS13	Personalized printed medication information		
AS99	Other—please specify under notes		

Comments (Insert comments as needed)

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

ANNEX 4. INSTRUCTIONS FOR COMPLETING PATIENT ADHERENCE RECORD

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

Folder No.	Date (dd/mm/yyyy) / /

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? Yes [ ] No [ ]

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? Yes [ ] No [ ]

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? Yes [ ] No [ ]

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? Yes [ ] No [ ]

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.

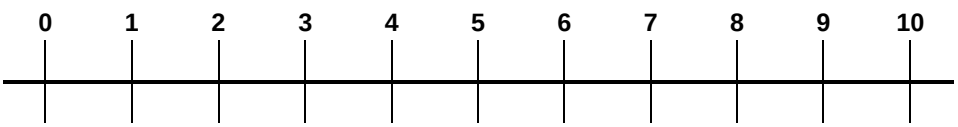
Assessing Adherence

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.*



Score
____%

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

Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken			Knows any additional instruction
			Morning (hour)	Evening (hour)	Judged correct (Y/N)	

Note: The grey shaded column is the judgment of the health care worker administering the questionnaire.

- 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 **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:

Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken			Knows any additional instruction
			Morning (hour)	Evening (hour)	Judged correct (Y/N)	
D4T	Y	Y	0715h	2000h	Y	Y
3TC	Y	Y	0715h	2000h	Y	Y

Efavirenz	Y	Y	0715h		N	Y

Pill Count

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

Calculated percentage adherence

$$\text{\% Adherence} = \frac{\text{Dispensed} - \text{Returned}}{\text{Expected to be taken}} \times 100 = \frac{\square - \square}{\square} \times 100 = \square\,\%$$

- 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 **dispensed**.
- Count the remaining tablets and write it in the space that says **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—

% Adherence =	120 – 17 / 108	**X 100 =**	95**%**

Adherence Assessment

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

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

Self-reporting	No to all questions	Yes to 1 question	Yes to 2 or more questions
VAS	95% or more	75–94%	Less than 75%
PIT—*Client knows the…*	Dose, Time, and Instructions	Dose and Time	Dose only or confused
Pill count	95% or more	75–94%	Less than 75%
Overall Adherence	High	Moderate	Low

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.

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

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)

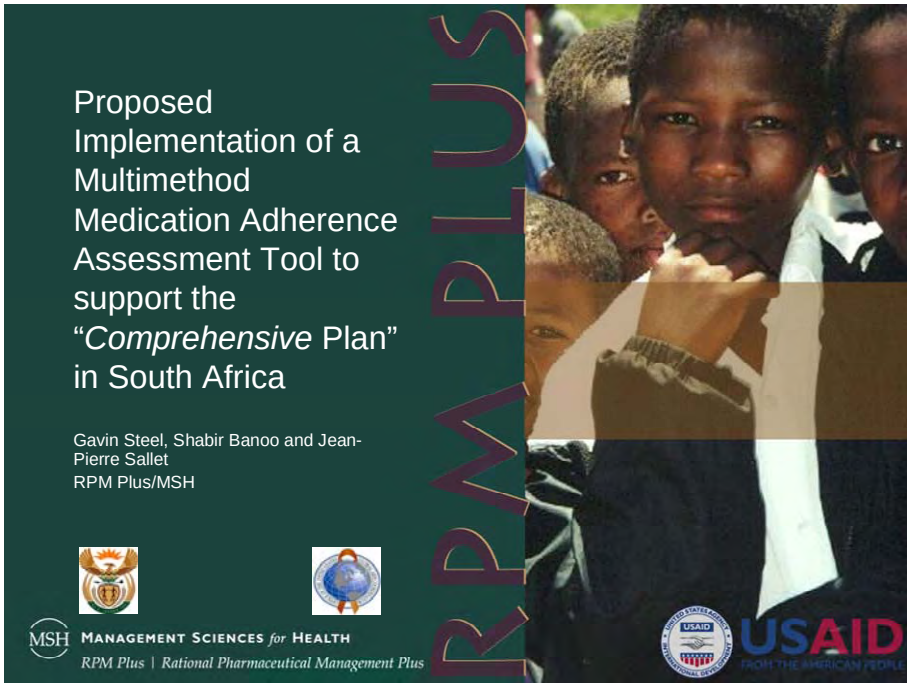
The comments section allows the pharmacist to record—

- 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.

ANNEX 5. RPM PLUS PRESENTATION AT THE NATIONAL/PROVINCIAL MEETING ON COMPREHENSIVE HIV/AIDS MANAGEMENT AND TREATMENT PLAN, MAY 31, 2007



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

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Objectives

- Prevent antimicrobial resistance
- Preserve first line therapy effectiveness through sustained high levels of adherence
- Support NDOH adherence strategy

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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

* Nwokike, J., G. Steel, and M. Joshi. 2006. *Analyzing Medication Adherence Measurement Tools in Predicting Antiretroviral Treatment Outcomes in Resource-limited Settings* (abstract). The XVI International AIDS Conference. August 13–18, Toronto. <www.msh.org/news_room/events/aids2006_pdf/02_aidsconf2006.pdf>.

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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

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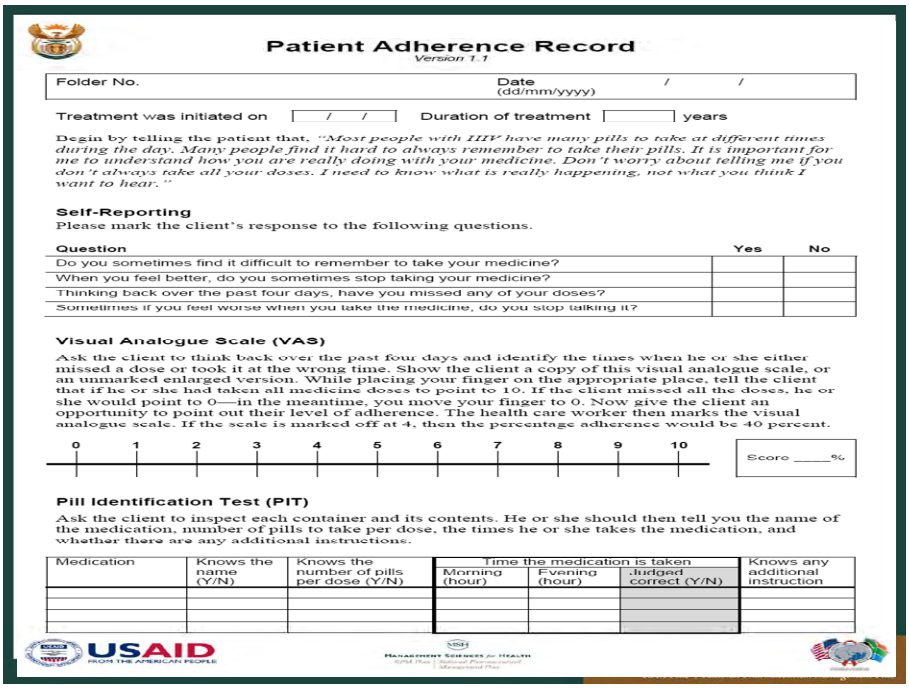

Patient Adherence Record

Version 1.1

Folder No. | Date (dd/mm/yyyy) / /

Treatment was initiated on / / Duration of treatment ____ 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.

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

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.

0 1 2 3 4 5 6 7 8 9 10

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.

Medication	Knows the name (Y/N)	Knows the number of pills per dose (Y/N)	Time the medication is taken: Morning (hour)	Evening (hour)	Judged correct (Y/N)	Knows any additional instruction

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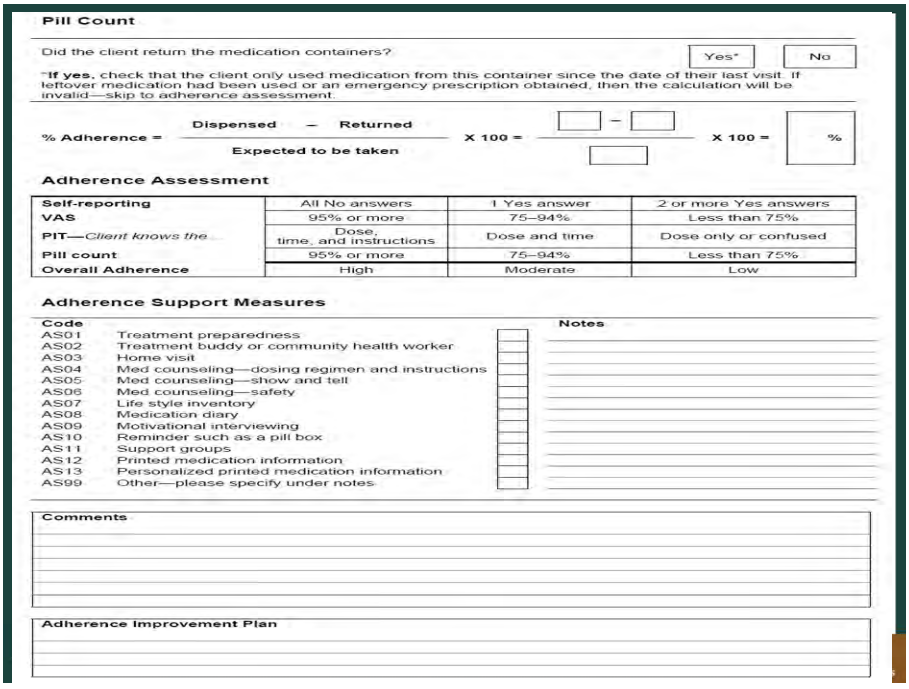

Pill Count

Did the client return the medication containers? Yes* No

*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—skip to adherence assessment.

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

Adherence Assessment

Self-reporting	All No answers	1 Yes answer	2 or more Yes answers
VAS	95% or more	75–94%	Less than 75%
PIT—*Client knows the*	Dose, time, and instructions	Dose and time	Dose only or confused
Pill count	95% or more	75–94%	Less than 75%
Overall Adherence	High	Moderate	Low

Adherence Support Measures

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

Comments

Adherence Improvement Plan

Composite assessment - triangulation

Self-reporting	All No answers	1 Yes answer	2 or more Yes answers
VAS	95% or more	75–94%	Less than 75%
PIT—*Client knows the...*	Dose, time, and instructions	Dose and time	Dose only or confused
Pill count	95% or more	75–94%	Less than 75%
Overall Adherence	High	Moderate	Low

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Method (3)

- To provide objective data to validate the tool, the following data was collected in a small group
  - Medication Event Monitoring System (MEMS)
  - Viral load and CD_4 count
  - A blinded pill count where patients were randomly assigned to receive an undisclosed quantity of medication

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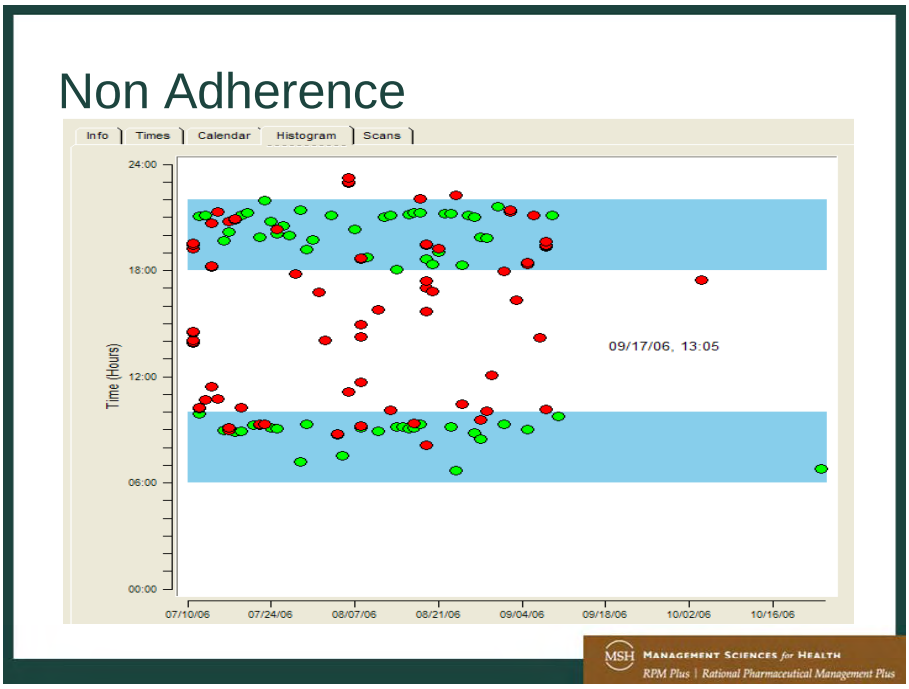
Non Adherence
Info
Times
Calendar
Histogram
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18:00
12:00
06:00
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Time (Hours)
09/17/06, 13:05
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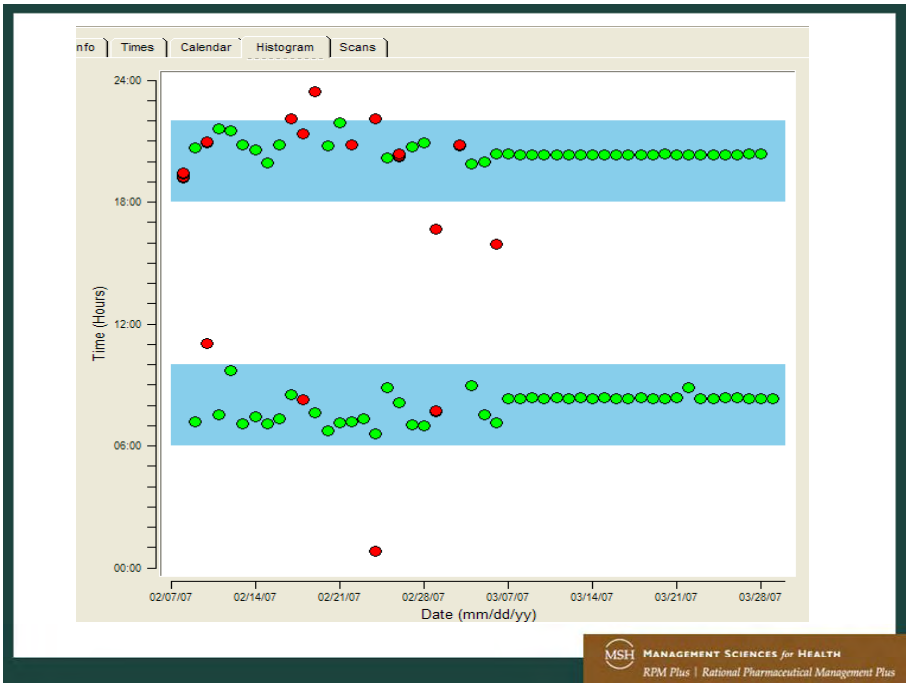
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Times
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Time (Hours)
02/07/07
02/14/07
02/21/07
02/28/07
03/07/07
03/14/07
03/21/07
03/28/07
Date (mm/dd/yy)
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Results—Feasibility

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

Note: N = 440

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Correlation of Measures

Adherence	MEMS	Self-report	Pill count	VAS	Multi-method
Low	15%	3%	0	3%	6%
Medium	18%	21%	19%	21%	36%
High	66%	76%	81%	76%	56%
Spearman		r = 0.53	r = 0.52	r = 0.41	r = 0.73

Multi method score r = 0.73 95% CI 0.5 – 0.85

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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%

Difference {MEMS – PC}	*Blinded*	*Non-blinded*
>10	31 %	
0 to 10	23%	20%
0	36%	70%
<0	9%	10%

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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.

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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

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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

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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

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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

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Other RPM Plus adherence support activities

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

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