Multiple Approaches to Monitor and Support Adherence to HIV Antiretroviral Therapy

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DOI:
10.33612/diss.879792708

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2024

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 9

General Discussion
Chapter 9

This thesis highlights the application of numerous adherence measures, comprising subjective and objective approaches either alone or in combination, to evaluate adherence to antiretroviral therapy (ART) as the main treatment for people living with human immunodeficiency virus (HIV). It demonstrates that the adherence rates varied across the different methods: the highest adherence estimate was provided by self-report questionnaires, a moderate estimate resulted from pill counting and prescription refill review, and the lowest estimate was provided by electronic monitoring devices. The thesis also suggests the potential use of emerging biological matrices, such as saliva and hair, to detect the presence of antiretroviral drug and to confirm recent and long-term ART adherence, respectively. Furthermore, it also proves the association between adherence to ART and viral suppression. Being less adherent to ART was found to increase the likelihood of having unsuppressed viral load. Female sex, secondary or lower education, and using multiple-tablet regimen (MTR) were predictors of suboptimal ART adherence, while younger age, female sex, and receiving MTR were among factors influencing treatment discontinuation. Finally, the thesis also explores different strategies to promote ART adherence, including the use of a technology-driven device (i.e., a smart blister package) and a practical adherence toolkit which may assist HIV care providers in identifying adherence barriers and selecting tailored interventions based on an individual’s problems and needs.

Measurement of Adherence to Antiretroviral Therapy

Various approaches have been recommended to measure adherence, depending on the component of adherence (i.e., initiation, implementation, and discontinuation) [1,2]. For treatment initiation, comparing the initial ART prescription and dispensing data is advisable [2]. Implementation can be studied with several methods such as self-report, pill counting, electronic monitoring (e.g., medication event monitoring system, MEMS), and drug presence/level testing [2,3]. In the case of persistence or discontinuation, pharmacy claims data are commonly used [4,5]. Notably, most studies in this thesis evaluate adherence for the implementation component and one study for the treatment persistence or discontinuation.

Variation in ART adherence estimates are provided by numerous adherence measures in the thesis, ranging from more accurate to less accurate methods. Detecting and quantifying the actual presence of the drug in the body may lead to more rigorous adherence results [6]. Direct measurement using venous blood sampling has been widely used; however, venepuncture is invasive, burdensome, and needs to be performed by a phlebotomist or other health care professional [7]. Therefore, utilizing alternative matrices that are less invasive may improve the acceptability and accessibility for patient sampling and reduce the burden of drug monitoring in routine practice. Chapter 2 provides an overview of evidence from the last two decades on the clinical applicability of emerging biological matrices, e.g., dried blood spots, saliva, and hair, for adherence monitoring of chronically administered drugs, including HIV medications.

The review highlights that hair is predominantly applied for long-term adherence monitoring and mostly applied in HIV studies. This finding supports the results of a systematic review that hair is suggested as a biomarker in monitoring long-term ART adherence because hair antiretroviral concentration could predict the virological responses [8]. The advantages of hair testing are that it is easy to collect, that it has a prolonged timeframe in which drug use can be retrospectively determined, and that it can
be stored at ambient temperature. Furthermore, saliva is another matrix applied for ART adherence monitoring. Saliva is considered a patient-friendly alternative matrix due to the ease of sampling and it being less-invasive. However, drug penetration into oral fluid is a prerequisite for the test to be useful. Antiretroviral drugs that are not extensively bound to protein and penetrate well into saliva could be measured using this matrix for adherence evaluation [9,10]. In most studies, non-adherence may be defined by a drug level under the lower limit of quantification (LLOQ) for the analytical method, where drug levels are undetectable and thus considered not present. For hair, the absence of the drug would mean the drug was not or was only very limitedly taken for longer periods [11–13]. For saliva, the absence of the drug in the matrix would mean the drug was not taken for several half-lives [14,15]. Moreover, high drug levels could also be indicative of non-adherence, as it could be the result of having taken several doses just before a clinical visit [16]. Thus, the times of both sampling and drug intake should be considered when interpreting drug measurements [17].

In general, drug-level monitoring is not part of routine care for people living with HIV in many developing countries, such as Indonesia [18,19]. High cost, scarcity of clinicians’ requests, and limited laboratory capacity and equipment appear to be major obstacles against application in practice [18,19]. Therefore, an easy-to-use and affordable assay with a preferably non-invasive matrix to monitor HIV treatment would be highly desirable. A study described in Chapter 3 attempts to explore the potential of a mobile microvolume ultraviolet/visible light (UV/Vis) spectrophotometer for quantification of antiretroviral drugs in saliva. Unfortunately, using the spectrophotometer to quantify tenofovir, lamivudine, and efavirenz in saliva appeared to be not feasible due to the relatively high LLOQ for tenofovir and efavirenz and matrix interference for efavirenz and lamivudine. Of importance, this study has demonstrated that compounds with low concentrations in saliva that have the maximum absorbance within the range of wavelengths of endogenous compounds of blank saliva (240–300 nm) are difficult to quantify in saliva directly by spectrophotometry. This might be a great obstacle for the monitoring of tenofovir, lamivudine, and efavirenz in saliva. The wavelength of maximum absorbance of these three drugs are relatively close to those of the blank saliva and the absorption peaks could overlap in the UV spectra. Furthermore, given that the total absorbance at the maximum wavelength exceeded the linear range, the assay could possibly be improved in the future by exploring possible strategies to bring the total signal at the wavelength of maximum absorption into the linear range for analysis, e.g., by diluting the saliva samples in blank (ultrapure water) or shortening the pathlength with the use of the drop tray or different cuvette sizes [20,21]. Once all data are within the validated range for analysis and if the interpatient variance of the blank matrix remains, derivative spectroscopy using the Savitzky-Golay filter may be applied. This may increase the resolution of the spectrum and decrease baseline shifts by filtering out the analyte signal from the total signal which, in turn, can increase the selectivity and specificity of the detection of analyte [22,23].

Next, electronic monitoring is the objective measure that provides more granular adherence data. This thesis evaluates the use of electronic monitoring devices for adherence measurement in two different observational studies performed in Indonesia (Chapter 4) and in the Netherlands (Chapter 7). A multi-method approach combining electronic monitoring with self-reporting and pill counting was performed to compare the measurement of medication adherence. For electronic monitoring, a pill bottle (Chapter 4)
and a blister package (Chapter 7) equipped with MEMS were utilized to record the time when a person opened and closed the bottle or the blister package. For self-reporting, two different adherence questionnaires were used: a validated self-reported adherence (SERAD) questionnaire [24,25] (Chapter 4) and a 5-item medication adherence report scale (MARS-5) [26,27] (Chapter 7). Significant differences were observed in overall adherence levels as measured by self-report, pill counting, and electronic monitoring in the two observational studies. These discrepancies were expected as differences in accuracy of the methods have been reported by other studies [3,28,29]. Self-reported adherence had the highest adherence estimate in the studies; however, this measure is prone to recall bias and overestimates adherence [28,29]. Pill counting exhibited a moderate adherence level, although it is subject to a desirability bias and does not provide a day-to-day variability [3,28]. Electronic monitoring showed the lowest adherence rate because it captures the bottle or blister package opening times as well as identifies treatment interruptions or the distribution of missed doses that cannot be provided by self-report or pill counting. Still, opening and closing the bottle or blister package does not actually reflect dose ingestion, especially when so-called “curiosity openings” occur, or multiple pills are taken out in advance. Therefore, a combined approach could minimize the shortcomings of these measures and low adherence levels suggested by the three methods need to be evaluated and acted upon by health care providers.

Given the complexity and the need for longitudinal assessment in HIV treatment, applying a combination of several adherence measures may provide more accurate results and a better understanding of the dynamic changes of ART adherence over time. This was evaluated through a longitudinal study of a cohort of people with HIV who were followed-up for six months at an Indonesian HIV clinic (Chapter 4). A significant increase in adherence was observed by pill counting during the first two months, whereas a considerable decrease was identified by electronic monitoring between 2–4 and 4–6 months. The Hawthorne effect (behavioural change due to awareness of being monitored) may impact the adherence behaviour during the first months, contributing to a higher ART adherence rate [30]. Furthermore, adherence that decreased between month 2–4 and 4–6, as captured by electronic monitoring, may suggest the possibility of treatment fatigue occurring among the treatment-experienced subjects following the long-term use of ART [30]. Compared to self-report and pill counting, electronic monitoring is considered the most objective method in measuring adherence and gives more in-depth information on medication taking behaviour. Although it might be less practical for daily practice, longitudinal monitoring with the use of a combination of adherence measures could capture the variation in ART adherence from different time points and angles.

Finally, for both treatment implementation and persistence/discontinuation, this thesis assessed ART adherence and persistence using pharmacy dispensing data obtained from the IADB.nl database (Chapter 6). The study revealed moderate rates of ART adherence (proportion of days covered) and persistence (prescriptions dispensed within an allowable 90-day gap) during the first year of treatment among Dutch people following ART initiation between 2000 and 2021. Number of people initiating single-tablet regimen (STR) was greater than those on MTR, and more STR patients had optimal ART adherence and persistence. The MTR group had a higher rate of switching between treatments, whereas the STR group had a higher rate of ART re-initiation within the first year.
HIV infection cannot be cured, but the virus replication can be diminished by the use of ART [31,32]. It requires lifelong treatment and thus medication adherence is warranted. Once initiated, ART should be taken consistently and continuously to achieve optimal treatment outcomes [3,32,33]. HIV treatment outcomes can be evaluated clinically by disease progression, immunologically by trends in CD4 counts over time, and virologically by measurement of HIV viral load [31,32]. The World Health Organization (WHO) has recommended viral load testing as the preferred monitoring approach to assess the efficacy of HIV treatment and to confirm the occurrence of virological failure (a persistently detectable viral load exceeding 1,000 copies/ml after at least six months of ART use) [32]. The aim of continuous ART taking, whether in treatment-naïve or treatment-experienced patients, is suppression of HIV viral load to lower than 1,000 copies/ml or undetectable levels [32].

A variation in the relationship between adherence to ART and HIV treatment outcomes in Indonesian patients was found based on the type of adherence measurement used in this thesis. For a study using self-reported adherence (Chapter 5), an increased odds of viral non-suppression was significantly associated with being less adherent to ART and the odds was about five times that of patients with a high ART adherence. The odds of low CD4 count in less adherent patients was about twice that of highly adherent patients. Notably, the prevalence of viral non-suppression or low CD4 count was higher among people who highly adhered to their ART compared to those who were less adherent.

For a study using a combination of self-report, pill counting, and electronic monitoring (Chapter 4), the odds of unsuppressed viral load or low CD4 count decreased with an increased rate of self-reported adherence, whereas the odds of viral non-suppression or low CD4 count elevated with an increased percentage of adherence by pill counting and electronic monitoring. However, the association between adherence by the three measures and treatment outcomes was not statistically significant. Mean adherence by pill counting and electronic monitoring was higher among individuals who had unsuppressed viral load or low CD4 count.

Many studies have reported that patients who have poor adherence to ART are likely to develop poor treatment outcomes [3,33–36]. However, in our two studies, patients with a high ART adherence experienced poorer treatment outcomes, suggesting that highly adherent patients did not necessarily have better treatment outcomes than those who were less adherent. This finding has clinical importance and is in line with the results of a meta-analysis from 43 studies across > 26 countries [3] that indicated that although optimal adherence to ART was associated with a lower risk of virologic failure, more patients from developing countries who were optimally adherent to ART experienced viral non-suppression. Unavailability of baseline antiretroviral drug resistance testing before ART initiation in resource-limited settings may potentially contribute to the increasing rates of detectable viral load in optimally adherent patients [3,37]. Therefore, the finding is of concern and draws attention to the need for enhanced surveillance and drug-resistance testing by the national HIV treatment programmes.

A number of studies have demonstrated that treatment interruptions during HIV treatment are still frequent, resulting in a higher rate of discontinuation [38–42]. The trend is also observed in a longitudinal study described in Chapter 6. The discontinuation rate was moderate during the twelve months following ART initiation, but only one-fifth of
non-persistent patients re-initiated ART within the same period after having interrupted treatment. Further research is needed into the reasons for this and its association with the treatment outcomes.

**Factors Affecting Adherence to Antiretroviral Therapy**

Adherence to ART is essential for reaching HIV viral suppression, provided the regimen prescribed is effective against the virus. Achieving at least 80% to 95% adherence is recommended to sustain adequate viral suppression [3,6,33,43]. Treatment adherence in people with HIV include initiating ART, taking ART everyday as prescribed, and keeping all clinical appointments [2,6]. It requires lifelong commitment between patients and health care providers to maintain optimal adherence. However, medication adherence is a dynamic behaviour and a multifactorial phenomenon. Patient, disease, treatment, social and economic, and health care system-related factors have been reported to associate with ART adherence [1,44]. However, predictors to adherence may differ across settings and population groups. This thesis determined factors influencing ART adherence in hospital and community settings as well as among different age groups (adolescent, adult, and older adult).

A cross-sectional study among adults and older adults attending a hospital-based HIV clinic in Indonesia (Chapter 5) yielded that those with secondary or lower education were associated with low ART adherence compared to those with college or university degrees. A similar finding has also been reported in previous studies [44,45]. Better education and health literacy may facilitate good communication with health care providers and increase retention of information provided, thereby enhancing medication adherence [44]. Literate individuals may have a greater understanding of ART efficacy and take their medicines correctly as prescribed to maintain therapeutic effect [46].

A longitudinal study among adolescents and adults who dispensed their ART prescriptions from community pharmacies in the Netherlands (Chapter 6) demonstrated that being female and using MTR were associated with having suboptimal ART adherence and treatment non-persistence. These findings are consistent with other studies [33,38,39,47–49]. Multifaceted social and behavioural challenges faced by women, e.g., HIV-related stigma, perceived discrimination, and depression, may lead to poor adherence to ART [47,48]. MTR may relate to regimen complexity and high tablet burden which have been reported as barriers to adherence and predictors of therapy discontinuation [33,38,39,49]. Moreover, the age of a patient was associated with treatment non-persistence. The study found that younger age increased the risk of treatment discontinuation within 12 months after starting ART. Lack of sufficient information about HIV and increased rates of mental health problems have been demonstrated to associate with incomplete treatment in adolescents with HIV [50]. In addition, youths may face HIV-related stigma and transition in care from paediatric to adult care settings that may result in rupture in care [38,51].

Forgetfulness and sleeping through dosing time were the most common reasons reported for missing ART doses in the three different studies (Chapters 4, 5, and 7). These reasons have also been reported as barriers to adherence in previous studies, regardless of ART regimen used or adherence level, as well as increasing the odds of having treatment interruption more than 48 hours or detectable viral load [52,53].

Most patients receiving ART regimens containing non-nucleoside/nucleotide reverse transcriptase inhibitor (NNRTI) and integrase strand transfer inhibitor (INSTI)
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in a hospital-based HIV clinic for at least six months (Chapter 5) were found to be highly adherent. Another study has reported the similar findings that patients using INSTI-based regimens have shown greater adherence and better persistence than other regimens due to better tolerability [38]. On the contrary, more patients on NNRTI and INSTI who dispensed their medicines from community pharmacies (Chapter 6) demonstrated suboptimal adherence and non-persistence one year after starting ART. In this study, underestimation of adherence rates among patients on NNRTI and INSTI in the community setting might be due to the occurrence of adverse drug events (e.g., gastrointestinal issues, weight gain, and insomnia) that hindered the patients from refilling their prescriptions and lack of reports from hospital-based outpatient pharmacies that provide HIV treatment. The differences between adherence rates among those on NNRTI and INSTI in the hospital and community settings may suggest that different clinic settings could affect treatment outcomes and retention in care. Although many clinics may offer similar HIV care and treatment, they often have unique identities that emerge from the structure of health care delivery, quality of the patient-provider relationship, academic affiliations, and funding sources [54]. Thus, further research could be performed to explore the reasons for adherence discrepancies in these groups.

Strategies to Promote Adherence to Antiretroviral Therapy

It is important for people living with HIV that they take ART everyday as prescribed and visit their HIV care provider regularly to ensure viral suppression. This thesis has addressed several strategies that could potentially support adherence to ART such as: simplifying regimen doses, providing reminder and feedback, and using digital technology such as an electronic smart blister. However, there is no one-size-fits-all solution for adherence, and strategies could be tailored to the specific needs and preferences of an individual.

Patients who received MTR were found to be susceptible to being less adherent and non-persistent during the first year of treatment. This underscores the importance of convenient regimens prescribed for patients initiating ART. The strategies of starting with fixed-dose combinations and once-daily dosing STR seem beneficial to increase the adherence and persistence in newly ART prescribed individuals [38,39]. As forgetfulness is the most reported reasons for missing ART doses, reminders can be beneficial for modifying the behaviour of unintentionally less adherent individuals who are willing to take the dose but forget it or are inaccurate in their intake behaviour [55,56]. The reminder system could be an alarm either built into the pill bottle or the blister package itself or be prompted by a (mobile) application. In systems incorporating data transfer to an online platform, individuals could directly access their own dosing history data. In the studies using a MEMS bottle (Chapter 4) and a smart blister package (Chapter 7), data transfer was performed by the pharmacists with a specific reading device connected to online adherence software. The data was then discussed with the individual during the consultation session.

Furthermore, the results of a usability study of an electronic dose pack (EDP), a novel smart blister package equipped with MEMS, elucidated that the EDP is perceived as a valued and usable tool to monitor and support medication adherence (Chapter 7). The adherence level as registered by the EDP was comparable with the other adherence measures (self-report and pill count), although some differences between the measures were observed. Qualitative data indicated that the EDP was perceived as easy to use, child-
safe, and giving no patient burden. Recommendations provided by the users were to adjust the package size, to incorporate reminders, and to give the participants direct insight into their performance. Notably, utilizing technology-driven devices for improving adherence requires investment and high costs, but this may be compensated by the reduced health care costs if individuals adhere to the treatment and sustain in optimal outcomes [57].

Nevertheless, selecting an adherence-enhancing strategy necessitates an early detection of non-adherence to ART and an understanding of factors affecting adherence. Given that adherence is a complex behaviour and influencing factors vary among individuals, this thesis developed a practical adherence toolkit to assist health care providers, particularly in Indonesia, in identifying the person-specific barriers and implement tailored interventions to improve adherence to HIV medications (Chapter 8). The adherence toolkit targets people living with HIV who have problems with sustaining their ART adherence both in community and hospital settings. The toolkit consists of a flowchart of adherence intervention, a validated self-reported adherence questionnaire to identify problems causing non-adherence, and an intervention wheel as a decision support tool that integrates HIV-medication-adherence-influencing factors and effective adherence-promoting approaches derived from systematic reviews and meta analyses [51,58–60], including previous studies conducted in Indonesia [45,61,62], in which each factor is related to specific (recommended) strategy.

**Methodological Limitations**

The thesis findings should be considered in the light of several methodological limitations. First, two observational studies were performed at a single centre in Indonesia (Chapters 4 and 5) limiting the generalizability of the study results to a larger population. A multicentre trial is therefore warranted in future studies to capture diverse population groups and larger HIV treatment centres. Second, the small sample size may not be adequate to detect a considerable relationship between ART adherence and HIV treatment outcomes. A larger number of study participants may be needed to assess correlation between adherence and treatment outcomes as well as factors influencing adherence or treatment outcomes in people receiving long-term ART. Third, the reasons underlying treatment interruption or discontinuation could not be discerned from the two observational studies (Chapters 4 and 6). Decisions on selecting the initial ART regimen and whether to discontinue are complex and result from a combination of clinician, patient, disease, and drug characteristics. Fourth, the studies (Chapters 5 and 6) have evaluated only patient, treatment, and disease-related factors affecting adherence. Other factors such as psychological, socioeconomic characteristics (e.g., monthly income, insurance, social support), and health care system-related factors may be further investigated in future studies.

**Recommendations for Practice**

HIV infection requires lifelong treatment, and it is important to ensure that people with HIV remain adherent to their HIV treatment and engage in care, so they will have not only longer but also healthier lives [6,31]. Therefore, medication adherence may act as a link between treatment and outcomes. All health care providers involved in HIV treatment and care, including medical doctors, nurses, and pharmacists, have the responsibility to monitor and promote adherence to HIV medications [32,63].
An extensive amount of research has resulted in the newer ART regimens with proven efficacy and less toxicity [31,32]. However, if people with HIV do not follow the regimens regularly as prescribed, elevated plasma viral load and disease progression could occur. Thus, medication adherence is an important issue to address, and we cannot exclusively blame the patient for not taking the medicines. Even though medication-taking behaviour is complex and individual, it involves the individual, health care providers, and multifactorial strategies to maintain it [51,58]. Health care providers involved in HIV care and treatment have the responsibility to recognise any issues interfering with the medication-taking behaviour and assist in identifying effective solutions [51,58]. A “blame-free” environment is therefore encouraged by involving the patient in the decision-making process.

Assessing ART adherence using self-report and pill counting approaches are still applicable in practice; however, the results should be interpreted carefully as the two methods are prone to recall and desirability bias. For more accurate results, health care providers may review prescription refill records, use electronic monitoring devices, or apply drug-level monitoring. They could refer to a quality-assessment tool for clinical validation of the analytical assays when choosing which emerging biological matrices are applicable for adherence monitoring (Chapter 2). The tool was developed to provide a quick overview of the drugs’ clinical validity based on sample size of published studies, performance of a cross-over test with a previously validated method, and the opinion of the authors that published the assays. Furthermore, opting for less frequent dosing with a fixed-dose combination for a single daily dose, applying reminder systems, and implementing technology-based interventions could be possible strategies offered to support adherence to ART. However, health care providers and health policy makers need to carefully consider which approach(es) to choose for routine implementation in a particular setting based on feasibility, acceptability, and health system organisation.

Furthermore, as this thesis found that highly adherent patients at an Indonesian HIV clinic experienced viral load non-suppression, this finding necessitates the advocacy of drug-resistance testing to be recommended in the national HIV programme particularly for treatment-naïve patients who will initiate ART and treatment-experienced patients who have high adherence to ART. Any virological failure could be early detected, and health care providers could select the appropriate treatment for the patients. HIV-1 genotypic resistance testing may be performed to NNRTI and nucleoside reverse transcriptase inhibitor (NRTI) drug classes, as they have been reported to be associated with mutations identified in Indonesian patients with virologic failure [64]. The HIVdb genotypic resistance interpretation algorithm by Stanford University can be used to infer antiretroviral drug susceptibility and resistance scores [65].

**Future Perspectives**

The recent introduction of an enzyme immunoassay for a qualitative drug level testing of antiretroviral drugs in plasma [66] and urine testing using dipstick technology [67,68] are promising and can be further explored with the use of non-invasive matrices in resource-limited settings. Furthermore, our group is working with a more selective analytical method, a liquid chromatography tandem mass spectrometry, to evaluate the use of dried blood spots, saliva, and urine withdrawn from people with HIV receiving tenofovir disoproxil fumarate-based ART regimen for pharmacokinetic-based adherence
monitoring with a limited sampling strategy. The results will generate evidence on the clinical application of emerging matrices for antiretroviral adherence monitoring in daily practice. Next, the applicability of an adherence toolkit to manage adherence to HIV medications will be evaluated in a cluster randomised controlled trial at 12 HIV clinics in Indonesia and followed-up for 12 months. The results will enable health care providers, people living with HIV, and policy makers to make an informed decision about the value of the adherence toolkit for being used in daily clinical practice. Interventions to promote adherence have been reported to decrease the economic burden of the health care system [69]. Therefore, future studies evaluating cost-effectiveness of adherence-promoting interventions implemented in people living with HIV are needed.
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References


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