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HIV Treatment Adherence - A Shared Burden for Patients, Health-Care Providers, and Other Stakeholders

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Abstract

Successful HIV treatment is contingent on sustained high levels of treatment adherence. Several barriers to optimal adherence have been documented. In this article, we first review the global burden of non-adherence among HIV/AIDS positive individuals on a public health scale. Second, we synthesized available evidence from different study designs and stratified across the European, African, and Asian literature to determine the factors influencing adherence to scheduled clinic appointments and medication non-adherence. Third, we discuss common measurement techniques that quantify the magnitude of non-adherence, their relative advantages and limitations in current practice. From January to May 2018, we reviewed guidelines, standard operating procedures, journal articles, and book chapters on treatment adherence among HIV patients receiving adherence to antiretroviral therapy (ART) globally. We searched PubMed, Medline, Google Scholar, and Cochrane Database of Systematic Reviews with the search terms "adherence," "adherence behavior," "medication adherence," and "HIV patients," or "HIV/AIDS," and "Antiretroviral Therapy" or "ART" or "ARVs" or "highly active ART " from 2000 to 2017. We also identified articles through searches of authors' files and previous research on HIV. We included only papers published in English in this review. We then generated a final list of reference on the basis of originality and the broad scope of this review. We found rich literature evidence of research findings and best practice recommendations on the importance of adherence in HIV/AIDS management, a general understanding of factors associated with non-adherence and approaches to investigating non-adherence behavior among different populations. We observed significant contextual differences exist with regard to barriers and burden of non-adherence among these populations. **(AIDS Rev. 2019;21:28-39)**

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Key words

Adherence. Treatment. HIV. AIDS. Antiretroviral Therapy.

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Introduction

Background narrative

"It was a bright and breezy early morning in April 2014; the clouds were still settling from the heavy rainfall that had been witnessed the previous night in Selangor and its environs. It was one of those mornings that required not only an extra motivation to get up from bed but also some doggedness to get through the traffic and waterlogged streets especially for those who commute by public transport. Confronting the cool breeze required an extra brazenness and courage; workers and students just had to draw motivation from somewhere to get going. Being a postgraduate student, the quest to complete my year-long research on-schedule and the understanding of how the timely completion of my studies takes me to the next level in my career were just enough motivation to start the day. It was needless to think about all the hassles I would normally face during my 45-60 min commute to the hospital where I was conducting my study and the uncertainty about how many patients I would be able to recruit into my study that day. I could imagine this was going to be one of those days when many patients, especially those who are frail or stable, may find it convenient to reschedule their clinic appointments. Regardless, this was not a time for procrastination, I had a job to do, I had to be there for the patients coming for their follow-up appointments and the new enrollees that would be receiving support in my study. On arriving the clinic at about 7.55 am, I noticed a couple of patients seated in the waiting area. Wow, that was early, I thought to myself. I rushed to prepare my room in anticipation of consultation starting at about 8.15 am. As I walked toward the nurses' station to review the files of patients scheduled for visit that morning, I noticed a middle-aged man seated in the waiting area, flanked by two ladies who seemed to be his wife and daughter. He looked pale, lethargic, and anxious. His face suggested to me that he needed immediate attention, so I spoke to the triage nurse who immediately took his vitals and other anthropometric measurements and scheduled for him to be one of the first few patients to be reviewed by the doctor. Shortly after, he was called to the consultation room, and as he stood up to go, I realized he could barely walk and had to be supported by the ladies that accompanied him. I asked the porter to bring a wheelchair to assist him to the doctor's room. After about 20 min of consultation by the doctor, he was referred to the nurse counsellor and thereafter to my room for enrollment into the antiretroviral therapy (ART) adherence support program. On arrival, I had a chat with Mr. Jivan (pseudonym) and as I explained the purpose of the study to him, he stopped me and asked to sign the consent form. Realizing that I was shocked by how he hadn't allowed me to finish explaining the study to him before signing the consent form, he said 'Dr, please don't be surprised, I know I have brought this (deterioration in health) upon myself by not complying with the advice of the health workers, not taking my medications regularly and not attending my clinic appointments. This is all my fault and I'm ready to make amend now. Please help me.' I reassured him of our help and support and completed all the necessary formalities to enroll him into the study. As he answered the baseline adherence questionnaire, it became clear that he had been started on ART about 3 weeks prior, but he failed to adhere to the medication schedule or attend follow-up clinic visit the week before. I was glad he had an insight to his problem, and we agreed on how to fit the medication schedule into his daily routine. We reinforced the importance of treatment support from his family and friends and linked him up with the local support group in the hospital. Seen on follow-up visit 2 weeks later, his condition had improved dramatically as he walked independently and looked brighter."

Narrated by author SAA

History of medication adherence in the context of HIV/AIDS

Historically, the concept of medication-taking in chronic medical conditions has been described with several terminologies. The quest to arrive at an all-encompassing description of patient's behavior of taking medications and adopting necessary lifestyle changes as part of their overall treatment has led researchers and medical interventionists to shift from terms such as compliance and concordance to adherence[1] - which describes a therapeutic alliance between the patient and clinician regarding a course of treatment. One of the earliest pivots of this conceptual evolution is the 2003 treatment adherence project sponsored by the World Health Organization (WHO) which described treatment adherence as "the extent to which a person's behavior - taking medications, following a diet, and/or executing lifestyle changes, corresponds with the agreed recommendations from a

health care provider[2]." Not only does adherence connote collaboration by emphasizing patient's choice and commitment to agreed recommendations but it also describes an active (by ensuring that patients own the treatment plan through participatory decision-making) and continuous process (a trend of patient's action about their health over time).

In the context of HIV/AIDS, treatment adherence is often used to describe both strict medication adherence and regular attendance of scheduled outpatient clinic appointments[2-4]. Medication adherence in HIV/AIDS has been defined by Jani as "the ability of a person living with HIV/AIDS to be involved in choosing, starting, managing, and maintaining a given therapeutic combination medication regimen to control viral replication and improve immune function[5]." Regular clinic attendance for drug pick-up, laboratory investigations and clinician assessment offer the opportunity to closely monitor treatment response (clinical, immunological, and virological), assess and address medication adherence challenges, and used by the WHO as an Early Warning Indicator (EWI) of HIV drug resistance among patients receiving ART around the world[6].

The goals of HIV treatment are to maximally and durably suppress plasma HIV RNA; restore and preserve immunologic function; reduce HIV-associated morbidity and prolong the duration and quality of survival; and prevent HIV transmission[7]. Strict adherence to the treatment plan (comprising combination antiretroviral regimen) is central to the achievement of these goals[8]. For example, a high level of sustained adherence is not only necessary to achieve viral suppression and improve immunological and clinical outcomes but also strict medication adherence decreases the risk of developing ARV drug resistance as well as reduces the risk of HIV transmission.

Adherence is a primary determinant of the effectiveness of treatment because poor adherence attenuates optimum clinical benefit. Optimal adherence increases the efficacy of interventions aimed at encouraging healthy lifestyles such as diet modification, improved physical activity, non-smoking, and safe sexual behaviors, and of the pharmacological-based risk-reduction interventions.

There appears to be a consensus in literature that minimum adherence levels of ≥95% are required for treatment success[9,10], although there have been reports of viral suppression at lower adherence levels and with non-nucleoside reverse transcriptase-based regimen[11]. Notwithstanding, the general understanding is that higher levels of adherence improve the probability of viral suppression and reduces disease progression and mortality.

Objectives

In this paper, we first review the global burden of medication non-adherence among HIV/AIDS positive individuals on a public health scale. Second, we rigorously synthesize available evidence from different study designs and stratified across the European, African, and Asian literature to determine the factors influencing adherence to scheduled clinic appointments and barriers to strict medication adherence among HIV/AIDS individuals. Third, we discuss common measurement techniques that aimed to quantify the magnitude of non-adherence, their key advantages and limitations in current practice.

Search strategy

From January to May 2018, we reviewed guidelines, standard operating procedures, journal articles, and book chapters on the treatment adherence among HIV patients receiving ART globally. We searched PubMed, Medline, Google Scholar, and Cochrane Database of Systematic Reviews with the search terms "adherence," "adherence behavior," "medication adherence," and "HIV patients" or "HIV/AIDS," and "Antiretroviral therapy" or "ART" or "ARVs" or "highly active ART (HAART)" from 2000 to 2017. We also identified articles through searches of authors' files and previous research on HIV. We included only papers published in English in this review. We then generated a final list of reference on the basis of originality and the broad scope of this review.

Burden of non-adherence

In 2016 an estimated 36.7 million people were living with HIV/AIDS worldwide, the majority of which are in low- and middle-income countries with sub-Saharan Africa being the most affected region. With advances in the scientific understanding of HIV, effective treatment with antiretroviral drugs can help control the virus; thus, persons infected with HIV can live healthy lives and reduce the risk of transmission to others[12]. As of July 2017, approximately 20.9 million people living with HIV had access to ART treatment worldwide[13,14] (Fig. 1).

Despite global scale-up efforts, adherence rates remain sub-optimal. The burden of non-adherence to

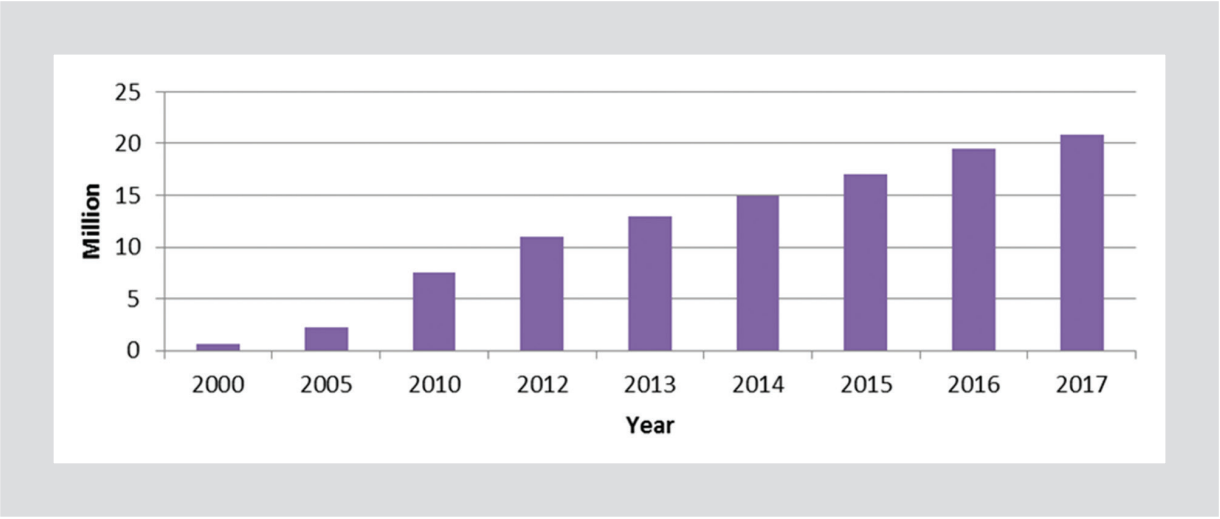

Figure 1. *Global prevalence of people with HIV receiving antiretroviral therapy. (Data source: global statistics HIV 2018[12], UNAIDS DATA 2018[13] and AIDS statistics by AVERT 2017[14]).*

HAART can be felt primarily in the patients' clinical outcomes and secondarily in health care workers, the stakeholders, and the health-care system at large. Non-adherence is a phenomenon that has been noted and studied in chronic diseases, and HIV is no exception especially given the social construct of a sexually transmitted disease and the attendant stigma associated with it. The burden is bound to be proportional to the rates of non-adherence because, in clinical scenarios, observational and interventional studies, non-adherence >80% culminates with detectable viraemia in most cases. Hence, there has been a slow but definite shift from the era of a cocktail of antiretroviral drugs to a pill a day to curb the pill burden and improve adherence, with medical technology researchers now favoring a pill a week and novel depot monthly injections that will drastically reduce non-adherence. Such research is bound to add to the burden on the available funds for managing this disease that has transitioned from a fatal one to a chronic one.

ART is an essential component and determinant of individual treatment success. Good clinical outcomes depend on consistent and good ART regimens. A 95% level of adherence to ART is required to achieve viral suppression and lower the rate of opportunistic infections[15]. For people living with HIV/AIDS; strict ART is the key to sustained HIV suppression. Adherence reduces the risk of drug resistance, improves overall health, quality of life, and survival[16]. Furthermore, it decreases the risk of HIV transmission[17]. Poor adherence leads to loss of virologic control, in turn, leading to the emergence of drug resistance and treatment failure. Previous studies have shown that adherence to scheduled clinic visit can be used as an objective proxy for adherence to medication between clinic visits[18]. Repeated missed appointments have been shown to result in non-adherence to medication, faster disease progression, and eventual treatment failure[19]. HIV positive clients who miss clinic appointments are often referred to as defaulters. In a study by Kimeu et al., authors reported that mean increase in CD4 counts at 6 months follow-up was seen among non-defaulters compare to defaulters[20]. They also reported a higher proportion of death among defaulters compared to non-defaulters[20]. Thus, defaulters are more likely to have poor clinical outcomes.

At the community level, non-adherence to ART makes HIV transmission more likely to occur[17,21]. In addition, non-adherence can substantially increase health-care costs related to hospitalization required to treat opportunistic infections[22]. A relationship exists between non-adherence and associated health-care costs. Medication non-adherence leads to poor outcomes, which then increase health-care service utilization and an overall health-care cost that is passed onto the patient. In most existing studies, only direct health-care costs are considered when estimating the impact of non-adherence and typically do not include indirect costs such as productivity and disability costs[23].

Direct health-care costs associated with non-adherence include hospital cost (health care and medicine cost) incurred due to increased morbidity and frequent hospital visits[24] and hospital-related costs that occur outside the hospital setting such as ambulatory care

costs, nursing home care costs and laboratory tests costs[25]. Indirect costs, on the other hand, include productivity costs that are incurred by the patient and society due to loss or impaired ability to work or engage in leisure activities due to morbidity and loss of economic productivity due to early death[26], social welfare costs that are given when individuals are unable to work (for example invalid benefit)[27], and costs to the patient's family, friends, and other associates that are involved with caring for the patient and that may occur if other patients are infected[28]. Report of a systematic review conducted to determine the economic impact of medication non-adherence across multiple disease groups showed a total unadjusted cost for non-adherent HIV patients ranged from $16,957 to $30,068[29] while non-adherence in AIDS was $30,532[30]. Studies in the United States have reported between $100 and $300 billion of avoidable health-care costs that are attributed to non-adherence in the US annually, representing 3%-10% of total US health-care costs[31,32].

Not having a formal salary or household income commonly associated with poverty has been reported to be a significant predictor of defaulting among patients on ART[33]. Economic impacts resulting from non-adherence have the potential to escalate thus worsening poverty of individuals and families, especially in countries most affected by the HIV epidemic.

One would assume that with widespread access to ART, there would be reduced need for HIV-related inpatient care. However, in low- and middle-income countries affected by the HIV epidemic, there is little published evidence in this regard[34]. Although HIV care is often provided on an outpatient basis, health-care facilities continue to treat serious HIV-related hospital admissions, and this is often resource-intensive and expensive. HIV-related opportunistic infections which are commonly associated with non-adherence are an important cause of hospital admissions and mortality in the era of ARTs. In a retrospective cohort study involving 1041 adult inpatient admission in a regional hospital in Johannesburg, close to half (45%) were known to be HIV positive. These patients accounted for at least 55% of all resources utilized and with further consideration of the fact that among patients of unknown HIV status some were bound to have been HIV positive. These figures thus represent the minimum burden placed on the hospital by HIV positive patients during the time of the study[34]. Similar high burden of HIV-related hospital admissions and mortality has been reported in studies conducted in Southern India[35], Northern Namibia,[36] and South-South Nigeria[37].

The HIV/AIDS epidemic poses a lot of challenges to the health systems of the developing countries that are most affected. HIV/AIDS increases overall health expenditures for both medical care and social support. HIV/AIDS can affect the health sector in various ways. These ways may range from the health workers themselves being infected with the HIV virus thus affecting the supply of their services (through absenteeism and deaths), a reduced moral of health professional resulting from the demanding health-care involved in caring for AIDS patients, attitudes of health care workers to HIV/AIDS patients that may reduce quality of care and an increase in health expenditures in both public and private sectors[38]. In most developing countries, budgets devoted to cover HIV/AIDS-related expenditures are insufficient and with the high demand for the effective treatment of HIV/AIDS-related diseases, demands for non-HIV/AIDS-related diseases remain unsatisfied thus resulting in the need for help from international donors to meet the health-care needs imposed by HIV/AIDS by these countries[38]. Non-adherence to ART by people living with HIV/AIDS increases demand and cost on/to the health systems (ART programs).

Stakeholders involved in HIV medication adherence are from various sectors; not limited to households and health. In the private sector, there is absenteeism and reduction of workers. There is reduced production in the agricultural sector especially as large numbers of HIV infected individuals in affected countries live in rural communities with farming as their source of livelihood. In education, there is increased absenteeism or death of teachers leading to a reduction in quality of education. On the other hand, the death of children, their parents or children being out of school to look after sick parents along with dropping out of school after the death of their parents reduce the demand for education. It is important that all stakeholders involved in the management of HIV infection; from patients to doctors/nurses to third-party players recognize and address the various factors that may potentially reduce treatment adherence.

Treatment adherence in HIV/AIDS

Evidence-based medicine that capitalized findings from rigorous clinical trials have conceptualized HIV/AIDS as a chronic manageable disease with the initiation of ARTs. ARTs have assured better prognosis through reduced opportunistic infections and the suppression of viral load in the circulation. These discoveries have triggered an invigoration of global

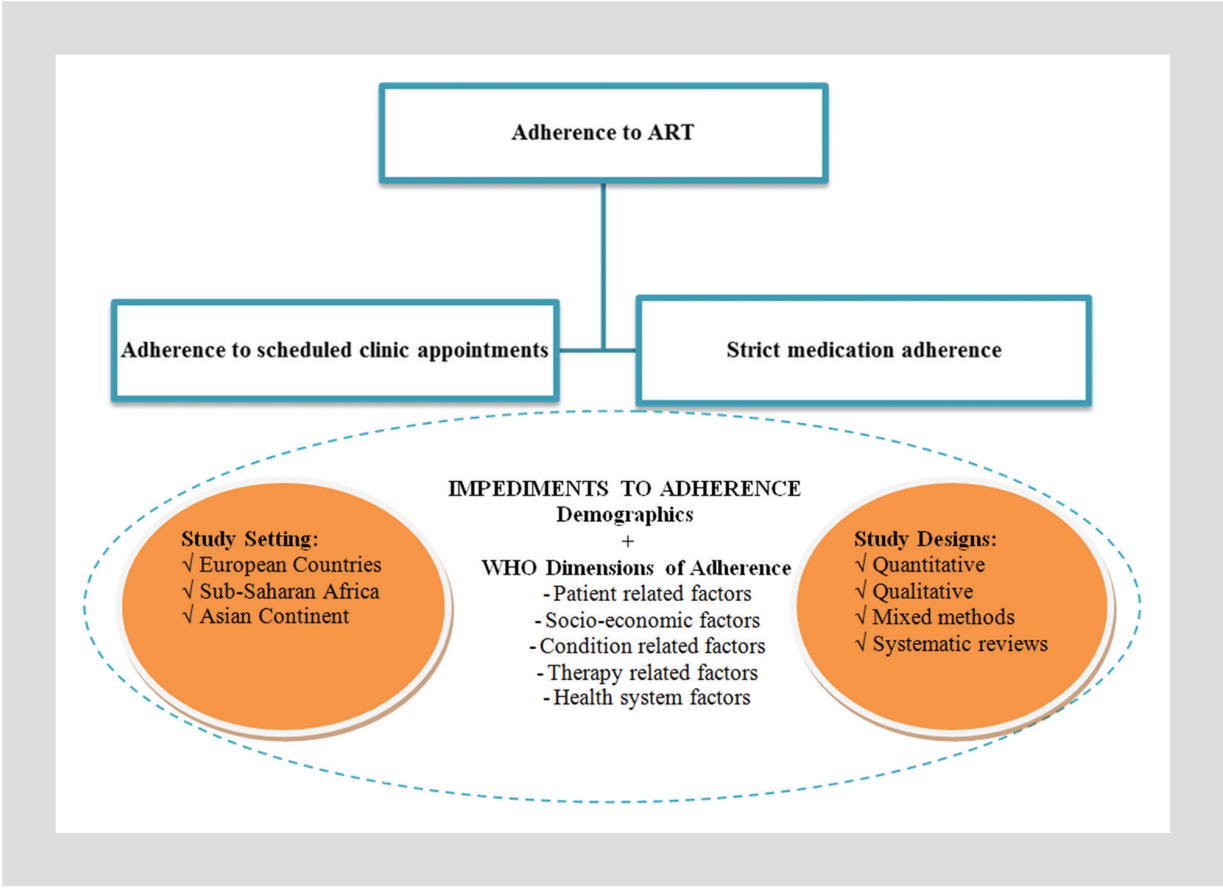

Figure 2. *The impediments to antiretroviral therapy adherence.*

public health workforce deployment to battle the HIV crisis with courage and determination. Major roll-out efforts have gained positive momentum for rapid scale-up interventions to initiate HIV-infected people with ARTs. Although the advent of ARTs has dramatically slowed disease progression, reduced mortalities, and incapacitated fatal infections to an otherwise more manageable disease, these regimens demand life-long strict adherence to achieve treatment success and prevent drug resistance. Abdulrahman et al.[3] conceptualized adherence to ART as a holistic approach comprising two key components - strict medication adherence and adherence to scheduled outpatient clinic appointments. There are significant proportions of HIV infected patients who have yet to reach the high levels of adherence required for treatment success[39]. Although research on adherence to ARTs is abundant, the difference in study designs, study settings, and measurement tools to identify potential factors associated with treatment adherence showed diverge, conflicting or mixed variations. The dense perplexity to understand the magnitude of the non-adherence problem on possible impediments or implementation failures on "medication taking" among HIV-infected individuals have summoned concerns among clinicians and public health advocates globally to reach a unified solution. Fig. 2 exhibits the impediments to ARTs adherence in literature.

Adherence to scheduled clinic appointments

In HIV/AIDS-infected patients, regular clinic attendance for medication refills, routine laboratory investigations, and clinician assessments are crucial to achieving treatment success and better prognosis. On-time appointment keeping and drug pickups are vital EWI monitored by the WHO in determining drug resistance profiles among HIV-infected patients attending ART clinics worldwide. In addition, adherence to scheduled clinic appointments provides the opportunity to primary caregivers for rapid detection of treatment failures. The bulk of investigations conduct-

ed to date was mainly quantitative study designs. Hitherto to these explicit efforts, most studies predicted non-adherent clinic attendance to be significantly related to sociodemographic, socioeconomic, health-care delivery systems, and patient- and provider-related factors, but these findings showed mixed variations across the European, African, and Asian sub-continent.

Sociodemographics and socioeconomic factors

Several cross-sectional studies found inconsistencies across sociodemographic and socioeconomic profiles affecting adherence to scheduled ART clinic attendance. Whereas older age, non-African-American ethnicity and high-income level were reported to influence regular clinic follow-ups in the United States and Brazil[40-42], older age and female gender were associated with missed clinic appointments in China[43]. In Malaysia, Indian ethnicity and heterosexual orientation were significant predictors of outpatient clinic attendance among HIV-positive patients receiving ARTs[44]. From the African perspective, a retrospective cohort analysis in Western Kenya found that missed clinic appointments were more likely to occur among those unemployed, smokers, and those with unknown disclosure status[20]. In a prospective study among the Ugandan cohort, younger HIV-infected patients were found to be less likely to achieve regular clinic attendance[45]. The Evidence for Elimination cluster-randomized trial evaluating point-of-care CD4 testing that included 1150 HIV-infected ART-naive pregnant and breastfeeding women attending antenatal care between January 2014 and June 2015 in Zimbabwe found that younger women were more likely to be non-adherent to continued care 360 days after ART initiation[46]. Structural barriers such as travel and financial constraints have contributed to missed or irregular clinic appointments. For those patients living in rural areas or resource limited settings, the cost of transportation relative to individual's income could be substantial; thus, the need to struggle to be equipped with other essential expenses for shelter, food, and education is tantamount. A qualitative study conducted in a Ugandan cohort concluded that the cost of transportation for monthly clinic visits was a potential barrier to regular clinic attendance[47]. Similar reasons were cited in another prospective study in the same setting[45].

Patient-related factors

Perceived social stigma and discrimination associated with positive HIV status were postulated to be an influencing factor of missed clinic appointments[44]. Patients' psychological vulnerabilities such as being depressed or unable to cope with stressful life situations as a consequence of the unstable social environment were attributed to irregular clinic attendance[45]. In addition, forgetfulness, commitments with work or other activities, the self-rated perception of ill health and religious beliefs was cited as potential barriers for missed clinic appointments as well[18,44,45].

Provider and health system factors

The bulk of studies from Asia reported that the distance from home to health facilities is a major factor for missed clinic appointments[48-55]. In addition, citing long delays or waiting time at clinics discouraged patients from adhering to future scheduled appointments[45]. Such impediments that de-motivated HIV-afflicted populations have also caused non-adherence to ART treatments[56]. From a qualitative study among 31 HIV-infected patients in Baltimore Maryland, clinician's availability, attitude and communication styles were hypothesized to influence negatively on scheduled HIV clinic attendance[57]. The influx of patients in public health facilities globally due to increased demand for health-care services has prompted health-care providers to execute rapid consultations, thus failing to convey critical information to patients as a result of interrupted patient-provider rapport.

It was postulated that patients' clinic attendance was influenced by unstable social living environment. HIV-infected individuals are often required to identify trusted family members, partners, and friends as treatment supporters to overcome potential social stigmatization. Trusted people may assist HIV-infected individuals with appointment keeping, provide emotional support and represent them when illness afflicts them, thus preventing them from defaulting clinics attendance for refills[45]. Studies in Asia found that system-level factors such as adherence to counseling, hospital-based support group and good family support were consistently associated with regular clinic attendance among HIV-positive patients receiving ARTs[58,59]. In Nepal, investigators conducted a 12-month retrospective cross-sectional analysis across 423 HIV-positive people to evaluate the association between perceived

family support and participation in support programs with regular clinic attendance. They found that good family support catalyzes greater adherence to regular clinic attendance[59]. Similarly, in Indonesia, Weaver et al.[58] through a qualitative approach found that increased level of social support experienced by ART-prescribed patients was positively associated with adherence. A similar scenario was highlighted from the European perspective, of which a 12-month retrospective analysis among 178 adult HIV-infected patients from the United States with limited family support showed greater clinic non-attendance rates[41]. Physical support from family or friends is crucial to ensure regular clinic attendance as it provides monetary support, transportation provision for commuting and appointments reminding[56,59].

Strict medication adherence

Adherence behavior (i.e., medication adherence) is a critical linkage between prescribed ART regimen and treatment outcome. When an HIV-infected individual is non-adherent, it is likely that even the most effective ART regimens fail[60]. Most studies on ART adherence exhibited that predictors and risk factors differ across different regions of the world, necessitating context-specific development of non-adherence profiles[61].

Sociodemographics and socioeconomic factors

Literature has highlighted varying patterns of adherence behaviors associated with patient demographics and socioeconomic predictors[60]. These inconsistencies were prevalent in countries with highly concentrated HIV epidemics as compared to countries with generalized HIV incidence patterns[60]. Concurrently, adherence behavior showed striking inconsistencies between low-, middle-, and high-income nations[22]. Resource rich-settings have consistently established that younger age, non-white ethnicity, low-income, lack of education, and insecure housing were positively associated with non-adherence behaviors[62,63]. In Asia, significant associations were found between adherence behavior with social (level of education, stigma, non-HIV disclosure, alcohol, or substance use) and economic (income and availability of health insurance) factors in resource limited settings, particularly in Nepal, Thailand, India, China, Cambodia, and Malaysia[56]. Findings from a systematic review on determinants of ART adherence among African adults reported that men, younger age, low literacy. and being unemployed were significant predictors of non-adherence[61].

Patient-related factors

The key reasons for not wanting to take ART medications by patients were forgetfulness, busy daily schedules, feeling sleepy after taking the medication and running out of medications[39,58,64,65]. Amplified by rumors and false beliefs that ARTs may cause harm and sexual arousals, patients were often predisposed to intentional non-adherent attitudes such as the decision to self-omit prescribed medications, or unintentional non-adherent attitudes such as decreased self-confidence toward ART treatment regimen[61]. Two studies in Asia identified religion and ritual obstacles among HIV-infected patients as factors that predispose them to self-omit prescribed medications[56,58]. Socio-cultural factors such as stigma and discrimination, fear of being recognized, fear of disclosure of status to the community, and stigmatization from family may cause sub-optimal adherence in HIV-infected patients[35,50,52,55,66,67]. To prevent unwanted disclosure, these patients hid their medications, leading to delayed or missed doses to prescribed ARTs[56]. It is worthy to note that negative perceptions over ARTs can exert control over self-motivations, thought processes and emotional states to influence adherence related behavior[56]. Using a mixed-method approach, a study in Nepal postulated that patients' belief, knowledge, and expectations regarding treatment strongly influenced their medical decision making[56]. That study revealed that very few patients believed that ART cured HIV and were unclear as to how long they should take ARTs. It is important for every patient to understand the importance of treatment goals and to adhere to prescribed ART regimen as inaccurate information and misconceptions toward disease and treatment would lead to poor therapeutic outcomes[56].

Provider and health system factors

Patient satisfaction with provider and health services is crucial to influence adherence behavior. A good patient-provider communication is essential for adherence behavior[16,68]. In an attempt to highlight the putative factors of medication non-adherence, a systematic review from Asia concluded that inaccessibility of services and the relationship with service provider were major barriers toward adherence behavior[56]. From the African perspective, non-adherence was observed when patients encountered unpleasant experi-

Table 1. Common measurement techniques, key advantages, and limitations

Measurement technique	Advantages	Limitations
1) Patient self-reports	1. The most common technique used by researchers given its' advantages of low cost (commonly used by resource limited settings) and design flexibility (allows cross-cultural adaptation–questionnaires suit individual language abilities) 2. Data collection is easy and helps to explore the magnitude of the problem (prevalence) and factors influencing the non-adherence problem (hypothesis generating) across different populations	1. Such approach may lead to recall bias (assuming that patients recall their behavior to provide an honest response) 2. Overestimates of adherence
2) Pill counts	1. Returning excess pills allow tangible evidence of non-adherence	1. Pill counts require patients to return medications packaging to the clinician. In such situations, there were high risks that patients tend to forget the packages or inadvertently discard them. Some patients engage in "pill dumping" to appear adherent. These situations may cause overestimates
3) Serum assay of drug levels	1. Measures the last dose taken	1. Expensive 2. Lack of general availability 3. The serum concentrations of nucleoside analogs may not reflect intracellular concentration of the active triphosphates 4. Provides information on recent doses and risks overestimates
4) Electronic pill caps	1. A monitoring system is inserted in the medication bottle caps to record accurately the date and time of opening and closing of the bottle	1. Interpretation of data assumes that a single dose is taken each time the bottle is opened, thus, leads to inaccuracies or overestimates if multiple doses are removed at once

ences with clinic staffs, rudeness, condemnation, and fatigue[61]. In addition, inappropriate health facility settings such as lack of privacy, crowded pharmacies, short doctor-patient communication due to multiple consultations, lost of patient records and long wait times were blamed to catalyze non-adherence behaviors[61]. With the influx of patient admissions in public hospitals, health-care providers often failed to convey critical information about medication use among patients and their effects on disease progression.

Therapeutic-related factors

ART regimens are often intricate and demand varying dosing schedules, complex regimen, meal restrictions, and adverse drug reactions[16,56,61,69]. The relatively short half-lives of non-nucleoside reverse transcriptase inhibitors and protease inhibitors had necessitated prescriptions with high dose frequencies and increased pill burden on HIV-infected patients, causing frustrations to adhere to agreed treatment plans[16]. Adverse drug reactions are important determinants in influencing adherence behaviors. The WHO defined an adverse drug reaction as "a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or modification of physiological function[70]." Using a qualitative approach among 34 HIV-infected persons in Nepal, Wasti et al.[56] reported that patients' non-adherence behaviors were related to medication side effects such as vomiting, diarrhea, body pain, and skin rashes. To further strengthen such claims, Li et al.[71] conducted a systematic review and qualitative meta-synthesis to conclude that visible drug reactions such as body changes, a buffalo hump, excess

sweating, darkening of the skin, body odor, hair loss, weight gain/loss, and skin rash increases the risk of unintentional HIV disclosure, disturbed routines, causing low self-esteem, self-stigmatization, and non-adherence to ARTs. Coherently, psychological impact associated with these adverse drug reactions such as being delusional and a feeling of being "killed" by taking ARTs has contributed to non-adherence[71]. In addition, efavirenz-containing regimens have been reported to result in neuropsychiatric reactions (e.g., dizziness, body heat, nightmares, and anxiety) which contributed to poor adherence[71,72].

Addressing the problems of non-adherence

Measuring and monitoring adherence

Valid and reliable tools are vital to quantify the extent of medication non-adherence precisely. Literature that explored medication non-adherence in HIV-infected persons to date has employed different methods of measurements. These variations have made the non-adherence phenomenon difficult to conclude, yet yielding multiple hurdles to execute appropriate interventions. Common techniques that investigators used to quantify the magnitude of the non-adherence problem in HIV-infected persons include patient self-reports, pill counts, measuring serum-assay drug levels, and the use of electronic pill caps. While each of these methodologies has its unique strengths, all of them have certain limitations[16]. Table 1 summarizes the key techniques used in adherence measurements.

Conclusion

Non-adherence places a significant burden on patients, caregivers, health-care providers, the health-care system and all stakeholders involved in HIV care and programming. Evidence proved that higher levels of adherence improves the probability of HIV suppression and reduces the risk of disease progression and mortality. Acknowledging rigorous research conducted over the past decade, we found rich literature evidence on findings incorporated to achieve the best practice recommendations on the importance of adherence in HIV/AIDS management. A general understanding of factors associated with non-adherence and approaches to investigating non-adherence behavior among different populations has highlighted a set of significant contextual differences that exist between barriers and burden of non-adherence among the HIV population. Our broad-spectrum review may be a platform of reference to help formulate and amalgamate a global consensus document to align fragmented efforts on scale-up interventions to reach optimal treatment-adherence among HIV populations worldwide while establishing research priorities and gold standards for reporting and validation.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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