

# The consequences of non-adherence to medicines

**Mekolle Enongene Julius**

**Africa Centre for HIV/AIDS Management  
Stellenbosch University, South Africa**

## **Abstract**

One of the main barriers to reaping the full benefits of prescription medications is known to be poor or non-adherence to treatment regimens. Many prescription drugs significantly lose effectiveness when patients don't follow the recommended treatment plan. Adherence problems are grave difficulties that have terrible effects on the patient and the healthcare system under discussion. Therefore, to stop the situation from getting worse, patients, healthcare professionals, and other stakeholders must work together.

## Introduction

A large proportion of patients only receive suboptimal benefit from their therapy, develop worse health outcomes with increased mortality and morbidity, all of which are connected with greater societal expenses, due to the relatively widespread problem of inadequate adherence to prescribed medications (1, 2). Suboptimal adherence or non-adherence is acknowledged as one of the key obstacles to enjoying the full impact of prescribed drugs. Patients' failure to adhere to the prescribed treatment regimen substantially reduces the effectiveness of many prescription medications. For some illnesses and/or patient groups, non-adherence rates are as high as 40 to 86 percent, leading to avoidable trips to emergency departments (EDs) and hospital admissions (3-6). According to estimates, between 4 and 11.4 percent of hospital admissions and 7.6 percent of ED visits are attributable to non-adherence (7, 8). According to these projections, greater adherence might greatly enhance health and lower healthcare expenses (6, 9).

It is suggested that pharmaceutical non-adherence is the evidence-based medicine's Achilles' heel (10). The WHO asserts that improvement in adherence interventions may significantly influence population health than improving particular medical treatments. Since failing to follow medical advice can be a serious issue, DSM-5 (APA 2013) includes it as a diagnostic category V15.81 (Z81.18). Fortunately, from the perspective of individualized pharmacotherapy and person-centered medicine, medication non-adherence is a diagnosable, preventable and treatable medical malady (11).

Antiretroviral therapy (ART) aims to reduce viral replication, restore or maintain immune function, and stop the virus from spreading further and consequently, the HIV disease natural history is subverted (12). However, ART is not curative; to maintain the suppression of HIV, it must be taken continuously (12). Though subject to fluctuation depending on the regimen, (13) near-perfect medication adherence of 95 percent is frequently quoted as vital for viral suppression. Meanwhile, persistent adherence to ART remains an up-hill task for a myriad of reasons (14, 15). Suboptimal adherence is complex (16), and numerous research studies have been done on methods to increase adherence to ART (17, 18). Although patients with HIV who

adhere to therapy have excellent outcomes (19, 20), non-adherence happens often in both high- and low-income settings. Viral load (21) and CD4 count (22) are two individual-level outcomes that poor ART adherence to has been shown to negatively affect in the literature. This paper emphasizes on the implications on the population of non-adherence to medications in general and to ART in particular.

### **1. Nonadherence, worsening health condition and mortality**

One of the most serious effects of not taking medications as prescribed is a deteriorating health condition that eventually results in death. Patients who are non-adherent frequently have increased symptoms, problems, and comorbidities, especially those who have chronic diseases. Over time, non-adherence can also lead to a faster rate of illness development, necessitating extended and rigorous care. If PLWHA don't adhere to treatment, their condition in the context of HIV can quickly degenerate into AIDS with resultant mortality.

In a systematic review of existing papers to determine the effects of non-adherence to COPD medication on clinical and financial outcomes, evidence from twelve complete studies showed unequivocally that non-adherent patients experienced higher hospitalizations, loss of productivity, poorer quality of life and mortality (23). Similarly, non-adhering patients were more likely to relapse and/or recurrence, experience more frequent emergency department (ED) visits, and hospitalization rates; more severe forms of depression; and lower response and remission rates, according to another systematic review looking at the clinical and financial impact of non-adherence to antidepressants in major depressive disorder (24). While depression was not associated with cardiovascular mortality, a study to understand the implication of medication non-adherence on the link between mortality risk and depression in heart failure found that non-adherence, but not depression, predicted all-cause mortality risk (hazard ratio 1.01; 95 percent confidence interval 1.004-1.02) when non-adherence was added to the model (25).

Three hundred thirty HIV-positive people were prospectively followed up for 16 months in one research. Clinical, para-clinical evaluations and adherence assessments were carried out. Findings showed no AIDS event among the high-adherence group compared to 8% in the

moderate-adherence group and 41% in the low-adherence group ( $P = 0.0012$ , log-rank test), concluding a strong link between ART adherence level and the risk of progression to AIDS among PLWHA (26). In a similar vein, a Cameroonian study that sought to identify the variables linked to an elevated risk of non-adherence among PLWHA found that participants with opportunistic infections had odds of being non-adherent that were 3.1 times greater.

In one Swiss HIV Cohort Study investigating the association between self-reported adherence to ART and cardiovascular events (including mortality) and non-cardiovascular-related death, (28) study participants ( $n=6,971$ ) were on ART between 2003 and 2018, had viral suppression for at least six months, and had no prior history of cardiovascular illness. With the aid of a standardized self-report, adherence was evaluated. Multivariate analysis showed a larger correlation between missed doses and mortality unrelated to cardiovascular disease. The authors came to the conclusion that among virally suppressed patients with HIV, insufficient ART adherence was strongly linked to an elevated risk for non-cardiovascular mortality (28).

## **2. Economic impact of non-adherence**

Despite reported non-adherence to long-term therapy for chronic illnesses, medications still constitute a cost-effective treatment option (29) and pharmaceutical non-adherence whether intentional or unintentional represents a different caliber of challenge in health economics.

The annual cost associated to medication non-adherence ranges from US\$100 to US\$290 billion (31) in the United States, €1.25 billion (32) in Europe, about \$A7 billion (33, 34) in Australia, and £339 in the United Kingdom. Also, it has been proposed that increasing adherence among the hypertensive population in the United Kingdom might lead to annual savings of more than £100 million (€116 million) (35). The predicted cost savings from reducing anti-diabetic medication non-adherence varies between \$661 million to \$1.16 billion (36). Additionally a typical non-adherent older adult patient also needs three more doctor visits annually, which raises treatment expenses by \$2,000 annually (37).

In a systematic review involving seventy-nine studies, to determine the economic impact of medication non-adherence across 14 disease groups, the key parameters for measurement of

the cost of non-adherence were total healthcare cost (83% of studies), inpatient costs (46%), outpatient costs (50%), pharmacy costs (70%), medical costs (29%), emergency department visit costs (27%) and hospitalization costs (18%). The study underscored how costly non-adherence to pharmaceutical regimens is for healthcare systems.

HIV/AIDS and poverty are connected in two ways: HIV/AIDS can deplete people in ways that make the disease worse, and poverty is a major factor in transmission (42). Malnutrition stems from poverty (43, 44). Additionally, poor adherence may result from insufficient transportation to access ART (45). A compromised immune system caused by the conjugated complication makes underprivileged populations more susceptible to advanced HIV diseases. On the other hand, PLWHA are more prone to fall into poverty as a result of the high expense of treatment or the lack of a reliable source of income (43, 44).

ART regimens provide good return on investment spent relative to varied recognized health care interventions according to cost-effectiveness analyses, even though HIV infection has evolved into an expensive manageable chronic disease in high-income countries, with annual unit cost per patient of approximately US\$20000 (38). Average ART cost per patient-year in low-income countries (LIC) according to one study was \$US792, \$US932 for middle-income countries (LMIC) and \$US1454 for upper-middle-income countries (UMIC). In all contexts, ARV medications accounted for the majority of ART costs (64 percent, 50 percent, and 47 percent in LIC, LMIC, and UMIC, respectively) (39). However, non-adherence promises to lay waste of such significant financial investment.

One Brazilian study that looked at the early adherence of PLWHA to ART for cost-effectiveness found that almost 80% of the adherent patients accounted for a smaller ratio cost-effectiveness relative to the minority non-adherent group. Furthermore, low adherence increased the probability of therapeutic failure and illness progression, which consequentially had a strong adverse influence on ARV therapy's cost-effectiveness (54).

### **3. Nonadherence complicating acquired HIV drug resistance**

When PLWHA have suboptimal adherence to ART, interruptions in treatment, insufficient medication bioavailability, or unfavorable drug combinations, acquired HIV drug resistance (ADR) may result (47). Since it can result in poor health outcomes for PLWHA and can be communicated to others (leading in transmitted HIV drug resistance), ADR is a major problem (47). Though the connection between emergence of drug resistance and poor adherence to ART has been broadly studied (48–50), it is important to keep in mind that this connection is intricate (47). Furthermore, based on antiretroviral (ARV) class used in the recommended regimen, the link between ART adherence and medication resistance is not constant (48).

Antiretroviral HIV drugs are currently divided into seven categories based on how they alter the HIV life cycle. These seven classes are: "integrase strand transfer inhibitors (INSTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), fusion inhibitors, CCR5 antagonists, post-attachment inhibitors, and nucleoside reverse transcriptase inhibitors (NRTIs)" (51). A few studies expanding on ADR below highlight some of these drug classes.

Based on a pool of studies addressing virologic failure among treatment-experienced and treatment-naive (INSTI- naive) persons, a 2020 systematic review evaluated published examples of resistance to Dolutegravir (DTG) (52). Pertaining to its effectiveness, high barrier to drug resistance and safety, DTG-based ART is a favored first- and second-line therapy regimen for PLWHA (52). Ten of the fifteen events of therapeutic failure that were discovered had measured DTG concentrations below optimum levels or had records of poor adherence (52). Researchers concluded that sub-optimal adherence may play a major role in emerging treatment resistance (52).

A 2011 Italian study looked at the relationships between adherence to ART and drug-related mutations in 40 HIV-positive individuals who were showing signs of treatment failure (53). Self-reporting was used to gauge adherence, and the authors computed the percentage of adherence for doses missed in the previous week, month, and three months (53). Participants were labeled as "very adherent" if they claimed to have taken all recommended doses and "non-adherent" if they had taken less than 80%. (53). Thirteen patients were not adherent, and

27 individuals were extremely adherent (53). The majority of subjects had genotypic resistance mutations, the authors discovered, despite a high self-reported therapy adherence (53).

#### **4. Non-adherence and transmissibility**

The HIV Undetectable=Untransmittable, or U=U concept has recently received overwhelming clinical support, solidifying it as a valid scientific theory. U=U denotes the inability of PLWHA to sexually transmit the virus to others when they take ART as directed every day to attain and maintain an undetectable viral load. Thus, effective HIV therapy is a potent weapon in the arsenal of HIV preventive goals, making it crucial in the fight to contain the epidemic (55). Based on this revolutionary scientific theory, HIV transmission to new people is likely the most visible result of non-adherence to ART (55), since it undermines the potential for ART to minimize transmissibility (56).

The major HPTN 052 clinical trial which followed more than 1,600 heterosexual couples for ten years provided conclusive proof that HIV transmission cannot occur through sexual contact when ART is consistently followed. According to HPTN 052, HIV transmission is virtually prevented when therapy for the virus is started and maintained early, when the immune system is still in a pretty good state. When ART reliably and persistently suppressed the virus in the HIV-positive spouse, no evidence of HIV transmission was seen. While there were occasional transmission events in the trial, new transmissions only happened when the partner with HIV was not completely virally suppressed because either they had recently started ART or their treatment was no longer effective and the virus was multiplying. The HPTN 052 findings, together with those of the START research financed by NIAID, influenced the WHO to suggest that every PLWHA should be enrolled to ART as soon as they are diagnosed in 2015 (57).

It was clearly shown in a 2017 German study of 233 males who had sex with HIV-positive men that adherence issues were linked to an elevated HIV transmission risk (58). Respondents were asked about their sexual behavior, health, and depressive symptoms after being divided into three risk groups: low (those who consistently achieved a viral load below the detection threshold), high (those who are ART-naive participants or those during a treatment-free interval with a low likelihood of transmitting resistant HIV strains), and another characterized high risk

group (those who are able to transmit ART resistance). Those in the second high risk transmission group were noticeably more likely to experience adherence issues in comparison to the low transmission risk group (58).

## **Conclusion**

Adherence issues constitute severe concerns that have devastating impact on both the patient and the healthcare system here discussed. Therefore conjugated efforts of patients, health care providers and other stakeholders are required to avert the growing problem.

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