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Antiretroviral Adherence Concepts and Strategies for Adults Accessing HIV Care

This evidence review is part of a series on HIV prevention and control produced by the National Collaborating Centre for Infectious Diseases. It is intended to inform public health practitioners and community-based workers and guide their practice.

Introduction

Adherence to HIV medications is an essential determinant of treatment success or failure. When taken properly, antiretroviral therapy (ART) dramatically improves an individual's health and allows the immune system to recover. According to a statistical model, the life expectancy of people living with HIV/AIDS (PHAs) would only be eight years shorter than that of individuals in the general population if they adhered to their medication regimens and received HIV care in line with guidelines (1).

However, full daily adherence is difficult because of long-term commitment to taking multiple drugs with different dosing requirements and drug side effects. Adherence means remembering to take medications as prescribed, at the right time, and in the right combination (2). Suboptimal adherence that fails to suppress an individual's viral load increases morbidity and mortality rates, emergency room visits (3), hospitalizations (1, 4), and promotes the development of HIV drug resistance (4).

Strategies to encourage ART adherence may save direct health care costs as well as improve individual health outcomes. Nachega and colleagues demonstrate that increasing resources for adherence strategies is associated with substantial cost savings for the entire health system (5). They estimate that improving adherence would decrease the mean total cost of medical care by US $85 per month among HIV-positive adults in a South African private clinic, thus providing evidence that strategies to promote adherence may be cost-saving (5).

Highlights

- PHAs who have access to behaviour interventions such as reminder messaging, education, and social support show improved adherence to antiretroviral therapies.
- Adherence to once-daily regimens is superior to twice-daily regimens.
- Health care providers should develop an individualized care plan with PHAs and provide follow-up services necessary for successful adherence.
- Health care providers should focus on improving communication skills, fostering trust, and working compassionately with their clients.

This Evidence Review explores the concepts of adherence and effective strategies to increase adherence to ART among adults living with HIV/AIDS (PHAs) who are already accessing medical care. Adherence in children and adolescents is not addressed in this Evidence Review.

Definitions

95% adherence: No more than two a missed monthly in a twice-a-day regime.

Fixed-dose combination: Two or more HIV medications combined in certain fixed doses in a single tablet.

Intermittent therapy: Antiretroviral treatment that is prescribed on and off at pre-specified time periods or is guided by CD4 cell counts.

Viral load: A measure of the number of virus particles present in the bloodstream, expressed as copies per millilitre.

Viral suppression: A viral load less than 50 copies/ml for long periods of time.

Viral rebound: The second of two consecutive viral load measurements (within 6 months) of more than 400 copies/ml after 26 weeks of initially achieving viral suppression on ART.

Part I: Background Concept of Adherence

What are the Rates of Adherence among Canadians?

In urban settings, around 50% of all known HIV-positive people used HIV treatment and care services, and most individuals were adherent to the ART prescribed (6). For example, in a study conducted in Vancouver, 84% of PHAs (N = 1715) who initiated triple combination regimens between 1996 and 2003 reported over 95% adherence (7). However, the study's inclusion criteria required at least three filled prescriptions prior to enrolment, allowing for possible bias in the selection of study participants. In a second Vancouver prospective study (N = 903), the adherence rate among PHAs was 79% during the initial six months; however, by 24–30 months, the adherence rate declined significantly to 72% (8). This study is one of many reporting that adherence declines over time (9–12).

Adherence rates for substance users and Aboriginal peoples are reported to be lower than for non-users and non-Aboriginals (13). HIV disproportionably affects Aboriginal peoples in Canada (14). Representing just 3% of Canada's population, Aboriginal peoples account for 5–8% of all individuals living with HIV and 6–12% of all new diagnoses in one year. Further, 53% of new HIV infections in Aboriginal peoples are associated with injection drug use (IDU) as compared to 14% among non-Aboriginals (15). In one study, Aboriginal participants were significantly less likely to adhere to therapy in the first year compared to non-Aboriginal participants (14).

Is 95% Adherence Necessary?

In the early era of antiretroviral combination therapy with protease inhibitors (PIs), researchers found that taking 95% or more of doses was required for full viral suppression (4, 16, 17). More recent recommendations state that virus suppression may be possible with lower adherence using ritonavir-boosted PI regimens (18) and non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens (19–22). Indeed, 70–90% adherence with NNRTI regimens may maintain viral suppression and prevent HIV drug resistance (19–22). Whereas missing a few doses may seem safe, sustained interruptions are not (22, 23). A 2008 case-control study estimated that there is a 50% chance of viral rebound only 15 days after ART discontinuation (23); more specifically, Ribaudo and colleagues found viral rebound between day 6 to 14 after discontinuation of NNRTI regimens, allowing for HIV mutation and replication (24).

Suboptimal ART adherence enables HIV to mutate, leading to the development of drug resistance. This is especially applicable to NNRTIs, namely efavirenez, nevirapine, and delavirdine, in which development of resistance to one agent confers high-level resistance to other NNRTIs (not true of etraverine). This is called cross or class resistance, and it means that some antiretroviral drugs will not work even if they have not been used before. Multi-resistant strains are resistant to two or more classes of drugs. NNRTIs, lamivudine (3TC), and integrase inhibitors (raltegravir and elvitegravir) have low barriers to resistance (25). In contrast, PIs have high genetic barriers to resistance (20). Understanding class-specific adherence-resistance relationships can help health care providers and clients tailor treatment to an individual's specific adherence pattern, thus minimizing the development of drug resistance (21). For a review of ART adherence pertaining to the development of class-specific antiretroviral resistance, refer to the article by Gardner and colleagues (22).

Clinicians should encourage patients to maintain a high adherence level for all antiretroviral regimens. However, for

clients who might take their medications irregularly with wide gaps between missed doses, it is recommended that clinicians prescribe boosted PIs regimens (21). For clients with moderate adherence, that is, with occasional gaps in missed doses being no more than two days, clinicians could prescribe NNRTIs-based regimens (21). Discussing with each patient what his/her particular preferences are regarding pill count, dosing times, and side effects, then tailoring the patient's antiretroviral therapy to these preferences, could increase adherence.

What are the Risk Factors that Impact Suboptimal Adherence?

The risk factors for suboptimal adherence can be categorized as social, economic, medical, and behavioural (2), and they can be attributed to the individual, the strength of the client-health care provider relationship, the drug regimen, or the clinical setting. The risk factors summarized and categorized by Reynolds (26) include the following:

- Cognitive and psychological function (e.g., depression, mental health, cognitive impairment, literacy, forgetfulness)
- Substance use of drugs or alcohol
- Disease progression and degree of symptoms
- Health care environment and material factors (e.g., access to care, financial concerns)
- Treatment experiences (e.g., regimen complexity, side effects, toxicity)
- Support from providers and others
- Informational resources (e.g., knowledge about HIV, medications, adherence).

Are Once-Daily ART Regimens Effective at Increasing Adherence?

Simplifying dosing regimens improves HIV adherence (27, 28). When PHAs are given therapies that are complex or that interfere with their lifestyle, adherence will often decrease (2). The most preferred ART regimen is one dose per day without food restrictions (29). In 2010, fixed-dose combinations include: Combivir (lamivudine [3TC]/zidovudine), Trizivir (abacavir [ABC]/3TC/zidovudine), Kaletra (lopinavir/ritonavir), Truvada (tenofovir/emtrictabine), and Atripla (tenofovir/emtricitabine/efavirenz) (30).

Many randomized control trials (RCTs) (29, 31, 32) and one pharmacy record study (33) have demonstrated viral suppression and improved adherence with once-daily dosing regimes compared to twice-daily dosing regimes. In a 2009 meta-analysis including 11 RCTs and 3029 participants, the adherence rate for once-daily dosing was found to be significantly higher than twice-daily dosing (27). In a 2001 review of 76 adherence studies, average adherence was 79% for once-daily dosing, 69% for twice daily, 65% for three times daily, and 51% for four times daily (34). However, this study was not specific to ART regimens.

Part II: Adherence Strategies

What Behavioural Strategies Effectively Increase Adherence?

Two meta-analyses indicate that some behavioural strategies to improve adherence are successful (35, 36). Recent and innovative research on couples-based and social support (37, 38), motivational interviewing techniques (39–41), patient education (42, 43), coordinated case management (44–46), and unannounced pill counts conducted by telephone (47) and during home visits (47–49) are effective at increasing adherence rates. Electronic monitoring devices (50) and peer support interventions (48) have shown poor results.

In a 2009 study, 31% of Ontario physicians recommended the use of pill boxes to their clients (51); however, few studies have assessed the use of pill boxes on HIV adherence rates. In a study by Kalichman et al., the use of a pill box among 39% of individuals on ART (N = 160) increased their likelihood of having an undetectable viral load and reduced incidence of missed medications (52). A study by Petersen et al. showed that pill box users increased their adherence to prescribed drug regimens by up to 5%. They were nearly twice as likely to have a viral load of 400 copies per millilitre or less. Pill box users also were 11% less likely than non-users to progress to AIDS during the course of the study (53).

According to a statistical model, the life expectancy of PHAs would only be eight years shorter than that of individuals in the general population if they adhered to their medication regimens and received HIV care in line with guidelines.

Medication "reminder packaging," which incorporates a date or time for a medication to be taken, can act as a reminder system to improve adherence. No HIV-specific reviews related to reminder packaging were found; however, two non-HIV-related systematic reviews concluded that reminder packaging resulted in a significant increase in the percentage of pills taken (54, 55).

Directly Observed Therapy

Ford and colleagues conducted a meta-analysis of directly observed therapy (DOT) verses self-administered treatment to promote adherence (56). Of the RCTs included for analysis, seven involved the general population (57–63), and four involved populations at high risk for non-adherence (substance users [64–66], the homeless [67], and prisoners [68]). These studies used viral suppression as the primary outcome, and they defined "directly observed" as supervised swallowing (N = 1862). Under this definition, only two studies fully qualified as being directly observed therapy; the remainder of the studies supervised only a portion of doses. Six studies used community or peer supporters as observers, and the others used health workers. The results of the meta-analysis show that there was no significant difference between DOT and self-administered treatment in achieving viral suppression. In addition, all secondary outcomes included in the meta-analysis (self-reported adherence, immunological change, loss to follow-up, all-cause mortality, mutations leading to resistance, and AIDS-defining events) were also not significantly different between the two adherence strategies.

Up to 70% of people who comply with their medication regimens do so because they see the provider as a caring advocate.

However, in a sub-analysis of the 2009 meta-analysis (56), DOT showed a marginal benefit compared to self-administration when groups at high risk of non-adherence were specifically examined (RR 1.31, p=0.046). Indeed, DOT studies have reported statistically significant findings in selected settings such as prisons (69), methadone maintenance (70, 71), needle-exchange programs (72), and in the community (40, 73, 74) among groups traditionally displaying high non-adherence. Supporters of DOT say that individuals benefit from the direct promotion of adherence, their interaction with the health system, and sustained retention in care (75). Further studies in these populations are warranted. Critiques of DOT programs state that they are very intensive, costly, and coercive to patient autonomy (56).

Social Support

Interventions that involve family members, particularly spouses, improved adherence (38, 76). In one study, a couple-based support intervention increased adherence although there were no changes in viral load or CD4 cell counts (37). Community-based support interventions for substance-users are effective (77, 78); however, improvement in adherence was only apparent if support was provided for a period of more than 4 months (4). For example, one peer support RCT conducted over a three-month period could not maintain adherence after intervention follow-up (48). In these studies, community support for adherence was defined as home care, support to family care givers, and continuing adherence counselling.

High adherence rates of over 90% found in sub-Saharan Africa may be the result of social contracts between partners, family members, friends, and health care providers (77). Due to economic obstacles to ART, such as user fees, laboratory test costs, and transportation costs associated with visits to HIV clinics, individuals must engage in monetary loans and social contracts to pay for their treatment. These social and monetary contracts obliged the individual to sustain ART adherence as a long-term health investment.

How can Health Care Providers Support Client Adherence?

A strong health care provider-client relationship that is based on open communication, participatory decision-making, and trust is predictive of adherence (78). Up to 70% of people who comply with their medication regimens do so because they see the provider as a caring advocate (2). PHAs with excellent adherence to ART reported that they: (a) believed adherence rates needed to be 90–100% for medication efficacy, (b) trusted their primary care providers, (c) took medications even when actively using drugs, (d) were open about their HIV status and received social support, (e) were motivated to stay healthy, and (f) were not depressed (78).

Prior to antiretroviral initiation, health care providers should discuss the barriers to adherence, such as alcohol abuse and depression, with their clients. Next, an adherence rate should be determined by using multiple assessment techniques (2, 79). The most popular method is a self-reported adherence questionnaire completed at every clinic visit (80). However, clinicians should inquire beyond the assessment of missed doses and gather information on other aspects of adherence such as knowledge of medication names and prescribed dosing regimens, special dietary instructions, and patterns of suboptimal adherence on weekends, mid-day, or when daily schedules change (36).

There are several limitations to self-reported patient adherence assessments, despite their practicality and low-cost. Self-report is susceptible to recall bias, potentially to social desirability bias (36), and has produced estimates of adherence that are 10–20% higher than those from electronic drug monitoring (81,

82). Despite these misgivings, two meta-analyses have found that self-reported ART adherence was significantly associated with improved viral load (36, 83).

Researchers are debating which recall period to use. While shorter recall periods are assumed to be more accurate, longer recall periods may be useful as once-daily dosing is increasingly used (84). Lu and colleagues compared 3-day, 7-day, and 1-month self-reports with electronic pill monitoring and found that over-reporting was significantly less for the 1-month recall period (9%) than for the 3-day (17%) or 7-day (14%) periods (85). They also found that questions rating adherence (from very poor to excellent) were more accurate than questions using frequencies or percentages. Their finding that one-month recall is more accurate than shorter recall periods is consistent with the finding of a meta-analysis that recall periods of 3 days or more were more accurate than those of 3 days or less (36).

Bangsberg suggests that ongoing adherence supervision can identify individual signature adherence patterns (21). For example, some patients may consistently take 70% of their medications, while others may have higher levels of adherence with intermittent treatment interruptions. Still others may have differential adherence to an individual medication due to side effects. As signature adherence patterns could be determined early during therapy, prior to viral rebound and drug resistance, it is important for the provider and patient to establish shared adherence goals (2, 21). Motivational interviews are successfully used by physicians to encourage patients to take medications properly (39, 40, 42). The interviews aim to build confidence, reduce ambivalence, and increase motivation for ART adherence (41).

Sustained adherence to first line ART regimens is necessary to achieve viral suppression. Once long-term viral suppression is achieved, the benefits are many: (a) the use of first line regimens can be sustained without the need to switch to more complex regimens (21), and (b) occasional lapses in adherence to the first line regimen would not be detrimental to the maintenance of viral suppression (86). In fact, Rosenblum and colleagues demonstrated that the level of adherence needed to maintain HIV suppression would decrease with longer duration of viral suppression (86).

What are the Gaps in the Research?

The evidence for adherence strategies and interventions is strong as it relates to benefits of once-daily dosing of ART regimens. However, further study is needed to evaluate whether DOT is effective in populations at high risk of non-adherence. More investigations are also needed to examine provider-client relationships and clinician training. The support role of individual, family, and community in influencing PHAs' adherence to ART needs further research. Furthermore, studies in specific HIV populations on the effectiveness of reminder packaging, unit-of use or fixed-dose pill packs, pill boxes, and telephone support with written correspondence for adherence are warranted.

What are the Conclusions?

Inconsistent adherence behaviours should be identified by health providers and modified prior to the start of ART to optimize adherence. Interventions to improve adherence behaviours include diagnosing and treating depression, treating drug and alcohol dependence, strengthening the provider-client relationship, and fostering social support through the incorporation of partners and family members into the care plan (21). Even though once-daily dosing is the most effective intervention found to date to maintain viral suppression over the long term, it should not be relied upon by health providers as the only effort to improve adherence (27). The optimal regimen should be chosen based on tolerability, potency, drug resistance, and the individual's "signature adherence patterns," and then it should be supplemented with behavioural interventions and ongoing adherence monitoring. The benefits of long-term viral suppression are the prevention of drug resistance, delaying of disease progression and improved survival.

Inconsistent adherence behaviours should be identified by health providers and modified prior to the start of ART to optimize adherence.

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