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Adherence to HIV combination therapy

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Abstract

The emergence of drug-resistant strains of HIV virus and treatment failure can result from non-adherence to antiretroviral therapy. While non-adherence to therapy is not a new issue or specific to HIV/AIDS, it has received renewed attention because of the complicated combination treatment regimens being prescribed. This paper reviews the relevant background literature on the contributions of social and behavioural science to non-adherence to HIV medications. Data indicating problems with adherence prior to combination therapy are reported. Despite limitations, even self-report assessments have already succeeded in showing that adherence to combination therapy is significantly related to HIV viral load. Recent research data are discussed. Implications of findings for counselling patients to increase their adherence are presented. © 2000 Elsevier Science Ltd. All rights reserved.

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The promising new combination therapies for HIV have profound implications for persons living with HIV infection. While much attention is focused on the beneficial effects of these therapies, there is concern that the complexity of the regimens, which often involve taking over two dozen pills, tablets or capsules a day, the need for total adherence and the long-term nature of the course of treatment may be resulting in problems with adherence. If these therapies are successful, they can result in levels of HIV viral load that are undetectable. But if the therapies are not adhered to, they are less successful and may lead to the development of resistant strains of virus. The emergence of resistant strains is problematic both for the patient affected but also to the public health, as these strains can be transmitted to others, limiting treatment alternatives.

In January 1998 when the "AIDS in Europe" Conference met in Paris, a general feeling of optimism was accompanied by a growing sense of realism. Public health authorities were reminded that the long-term effects of new therapies were still largely unknown. Clinicians, more and more often, insisted that therapeutic effectiveness was crucially linked to patient behaviours. In particular, adherence to treatment was judged to be a necessary condition for success. In the few reports that were available, non-adherence was associated with higher levels of viral load and treatment breakthrough (Deeks et al., 1997; Hecht et al., 1998a,

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b). A few months later when the 12th World AIDS Conference met in Geneva, adherence was definitely an issue of primary importance. In contrast to the previous World AIDS Conference in Vancouver, where only a handful of papers discussed adherence, more than 190 papers, from investigators from various disciplines and from throughout the globe, focused on adherence at the meeting in Geneva.

This paper will address this social and behavioural issue that is critical to AIDS clinical research and care. First, some background on adherence to treatments in general will be discussed. Second, the major findings in adherence to combination therapy in HIV will be presented. Third, implications of these findings for HIV research and care will be outlined.

Background to adherence or compliance: A social and behavioural science perspective

Biomedical scientists involved in clinical trial research and health care providers charged with treating persons living with HIV are turning to social and behavioural scientists for assistance with adherence. In particular, there is interest in understanding the factors that account for patients' difficulties in adhering to care. While some social and behavioural scientists have become very involved in developing measures of adherence, studying explanatory factors and developing programs to modify patient adherence, others (Giami, 1996; Abelhauser, 1998), have argued, "l'arbre qui cache la forêt."

When considering background research on adherence, it is important to discuss "compliance." Earlier research addressing "the extent to which the patient's behaviour (in terms of taking medications, following diets, or other life style changes) coincides with medical or health advice" (Haynes et al., 1979) referred to patient "compliance" (Haynes et al., 1979). The term "compliance," however, was viewed by some as containing a value statement and a directional bias which assumed that physician guidelines were accurate and patient response was measured according to these guidelines. Some suggested that this perspective allowed for subtle elements of blame to enter the discourse and as such, focused theoretical explanations on patient characteristics, most notably patient failings (Ley, 1988; Tuckett et al., 1986) "Adherence" was thought to convey more of a partnership between the physician and patient. This perspective allowed for less value judgement and a more comprehensive examination of factors related to adherence, including characteristics of the regimen, provider behaviours, and social and environmental factors.

Adherence became a topic of considerable research by multidisciplinary teams beginning in the 1970s when it was discovered that as many as 50% of patients with hypertension were not taking sufficient amounts of their antihypertensive medication to have their blood pressure under control (Haynes et al., 1979). Research in other areas of medicine demonstrated that non-adherence was common, particularly when treatments were long-term (Myers and Midence, 1998) such as diabetes (Warren and Hixenbaugh, 1998), and asthma (Hand, 1998) or hypertension. Indeed, despite considerable attention to the problem, adherence to antihypertensive medications continues to be a challenge (Gidron, 1998). While adherence was a major topic of research in health psychology and behavioural medicine in certain countries, it may have received less attention in Europe, particularly in France. Ten years ago, more than 4000 scientific papers had already been listed in the Index Medicus and other bibliographic collections. This reflects a dramatic increase from 25 related publications in the 1950s and 168 in the 1960s (Ley, 1988). Most of these papers were attempts to identify and control determinants of non-adherence to regimens necessary to the management of chronic conditions, with attention to patient knowledge of the disease and regimen, motivation to adhere and strategies to remember medication based on social and behavioural science.

One of the most consistent findings in the adherence literature is that there is a direct association between poor adherence and the complexity of drug regimens, the number of different medications included in the regimen and the extent to which the regimen interferes with the patient's daily life (Mehta et al., 1997; Miller, 1997). Another well-documented observation is that the best adherence is found when medications relieve symptoms, while poor adherence occurs when medications produce side effects in persons without current symptoms (Mehta et al., 1997; Morin and Moatti, 1996; Munzenberger et al., 1997).

Adherence and emergence of drug resistant virus

All recently published treatment guidelines (Carpenter et al., 1997; Dormont, 1997, 1998) have a twofold orientation: positive recommendations and warnings. On the positive side, they confirm the prognostic value of viral load and CD4+ level. The guidelines clearly indicate that one criterion and operational objective for evaluating drug effectiveness is the lowering of viral load, optimally to below a detectable level. The other goal is to rebuild the immune system, which is reflected, in part, by the CD4 lymphocyte level. Most guidelines recommend initial treatment as early as possible, but this recommendation is not received with-

out controversy, particularly in Europe. Regardless of the debates as to the timing of when to initiate treatment, there is agreement on the importance of warning that non-adherence is a leading cause of treatment failure. That is, intermittent adherence can result in the emergence of treatment failure and drug-resistant strains of the HIV virus. When protease inhibitors are used, cross-resistance can occur even with short-term non-adherence. If initial treatment fails because of undetected non-compliance practices, the cross-resistance makes it extremely difficult to find other effective treatments (Dormont, 1998). The development of drug resistant strains affects the individual patient and also poses a threat to the general public health if the drug-resistant strain is transmitted to others (Mehta et al., 1997). The importance of this latter caution was brought to the forefront in the 12th World AIDS Conference in Geneva where the initial cases of uninfected individuals becoming infected with multi-drug resistant strains of HIV was reported (Hecht et al., 1998a, b).

The challenge of non-adherence

The new focus on adherence begs two questions. First, what are the levels of adherence that have been seen? Second, how much adherence is necessary to prevent treatment failure? Even the most casual awareness of the factors associated with non-adherence to other conditions should have sent out an alert as the full extent of the medications involved in combination therapy became apparent. Research on adherence over recent decades, independent of HIV/AIDS indicated that adherence decreased as the number of pills, capsules or tablets increased. Similarly, adherence decreased as the number of doses per day increased, any medication side effects increased, and the regimen interfered with daily life (Mehta et al., 1997; Miller, 1997; Morin and Moatti, 1996; Munzenberger et al., 1997). The combination therapies for HIV/AIDS are replete with these factors as patients attempt to lead ordinary lives. The adherence regimen of combination therapies is not limited to the drugs themselves, but also applies to daily living adjustments that provide pre-requisite conditions for drug efficacy. Specifically, the combination therapies require patients to take a great number of pills, multiple times per day, and take care to adhere to complex timing of doses in conjunction with eating, fat content of meals and intake of fluids. Furthermore, the combination therapies are often associated with severe side effects including transient reactions such as diarrhoea, fatigue, nausea and vomiting, as well as longer lasting effects including oral numbness and peripheral neuropathy (Baker, 1996; Dormont, 1998). Indeed, combination therapies are perhaps the most complex series of regimens that have ever been prescribed under conditions of continuous and open-ended treatment for a large and diverse patient population. Not only are they complex but they combine some of the most powerful barriers to adherence.

Non-adherence — assessment

Determining the level of non-adherence among patients living with HIV/AIDS is complicated by the general methodological difficulties of adherence assessment. There is no "gold standard" of adherence assessment. Self-reported measures of medication adherence are subject to social desirability and recall bias. Despite these weaknesses, this approach has been shown to give satisfactory concurrent and predictive validity when used in a controlled design and multi-method approach (Brooks et al., 1996; Morisky et al., 1986). Other methods of assessing adherence include electronic monitoring, pill counts, blood levels and refill history. All of these methods have strengths and weaknesses. Most of the adherence literature in HIV/AIDS has relied on self-report, which is likely to under-estimate the problem. As will be discussed later, however, research shows that this approach to assessing adherence is significantly associated with viral load (Hecht et al., 1998a, b; Nieuwkerk et al., 1998; Weidle et al., 1998).

At the time of the European Conference in January 1998, most published empirical data had been collected prior to combination therapy. These data reported on the study of potential or actual barriers to adherence, most commonly to monotherapy with zidovudine (AZT). While scarce, these previous studies provided useful perspectives for describing, explaining and modifying adherence problems among HIV-infected persons. In five American studies providing sufficient data on adherence to AZT for an analysis, 80% adherence was achieved by 42% of patients when examined over the past month (Singh et al., 1996). When only the last week is considered, the percent of patients adhering to care increased to 67% (Samet et al., 1992). Similar data were reported from a Spanish cohort (1990–1996) using several medical criteria. It was estimated that long-term follow-up and compliance was achieved only in 47.6% of patients (Knobel et al., 1997).

In addition to adherence to regimens, adherence to care also involves keeping appointments or remaining in clinical trials. Here too, there were early indications of problems of non-adherence, prior to combination therapy. For example in the French–English "Delta trial", which compared monotherapy and dual therapy, drop-out rates were significant and created

problems in data interpretation in the last phase of the trial. It was observed that 65% of patients stopped following the initial randomized treatment condition. Only 13% of the drop-outs could be explained by either clinical factors or patient death (Chambon, 1995; Yeni, 1995). It is generally estimated that at least 30% of enrolled patients drop out or are lost at follow-up in HIV clinical trials and this is only the most visible aspect of non-adherence. This level of non-adherence is important because it threatens the integrity of clinical research.

Non-adherence — scope of the problem

The existing surveys of adherence to combination therapy indicate that adherence is likely to be a significant problem. Two such preliminary surveys were reported on at the European Conference. Both of these used a self-report instrument designed specifically to assess the extent and reasons for non-adherence. The first of these was a study conducted at San Francisco General Hospital (Hecht et al., 1998a, b). AIDS outpatients seen during January and February 1997 were given questionnaires to complete. These questionnaires used a strategy to assess adherence that was recommended by Jacqueline Dunbar-Jacob and colleagues (1995) which asks about how many medications are missed, working back from "yesterday" to the "day before yesterday." A group of 134 patients on combination therapy with protease inhibitors and who had a viral load taken during their visit were studied. Of the group, slightly more than 10% reported missing at least one dose "yesterday," and 30% reported missing at least one dose over the three most recent days. Of particular relevance to the field, a significant, linear relationship was observed between self-report of non-adherence and viremia. Specifically, of the patients reporting between 90 and 100% adherence over the recent past, approximately 60% had undetectable viral loads. Alternatively, of the patients reporting less that 80% adherence, only about 35% had undetectable viral loads. This relationship between the report of non-adherence and virologic outcomes is important as it validates the use of straightforward assessments of non-adherence.

The second survey examining the extent of non-adherence was conducted by the Recruitment, Adherence and Retention Subcommittee of the Outcomes Committee of the United States' AIDS Clinical Trials Group (ACTG). This survey involved 10 ACTG sites and 75 patients. The results were strikingly similar to those observed at San Francisco General Hospital. In particular, slightly more than 10% of the patients reported missing at least one dose of their medication each day over several sequential days (Chesney and Ickovics, 1997). Since these reports, others have found levels of non-adherence to be at this level or slightly higher (Weidle et al., 1998).

Social and behavioural factors in non-adherence

Interest in developing strategies to address non-adherence has led to investigations of its correlates. Sociodemographic factors are among the earliest variables to be examined. As is common throughout the adherence literature, non-adherence to HIV therapy is not consistently associated with demographic characteristics (Eldred et al., 1997; Morin and Moatti, 1996; Singh et al., 1996). For example, male gender seemed in some studies associated with decreased adherence, especially when associated with mental illness and age (Mehta et al., 1997). Gender often reflects a number of conditions and should not be overlooked. In fact, the impact of gender on adherence relies heavily on the context and social situations in which individuals interact. For example, it has been noticed that in some cases women were missing more doses and clinic visits than men (Ohmit et al., 1998). This difference could be explained by the fact that those women had to manage difficult family and child-care responsibilities. Indeed, when free on-site childcare was provided, adherence with scheduled visits improved immediately (Kissinger et al., 1995; Mehta et al., 1997).

Persons with HIV who live "marginal" lifestyles, use illicit drugs, and have lower socio-economic status have been a group that professionals thought would be at risk for non-adherence. All too often there are common representations among professional care-givers of this patient group which postulate that drug users are unable and/or unwilling to comply with long and complex regimens (Morin and Moatti, 1996). In fact, empirical results show a complex picture. Compared to other groups in a Swiss cohort study (Broers et al., 1994). Injection Drug Users tended to access medical care later in the course of their disease, received less positive thinking toward disease and received less preventive treatment. But once IDU's did accept antiviral treatment, they were as compliant as patients from other risk groups. Former IDU's and patients receiving methadone treatment started zidovudine therapy more often and complied better with treatment than those actively using drugs.

Personality psychology has proposed relationships to adherence. The data are sketchy and no empirical studies have been reported. Vincintini et al. (1998) noted that personality disorders did not show relationships with adherence behaviours. However, stress or depressed mood, long known to predict non-adherence in

conditions other than HIV/AIDS (Dunbar-Jacob et al., 1995), is consistently associated with non-adherence to HIV therapy (Gifford et al., 1998; Hirschhorn et al., 1998; Klosinski and Brooks, 1998).

Another tradition in adherence research has been to develop a treatment model for non-adherence. The most common models proposed are the Health Belief Model (Rosenstock, 1974), the Health Decision Model (Eraker et al., 1984), and the Theory of Reasoned Action (Terry et al., 1993). These models introduce "subjective" variables such as "perceived severity" of disease, perceived "susceptibility" or perceived "barriers" to health and illness behaviour. The models have been widely criticized however, especially by European social scientists who argue that they study rationalization processes and work with an individualistic approach.

In contrast to studies of personality and personality disorder, there has been considerable attention to studies identifying barriers to care and reasons for missing medications. A number of studies have explored reasons for non-adherence to medications with considerable consistency (e.g. Brigido et al., 1998). In general, these include:

Forgetfulness and mental problems
Social context which often mitigates against the demands of the regimen
Daily routines
Breaks in routines
Treatment side effects and their severity
Psychological mood, most notably negative mood measures.
Economic barriers
Practical barriers such as distance to pharmacy outlets or medical resources.

Focus should not be limited to an individual paradigm aimed at the "patient." A more comprehensive approach would allow for an understanding from at least three perspectives, including the patient and associated variables, the provider and the potion (Sherr, 1998).

Intervention

As research to identify factors associated with adherence proceeds, and given the urgency of patients on these medications, there is pressure on social and behavioural scientists to provide assistance in modifying this behaviour. Numerous programs incorporating these ideas were presented at the 12th World AIDS Conference in Geneva. These programs are available for the patient and the team consisting of the clinician, nurse and nurse practitioner, pharmacist, social worker/psychologist, and nutritionist. In most instances, they incorporate the following elements:

Clarify the regimen — patients can't adhere unless they clearly know and understand the regimen they are to follow. Analyse and problem-solve risk behaviour — strategies might include:

Modifying the schedule,
Simplifying the regimen
Introducing devices to encourage memory, and
Referring to care.

Physicians and nurses can identify the problem but need to refer patients to professionals to obtain treatment for depressed mood and alcohol and illicit drug use.

Almost all of the studies reported at the retrovirology meeting were descriptive. One important exception was a randomized trial of a hospital-based pharmacy intervention (Knobel et al., 1998). Incorporating the key elements of adherence counselling described above, the intervention showed that patients who receive individual advice and support from the pharmacist improved adherence and showed a tendency toward improved disease outcome.

In this paper, we provided background to non-adherence in HIV/AIDS. We presented the major findings in adherence to combination therapy. We have also given a brief update on the implications of the findings for counselling patients to increase their adherence. While efforts to simplify regimens, reduce toxicity, and create combinations of medications are underway, we can assume that pressure to intervene will continue, and if anything, increase. Efforts to intervene will undoubtedly be multidisciplinary in nature. What will draw these teams together will, in all likelihood, be a shared recognition that adherence is essential to treatment effectiveness.

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