REPORT ON ADHERENCE TO MEDICATIONS IN CHILDREN

Executive summary

There is a large literature on adherence to medicines in both adults and children. While there are a number of strategies that can be used to try to improve adherence rates, none has proved effective in all settings and in all clinical conditions. Most of the effective interventions have been complex, multifaceted interventions. The methods are often labour intensive, and many will incur increased costs to the health care system.

Various authors have attempted to classify the factors associated with non-adherence. The key themes are patient/family factors, disease factors (including beliefs about the medication and its usefulness for treating disease), regimen factors (relating to daily schedules) and interpersonal relationships (with family and health care providers). A recurring theme is the importance of good communication between health care providers and patients.

All adherence is predicated on ensuring access to affordable medicines, and reliable drug supply and distribution networks so that treatment can be followed. Strategies that are practical for routine clinical use are required. There are some conclusions that can be drawn from the literature.

1. Simplifying dosage regimens (both dosage frequency and numbers of tablets) is important in improving adherence in both adults and children. Once daily and twice daily regimens are associated with better adherence than three and four times daily schedules. There is limited formal trial evidence to support the use of fixed dose combinations to improve adherence, but pill burden is a substantial issue, particularly in HIV infection. Fixed dose combination preparations offer programmatic benefits with easier storage and distribution of medicines. In addition, they reduce the chances of use of only some of the drugs in the treatment regimen, and may, in the longer term, help reduce the development of resistance.
2. There is some evidence that adherence tools such as pillboxes to organise doses, and organising cues to remind patients to take medicines improve medicines adherence. While the quantitative benefits appear to be small, they may be a relatively cheap intervention.
3. Poor access to medicines because of geographic or cost issues compromises adherence. Geographic access may be addressed by decentralisation of diagnostic and treatment services. However, decentralisation of services requires improved local supervision and support to ensure that appropriate services can be provided.
4. Physicians contribute to poor adherence by prescribing complex regimens, failing to adequately explain benefits and side effects of a medication, not giving consideration to the patient's lifestyle or the cost of the medications and having poor therapeutic relationships with their patients. Health care

providers need to spend time with patients to provide information and education, to enquire about difficulties with managing treatment regimens, and to provide advice or alternatives to deal with side effects of therapy.

Specifically relating to children

Quantitative evidence suggests that adherence in children is lower than in adults, and that adolescents are less adherent than younger children. Many of the factors influencing adherence in paediatrics are similar to those seen in adult patient populations. The need for a caregiver (most often a parent) to be involved adds an extra dimension to the problems of adherence in children.

1. Convenient and simplified dosing regimens, appropriate and palatable formulations are key aspects that need to be addressed. The family's ability to cope with the regimen (scheduling, discomfort associated with the treatment, side effects and costs) need to be considered.
2. Parents' beliefs about the seriousness of the illness and about the medications and treatments prescribed influence adherence. Good communication with health care providers is a key factor. Patients and families need to understand the nature of the illness, the likely course of disease, the value of the therapeutic treatments offered and the importance of adherence to the prescribed regimens.
3. With evidence of poorer adherence in adolescents, teenagers need to be supported to make the transition to take responsibility for their own medicines.

Adherence in HIV/AIDS

Given the importance of adherence rates of around 95% in HIV treatment regimens, studies of adherence to therapy in HIV/AIDS, barriers and facilitators of adherence both in adult and paediatric populations have been extensively studied and reported.

1. Costs of medicines (including costs associated with accessing care and medicines), not disclosing HIV status to a loved one for fear of being stigmatized, alcohol abuse and difficulty in following complex regimens have been identified as important factors negatively affecting adherence.
2. Promising strategies for improving adherence to HAART studied in RCTs include pharmacist-led individualised interventions, cognitive-behavioural educational interventions based on self-efficacy theory, and cue-dose training in combination with monetary reinforcement. Trials have also investigated the use of handheld devices, two-way pagers, medication vials equipped with alarms, and the enhancement of social and emotional support. While variously effective, all of these proposals have limited application in resource-poor settings.
3. Qualitative studies in developing countries have identified several facilitators of adherence. These include having a sense of self-worth and accepting one's seropositivity (such patients may be more inclined to disclose HIV status to trusted family and friends), and understanding the benefits of treatment and

strict adherence, use of reminder tools and simple regimens (techniques for taking control and managing medicines better). De-stigmatizing disease to enhance disclosure requires changing of attitudes and acceptance within communities, which may be facilitated by education and information. The medication issues can be addressed, in part, by increased health worker awareness of possible barriers to adherence and improved communication with patients and their families on how these might be addressed.

4. Directly observed therapy with antiretrovirals (DOT-ART) appears to show promise as an intervention to improve adherence to therapy in HIV. One of the major difficulties is that, unlike tuberculosis where DOTS is standard practice in many settings, antiretroviral therapy is lifelong rather than time limited. There is evidence that both family and community DOT supporters can achieve good treatment outcomes, highlighting the fact that not all care needs to be provided at a health care facility; families and communities have an important role to play. Allowing patients to choose their own treatment supporter can also facilitate supervision that is most appropriate to their daily lives. Making therapies easy to include in routine activities has been identified as an important mechanism to improve adherence.

Background

The World Health Organization (2003) defines adherence as 'the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider'. Osterberg and Balschke (2005) note that the term adherence has become preferred to the term compliance because compliance implies the patient is passively following orders, adherence can imply a treatment plan agreed by both patient and physician.

Measuring adherence may take a number of forms. Direct methods include directly observed therapy, measurement of the drug or its metabolite in blood, or measurement of a biological marker in the urine. Direct approaches, although more accurate at assessing compliance, are expensive, burdensome to the provider and may be susceptible to distortion by the patient. Indirect methods of assessing adherence include the use of patient questionnaires and patient self-reports, pill counts, rates of prescription refills, assessment of patient's clinical response, the use of electronic medication monitors, measurement of physiologic markers and patient diaries. Measurement of medication adherence in children largely relies on questioning (or questionnaires) for parents, caregivers or sometimes teachers. Osterberg and Balschke note that questioning of the patient can be susceptible to misinterpretation and can lead to overestimation of patient's adherence to therapy, and pill counts can be manipulated by the patient. The use of electronic monitoring is expensive and does not provide a useful solution in most clinical settings. In addition, the methods generally don't reveal whether or not the patient consumed the medicine, simply that the container was opened. Adherence estimates based on prescription refills assume purchase is related to consumption and relies on access to adequate documentation on prescription purchases.

The evidence around adherence to medicines is complex and solutions recommended to improve adherence usually multi-faceted. Given the WHO focus on better medicines for children, this review was commissioned to summarise the available evidence on adherence to medicines in children.

Literature review

The literature review for this report was not undertaken as a formal systematic review. A preliminary search identified a large literature on the topic of adherence to medications in both adults and children and a number of systematic reviews addressing specific aspects of adherence. Therefore, this review is based on a number of systematic reviews (some of which were Cochrane reviews) addressing various quantitative and qualitative aspects of medication compliance, and applied to medicines in general as well as to particular clinical conditions. Where appropriate, additional studies that have updated existing reviews or contribute useful information have been included in this report.

Much of the evidence has been derived in adult populations. However, as there are considerable overlaps in the issues that are relevant to adherence to medication in adults and children, literature on both patient populations are presented. Given the particular imperative for high adherence rates in human immunodeficiency virus / acquired immunodeficiency syndrome (HIV/AIDS), this clinical area is examined in more detail in this report.

Results

Quantitative measures of adherence

Claxton et al (2001) identified 76 studies conducted between 1986 and 2000 which used electronic monitors (claimed to be the most accurate measure of compliance) to assess adherence. Compliance with once-daily, twice-daily, three times-daily, and four times-daily dosing regimens was assessed. The authors defined two major categories of compliance rates: dose-taking (taking the prescribed number of pills each day) and dose-timing (taking pills within the prescribed time frame).

The mean dose-taking compliance estimated from these studies was 71% (range, 34%-97%). Adherence rates declined as the number of daily doses increased: 1 dose 79% ± 14%, 2 doses 69% ± 15%, 3 doses 65% ± 16%, 4 doses 51% ± 20% (P < 0.001 among dose schedules). Compliance was significantly higher for once-daily versus three or four-times-daily dose regimens, however, there were no significant differences in compliance between once-daily and twice-daily regimens or between twice-daily and three times-daily regimens.

Only 14 of the studies in the Claxton review reported dose-timing results. The mean dose-timing compliance was 59% ± 24%; more frequent dosing was associated with lower compliance rates. These authors concluded that simpler, less frequent dosing regimens resulted in better compliance across a variety of therapeutic classes of medicines.

Di Matteo (2004a) has conducted a quantitative review of 50 years of research (1948-1998) into patient adherence to medical recommendations. This review identified 569 studies which quantified adherence to a medically prescribed treatment or preventive measure (exercise, diet, medication, health-related behaviour, screening, vaccination and appointment). An additional 164 studies correlated one or more demographic measures with adherence, the most commonly assessed variables were age, gender, education and income.

Across the 569 quantitative studies, adherence ranged from 4.6% to 100% (median 76%, average 75.2%). Di Matteo concluded that larger studies reported lower adherence than small studies, and studies of adults (n = 401) yielded higher adherence rates than studies of paediatric patients (n = 116) (76.8% vs 70.2%). In the 8 studies identified assessing adherence in HIV, mean adherence was reported as 88.3% (95% CI 78.9%, 95.2%). This was the highest rate of adherence in the 17 clinical conditions considered in this review. In the analysis of correlation with demographic variables, DiMatteo concluded that the age-adherence relationship was stronger in paediatric than adult samples, with a trend for adolescents to be less adherent than younger children. Overall, the correlations between adherence and socio-demographic factors were generally modest in magnitude.

Lowry et al (2005) reported that both intentional and unintentional non-adherence are common in antihypertensive therapy (31% and 9% respectively in a Veteran's Study population) and related to perceived adverse effects of medicines. These authors argue that different interventions are likely to be required to improve adherence in each case.

Barber et al (2004) examined compliance with new medicines in elderly patients (aged >75 years), measuring self-reported adherence, causes of non-adherence, problems with medication and patient information needs. A significant proportion of patients newly started on a chronic medication quickly become non-adherent, often intentionally so. Many have problems with their medication and information needs. While not specifically addressing methods for improving adherence, Barber et al concluded that patients needed more support when starting on new medication for a chronic condition and new services may be required to provide this.

Osterberg and Balschke (2005) describe six general patterns of medication taking by patients with chronic illness. About one-sixth take virtually all doses, one-sixth take almost all doses, one sixth take most doses, one-sixth have infrequent periods of not taking medication, one-sixth have more frequent times of being medication-free whilst the remainder take little or no medication.

Relationships between measures of adherence and clinical outcomes

Adherence rates are usually higher for acute conditions than chronic illnesses and there is no agreed position on what constitutes adequate adherence. While rates of adherence (e.g. percentage of doses actually taken over a specified period) of 80% or more may be satisfactory in some clinical conditions, adherence rates of 95% or more

are generally required with HIV infection to suppress viral replication and reduce the development of resistance (Chesney 2003, Ivkovics and Meade 2002).

Blackburn et al (2005) used linked administrative health databases to investigate the relationship between adherence to statin therapy and cardiovascular outcomes. Among all 1056 patients in the analysis, adherence was not associated with a reduction of the primary end point (composite of myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafts (CABG), and death.). However, patients in the adherent group (>80% doses) were half as likely to experience a subsequent myocardial infarction as the patients in the non-adherent group (<60% doses; hazard ratio [HR] 0.45, 95% CI 0.20 to 0.99).

A more recent study by Rasmussen et al (2007) explored the relationship between drug adherence and mortality in 31,455 survivors of acute myocardial infarction (AMI) aged over 65 years. These authors identified a dose-response-type adherence-mortality association among statin users, with a less pronounced effect for beta-blockers. For statins, the risk of mortality was highest for low adherers (<40%) compared to high adherers to therapy (>80% days covered); adjusted hazard ratio 1.25 (95% CI 1.09 to 1.42). The authors of this study suggest that survival advantages associated with improved adherence post-AMI are drug-class effects, i.e. moderated by drug effects rather than 'healthy adherer' behavioural attributes.

Thus, there is evidence at least in some clinical areas that failure to adhere to prescribed treatment regimens is associated with adverse clinical outcomes. Therefore, efforts to improve adherence rates are likely to result in improved health outcomes.

Interventions to improve adherence to medicines

Haynes et al (2007) conducted a Cochrane review examining the evidence from randomised controlled trials (RCTs) on interventions to assist patients to follow prescriptions for medications for medical problems (including mental disorders). Eligible studies reported on both medication adherence and treatment outcome, and with at least 80% follow-up of each group studied. For long-term treatments, studies with positive initial findings had to report results for at least six months follow-up.

Interventions tested in these studies were diverse and included:
  (i)   more instruction for patients (e.g., verbal, written material, visual material and programmed learning)
  (ii)   counselling, about the patients' target disease, the importance of therapy and compliance with therapy, the possible side-effects, Tools for Health and Empowerment (THE) course, etc.
  (iii) automated telephone, computer-assisted patient monitoring and counseling manual telephone follow-up
  (iv)   family intervention
  (v)   various ways to increase the convenience of care, e.g., provision at the worksite or at home

(vi)   simplified dosing

(vii)   involving patients more in their care through self-monitoring of their blood pressure

(viii)   reminders, e.g., tailoring the regimen to daily habits

(ix)   special 'reminder' pill packaging

(x)   dose-dispensing units of medication and medication charts

(xi)   appointment and prescription refill reminders

(xii)   reinforcement or rewards for both improved adherence and treatment response, e.g., reduced frequency of visits and partial payment for blood pressure monitoring equipment

(xiii)   different medication formulations, such as tablet versus syrup

(xiv)   crisis intervention conducted when necessary, e.g., for attempted suicide, aggressive and destructive behaviour

(xv)   direct observation of treatments (DOTS) by health workers or family members, lay health mentoring

(xvi)   comprehensive pharmaceutical care services, such as Pharmacist's Management of Drug-Related Problems (PMDRP)

(xvii)   psychological therapy e.g., cognitive behaviour therapy

Eight studies concerned short-term conditions, acute infections in all cases (Helicobacter-pylori infection (n=3), seasonal rhinitis and asthma (n=1), Streptococcal pharyngitis (n=1), malaria (n=1), acute infection (n=1) and use of macrolide antibiotics (n=1). Four of nine interventions (8 RCTs) showed an effect on both adherence and at least one clinical outcome. In one RCT, there were significant improvements in patient compliance, but this did not enhance the clinical outcome.

A narrow range of disorders was studied for long-term conditions (hypertension n=7, schizophrenia or acute psychosis (n=10), asthma and/or chronic obstructive pulmonary disease (n=10), rheumatoid arthritis (n=2), epilepsy (n=1), hyperlipidemia (n=3), ischaemic heart disease (n=1), depression (n=2), HIV (n=6), diabetes (n=2), tuberculosis (TB) (n=1), oral anticoagulant therapy (n=1), contraception (n=1), and complex regimens in the elderly (n=2). In 26 of 58 interventions (49 RCTs), there were improvements in adherence, but only 18 interventions led to improvement in at least one treatment outcome. Almost all of the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care. Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. Six studies showed that telling patients about adverse effects of treatment did not affect their adherence.

The authors concluded that improving short-term adherence is relatively successful with a variety of simple interventions. However, current methods of improving adherence for chronic health problems are mostly complex and not very effective.

Interventions to improve adherence to medicines in specific clinical conditions

Hypertension

A Cochrane review (Schroeder et al 2004) examined interventions used in RCTs to improve compliance with antihypertensive medications in adults. Thirty-eight trials testing 58 interventions were included in the review. Studies were conducted in nine different countries over the period 1975-2000. Simplifying dosing regimens increased adherence in seven out of nine studies (relative increase in adherence 8% to 19.6%). Motivational strategies showed positive benefits in 10 out of 24 studies, with generally small increases in adherence (maximum increase 23%). Complex interventions involving more than one technique increased adherence in eight out of 18 studies (increases 5% to 41%). Patient education alone seemed largely unsuccessful in this clinical condition. While reducing the number of daily doses appears to be effective in increasing adherence, there is less evidence of an effect on blood pressure reduction.

Lipid lowering drugs

A Cochrane review (Schedlbauer et al 2004) assessed interventions to improve adherence to lipid lowering drugs. The interventions in the eight RCTs identified could be grouped into four categories: simplification of drug regimen, patient information/education, intensified patient care such as reminders, and complex behavioural interventions (e.g. group sessions). Changes in adherence reported in the studies ranged from a decrease in adherence by 3% to increase in adherence by 25%. Three studies reported significantly improved adherence through simplification of drug regimen, improved patient information/education, and reminders. These results do not suggest any advantage of one particular type of intervention.

Petrilla et al (2005) reviewed evidence-based interventions to improve patient compliance with antihypertensive and lipid-lowering medications. Of 22 interventions examined, 12 demonstrated a significant improvement in compliance. Recommended interventions included fixed-dose combination drugs, once-daily or once-weekly dosing schedules, unit-dose packaging, educational counselling by telephone, case management by pharmacists, treatment in pharmacist- or nurse-operated disease management clinics, mailed refill reminders, self-monitoring, dose-tailoring, rewards and various combination strategies. Personalised, patient-focused programs that involved frequent contact with health professionals or a combination of interventions were the most effective at improving compliance. Less-intensive strategies, such as prescribing products that simplify the medication regimen or sending refill reminders, achieved smaller improvements in compliance but may be cost-effective due to their low cost.

Type 2 diabetes

Vermeire et al (2005) examined evidence from randomized controlled trials, controlled clinical trials, before-after studies and epidemiological studies on interventions to improve adherence to treatment recommendations in patients with

type 2 diabetes. Amongst 21 studies included in the review, nurse led interventions, home aids, diabetes education, pharmacy led interventions, adaptation of dosing and frequency of medication taking showed a small effect on a variety of outcomes including HbA1c. However, there were no data on any relationship between adherence and mortality and morbidity, or on quality of life. The authors concluded that current efforts to improve or to facilitate adherence of people with type 2 diabetes to treatment recommendations do not show either significant effects or harms. The available studies did not identify any intervention which clearly enhanced adherence to treatment recommendations in type 2 diabetics.

Tuberculosis (TB)

Thiam et al (2007) conducted a cluster randomized trial at 16 government district health centres in Senegal, Africa, to examine the impact of a 'contextualised' intervention to improve adherence to TB treatment. The intervention included four components - improving counselling and communication between health personnel and patients, decentralizing treatment to remote health posts and involving community health workers, by giving patients the opportunity to choose their treatment supporter, thus strengthening the directly observed therapy (DOT) strategy and reinforcing supervision of health posts by the district health centres.

In this study of 1522 patients, the intervention was associated with improved treatment outcomes (proportion cured and successfully completing 8 months treatment; adjusted risk ratio RR 1.18; 95% CI 1.03, 1.34) and a reduction in the proportion of patients defaulting from treatment (5.5% vs 16.8%; adjusted RR 0.43; 95% CI 0.21, 0.89). The authors suggest that this intervention could be generalized to other TB programs in resource poor settings.

Fixed-dose combinations, unit dose packaging of medications and reminder packaging to improve adherence

Connor et al (2004) conducted a systematic review to investigate the impact of fixed-dose combination pills or unit-of-use packaging to improve adherence. While not published as a Cochrane review, the review describes similarly rigorous study methods. Fifteen eligible studies (1980-2002) were identified; fixed-dose combination pills were used in three trials, unit-of-use packaging was used in the remaining 12 studies. Thirteen studies reported at least one measure of medication adherence, seven reported clinically relevant or intermediate end-points.

Of the three studies using fixed-dose combinations, two were conducted in patients with TB and one in an HIV population. Based on a combination of self-reports, pill counting and urine testing, one of the TB studies concluded a significant difference in the proportion of patients with sputum conversion at 8 weeks in the fixed-dose combination group, but no difference in medication compliance at 8 weeks or 6 months. The second study in TB patients was too small to show statistically significant differences, although trends favoured the fixed-dose combination group (differences in sputum conversion at 8 weeks, compliance, radiological improvement at 2 years). With 50% loss to follow-up of study subjects, the improvements in

compliance were not thought to be clinically important. In the study of HIV patients, self-reported adherence was significantly improved in the intervention group, while there was a non-significant trend towards improvement in clinical outcomes.

Ten of the 12 studies on unit-of-use packaging were conducted in developed country settings and in a variety of clinical areas (hypertension, diabetes, vitamin use for disease prevention, elderly patients). These trials used calendar-blister packaging or a pill organizer (e.g. Dosett box). Two of three trials showed a benefit of the packaging in hypertensive patients when combined with patient education (compared to education alone). One study demonstrated a significant reduction in HbA1c and diastolic blood pressure in poorly controlled diabetic patients when calendar-blister packs were used in conjunction with written instructions. However, there were no measures of adherence reported in this study. In three of five trials of medication aids for geriatric patients, there were improvements in adherence as measured by pill counts. However, all studies had methodological weaknesses (too small, too short, not accounting for study design in analysis) making it difficult to generalize the results of these studies.

In the two studies conducted in economically developing countries, data on clinical outcomes were not reported and the study design was not accounted for in the analysis. While there were reported advantages in storage, handling and preservation of medication in calendar-blister packs, no differences were reported in adherence in an Indian trial of patients being treated for leprosy. Prepackaging of three day courses of medication for malaria was tested in a trial in Ghana - significant improvements in adherence was reported for the unit-of-use packaging group (based on self-reports and medication checks). This study also reported reductions in the total costs of treatment and time spent by patients waiting at the clinic.

Overall, Connor et al conclude that there is some evidence that fixed-dose combinations and unit-of-use packaging are likely to improve compliance in some clinical settings. However, the potential size of the benefits remains unclear.

Legoretta et al (2005) used US Medicare claims data to compare patients treated with a fixed dose combination of lamivudine and zidovudine with administration of the individual components given separately. Pharmacy claims data provided the mechanism for assessing adherence in the two groups of patients. Mean adherence across all prescriptions for study therapy was higher for patients on the combined therapy (85%) than for patients taking the drugs separately (75%). Using multiple regression analyses to adjust for covariates, these authors concluded that the combined therapy significantly reduced the risk of adherence failure by two-thirds (defined by the 95% threshold) – adjusted OR 0.33 (95% CI 0.16, 0.63).

Unit-dose packaging of antimalarial medicines

Based on the expectation that unit-dose packaging of antimalarial drugs may improve malaria cure by making it easier for patients to take their treatment correctly, Orton and Barnisch (2005) conducted a Cochrane review which examined evidence

from RCTs, cluster-RCTs, quasi-RCTs, and controlled before-and-after studies of unit-dose packaging of drugs for the treatment of uncomplicated malaria. Four studies, all of poor methodological quality were identified – three quasi-RCTs (895 participants) and one cluster-RCT (6 health facilities). None of the studies adequately assessed treatment failure. Unit-dose packaged drugs (in conjunction with prescriber training and patient information) appeared to be associated with higher participant-reported treatment adherence in all trials. A meta-analysis of two trials (596 participants) showed that participant-reported treatment adherence was higher with blister-packed tablets compared with tablets in paper envelopes (RR 1.18, 95 % CI 1.12 to 1.25). Two trials using tablets in sectioned polythene bags as the intervention also noted an increase in participant-reported treatment adherence: the cluster-RCT (6 clusters) compared it with tablets in paper envelopes, and the other trial compared it with syrup in bottles (RR 2.15, 1.76 to 2.61; 299 participants). Overall, the authors concluded that there is insufficient evidence to determine the effect of unit-dose packaged antimalarial drugs on treatment failure.

Reminder packaging

Heneghan et al (2006) conducted a Cochrane review looking at the evidence for reminder packaging as a useful intervention to improve adherence to long-term medications (medicines to be taken for one month or more). Medication 'reminder packaging' incorporates a date or time for a medication to be taken in the packaging. Eight studies containing data on 1,137 participants were included in the review. Reminder packaging showed a significant increase in the percentage of pills taken, weighted mean difference 11% (95% CI 6% to 17%). No appropriate data were available for meta-analysis by clinical outcomes; the most common outcome reported was blood pressure (3 trials). The authors concluded that reminder packing may represent a simple method for improving adherence for patients with selected clinical conditions.

Directly observed therapy (DOT) as a means of improving adherence

Tuberculosis

Directly observed therapy is a policy that has been introduced to encourage adherence to treatment regimens in tuberculosis. Volmink and Garner (2006) conducted a Cochrane review to examine the evidence in support of this policy. Randomized and quasi-randomized controlled trials comparing a health worker, family member, or community volunteer routinely observing people taking antituberculous drugs compared with routine self administration of treatment at home were identified for this review. Patients either required treatment for clinically active tuberculosis or medication for preventing active disease.

These authors reported the results of 10 studies with 3985 participants. There was no statistically significant difference between DOT and self administration of treatment for the number of people cured (RR 1.02, 95% CI 0.86 to 1.21, based on 1603 participants and 4 trials) or completed treatment (RR 1.06, 95% CI 1.00 to 1.13). Stratifying the location of the DOT by home or at a clinic suggests a possible small

effect with home-based DOT (RR 1.10, 95% CI 1.02 to 1.18; 1365 participants, 3 trials). Two small trials of tuberculosis prophylaxis in intravenous drugs users found no statistically significant difference between DOT and self administration (199 participants, 1 trial), or a choice of location for DOT for completion of treatment (108 participants, 1 trial). Overall, Volmink and Garner conclude that the results of randomized controlled trials conducted in low-, middle-, and high-income countries provide no assurance that directly observed therapy compared with self-administered treatment has any quantitatively important effect on cure or treatment completion in people receiving treatment for tuberculosis.

Despite the observations of this Cochrane review, the use of DOTS in tuberculosis has become an important component of TB management strategies around the world. Its perceived effectiveness in improving treatment completion rates and therefore clinical outcomes has led to the suggestion that directly observed treatment may be a useful technique to improve adherence with HIV medicines, where high adherence levels are even more important (see section on HIV medicines).

Adherence with HIV medicines

Quantitative estimates of adherence in HIV

Mills et al (2006a) have conducted a systematic review and meta-analysis of studies conducted up to April 2006 evaluating adherence to anti-retroviral therapy (ART) in Sub-Saharan Africa and North America. Included studies had to have reported a threshold for adherence (100%, >95%, >90%, >80%) and reflect general, not highly selected, HIV populations in North America and Africa. The analysis included 31 North American studies (28 full text articles, 3 abstracts) and 27 African studies (9 full text articles, 18 abstracts). The combined continent analysis yielded an estimate of adherence to ART of 64% (95% CI 59%-70%) but there was significant heterogeneity between the studies. The pooled estimate for the American studies was 55% (95% CI 49%-62%) and for the African studies was 77% (95% CI 68%-85%), indicating a statistically significant higher level of ART adherence in Africa. The authors also assessed the impact of free access to care on adherence to ART. They concluded that free access to care was not associated with higher ART adherence in Africa (16 studies; 74% with 95% CI 64%-82%) than in North America (24 studies; 82% with 95% CI 67%-93%).

Mills et al conclude from their findings that ART adherence rates in Africa in early treatment programs are favourable. However, they note that complexity of treatment regimens (a factor influencing non-adherence) is likely to be higher in North America. In addition, the African experience reported is likely to reflect early programs with limited therapy options and results may not be able to be generalised to the larger HIV populations in Africa. Studies using patient recall and pill counts to assess adherence found similar rates in both North American and African papers included in the review. The authors suggest that the results are contrary to sentiments that have been expressed about likely adherence in African HIV populations. Mills et al suggest that the poor adherence rates in impoverished North American patients may relate to poor patient-clinician relationships, untreated depression, substance abuse

and other factors that are common among poor individuals in the North American setting rather than poverty itself.

Mills et al suggest that the most important and prevalent factors reported to negatively affect adherence in sub-Saharan Africa are cost, not disclosing HIV status to a loved one or fear of being stigmatized, alcohol abuse, and difficulty in following complex regimens. They note that HIV status disclosure in a community with access in ART may result in improved uptake of voluntary counselling and testing, help decrease the stigma and improve adherence. Mills et al suggest there are three important policy implications of their analysis:

(i) expectation of poor compliance in Africa is not an evidence-based rationale for delaying the expansion of ART programs in resource-poor settings

(ii) the focus should be maintenance of ART adherence rates by increasing access to affordable ART and establishing reliable drug supply and distribution networks from the pharmacy to the individual patient

(iii) understanding culturally specific barriers to adherence will be important in developing evidence-based interventions targeted at the individuals with poor ART adherence.

Bartlett et al (2000) performed a meta-analysis of clinical trials conducted in HIV-1 infected, antiretroviral naïve adults receiving triple drug therapy. The trials represented 29 treatment groups and 19 unique regimens from 22 trials. There was a statistically significant univariate trend towards a lower percentage of patients with HIV-1 RNA less than or equal to 50 copies/ml at 48 weeks and higher pill burden. The authors conclude that this observed association suggests that pill burden is a potential barrier to optimum drug adherence and that simplified dosage regimens may improve adherence.

Stone et al (2001) conducted a cross-sectional study of women living with HIV/AIDS and enrolled in the HIV Epidemiologic Research (HER) Study. A multivariate logistic regression model showed that patients with less complex regimens (twice daily or less in frequency, no food-dosing restrictions) who correctly understood the dosing and food restrictions were less likely to have skipped doses in the previous 3 days than those with more complex regimens (OR 0.4, 95% CI 0.2-0.7). These authors conclude that simplifying ART regimens may have an important role in improving adherence.

Qualitative assessment of adherence in HIV

In a companion study, Mills et al (2006b) have conducted a systematic review of patient-reported barriers and facilitators for adherence to highly active antiretroviral therapy (HAART). The review included 37 qualitative studies (focus groups, semi-structured interviews, open-ended questioning) and 47 using a quantitative methodology (surveys which also used structured questionnaires or structured interviews to determine potential factors). Of the 84 studies, only 12 were conducted in developing country settings; two of these were qualitative studies.

Important barriers in both developed and developing country settings were fear of disclosure, concomitant substance abuse, forgetfulness, suspicions of treatment, regimens that are too complicated, numbers of pills required, decreased quality of life, work and family responsibilities, falling asleep and access to medication.

Thirty-three individual themes of barriers were recorded in 34 qualitative studies conducted in developed countries. A more detailed summary of the barriers identified is shown in the following table (Table 1).

Table 1: Barriers to adherence with HIV medicines from 34 qualitative studies (developed countries)

Category	Barrier (Number of studies reporting)
Patient-related	Fear of disclosure and wanting to avoid taking medicines in public places (23)
	Feeling depressed, hopeless or overwhelmed (18)
	Having a concurrent addiction (14)
	Forgetting to take the medication at the specified time (11)
	Being suspicious of the treatment/medical establishment (9)
	Wanting to be free of medications or preferring a natural approach (10)
	Feeling that treatment is a reminder of HIV status (8)
	Wanting to be in control (7)
	Not understanding treatment instructions (5)
	Still having doubt or not being able to accept HIV status (5)
	Lack of self-worth (4)
	Financial constraints (3)
	Being homeless (2)
	Having other concurrent illnesses affecting adherence (1)
Beliefs about medication	Side effects (either real or anticipated) (27)
	Complicated regimens (12)
	Taste, size, dosing frequency and/or pill count (12)
	Adherence was negatively affected when individuals prescribed HAART felt healthy (9)
	Doubting the efficacy of HAART (7)
	Having a decreased quality of life (6)
	Uncertainty of long-term effects (6)
	Unwanted changes in body image (5)
Daily schedules	Disruptions in routine or having a chaotic schedule (16)
	Finding HAART too inconvenient or difficult to incorporate (14)
	Difficulties co-ordinating adherence with work, family or care-giving responsibilities (11)
	Difficulty in balancing the numerous strict dietary requirements associated with HAART (7)
	Sleeping through a dose (6)
	Being away from home and not bringing medication (6)
	Being too distracted or busy(5)
	Having no time to refill prescriptions, pharmacy-related problems (4)
	Difficulties with a particular dose, particularly middle-of-day or early-morning dose (4)

Category	Barrier (Number of studies reporting)
Interpersonal relationships	Lack of trust or dislike of health care provider (12)
	Social isolation (10)
	Negative publicity regarding HAART or the medical establishment (9)
	Discouraging social network (5)

Source: Mills et al, PLoS Med 2006;3(11):e348

The review notes that there were three barriers described in qualitative reports but not in quantitative studies – having suspicions about HAART, wanting to be in control, and doubting or having difficulty in accepting one's HIV status.

Important facilitators reported in developed country settings included having a sense of self-worth, seeing the positive effects of antiretrovirals, accepting their seropositivity, understanding the need for strict adherence, making use of reminder tools, and having a simple regimen. A more detailed summary of the facilitators identified from 23 studies is shown in the following table (Table 2).

Table 2: Facilitators to adherence with HIV medicines from 23 qualitative studies (developed countries)

Category	Barrier (Number of studies reporting)
Patient-related	Having self worth (15)
	Medication taking priority over substance use (4)
	Seeing positive results when adhering to HAART (6)
	Acceptance of HIV-seropositivity (8)
Beliefs about medication	Belief in the efficacy of HAART and "having faith" in treatment (12)
	Understanding the need for strict compliance (9)
	Having a simple regimen (3)
Daily schedules	Learning to balance HAART with daily schedules (12)
	Having a routine in which taking antiretrovirals could be easily incorporated (11)
	Use of reminder tools (7)
Interpersonal relationships	Having a trusting relationship with a health care provider (17)
	Openly disclosing HIV status to family and friends, having a strong support network (18)
	Living for someone, especially children (9)
	Being actively involved in treatment decision making (4)
	Using friends and family as reminders (6)

Source: Mills et al, PLoS Med 2006;3(11):e348

Four themes for facilitation were identified in the qualitative studies but not mentioned in the qualitative studies – having medication taking priority over substance abuse, having a simple regimen, using reminder tools and living for someone.

Eighteen specific barriers were identified in two studies conducted in developing countries (Table 3).

Table 3: Barriers to adherence with HIV medicines from 2 qualitative studies (developing countries)

Category	Barrier (Number of studies reporting)
Patient-related	Having a co-existing substance addiction, simply forgetting, financial constraints (2) Fear of disclosure (1) Difficulty understanding treatment instructions and the need for compliance (1) Presence of concurrent diseases or illnesses, including malnutrition (1)
Beliefs about medication	Side effects, real or anticipated (1) Complicated regimens (1) Taste, size and frequency of dosing (1) Having doubts about HAART efficacy (1) Feeling fine or healthy (1) Decreased quality of life while taking medications, feeling too sick (1) Being uncertain about long-term effects of HIV treatment (1)
Daily schedules	Trouble incorporating work and family responsibilities with HAART (2) Transportation difficulties (long distances to receive treatment) (2) Running out of medications or irregular supply (1) Being away from home (1) Too busy or distracted to comply properly (1)

Source: Mills et al, PLoS Med 2006;3(11):e348

With the exception of transportation difficulties (long distances to receive treatment), these barriers were similar to those reported in developed country settings.

No facilitators of adherence were discussed in any study conducted in a developing country setting. None of the 10 quantitative studies enquired of difficulties with morning or afternoon doses, work or family responsibilities or listed inconvenience as a barrier.

Mills et al conclude that despite the paucity of evidence from developing country settings, many barriers to adherence can be addressed with patients through discussion and education regarding treatment benefits to health. These authors suggest that in developing country settings, access to medications is the greatest concern. Reports of barriers from more than one study give some confidence in the generalizability of the findings of the review. The authors note that one of the potential limitations of the review is that they did not evaluate patients' perceptions of what adherence meant to them – acceptance, execution or persistence of drug therapy. Further, the limited information from developing countries will be drawn from early adopters of ART. Mills et al note that these individuals may not be representative of the larger epidemic and may not have experienced the longer-term side effects of therapy.

Mills et al suggest that their findings should influence adherence program delivery methods in developing country settings. Issues such as fear of disclosure, suspicions about treatment, forgetfulness and irregular supply were important barriers identified by large proportions of the populations studied. Patient level adherence can only be assessed when a steady supply of medication exists. The authors conclude that given the many factors identified in the review, clinicians should use the information to engage in open discussion with patients to promote adherence and identify barriers and facilitators within their own populations. Barriers to adherence are consistently found across all settings.

A more recent study by Glass et al (2006) concluded that younger age, lack of social support and complexity of therapy are important factors related to non-adherence. These authors suggest that investment in behavioural dimensions of HIV is crucial to improve adherence in ART recipients.

Yuan et al (2006) have investigated reasons for discontinuation of treatment regimens in a US cohort of 3414 anti-retroviral HAART naïve patients. During a median follow-up of 211 days, 18.4% reported discontinuation due to drug toxicity, 13.4% because of non-compliance and 7.5% because of treatment failure. Black ethnicity, current smoking, high pill burden and recent viral control were all predictive of discontinuation. In this study, high pill burden (>15 pills per day), considered a surrogate for regimen complexity, and the most recent poor viral control (HIV RNA) were found to be consistently associated with a higher likelihood of discontinuation. The authors suggest that identification of risk factors and simplification of treatment regimens for those at higher risk of discontinuation are needed to improve adherence and maximise the effectiveness of HAART regimens.

An earlier study by Maggiolo et al (2002) has drawn similar conclusions. Their observational cross-sectional study of 623 patients in Italy concluded that older age, lower numbers of pills, fewer daily doses and shorter time on therapy were factors associated with adherent behaviour. Forgetfulness, being away from home, and problems with dosage schedule were the most frequent causes of non-adherence. This study also showed that adherent patients were more likely to have undetectable viral load than nonadherent patients (76.5% vs 55.3%; p< 0.0001). The authors concluded that simpler regimens with smaller numbers of pills and doses may help compliance with therapy.

Role of patient education and support in improving adherence in HIV

Rueda et al (2006) conducted a Cochrane review of the research literature (RCTs) on the effectiveness of patient support and education to improve adherence to HAART. Only those studies that measured adherence at a minimum of six weeks were included. The authors identified 19 studies (2,159 participants) for inclusion in the review. Study heterogeneity with respect to populations, interventions, comparison groups, outcomes, and length of follow-up precluded combining study results. The populations ranged from general HIV-positive populations to studies focusing exclusively on children, women, Latinos, or adults with a history of alcohol dependence, to studies focusing almost exclusively on men. Study interventions

included cognitive behavioral therapy, motivational interviewing, medication management strategies, and interventions indirectly targeting adherence, such as programs directed to reduce risky sexual behaviours. Ten of the 19 studies demonstrated a beneficial effect of the intervention on adherence. Rueda et al found that interventions targeting practical medication management skills, those administered to individuals rather than groups, and those interventions delivered over 12 weeks or more were associated with improved adherence outcomes. Interventions targeting marginalized populations such as women, Latinos, or patients with a past history of alcoholism were not successful at improving adherence. The authors were unable to determine whether effective adherence interventions were associated with improved virological or immunological outcomes.

Structured treatment interruptions (STI) to improve adherence in HIV

Issues such as the pill burden in HIV, problems with adherence to treatment, the development of resistance and treatment failure as well as the development of drug toxicities have given rise to interest in the use of structured treatment interruptions (STI) in HIV. STI are defined as one or more planned, timing pre-specified, cyclical interruptions in ART. STI have been attempted in monitored clinical settings in eligible participants. Pai et al (2005) conducted a Cochane review examining the evidence from high quality randomized controlled trials on the use of STI in the management of chronic suppressed HIV infection. STI strategies were classified either as a timed-cycle STI strategy (where there is a defined period off therapy) or a CD4-guided STI strategy. Data from 33 studies were included in the review (18 RCTs and non-randomized controlled trials, and 15 single arm trials).

The authors note that timed-cycle STI fell out of favor due to reports of development of resistance in many studies. In addition, there were no significant immunological and virological benefits, and no reduction in toxicities, reported in these studies. Although CD4-guided STI strategy has reported favorable outcomes in the short term, the long-term safety, efficacy and tolerability of this strategy has not been fully investigated.

Pai et al conclude that based on the studies reviewed, the evidence to support the use of timed-cycle STI and CD4-guided STI cycles as a standard of care in the management of chronic suppressed HIV infection is inconclusive.

Other interventions to promote adherence in HIV

Ostrop and Gill (2000) investigated several tools to enhance adherence and persistence with antiretroviral therapy - individualized schedules, dosettes and electronic reminder devices, which were offered free of charge to all patients. Thirty-nine of 64 subjects in the study used at least one adherence tool. The median adherence in those using tools was 95%; and did not differ significantly for schedules (95%) and dosettes (94%). Median adherence with electronic reminders was 76%. The authors concluded that using individualizing strategies, including adherence tools in addition to counselling and follow-up could produce good adherence rates and persistence with antiretroviral therapy.

Stenson et al (2005) report on the implementation of a three step workplace-based ART counselling programme in South Africa. This early evaluation of the program suggests that participants HIV/ART knowledge was good (90% answered 6/7 questions correctly). Participant recommendations for the program were that it be ongoing, and that the counselling need to be respectful, promote HIV testing, address the issues of infected partners and stigma. Participating health care professionals identified additional training needs including counselling of family and friends, family planning, sexually transmitted diseases and running support groups. The authors conclude that the program appears to prepare patients well for ART, and that counselling should be offered at every clinic visit.

Role of DOT-ART to improve adherence in HIV

Mills et al (2006a) comment on the role of interventions such as directly observed therapy of antiretroviral therapy (DOT-ART). In settings with high HIV disclosure rates, community-based DOT-ART with a patient-nominated supporter has been shown to improve or maintain high levels of ART adherence (Farmer 2001, Severe 2005). However, these observations need to be confirmed in well conducted RCTs. Long-term clinic based DOT-ART is not likely to be feasible due to the lifelong nature of treatment of HIV and long transportation distances in rural settings.

Several studies have assessed the use of directly observed antiretroviral therapy (Page-Shipp et al 2004, Libamba et al 2005, White et al 2006).

In their study of the attitudes of HIV-infected miners in South Africa to DOT-ART, Page-Shipp et al (2004) concluded that the strategy was not an immediately popular concept with their clients, primarily more because of a desire to retain responsibility for their own treatment rather than an unwillingness to disclose their status. If DOT-ART were to be the standard mode of delivery for ART programmes, these issues would need to be addressed.

In the pilot study by White et al of directly observed antiretroviral therapy in prisoners, the strongest correlation between inmates' beliefs and their adherence was between "positive beliefs about protease inhibitors". Libamba et al (2005) report adopting several of the principles of TB-DOTS for delivering ART in Malawi: case finding and registration, treatment, monitoring, drug procurement, staffing and the issue of free drugs in an attempt to improve uptake of HIV programs and increase adherence to therapy.

Adherence to medicines in paediatric populations

Adherence in children provides particular challenges and requires a compliant child and a committed parent or caregiver. However a young child may refuse to take the medication for a variety of reasons such as an inability to swallow tablets, an aversion to the taste, feeling unwell and hence refusing to co-operate. Also, there may simply be an antagonism to the person delivering the therapy. Adolescent patients are particularly problematic because of their psychosocial and lifestyle

issues. Factors influencing adherence are similar to those in adults, although the involvement of a caregiver adds an extra dimension.

Studies that have been conducted in paediatric populations suggest that rates of adherence to medicines in children are similar to those in adults (around 50% and decreasing over time). Di Matteo (2004a) concluded that studies of adults (n = 401) yielded higher adherence rates than studies of paediatric patients (n = 116) (76.8% vs 70.2%). In the analysis of correlation with demographic variables, DiMatteo concluded that the age-adherence relationship was stronger in paediatric than adult samples, with a trend for adolescents to be less adherent than younger children.

Osterberg and Balschke (2005) note that few interventions have successfully improved adherence in children; those that have usually have used a behavioural intervention or combination of behavioural and other interventions. Tokens or other rewards for taking medications have been used successfully to improve adherence and are simple reinforcement strategies that can be used by parents and caregivers. Behavioural interventions by contrast generally require resources and staff and may be impractical in resource- poor settings. The use of more palatable formulations has also been used successfully to improve adherence and mobilising social supports with families, schools and communities has been shown to be effective. Improved communication between health professionals their child patients and care-givers or parents can only improve adherence.

DiMatteo's (2004b) qualitative review of the empirical evidence on paediatric adherence examines the issues of communication, patient disease, type of regimen and beliefs held about it, patient's (and family's) habits, experiences and supports, and the health professional-patient-family relationship. DiMatteo suggests that adherence is dependent on a number of factors that relate directly or indirectly to communication. Families must accept the importance of taking the medication as prescribed and reporting side effects. DiMatteo suggests written summaries of medications and methods for assessing and tracking adherence are of value. The presentation of information to the family is vital to observance of the regimen and giving information to the child is essential for coping with the illness. This must be tempered with recognition of both the developmental and the intellectual capacity of the child. The older the child, the more likely the understanding of the complexities of the information.

Trust in the health professional-patient relationship is central to truthful reporting of adherence and is associated with better adherence. DiMatteo notes that beliefs and attitudes are among the most well studied predictors of adherence to preventive and treatment regimens - parents' beliefs about the seriousness of the illness and about the medications or treatments prescribed will influence adherence. Relatively little is known about the impact of children's own health beliefs. Parents model health behaviours and coping skills and establish behavioural norms for their children. These will influence adherence - anxiety and depression in the caregiver will be transmitted to the child and can adversely affect adherence. Peer influences will also affect adherence to treatment regimens. In the case of children, the patient's developmental and physical growth patterns can affect both physical and emotional

stress levels. The developmental changes bring challenges in clinical practice as parental supervision is reduced, and responsibility is transferred to the adolescent.

In chronic diseases, adherence will be influenced by the extent to which families can cope with the regimen (scheduling, discomfort, side effects and costs). DiMatteo notes that cognitive modification and behavioural management strategies may be required for more difficult long-term adherence. Assistance such as reducing the complexity of regimens, side effects and costs are essential to integrating treatment regimens into family life. Di Matteo notes there is growing awareness of the effects of illness on sibling relationships, producing impressive maturity in some cases but placing great pressures on well children in others. Social and family support are key factors in pediatric adherence, with roles for 'supportive others' as well as immediate family.

DiMatteo notes that research on interventions to improve communication, health behaviour and adherence in paediatric settings is sparse. Parents and families need to understand what they are being asked to do and given the opportunity to provide feedback on their experience of the regimen. Sources of resistance need to be identified, and beliefs in the efficacy and benefits of treatment enhanced. The influence of others (family, friends, cultural group) need to be recognised.

DiMatteo concludes that interventions to improve paediatric health behaviour need to be broad in form and strategy (combining cognitive reframing, constructive thinking and planning, family therapy and behavioural management including goal setting, shaping and rewards). Interventions should target specific health behaviours, tailored to provide individualised solutions to practical problems as well as characteristics of family and child. Tailoring the regimen to the specific demands of the disease is essential - educational strategies work best for some diseases, behavioural and multi-component strategies work best for others. DiMatteo notes that ultimately, long-term health behaviour and chronic illness management require pediatric patients to learn to care for themselves and children need to be assisted in this transition.

Interventions to improve adherence to medicines in specific paediatric clinical conditions

Asthma

Children with asthma may receive both preventer medication (to be taken every day) and reliever medication (which are only taken when the child is symptomatic). Confusion as to which therapy is taken when may lead to inadvertent non-adherence. Communication is important if this problem is to be averted.

Graves et al (2006) examined recent studies to identify characteristics of interventions that might enhance adherence in young children with asthma. Based on five studies, the authors concluded that it was important to consider the strain on the caregiver role when developing the treatment regimen, to provide devices that parents and children can use, to monitor adherence with electronic monitoring, and to address

parents' concerns and perceptions about treating prodromal symptoms of an asthma exacerbation. Parents are often hesitant to treat cough symptoms, so specific training components may be needed.

Bartlett et al (2002) conducted a small pilot project testing an intervention that used social learning strategies (e.g., goal-setting, monitoring, feedback, reinforcement, and enhanced self-efficacy) and targeted known barriers to individualize a family-based asthma action plan. Families of 15 asthmatic children participated, received up to five home visits by a nurse, and used electronic monitors children's metered dose inhaler (MDI) to provide immediate feedback on medication adherence to the families and validate medication use. Within four weeks, the number of children who were using their medications appropriately doubled from 28.6% to 54.1% (90% increase; p = 0.004).

Chronic rheumatic disease

Rapoff (2006) reviews the available evidence on the management of adherence in chronic rheumatic disease in children and adolescents. Studies conducted suggest that adherence varies widely across patient samples and methods of assessing adherence, but appear less than optimal. In addition, Rapoff reviews studies that identify risk factors for paediatric non-adherence, which can be broadly classified into patient/family factors, disease and regimen factors. The table (page 308) from the paper is reproduced here and identifies both risk factors and possible approaches to improve adherence (Table 4).

Table 4: Factors associated with non-adherence to pediatric medical regimens and possible approaches to improve adherence

Factor	Intervention implications
Patient/family factors	
Low socio-economic status	Target low SES families for intervention; social work consult to link with financial and social resources
Lack of knowledge	Intensive education about disease, treatments and importance of adherence
Low self-esteem and autonomy	Encourage care-givers to promote autonomy and provide positive reinforcement for family efforts to manage regimens
Family dysfunction	Refer for family therapy
High family stress and poor coping	Teach stress management strategies to patients and families (e.g. relaxation therapy)
Low motivation and lack of provider support	Provide support to families and positive reinforcement for managing regimens
Disease factors	
Decrements in adherence over time	Monitor adherence and intervene when adherence starts to drop and is compromising efficacy of treatment
Patient asymptomatic, in remission or has mild disease	Emphasize value of full adherence to prevent symptoms, continue remission or control disease
Disease perceived as less severe by the family	Address long-term negative consequences of uncontrolled disease, balanced with encouragement to continue treatments

Regimen factors	
Complex and costly regimens	Simplify regimens and provide cost-effective care
Late onset of subspecialty care and fewer visits	Educate community physicians about the importance of early identification and referral to rheumatologists, increase visits
Lack of provider attention to adherence issues	Routinely question about adherence issues and address barriers to adherence
Negative side effects	Assess for side effects and provide alternatives for controlling them

Source: Table 2, page 308 Rapoff MA. Best Practice & Research Clinical Rheumatology 2006;20(2):301-314.

Many of the solutions proposed reflect the setting for most of the studies, well resourced developed country settings. The applicability of the some of the proposed interventions for resource-poor settings is doubtful. None-the-less, the general principles of considering family, disease and regimen factors to promote adherence are useful ways to consider possible interventions in all settings.

Tuberculosis (TB)

Cass et al (2005) reported on a structured behavioral intervention which included techniques of self-monitoring and positive reinforcement, to increase children's adherence to treatment for latent tuberculosis infection. Children participating in the program were reported to be 2.4 times more likely to complete therapy than those who did not receive the intervention.

Malaria

A study by Conteh et al (2007) has focused on the issue of provider communication as a potential influence on adherence to malaria treatment in Gambia. Exit interviews were conducted immediately after the consultation with the health care provider with 1337 caretakers of children aged 10 years or less. The authors report substantial mismatch between caretakers' and providers' interpretations of the clinic visit (both diagnosis and treatment regimen). Importantly, the results of this study showed a delay in the administration of the first dose of antimalarial. Local Gambian Ministry of Health Guidelines specify that the first dose of antimalarial should be given under supervision. However, only 9% of patients prescribed antimalarials were given their first dose at the clinic; most caretakers reported intention to administer the dose when they got home. The authors of this study conclude that pre-packaged blister packs of medicines could potentially provide far greater benefit than their additional cost, as in this study the delivery and management of treatment for non-severe malaria was rarely executed according to the primary health care setting protocol. In addition, verbal communication between caretakers and health care providers needs to be strengthened if adherence levels to antimalarial drugs (in this case) are to improve.

Adherence with HIV medicines

A study by Wiener et al (2004) compared three methods of assessing adherence to HIV medicines in adolescents. The study used clinical nurse rating, a Retrospective Self-Report Interview (using two different scoring criteria), and a 24-hour recall phone interview, chosen because of their potential to be integrated within a clinical setting. Reported perfect adherence to protease inhibitors ranged from 31% to 54% depending on the measure used and there was little agreement between the measures.

Gibb et al (2003) used questionnaires completed at 4, 12, 24 and 48 weeks by caregivers of previously untreated HIV-infected children participating in the European PENTA 5 trial. In this study, nelfinavir was reported to be the most difficult drug to take, although this difficulty diminished over time. Comments on difficulties in taking and remembering drugs related to fear of disclosure and to unpleasant drug characteristics. In this study, full adherence was reported more frequently in children older than 10 years and those with symptomatic HIV disease. These authors note that more children reporting full adherence achieved HIV RNA <400 copies/ml.

Reddington et al (2000) used an interview study of 90 caregivers of children with HIV to identify interventions likely to improve adherence to HIV medicines. In this study, children whose caregivers reported no missed doses in the previous week (adherent) were more likely to have an HIV viral load <400 copies/ml (50% vs. 24%, P = 0.04). Nonadherent caregivers (who reported 1 or more missed doses in the previous week) were more likely than adherent caregivers to feel that full adherence is impossible (44% vs. 12%, P = 0.001), to express the need for more help with medication administration (26% vs. 6%, P = 0.02) and were less likely to have informed the school (or day-care) about the child's HIV infection (42% vs. 67%, P = 0.05). Six of 10 potential interventions were rated by a majority of respondents as "very helpful": better tasting medications (81%); longer dosing intervals (72%); medications that did not require refrigeration (63%); access to 24-h telephone advice (62%); a follow-up call from a health care provider (57%); and a pill organizer (56%). Reddington et al conclude that modifications to improve the convenience and palatability of HIV medicines and increased access to medical advice are likely to be the most helpful interventions to improve adherence.

Mellins et al (2004) used a battery of psychological assessments and self-report adherence data in their study of caregivers and 48 HIV infected children aged 7 years or more. Missed doses in the past month were reported by 40% caregivers and 56% of children. In univariate analyses conducted, non-adherence was significantly associated with older age child, worse parent-child communication, higher caregiver stress, lower caregiver quality of life, and worse caregiver cognitive functioning. There were borderline associations between non-adherence and increased child responsibility for medications, HIV disclosure to the child, and child stress. In multivariate analyses, the factors most strongly associated with nonadherence were worse parent-child communication, higher caregiver stress, less disclosure to others, and quality of life. Mellins et al conclude that efforts to improve children's adherence

to complex antiretroviral regimens requires addressing developmental, psychosocial and family factors.

Wrubel et al (2005) investigated adherence to HIV medicines in children from the perspective of the caregiver mothers. Interviews with 71 maternal caregivers in the USA showed that influences on adherence were complex and involved both contextual and longitudinal factors. All but one of the 38 biological mothers was positive for HIV. In 14 cases, the mothers reported that the medication reinforced their guilt by persistently reminding them that they had infected their child. Adherence practices were affected in a positive way by mothers' commitment to adherence, and in a negative way by feelings of stigma and guilt, by the effects of bereavement on children and by children adopting their mothers' attitudes about medications. The interactive process of giving medication was shaped by children's behavior, mothers' developmental expectations for children, and, for mothers with HIV, their adherence for themselves. However, the mother's well being often suffered because of the need to strictly adhere to giving (HIV) medication to their children.

Side-effects also interfered with adherence in this population of patients. Post-medication diarrhea was often countered by the care-giver with-holding the morning medication so the child did not have diarrhea at school. Medication-induced vomiting exacerbated aversion to taking the medicine which was already problematic because of poor palatability.

Family counselling is likely to offer some benefits in this setting. But this is time consuming and costly so will not be practical in resource-poor countries.

Hammami et al (2004) performed a qualititative study of 11 caregivers to assess factors influencing adherence to HAART in a pediatric population in Belgium. This study identified three main factors influencing adherence: adherent patients were found to internalize the medical information to a stronger extent than less-adherent patients. Adherent patients showed stronger motivation to stick to the medical regimen on the basis of personal cost-benefit analyses, i.e., perceived benefits outweighed the costs or difficulties experienced. Adherent patients developed greater problem-solving capacities, i.e., ways to deal with practical complications of medication intake. The interviews also suggested a fourth, more dynamic component: knowledge, motivation, and capacities evolved in a progressive way, related to individual stages of coping with HIV. The authors concluded that the data suggest that coping with HIV and the process of establishing good adherence may be interrelated.

Pontali (2005) has considered adherence to HAART in children. Key interventions centred on the patient and his or her family are the tailoring of the HAART regimen to the daily activities of the child and family and implementing an intensive education program on adherence for the child and caregiver prior to starting the treatment. Specific medication related issues such as pharmacokinetic and pharmacodynamic properties, taste, palatability and food interactions cannot be solved by clinicians and families; rather greater commitment from the

pharmaceutical industry is required and innovative solutions sought. Pontali suggests that an adherence strategy or program should be part of all institutions working in paediatric HIV infection. He notes that most of the necessary interventions can be easily implemented but require trained and committed staff (and institutions) and time to be spent with patients and their caregivers.

Williams et al (2006) have examined factors associated with nonadherence to antiretroviral therapy. Of 2088 US and Puerto Rican children and adolescents in the study, 84% of care-givers reported complete adherence in the past 3 days. The median viral load was approximately 10 times higher among nonadherent than adherent children, and the strength of the association increased with age. Factors associated with at least marginally significant increases in nonadherence were increasing age particularly in adolescence which itself can be a time of immense emotional turmoil, female gender, detectable HIV viral load, occurrence of recent stressful life events, repeating a grade at school, diagnosis of depression or anxiety. Factors associated with improved adherence included having an adult other than a parent as the primary caregiver, using a buddy system to help to remember to take ART medications, higher caregiver education level, previous adherence assessments, and taking antipsychotic medications. The authors suggest these findings highlight the importance of evaluating and supporting the family environment to optimise adherence.

Brackis-Cott et al (2003) used a questionnaire to assess ten USA primary care medical providers' (5 physicians and 5 nurses) views regarding adherence to antiretroviral therapy among perinatally HIV-infected children. The providers felt they were able to identify several helpful communication strategies in theory, but they were not able to consistently implement them in practice. They commented that many families were also struggling with poverty, mental health and substance use problems, additional HIV disease in the family, and disclosure issues, all of which can contribute to problems in disease management and adherence to treatment.

Costs of adherence support interventions

Schackman et al (2005) have made an attempt to estimate the direct and indirect costs associated with providing various adherence support interventions for patients with HIV. Data for this cross-sectional study were collected from 9 treatment sites testing 13 adherence interventions (including group sessions, pill organizers, physical/auditory reminders such as pagers, home visits, scheduling separate adherence appointments, staff adherence training sessions). Data elements reported were types of services delivered at the encounter, service delivery setting, provider, intervention delivery mode, adherence tools used, time spent on adherence intervention, travel time, incentive structures, cost of adherence tools, administrative time for scheduling adherence appointments, time for staff adherence training sessions. This study estimated a median direct cost per month of $35 ($5 - $58) per patient and included direct provider costs (66%), incentives (17%), reminders and other tools (8%). From a societal perspective (which included patient time and travel costs), the median direct cost per month per patient was $47 ($24-$114) in 2002 US dollars. The authors argue that in the US setting this expenditure would meet current

cost-effectiveness thresholds. They argue that incorporating adherence interventions into HIV care can delay the development of HIV drug resistance and lead to improved life expectancy and quality of life. Schackman et al argue that although budgets for HIV care may increase in the short-term, the dollars spent on life-saving HIV medications will be used more effectively. Cost-effective solutions that can be instituted in resource-poor settings need to be found.

Summary

The importance of adherence to medicines is exemplified by the large numbers of studies and systematic reviews conducted on this topic. The consistent conclusion is that there are a number of strategies that can be used to try to improve adherence rates but none has proved effective in all settings and in all clinical conditions. Adherence is a behavioural attribute shaped and influenced by many things, and therefore modifying adherence behaviour will be difficult. Most of the interventions shown to be effective have been complex, multifaceted interventions targeting more than one aspect contributing to suboptimal treatment adherence. Successful methods to increase adherence are often complex and labour intensive, and will often also result in increased costs to the health care system.

One of the major Cochrane reviews (Haynes et al 2007) on adherence in short-term and long-term chronic conditions concluded that improving short-term adherence was relatively successful, although benefits in clinical outcomes were generally not shown. Methods for improving adherence for chronic health conditions tend to be complex and not very effective. Studies in specific clinical areas have not identified interventions that have worked consistently.

Several of the reviews on adherence have attempted to identify useful categorizations for the influences on adherence as a means to systematically identify interventions that might target these influences. In his review of adherence in chronic rheumatic diseases in children, Rapoff (2006) classifies the factors associated with nonadherence as patient/family factors, disease factors and regimen factors. In a review of patient reported barriers and facilitators for adherence to HAART, Mills et al (2006b) categorize the influences as patient-related, beliefs about medication, issues relating to daily schedules and interpersonal relationships (with family and health care providers).

Reflecting similar themes, Osterberg and Blaschke (2005) suggest methods to improve adherence can be grouped into four categories - patient education, improved dosing schedules, increased hours when the clinic is open (reflecting increased access), and improved communication between physicians and patients. Strategies that are practical for routine clinical use are required.

Lienhardt and Rustomjee (2006) suggest that solutions to the problems of non-adherence need to address socio-cultural barriers, economic barriers, geographical constraints and health system barriers. However, sitting behind these categories of factors are a complex of psycho-social, medical and health service organizational

issues that will likely contribute to non-adherence to a differing extent in individual patients.

There are however some key themes that can be identified from the literature.

Simplifying dosage regimens (both dosage frequency and numbers of tablets) is an important step in improving adherence to medicines in both adult and paediatric patient populations. There is trial evidence that once daily and twice daily regimens are associated with better adherence than three and four times daily schedules. There is limited formal trial evidence to support the use of fixed dose combinations as a mechanism to improve adherence, but numerous studies have identified pill burden as an issue, particularly in HIV infection. At a programmatic level, the use of fixed dose combination preparations is also likely to facilitate improved storage and distribution of medicines, an important consideration in resource-poor settings. Where multi-drug therapies are important for treatment (e.g. tuberculosis, malaria, HIV), fixed dose combination preparations are likely reduce the chances of use of only some of the drugs in the treatment regimen, and in the longer term, help reduce the development of resistance that occurs in these infectious diseases.

There is some evidence that adherence tools such as pillboxes to organise doses, and organising cues to remind patients to take medicines will assist in improving medicines adherence. However the quantitative benefits of these appear to be small. They may however be a relatively cheap intervention and a useful adjunct to other educational and informational activities to improve adherence. While directly observed therapy (DOT) has been widely adopted as a policy for medicine administration in tuberculosis treatment, there is in fact little evidence from randomised controlled trials to support the policy. However, it has been suggested as one possible approach for improving adherence to HIV therapy.

Access is an important issue, particularly in developing country settings. Access may be geographical access as well as economic access. Economic barriers can be moderated by the integration of care for diseases into public health services, where diagnostic and treatment services are free, or costs take account of the ability of individuals to pay for their care. Geographical constraints can be addressed by decentralisation of diagnostic and treatment services. Thiam et al (2007) report on qualitative studies which conclude that in areas in which patients live far from health centres the positive effect of free treatment may be offset by indirect transportation costs and patients may prefer to give up treatment due to these costs. Decentralisation of services means that local health services need to be adequately supported, supplied and supervised to ensure that appropriate services can be provided.

A recurring theme in the literature on adherence is the importance of the patient-family-health care provider relationship. Trust and good communication are essential. Health care providers need to spend time with patients to provide information and education, to enquire about difficulties with managing treatment regimens, and to provide advice or alternatives to deal with side effects of therapy. Physicians contribute to poor adherence by prescribing complex regimens, failing to

adequately explain benefits and side effects of a medication, not giving consideration to the patient's lifestyle or the cost of the medications and having poor therapeutic relationships with their patients (Osterberg and Blaschke 2005).

Adherence to medicines in children:

There is some quantitative evidence to suggest that adherence in children is lower than in adults, and trends that suggest that adolescents will be less adherent than younger children. Many of the factors influencing adherence in paediatrics are similar to those seen in adult patient populations. Convenient and simplified dosing regimens, appropriate and palatable formulations are key aspects that need to be addressed. The need for a caregiver, most often a parent, to be involved adds an extra dimension to the problems of adherence in children.

While little is known about children's health beliefs and its impact on adherence to therapy, there is much more evidence to show that parents' beliefs about the seriousness of the illness and about the medications and treatments prescribed will influence adherence (DiMatteo 2004b). In chronic illness, not only are parental beliefs and attitudes important, but also the family's ability to cope with the regimen (scheduling, discomfort associated with the treatment, side effects and costs). Social and family supports are key factors in improving and maintaining paediatric adherence. Families need to be supported and education provided so that patients and families understand the nature of the illness, the likely course of disease, the value of the therapeutic treatments offered and the importance of adherence to the prescribed regimens.

Improving adherence in children also requires recognition of the different stages of psychosocial development of the patients. Adolescents are particularly challenging as they increasingly take responsibility for their own medicines and disease management and need to deal with peer pressures and their perceptions of their place in the world. Ultimately, paediatric patients need to learn to care for themselves and children need to be assisted in the transition.

Adherence in HIV/AIDS

Given the importance of adherence rates of around 95% in HIV treatment regimens, studies of adherence to therapy in HIV/AIDS, barriers and facilitators of adherence both in adult and paediatric populations have been extensively studied and reported.

In their quantitative study, Mills et al (2006a) identify cost, not disclosing HIV status to a loved one or fear of being stigmatized, alcohol abuse and difficulty in following complex regimens as important and prevalent factors negatively affecting adherence in sub-Saharan Africa. Of these, simplifying treatment regimens (frequency and numbers of pills) and cost of medicines may be the easiest to address. All adherence is predicated on ensuring access to affordable medicines, and reliable drug supply and distribution networks so that treatment can be followed. Having to travel long distances to access care and medicines will negatively affect adherence to treatment regimens.

Promising strategies for improving adherence to HAART studied in RCTs include pharmacist-led individualised interventions, cognitive-behavioural educational interventions based on self-efficacy theory, and cue-dose training in combination with monetary reinforcement. Trials have also investigated the use of handheld devices, two-way pagers, medication vials equipped with alarms, and the enhancement of social and emotional support. While variously effective, all of these proposals have limited application in resource-poor settings.

Qualitative studies in developing countries have identified a range of barriers to adherence to HIV treatment. Facilitators to adherence include having a sense of self-worth and accepting one's seropositivity (such patients may be more inclined to disclose HIV status to trusted family and friends), and understanding the benefits of treatment and strict adherence, use of reminder tools and simple regimens (techniques for taking control and managing medicines better). De-stigmatizing disease to enhance disclosure requires changing of attitudes and acceptance within communities, which may be facilitated by education and information. The medication issues can be addressed, in part, by increased health worker awareness of possible barriers to adherence and improved communication with patients and their families on how these might be addressed.

Directly observed therapy with antiretrovirals (DOT-ART) appears to show promise as an intervention to improve adherence to therapy in HIV. One of the major difficulties is that, unlike tuberculosis where DOTS is standard practice in many settings, antiretroviral therapy is lifelong, rather than time limited as occurs with TB. There is evidence that both family and community DOT supporters can achieve good treatment outcomes, highlighting the fact that not all care needs to be provided at a health care facility; families and communities have an important role to play. Allowing patients to choose their own treatment supporter can also facilitate supervision that is most appropriate to their daily lives. Making therapies easy to include in routine activities has been identified as an important mechanism to improve adherence.

Conclusion

There are no "magic bullets" or single interventions that are guaranteed to improve adherence and maintain it longterm. The need for specific programs to improve adherence in chronic conditions is a recurring theme in the literature. These programs need to be tailored to individual needs, recognizing the patient/family, disease and regimen factors relevant in each case. These programs are not without cost, particularly those of time of health care providers for both training and improved communication with and education of patients (and caregivers in the case of children). Questions about adherence and difficulties faced in adhering to regimens need to be an integral part of all interactions with health care providers. Funding streams, including donor programs, need to consider integration of adherence support programs into their work to ensure that the large amounts of money spent on medicines is used most effectively to improve health outcomes.

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