Assessing and improving adherence with multidrug therapy

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Summary

Introduction: Adherence with multidrug therapy (MDT) in the treatment of leprosy is important to minimise the risk of relapse and avoid the emergence of drug resistance. Adherence is defined as the extent to which the patient’s behaviour matches recommendations from the prescriber. This paper reviews the methods for assessing adherence with MDT in leprosy, and community approaches to improving adherence based on evidence from the treatment of tuberculosis (TB) and HIV, as well as leprosy.

Methods: To identify and summarise the available literature regarding the assessment of treatment regularity in leprosy, a literature search of MEDLINE was conducted using the following search terms: ‘leprosy’ AND (‘adherence’ OR ‘compliance’ OR ‘concordance’). To identify evidence for interventions that have involved community members in HIV, TB or leprosy adherence support, a literature search was conducted using the key terms and medical subject headings ‘treatment or adherence’ ‘community,’ ‘HIV, TB or Leprosy’ and ‘low and middle income countries’ combined using Boolean operators.

Results: Leprosy programmes routinely use defaulting and treatment completion as proxy measures of adherence as recommended by the WHO global strategy. However, a number of other methods have been used to assess adherence including questionnaires, pill counts, as well as direct measures based on testing urine for the presence of dapsone. Direct methods were extensively used during the dapsone mono-therapy era but there is little evidence of their use in MDT. Use of multiple methods of assessing adherence improves the accuracy and reliability of the results. Community activities in TB and HIV such as variants of treatment observation, and/or wider programmes of counselling or direct support to the patient or their family or to increase community or social support were shown to improve treatment
Outcomes evaluated included treatment default and completion, clinical indicators, and adherence (pill-count, self report).

Conclusions: Adherence is very important in leprosy and regular assessment of medication adherence together with constructive feedback and counselling of patients is likely to be beneficial. Leprosy programme can learn from adherence support interventions developed by both TB and HIV programmes.

Introduction

Adherence with multidrug therapy (MDT) in the treatment of leprosy is important to minimise the risk of relapse and avoid the emergence of drug resistance. Poor adherence with MDT has also been associated with the risk of reactions and disability. Adherence has been defined as the extent to which the patient’s behaviour matches recommendations from the prescriber. Leprosy programmes routinely use treatment completion and defaulter rates as proxy measures of treatment adherence in leprosy which focus on the health service delivery aspect of adherence. This is extremely important as a major cause of poor adherence is the interruption of the supply of drugs due to logistical or cost reasons. Accompanied MDT is one initiative that can ensure drug supply to patients.

Leprosy programmes perform well on treatment delivery, as measured by treatment completion rates, through the uninterrupted provision of high quality MDT in blister packs free at the point of delivery. The supervised monthly dose, the use of blister packs, and shortened regimens are all health system factors that can improve adherence. In contrast, there is relatively little evidence on adherence with MDT after delivery to the patient. There were many studies published assessing adherence with dapsone monotherapy in the era of widespread dapsone resistance but since MDT was introduced the topic has been neglected. Few studies assessing adherence have been published in the past 15 years but a recent study from India has indicated that the issue demands further study.

Defaulting in leprosy treatment occurs early in the treatment and the causes can be related to health care provision, the treatment and the patient. Socio-economic, life circumstances and social stigma are important factors in non-adherence. In India, loss of wages, adverse drug reactions and social stigma have been identified as key factors. Acknowledgement of the diagnosis and disclosure of the diagnosis have also been shown to be important to adherence. The World Health Organisation (WHO) report on adherence to long-term therapies stress the need for social support for patients rather than blame and advocate multidisciplinary approaches to involve families, communities and patient organisations to improve adherence.

This paper reviews the methods for assessing adherence with MDT in leprosy and community approaches to improving adherence based on evidence from the treatment of tuberculosis (TB) and HIV, as well as leprosy.

Assessment of Medication Adherence in Leprosy

Since the emergence of drug resistant strains of Mycobacterium leprae, the WHO has greatly emphasised the need to ensure that patients with leprosy complete their treatment on time. The potential spread of rifampicin-resistant M. leprae is considered one of the most serious

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threats that could impede the ongoing efforts to further reduce the disease burden in leprosy endemic countries. Therefore, WHO advocates the use of timely and effective measures to combat the problem of drug resistance, which includes the monitoring of medication adherence amongst patients with leprosy.

METHODS

There is no agreed ‘gold standard’ measure of adherence and the definition of adherence varies markedly between studies. Direct measures of adherences include examinations of blood, urine or other bodily fluids for the presence of a drug or metabolite. Indirect measures include questionnaires, pill counts and analysis of pharmacy records. Whichever measure is used, there is evidence that simultaneous use of different assessment methods improves the accuracy and reliability of results obtained. To identify and summarise the available literature regarding the assessment of treatment regularity in leprosy, a literature search of MEDLINE was conducted using the following search terms: ‘leprosy’ AND (‘adherence’ OR ‘compliance’ OR ‘concordance’) in the paper title or abstract.

TREATMENT DEFAULT

One of the most frequently used proxy measures of medication adherence in leprosy is that of treatment default. The WHO uses this indirect measure to identify patients who have not completed their treatment on time and as an indicator of the quality of leprosy services. Patients with paucibacillary (PB) and multibacillary (MB) leprosy must complete their courses of multi-drug therapy (MDT) within a maximum time-frame of 9 and 18 months, respectively. Any patients who do not achieve this target are labelled as treatment defaulters.

In a retrospective assessment for treatment default amongst patients registered in Northern Mozambique between 1993 and 1997, 378 (40.8%) did not complete treatment. A similar treatment default rate was found in New Delhi, India, with greater than 50% of assessed patients not completing treatment on time. In the same geographical area, between 2000 and 2009, a treatment default rate of 19.8% was reported amongst children of less than 14 years of age. However, not all studies have found high treatment default rates. A Brazilian study retrospectively assessed medication adherence amongst 1,469 cases registered between 2001 and 2007 and identified 48 defaulters, equating to a default rate of 3.4%.

QUESTIONNAIRES

Questionnaires can be used to indirectly assess medication adherence. In a study of 56 patients registered in Hyderabad, India, in 2009, 13 patients (25%) were found to be non-adherent following assessment by an interviewer-administered patient self-report questionnaire. Similarly, 30% of 233 study subjects were non-adherent as determined by pre-tested interviews conducted in Cebu, Philippines.

PILL COUNTS, BLISTER PACKS AND ANALYSIS OF PHARMACY RECORDS

Pharmacy-related resources have also been useful in assessing medication adherence. Nine percent of patients with leprosy in Raipur City, India, were found to be non-adherent...
according to the results of pill counts. Blister packs have also been used to measure adherence and are recommended by the WHO as a means to improve adherence. Forty percent of patients in Western Sudan did not collect enough medication to complete treatment, according to their treatment records.

**DIRECT MEASURES OF MEDICATION ADHERENCE**

The most commonly used direct measures of adherence in the treatment of leprosy involve testing urine specimens for the presence of dapsone, which is taken daily in MDT. The most popular methods include the dapsone tile test, the dapsone:creatinine (D:C) ratio test and the urine spot test. Huikeshoven et al. found that urine spot tests will be negative after an average of three missed doses of dapsone. Although it was reported that the quantitative D:C ratio test appeared to be more sensitive than the qualitative urine spot test in detecting non-adherence, the latter was more specific and considered the method of choice when rapidity and reproducibility are the prime objectives and sensitivity can be marginally compromised. Other authors agree that the urine spot test is relatively simple, easily performed in field conditions and that results correlate well with those of the D:C ratio test.

Numerous studies have used the urine spot test in field conditions and the vast majority show significant levels of non-adherence amongst patients with leprosy. In 2009, 13 out of 52 patients (25%) in Hyderabad, India, were found to be non-adherent according to the urine spot test. A study conducted in Kaduna State, Nigeria, which was published in 1995, showed that 20% of 258 patients were non-adherent. In 1991, a study was published that found 55 out of 341 (16·1%) outpatients treated in Eastern Nepal were non-adherent. In 1989, a study was published that found 45 out of 337 (13·3%) Nepalese patients were non-adherent. In 1988, a study was published that found 45·4% of 366 patients in Agra, India, were non-adherent. Authors that used the dapsone tile test or the D:C ratio test to measure adherence obtained similar results. Using the D:C ratio, a study in 1993 found 82 out of 294 (28%) patients in Mumbai, India, were irregular in consuming dapsone. In another study in the same geographical area, 65% of patients were non-adherent to treatment on repeat testing with the dapsone tile test. The findings are summarised in Table 1.

**Table 1.** Studies directly assessing medication adherence in the treatment of leprosy

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Date published</th>
<th>Geographical area</th>
<th>Measure of adherence used</th>
<th>Non-adherence rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiand et al.</td>
<td>2009</td>
<td>India</td>
<td>Urine spot test</td>
<td>13 out of 52 patients (25%)</td>
<td>4</td>
</tr>
<tr>
<td>Lammers et al.</td>
<td>1995</td>
<td>Nigeria</td>
<td>Urine spot test</td>
<td>20% of 258 patients</td>
<td>37</td>
</tr>
<tr>
<td>van Trier et al.</td>
<td>1991</td>
<td>Nepal</td>
<td>Urine spot test</td>
<td>55 out of 341 (16·1%) outpatients</td>
<td>20</td>
</tr>
<tr>
<td>Roche et al.</td>
<td>1989</td>
<td>Nepal</td>
<td>Urine spot test</td>
<td>45 out of 337 (13·3%) patients</td>
<td>33</td>
</tr>
<tr>
<td>Girdhar et al.</td>
<td>1988</td>
<td>India</td>
<td>Urine spot test</td>
<td>45·4% of 366 patients</td>
<td>34</td>
</tr>
<tr>
<td>Revankar et al.</td>
<td>1993</td>
<td>India</td>
<td>D:C ratio test</td>
<td>82 out of 294 (28%) patients</td>
<td>29</td>
</tr>
<tr>
<td>Naik et al.</td>
<td>1990</td>
<td>India</td>
<td>Dapsone tile test</td>
<td>65% of patients</td>
<td>22</td>
</tr>
</tbody>
</table>
Community Based Support for Medication Adherence

Achieving adequately high levels of adherence is challenging. Patients in Low and Middle Income Countries (LMICs) face many additional barriers including limited resources and weak health systems. Factors such as high travel costs and lost wages due to waiting times have been found to be particularly relevant to adherence to antiretroviral treatment (ART) in African settings. Stigma and lack of disclosure can mean that patients do not receive adequate support from family and community. Treatment of HIV and tuberculosis (TB) faces similar constraints and challenges and provides useful examples of interventions for leprosy. Approaches used in HIV and TB include task shifting to non-health workers and community based interventions with involvement of community members. Different forms of community based treatment support have been advocated ranging from simple interventions using direct observation by a community member through to more complex programmes which include social or financial support.

METHODS

The aim of this review was to capture evidence for interventions that have involved community members in HIV, TB or leprosy adherence support in LMICs. Studies were included that described any combination of individual or collective community activity in delivery of care, decisions about how care should be delivered or what care should be provided. This included interventions that involved peers and community lay health workers (LHW), though not studies that exclusively involved family members. Study designs included randomised controlled trials, controlled before and after with one or more control groups, interrupted time series or controlled clinical trials. MEDLINE and Embase were searched. Key terms and medical subject headings used to capture ‘treatment or adherence’ ‘community,’ ‘HIV, TB or Leprosy’ and ‘low and middle income countries’ were combined using Boolean operators.

INTERVENTIONS TO IMPROVE ADHERENCE

Studies retrieved were set in Indonesia, Iraq, Kenya, Mozambique, Nepal, South Africa, Tanzania, Thailand and Uganda. Both rural and urban settings were included. Conditions included TB and HIV/AIDS. No leprosy studies were found.

Activities were broadly characterised as variants of treatment observation, and/or wider programmes of counselling or direct support to the patient or their family or to increase community or social support. Outcomes evaluated included routine treatment outcomes such as treatment default and completion for TB, clinical indicators for HIV (e.g. CD4 and viral load) and adherence (pill-count, self report).

Many studies compared community direct observation to observation at the health facility, family and/or self-administered treatment. Treatment observers in the intervention arms included forms of LHWs, trained volunteers, former patients, shop workers and lay leaders and community members. Where there was an option of family or community member the latter were used infrequently. Treatment observers were chosen either by patients, clinic staff or lay leaders.
Two of these studies found significant improvements in cure and completion rates\(^{42,53}\) and five were equivalent\(^{45,49–52}\) though mortality rates were significantly lower for one.\(^{50}\)

Where analysed, community DOT was less costly\(^{45,49,51}\) but community perspective revealed increased financial burden to patients\(^{57}\) or treatment supervisors.\(^{58}\)

Some interventions combined direct observation with additional support to deliver ART. Peers observed treatment, provided education and increased access to social support and community groups.\(^{44}\) Patient nominated supporters were given additional training and provided once daily DOT.\(^{48}\) Results were mixed. Modified DOT had significant improvements in adherence in both the 7 day measure (94·4% vs. 87·7%, % difference 6·8, 95% CI 0·9 to 12·9) and the 30 day measure (95·2% vs. 88·5%, % difference 6·6, 95% CI 0·6 to 12·6) but less than the 10% deemed clinically relevant.\(^{44}\)

More complex interventions for TB services include comparison of direct observation by household members to a programme supplemented by decentralised care and community support by providing education to the community and supervision at the local health service.\(^{41}\) Another study used a holistic programme of care delivered by LHWs chosen by the community and trained in primary health care, HIV/AIDS and social development. LHWs provided either DOT and/or a mentoring role, acted as an advocate for the community and contributed to the development of health committees. Sustainability was supported through development of income generating activities by villagers.\(^{47,59}\) Both studies demonstrated significant improvements in TB treatment outcomes for new patients.\(^{41,47}\) An overall reduction in costs was noted but the community cost was unknown.\(^{60}\)

A smaller group of studies evaluated interventions that had no direct observation component. A multi-faceted programme with a treatment supporter, treatment buddy (family or friend) and lay adherence counsellor providing adherence support to TB patients was compared to DOT (health facility, community or workplace). This found small increases in smear conversion at 2 and 3 months for new smear positive patients (Incidence rate ratio (IRR) 1·08 95% CI 1·00–1·07 and IRR 1·08, 95% CI 1·02–1·04 respectively).\(^{46}\) A similarly complex package of facility and home based counselling, clinical services, adherence monitoring and social support delivered through community based peer health workers was evaluated for HIV. This showed significant reductions in virological failure from 96 weeks onwards.\(^{54}\) An intervention using patient selected treatment supporters (family, friends or neighbours) who received education and who were required to commit to supporting patients in HIV, ART and other practical needs found increased likelihood of optimal adherence (OR = 4·51, 95% CI 1·22–1·62, exact \(P = 0·027\)), though there was no significant differences in mean adherence.\(^{55}\) Community based care provided by people living with HIV/AIDS (PLWAs) supported with personal digital assistants (PDA)s who visited patients monthly were shown to provide equivalent outcomes to facility based care, however only adherent clients were eligible to enrol in the study.\(^{43}\)

Discussion

The current WHO strategy uses treatment default rates as a proxy for overall medication adherence and as an indicator of the quality of leprosy services. However, labelling a patient as a treatment defaulter does not provide any information about when during treatment defaulting occurs\(^{5}\) and is of little use in preventing irregularity in drug intake. In 1992, Becx-Bleumink found that whilst 82·6% of 963 patients attended clinic in Ethiopia with
100% regularity, 12.7%, 3.6%, and 1.1% missed one, two, or three clinic appointments, respectively. Under the current guidelines, none of these patients would be labelled as treatment defaulters, despite the likely irregularities in drug intake. It is true that occasionally iatrogenic factors take precedence and therapy is discontinued in the hope of controlling medication side effects or a leprosy reaction but, nonetheless, irregular intake of medications is usually due to poor adherence.

To improve medication adherence, it has been proposed that drug intake should be checked periodically by pill counts or a simple urine spot test whenever possible. There are numerous examples in the published literature of the successful implementation of such initiatives. In 1994, Naik et al. found that about 10% of 2952 urine specimens from patients with leprosy in Mumbai, India, tested negative according to the dapsone tile test. Following constructive feedback and counselling of patients showing poor medication adherence, an improvement in drug intake was found in over 80% of cases. Similarly, in an earlier study by Naik et al., 52% of those patients who tended to be irregular in their drug intake according to the dapsone tile test became adherent after counselling. In the United States, Piscitelli et al. used the D:C ratio test to show that overall adherence over a 6-year period was 81.6%, which was significantly better than the baseline compliance in the leprosy clinic of 46.7%.

In summary, a variety of studies using different measures of adherence have been published, which show that poor drug intake is endemic amongst patients with leprosy. This is of concern because irregularity with treatment is considered to be contributory to the persistent infectivity of old cases and is likely to facilitate the emergence of drug resistant strains of M. leprae. Regular assessment of medication adherence together with constructive feedback and counselling of patients with poor adherence is likely to be beneficial and may improve the effectiveness of the global strategy to reduce the disease burden due to leprosy. Integrated settings can improve adherence due to closer supervision.

Ensuring adequately high adherence in the context of limited resources is difficult. Focussing on providing support in and by the community has the potential to address many of the barriers. Cross fertilisation between HIV and TB adherence support interventions demonstrates that much can be learnt from other programmes. However with all these interventions it is also important to ensure that they do not have a negative impact on patients or community members for example by increasing costs, leading to stigma or burdening particular groups disproportionately.

Community based DOT without additional interventions used for TB showed at least equivalent outcomes. Though use of community member observation was low where the option of a family member existed, it may be an important option to ensure that patients are able to access this support when no family member is available, particularly as isolated patients may be those most vulnerable to poor adherence. These programmes have the potential to mitigate some of the negative consequences of facility based programmes such as the costs but caution is needed to ensure that these are not displaced to the community.

The evidence for modified direct observation programmes used for HIV was mixed but components of these interventions may be useful given the improvements found. This is reinforced by the positive findings from the TB programmes that used a more holistic approach which involved the wider community in support as well as direct observation of treatment. Increased social support can be associated with better outcomes for physical and mental health and this may be mechanism behind positive outcomes. Of the studies that used adherence support interventions without a direct observation component those using community based peer health workers demonstrated positive results.
Accompanied MDT for leprosy was introduced in 2000 whereby the entire supply of MDT drugs would be provided and someone close to or important to the patient would assume responsibility for helping complete the full course of treatment. The approach was seen as controversial and lacking in evidence, although an evaluation of the approach in Madagascar showed promise.

The determinants of adherence are multi-factorial and adherence support interventions may need to address multiple barriers. Using programmes that provided a wider range of support and engaged the wider community with or without elements of direct observation delivered clinically relevant improvements in many cases. These interventions may be more suitable for adaptation for leprosy and also have the potential to bring about wider benefits both to the patients and their community.

References

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