All non-adherence is equal, but is some more equal than others? TB in the digital era.

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Take-home message: Digital adherence technologies (DATs) provide a wealth of information on dose-by-dose anti-TB medication-taking. Studies of DAT data should place non-adherence in standardised taxonomic frameworks in order to best inform intervention and regimen design.

Abstract

Adherence to treatment for tuberculosis (TB) has been a concern for many decades, resulting in the World Health Organization's recommendation of the direct observation of treatment in the 1990s. Recent advances in digital adherence technologies (DATs) have renewed discussion on how to best address non-adherence, as well as offering important information on dose-by-dose adherence patterns and their variability between countries and settings. Previous studies have largely focussed on percentage thresholds to delineate sufficient adherence, but this is misleading and limited, given the complex and dynamic nature of adherence over the treatment course. Instead, we apply a standardised taxonomy- as adopted by the international adherence community- to dose-by-dose medication-taking data, which divides missed doses into a) late/non-initiation (starting treatment later than expected/not starting), b) discontinuation (ending treatment early), and c) suboptimal implementation (intermittent missed doses). Using this taxonomy, we can consider the implications of different forms of non-adherence for intervention and regimen design. For example, can treatment regimens be adapted to increase the 'forgiveness' of common patterns of suboptimal implementation to protect against treatment failure and the development of drug resistance? Is it reasonable to treat all missed doses of treatment as equally problematic and equally common when deploying DATs? Can DAT data be used to indicate the patients that need enhanced levels of support during their treatment course? Critically, we pinpoint key areas where knowledge regarding treatment adherence is sparse and impeding scientific progress.

Introduction

Many decades after initial trials of antimicrobials for TB,[1] the standard treatment for drug sensitive disease remains lengthy at six months; regimens for drug resistant disease can last for two years.[2] Concerns about adherence to treatment over such long periods - and the implications of that non-adherence - led to the World Health Organization (WHO) recommendation of directly observed treatment (DOT) in 1994.[3, 4]

In recent years, digital adherence technologies (DATs; including SMS-based reminders, video supported therapy [VOT], and medication monitor boxes) have increasingly been tested as remote alternatives to DOT/other standards of care as they may be cheaper, more acceptable, and less financially and temporally burdensome.[5, 6] DATs provide healthcare workers with regular, up-to-date, information on how medication has been taken (either accessed at each appointment or remotely each day). DATs can be provided in different ways, e.g. to all patients as the sole source of support or as part of a package of interventions that is personalised to an individual's needs.[7] Intervention packages may be reviewed as a result of appointment-by-appointment (or remote dose-by-dose) evaluation of DAT data that demonstrates the need for enhanced treatment support.[8, 9] Such reviews could also help to determine the patients least in need of dose-by-dose monitoring i.e. providing a 'step-down' approach during treatment.

Like DOT, DATs are interventions to promote dose-taking that assumes all doses are of equal importance. This one-size-fits-all approach latently assumes that missed doses are essentially interchangeable i.e. that each is of equal importance in terms of its clinical implications. This may not be the case; early stage adherence when bacterial loads are higher may be more important than late stage, for example. Additionally, it is assumed that DOT and DATs work equally well across the entire treatment period, which is not always the case.[10]

The advent of DATs provides a unique moment to reassess our global approach to non-adherence to anti-TB medications. Assuming that DAT event monitoring is equivalent to dose-taking, DAT devices provide rich digital datasets of date- and time-stamped information that have not previously been available to the research community. Key lessons about anti-TB medication-taking and best practice for DAT deployment can be learnt, in order to avoid a simple duplication of our current global DOT approach and better personalise clinical care.

In this paper, we take the opportunity of ongoing global evaluation and roll-out of DATs to review and refine a classification of non-adherence to treatment, examine the evidence for the global burden and association of different types of non-adherence with treatment outcomes, and consider what this refined classification of non-adherence means for intervention and regimen design and deployment.

What is non-adherence?

In this paper, we adopt a definition of adherence that emphasises the patient's role in agreeing a treatment plan i.e.:

> *Adherence- when a patient's dose-taking, at any stage during treatment, matches mutually agreed recommendations from the prescriber.*[11]

Therefore, non-adherence represents a divergence from this agreement.

Traditionally, TB research has assessed non-adherence using simple 80-90% thresholds of doses taken across the duration of treatment. To date, few studies have determined whether 80-90% is the optimal point of inflection. Furthermore, this simple binary classification masks extensive complexity across the treatment period. Given this complexity, it is essential to lay out definitions and descriptors.[12, 13] In 2010, partly co-ordinated by the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP), a new taxonomy for

non-adherence was launched.[14] This is the only globally accepted taxonomy for non-adherence, which consists of three core concepts, which are mappable using dose-by-dose data, such as that provided by DATs (Figure 1a) and b)):

1) Initiation, which tracks when the first dose of a regimen is taken relative to the intended start date.
2) Discontinuation, which documents the cessation of treatment.
3) Implementation- how doses are taken during the period of persistence (the timeframe between initiation and discontinuation) i.e. intermittent missed doses (treatment gaps).

As a condition with a time-limited treatment period, TB lends itself to this definitions framework. Drug-sensitive TB is treated for six months with an all-oral regimen, starting with four drugs administered over two months (initiation phase; not to be confused with treatment initiation), followed by two drugs over four months (continuation phase).[15] It is usually dosed daily; in some places, thrice-weekly regimens (although problematic in their own right, see below) are utilised to allow to make DOT less burdensome on both the patient and the healthcare system. Fixed dose combination (FDC) pills are used in many settings. Thus the number of treatment doses expected to be taken in a week can vary from place to place and patient to patient; the number of pills this represents will also vary depending upon a patient's weight. For drug-resistant TB, both regimens themselves and their dosing becomes more complex, and treatment more lengthy.[16]

Within the context of non-adherence to TB treatment, the core concepts can be mapped as follows:

1) Late initiation of, or not initiating, treatment: this charts the time frame between the intended treatment start date after a patient is informed of their diagnosis and the first dose being taken. The reasons for issues with initiation are multifactorial. Delays can be due to a lag in, or non-acquisition of, medication, as well as provided medication not being taken. Non-initiation may be driven by failures in the access of/linkage to care cascade with drivers and consequences that are, therefore, different from late initiation.
2) Early discontinuation of treatment e.g. due to loss to follow-up (LFU; previously known as default).[17]
3) Suboptimal implementation,[12] i.e. the form of non-adherence that has been the focus of both observational studies and clinical trials.

Of note, LFU - as defined by the WHO[17] - is not a clear-cut proxy for early discontinuation of treatment. This is because it is both a standardised end-of-treatment outcome that is reported within surveillance systems (treatment is interrupted for two consecutive months or more), as well as occurring when a TB patient does not start treatment ('initial LFU' or 'pre-treatment LFU').[18, 19] LFU thus a) contains some non-initiation and b) is not the only form of discontinuation due to the time constriction placed upon it. Furthermore, LFU documents non-engagement with clinical appointments, not medication-taking *per se*.

In the next sections, we will discuss how the effect of the three core concepts of non-adherence on TB control depends on two factors: 1) the prevalence of each kind of non-adherence and 2) the impact of each type on treatment outcomes. Throughout this paper, we use a previously published dataset of DAT data to provide a worked example of the concepts that we illustrate (Table 1).

Late or non-initiation

What is the global burden?

Among our core components of non-adherence, non-initiation is arguably most on the global map, as a component part of the WHO's campaign to find and treat the 'missing millions'.[20] The precise number of patients not starting treatment is unknown, although WHO estimates treatment coverage to be 69% globally.[21] For rifampicin-resistant TB, Boyd *et al.* have estimated a similar global mean of 76% of individuals initiating treatment, among those diagnosed.[22] In a review of studies undertaken in low-income and lower-middle-income countries, or those with a high burden of TB, MacPherson *et al.* projected that 18% of individuals do not initiate treatment after diagnosis in African nations and 13% in Asian nations.[18] A later study estimated the figure to be 12% in South Africa.[19]

A series of systematic reviews and meta-analyses have examined temporal delays in treatment initiation (the time frame between diagnosis and the start of treatment). In India among pulmonary TB patients, median delay was 2·5 days (IQR 1·9-3·6)[23] and in the Eastern Mediterranean Region zero to two days.[24] In comparison, a recent observational study from China found the median time from TB diagnosis to MDR TB treatment was six months.[25] This is because the situation in drug resistant disease is additionally complex, as patients may start on the six month regimen whilst waiting for drug sensitivity testing results before their treatment is adjusted (proving a window for further drug resistance to develop),[16] and sourcing second-line drugs may take time.

What is the relationship with treatment outcomes?

Examining the relationship between initiation of treatment and treatment outcomes is complicated by the different measures of lateness used in the literature. In many papers, an overall figure of the delay between symptoms and the start of treatment was quoted, rather than delays between diagnosis and the start of treatment (Figure 2). *In sensu stricto*, we sought to document delays between diagnosis (preferably when it was received by the patient) and the start of treatment only.

In a 2018 review, Melsew *et al.* examined the impact of delays in starting treatment on patient infectiousness.[26] Among eight studies, four found evidence for an association between delays in treatment initiation after the onset of symptoms (with a roughly doubling of the odds of infectiousness), three found no evidence for an association, and one found mixed evidence. The delays charted were from less than a fortnight to more than 90 days.

Evidence from Ethiopia documented a doubling in the adjusted relative risk of treatment failure, death or LFU among those for whom delay was >30 days.[27] This study used a measure of 'overall delay' (from the start of symptoms to the start of treatment) with a median of 55 days (inter-quartile range [IQR] 32-100) documented. Of this, 22 days (9-48) were classed as 'provider delay' i.e. the time post-presentation at a healthcare facility between diagnosis and the start of treatment.

Among MDR patients in Myanmar, in a univariable analysis where treatment delay was classified as between the date of MDR-TB confirmation and the date of treatment initiation, the median treatment delay for patients with poor treatment outcomes (lost to follow up, failed, died) was 144 days, which was longer than among patients who achieved successful treatment outcomes (102 days).[28] In an adjusted analysis comparing the impact of long (≥median of 152 days) versus short (<median) delays, this association was not retained.

In MDR TB patients in China results were also mixed, this time depending upon the measure of delay used. The time between TB diagnosis to the start of MDR treatment showed some effect, albeit with a null-inclusive confidence interval, whereas shorter delays (≤60 days) after the performance of DST showed a doubling or more in the likelihood of a positive treatment outcome, depending upon the other factors adjusted for.[25]

Discontinuation

What is the global burden?

Due to the substantial overlap with LFU and the use of this measure as a standardised reporting outcome, the estimates of the global burden of discontinuation have been captured in many studies. An individual patient data meta-analysis of 9,000 MDR TB patients from 23 countries suggested around a sixth were lost to follow up, with a median timing of seven months.[29] In an older systematic review not specifically for drug-resistant disease, Kruk *et al.* documented likelihoods of LFU of 7-54% and timings of between 42 and 85 days in low- and middle-income settings.[30] There was large amounts of variation between countries and regions. Approaches that include a precise analysis of when discontinuation from treatment occurs and how this relates to LFU should become more common as dose-by-dose monitoring systems are rolled out globally.

What is the relationship with treatment outcomes?

Determining the relationship between discontinuation and treatment outcomes is complex, given the use of LFU both as a marker of discontinuation and a negative surveillance outcome.[17] Useful sources of data include the randomised controlled trials (RCTs) that developed the standard regimen we use today. Historically, it was the addition of rifampicin and then pyrazinamide which allowed treatment to be shortened to six months;[31] further studies showed an important increase in the likelihood of post-treatment relapse when treatment was reduced to four months.[32]

In recent years, several RCTs have sought to shorten the treatment of drug sensitive TB to four months by including fluoroquinolones, but, as yet, none have demonstrated non-inferiority.[33-35] Pooled analyses have indicated that such regimens may be non-inferior in particular patient groups, indicating the need for stratified treatment approaches.[36] Although such regimens are intended to reduce non-adherence by shortening overall duration, this may increase the sensitivity of such regimens to suboptimal implementation i.e. the importance of each dose in the regimen may be increased, relative to a longer regimen, making each missed dose more problematic.

Critically, well-designed studies using dose-by-dose monitoring systems such as DATs together with robust treatment outcome collection will go a long way towards answering remaining questions in this area.

Suboptimal implementation

What is the global burden?

Until recently, suboptimal implementation for anti-TB treatment has been assessed through the differentially reliable self-reported or questionnaire-derived methods (for example [37, 38]) and DOT (e.g. [10, 39-41]). Study protocols also used various thresholds to classify non-adherence, and often reported a mixture of suboptimal implementation and discontinuation in their analyses.

To date, the burden of suboptimal implementation is suggested to be highly variable between countries and regions, e.g. 21·3% in pooled estimate from Ethiopia versus 90·8% in the Philippines, although differences will partly be protocol-dependent.[41, 42] Approaches that include a precise analysis of the types of suboptimal implementation displayed by patients should become more common as dose-by-dose monitoring systems are rolled out globally,[43] e.g. examining the lengths of gaps displayed and when they occur during treatment.[12, 44] For example, in a recent study in China, 47·2% of 780 patients had a dosing gap of a week or more and 95·9% some form of suboptimal implementation (Table 1).[12]

What is the relationship with treatment outcomes?

There has been substantial interest in the relationship between suboptimal implementation and various intermediate and final treatment outcomes. Largely using simple percentage adherence thresholds across the entire treatment period, suboptimal implementation has been associated with unsuccessful treatment outcomes in a variety of settings from Malawi to Israel, in both observational and randomised controlled trial datasets, and using a variety of methods to define and measure implementation.[36, 44-49] In observational datasets from Russia and the US, this association extends to the development of drug resistance,[50, 51] although in simulations it has not been consistently proven.[52] Recurrence of TB disease among pulmonary TB patients was higher with worse implementation in both the Yemen and Vietnam.[53, 54]

Moving beyond adherence thresholds, in MDR TB patients in Armenia and Abkhazia on DOT, Bastard *et al.* noted the criticality of gap length and the time between gaps. Odds of negative outcomes (treatment failure, death or default) nearly quadrupled with interruptions of three or more days and also short periods (<10 days) between gaps.[44] From a different angle in drug-sensitive pulmonary TB, Johnston *et al.*'s meta-regression found that treatment failure, acquired drug resistance, and relapse were more common with thrice-weekly versus daily dosing.[55] The Imperial *et al.* pooled meta-analysis looked at the impact of a six days in seven versus a seven days in seven dosing strategy and found that the former increased the likelihood of an unfavourable outcome (broadly death, treatment failure, a lack of culture conversion, relapse, adverse events), as well as the implications of different adherence thresholds within this.[36]

As for discontinuation, well-designed studies using DATs or other dose-by-dose monitoring systems will be essential to answer the remaining questions in this area.

What do different types of non-adherence mean for intervention and regimen design and deployment?

Effectively preventing non-adherence to treatment not only requires interventions appropriately tailored to patients and healthcare systems, but also the type of non-adherence commonly displayed. Critically, the types of non-adherence displayed and their relationship to treatment outcomes may vary by population group e.g. people living with HIV, individuals with other comorbidities, children and the elderly. Elucidating these relationships requires setting-by-setting data collection using tools such as DATs. This should include how variability in adherence throughout treatment determines the need for 'step-up' interventions.

Late or non-initiation

Non-initiation of treatment after diagnosis can be due to a large number of complex factors, including the lack of accessibility of treatment - e.g. due to costs associated with attending the clinic; under-resourced or poorly functioning facilities; and stigma/lack of awareness of TB.[56-58] Here, interventions include broad systems-strengthening factors that will benefit the entire care cascade, such as better financing of healthcare systems; the provision of free TB drugs to everyone; and the removal of other financial barriers e.g. through cash transfer programmes,[59] as well as 'pull factors' such as improvement of the quality of care; increasing awareness of/decreasing stigma around TB; and improving case detection/outreach. Factors such as strengthening the care cascade and reducing stigma may reduce late initiation, too.

Discontinuation

If discontinuation occurs early enough, even if it is relatively uncommon, it can form a large proportion of missed doses during treatment (Figure 1c). As documented above, early discontinuation is also known to be highly detrimental to treatment outcomes. Therefore, settings should consider the relative burden of discontinuation versus other forms of non-

adherence when planning for effective interventions to implement (Table 1).

When it comes to intervention design, a single intervention may not address all discontinuation, as the drivers are not the same for every patient and sometimes reflect disengagement with care, rather than treatment.

One of the key implications for the development of shorter treatment regimens is their potential to reduce discontinuation,[60] simply by reducing overall duration (Table 1).

Suboptimal implementation and interventions

Intelligent intervention design should be influenced by the common form of suboptimal implementation (including long versus short gaps and erratic versus regular missed doses; Figure 1d), their causes (i.e. treatment-related, individual knowledge and perceptions, social factors, systems issues, temporal factors, and structural factors.[61-64] Also influential, is whether non-adherence is intentional or unintentional,[11] however; making the distinction on an individual basis can be difficult and potentially fruitless.

To date, many interventions have sought to target individual-level cognitive or behavioural factors such as forgetfulness or 'misconceptions' through SMS reminder systems, medication monitor box alarms, or the regular need to report for DOT or VOT.[43] More complex interventions are required to deal with multifactorial causes of non-adherence,[7] such as rapid reporting and support systems. As TB tends to affect socially and economically deprived groups, interventions that focus on individual agency and behaviour- but do not account for social and structural barriers to care (as well as factors that influence a patient's ability to take medication regularly) - are destined to work primarily for those who already have better capacity and social circumstances.[65]

Critically, adherence to treatment is dynamic and can change in response to events and life circumstances of all kinds over time,[66] producing ever-varying patterns of suboptimal implementation. Dose-by-dose monitoring systems that are accessible to healthcare services can be used to promote rapid responsiveness to the frequency and length of gaps that occur during treatment (Table 1), as part of the partnership between patients and healthcare providers.[67]

Polypharmacy is of substantial concern as a cause of non-adherence,[68] and therefore population groups for whom this is an issue should have special consideration in intervention design.

Suboptimal implementation and regimen forgiveness

The 'forgiveness' of treatment regimens reflects their ability to withstand unexpected gaps in dosing.[69] Forgiveness varies from drug to drug, depending on pharmacokinetic parameters, thus each drug will respond individually to different patterns of suboptimal implementation. The development of drug resistance is a key consideration; differing gap lengths can lead to divergent results. Within multidrug regimens, such as those used for TB, the maintenance of sufficient drug blood levels to achieve an antibacterial effect depends upon the metabolism of all the component drugs and thus how they behave in combination. Dosing strategies may potentially be alterable to overcome non-forgiveness, but this should be undertaken in light of considerations surrounding the patient's medication-taking burden (e.g. the number of times doses need to be taken in a day) and whether or not combined pills containing different drugs of different characteristics are used.[70, 71]

We provide two illustrations: not taking any treatment at a given time point versus not taking some of the drugs.

When all drugs are omitted at the same time, the implications of longer and shorter breaks

should be considered separately. Longer gaps from treatment (four days or more) can allow bacteria to restart replication. It is currently unknown how such an increase in the bacterial burden may affect treatment outcomes; it may prolong the treatment length required for a cure. Here, replication after previous exposure to antibiotics may facilitate the emergence of resistance.

Shorter breaks (one to two days; Table 1) may be a problem when different drugs within a combination regimen have different pharmacokinetic properties and therefore some may take a considerably longer time to clear and/or reach their therapeutic levels when the regimen is re-started. As a result, drug concentrations after the first dose and at steady state will differ considerably in some tissues or plasma. For example, Strydom *et al.* have illustrated the effects of the slower accumulation of certain drugs in a pharmacokinetics study on TB patients undergoing lung resection surgery.[72] In the most detailed study of its kind, the authors demonstrated that drug concentrations after the first dose of a drug differ from those at steady state - at least in some tissues - for ethambutol (shown in a different study[73]), pyrazinamide, moxifloxacin, and linezolid. This was not the case for isoniazid, rifampicin, and kanamycin. More studies of this type will help us understand how TB drugs accumulate and behave in relevant lesion types.

During instances when all drugs are omitted at the same time, the drug that clears more slowly will be still present after others, resulting in effective monotherapy during the gap. Even with perfect adherence, it is known that there are periods of effective monotherapy within each day.[72] The impact of such short bouts of monotherapy on the emergence of resistance is largely unknown. Drugs that require multiple days to reach their steady state levels may be below their therapeutic ranges for days after treatment resumes. Frequent short gaps may therefore keep levels below the therapeutic range for a longer period. Illustrations of how this would impact rifampicin and moxifloxacin levels in the lungs are presented (Figure 3).

If FDCs are not used, it is also possible to suboptimally implement specific components of the regimen. During the continuation phase of treatment, suboptimal implementation of one drug will lead to monotherapy; the risk of drug resistance posed by monotherapy was illustrated by one of the first rifampicin trials in 1968.[74, 75] As a result, the current ethical maximum for monotherapy studies is 14 days.[76]

Further data in this area are required to better understand how gap lengths, timings and frequencies of suboptimal implementation carry the most risk for the emergence of resistance or in prolonging treatments, and how this is influenced by patient-by-patient variability in pharmacokinetics (e.g. isoniazid acetylator status) and clinical characteristics known to influence treatment success.[36]

The relationship between different types of non-adherence

In addition to considering the different types of non-adherence in isolation, the relationships between them also have important implications for intervention design. For example, an approximate doubling in the likelihood of discontinuation in the presence of suboptimal implementation of <80% versus ≥90% during the initiation phase of treatment has been demonstrated in data from China (Table 1).[9, 12] Early-stage dose-by-dose monitoring data from DATs could thus be highly valuable at indicating the patients who will later be in need of additional adherence support.

Latent tuberculosis

In our consideration of adherence to TB treatment up to this point, our focus has been on TB disease. Needless to say, the issues raised are equally important for latent tuberculosis infection (LTBI) and preventive treatment; there is still a need for a standardised taxonomic framework within which to discuss non-adherence. Unlike for drug sensitive TB disease,

adherence studies for LTBI need to take into account the different WHO-recommended regimen lengths and dosing patterns when applying this framework.[77]

Numerous studies have documented how adherent patients are to LTBI treatment; such studies have a far greater focus on non-initiation than studies of treatment for TB disease, given the interest in a) patients declining take proferred treatment or b) not being offered treatment.[78, 79] Additionally, the nature of LTBI makes treatment completion the marker of choice for treatment success by National TB Programmes, thus the proportion of patients completing treatment has been extensively reviewed.[78-81] For both non-initiation and discontinuation, levels were highly variable between studies (7-99% and 4-100%, respectively). A global consensus as to which non-adherence patterns can be safely tolerated for LTBI regimens of different lengths is urgently needed. As with TB disease, this should also influence the design of interventions to promote adherence, as well as decisions on which regimens will be most effective in a given population group (balancing cost; the length of the regimen, its adverse event profile and the implications for adherence; and regimen efficacy).

Conclusion

As a global TB community, we find ourselves at a crossroads when it comes to treatment adherence. Through DATs, remote dose-by-dose treatment monitoring has become accessible like never before, and we have a substantial opportunity to deploy precision medicine approaches to develop and target adherence-promoting interventions. In the COVID-19 era, remote monitoring tools are all the more important for TB control due to the need to reduce patient contact with healthcare services (and we also note the likely impact of the disruption of the pandemic on adherence itself).

Important information is, however, missing. Further studies using tools such as DATs need to be rapidly undertaken to fill critical gaps in our knowledge where only limited data exist (Table 2). It is essential that interventions are not adopted at the national scale without rigorous effectiveness and cost-effectiveness studies, such as that being undertaken by the ASCENT project across five countries.[82] During adoption, careful programmatic management is also required to avoid the wasteful parallel development of digital tools to report and manage DAT data.[83]

Although we advocate in this paper for non-adherence to be considered as three separate issues, it is important to note that the underlying causes of each component may be similar and that each component may be inter-related. Effective interventions (such as those taking a stepped approach to enhanced treatment support e.g. by more frequent contact with health systems or resolution of insecure housing, etc.), may work across several components of non-adherence, but this will not been known unless data are analysed in this fashion. Trials of different interventions should also seek to separate their impact on the different components of non-adherence.[13]

The data that arise from studies such as those we propose will raise crucial questions for the future of TB control. For example, are levels of particularly problematic adherence issues low enough globally that it is not necessary to watch patients taking every single dose of their medication? Or should all patients be observed during the initiation phase, given the medication burden, higher replicating mycobacterial load, and connection between early suboptimal adherence and discontinuation, then allowed to self-medicate if no issues are observed? Can culturally-adapted menus of interventions be developed to address the common forms of non-adherence for any given setting? Can we build predictive models to determine which patients are most likely to suffer from which problematic non-adherence issues?

To date, the TB literature has largely treated all missed doses of treatment as equally problematic and equally common. By harnessing the power of dose-by-dose adherence data, particularly through DATs, we can determine which patterns of missingness are ‘more equal than others’ - a finding that could revolutionise our approach to non-adherence.

Declaration of interests

HRS reports grants from Medical Research Council, UK, grants from National Institute for Health Research, UK, during the conduct of the study; other from Korean CDC and Johnson and Johnson (makers of Bedaquiline), other from Latvian Society Against Tuberculosis (funding through Otsuka and Johnson and Johnson), outside the submitted work. MF reports grants from Medical Research Council, UK, during the conduct of the study. ASK reports grants from World Health Organization, grants from Medical Research Council, UK, grants from National Institute of Health Research, UK, grants from Economic and Social Research Council, UK, grants from The Bloomsbury SET (Research England), grants from The Colt Foundation, UK, grants from Viiv Healthcare, USA, personal fees from The Aurum Institute, South Africa, personal fees from Edanz Group, Japan, personal fees from Pastest, UK, personal fees from The University of Cape Town, South Africa, non-financial support from Kyoto University, Japan, non-financial support from Vital Strategies, Singapore, non-financial support from Bloomberg Philanthropies, USA, other from Bill & Melinda Gates Foundation, USA, outside the submitted work. MCIL reports grants from National Institute for Health Research, UK, during the conduct of the study. All other authors have no conflicts of interest.

Funding

HRS and MF are supported by the Medical Research Council [MR/R008345/1]. HRS, ASK and MCIL are supported by the National Institute for Health Research (NIHR) Health Technology Assessment Programme, UK grant number 16/88/06. The views expressed are those of the author(s) and not necessarily those of the National Health Service, UK, the NIHR or the Department of Health and Social Care. The funders did not play a role in the writing of the manuscript or the decision to submit for publication. None of the authors have been paid to write this article by a pharmaceutical company or other agency. The corresponding author had full access to all the data in the study and has final responsibility for the decision to submit for publication.

Authors contributions

All authors contributed to the conception of the work. MF, HRS, AM and PAzW contributed to the acquisition, analysis and interpretation of data/literature for the work. All authors drafted the work/revised it critically for important intellectual content. All authors give final approval of the manuscript version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Table 1. The implications of non-adherence patterns for intervention and regimen design: worked example from China

In a study of 780 patients from a pragmatic cluster-randomized trial in China of electronic reminders to improve treatment adherence,[9, 12] data were taken from the control arm of the trial (electronic reminders set to silent, thus no intervention to promote adherence). Medication monitor boxes provided granular data as to whether each individual dose was taken (box opening used as a proxy). Treatment was dosed every other day. All patients initiated treatment within this study. Decision making as which type of non-adherence should be targeted by interventions will also depend upon the relative impact of each form of non-adherence on outcomes.[84]

Domain	Suboptimal implementation	Discontinuation
Number of participants affected	748/780 (95.9%) of all participants suboptimally implemented their treatment.	235/780 (30.1%) of all participants discontinued early.
Number of doses missed	9,487/16,794 (56.4%) missed doses were due to suboptimal implementation.	7,307/16,794 (43.5%) missed doses were due to early discontinuation.
Patterns displayed	The median gap length per patient was one dose, with a maximum number of gaps per participant of 24. 176/780 individuals (22.6%) had gaps of seven doses (a fortnight) or more. Suboptimal implementation increased over time.	5.1% of individuals had discontinued treatment by the end of month two,14.4% by the end of month four, 18.2% by the end of month five, 36.3% by the end of month six (including individuals missing only their last dose).
Link between suboptimal implementation and discontinuation?	Missed doses in the initiation phase due to suboptimal implementation associated with increased risk of discontinuation in the continuation phase.	
Implications for intervention and regimen design	The causes of large numbers of short gaps need to be ascertained and addressed by an effective intervention.	Given the burden of discontinuation and when it occurs, shortened regimens may have been helpful in this setting. Early stage suboptimal implementation could act as an indicator of patients who require an intervention to prevent discontinuation.

Table 2. Summary of knowledge gaps

Area	Missing information	Impact
Global burden of different types of non-adherence	A better determination of the distribution of non-adherence between late/non-initiation, suboptimal implementation and discontinuation Whether there are substantial differences between (and within) countries. Who displays each pattern Why different patterns are displayed	Stratification of settings/populations on the basis of the interventions that might be useful, including changes to healthcare processes and systems Intelligent intervention design
Trials vs. normal treatment pathway	The extent to which non-adherence varies between clinical trials and in normal care settings	Aids decision-making surrounding the adoption of new regimens (operational efficacy)
Suboptimal implementation patterns	Improved estimates of the frequency and types of suboptimal implementation, explicitly excluding doses missed due to discontinuation Variability in patterns between settings and patients Causes of these patterns	Stratification of settings (e.g. by healthcare system)/populations (e.g. by patient characteristics) on the basis of the interventions that might be useful Intelligent intervention design
Relationship between the different components of adherence	Whether early-stage indicators of non-adherence can predict later issues with non-adherence	Inform clinicians as to which non-adherence patterns should trigger active intervention
Relationship between patterns and patient outcomes	Specific mapping of how different non-adherence types and patterns impact treatment failure (and the need to restart treatment) and the development of drug resistance, in order to prioritise cost-effective intervention development and roll-out	Stratification of settings/populations on the basis of the interventions that might be useful and when they should be 'stepped up' Intelligent intervention design Inform clinicians as to which non-adherence patterns should trigger active intervention
Regimen forgiveness	The impact of the commonly displayed adherence patterns on forgiveness The implications of non-adherence to each drug within the multidrug regimen	Inform regimen design

Figure legends

Figure 1. The different components of non-adherence to treatment

Using the standard taxonomy described by Vrijens *et al.*,[14] it is possible to distinguish between the first and last prescribed doses of medication and the first and last doses taken. In terms of sources of non-adherence- panel a)- firstly individuals may initiate treatment later than agreed with their clinician. Secondly, treatment may be discontinued early i.e. before the last prescribed dose. Persistence is the period between initiation and discontinuation. Thirdly- panel b)- non-adherence arises from how individuals implement their medication; doses may be missed intermittently. In this diagram, the complete regimen is only 10 doses. Adapted from Vrijens *et al.*[14] Panel c) illustrates the impact of discontinuation within an illustrated population of eight patients taking six doses of treatment each before treatment is stopped. 38% (1 - 3) discontinue their treatment early, all at different time points. 75% of patients (3-8) display some form of suboptimal implementation. Despite this, doses missed due to discontinuation make up half of non-adherence across the entire patient population. Panel d) illustrates different types of suboptimal implementation. Patient 1- short, irregular, gaps. Patient 2- long, irregular, gaps. Patient 3- regular gaps. Treatment is not stopped after the last illustrated dose. Green- dose taken, white- missed due to suboptimal implementation, orange- missed due to discontinuation.

Figure 2. Cascade of care until the start of tuberculosis treatment

*These two time points may be on the same day. †For drug resistant tuberculosis patients, drug sensitivity testing results may not be available until after treatment for drug sensitive disease is initiated, necessitating a chance in regimen.

Figure 3. Different patterns in suboptimal implementation lead to divergent results.

Rifampicin (red, 600mg dose) and moxifloxacin (black, 400mg dose) concentrations were modelled in uninvolved lung tissues. This combination is currently being investigated in clinical trials,[85] but the two drugs have very different pharmacokinetic properties. The three different plots show the same suboptimal implementation patterns as Figure 1d). Patient 1- short, irregular gaps. Patient 2- long, irregular gaps. Patient 3- regular gaps. The different shaded areas indicate different issues with drug concentrations. Cream indicates periods where only moxifloxacin is above the minimum inhibitory concentration (MIC). Above the MIC the drug either stops replication completely or eliminates bacteria, therefore during these periods there is an effective moxifloxacin monotherapy. Grey areas are periods where no drug is above the MIC; as a result, bacteria may eventually restart replication. Dark blue periods are when moxifloxacin concentrations do not reach the levels (therapeutic range) expected during proper adherence. In these cases, bacterial elimination rates for the given period may be lower than expected, therefore possibly delaying the time it takes to clear bacteria. The presented MIC cut-offs are mainly for illustration purposes, to indicate time periods where adverse events may occur due to differences in concentrations, rather than capturing events on a bacterial population level. Bacterial population dynamics are governed by multiple factors in addition to drug concentrations e.g. the post-antibiotic effect. For instance, growth rates of bacteria may be affected by the post-antibiotic effect.[86] Furthermore, selection of resistance mechanisms also occurs at sub-MIC concentrations.[87] The plots were made with the model and parameters published by Strydom *et al*.[72]